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# Guide to Receptors and Channels (GRAC), 5th edition

## Abstract

The Fifth Edition of the 'Guide to Receptors and Channels' is a compilation of the major pharmacological targets divided into seven sections: G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside suggestions for further reading. Available alongside this publication is a portal at <http://www.GuideToPharmacology.org> which is produced in close association with NC-IUPHAR and allows free online access to the information presented in the Fifth Edition.

## Introduction

The great proliferation of drug targets in recent years has driven the need to provide a logically-organised synopsis of the nomenclature and pharmacology of these targets. This is the underlying reason for this 'Guide to Receptors and Channels', distributed with the *British Journal of Pharmacology*, and produced in association with NC-IUPHAR, the Nomenclature Committees of the International Union of Basic and Clinical Pharmacology. Thanks to a closer collaboration between the British Pharmacological Society and NC-IUPHAR, a free online portal containing the information presented in the Guide to Receptors and Channels has been established at <http://www.GuideToPharmacology.org>. The new portal gathers in one place the previously separate information on drug targets of GRAC and IUPHAR-DB, the database produced by NC-IUPHAR. Over time, these will steadily be integrated and the portal will be developed as a one-stop-shop for information on drug targets and other information of assistance to pharmacology and drug development in both academia and industry. The free online portal has been created by the IUPHAR Database Team (Joanna Sharman, Chido Mpamhanga, Adam Pawson, Helen Benson, Vincent Bombail and Tony Harmar) in the Centre for Cardiovascular Science, University of Edinburgh.

Our intent is to produce an authoritative but user-friendly publication, which allows a rapid overview of the key properties of a wide range of established or potential pharmacological targets. The aim is to provide information succinctly, so that a newcomer to a particular target group can identify the main elements 'at a glance'. It is not our goal to produce all-inclusive reviews of the targets presented; references to these are included in the Further Reading sections of the entries or, for many targets, the website of NC-IUPHAR (<http://www.iuphar-db.org>) provides extensive information. The 'Guide to Receptors and Channels' presents each entry, typically a circumscribed target class family on, wherever possible, a single page, so as to allow easy access and rapid oversight.

Targets have been selected for inclusion where there is sufficient pharmacological information to allow clear definition or where, in our view, there is clear interest in this molecular class from the pharmacological community. Our philosophy has been to present data on human proteins wherever possible, both in terms of structural information and pharmacology. To this end, the Ensembl ID allows rapid access through a free online database (<http://www.ensembl.org>) to genomes from many other species, including mouse and rat. From this database, links are also provided to structural information in a number of formats. Where structural or pharmacological information is not available for human targets, we have used data from other species, as indicated. A priority in constructing these tables was to present agents which represent the most selective and which are available by donation or from commercial sources, now or in the near future.

The Guide is divided into seven sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear receptors, transporters and enzymes. In comparison with the Fourth Edition of the 'Guide to Receptors and Channels' (Alexander *et al.*, 2009), we have added a number of new records, expanding the total to include over 1600 protein targets. The expansion for the Fifth Edition comes primarily from including the full complement of transporters defined in the human genome, as well as increasing the content on enzymes. As in the Fourth Edition, we have also included lists of 'orphan' G protein-coupled and nuclear receptors. The preliminary pairings for orphan GPCR and nuclear receptors provide information on targets, where there is some evidence for an endogenous ligand or a link to a disease or disorder.

The Editors of the Guide have compiled the individual records, taking advice from many Consultants (listed on page S3). With each record, an indication is given of the status of the nomenclature, as proposed by NC-IUPHAR, published in *Pharmacological Reviews*. Where this guidance is lacking, advice from several prominent, independent experts has been obtained to produce an authoritative consensus, which attempts to fit in within the general guidelines from NC-IUPHAR (Vanhoutte *et al.*, 1996). Tabulated data provide ready comparison of selective agents and probes (radioligands and PET ligands, where available) within a family of targets and additional commentary highlights whether species differences or ligand metabolism are potential confounding factors. We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2011). Guide to Receptors and Channels (GRAC), 5<sup>th</sup> edn. *Br J Pharmacol* **164** (Suppl. 1): S1–S324.

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### References

- Alexander SPH, Mathie A, Peters JA (2009). Guide to Receptors and Channels (GRAC), 4th Edition. *Br J Pharmacol* **158**: S1–S239.
- Vanhoutte PM, Humphrey PPA, Spedding M (1996). X. International Union of Pharmacology recommendation for nomenclature of new receptor subtypes. *Pharmacol Rev* **48**: 1–2.

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# G PROTEIN-COUPLED RECEPTORS

**Overview:** The completion of the Human Genome Project allowed the identification of a large family of proteins with a common motif of seven groups of 20–24 hydrophobic amino acids arranged as  $\alpha$ -helices. Approximately 800 of these seven transmembrane (7TM) receptors have been identified of which over 300 are non-olfactory receptors (see Fredriksson *et al.*, 2003; Lagerstrom and Schioth, 2008). Subdivision on the basis of sequence homology allows the definition of rhodopsin, secretin, adhesion, glutamate and Frizzled receptor families. NC-IUPHAR recognizes Classes A, B, and C, which equate to the rhodopsin, secretin, and glutamate receptor families.

The nomenclature of 7TM receptors is commonly used interchangeably with G protein-coupled receptors (GPCR), although the former nomenclature recognises signalling of 7TM receptors through pathways not involving G proteins. For example, adiponectin and membrane progesterin receptors have some sequence homology to 7TM receptors but signal independently of G proteins and appear to reside in membranes in an inverted fashion compared to conventional GPCR. Additionally, the NPR-C natriuretic peptide receptor (see Page S195) has a single transmembrane domain structure, but appears to couple to G proteins to generate cellular responses. The 300+ non-olfactory GPCR are the targets for the majority of drugs in clinical usage (Overington *et al.*, 2006), although only a minority of these receptors are exploited therapeutically.

Signalling through GPCR is enacted by the activation of heterotrimeric GTP-binding proteins (G proteins), made up of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, where the  $\alpha$  and  $\beta\gamma$  subunits are responsible for signalling. The  $\alpha$  subunit (tabulated below) allows definition of one series of signalling cascades and permits grouping of GPCRs to suggest common cellular, tissue and behavioural responses.  $G\beta\gamma$  subunits (tabulated below) also are able to signal, in a manner independent of the  $G\alpha$  subunits. Recently, the concept of agonist bias, or functional selectivity, has arisen (see Kenakin and Miller, 2010), which suggests that particular agonists, or allosteric modulators, may be able to promote post-receptor signalling through one cascade at the expense of an alternative. This has complicated the scenario for classification of GPCR. For the purposes of the Guide to Receptors and Channels, 'Principal transduction' is limited to the predominant established  $G\alpha$  signalling.

**$G\alpha_s$  family:**  $\beta_1$ -adrenoceptors (see Page S26) in the heart couple principally through  $G\alpha_s$  to activate adenylyl cyclase activity (see Page S288) and elevate intracellular cyclic AMP levels. This in turn leads to activation of protein kinase A (see Page S310) and the consequent phosphorylation and enhancement of function of voltage-gated calcium channels ( $Ca_v1.2$ , see Page S142). This, in turn leads to the observed action of noradrenaline (norepinephrine) or adrenaline (epinephrine) in increasing cardiac rate and force of contraction. The identification of other  $G_s$ -coupled GPCR in the heart would allow prediction of a similar effect on heart rate and force through the same mechanisms. In other tissues,  $G_s$ -coupled receptors would be predicted to evoke smooth muscle relaxation (e.g.  $\beta_2$ -adrenoceptors in bronchioles, Page S26), enhance secretion (e.g.  $H_2$  histamine receptors in gastric parietal cells, Page S70), stimulate lipolysis in adipocytes (e.g.  $\beta_3$ -adrenoceptors, Page S26) and inhibit platelet aggregation (e.g. IP prostanoid receptors, Page S97).

Nomenclature	HGNC nomenclature	Other names	Ensembl ID
$\alpha_s$	<i>GNAS</i>	Stimulatory G protein	ENSG00000087460
$\alpha_{olf}$	<i>GNAL</i>	Olfactory type	ENSG00000141404

**G $\alpha_i$  family:** M<sub>2</sub> muscarinic acetylcholine receptors (see Page S20) in the heart couple *via* G $\alpha_i$  subunits to inhibit adenylyl cyclase activity (see Page S288). Vagal innervation targets these receptors, primarily in the atria, to counteract the effects of noradrenaline and adrenaline in the cardiac myocyte, leading to a reduction in heart rate and force of contraction. In addition, G $\alpha_i$  subunits and G $\beta\gamma$  subunits (see below) enhance potassium channel opening (K<sub>ir2.x</sub>, see Page S158). The ensuing hyperpolarization of the cardiac myocyte leads to a reduction in voltage-gated L-type calcium channel activity and a consequent inhibition of rate and force of cardiac contraction – the manifestation of vagal nerve stimulation. In other tissues, G<sub>i</sub>-coupled receptors would be predicted to inhibit neurotransmitter release (e.g.  $\mu$  opioid receptors, Page S88, on parasympathetic nerve terminals in the small intestine), inhibit lipolysis in adipocytes (e.g. A<sub>1</sub> adenosine receptors, Page S22) and enhance platelet aggregation (e.g. P2Y<sub>12</sub> receptors, Page S91).

In the retina, transducin ( $\alpha_t$ ) subunits allow coupling to a cyclic GMP-specific phosphodiesterase, PDE6 (see Page S290). This reduces cellular cyclic GMP levels leading to a reduction of currents through cyclic nucleotide-gated channels (CNG, Page S153) and subsequent decrease of the 'dark' current.

Nomenclature	HGNC nomenclature	Other names	Ensembl ID
$\alpha_{i1}$	<i>GNAI1</i>	Inhibitory G protein $\alpha$ subunit	ENSG00000127955
$\alpha_{i2}$	<i>GNAI2</i>	Inhibitory G protein $\alpha$ subunit	ENSG00000114353
$\alpha_{i3}$	<i>GNAI3</i>	Inhibitory G protein $\alpha$ subunit	ENSG00000065135
$\alpha_{t1}$	<i>GNAT1</i>	Transducin 1 $\alpha$ subunit	ENSG00000114349
$\alpha_{t2}$	<i>GNAT2</i>	Transducin 2 $\alpha$ subunit	ENSG00000134183
$\alpha_{t3}$	<i>GNAT3</i>	Gustducin $\alpha$ subunit	ENSG00000214415
$\alpha_o$	<i>GNAO1</i>	$\alpha$ other	ENSG00000087258
$\alpha_z$	<i>GNAZ</i>	–	ENSG00000128266

**G $\alpha_q$  family:** M<sub>3</sub> muscarinic acetylcholine receptors (see Page S20) in bronchial smooth muscle couple *via* G $\alpha_{q/11}$  subunits to stimulate phospholipase C- $\beta$  activity (see Page S302). This leads to an elevation of intracellular calcium ions through inositol 1,4,5-trisphosphate action at IP<sub>3</sub> receptors (see Page S157), activation of protein kinase C (see Page S311) and the consequent smooth muscle contraction and reduced airway conductance. In other tissues, G<sub>q</sub>-coupled receptor activation leads to increased platelet aggregation (e.g. P2Y<sub>1</sub> receptors, Page S91).

Lysophosphatidic acid receptors (see Page S76) and proteinase-activated receptors (see Page S95) are examples of GPCR which couple through multiple G protein families, including G $\alpha_{12/13}$  leading to activation of a guanine nucleotide exchange factor, or GEF, for the Rho family of low molecular GTP-binding proteins (ENSM00500000269651), the subsequent activation of Rho kinase (see Page S313) and regulation of the cytoskeleton, leading to cellular shape changes and/or migration.

Nomenclature	HGNC nomenclature	Ensembl ID
$\alpha_q$	<i>GNAQ</i>	ENSG00000156052
$\alpha_{11}$	<i>GNA11</i>	ENSG00000088256
$\alpha_{12}$	<i>GNA12</i>	ENSG00000146535
$\alpha_{13}$	<i>GNA13</i>	ENSG00000120063
$\alpha_{14}$	<i>GNA14</i>	ENSG00000156049
$\alpha_{15}$	<i>GNA15</i>	ENSG00000060558

GNAQP1 is a pseudogene (ENSG00000214077).

**G $\beta\gamma$  subunits:** although  $\beta$  and  $\gamma$  subunits are synthesised as separate entities, they are considered to generate a complex which is essentially biologically irreversible. Acylation and prenylation ensure an association with the plasma membrane, where G $\beta\gamma$  subunits may regulate ion channel activities, or recruit members of the G protein-coupled receptor kinase family, also known as  $\beta$ -adrenoceptor kinases (see Page S310). Phosphorylation of particular cytoplasmic serine/threonine residues of GPCR allows binding of  $\beta$ -arrestin (ENSM00250000000572). These proteins act as scaffolding partners facilitating internalization of GPCR as a mechanism of desensitization, or coupling to alternative signalling pathways (e.g. MAP kinases, see Page S312).

Nomenclature	HGNC nomenclature	Ensembl ID
$\beta_1$	<i>GNB1</i>	ENSG00000078369
$\beta_2$	<i>GNB2</i>	ENSG00000172354
$\beta_3$	<i>GNB3</i>	ENSG00000111664
$\beta_4$	<i>GNB4</i>	ENSG00000114450
$\beta_5$	<i>GNB5</i>	ENSG00000069966



Nomenclature	HGNC nomenclature	Ensembl ID
$\gamma 2$	<i>GNG2</i>	ENSG00000186469
$\gamma 3$	<i>GNG3</i>	ENSG00000162188
$\gamma 4$	<i>GNG4</i>	ENSG00000168243
$\gamma 5$	<i>GNG5</i>	ENSG00000174021
$\gamma 7$	<i>GNG7</i>	ENSG00000176533
$\gamma 8$	<i>GNG8</i>	ENSG00000167414
$\gamma 10$	<i>GNG10</i>	ENSG00000242616
$\gamma 11$	<i>GNG11</i>	ENSG00000127920
$\gamma 12$	<i>GNG12</i>	ENSG00000172380
$\gamma 13$	<i>GNG13</i>	ENSG00000127588
$\gamma t1$	<i>GNGT1</i>	ENSG00000127928
$\gamma t2$	<i>GNGT2</i>	ENSG00000167083

GNB1L (ENSG00000185838) and GNB2L1 (ENSG00000204628) are described as G $\beta$ -like proteins on the basis of sequence homology. Four G $\gamma$  pseudogenes are defined in the human genome (GNG5P1, ENSG00000213536; GNG5P2, ENSG00000133136; GNG5P3, ENSG00000254949; GNG5P5, ENSG00000234590).

### Further Reading

- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288.
- Fredholm BB, Hokfelt T, Milligan G (2007). G-protein-coupled receptors: an update. *Acta Physiol* 190: 3–7.
- Fredriksson R, Lagerstrom MC, Lundin LG, Schioth HB (2003). The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Mol Pharmacol* 63: 1256–1272.
- Hill SJ, Williams C, May LT (2010). Insights into GPCR pharmacology from the measurement of changes in intracellular cyclic AMP; advantages and pitfalls of differing methodologies. *Br J Pharmacol* 161: 1266–1275.
- Kenakin T (2010). Being mindful of seven-transmembrane receptor ‘guests’ when assessing agonist selectivity. *Br J Pharmacol* 160: 1045–1047.
- Kenakin T, Miller LJ (2010). Seven transmembrane receptors as shapeshifting proteins: the impact of allosteric modulation and functional selectivity on new drug discovery. *Pharmacol Rev* 62: 265–304.
- Kenakin TP (2009). Cellular assays as portals to seven-transmembrane receptor-based drug discovery. *Nat Rev Drug Discov* 8: 617–626.
- Lagerstrom MC, Schioth HB (2008). Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat Rev Drug Discov* 7: 339–357.
- Milligan G (2009). G protein-coupled receptor hetero-dimerization: contribution to pharmacology and function. *Br J Pharmacol* 158: 5–14.
- Overington JP, Al-Lazikani B, Hopkins AL (2006). How many drug targets are there? *Nat Rev Drug Discov* 5: 993–996.
- <http://www.iuphar-db.org/>

# Orphan G protein-coupled receptors

## Preliminary pairings

While the remainder of this section focuses on those GPCR for which there is substantial pharmacological information, or interest, listed below are a number of putative GPCR identified by IUPHAR (Foord *et al.*, 2005), for which only preliminary evidence for an endogenous ligand has been published, or for which there exists a potential link to a disease, or disorder. The GPCR in the table below are all Class A, rhodopsin-like GPCR.

IUPHAR name	Ensembl ID	Other names	Putative endogenous ligand	Comment
CCRL2	ENSG00000121797	Chemokine (C-C motif) receptor-like 2, HCR, CRAM-B, CKRX, CRAM-A, CCR11, Cmkbr112, L-CCR, CRAM	Chemerin (Zabel <i>et al.</i> , 2008)	–
GPR1	ENSG00000183671	–	Chemerin (Barnea <i>et al.</i> , 2008)	Reported to act as a co-receptor for HIV (Shimizu <i>et al.</i> , 1999)
GPR3	ENSG00000181773	ACCA	Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)	Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> (Eggerickx <i>et al.</i> , 1995). Gene disruption results in premature ovarian aging (Ledent <i>et al.</i> , 2005), reduced $\beta$ -amyloid deposition (Thathiah <i>et al.</i> , 2009) and heightened pain behaviours (Ruiz-Medina <i>et al.</i> , 2011) in mice
GPR4	ENSG00000177464	–	Protons (Ludwig <i>et al.</i> , 2003; Tobo <i>et al.</i> , 2007; Liu <i>et al.</i> , 2010a)	An initial report suggesting activation by lysophosphatidylcholine, sphingosylphosphorylcholine (Zhu <i>et al.</i> , 2001) has been retracted (Zhu <i>et al.</i> , 2005). Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation (Yang <i>et al.</i> , 2007)
GPR6	ENSG00000146360	–	Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)	Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> and to be located intracellularly (Padmanabhan <i>et al.</i> , 2009)
GPR12	ENSG00000132975	GPCR21, Gpcr01, Gpcr12, Gpcr20	Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)	Gene disruption results in dyslipidemia and obesity (Bjursell <i>et al.</i> , 2006)
GPR15	ENSG00000154165	BOB	–	Reported to act as a co-receptor for HIV (Edinger <i>et al.</i> , 1997)
GPR17	ENSG00000144230	R12	Dual leukotriene and UDP receptor (Ciana <i>et al.</i> , 2006)	Reported to antagonize CysLT1 receptor signalling <i>in vivo</i> and <i>in vitro</i> (Maekawa <i>et al.</i> , 2009)
GPR20	ENSG00000204882	–	–	Reported to inhibit adenylyl cyclase constitutively through G <sub>i/o</sub> (Hase <i>et al.</i> , 2008)
GPR22	ENSG00000172209	–	–	Reported to inhibit adenylyl cyclase constitutively through G <sub>i/o</sub> ; gene disruption results in increased severity of functional decompensation following aortic banding (Adams <i>et al.</i> , 2008). Identified as a susceptibility locus for osteoarthritis (Evangelou <i>et al.</i> , 2011, Kerkhof <i>et al.</i> , 2010, Valdes and Spector, 2010)
GPR26	ENSG00000154478	–	–	Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> (Jones <i>et al.</i> , 2007)

IUPHAR name	Ensembl ID	Other names	Putative endogenous ligand	Comment
GPR31	ENSG00000120436	bA517H2.2	12(S)-Hydroxyeicosatetraenoic acid (Guo <i>et al.</i> , 2011)	
GPR34	ENSG00000171659	–	Lysophosphatidylserine (Sugo <i>et al.</i> , 2006), but fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)	Gene disruption results in an enhanced immune response (Liebscher <i>et al.</i> , 2011)
GPR35	ENSG00000178623	–	Kynurenic acid (Wang <i>et al.</i> , 2006); lysophosphatidic acid (Oka <i>et al.</i> , 2010)	Reported to respond to the phosphodiesterase inhibitor zaprinast (Taniguchi <i>et al.</i> , 2006) the chloride channel blocker 5-nitro-2-(3-phenylpropylamino) benzoic acid (Taniguchi <i>et al.</i> , 2008), the pharmaceutical adjuvant pamoic acid (Zhao <i>et al.</i> , 2010) and tyrosine kinase inhibitor tyrphostins (Deng <i>et al.</i> , 2011)
GPR37	ENSG00000170775	PAELR, EDNRBL, Endothelin B receptor-like protein 1, Parkin-associated endothelin receptor-like receptor	Head activator peptide (Rezgaoui <i>et al.</i> , 2006)	Reported to associate and regulate the dopamine transporter (Marazziti <i>et al.</i> , 2007) and to be a substrate for parkin (Marazziti <i>et al.</i> , 2009). Gene disruption results in altered striatal signalling (Marazziti <i>et al.</i> , 2011)
GPR39	ENSG00000183840		Zn <sup>2+</sup> (Holst <i>et al.</i> , 2007)	Obestatin was reported initially as an endogenous ligand (Zhang <i>et al.</i> , 2005), but subsequent studies failed to reproduce these findings. Has been reported to be down-regulated in adipose tissue in obesity-related diabetes (Catalan <i>et al.</i> , 2007). Gene disruption results in obesity (Petersen <i>et al.</i> , 2011)
GPR50	ENSG00000102195	Melatonin-related receptor, H9, MTNRL	–	A potential orthologue of an avian melatonin receptor (Dufourny <i>et al.</i> , 2008)
GPR63	ENSG00000112218	PSP24B	Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)	
GPR65	ENSG00000140030	TDAG8, T-cell death associated gene 8	Protons (Wang <i>et al.</i> , 2004; Ihara <i>et al.</i> , 2010)	Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease (Kotlyan <i>et al.</i> , 2009)
GPR68	ENSG00000119714	OGR1	Protons (Ludwig <i>et al.</i> , 2003; Liu <i>et al.</i> , 2010b)	–
GPR75	ENSG00000119737	WI-31133	RANTES (Ignatov <i>et al.</i> , 2006)	–
GPR84	ENSG00000139572	EX33	Medium chain fatty acids (Wang <i>et al.</i> , 2006)	–
GPR87	ENSG00000138271	GPR95	Lysophosphatidic acid (Tabata <i>et al.</i> , 2007)	–
GPR88	ENSG00000181656	STRG	–	Gene disruption results in altered striatal signalling (Logue <i>et al.</i> , 2009)
GPR120	ENSG00000186188		Free fatty acids (Katsuma <i>et al.</i> , 2005; Hirasawa <i>et al.</i> , 2005)	–
GPR132	ENSG00000183484	G2A	Protons (Murakami <i>et al.</i> , 2004)	Reported to respond to lysophosphatidylcholine (Kabarowski <i>et al.</i> , 2001), but later retracted (Witte <i>et al.</i> , 2005)
GPR143	ENSG00000101850	OA1	L-DOPA (Lopez <i>et al.</i> , 2008)	Loss-of-function mutations underlie ocular albinism type 1 (Bassi <i>et al.</i> , 1995)

IUPHAR name	Ensembl ID	Other names	Putative endogenous ligand	Comment
GPR149	ENSG00000174948	PGR10, IEDA		Gene disruption results in enhanced fertility (Edson <i>et al.</i> , 2010)
GPR161	ENSG00000143147	RE2	–	Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish (Leung <i>et al.</i> , 2008)
GPR183	ENSG00000169508	EBI2, Epstein-Barr virus induced gene 2, lymphocyte-specific G protein-coupled receptor	Oxysterols (Hannedouche <i>et al.</i> , 2011; Liu <i>et al.</i> , 2011)	–
GPRC <sub>6</sub>	ENSG00000173612	GPRC6A	Basic amino acids, such as L-arginine, L-lysine and L-ornithine (Wellendorph <i>et al.</i> , 2005)	–
LGR4	ENSG00000205213	Leucine-rich repeat-containing G-protein coupled receptor 4, GPR48	R-spondins (Carmon <i>et al.</i> , 2011; de Lau <i>et al.</i> , 2011)	Gene disruption leads to multiple developmental disorders (Luo <i>et al.</i> , 2009; Jin <i>et al.</i> , 2008; Song <i>et al.</i> , 2008; Weng <i>et al.</i> , 2008)
LGR5	ENSG00000139292	Leucine-rich repeat-containing G-protein coupled receptor 5, GPR49, GPR67, FEX, HG38	R-spondins (Carmon <i>et al.</i> , 2011; de Lau <i>et al.</i> , 2011)	–
LGR6	ENSG00000133067;	FLJ14471, VTS20631	R-spondins (Carmon <i>et al.</i> , 2011; de Lau <i>et al.</i> , 2011)	–
MAS1	ENSG00000130368	Mas	Angiotensin-(1-7) (Santos <i>et al.</i> , 2003)	
MRGPRD	ENSG00000172938	TGR7, Mas-related GPR member D, MrgD	β-Alanine (Shinohara <i>et al.</i> , 2004)	Potentially exists as a heteromer with MRGPRE (Milasta <i>et al.</i> , 2006)
MRGPRX1	ENSG00000170255	SNSR4, Mas-related GPR member X1, MrgX1	BAM8-22 (Chen and Ikeda, 2004)	Reported to mediate the sensation of itch (Liu <i>et al.</i> , 2009; Sikand <i>et al.</i> , 2011)
MRGPRX2	ENSG00000183695	Mas-related GPR member X2, MrgX2	PAMP (Kamohara <i>et al.</i> , 2005), cortistatin (Robas <i>et al.</i> , 2003)	–
P2RY10	ENSG00000078589	Purinergic receptor, P2Y10, P2Y-like	Sphingosine 1-phosphate and lysophosphatidic acid (Murakami <i>et al.</i> , 2008)	–
OXGR1	ENSG00000165621	GPR80, GPR99, P2Y15	2-Oxoglutarate (He <i>et al.</i> , 2004)	–
SUCNR1	ENSG00000198829	GPR91	Succinate (He <i>et al.</i> , 2004; Hogberg <i>et al.</i> , 2011)	–

#### Additional 'orphan' GPCRs

In the set of tables below, putative GPCR with as-yet unidentified endogenous ligands are listed.

#### Class A orphan GPCR

IUPHAR name	Ensembl ID	Other names
GPR19	ENSG00000183150	GPR-NGA
GPR21	ENSG00000188394	–
GPR25	ENSG00000170128	–
GPR27	ENSG00000170837	SREB1, super-conserved receptor expressed in brain 1
GPR33	ENSMUSG00000035148	Pseudogene in man
GPR37L1	ENSG00000170075	Endothelin B receptor-like protein 2, ETBR-LP-2, G-protein coupled receptor 37-like 1, CAG-18, DOKist8
GPR45	ENSG00000135973	PSP24

IUPHAR name	Ensembl ID	Other names
GPR52	ENSG00000203737	–
GPR61	ENSG00000156097	BALGR, GPCR3
GPR62	ENSG00000180929	GPCR8
GPR78	ENSG00000155269	–
GPR82	ENSG00000171657	–
GPR83	ENSG00000123901	GPR72, KIAA1540, glucocorticoid-induced receptor, GIR, RP105, RP39, RP82
GPR85	ENSG00000164604	SREB2, Super Conserved Receptor Expressed in Brain 2, Srep2, MGC105281
GPR101	ENSG00000165370	GPCR6, RGD1564196
GPR135	ENSG00000181619	HUMNPIIY20, PAFR
GPR139	ENSG00000180269	PGR3, GPRg1
GPR141	ENSG00000187037	PGR13
GPR142	ENSG00000257008	PGR2, KIF19
GPR146	ENSG00000164849	PGR8
GPR148	ENSG00000173302	PGR6, brain and testis restricted GPCR
GPR150	ENSG00000178015	PGR11
GPR151	ENSG00000173250	PGR7, GALR4, GPCR-2037
GPR152	ENSG00000175514	PGR5
GPR153	ENSG00000158292	PGR1
GPR160	ENSG00000173890	GPCR150, GPCR1
GPR162	ENSG00000110811	A-2, GRCA
GPR171	ENSG00000174946	H963
GPR173	ENSG00000184194	Super conserved receptor expressed in brain 3, SREB3
GPR174	ENSG00000147138	FKSG79
GPR176	ENSG00000166073	Gm1012, HB954
GPR182	ENSG00000166856	adrenomedullin receptor, hrhAMR, AM-R, G10-D, Gpcr17, Gpcr22, MB10, NOW, ADMR
MAS1L	ENSG00000204687	MAS-L, MRG, dj994E9.2, MAS-R, MGC119987, MAS1 oncogene-like
MGRPRX3	ENSG00000179826	MAS-related GPR, member X3, Mrga10, SNSR1, SNSR2, MRGX3, sensory neuron-specific G-protein coupled receptor 1/2
MGRPRX4	ENSG00000179817	MAS-related GPR, member X4, MRGX4, SNSR5, SNSR6, sensory neuron-specific G-protein coupled receptor 5/6
MRGPRE	ENSG00000184350	MAS-related GPR, member E, mrgE, GPR167, MGC138408
MRGPRF	ENSG00000172935	GPR168, GPR140, MGC21621, mrgF, MAS-related GPR, member F, RTA
MRGPRG	ENSG00000182170	MAS-related GPR, member G, GPR169, mrgG, MRGG, EBRT2
OPN3	ENSG00000054277	Opsin-3, Encephalopsin, Panopsin, ECPN, ERO, NMO-1
OPN5	ENSG00000124818	GPR136, neuropsin, PGR12, TMEM13
P2RY8	ENSG00000182162	purinergic receptor P2Y, G-protein coupled, 8, P2Y8, MGC50878

### Class B Orphan GPCR

IUPHAR name	Ensembl ID	Other names
GPR157	ENSG00000180758	FLJ12132

**Adhesion GPCRs:** Adhesion GPCRs are structurally identified on the basis of a large extracellular region, similar to the Class B GPCR, but which is linked to the 7TM region by a 'stalk' motif containing a GPCR proteolytic site. The N-terminus often shares structural homology with proteins such as lectins and immunoglobulins, leading to the term adhesion GPCR (see Fredriksson *et al.*, 2003; Yona *et al.*, 2008).

IUPHAR name	Ensembl ID	Other names	Comment
BAI1	ENSG00000181790	Brain-specific angiogenesis inhibitor 1	Reported to respond to phosphatidylserine (Park <i>et al.</i> , 2007)
BAI2	ENSG00000121753	Brain-specific angiogenesis inhibitor 2	–
BAI3	ENSG00000135298	Brain-specific angiogenesis inhibitor 3	–
CD97	ENSG00000123146	Leukocyte antigen CD97	–
CELSR1	ENSG00000075275	Cadherin EGF LAG seven-pass G-type receptor 1, flamingo homolog 2, hFmi2	–
CELSR2	ENSG00000143126	Cadherin EGF LAG seven-pass G-type receptor 2, epidermal growth factor-like 2, multiple epidermal growth factor-like domains 3, flamingo 1	–
CELSR3	ENSG00000008300	Cadherin EGF LAG seven-pass G-type receptor 3, flamingo homolog 1, hFmi1, multiple epidermal growth factor-like domains 2, epidermal growth factor-like 1	–
ELTD1	ENSG00000162618	EGF, latrophilin and seven transmembrane domain-containing protein 1, EGF-TM7-latrophilin-related protein, ETL	–
EMR1	ENSG00000174837	EGF-like module-containing mucin-like hormone receptor-like 1, cell surface glycoprotein EMR1, EMR1 hormone receptor	–
EMR2	ENSG00000127507	EGF-like module-containing mucin-like hormone receptor-like 2, EGF-like module EMR2, CD312 antigen	–
EMR3	ENSG00000131355	EGF-like module-containing mucin-like hormone receptor-like 3, EGF-like module-containing mucin-like receptor EMR3	–
GPR56	ENSG00000205336	TM7LN4, TM7XN1	Reported to bind tissue transglutaminase 2 (Xu <i>et al.</i> , 2006) and collagen, which activates the G <sub>12/13</sub> pathway (Luo <i>et al.</i> , 2011)
GPR64	ENSG00000173698	HE6	–
GPR97	ENSG00000182885	Pb99, PGR26	–
GPR98	ENSG00000164199	VLGR1, FEB4, KIAA0686, USH2C, Frings, MASS1, monogenic audiogenic seizure susceptibility 1 homolog	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder (Jacobson <i>et al.</i> , 2008)
GPR110	ENSG00000153292	hGPCR36, PGR19	–
GPR111	ENSG00000164393	hGPCR35, PGR20	–
GPR112	ENSG00000156920	RP1-299I16, PGR17	–
GPR113	ENSG00000173567	hGPCR37, PGR23	–
GPR114	ENSG00000159618	PGR27	–
GPR115	ENSG00000153294	FLJ38076, PGR18	–
GPR116	ENSG00000069122	DKFZp564O1923, KIAA0758	–
GPR123	ENSG00000197177	KIAA1828	–
GPR124	ENSG00000020181	Tumour endothelial marker 5	–
GPR125	ENSG00000152990	PGR21	–
GPR126	ENSG00000112414	FLJ14937	–
GPR128	ENSG00000144820	FLJ14454	–
GPR133	ENSG00000111452	PGR25	–
GPR144	ENSG00000180264	PGR24	–
LPHN1	ENSG00000072071	Lectomedin-2, LEC2, latrophilin-1, calcium-independent $\alpha$ -latrotoxin receptor 1	–
LPHN2	ENSG00000117114	Lectomedin-1, LEC1, latrophilin-2, calcium-independent $\alpha$ -latrotoxin receptor 2, latrophilin homolog 1	–
LPHN3	ENSG00000150471	Lectomedin-3, LEC3, Latrophilin-3, calcium-independent $\alpha$ -latrotoxin receptor 3, l	–

## Class C Orphan GPCR

IUPHAR name	Ensembl ID	Other names
GPR156	ENSG00000175697	PGR28, GABABL
GPR158	ENSG00000151025	KIAA1136
GPR179	ENSG00000188888	GPR158L1
GPRC5A	ENSG00000013588	RAIG <sub>1</sub> , Retinoic acid-induced protein 3, retinoic acid-induced gene 1 protein, orphan G-protein-coupling receptor PEIG-1
GPRC5B	ENSG00000167191	RAIG <sub>2</sub> , Retinoic acid-induced gene 2 protein, A-69G12.1
GPRC5C	ENSG00000170412	RAIG <sub>3</sub> , Retinoic acid-induced gene 3 protein,
GPRC5D	ENSG0000011291	RAIG <sub>4</sub> , G-protein coupled receptor family C group 5 member D

## Taste receptors

Whilst the taste of acid and salty foods appears to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin (G $\alpha_{13}$ , see Page S6) and G $\alpha_{14}$ -mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involvement of PLC $\beta$ 2 (Zhang *et al.*, 2003), TRPM5 (Zhang *et al.*, 2003) and IP<sub>3</sub> (Hisatsune *et al.*, 2007) receptors in post-receptor signalling of taste receptors.

Although predominantly associated with the oral cavity, taste receptors are also located elsewhere, including further down the gastrointestinal system, in the lungs and in the brain.

Sweet/Umami: T1R3 acts as an obligate partner in T1R1/T1R3 and T1R2/T1R3 heterodimers, which sense umami or sweet, respectively. T1R1/T1R3 heterodimers respond to L-glutamate and may be positively allosterically modulated by 5'-nucleoside monophosphates, such as GMP (Li *et al.*, 2002). T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin (Nelson *et al.*, 2001).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
T1R1	<i>TAS1R1</i>	ENSG00000173662	GPR70, TR1
T1R2	<i>TAS1R2</i>	ENSG00000179002	GPR71, TR2
T1R3	<i>TAS1R3</i>	ENSG00000169962	–

Bitter: the composition and stoichiometry of bitter taste receptors is not yet established. Bitter receptors appear to separate into two groups, with very restricted ligand specificity or much broader responsiveness. For example, T2R5 responded to cycloheximide, but not 10 other bitter compounds (Chandrashekar *et al.*, 2000), while T2R14 responded to at least eight different bitter tastants, including (-)- $\alpha$ -thujone and picrotoxinin (Behrens *et al.*, 2004).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
T2R1	<i>TAS2R1</i>	ENSG00000169777	TRB7
T2R3	<i>TAS2R3</i>	ENSG00000127362	–
T2R4	<i>TAS2R4</i>	ENSG00000127364	–
T2R5	<i>TAS2R5</i>	ENSG00000127366	–
T2R7	<i>TAS2R7</i>	ENSG00000121377	TRB4
T2R8	<i>TAS2R8</i>	ENSG00000121314	TRB5
T2R9	<i>TAS2R9</i>	ENSG00000121381	TRB6
T2R10	<i>TAS2R10</i>	ENSG00000121318	TRB2
T2R13	<i>TAS2R13</i>	ENSG00000212128	TRB3
T2R14	<i>TAS2R14</i>	ENSG00000212127	TRB1
T2R16	<i>TAS2R16</i>	ENSG00000128519	–
T2R19	<i>TAS2R19</i>	ENSG00000212124	T2R23, TAS2R23, TAS2R48
T2R20	<i>TAS2R20</i>	ENSG00000255837	T2R56, TAS2R49
T2R24	<i>TAS2R24</i>	ENSG00000186136	hT2R55, T2R55, TAS2R55

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
T2R30	TAS2R30	ENSG00000256188	TAS2R47
T2R31	TAS2R31	ENSG00000256436	T2R53, TAS2R44
T2R39	TAS2R39	ENSG00000236398	–
T2R40	TAS2R40	ENSG00000221937	GPR60
T2R51	TAS2R50	ENSG00000212126	–
T2R52	TAS2R43	ENSG00000255374	–
T2R54	TAS2R46	ENSG00000226761	–
T2R59	TAS2R41	ENSG00000221855	–
T2R60	TAS2R60	ENSG00000185899	–
T2R61	TAS2R38	ENSG00000257138	PTC

### Further Reading

- Andres-Barquin PJ, Conte C (2004). Molecular basis of bitter taste: the T2R family of G protein-coupled receptors. *Cell Biochem Biophys* **41**: 99–112.
- Bachmanov AA, Beauchamp GK (2007). Taste receptor genes. *Annu Rev Nutr* **27**: 389–414.
- DeSimone JA, Lyall V (2006). Taste receptors in the gastrointestinal tract III. Salty and sour taste: sensing of sodium and protons by the tongue. *Am J Physiol Gastrointest Liver Physiol* **291**: G1005–G1010.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288.
- Fredriksson R, Lagerstrom MC, Lundin LG, Schiöth HB (2003). The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Mol Pharmacol* **63**: 1256–1272.
- Kinnamon SC (2011). Taste receptor signaling – from tongues to lungs. *Acta Physiol (Oxf)* in press.
- Lagerstrom MC, Schiöth HB (2008). Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat Rev Drug Discov* **7**: 339–357.
- Meyerhof W (2005). Elucidation of mammalian bitter taste. *Rev Physiol Biochem Pharmacol* **154**: 37–72.
- Overington JP, Al-Lazikani B, Hopkins AL (2006). How many drug targets are there? *Nat Rev Drug Discov* **5**: 993–996.
- Renwick AG, Molinary SV (2010). Sweet-taste receptors, low-energy sweeteners, glucose absorption and insulin release. *Br J Nutr* **104**: 1415–1420.
- Rozengurt E (2006). Taste receptors in the gastrointestinal tract. I. Bitter taste receptors and  $\alpha$ -gustducin in the mammalian gut. *Am J Physiol Gastrointest Liver Physiol* **291**: G171–G177.
- Rozengurt E, Sternini C (2007). Taste receptor signaling in the mammalian gut. *Curr Opin Pharmacol* **7**: 557–562.
- Temussi PA (2009). Sweet, bitter and umami receptors: a complex relationship. *Trends Biochem Sci* **34**: 296–302.
- Tepper BJ (2008). Nutritional implications of genetic taste variation: the role of PROP sensitivity and other taste phenotypes. *Annu Rev Nutr* **28**: 367–388.
- Yarmolinsky DA, Zuker CS, Ryba NJ (2009). Common sense about taste: from mammals to insects. *Cell* **139**: 234–244.
- Yona S, Lin HH, Siu WO, Gordon S, Stacey M (2008). Adhesion-GPCRs: emerging roles for novel receptors. *Trends Biochem Sci* **33**: 491–500.

### References

- Adams JW *et al.* (2008). *Am J Physiol Heart Circ Physiol* **295**: H509–H521.
- Barnea G *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 64–69.
- Bassi MT *et al.* (1995). *Nat Genet* **10**: 13–19.
- Behrens M *et al.* (2004). *Biochem Biophys Res Commun* **319**: 479–485.
- Bjursell M *et al.* (2006). *Biochem Biophys Res Commun* **348**: 359–366.
- Carmon KS *et al.* (2011). *Proc Natl Acad Sci U S A* **108**: 11452–11457.
- Catalan V *et al.* (2007). *Clin Endocrinol (Oxf)* **66**: 598–601.
- Chandrashekar J *et al.* (2000). *Cell* **100**: 703–711.
- Chen H, Ikeda SR (2004). *J Neurosci* **24**: 5044–5053.
- Ciana P *et al.* (2006). *EMBO J* **25**: 4615–4627.
- de Lau W *et al.* (2011). *Nature* **476**: 293–297.
- Deng H *et al.* (2011). *FEBS Lett* **585**: 1957–1962.
- Dufourny L *et al.* (2008). *BMC Evol Biol* **8**: 105.
- Edinger AL *et al.* (1997). *Proc Natl Acad Sci U S A* **94**: 14742–14747.
- Edson MA *et al.* (2010). *Endocrinology* **151**: 358–368.
- Eggerickx D *et al.* (1995). *Biochem J* **309**: 837–843.
- Evangelou E *et al.* (2011). *Ann Rheum Dis* **70**: 349–355.
- Guo Y *et al.* (2011). *J Biol Chem* **286**: 33832–33840.
- Hannedouche S *et al.* (2011). *Nature* **475**: 524–527.
- Hase M *et al.* (2008). *J Biol Chem* **283**: 12747–12755.
- He W *et al.* (2004). *Nature* **429**: 188–193.
- Hirasawa A *et al.* (2005). *Nat Med* **11**: 90–94.
- Hisatsune C *et al.* (2007). *J Biol Chem* **282**: 37225–37231.
- Hogberg C *et al.* (2011). *J Thromb Haemost* **9**: 361–372.
- Holst B *et al.* (2007). *Endocrinology* **148**: 13–20.
- Ignatov A *et al.* (2006). *Br J Pharmacol* **149**: 490–497.
- Ihara Y *et al.* (2010). *Proc Natl Acad Sci U S A* **107**: 17309–17314.
- Jacobson SG *et al.* (2008). *Hum Mol Genet* **17**: 2405–2415.
- Jin C *et al.* (2008). *Invest Ophthalmol Vis Sci* **49**: 4245–4253.
- Jones PG *et al.* (2007). *Biochimica et Biophysica Acta* **1770**: 890–901.
- Kabarowski JH *et al.* (2001). *Science* **293**: 702–705.
- Kamohara M *et al.* (2005). *Biochem Biophys Res Commun* **330**: 1146–1152.
- Katsuma S *et al.* (2005). *J Biol Chem* **280**: 19507–19515.
- Kerkhof HJ *et al.* (2010). *Arthritis Rheum* **62**: 499–510.
- Kottyan LC *et al.* (2009). *Blood* **114**: 2774–2784.
- Ledent C *et al.* (2005). *Proc Natl Acad Sci U S A* **102**: 8922–8926.
- Leung T *et al.* (2008). *Dev Biol* **323**: 31–40.
- Li X *et al.* (2002). *Proc Natl Acad Sci U S A* **99**: 4692–4696.
- Liebscher I *et al.* (2011). *J Biol Chem* **286**: 2101–2110.
- Liu C *et al.* (2011). *Nature* **475**: 519–523.
- Liu JP *et al.* (2010a). *Pharmacol Res* **61**: 499–505.
- Liu JP *et al.* (2010b). *Am J Physiol Heart Circ Physiol* **299**: H731–H742.
- Liu Q *et al.* (2009). *Cell* **139**: 1353–1365.
- Logue SF *et al.* (2009). *Mol Cell Neurosci* **42**: 438–447.
- Lopez VM *et al.* (2008). *PLoS Biol* **6**: e236.
- Ludwig MG *et al.* (2003). *Nature* **425**: 93–98.
- Luo J *et al.* (2009). *Development* **136**: 2747–2756.
- Luo R *et al.* (2011). *Proc Natl Acad Sci U S A* **108**: 12925–12930.
- Maekawa A *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 11685–11690.
- Marazziti D *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 9846–9851.



- Marazziti D *et al.* (2009). *FASEB J* **23**: 1978–1987.
- Marazziti D *et al.* (2011). *FASEB J* **25**: 2071–2081.
- Milasta S *et al.* (2006). *Mol Pharmacol* **69**: 479–491.
- Murakami N *et al.* (2004). *J Biol Chem* **279**: 42484–42491.
- Nelson G *et al.* (2001). *Cell* **106**: 381–390.
- Oka S *et al.* (2010). *Biochem Biophys Res Commun* **395**: 232–237.
- Padmanabhan S *et al.* (2009). *FEBS Lett* **583**: 107–112.
- Park D *et al.* (2007). *Nature* **450**: 430–434.
- Petersen PS *et al.* (2011). *FASEB J* in press.
- Rezgaoui M *et al.* (2006). *J Cell Sci* **119**: 542–549.
- Robas N *et al.* (2003). *J Biol Chem* **278**: 44400–44404.
- Ruiz-Medina J *et al.* (2011). *Neuropharmacology* **61**: 43–50.
- Santos RA *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 8258–8263.
- Shimizu N *et al.* (1999). *J Virol* **73**: 5231–5239.
- Shinohara T *et al.* (2004). *J Biol Chem* **279**: 23559–23564.
- Sikand P *et al.* (2011). *J Neurosci* **31**: 7563–7567.
- Song H *et al.* (2008). *J Biol Chem* **283**: 36687–36697.
- Sugo T *et al.* (2006). *Biochem Biophys Res Commun* **341**: 1078–1087.
- Tabata K *et al.* (2007). *Biochem Biophys Res Commun* **363**: 861–866.
- Taniguchi Y *et al.* (2006). *FEBS Lett* **580**: 5003–5008.
- Taniguchi Y *et al.* (2008). *Pharmacology* **82**: 245–249.
- Thathiah A *et al.* (2009). *Science* **323**: 946–951.
- Tobo M *et al.* (2007). *Cell Signal* **19**: 1745–1753.
- Valdes AM, Spector TD (2010). *Curr Opin Rheumatol* **22**: 139–143.
- Wang J *et al.* (2006). *J Biol Chem* **281**: 22021–22028.
- Wang JQ *et al.* (2004). *J Biol Chem* **279**: 45626–45633.
- Wellendorph P, Hansen KB *et al.* (2005). *Mol Pharmacol* **67**: 589–597.
- Weng J *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 6081–6086.
- Witte ON *et al.* (2005). *Science* **307**: 206.
- Xu L *et al.* (2006). *Proc Natl Acad Sci U S A* **103**: 9023–9028.
- Yang LV *et al.* (2007). *Mol Cell Biol* **27**: 1334–1347.
- Yin H *et al.* (2009). *J Biol Chem* **284**: 12328–12338.
- Zabel BA *et al.* (2008). *J Exp Med* **205**: 2207–2220.
- Zhang JV *et al.* (2005). *Science* **310**: 996–999.
- Zhang Y *et al.* (2003). *Cell* **112**: 293–301.
- Zhao P *et al.* (2010). *Mol Pharmacol* **78**: 560–568.
- Zhu K *et al.* (2001). *J Biol Chem* **276**: 41325–41335.
- Zhu K *et al.* (2005). *J Biol Chem* **280**: 43280.

# 5-HT (5-Hydroxytryptamine)

5-HT receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors (Hoyer *et al.*, 1994) and subsequently revised (Hartig *et al.*, 1996)] are, with the exception of the ionotropic 5-HT<sub>3</sub> class, GPCR where the endogenous agonist is 5-HT. The diversity of metabotropic 5-HT receptors is increased by alternative splicing that produces isoforms of the 5-HT<sub>2A</sub> (non-functional), 5-HT<sub>2C</sub> (non-functional), 5-HT<sub>4</sub>, 5-HT<sub>6</sub> (non-functional) and 5-HT<sub>7</sub> receptors. Unique amongst the GPCRs, RNA editing produces 5-HT<sub>2C</sub> receptor isoforms that differ in function, such as efficiency and specificity of coupling to G<sub>q/11</sub> and also pharmacology (reviewed by Bockaert *et al.*, 2006; Werry *et al.*, 2008). Most 5-HT receptors (except 5-HT<sub>1e</sub> and 5-HT<sub>5a/sb</sub>) play specific roles mediating functional responses in different tissues (reviewed by Villalón and Centurión, 2007; Ramage and Villalón, 2008).

Nomenclature	5-HT <sub>1A</sub>	5-HT <sub>1B</sub>	5-HT <sub>1D</sub>	5-HT <sub>1e</sub>
Other names	–	5-HT <sub>1Dβ</sub>	5-HT <sub>1Dα</sub>	–
Ensembl ID	ENSG00000178394	ENSG00000135312	ENSG00000179546	ENSG00000168830
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Selective agonists (pK)	8-OH-DPAT (8.4–9.4), U92016A (9.7) F15599 (8.6, Newman-Tancredi <i>et al.</i> , 2009)	L694247 (9.2), CP94253 (8.7), sumatriptan (6.5–8.1), elipripran (8.0)	PNU109291 (9.0 – gorilla, Ennis <i>et al.</i> , 1998) sumatriptan (8.0–8.7), eletriptan (8.9), L694247 (9.0, Wurch <i>et al.</i> , 1998)	BRL-54443 (8.7, Brown <i>et al.</i> , 1998)
Selective antagonists (pK)	(±)WAY100635 (7.9–9.2), (S)-UH301 (7.9–8.6), NAD299 (robalzotan, 9.2)	SB236057 (8.2, inverse agonist, Middlemiss <i>et al.</i> , 1999), SB224289 (inverse agonist, 8.2–8.6), GR55562 (pK <sub>B</sub> 7.4, Hoyer <i>et al.</i> , 2002)	SB714786 (9.1) BRL15572 (7.9)	–
Probes (K <sub>D</sub> )	[ <sup>3</sup> H]WAY100635 (0.3 nM, Khawaja <i>et al.</i> , 1997), [ <sup>3</sup> H]NAD299 (0.16 nM), [ <sup>3</sup> H]8-OH-DPAT (0.4 nM), [ <sup>3</sup> H]F13640 (1.4 nM, Heusler <i>et al.</i> , 2010) [ <sup>11</sup> C]WAY100635 (PET ligand), p-[ <sup>18</sup> F]MPPF (PET ligand)	[N-methyl- <sup>3</sup> H <sub>3</sub> ]-AZ10419369 (0.37 nM, Maier <i>et al.</i> , 2009) [ <sup>3</sup> H]alniditan (2.0–2.4 nM) [ <sup>3</sup> H]eletriptan (3 nM), [ <sup>3</sup> H]sumatriptan (11 nM) [ <sup>125</sup> I]GTI, [ <sup>3</sup> H]GR125743 (2.6 nM, Xie <i>et al.</i> , 1999), [ <sup>11</sup> C]AZ10419369 (PET ligand)	[ <sup>3</sup> H]alniditan (1.2–1.4 nM) [ <sup>3</sup> H]eletriptan (0.9 nM), [ <sup>3</sup> H]sumatriptan (7 nM), [ <sup>125</sup> I]GTI, [ <sup>3</sup> H]GR125743 (2.8 nM, Xie <i>et al.</i> , 1999)	[ <sup>3</sup> H]5-HT (6 nM)

Nomenclature	5-HT <sub>1F</sub>	5-HT <sub>2A</sub>	5-HT <sub>2B</sub>	5-HT <sub>2C</sub>
Other names	5-HT <sub>1Eβ</sub> , 5-HT <sub>6</sub>	D, 5-HT <sub>2</sub>	5-HT <sub>2F</sub>	5-HT <sub>1C</sub>
Ensembl ID	ENSG00000179097	ENSG00000102468	ENSG00000135914	ENSG00000147246
Principal transduction	G <sub>i/o</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>
Selective agonists (pK)	LY344864 (8.2, Phebus <i>et al.</i> , 1997) LY334370 (8.7), LY573144 (8.7, Nelson <i>et al.</i> , 2010), BRL-54443 (8.9, Brown <i>et al.</i> , 1993), elipripran (8.0), sumatriptan (7.2–7.9)	DOI (7.4–9.2)	DOI (7.6–7.7), Ro600175 (8.3), BW723C86 (7.3–8.6)	DOI (7.2–8.6), Ro600175 (7.7–8.2) WAY163909 (8.0, Dunlop <i>et al.</i> , 2005) Locaserin (7.8, Thomsen <i>et al.</i> , 2008)
Selective antagonists (pK)	–	ketanserin (8.1–9.7), MDL100907 (9.4)	RS127445 (9.0), EGIS-7625 (9.0)	SB242084 (8.2 – 9.0), RS102221 (8.3–8.4) FR260010 (8.9, Harada <i>et al.</i> , 2006)
Probes (K <sub>D</sub> )	[ <sup>3</sup> H]LY334370 (0.5 nM), [ <sup>125</sup> I]LSD	[ <sup>3</sup> H]ketanserin (0.2–1.3 nM), [ <sup>3</sup> H]RP62203 (fananserin, 0.13 nM – rat, Malgouris <i>et al.</i> , 1993), [ <sup>11</sup> C]M100907 (PET ligand), [ <sup>18</sup> F]altanserin (PET ligand)	[ <sup>3</sup> H]5-HT (8 nM – rat) [ <sup>3</sup> H]mesulergine (5–10 nM), [ <sup>3</sup> H]LSD (5–10 nM), [ <sup>125</sup> I]DOI (20–25 nM)	[ <sup>3</sup> H]mesulergine (0.5–2.2 nM), [ <sup>125</sup> I]DOI (6–25 nM), [ <sup>3</sup> H]LSD

Nomenclature	5-HT <sub>4</sub>	5-HT <sub>5a</sub>	5-HT <sub>5b</sub>	5-HT <sub>6</sub>
Other names	–	5-HT <sub>5α</sub>	–	–
Ensembl ID	ENSG00000164270	ENSG00000157219	ENSMUSG00000050534	ENSG00000158748
Principal transduction	G <sub>s</sub>	G <sub>i</sub> /G <sub>o</sub> ?	None identified	G <sub>s</sub>
Selective agonists (pK <sub>i</sub> )	BIMU8 (7.3), ML10302 (7.9–9.0), RS67506 (8.8–guinea-pig, Eglen <i>et al.</i> , 1995)	–	–	WAY181187 (8.7, Schechter <i>et al.</i> , 2008) E6801 (partial agonist, 8.7, Holenz <i>et al.</i> , 2005)
Selective antagonists (pK <sub>i</sub> )	GR113808 (9.3–10.3), SB204070 (9.8 – 10.4), RS100235 (8.7–12.2)	SB699551 (8.2)	–	SB399886 (9.4, Hirst <i>et al.</i> , 2006) SB271046 (8.9), SB357134 (8.5, Bromidge <i>et al.</i> , 2001), Ro630563 (7.9–8.4)
Probes (K <sub>D</sub> )	[ <sup>3</sup> H]GR113808 (50 – 200 pM), [ <sup>125</sup> I]SB207710 (86 pM – piglet, Brown <i>et al.</i> , 1993), [ <sup>3</sup> H]RS57639 (0.25 nM–guinea-pig, Bonhaus <i>et al.</i> , 1997) [ <sup>11</sup> C] SB207145 (PET ligand)	[ <sup>3</sup> H]5-CT (2.5 nM), [ <sup>125</sup> I]LSD (0.2 nM)	[ <sup>3</sup> H]5-CT, [ <sup>125</sup> I]LSD	[ <sup>125</sup> I]SB258585 (1.0 nM, Hirst <i>et al.</i> , 2000), [ <sup>3</sup> H]Ro630563 (5 nM, Boess <i>et al.</i> , 1998), [ <sup>3</sup> H]5-CT, [ <sup>125</sup> I]LSD (2 nM)

Nomenclature	5-HT <sub>7</sub>
Other names	5-HT <sub>1</sub> -like, 5-HT <sub>1V</sub> , orphan
Ensembl ID	ENSG00000148680
Principal transduction	G <sub>s</sub>
Selective agonists (pK <sub>i</sub> )	E55888 (8.6, Brenchat <i>et al.</i> , 2009)
Selective antagonists (pK <sub>i</sub> )	SB656104 (8.7, Forbes <i>et al.</i> , 2002), SB269970 (8.6–8.9 Thomas <i>et al.</i> , 2000), SB258719 (7.5)
Radioligands (K <sub>D</sub> )	[ <sup>3</sup> H]SB269970 (1.2 nM, Thomas <i>et al.</i> 2000), [ <sup>3</sup> H]5-CT (0.4 nM, Thomas <i>et al.</i> , 2000) [ <sup>3</sup> H]LSD (3 nM), [ <sup>3</sup> H]5-HT (1–8 nM)

Tabulated pK<sub>i</sub> and K<sub>D</sub> values refer to binding to human 5-HT receptors unless indicated otherwise. Unreferenced values are extracted from the NC-IUPHAR database ([www.iuphar-db.org](http://www.iuphar-db.org)). The nomenclature of 5-HT<sub>1B</sub>/5-HT<sub>1D</sub> receptors has been revised (Hartig *et al.*, 1996). Only the non-rodent form of the receptor was previously called 5-HT<sub>1DB</sub>. The human 5-HT<sub>1B</sub> receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS181 is a selective antagonist of the rodent 5-HT<sub>1B</sub> receptor. Fananserin and ketanserin bind with high affinity to dopamine D4 and histamine H<sub>1</sub> receptors respectively, and ketanserin is a potent α1 adrenoceptor antagonist, in addition to blocking 5-HT<sub>2A</sub> receptors. The human 5-HT<sub>5A</sub> receptor has been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells (Noda *et al.*, 2003). The human orthologue of the mouse 5-HT<sub>5b</sub> receptor is non-functional due to interruption of the gene by stop codons. The 5-HT<sub>1c</sub> receptor appears not to have been cloned from mouse, or rat, impeding definition of its function. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT<sub>1P</sub>, has been described (Gershon, 1999).

**Abbreviations:** 5-CT, 5-carboxamidotryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; [N-methyl-<sup>3</sup>H<sub>3</sub>]AZ10419369, 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4H-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; BIMU8, (endo-N-8-methyl-8-azabicyclo [3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1H-benzimidazol-1-carboxamide hydrochloride; BRL15572, 3-[4-(3-chlorophenyl) piperazin-1-yl]-1,1-diphenyl-2-propanol; BRL54443, 5-hydroxy-3-(1-methylpiperidin-4-yl)-1H-indole; BW723C86, 1-[5-(2-thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride; CP94253: 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypropylrolo[3, 2-b] pyridine; E6801, 6-chloro-N-(3-(2-dimethylamino)ethyl)-1H-indol-5-yl)imidazo[2,1-*b*]thiazole-5-sulfonamide; E55888, dimethyl-2-[3-(1,3,5-trimethyl-1H-pyrazol-4-yl)-phenyl]-ethyl]-amine; EGIS-7625, 1-benzyl-4-[(2-nitro-4-methyl-5-amino)-phenyl]-piperazine; F13640, 3-chloro-4-fluoro-phenyl-[4-fluoro-4-[(5-methyl-piperidin-2-ylmethyl)-amino]-methyl]piperidin-1-yl]-methanone ; F15599, 3-chloro-4-fluorophenyl-(4-fluoro-4-[(5-methylpyrimidin-2-ylmethyl)-amino]-methyl)-piperidin-1-yl)-methanone; FR260010, (N-[3-(4-methyl-1H-imidazol-1-yl)phenyl]-5,6-dihydrobenzo[h]quinazolin-4-amine; GR55562, 3-[3-(dimethylamino)propyl]-4-hydroxy-N-[4-(4-pyridinyl)phenyl]benzamide; GR113808, [1-2-(methylsulphonyl)amino]ethyl]-4-piperidinylmethyl-1-methyl-1H-indole-3-carboxylate; GR125743, *n*-[4-methoxy-3-(4-methyl-1-piperidinyl)phenyl]-3-methyl-4-(4-pyrindinyl)benzamide; GTI, 5-hydroxytryptamine-5-O-carboxymethylglycyltyrosinamide; L694247, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl] ethanamine; LY334370, 5-(4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate; LY344864, N-[(6R) -6-dimethylamino-6,7,8,9-tetrahydro-5H-carbazo-3-yl]-4- fluorobenzamide; LY573144, 2,4,6-trifluoro-N-[6-[(1-methylpiperidin-4-yl)carbonyl]pyridin-2-yl]benzamide; MDL100907, (+/-)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; NAD299, (R)-3-N,N-dicyclobutylamino-8-fluoro-[6-3H]-3,4-dihydro-2H-1-benzo pyran-5-carboxamide; NAS181, (R)-(+)-2-[[[3-(morpholinomethyl)-2H-chromen-8-yl]oxy]methyl] morpholine methane sulfonate; p-[<sup>18</sup>F]MPPF 4-(2'-methoxyphenyl)-1-[2'-(N-2'-pyridinyl)-p-fluorobenzamido]-ethyl piperazine; PNU109291, (S)-3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-1H-2-benzopyran-6-carboximide; RP62203, 2-[3-(4-(4-fluorophenyl)-piperazinyl)propyl]naphto[1,8-*ca*]isothiazole-1,1-dioxide; Ro600175, (S)-2-(6-chloro-5-fluoroindol-1-yl)-1-methylethylamine; Ro630563, 4-amino-N-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; RS57639, 4-amino-5-chloro-2-methoxy benzoic acid 1-(3-[2,3-dihydrobenzo[1,4]dioxin-6-yl)-propyl]-piperidin-4-yl methyl ester; RS67506, 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-(2-methyl sulphonylamino)ethyl-4-piperidinyl]-1-propanone hydrochloride; RS100235, 1-(8-amino-7-chloro-1,4-benzodioxan-5-yl)-5-[(3-(3,4-dimethoxyphenyl)prop-1-yl)piperidin-4-yl]propan-1-one; RS102221, 8-[5-(5-amino 2,4-dimethoxyphenyl) 5-oxopentyl]-1,3,8-triazaspiro

[4,5]decane-2,4-dione; **RS127445**, (2-amino-4-(4-fluorophenyl-1-yl)-6-isopropylpyrimidine); **SB204070**, 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate; **SB207710**, 1-butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate; **SB224289**, 1'-methyl-5[[2'-methyl-4'-5-methyl-1,2,4-oxadiazol-3-yl]biphenyl-4-yl]carbonyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]oxalate; **SB236057**, 1'-ethyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indol-3,4'-piperidine]; **SB242084**, 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl] indoline; **SB258585**, 4-iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]-benzenesulphonamide; **SB258719**, (R)-3,N-dimethyl-N-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzene sulphonamide; **SB269970**, (R)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonyl)phenol; **SB271046**, 5-chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide; **SB357134**, N-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB-399885**, N-[3,5-dichloro-2-(methoxyphenyl)-4-(methoxy)-3-(1-piperazinyl)benzenesulphonamide]; **SB656104**, 6-(R)-2-[2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl-1H-indole hydrochloride; **SB699551**, 3-cyclopentyl-N-[2-(dimethylamino)ethyl]-N-[(4'-{[(2-phenylethyl)amino]methyl}-4-biphenyl)methyl]propanamide dihydrochloride; **SB714786**, 2-methyl-5-[(2-[4-(8-quinolinylmethyl)-1-piperazinyl]ethyl)oxy]quinoline; **UH301**, 5-fluoro-8-hydroxy-2-(dipropylamino) tetralin; **U92016A**, (+)-R)-2-cyano-N,N-dipropyl-8-amino-6,7,8,9-tetrahydro-3H-benz[e]indole; **WAY100635**, N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexanecarboxamide trichloride, **WAY163909**, (7bR, 10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1h]indole; **WAY-181187**, 2-[1-(6-chloroimidazo[2,1-b]thiazol-5-ylsulfonyl)-1H-indol-3-yl]ethylamine

## Further Reading

- Aloyo VJ, Berg KA, Spampinato U, Clarke WP, Harvey JA (2009). Current status of inverse agonism at serotonin<sub>2A</sub> (5-HT<sub>2A</sub>) and 5-HT<sub>2C</sub> receptors. *Pharmacol Ther* **121**: 160–173.
- Barnes NM, Sharp T (1999). A review of central 5-HT receptors and their function. *Neuropharmacology* **38**: 1083–1152.
- Berger M, Gray JA, Roth BL (2009). The expanded biology of serotonin. *Annu Rev Med* **60**: 355–366.
- Bockaert J, Claeysen S, Becamel C, Dumuis A, Marin P (2006). Neuronal 5-HT metabotropic receptors: fine-tuning of their structure, signaling, and roles in synaptic modulation. *Cell Tissue Res* **326**: 553–572.
- Bockaert J, Claeysen S, Compan V, Dumuis A (2008). 5-HT<sub>4</sub> receptors: history, molecular pharmacology and brain functions. *Neuropharmacology* **55**: 922–931.
- Bojarski AJ (2006). Pharmacophore models for metabotropic 5-HT receptor ligands. *Curr Top Med Chem* **6**: 2005–2026.
- Bonasera SJ, Tecott LH (2000). Mouse models of serotonin receptor function: toward a genetic dissection of serotonin systems. *Pharmacol Ther* **88**: 133–142.
- Bureau R, Boulouard M, Dauphin F, Lezoualc'h F, Rault S (2010). Review of 5-HT<sub>1A</sub>R ligands: state of art and clinical applications. *Curr Top Med Chem* **10**: 527–553.
- Caliendo G, Santagada V, Perissutti E, Fiorino F (2005). Derivatives as 5HT<sub>1A</sub> receptor ligands – past and present. *Curr Med Chem* **12**: 1721–1753.
- Fink KB, Göthert M (2007). 5-HT receptor regulation of neurotransmitter release. *Pharmacol Rev* **59**: 360–417. <http://www.ncbi.nlm.nih.gov/pubmed/18160701>?ordinalpos=69&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\_ResultsPanel.Pubmed\_RVDDocSum
- Gershon MD (1999). Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* **13**: Suppl 2, 15–30.
- Glennon RA, Siripurapu U, Roth BL, Kolanos R, Bondarev ML, Sikazwe D, Lee M, Dukat M (2010). The medicinal chemistry of 5-HT<sub>6</sub> receptor ligands with a focus on arylsulfonyltryptamine analogs. *Curr Top Med Chem* **10**: 579–595.
- Gupta S, Villalón CM (2010). The relevance of preclinical research models for the development of antimigraine drugs: focus on 5-HT<sub>1B/1D</sub> and CGRP receptors. *Pharmacol Ther* **128**: 170–190.
- Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ *et al.* (1994). International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* **46**: 157–203.
- Hartig PR, Hoyer D, Humphrey PP, Martin GR (1996). Alignment of receptor nomenclature with the human genome: classification of 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptor subtypes. *Trends Pharmacol Sci* **17**: 103–105.
- Heal DJ, Smith SL, Fisas A, Codony X, Buschmann H (2008). Selective 5-HT<sub>6</sub> receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. *Pharmacol Ther* **117**: 207–231.
- Hoyer D, Hannon JP, Martin GR (2002). Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* **71**: 533–554.
- Jensen NH, Cremers TI, Sotty F (2010). Therapeutic potential of 5-HT<sub>2C</sub> receptor ligands. *ScientificWorldJournal* **10**: 1870–1885.
- King MV, Marsden CA, Fone KC (2008). A role for the 5-HT<sub>1A</sub>, 5-HT<sub>4</sub> and 5-HT<sub>6</sub> receptors in learning and memory. *Trends Pharmacol Sci* **29**: 482–492.
- Lezoualc'h F, Jockers R, Berque-Bestel I (2009). Multivalent-based drug design applied to serotonin 5-HT<sub>4</sub> receptor oligomers. *Curr Pharm Des* **15**: 719–729.
- Kitson SL (2007). 5-hydroxytryptamine (5-HT) receptor ligands. *Curr Pharm Des* **13**: 2621–2637.
- Lanfume L, Hamon M (2004). 5-HT<sub>1</sub> receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 1–10.
- Leopoldo M, Lacivita E, Berardi F, Perrone R, Hedlund PB (2011). Serotonin 5-HT<sub>7</sub> receptor agents: structure-activity relationships and potential therapeutic applications in central nervous system disorders. *Pharmacol Ther* **129**: 120–148.
- Leysen JE (2004). 5-HT<sub>2</sub> receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 11–26.
- Nelson DL (2004). 5-HT<sub>5</sub> receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 53–58.
- Pauwels PJ (2000). Diverse signalling by 5-hydroxytryptamine (5-HT) receptors. *Biochem Pharmacol* **60**: 1743–1750.
- Ramage AG, Villalón CM (2008). 5-Hydroxytryptamine and cardiovascular regulation. *Trends Pharmacol Sci* **29**: 472–481.
- Sanger GJ (2008). 5-hydroxytryptamine and the gastrointestinal tract: where next? *Trends Pharmacol Sci* **29**: 465–471.
- Saxena PR, De Vries P, Villalón CM (1998). 5-HT<sub>1</sub>-like receptors: a time to bid good-bye. *Trends Pharmacol Sci* **19**: 311–316.
- Thomas DR, Hagan JJ (2004). 5-HT<sub>7</sub> receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 81–90.
- Thomas DR (2006). 5-HT<sub>5A</sub> receptors as a therapeutic target. *Pharmacol Ther* **111**: 707–714.
- Villalón CM, Centurión D (2007). Cardiovascular responses produced by 5-hydroxytryptamine: a pharmacological update on the receptors/mechanisms involved and therapeutic implications. *Naunyn Schmiedeberg's Arch Pharmacol* **376**: 45–63.
- Volk B, Nagy BJ, Vas S, Kostyalik D, Simig G, Bagdy G (2010). Medicinal chemistry of 5-HT<sub>5A</sub> receptor ligands: a receptor subtype with unique therapeutic potential. *Curr Top Med Chem* **10**: 554–578.
- Ward SE, Watson JM (2010). Recent advances in the discovery of selective and non-selective 5-HT<sub>1D</sub> receptor ligands. *Curr Top Med Chem* **10**: 479–492.
- Werry TD, Loiacono R, Sexton PM, Christopoulos A (2008). RNA editing of the serotonin 5HT<sub>2C</sub> receptor and its effects on cell signalling, pharmacology and brain function. *Pharmacol Ther* **119**: 7–23.
- Woolley ML, Marsden CA, Fone KC (2004). 5-HT<sub>6</sub> receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 59–79.

## References

- Boess FG *et al.* (1998). *Mol Pharmacol* **54**: 577–583.
- Bonhaus DW *et al.* (1997). *Neuropharmacology* **36**:671–679.
- Brenchat A *et al.* (2009). *Pain* **141**: 239–247.
- Bromidge SM *et al.* (2001). *Bioorg Med Chem Lett* **11**:55–58.
- Brown AM *et al.* (1993). *Br J Pharmacol* **110**: 10P.
- Brown AM *et al.* (1998). *Br J Pharmacol* **123**: 233P.
- Dunlop J *et al.* (2005). *J Pharmacol Exp Ther* **313**: 862–869.
- Eglen RM *et al.* (1995). *Br J Pharmacol* **115**:1387–1392.
- Ennis MD *et al.* (1998). *J Med Chem* **41**:2180–2183.
- Forbes IT *et al.* (2002). *Bioorg Med Chem Lett* **12**: 3341–3344.
- Harada K *et al.* (2006). *Eur J Pharmacol* **553**: 171–184.
- Heusler P *et al.* (2010). *Naunyn Schmiedebergs Arch Pharmacol* **382**: 321–330.
- Hirst WD *et al.* (2000). *Br J Pharmacol* **130**: 1597–1605.
- Hirst WD *et al.* (2006). *Eur J Pharmacol* **553**: 109–119.
- Holenz J *et al.* (2005). *J Med Chem* **48**: 1781–1795.
- Khawaja X *et al.* (1997). *Life Sci* **60**: 653–665.
- Malgouris C *et al.* (1993). *Eur J Pharmacol* **233**: 37–45.
- Maier DL *et al.* (2009). *J Pharmacol Exp Ther* **330**: 342–351.
- Middlemiss DN *et al.* (1999). *Eur J Pharmacol* **375** :359–365.
- Nelson DL *et al.* (2010). *Cephalalgia* **30**: 1159–1169.
- Newman-Tancredi A *et al.* (2009). *Br J Pharmacol* **156**: 338–353.
- Noda M *et al.* (2003). *J Neurochem* **84**: 222–232.
- Phebus LA *et al.* (1997). *Life Sci* **61**: 2117–2126.
- Schechter LE *et al.* (2008). *Neuropsychopharmacology* **33**: 1323–1335.
- Thomas DR *et al.* (2000). *Br J Pharmacol* **130**: 409–417.
- Thomsen WJ *et al.* (2008). *J Pharmacol Exp Ther* **325**: 577–587.
- Wurch T *et al.* (1998). *Mol Pharmacol* **54**: 1088–1096.
- Xie Z *et al.* (1999). *FEBS Lett* **456**: 63–67.

# Acetylcholine (muscarinic)

**Overview:** Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors, Caulfield and Birdsall, 1998) are GPCR of the Class A, rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42, its structural analogues AC-260584 and 77-LH-28-1, desmethylozapine, TBPB and LuAE51090 have been described as functionally selective agonists of the M<sub>1</sub> receptor subtype *via* binding in a mode distinct from that utilized by non-selective agonists (Spalding *et al.*, 2002, 2006; Sur *et al.*, 2003; Langmead *et al.*, 2006, 2008; May *et al.*, 2007; Jones *et al.*, 2008; Lebon *et al.*, 2009; Avlani *et al.*, 2010; Sams *et al.*, 2010). There are two pharmacologically characterised allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine, and the other binds KT5720, WIN62,577, WIN51,708 and staurosporine (Lazareno *et al.*, 2000, 2002). There are selective enhancers of acetylcholine binding and action; brucine, BQCA, KT5720, VU0090157, VU0029767 and ML169 (VU0405652) at M<sub>1</sub> receptors, PG135 at M<sub>2</sub> receptors, N-chloromethylbrucine and WIN62,577 at M<sub>3</sub> receptors and thiochrome, LY2033298, VU0152099 and VU0152100 at M<sub>4</sub> receptors, and VU0238429 at M<sub>5</sub> receptors (Birdsall and Lazareno, 2005; Brady *et al.*, 2008; Chan *et al.*, 2008; Shirey *et al.*, 2008; Bridges *et al.*, 2009; Ma *et al.*, 2009; Marlo *et al.*, 2009; Reid *et al.*, 2011). LY2033298 has also been shown to activate the M<sub>4</sub> receptor directly *via* an allosteric site (Nawaratne *et al.*, 2008; 2010; Leach *et al.*, 2010; 2011). The allosteric site for gallamine and strychnine on M<sub>2</sub> receptors can be labelled by [<sup>3</sup>H]dimethyl-W84 (Tränkle *et al.*, 2003). McN-A-343 is a functionally selective partial agonist that appears to interact in a bitopic mode with both the orthosteric and an allosteric site on the M<sub>2</sub> muscarinic receptor (Valant *et al.*, 2008). THR-160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M<sub>2</sub> receptors by binding both to the orthosteric and a nearby allosteric site (Steinfeld *et al.*, 2007; Antony *et al.*, 2009). VU0255035 is a recently described competitive orthosteric antagonist with selectivity for the M<sub>1</sub> receptor (Sheffler *et al.*, 2009), and LY593093 has recently been described as a selective orthosteric partial agonist of the M<sub>1</sub> receptor (Watt *et al.*, 2011).

Nomenclature	M <sub>1</sub>	M <sub>2</sub>	M <sub>3</sub>
Ensembl ID	ENSG00000168539	ENSG00000181072	ENSG00000133019
Principal transduction	G <sub>q/11</sub>	G <sub>i/o</sub>	G <sub>q/11</sub>
Antagonists (pK <sub>i</sub> )	MT7 (10.9-11.0), 4-DAMP (9.2), triptiramine (8.8), darifenacin (8.3), pirenzepine (6.3-8.3), VU0255035 (7.8), guanylpirenzepine (7.7), AFDX384 (7.3-7.5), MT3 (6.5-7.1), himbacine (6.7-7.1), AFDX116 (6.2)	triptiramine (9.6), AFDX384 (8.0-9.0), 4-DAMP (8.3), himbacine (7.9-8.4), darifenacin (7.3-7.6), AFDX116 (6.7-7.3), VU0255035 (6.2), pirenzepine (4.9-6.4), MT3 (<6), guanylpirenzepine (5.6), MT7 (<5)	4-DAMP (9.3), darifenacin (9.1), AFDX384 (7.2-7.8), triptiramine (7.1-7.4), himbacine (6.9-7.2), pirenzepine (5.6-6.7), guanylpirenzepine (6.5), VU0255035 (6.1), AFDX116 (6.1), MT3 (<6), MT7 (<5)
Probes (K <sub>D</sub> )	[ <sup>3</sup> H]NMS (80-150 pM), [ <sup>3</sup> H]QNB (15-60 pM), [ <sup>3</sup> H]pirenzepine (3-15 nM), ( <i>R,R</i> )-quinuclidinyl-4-[ <sup>18</sup> F]-fluoromethyl-benzilate (PET ligand), [ <sup>11</sup> C]xanomeline (PET ligand), [ <sup>11</sup> C]butylthio-TZTP (PET ligand)	[ <sup>3</sup> H]NMS (200-400 pM), [ <sup>3</sup> H]QNB (20-50 pM), [ <sup>18</sup> F]FP-TZTP (PET ligand),	[ <sup>3</sup> H]NMS (150-250 pM), [ <sup>3</sup> H]QNB (30-90 pM), [ <sup>3</sup> H]darifenacin (300 pM)

Nomenclature	M <sub>4</sub>	M <sub>5</sub>
Ensembl ID	ENSG00000180720	ENSG00000184984
Principal transduction	G <sub>i/o</sub>	G <sub>q/11</sub>
Antagonists (pK <sub>i</sub> )	4-DAMP (8.9), MT3 (8.7), AFDX384 (8.0-8.7), AFDX116 (7-8.7), himbacine (7.9-8.2), triptiramine (7.8-8.2), darifenacin (8.1), pirenzepine (5.9-7.6), guanylpirenzepine (6.5), VU0255035 (5.9), MT7 (<5)	4-DAMP (9.0), darifenacin (8.6), triptiramine (7.3-7.5), guanylpirenzepine (6.8), pirenzepine (6.2-6.9), himbacine (5.4-6.5), AFDX384 (6.3), AFDX116 (5.3-5.6), VU0255035 (5.6), MT3 (<6), MT7 (<5)
Probes (K <sub>D</sub> )	[ <sup>3</sup> H]NMS (50-100 pM), [ <sup>3</sup> H]QNB (20-80 pM)	[ <sup>3</sup> H]NMS (500-700 pM), [ <sup>3</sup> H]QNB (20-60 pM)

Antagonist data tabulated are pK<sub>i</sub> values determined for human recombinant receptors. MT3 (m4-toxin) and MT7 (m1-toxin1) are toxins contained with the venom of the Eastern green mamba (*Dendroaspis augusticeps*) (see Potter *et al.*, 2004; Servent and Fruchart-Gaillard, 2009).

**Abbreviations:** 77-LH-28-1, 1-[3-(4-butyl-1-piperidinyl)propyl]-3,4-dihydro-2(1H)-quinolinone; AC-42, 4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride; AC-260584, 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one; AFDX116 (otenzepad), 1-[2-[2-(diethylaminomethyl)piperidin-1-yl]acetyl]-5H-pyrido[2,3-b][1,4]benzodiazepin-6-one; AFDX384, (±)-5,11-dihydro-11-[[2-[2-[dipropylamino)methyl]-1-piperidinyl]ethyl]amino]carbonyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one; BQCA, benzyl quinolone carboxylic acid; Butylthio-TZTP, butylthio-thiadiazolyltetrahydro-1-methyl-pyridine; Dimethyl-W84, N,N'-bis[3-(1,3-dihydro-1,3-dioxo-4-methyl-2H-isoindol-2-yl)propyl]-N,N,N',N'-tetramethyl-1,6-hexanediaminium diiodide; FP-TZTP, [3-(3-(3-Fluoropropyl)thio)-1,2,5-thiadiazol-4-yl]-1,2,5,6-tetrahydro-1-methylpyridine; 4-DAMP, 4-diphenylacetoxo-N-methylpiperidine methiodide; Hybrid 1, 2-[3-[1-(6-{1,1-dimethyl-1-[4-(isoxazol-3-yloxy)but-2-ynyl]-ammonium]hexyl)-1,1-dimethylammonio]propyl]isoindoline-1,3-dione dibromide; Hybrid 2, 2-[3-[1-(6-{1,1-dimethyl-1-[4-(isoxazol-3-yloxy)but-2-ynyl]-ammonium]hexyl)-1,1-dimethylammonio]-2,2-dimethylpropyl]-benzo[de]isoquinoline-1,3-dione dibromide; KT5720, (9S,10S,12R)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1H-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*ij*][1,6]benzodiazocine-10-carboxylic acid hexyl ester; LuAE51090, N-[1-[3-(3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)propyl]piperidin-4-yl]-2-phenylacetamide; LY2033298, 3-amino-5-chloro-6-methoxy-4-methyl-thieno(2,3-*b*)pyridine-2-carboxylic acid cyclopropylamide; LY593093, N-[(1R,2R)-6-((1E)-1-[4-(4-fluorobenzyl)(methyl)amino]ethylidene)amino]-2-hydroxy-2,3-dihydro-1H-inden-1-yl]biphenyl-4-carboxamide; McN-A-343, 4-(3-chlorophenyl) carbamoyloxy-2-butynyltrimethyl ammonium chloride; ML169 (or VU0405652), 2-((1-(5-bromo-2-fluorobenzyl)-1H-indol-3-yl)sulfonyl-N-(5-methylisoxazol-3-yl)acetamide; NMS, N-methylscopolamine; PG135, (3aS,12R,12aS,12bR)-2-amino-2,3,3a,4,11,12a,12b-octahydro-10-hydroxyisoquinolo[2,1,8-*lma*]carbazol-5(1H)-one hydrochloride; QNB, 3-quinuclidinylbenzilate; TBPB, 1-(1'-2-methylbenzyl)-1,4'-bipiperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one; THR-160209, 4-[N-[7-(3-(S)-(1-carbamoyl-1,1-diphenylmethyl)

pyrrolidin-1-yl]hept-1-yl]-N-(n-propyl)amino]-1-(2,6-dimethoxy-benzyl)piperidine; VU0029767, (E)-2-(4-ethoxyphenylamino)-N'-((2-hydroxynaphthalen-1-yl)methylene)acetohydrazide; VU0090157, cyclopentyl 1,6-dimethyl-4-(6-nitrobenzo[d][1,3]-dioxol-5-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate; VU0152099, 3-amino-N-(benzo[d][1,3]dioxol-5-ylmethyl)-4,6-dimethylthieno[2,3-b]pyridine carboxamide; VU0152100, 3-amino-N-(4-methoxybenzyl)-4,6-dimethylthieno[2,3-b]pyridine carboxamide; VU0238429, structure not available; VU0255035, N-(3-oxo-3-(4-(pyridine-4-yl)piperazin-1-yl)propyl)-benzo[c][1,2,5]thiadiazole-4 sulfonamide; WIN51,708, 17- $\beta$ -hydroxy-17- $\alpha$ -ethynyl-5- $\alpha$ -androstano[3,2-b]pyrimido[1,2-a]benzimidazole; WIN62,577, 17- $\beta$ -hydroxy-17- $\alpha$ -ethynyl- $\Delta^4$ -androstano[3,2-b]pyrimido[1,2-a]benzimidazole

### Further Reading

- Abrams P, Andersson KE, Buccafusco JI, Chapple C, De Groat WC, Fryer AD *et al.* (2006). Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol* **148**: 565–578.
- Andersson KE (2011). Muscarinic acetylcholine receptors in the urinary tract. *Handb Exp Pharmacol* **202**: 319–344.
- Birdsall NJM, Lazareno S. (2005). Allosterism at muscarinic receptors: ligands and mechanisms. *Mini Rev Med Chem* **5**: 523–543.
- Brown DA (2010). Muscarinic acetylcholine receptors (mAChRs) in the nervous system: some functions and mechanisms. *J Mol Neurosci* **41**: 340–346.
- Caulfield MP, Birdsall NJM. (1998). International Union of Pharmacology. XVII Classification of muscarinic acetylcholine receptors. *Pharmacol Rev* **50**: 279–290.
- Conn PJ, Christopoulos A, Lindsley CW (2009a) Allosteric modulators of GPCRs: A novel approach for the treatment of CNS disorders. *Nature Rev Drug Discover* **8**: 41–54.
- Conn PJ, Jones CK, Lindsley CW (2009b). Subtype-selective allosteric modulators of muscarinic receptors for the treatment of CNS disorders. *Trends Pharmacol Sci* **30**: 148–155.
- De Amici M, Dallanocce C, Holzgrabe U, Tränkle C, Mohr K (2010). Allosteric ligands for G protein-coupled receptors: A novel strategy with attractive therapeutic opportunities. *Med Res Rev* **30**: 463–549.
- Digby GJ, Shirey JK, Conn PJ (2010). Allosteric activators of muscarinic receptors as novel approaches for treatment of CNS disorders. *Mol Biosyst* **6**: 1345–1354.
- Eckelman WC (2006). Imaging of muscarinic receptors in the central nervous system. *Curr Pharm Des* **12**: 3901–3913.
- Eglen RM (2005) Muscarinic receptor subtype pharmacology and physiology. *Prog Med Chem* **43**: 105–136.
- Eglen RM (2006). Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. *Auton Autocoid Pharmacol* **26**: 219–233.
- Gregory KJ, Sexton PM, Christopoulos A (2007) Allosteric modulation of muscarinic acetylcholine receptors. *Curr Neuropharmacol* **5**: 157–167.
- Holzgrabe U, De Amici M, Mohr K (2006). Allosteric modulators and selective agonists of muscarinic receptors. *J Mol Neurosci* **30**: 165–168.
- Ishii M, Kurachi Y (2006). Muscarinic acetylcholine receptors. *Curr Pharm Des* **12**: 3573–3581.
- Langmead CJ, Watson J, Reavill C (2008). Muscarinic acetylcholine receptors as CNS drug targets. *Pharmacol Ther* **117**: 232–243.
- Mohr K, Tränkle C, Kostenis E, Barocelli E, De Amici M, Holzgrabe U (2010). Rational design of dualsteric GPCR ligands: quests and promise. *Br J Pharmacol* **159**: 997–1008.
- Nathanson NM (2008). Synthesis, trafficking, and localization of muscarinic acetylcholine receptors. *Pharmacol Ther* **119**: 33–43.
- Peretto I, Petrillo P, Imbimbo BP (2009). Medicinal chemistry and therapeutic potential of muscarinic M<sub>3</sub> antagonists. *Med Res Rev* **29**: 867–902.
- Potter LT, Flynn DD, Liang JS, McCollum MH (2004). Studies of muscarinic neurotransmission with antimuscarinic toxins. *Prog Brain Res* **145**: 121–128.
- Servent D, Fruchart-Gaillard C (2009). Muscarinic toxins: tools for the study of the pharmacological and functional properties of muscarinic receptors. *J Neurochem* **109**: 1193–1202.
- Tobin G, Giglio D, Lundgren O (2009) Muscarinic receptor subtypes in the alimentary tract. *J Physiol Pharmacol* **60**: 3–21.
- Valant C, Sexton PM, Christopoulos A (2009) Orthosteric/allosteric bitopic ligands: Going hybrid at GPCRs. *Mol Int* **9**: 125–135.
- Wess J, Eglen RM, Gautam D (2007). Muscarinic acetylcholine receptors: mutant mice provide new insights for drug development. *Nat Rev Drug Discov* **6**: 721–733.

### References

- Avlani VA *et al.* (2010). *Mol Pharmacol* **78**: 94–104.
- Antony J *et al.* (2009). *FASEB J* **23**: 442–450.
- Brady AE *et al.* (2008). *J Pharmacol Exp Ther* **327**: 941–953.
- Bridges TM *et al.* (2009). *J Med Chem* **52**: 3445–3448.
- Chan WY *et al.* (2008). *Proc Natl Acad Sci USA* **105**: 10978–10983.
- Jones CK *et al.* (2008). *J Neurosci* **28**: 10422–10433.
- Langmead CJ *et al.* (2006). *Mol Pharmacol* **69**: 236–246.
- Langmead CJ *et al.* (2008). *Br J Pharmacol* **154**: 1104–1115.
- Lazareno S *et al.* (2000). *Mol Pharmacol* **58**: 194–207.
- Lazareno S *et al.* (2002). *Mol Pharmacol* **62**: 1492–1505.
- Leach K *et al.* (2010). *Neuropsychopharmacology* **35**: 855–869.
- Leach K *et al.* (2011). *Mol Pharmacol* **79**: 855–865.
- Lebon G *et al.* (2009). *Mol Pharmacol* **75**: 331–341.
- Ma L *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 15950–15955.
- May LT *et al.* (2007). *Mol Pharmacol* **72**: 463–476.
- Marlo JE *et al.* (2009). *Mol Pharmacol* **75**: 577–588.
- Nawaratne V *et al.* (2008). *Mol Pharmacol* **74**: 1119–1131.
- Nawaratne V *et al.* (2010). *J Biol Chem* **285**: 19012–19021.
- Reid PR *et al.* (2011). *Bioorg Med Chem Lett* **21**: 2697–2701.
- Sams AG *et al.* (2010). *J Med Chem* **53**: 6386–6397.
- Sheffler DJ *et al.* (2009). *Mol Pharmacol* **76**: 356–368.
- Shirey JK *et al.* (2008). *Nat Chem Biol* **4**: 42–50.
- Spalding TA *et al.* (2002). *Mol Pharmacol* **61**: 1297–1302.
- Spalding TA *et al.* (2006). *Mol Pharmacol* **70**: 1974–1983.
- Steinfeld T *et al.* (2007). *Mol Pharmacol* **72**: 291–302.
- Sur C *et al.* (2003) *Proc Natl Acad Sci USA* **100**: 13674–13679.
- Tränkle C *et al.* (2003). *Mol Pharmacol* **64**: 180–190.
- Valant C *et al.* (2008). *J Biol Chem* **283**: 29312–29321.
- Watt ML *et al.* (2011). *J Pharmacol Exp Ther* **338**: 622–632.

# Adenosine

**Overview:** Adenosine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adenosine Receptors; Fredholm *et al.*, 2011) are activated by the endogenous ligand adenosine (potentially inosine also at A<sub>3</sub> receptors). NECA is a non-selective agonist, while XAC and CGS15943 display submicromolar affinity for antagonism of all four adenosine receptors (Klotz *et al.*, 1998; Ongini *et al.*, 1999). Crystal structures for the antagonist-bound and agonist-bound A<sub>2A</sub> adenosine receptors have been described (Jaakola *et al.*, 2008; Xu *et al.*, 2011).

Nomenclature	A <sub>1</sub>	A <sub>2A</sub>	A <sub>2B</sub>	A <sub>3</sub>
Ensembl ID	ENSG00000163485	ENSG00000128271	ENSG00000170425	ENSG00000121933
Principal transduction	G <sub>i/o</sub>	G <sub>s</sub>	G <sub>s</sub>	G <sub>i/o</sub>
Selective agonists	CPA, CCPA, S-ENBA, GR79236	CGS21680, HENECA, ATL-146e (Peirce <i>et al.</i> , 2001)	Bay60-6583 (Eckle <i>et al.</i> , 2007)	CI-IB-MECA, IB-MECA
Selective antagonists	PSB36 (9.8, Abo-Salem <i>et al.</i> , 2004), DPCPX (8.5), SLV320 (9.0, Kalk <i>et al.</i> , 2007)	SCH442416 (10.3, Todde <i>et al.</i> , 2000), ZM241385 (9.0), SCH58261 (7.9–9.5)	PSB603 (9.3, Borrmann <i>et al.</i> , 2009), MRS1754 (8.7), MRS1706 (8.4), PSB1115 (7.7)	MRS1220 (8.8), VUF5574 (8.4, van Muijlwijk-Koezen <i>et al.</i> , 2000), MRS1523 (7.7), MRS1191 (7.0)
Probes	[ <sup>3</sup> H]-CCPA, [ <sup>3</sup> H]-DPCPX (0.6–1.2 nM)	[ <sup>3</sup> H]-CGS21680, [ <sup>3</sup> H]-ZM241385 (0.8 nM)	[ <sup>3</sup> H]-MRS1754 (1.1 nM)	[ <sup>125</sup> I]-AB-MECA (0.6 nM)

Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A<sub>2B</sub> adenosine receptor (ENSG00000182537) with 79% identity to the A<sub>2B</sub> adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor. DPCPX also exhibits antagonism at A<sub>2B</sub> receptors (pK<sub>i</sub> ca. 7, Alexander *et al.*, 1996; Klotz *et al.*, 1998). HENECA also shows activity at A<sub>3</sub> receptors (Varani *et al.*, 1998). Antagonists at A<sub>3</sub> receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A<sub>3</sub> receptor. In the absence of other adenosine receptors, [<sup>3</sup>H]-DPCPX and [<sup>3</sup>H]-ZM241385 can also be used to label A<sub>2B</sub> receptors (K<sub>D</sub> ca. 30 and 60 nM, respectively). [<sup>125</sup>I]-AB-MECA also binds to A<sub>1</sub> receptors (Klotz *et al.*, 1998). [<sup>3</sup>H]-CGS21680 is relatively selective for A<sub>2A</sub> receptors, but may also bind to other sites in cerebral cortex (Johansson and Fredholm, 1995; Cunha *et al.*, 1996). [<sup>3</sup>H]-NECA binds to other non-receptor elements, which also recognise adenosine (e.g. Lorenzen *et al.*, 1996). XAC-BY630 has been described as a fluorescent antagonist for labelling A<sub>1</sub> adenosine receptors in living cells, although activity at other adenosine receptors was not examined (Bridson *et al.*, 2004).

**Abbreviations:** AB-MECA, N<sup>6</sup>-(4-aminobenzyl)-adenosine-5'-N-methyluronamide; ATL-146e, 4-[3-[6-amino-9-(5-ethylcarbamoyl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl]-prop-2-ynyl]-cyclohexanecarboxylic acid methyl ester; Bay 60-6583, 2-(6-amino-3,5-dicyano-4-(4-(cyclopropylmethoxy)phenyl)pyridin-2-ylthio)acetamide; CCPA, 2-chloro-N<sup>6</sup>-cyclopentyladenosine; CGS15943, 5-amino-9-chloro-2-(2-furyl)1,2,4-triazolo[1,5-c]quinazoline; CGS21680, 2-(4-[2-carboxyethyl]-phenethylamino)adenosine-5'-N-ethyluronamide; CI-IB-MECA, 2-chloro-N<sup>6</sup>-(3-iodobenzyl)adenosine-5'-N-methyluronamide; CPA, N<sup>6</sup>-cyclopentyladenosine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; GR79236, N-[(1s,2s)-2-hydroxycyclopentyl adenosine; HENECA, 2-(1-(E)-hexenyl)adenosine-5'-N-ethyluronamide; MRS1191, 1,4-dihydro-2-methyl-6-phenyl-4-(phenylethynyl)-3,5-pyridinedicarboxylic acid, 3-ethyl 5-(phenylmethyl) ester; MRS1220, 9-chloro-2-(2-furyl)5-phenylacetylaminol[1,2,4]triazolo[1,5c]quinazoline; MRS1523, 2,3-ethyl-4,5-dipropyl-6-phenylpyridine-3-thiocarboxylate-5-carboxylate; MRS1706, N-(4-acetylphenyl)-2-(4-[2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl]phenoxy)acetamide; MRS1754, 8-(4-[[4-(4-cyanophenyl)carbamoylmethyl]oxy]phenyl)-1,3-di(n-propyl)xanthine; NECA, adenosine-5'-N-ethyluronamide; PSB1115, 4-[2,3,6,7-tetrahydro-2,6-dioxo-1-propyl-1H-purin-8-yl]benzenesulphonic acid; PSB36, 1-butyl-8-(3-noradamantanyl)-3-(3-hydroxypropyl)xanthine; PSB603, 8-[4-[4-(4-chlorophenyl)piperazine-1-sulfonyl]phenyl]-1-propylxanthine; S-ENBA, (2S)-N<sup>6</sup>-(2-endonorbanyl)adenosine; SCH442416, 2-(2-furanyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo [4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine; SCH58261, 5-amino-2-(2-furyl)-7-phenylethylpyrazolo[4,3-e]-1,2,4-triazolo[1,5c]pyrimidine; SLV320, trans-4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexanol; VUF5574, N-(2-methoxyphenyl)-N-(2-[3-pyridyl]quinazolin-4-yl)urea; XAC, 8-(4-[[[2-aminoethyl]amino]carbonyl]methyl]oxy]phenyl)-1,3-dipropylxanthine; also known as xanthine amine congener; XAC-BY630, N-(2-aminoethyl)-2-[4-(2,6-dioxo-1,3-dipropyl-7H-purin-8-yl)phenoxy]acetamide; ZM241385, 4-(2-[7-amino-2-(2-furyl)]{1,2,4}triazolo[2,3-a]{1,3,5}triazin-5-yl amino)ethyl)phenol

## Further Reading

- Fredholm BB, IJzerman AP, Jacobson KA, Linden J, Muller CE (2011). International Union of Basic and Clinical Pharmacology. LXXXI. Nomenclature and classification of adenosine receptors – an update. *Pharmacol Rev* 63: 1–34.
- Gessi S, Merighi S, Sacchetto V, Simioni C, Borea PA (2011). Adenosine receptors and cancer. *Biochim Biophys Acta* 1808: 1400–1412.
- Goblyos A, IJzerman AP (2011). Allosteric modulation of adenosine receptors. *Biochim Biophys Acta* 1808: 1309–1318.
- Headrick JP, Peart JN, Reichelt ME, Haseler LJ (2011). Adenosine and its receptors in the heart: Regulation, retaliation and adaptation. *Biochim Biophys Acta* 1808: 1413–1428.
- Kumar V, Sharma A (2009). Adenosine: An endogenous modulator of innate immune system with therapeutic potential. *Eur J Pharmacol* 616: 7–15.
- Lasley RD (2011). Adenosine receptors and membrane microdomains. *Biochim Biophys Acta* 1808: 1284–1289.
- Mundell S, Kelly E (2011). Adenosine receptor desensitization and trafficking. *Biochim Biophys Acta* 1808: 1319–1328.
- Ponnoth DS, Mustaffa SJ (2011). Adenosine receptors and vascular inflammation. *Biochim Biophys Acta* 1808: 1429–1434.
- Wei CJ, Li W, Chen JF (2011). Normal and abnormal functions of adenosine receptors in the central nervous system revealed by genetic knockout studies. *Biochim Biophys Acta* 1808: 1358–1379.
- Zhou Y, Schneider DJ, Blackburn MR (2009). Adenosine signaling and the regulation of chronic lung disease. *Pharmacol Ther* 123: 105–116.



## References

- Abo-Salem OM *et al.* (2004). *J Pharmacol Exp Ther* **308**: 358–366.
- Alexander SPH *et al.* (1996). *Br J Pharmacol* **119**: 1286–1290.
- Borrmann T *et al.* (2009). *J Med Chem* **52**: 3994–4006.
- Briddon SJ *et al.* (2004). *Proc Natl Acad Sci U S A* **101**: 4673–4678.
- Cunha RA *et al.* (1996). *Naunyn-Schmiedeberg's Arch Pharmacol* **353**: 261–271.
- Eckle T *et al.* (2007). *Circulation* **115**: 1581–1590.
- Jaakola VP *et al.* (2008). *Science* **322**: 1211–1217.
- Johansson B, Fredholm, BB (1995). *Neuropharmacology* **34**: 393–403.
- Kalk P *et al.* (2007). *Br J Pharmacol* **151**: 1025–1032.
- Klotz K-N *et al.* (1998). *Naunyn-Schmiedeberg's Arch Pharmacol* **357**: 1–9.
- Lorenzen A *et al.* (1996). *Biochem Pharmacol* **52**: 1375–1385.
- Ongini E *et al.* (1999). *Naunyn-Schmiedeberg's Arch Pharmacol* **359**: 7–10.
- Peirce SM *et al.* (2001). *Am J Physiol Heart Circ Physiol* **281**: H67–H74.
- Todde S *et al.* (2000). *J Med Chem* **43**: 4359–4362.
- van Muijlwijk-Koezen JE *et al.* (2000). *J Med Chem* **43**: 2227–2238.
- Varani K *et al.* (1998). *Life Sci* **63**: PL81–PL87.
- Xu F *et al.* (2011). *Science* **332**: 322–327.

# Adrenoceptors, $\alpha_1$

**Overview:**  $\alpha_1$ -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are GPCR activated by the endogenous agonists adrenaline and noradrenaline with equal potency. Phenylephrine, methoxamine and cirazoline are agonists selective for  $\alpha_1$ -adrenoceptors relative to  $\alpha_2$ -adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are antagonists considered selective for  $\alpha_1$ -adrenoceptors relative to  $\alpha_2$ -adrenoceptors. [ $^3$ H]-Prazosin (0.25 nM) and [ $^{125}$ I]-HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the  $\alpha_1$ -adrenoceptors exist, some of which may display a different spectrum of signalling properties. One polymorphism of the  $\alpha_{1A}$ -adrenoceptor has been described but is not associated with disease.

Nomenclature	$\alpha_{1A}$	$\alpha_{1B}$	$\alpha_{1D}$
Other names	$\alpha_{1a}$ , $\alpha_{1c}$	$\alpha_{1b}$	$\alpha_{1A/D}$ , $\alpha_{1a/d}$
Ensembl ID	ENSG00000120907	ENSG00000170214	ENSG00000171873
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>
Selective agonists	A61603, dabuzalgron (Blue <i>et al.</i> , 2004)	–	–
Selective antagonists	Tamsulosin (10.5), silodosin (10.4), (+)niguldipine (10.0), SNAP5089 (9.7)	–	BMY7378 (8.4)

The clone originally called the  $\alpha_{1C}$ -adrenoceptor corresponds to the pharmacologically defined  $\alpha_{1A}$ -adrenoceptor (see Hieble *et al.*, 1995). Some tissues possess  $\alpha_{1A}$ -adrenoceptors that display relatively low affinity in functional and binding assays for prazosin ( $pK_i < 9$ ) that might represent different receptor states (termed  $\alpha_{1L}$ -adrenoceptors, Ford *et al.*, 1997; Morishima *et al.*, 2007).  $\alpha_{1A}$ -Adrenoceptor C-terminal splice variants form homo and heterodimers, but fail to generate a functional  $\alpha_{1L}$ -adrenoceptor (Ramsay *et al.*, 2004). Recent studies suggest that the  $\alpha_{1L}$ -adrenoceptor phenotype may result from the interaction of  $\alpha_{1A}$ -adrenoceptors with cysteine-rich epidermal growth factor-like domain 1 $\alpha$  (CRELD1 $\alpha$ ) (Nishimune *et al.*, 2010).  $\alpha_{1D}$ -Adrenoceptors form heterodimers with  $\alpha_{1B}$ - or  $\beta_2$ -adrenoceptors that show increased cell-surface expression (Uberti *et al.*, 2005). Heterodimers formed between  $\alpha_{1D}$ - and  $\alpha_{1B}$ -adrenoceptors have distinct functional properties (Hague *et al.*, 2004).  $\alpha_{1D}$ -Adrenoceptors are mainly located intracellularly. (+)Niguldipine also has high affinity for L-type Ca<sup>2+</sup> channels.

Signalling is predominantly via G<sub>q/11</sub> but  $\alpha_1$ -adrenoceptors also couple to G<sub>i/o</sub>, G<sub>s</sub>, and G<sub>12/13</sub>. Several ligands activating  $\alpha_{1A}$ -adrenoceptors display ligand directed signalling bias. For example, oxymetazoline is a full agonist for extracellular acidification rate (ECAR) and a partial agonist for Ca<sup>2+</sup> release but does not stimulate cAMP production. Phenylephrine is biased toward ECAR versus Ca<sup>2+</sup> release or cAMP accumulation but not between Ca<sup>2+</sup> release and cAMP accumulation (Evans *et al.*, 2011). There are also differences between subtypes in coupling efficiency to different pathways – e.g. coupling efficiency to Ca<sup>2+</sup> signalling is  $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$  but for MAP kinase signalling is  $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$ . The subtypes also seem to show differences in regulation.

**Abbreviations:** A61603, N-(5-[4,5-dihydro-1H-imidazol-2-yl]-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide hydrobromide; BMY7378, 8-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-8-azaspiro[4,5]decane-7,9-dione dihydrochloride; HEAT, 2- $\beta$ -4-hydroxy-3-iodophenylethylaminomethyltetralone; RS17053, N-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro- $\alpha$ , $\alpha$ -dimethyl-1H-indole-3-ethanamide; silodosin, (-)-(*R*)-1-(3-hydroxypropyl)-5-(2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino)propyl)indoline-7-carboxamide, also known as KMD3213; SNAP5089, 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate-N-[3-(4,4-diphenylpiperidin-1-yl)propyl]amide methyl ester

## Further Reading

- Andersson KE, Gratzke C (2007). Pharmacology of  $\alpha_1$ -adrenoceptor antagonists in the lower urinary tract and central nervous system. *Nat Clin Pract Urol* 4: 368–378.
- Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP *et al.* (1994). International Union of Pharmacology IV. Nomenclature of adrenoceptors. *Pharmacol Rev* 46: 121–136.
- Cotecchia S (2007). Constitutive activity and inverse agonism at the  $\alpha_1$ adrenoceptors. *Biochem Pharmacol* 73: 1076–1083.
- Cotecchia S (2010). The  $\alpha_1$ -adrenergic receptors: diversity of signaling networks and regulation. *J Recept Signal Transduct Res* 30: 410–419.
- Hein L (2006). Adrenoceptors and signal transduction in neurons. *Cell Tissue Res* 326: 541–551.
- Hein P, Michel MC (2007). Signal transduction and regulation: are all  $\alpha_1$ -adrenergic receptor subtypes created equal? *Biochem Pharmacol* 73: 1097–1106.
- Hieble JP, Bylund DB, Clarke DE, Eikenburg DC, Langer SZ, Lefkowitz RJ *et al.* (1995). International Union of Pharmacology. X. Recommendation for nomenclature of  $\alpha_1$ -adrenoceptors: consensus update. *Pharmacol Rev* 47: 267–270.
- Kojima Y, Sasaki S, Hayashi Y, Tsujimoto G, Kohri K (2009). Subtypes of  $\alpha_1$ -adrenoceptors in BPH: future prospects for personalized medicine. *Nat Clin Pract Urol* 6: 44–53.
- Koshimizu TA, Tanoue A, Tsujimoto G (2007). Clinical implications from studies of  $\alpha_1$  adrenergic receptor knockout mice. *Biochem Pharmacol* 73: 1107–1112.
- Perez DM (2007). Structure-function of  $\alpha_1$ -adrenergic receptors. *Biochem Pharmacol* 73: 1051–1062.

## References

- Blue DR *et al.* (2004). *BJU Int* 93: 162–170.
- Evans BA *et al.* (2011). *Mol Pharmacol* 79: 298–307.
- Ford APDW *et al.* (1997). *Br J Pharmacol* 121: 1127–1135.
- Hague C *et al.* (2004). *J Pharmacol Exp Ther* 309: 388–397.
- Morishima S *et al.* (2007). *J Urol* 177: 377–381.
- Nishimune A *et al.* (2010). *J Pharmacol Sci* 113: 169–181.
- Ramsay D *et al.* (2004). *Mol Pharmacol* 66: 228–239.
- Uberti MA *et al.* (2005). *J Pharmacol Exp Ther* 313: 16–23.

# Adrenoceptors, $\alpha_2$

**Overview:**  $\alpha_2$ -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; Bylund *et al.*, 1994) are GPCR activated by endogenous agonists with a relative potency of adrenaline>noradrenaline. UK14304 (brimonidine) and BHT920 are agonists selective for  $\alpha_2$ -adrenoceptors relative to  $\alpha_1$ -adrenoceptors. Rauwolscine (9.0) and yohimbine (9.0) are antagonists selective for  $\alpha_2$ -adrenoceptors relative to  $\alpha_1$ -adrenoceptors. [<sup>3</sup>H]-rauwolscine (1 nM), [<sup>3</sup>H]-UK14304 (5 nM) and [<sup>3</sup>H]-RX821002 (0.5 nM and 0.1 nM at  $\alpha_{2C}$ ) are relatively selective radioligands. There is species variation in the pharmacology of the  $\alpha_{2A}$ -adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine  $\alpha_{2A}$ -adrenoceptors compared to the human receptor. These  $\alpha_{2A}$  orthologues are sometimes referred to as  $\alpha_{2D}$ -adrenoceptors. Multiple mutations of  $\alpha_2$ -adrenoceptors have been described, some of which are associated with alterations in function. The effects of classical (not subtype selective)  $\alpha_2$ -adrenoceptor agonists such as clonidine, guanabenz and UK14304 (brimonidine) on central baroreflex control (hypotension and bradycardia), hypnotic, analgesic, seizure modulation and platelet aggregation are mediated by  $\alpha_{2A}$ -adrenoceptors. The roles of  $\alpha_{2B}$  and  $\alpha_{2C}$ -adrenoceptors are less clear but the  $\alpha_{2B}$  subtype appears to be involved in neurotransmission in the spinal cord and  $\alpha_{2C}$  in regulating catecholamine release from adrenal chromaffin cells.

Nomenclature	$\alpha_{2A}$	$\alpha_{2B}$	$\alpha_{2C}$
Other names	$\alpha_{2D}$	–	–
Ensembl ID	ENSG00000150594	ENSG00000222040	ENSG00000184160
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Selective agonists	Oxymetazoline	–	–
Selective antagonists	BRL44408 (8.0, Young <i>et al.</i> , 1989)	Imiloxan (7.3, Michel <i>et al.</i> , 1990)	JP1302 (7.8, Sallinen <i>et al.</i> , 2007)

Oxymetazoline is a reduced efficacy agonist. ARC239 (pK<sub>i</sub> 8.0) and prazosin (pK<sub>i</sub> 7.5) show selectivity for  $\alpha_{2B}$ - and  $\alpha_{2C}$ -adrenoceptors over  $\alpha_{2A}$ -adrenoceptors. Binding sites for imidazolines, distinct from  $\alpha_2$ -adrenoceptors, have been identified and classified as I<sub>1</sub>, I<sub>2</sub> and I<sub>3</sub> sites and catecholamines have a low affinity for these sites. I<sub>1</sub>-imidazoline receptors are involved in central inhibition of sympathetic tone, I<sub>2</sub>-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I<sub>3</sub>-imidazoline receptors regulate insulin secretion from pancreatic  $\beta$ -cells.

**Abbreviations:** ARC239, 2-(2,4-[O-methoxyphenyl]-piperazin)-1-yl; BHT920, 6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepine; BRL44408, 2-(4,5-dihydro-1H-imidazol-2-ylmethyl)-1-methyl-1,3-dihydroisoindole; JP1302, N-(4-[4-methyl-1-piperazinyl]phenyl)-9-acridinamine dihydrochloride; MK912, (2S,12bS)1',3'-dimethylspiro(1,3,4,5',6',6',7,12b-octahydro-2H-benzo[b]furo[2,3-a]quinolizine)-2,4'-pyrimidin-2'-one; RX821002, 2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline; UK14304, 5-bromo-6-[2-imidazolin-2-ylamino]quinoxaline, also known as brimonidine

## Further Reading

- Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP *et al.* (1994). International Union of Pharmacology IV. Nomenclature of adrenoceptors. *Pharmacol Rev* 46: 121–136.
- Gyires K, Zadori ZS, Torok T, Matyus P (2009).  $\alpha_2$ -Adrenoceptor subtypes-mediated physiological, pharmacological actions. *Neurochem Int* 55: 447–453.
- Hein L (2006). Adrenoceptors and signal transduction in neurons. *Cell Tissue Res* 326: 541–551.
- Knaus AE, Muthig V, Schickinger S, Moura E, Beetz N, Gilsbach R *et al.* (2007).  $\alpha_2$ -adrenoceptor subtypes – unexpected functions for receptors and ligands derived from gene-targeted mouse models. *Neurochem Int* 51: 277–281.
- Philipp M, Hein L (2004). Adrenergic receptor knockout mice: distinct functions of 9 receptor subtypes. *Pharmacol Ther* 101: 65–74.

## References

- Michel AD *et al.* (1990). *Br J Pharmacol* 99: 560–564.
- Sallinen J *et al.* (2007). *Br J Pharmacol* 150: 391–402.
- Young P *et al.* (1989). *Eur J Pharmacol* 168: 381–386.

# Adrenoceptors, $\beta$

**Overview:**  $\beta$ -Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, see Bylund *et al.*, 1994) are GPCR activated by the endogenous agonists adrenaline and noradrenaline. Isoprenaline is a synthetic agonist selective for  $\beta$ -adrenoceptors relative to  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors, while propranolol ( $pK_i$  8.2–9.2) and cyanopindolol ( $pK_i$  10.0–11.0) are relatively selective antagonists.  $\beta_3$ -Adrenoceptors are relatively resistant to blockade by propranolol ( $pK_i$  5.8–7.0), but can be blocked by high concentrations of bupranolol ( $pK_i$  8.65, Sato *et al.*, 2008). Numerous polymorphisms exist for the  $\beta_1$ - and  $\beta_2$ -adrenoceptors and some of these are associated with alterations in signalling in response to agonists. These polymorphisms are likely to be associated with disease susceptibility and altered responses to drugs. The X-ray crystal structures have recently been described of the agonist bound (Warne *et al.*, 2011) and antagonist bound forms of the  $\beta_1$ - (Warne *et al.*, 2008), agonist-bound (Cherezov *et al.*, 2007) and antagonist-bound forms of the  $\beta_2$ -adrenoceptor (Rosenbaum *et al.*, 2011; Rasmussen *et al.*, 2011a), as well as agonist-bound, G<sub>s</sub> protein-coupled  $\beta_2$ -adrenoceptor (Rasmussen *et al.*, 2011b).

Nomenclature	$\beta_1$	$\beta_2$	$\beta_3$
Other names	–	–	atypical $\beta$
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000188778
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Rank order of potency	Noradrenaline>adrenaline	Adrenaline> noradrenaline	Noradrenaline =adrenaline
Selective agonists	Noradrenaline, xamoterol, RO363, denopamine	Procaterol, salbutamol, zinterol, salmeterol, formoterol, terbutaline, fenoterol (Baker, 2010)	BRL37344, CL316243, CGP12177A, carazolol, L742791, L755507, SB251023
Selective antagonists	CGP20712A (8.5–9.3), betaxolol (8.5), atenolol (7.6)	ICI118551 (8.3–9.2)	SR59230A (8.8), L748337 (8.4)
Probes	[ <sup>125</sup> I]-ICYP (20–50 pM)+70 nM ICI118551	[ <sup>125</sup> I]-ICYP (20–50 pM)+100 nM CGP20712A	[ <sup>125</sup> I]-ICYP (0.5 nM)

Noradrenaline, xamoterol and RO363 are agonists that show selectivity for  $\beta_1$ - relative to  $\beta_2$ -adrenoceptors. Pharmacological differences exist between human and mouse  $\beta_3$ -adrenoceptors, and the 'rodent selective' agonists BRL37344 and CL316243 have low efficacy at the human  $\beta_3$ -adrenoceptor whereas CGP12177A and L755507 activate human  $\beta_3$ -adrenoceptors (Sato *et al.*, 2008). All  $\beta$ -adrenoceptors couple to G<sub>s</sub> (activating adenylyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate other G proteins such as G<sub>i</sub> and many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at  $\beta_1$ - and  $\beta_2$ -adrenoceptors are agonists at  $\beta_3$ -adrenoceptors (CL316243, CGP12177A and carazolol). Many 'antagonists' appear to be able to selectively activate mitogen-activated protein kinase pathways (Baker *et al.*, 2003a; Galandrin and Bouvier, 2006; Galandrin *et al.*, 2008; Sato *et al.*, 2007; Sato *et al.*, 2008; Evans *et al.*, 2010) and display ligand-directed signalling bias. Bupranolol appears to act as a neutral antagonist in most systems so far examined. SR59230A has reasonably high affinity at  $\beta_3$ -adrenoceptors (Manara *et al.*, 1996), but does not discriminate well between the three  $\beta$ -adrenoceptor subtypes (Candelore *et al.*, 1999) and has been reported to have lower affinity for the  $\beta_3$ -adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

The  $\beta_3$ -adrenoceptor has introns, but splice variants have only been described for the mouse (Evans *et al.*, 1999), where the isoforms display different signalling characteristics (Hutchinson *et al.*, 2002). There are 3  $\beta$ -adrenoceptors in turkey (termed the t $\beta$ , t $\beta$ 3c and t $\beta$ 4c) that have a pharmacology that differs from the human  $\beta$ -adrenoceptors (Baker, 2011). The 'putative  $\beta_3$ -adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP12177A and other nonconventional partial agonists at  $\beta_1$ -adrenoceptors, since 'putative  $\beta_3$ -adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking  $\beta_1$ -adrenoceptors (Konkar *et al.*, 2000; Kaumann *et al.*, 2001).

Radioligand binding with [<sup>125</sup>I]-ICYP can be used to define  $\beta_1$ - or  $\beta_2$ -adrenoceptors when conducted in the presence of a 'saturating' concentration of either a  $\beta_1$ - or  $\beta_2$ -adrenoceptor-selective antagonist. [<sup>3</sup>H]-CGP12177 or [<sup>3</sup>H]-dihydroalprenolol can be used in place of [<sup>125</sup>I]-ICYP. Binding of a fluorescent analogue of CGP12177 to  $\beta_2$ -adrenoceptors in living cells has been described (Baker *et al.*, 2003b). [<sup>125</sup>I]-ICYP at higher (nM) concentrations can be used to label  $\beta_3$ -adrenoceptors in systems where there are few if any other  $\beta$ -adrenoceptor subtypes.

**Abbreviations:** BRL37344, sodium 4-(2-[2-hydroxy-3-chlorophenyl]ethylamino)propyl)phenoxyacetate; CGP12177A, (-)-4-(3-tert-butylamino-2-hydroxypropoxy)-benzimidazol-2-one; CGP20712A, 2-hydroxy-5-(2-[[2-hydroxy-3-(4-[1-methyl-4-trifluoromethyl-2-imidazolyl]phenoxy)propyl]amino]ethoxy)benzamide; CL316243, disodium (R,R)-5-(2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl)-1,3-benzodioxole-2,2-dicarboxylate; ICYP, iodocyanopindolol; L742791, (S)-N-(4-[2-(3-[4-hydroxyphenoxy]-2-hydroxypropyl)amino]ethyl)phenyl)-4-iodobenzenesulfonamide; L748337, N-[[3-[(2S)-2-hydroxy-3-[[2-[4-[(phenylsulfonyl)amino]phenyl]ethyl]amino]propoxy]phenyl]methyl]-acetamide]; RO363, (-)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propanol)oxalate; SB251023, (4-[1-[2-(S)-hydroxy-3-(4-hydroxyphenoxy)-propylamino]cyclopentylmethyl]phenoxy)methyl]phenylphosphonic acid lithium salt; SR59230A, 3-(2-ethylphenoxy)-1-[[1s]-1,2,3,4-tetrahydronaphth-1-ylamino]-2S-propanol oxalate

## Further Reading

- Ahles A, Engelhardt S (2009). Polymorphisms determine  $\beta$ -adrenoceptor conformation: implications for cardiovascular disease and therapy. *Trends Pharmacol Sci* 30: 188–193.
- Baker JG, Hill SJ, Summers RJ (2011) Evolution of  $\beta$ -blockers: from anti-anginal drugs to ligand-directed signaling. *Trends Pharmacol Sci* 32: 227–234.
- Brodde OE (2008).  $\beta_1$  and  $\beta_2$  adrenoceptor polymorphisms: Functional importance, impact on cardiovascular diseases and drug responses. *Pharmacol Ther* 117: 1–29.
- Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP *et al.* (1994). International Union of Pharmacology IV. Nomenclature of adrenoceptors. *Pharmacol Rev* 46: 121–136.

- Cazzola M, Molimard M (2010). The scientific rationale for combining long-acting  $\beta_2$ -agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* **23**: 257–267.
- Evans BA, Sato M, Sarwar M, Hutchinson DS, Summers RJ (2010) Ligand directed signaling at  $\beta$ -adrenoceptors *Br J Pharmacol* **159**: 1022–1038.
- Kaumann AJ, Molenaar P (2008). The low-affinity site of the  $\beta_1$ -adrenoceptor and its relevance to cardiovascular pharmacology. *Pharmacol Ther* **118**: 303–336.
- Mason RP, Giles TD, Sowers JR (2009). Evolving mechanisms of action of  $\beta$  blockers: focus on nebivolol. *J Cardiovasc Pharmacol* **54**: 123–128.
- Michel MC, Harding SE, Bond RA (2011). Are there functional  $\beta$ -adrenoceptors in the human heart? *Br J Pharmacol* **162**: 817–822.
- Moens AL, Yang R, Watts VL, Barouch LA (2010).  $\beta_3$ -adrenoreceptor regulation of nitric oxide in the cardiovascular system. *J Mol Cell Cardiol* **48**: 1088–1095.
- Mustafi D, Palczewski K (2009). Topology of class A G protein-coupled receptors: insights gained from crystal structures of rhodopsins, adrenergic and adenosine receptors. *Mol Pharmacol* **75**: 1–12.
- Patel CB, Noor N, Rockman HA (2010). Functional selectivity in adrenergic and angiotensin signaling systems. *Mol Pharmacol* **78**: 983–992.
- Pluim BM, de Hon O, Staal JB, Limpens J, Kuipers H, Overbeek SE *et al.* (2011).  $\beta$ -Agonists and physical performance: a systematic review and meta-analysis of randomized controlled trials. *Sports Med* **41**: 39–57.
- Rosenbaum DM, Rasmussen SG, Kobilka BK (2009). The structure and function of G-protein-coupled receptors. *Nature* **459**: 356–363.
- Walker JK, Penn RB, Hanania NA, Dickey BF, Bond RA (2011). New perspectives regarding  $\beta_2$ -adrenoceptor ligands in the treatment of asthma. *Br J Pharmacol* **163**: 18–28.

## References

- Baker JG *et al.* (2003a). *Mol Pharmacol* **64**: 1357–1369.
- Baker JG *et al.* (2003b). *Br J Pharmacol* **139**: 232–242.
- Baker JG (2010). *Br J Pharmacol* **160**: 1048–1061.
- Baker JG (2011). *PLoS ONE* **5**(11): e15487.
- Candelore MR *et al.* (1999). *J Pharmacol Exp Ther* **290**: 649–655.
- Cherezov V *et al.* (2007). *Science* **318**: 1258–1265.
- Evans BA *et al.* (1999). *Br J Pharmacol* **127**: 1525–1531.
- Galandrin S *et al.* (2008). *Mol Pharmacol* **74**: 162–172.
- Galandrin S, Bouvier M (2006). *Mol Pharmacol* **70**: 1575–1584.
- Hutchinson DS *et al.* (2002). *Br J Pharmacol* **135**: 1903–1914.
- Kaumann AJ *et al.* (2001). *Naunyn-Schmiedeberg's Arch Pharmacol* **363**: 87–93.
- Kaumann AJ, Molenaar P (1996). *Br J Pharmacol* **118**: 2085–2098.
- Konkar AA *et al.* (2000). *Mol Pharmacol* **57**: 252–258.
- Manara L *et al.* (1996). *Br J Pharmacol* **117**: 435–442.
- Rasmussen SG *et al.* (2011a). *Nature* **469**: 175–180.
- Rasmussen SG *et al.* (2011b). *Nature* **477**: 549–555.
- Rosenbaum DM *et al.* (2011). *Nature* **469**: 236–240.
- Sato M *et al.* (2007). *Mol Pharmacol* **72**: 1359–1368.
- Sato M *et al.* (2008). *Mol Pharmacol* **74**: 1417–1428.
- Warne T *et al.* (2008). *Nature* **454**: 486–491.
- Warne T *et al.* (2011). *Nature* **469**: 241–244.

# Anaphylatoxin

**Overview:** anaphylatoxin receptors (provisional nomenclature) are activated by the endogenous ~75 amino-acid anaphylatoxin polypeptides C3a (ENSG00000125730) and C5a (ENSG00000106804), generated upon stimulation of the complement cascade.

Nomenclature	C3a	C5a
Other names	AZ3B, HNFAG09	CD88
Ensembl ID	ENSG00000171860	ENSG00000134830
Principal transduction	G <sub>ij/or</sub> , G <sub>z</sub>	G <sub>ij/or</sub> , G <sub>z</sub> , G <sub>16</sub> (Buhl <i>et al.</i> , 1993)
Rank order of potency	C3a>C5a (Ames <i>et al.</i> , 1996)	C5a, C5a des Arg>C3a (Ames <i>et al.</i> , 1996)
Selective agonists	Trp-Trp-Gly-Lys-Lys-Tyr-Arg-Ala-Ser-Lys-Leu-Gly-Leu-Ala-Arg (Ames <i>et al.</i> , 1997)	Phe-Lys-Pro-Cha-Cha-Phe-Lys-D-Cha-Cha-D-Arg (Konteatis <i>et al.</i> , 1994), S19 (Yamamoto, 2000)
Selective antagonists	SB290157 (pIC <sub>50</sub> 7.5, Ames <i>et al.</i> , 2001)	NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg (Konteatis <i>et al.</i> , 1994), AcPhe-Orn-Pro-D-Cha-Trp-Arg (Wong <i>et al.</i> , 1998), W54011 (8.7, Sumichika <i>et al.</i> , 2002), CHIPS (Postma <i>et al.</i> , 2004)
Probes	[ <sup>125</sup> I]-C3a	[ <sup>125</sup> I]-C5a

SB290157 has also been reported to have agonist properties (Mathieu *et al.*, 2005). A putative chemoattractant receptor termed C5L2 (also known as GPR77, ENSG00000134830) binds [<sup>125</sup>I]-C5a, with no clear signalling function, but a putative role opposing inflammatory responses (Cain and Monk, 2002; Gao *et al.*, 2005; Gavriluk *et al.*, 2005). Binding to this site may be displaced with the rank order C5a des Arg>C5a (Cain and Monk, 2002; Okinaga *et al.*, 2003), while there is controversy over the ability of C3a and C3a des Arg to compete (Kalant *et al.*, 2003; Okinaga *et al.*, 2003; Honczarenko *et al.*, 2005; Kalant *et al.*, 2005). C5L2 appears to lack G protein signalling and has been termed a decoy receptor (Scola *et al.*, 2009).

**Abbreviations:** BOC-PLPLP, Boc-Phe-Leu-Phe-Leu-Phe; CHIPS, chemotaxis inhibitory protein of *Staphylococcus aureus*; SB290157, N<sup>2</sup>-([2,2-diphenylethoxy]acetyl)-L-arg; W54011, N-(4-dimethylaminophenyl)methyl-N-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-carboxamide hydrochloride

## Further Reading

Ali H (2010). Regulation of human mast cell and basophil function by anaphylatoxins C3a and C5a. *Immunol Lett* **128**: 36–45.  
 Hajishengallis G (2010). Complement and periodontitis. *Biochem Pharmacol* **80**: 1992–2001.  
 Manthey HD, Woodruff TM, Taylor SM, Monk PN (2009). Complement component 5a (C5a). *Int J Biochem Cell Biol* **41**: 2114–2117.  
 Monk PN, Scola AM, Madala P, Fairlie DP (2007). Function, structure and therapeutic potential of complement C5a receptors. *Br J Pharmacol* **152**: 429–228.  
 Sacks SH (2010). Complement fragments C3a and C5a: the salt and pepper of the immune response. *Eur J Immunol* **40**: 668–670.  
 Ward PA (2009). Functions of C5a receptors. *J Mol Med (Berl)* **87**: 375–378.

## References

- Ames RS *et al.* (1996). *FEBS Lett* **395**: 157–159.  
 Ames RS *et al.* (1997). *Immunopharmacology* **38**: 87–92.  
 Ames RS *et al.* (2001). *J Immunol* **166**: 6341–6348.  
 Buhl AM *et al.* (1993). *FEBS Lett* **323**: 132–134.  
 Cain SA, Monk, PN (2002). *J Biol Chem* **277**: 7165–7169.  
 Gao H *et al.* (2005). *FASEB J* **19**: 1003–1005.  
 Gavriluk V *et al.* (2005). *J Neurochem* **92**: 1140–1149.  
 Honczarenko M *et al.* (2005). *Leukemia* **19**: 1682–1683.  
 Kalant D *et al.* (2003). *J Biol Chem* **278**: 11123–11129.  
 Kalant D *et al.* (2005). *J Biol Chem* **280**: 23936–23944.  
 Konteatis ZD *et al.* (1994). *J Immunol* **153**: 4200–4205.  
 Mathieu MC *et al.* (2005). *Immunol Lett* **100**: 139–145.  
 Okinaga S *et al.* (2003). *Biochemistry* **42**: 9406–9415.  
 Postma B *et al.* (2004). *J Immunol* **172**: 6994–7001.  
 Scola AM *et al.* (2009). *Mol Immunol* **46**: 1149–1162.  
 Sumichika H *et al.* (2002). *J Biol Chem* **277**: 49403–49407.  
 Wong AK *et al.* (1998). *J Med Chem* **41**: 3417–3425.  
 Yamamoto T (2000). *Pathol Int* **50**: 863–871.

# Angiotensin

**Overview:** The actions of angiotensin II (Ang II) are mediated by AT<sub>1</sub> and AT<sub>2</sub> receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; see de Gasparo *et al.*, 2000), which have around 30% sequence similarity. AT<sub>1</sub> receptors are predominantly coupled to G<sub>q/11</sub>, however they are also linked to arrestin recruitment and stimulate G protein independent arrestin signalling (Luttrell and Gesty-Palmer 2010). Most species express a single AT<sub>1</sub> gene, but two related AT<sub>1A</sub> and AT<sub>1B</sub> receptor genes are expressed in rodents. The AT<sub>2</sub> receptor counteracts several of the growth responses initiated by the AT<sub>1</sub> receptors. The AT<sub>2</sub> receptor is much less abundant than the AT<sub>1</sub> receptor in adult tissues and is upregulated in pathological conditions. Endogenous ligands are Ang II and angiotensin III (Ang III), while angiotensin I is weakly active in some systems.

Nomenclature	AT <sub>1</sub>	AT <sub>2</sub>
Ensembl ID	ENSG00000144891	ENSG00000180772
Principal transduction	G <sub>q/11</sub>	G <sub>i</sub> / G <sub>o</sub> , Tyr & Ser/Thr phosphatases
Selective agonists	L162313	[p-NH <sub>2</sub> -Phe <sup>6</sup> ]-Ang II, CGP42112
Selective antagonists	EXP3174, eprosartan, valsartan, irbesartan, losartan, candesartan	PD123319, PD123177
Probes	[ <sup>3</sup> H]-A81988, [ <sup>3</sup> H]-L158809, [ <sup>3</sup> H]-eprosartan, [ <sup>3</sup> H]-losartan, [ <sup>125</sup> I]-EXP985	[ <sup>125</sup> I]-CGP42112

There is also evidence for an AT<sub>4</sub> receptor that specifically binds angiotensin IV and is located in the brain and kidney. An additional putative endogenous ligand for the AT<sub>4</sub> receptor has been described (LVV-hemorphin, a globin decapeptide) (Moeller *et al.*, 1997). The AT<sub>1</sub> and bradykinin B2 receptors have been proposed to form a heterodimeric complex (Abdalla *et al.*, 2000). The antagonist activity of CGP42112 has also been reported (Lokuta *et al.*, 1995). Novel AT<sub>1</sub> receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesized. The best of these compounds bind to AT<sub>1</sub> receptors with nanomolar affinity and are slightly more potent than losartan in functional studies (Cappelli *et al.*, 2004).

**Abbreviations:** **A81988**, 2(*N*-propyl-*N*-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methylamino)pyridine-3-carboxylate; **candesartan**, 2-ethoxy-3-[[4-[2-(2*H*-tetrazol-5-yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid; **CGP42112A**, nicotinic acid-Tyr-(*N*-benzoylcarbonyl-Arg)-Lys-His-Pro-Ile-OH; **eprosartan**, (E)-α-[(2-butyl-1-[(4-carboxyphenyl)methyl]-1*H*-imidazol-5-yl)methylene]-2-thiophenepropanoate; **EXP3174**, *n*-butyl-4-chloro-1-[(2'-[1*H*-tetrazol-5-yl]biphenyl-4-yl)methyl]imidazole-5-carboxylate; **EXP985**, *N*-(2-[4-hydroxy-3-iodophenyl]ethyl)-4-chloro-2-propyl-1-[(2'-[1*H*-tetrazol-5-yl]biphenyl-4-yl)methyl]imidazole-5-carboxamide; **irbesartan**, 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one; **L158809**, 5,7-dimethyl-2-ethyl-3-(2-[1*H*-tetrazol-5-yl]biphenyl-4-yl)imidazo[4,5-*b*]pyridine; **L162313**, 5,7-dimethyl-2-ethyl-3-[[4-[2(*n*-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]imidazo[4,5,6]pyridine; **losartan**, 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2'-[1*H*-tetrazol-5-yl]biphenyl-4-yl)methyl]imidazole, also known as Dup 753; **PD123177**, 1-(4-amino-3-methylphenyl)methyl-3-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **PD123319**, (S)-1-(4-[dimethylamino]-3-methylphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **valsartan**, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine

## Further Reading

- Aldiger JC, Ghannad E (2002). Exploring AT<sub>1</sub> and AT<sub>2</sub> angiotensin II receptors in humans. *Drugs* **62**: 11–19.
- Carey RM (2005). Update on the role of the AT<sub>2</sub> receptor. *Curr Opin Nephrol Hypertens* **14**: 67–71.
- Cheung BM (2006). Therapeutic potential of angiotensin receptor blockers in hypertension. *Expert Opin Investig Drugs* **15**: 625–635.
- Croom KE, Plosker GL (2008). Irbesartan: a review of its use in hypertension and diabetic nephropathy. *Drugs* **68**: 1543–1569.
- De Gasparo M (2002). AT<sub>1</sub> and AT<sub>2</sub> angiotensin (II) receptors: key features. *Drugs* **62**: 1–10.
- De Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T (2000). International Union of Pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev* **52**: 415–472.
- Ferrario CM, Chappell MC (2004). Novel angiotensin peptides. *Cell Mol Life Sci* **61**: 2720–2727.
- Jones ES, Vinh A, McCarthy CA, Gaspari T, Widdop RE (2008). AT<sub>2</sub> receptors: functional relevance in cardiovascular disease. *Pharmacol Ther* **120**: 292–316.
- Kintscher U, Foryst-Ludwig A, Unger T (2008). Inhibiting angiotensin type 1 receptors as a target for diabetes. *Expert Opin Ther Targets* **12**: 1257–1263.
- Kusserow H, Unger T (2004). Vasoactive peptides, their receptors and drug development. *Basic Clin Pharmacol Toxicol* **94**: 5–12.
- Luttrell LM, Gesty-Palmer D (2010). Beyond desensitization: Physiological relevance of arrestin-dependent signaling. *Pharm Rev* **62**: 305–330.
- Ma TK, Kam KK, Yan BP, Lam YY (2010). Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status. *Br J Pharmacol* **160**: 1273–1292.
- Maggioni AP (2006). Efficacy of angiotensin receptor blockers in cardiovascular disease. *Cardiovasc Drugs Ther* **20**: 295–308.
- Nouet S, Nahmias C (2000). Signal transduction from the angiotensin II AT<sub>2</sub> receptor. *Trends Endocrinol Metab* **11**: 1–6.
- Ram CV (2008). Angiotensin receptor blockers: current status and future prospects. *Am J Med* **121**: 656–663.
- Rashid AJ, O'Dowd BF, George SR (2004). Minireview: diversity and complexity of signaling through peptidergic G protein-coupled receptors. *Endocrinology* **145**: 2645–2652.
- Unger T (1999). The angiotensin type 2 receptor: variations on an enigmatic theme. *J Hypertens* **17**: 1775–1786.
- Zaman MA, Oparil S, Calhoun DA (2002). Drugs targeting the renin-angiotensin-aldosterone system. *Nat Rev Drug Discov* **1**: 621–636.

## References

- Abdalla S *et al.* (2000). *Nature* **407**: 94–98.
- Cappelli A *et al.* (2004). *J Med Chem* **47**: 2574–2586.
- Lokuta AJ *et al.* (1995). *J Biol Chem* **269**: 4832–4838.
- Moeller I *et al.* (1997). *J Neurochem* **68**: 2530–2537.

# Apelin

**Overview:** The apelin receptor (APJ, nomenclature as agreed by NC-IUPHAR on apelin receptors, Pitkin *et al.*, 2010) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36, apelin-13 and (Pyr<sup>1</sup>)apelin-13 are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (ENSG00000171388) by a so far unidentified enzymatic pathway (Tatemoto *et al.*, 1998).

Nomenclature	APJ
Other names	Apelin receptor, angiotensin receptor-like 1
Ensembl ID	ENSG00000134817
Principal transduction	G <sub>i/o</sub>
Rank order of potency	[Pyr <sup>1</sup> ]apelin-13 ≥ apelin-13 > apelin-36 (Tatemoto <i>et al.</i> , 1998; Fan <i>et al.</i> , 2003)
Selective agonists	[Pyr <sup>1</sup> ]apelin-13, apelin-13, apelin-17, apelin-36
Probes	[ <sup>125</sup> I]-[Pyr <sup>1</sup> ]Apelin-13 (0.3 nM, Katugampola <i>et al.</i> , 2001), [ <sup>125</sup> I]-apelin-13 (Fan <i>et al.</i> , 2003), [ <sup>3</sup> H]-[Pyr <sup>1</sup> ][Met(0 <sup>11</sup> )]apelin-13 (Medhurst <i>et al.</i> , 2003), [ <sup>125</sup> I]-[Nle <sup>75</sup> ,Tyr <sup>77</sup> ]apelin-36 (Kawamata <i>et al.</i> , 2001), [ <sup>125</sup> I]-[Glp <sup>65</sup> Nle <sup>75</sup> ,Tyr <sup>77</sup> ]apelin-13 (Hosoya <i>et al.</i> , 2000)

Potency order determined for heterologously expressed human APJ receptor (pD<sub>2</sub> values range from 9.5 to 8.6). APJ may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function (Cayabyab *et al.*, 2000). A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* (Lee *et al.*, 2005), however this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant APJ receptor (Fan *et al.*, 2003).

## Further Reading

- Chandrasekaran B, Dar O, McDonagh T (2008). The role of apelin in cardiovascular function and heart failure. *Eur J Heart Fail* **10**: 725–732.
- Davenport AP, Pitkin SL, Maguire JJ. (2007). Apelins. In: Offermanns S, Rosenthal W (eds). *Encyclopedic Reference of Molecular Pharmacology*. Springer: Berlin, pp. 201–206.
- Japp AG, Newby DE (2008). The apelin-APJ system in heart failure: pathophysiologic relevance and therapeutic potential. *Biochem Pharmacol* **75**: 1882–1892.
- Langelaan DN, Bebbington EM, Reddy T, Rainey JK (2009). Structural insight into G-protein coupled receptor binding by apelin. *Biochemistry* **48**: 537–548.
- Lee DK, George SR, O'Dowd BF (2006). Unravelling the roles of the apelin system: prospective therapeutic applications in heart failure and obesity. *Trends Pharmacol Sci* **27**: 190–194.
- Pitkin SL, Maguire JJ, Bonner TI, Davenport AP (2010). International Union of Basic and Clinical Pharmacology. LXXIV. Apelin receptor nomenclature, distribution, pharmacology, and function. *Pharmacol Rev* **62**: 331–342.
- Sorli SC, van den Berghe L, Masri B, Knibiehler B, Audigier Y. (2006). Therapeutic potential of interfering with apelin signalling. *Drug Discov Today* **11**: 1100–1106.

## References

- Cayabyab M *et al.* (2000). *J Virol* **74**: 11972–11976.
- Fan X *et al.* (2003). *Biochemistry* **42**: 10163–10168.
- Hosoya M *et al.* (2000). *J Biol Chem* **275**: 21061–21067.
- Katugampola SD *et al.* (2001). *Br J Pharmacol* **132**: 1255–1260.
- Kawamata Y *et al.* (2001). *Biochim Biophys Acta* **1538**: 162–171.
- Lee DK *et al.*, (2005). *Endocrinology* **146**: 231–236.
- Medhurst AD *et al.* (2003). *J Neurochem* **84**: 1162–1172.
- Tatemoto K *et al.* (1998). *Biochem Biophys Res Commun* **251**: 471–476.



# Bile acid

**Overview:** The bile acid receptor (GPBA, provisional nomenclature) responds to bile acids produced during the liver metabolism of cholesterol.

Nomenclature	GPBA
Other names	GPBAR1, BG37, GPCR19, GPR131, M-BAR, MGC40597, TGR5
Ensembl ID	ENSG00000179921
Principal transduction	G <sub>s</sub> (Maruyama <i>et al.</i> , 2002)
Rank order of potency	Lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid (Maruyama <i>et al.</i> , 2002; Kawamata <i>et al.</i> , 2003)
Selective agonists	Oleanolic acid (Sato <i>et al.</i> , 2007), betulinic acid (Genet <i>et al.</i> , 2010)

The triterpenoid natural product betulinic acid has also been reported to inhibit inflammatory signalling through the NFκB pathway (Takada and Aggarwal, 2003). Disruption of GPBA expression is reported to protect from cholesterol gallstone formation (Vassileva *et al.*, 2006).

## Further Reading

- Fiorucci S, Cipriani S, Baldelli F, Mencarelli A (2010). Bile acid-activated receptors in the treatment of dyslipidemia and related disorders. *Prog Lipid Res* **49**: 171–185.
- Fiorucci S, Mencarelli A, Palladino G, Cipriani S (2009). Bile-acid-activated receptors: targeting TGR5 and farnesoid-X-receptor in lipid and glucose disorders. *Trends Pharmacol Sci* **30**: 570–580.
- Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B (2009). Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev* **89**: 147–191.
- Nguyen A, Bouscarel B (2008). Bile acids and signal transduction: role in glucose homeostasis. *Cell Signal*, **20**: 2180–2197.
- Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K (2011). The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. *J Hepatol* **54**: 1263–1272.
- Sato H, Macchiarulo A, Thomas C, Gioiello A, Une M, Hofmann AF *et al.* (2008). Novel potent and selective bile acid derivatives as TGR5 agonists: biological screening, structure-activity relationships, and molecular modeling studies. *J Med Chem* **51**: 1831–1841.
- Thomas C, Auwerx J, Schoonjans K (2008). Bile acids and the membrane bile acid receptor TGR5 – connecting nutrition and metabolism. *Thyroid*, **18**: 167–174.
- Tiwari A, Maiti P (2009). TGR5: an emerging bile acid G-protein-coupled receptor target for the potential treatment of metabolic disorders. *Drug Discov Today*, **14**: 523–530.
- Wei J, Qiu DK, Ma X (2009). Bile acids and insulin resistance: implications for treating nonalcoholic fatty liver disease. *J Dig Dis*, **10**: 85–90.

## References

- Genet C *et al.* (2010). *J Med Chem* **53**: 178–190.
- Kawamata Y *et al.* (2003). *J Biol Chem* **278**: 9435–9440.
- Maruyama T *et al.* (2002). *Biochem Biophys Res Commun* **298**: 714–719.
- Sato H *et al.* (2007). *Biochem Biophys Res Commun* **362**: 793–798.
- Takada Y, Aggarwal BB (2003). *J Immunol* **171**: 3278–3286.
- Vassileva G *et al.* (2006). *Biochem J* **398**: 423–430.

# Bombesin

**Overview:** Bombesin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, Jensen *et al.*, 2008) are activated by the endogenous ligands gastrin-releasing peptide (GRP), neuromedin B (NMB) and GRP-18-27 (previously named neuromedin C). Bombesin is a tetradecapeptide, originally derived from amphibians. These receptors couple primarily to the G<sub>q/11</sub> family of G proteins (but see also Jian *et al.*, 1999). Activation of BB<sub>1</sub> and BB<sub>2</sub> receptors causes a wide range of physiological actions, including the stimulation of tissue growth, smooth-muscle contraction, secretion and many central nervous system effects (Tokita *et al.*, 2002). A physiological role for the BB<sub>3</sub> receptor has yet to be fully defined although receptor knockout experiments suggest a role in energy balance and the control of body weight (see Jensen *et al.*, 2008).

Nomenclature	BB <sub>1</sub>	BB <sub>2</sub>	BB <sub>3</sub>
Other names	NMB-R, BB1	GRP-R, BB2	BRS-3, bb3
Ensembl ID	ENSG00000135577	ENSG00000126010	ENSG00000102239
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>
Selective agonists	NMB	GRP	[D-Tyr <sup>6</sup> ,Apa-4Cl <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ] bombesin <sub>6-14</sub> ,
Selective antagonists	PD165929, dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH <sub>2</sub> , dNal-Cys-Tyr-dTrp-Lys-Val-Cys-Nal-NH <sub>2</sub> , PD168368	[D-Phe <sup>6</sup> ,Cpa <sup>14</sup> ,ψ13-14]Bn <sub>6-14</sub> , JMV594, Ac-GRP <sub>20-26</sub> methyl ester	–
Probes	[ <sup>125</sup> I]-BH-NMB, [ <sup>125</sup> I]-[Tyr <sup>4</sup> ]bombesin	[ <sup>125</sup> I]-[DTyr <sup>6</sup> ]bombesin-6-13-methyl ester, [ <sup>125</sup> I]-GRP, [ <sup>125</sup> I]-[Tyr <sup>4</sup> ]bombesin	[ <sup>125</sup> I]-[Tyr <sup>6</sup> ,βAla <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ] bombesin-6-14

All three subtypes may be activated by [dPhe<sup>6</sup>,βAla<sup>11</sup>,Phe<sup>13</sup>,Nle<sup>14</sup>]bombesin-6-14 (Mantey *et al.*, 1997). [D-Tyr<sup>6</sup>, Apa-4Cl, Phe<sup>13</sup>, Nle<sup>14</sup>] bombesin-6-14, has more than 200-fold selectivity for BB<sub>3</sub> receptors over BB<sub>1</sub> and BB<sub>2</sub> (Mantey *et al.*, 2004).

**Abbreviations:** PD165929, 2-[3-(2,6-diisopropylphenyl)-ureido]3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-proprionate, PD168368, 3-(1H-indol-3-yl)-2-methyl-2-[3(4-nitro-phenyl)-ureido]N-(1-pyridin-2-yl-cyclohexylmethyl)-proprionamide, JMV594 H-D-Phe,Gln,Trp,Ala,Val,Gly,His-NH-CH[CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>]-CHOH-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>.

## Further Reading

- Batthey J, Wada E (1991). Two distinct receptor subtypes for mammalian bombesin receptors. *Trends Neurosci* **14**: 524–528.
- Iwabuchi M, Ui-Tei K, Yamada K, Matsuda Y, Sakai Y, Tanaka K, Ohki-Hamazaki H (2003). Molecular cloning and characterisation of avian bombesin-like peptide receptors: new tools for investigating molecular basis of ligand selectivity. *Br J Pharmacol* **139**: 555–566.
- Jensen RT, Batthey JF, Spindel ER, Benya RV (2008). International Union of Pharmacology. LXVIII. Mammalian bombesin receptors: nomenclature, distribution, pharmacology, signaling and function in normal and disease states. *Pharmacol Rev* **60**: 1–42.
- Jensen R, Coy D (1991). Progress in the development of potent bombesin receptor antagonists. *Trends Pharmacol Sci* **12**: 13–18.
- Kroog GS, Jensen RT, Batthey JF (1995). Bombesin receptors. *Med Res Rev* **15**: 389–417.
- Moody TW, Merali Z (2004). Bombesin-like peptides and associated receptors within the brain: distribution and behavioural implications. *Peptides* **25**: 511–520.
- Moody TW, Mantey SA, Pradhan TK, Schumann M, Nakagawa T, Martinez A *et al.* (2004). Development of high affinity camptothecin–bombesin conjugates that have targeted cytotoxicity for bombesin receptor-containing tumor cells. *J Biol Chem* **279**: 23580–23589.
- Ohki-Hamazaki H (2000). Neuromedin B. *Prog Neurobiol* **62**: 297–312.
- Ohki-Hamazaki H, Iwabuchi M, Maekawa F (2005). Development and function of bombesin-like peptides and their receptors. *Int J Dev Biol* **49**: 293–300.
- Roesler R, Henriques JA, Schwartsmann G (2006). Gastrin-releasing peptide receptor as a molecular target for psychiatric and neurological disorders. *CNS Neurol Disord Drug Targets* **5**: 197–204.
- Tokita K, Hocart SJ, Coy DH, Jensen RT (2002). Molecular basis of the selectivity of gastrin-releasing peptide receptor for gastrin-releasing peptide. *Mol Pharmacol* **61**: 1435–1443.
- Weber D (2003). Design of selective peptidomimetic agonists for the human orphan receptor BRS-3. *J Med Chem* **46**: 1918–1930.
- Weber HC (2009). Regulation and signaling of human bombesin receptors and their biological effects. *Curr Opin Endocrinol Diabetes Obes* **16**: 66–71.
- Zhou J, Chen J, Mokotoff M, Ball ED (2004). Targeting gastrin-releasing peptide receptors for cancer treatment. *Anti-cancer Drugs* **15**: 921–927.

## References

- Jian XY *et al.* (1999). *J Biol Chem* **274**: 11573–11581.
- Mantey SA *et al.* (1997). *J Biol Chem* **272**: 26062–26071.
- Mantey SA *et al.* (2004). *J Pharmacol Exp Ther* **310**: 1161–1170.

# Bradykinin

**Overview:** Bradykinin (or kinin) receptors (nomenclature recommended by the NC-IUPHAR subcommittee on bradykinin (kinin) receptors, Leeb-Lundberg *et al.*, 2005) are activated by the endogenous peptides bradykinin (BK), [des-Arg<sup>9</sup>]BK, Lys-BK (kallidin), Lys-[des-Arg<sup>9</sup>]BK, T-kinin (Ile-Ser-BK), [Hyp<sup>3</sup>]BK and Lys-[Hyp<sup>3</sup>]BK. The variation in affinity or inactivity of B<sub>2</sub> receptor antagonists could reflect the existence of species homologues of B<sub>2</sub> receptors.

Nomenclature	B <sub>1</sub>	B <sub>2</sub>
Ensembl ID	ENSG00000100739	ENSG00000168398
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	Lys-[des-Arg <sup>9</sup> ]BK > [des-Arg <sup>9</sup> ]BK = Lys-BK > BK	Lys-BK ≥ BK >> [des-Arg <sup>9</sup> ]BK, Lys-[des-Arg <sup>9</sup> ]BK
Selective agonists	Lys-[des-Arg <sup>9</sup> ]BK, Sar[D <sup>8</sup> Phe <sup>8</sup> ][des-Arg <sup>9</sup> ]BK	[Phe <sup>8</sup> , ψ(CH <sub>2</sub> -NH)Arg <sup>9</sup> ]BK, [Hyp <sup>3</sup> , Tyr(Me) <sup>8</sup> ]BK
Selective antagonists	B9958 (9.2, Regoli <i>et al.</i> , 1998), R914 (8.6, Gobeil <i>et al.</i> , 1999), R715 (8.5, Gobeil <i>et al.</i> , 1996a), Lys-[Leu <sup>8</sup> ][des-Arg <sup>9</sup> ]BK (8.0)	Icatibant (8.4, Gobeil <i>et al.</i> , 1996b), FR173657 (8.2, Rizzi <i>et al.</i> , 1997), LF160687 (Pruneau <i>et al.</i> , 1999)
Probes	[ <sup>3</sup> H]-Lys-[des-Arg <sup>9</sup> ]BK (0.4 nM), [ <sup>3</sup> H]-Lys-[Leu <sup>8</sup> ][des-Arg <sup>9</sup> ]BK, [ <sup>125</sup> I]-Hpp-desArg <sup>9</sup> HOE140 (0.1 nM)	[ <sup>3</sup> H]-BK (0.2 nM), [ <sup>3</sup> H]-NPC17731 (50–900 pM), [ <sup>125</sup> I]-[Tyr <sup>8</sup> ]BK

**Abbreviations:** B9958, Lys-Lys[Hyp<sup>3</sup>, Cpg<sup>5</sup>, dTic<sup>7</sup>, Cpg<sup>8</sup>][des-Arg<sup>9</sup>]BK; FR173657, (E)-3-(6-acetamido-3-pyridyl)-N-(N-[2,4-dichloro-3-((2-methyl-8-quinolinyl)oxymethyl)phenyl]-N-methylaminocarbonyl-methyl)acrylamide; Icatibant, DArg[Hyp<sup>3</sup>, Thi<sup>5</sup>, DTic<sup>7</sup>, Oic<sup>8</sup>]BK, also known as HOE140; LF160687, 1-([2,4-dichloro-3-((2,4-dimethylquinolin-8-yl)oxy)methyl]phenyl)sulfonyl)-N-(3-[[4-(aminoimethyl)phenyl]carbonylamino]propyl)-2(S)-pyrrolidinecarboxamide; NPC17731, DArg[Hyp<sup>3</sup>, DHypE(transpropyl)<sup>7</sup>, Oic<sup>8</sup>]BK; R715, AcLys[D Nal<sup>7</sup>, Ile<sup>8</sup>][des-Arg<sup>9</sup>]BK; R914, AcLys-Lys-([αMe]Phe<sup>5</sup>δ-βNal<sup>7</sup>, Ile<sup>8</sup>)desArg<sup>9</sup>BK

## Further Reading

- Campos MM, Leal PC, Yunes RA, Calixto JB (2006). Non-peptide antagonists for kinin B1 receptors: new insights into their therapeutic potential for the management of inflammation and pain. *Trends Pharmacol Sci* 27: 646–651.
- Calixto JB, Medeiros R, Fernandes ES, Ferreira J, Cabrini DA, Campos MM (2004). Kinin B<sub>1</sub> receptors: key G-protein-coupled receptors and their role in inflammatory and painful processes. *Br J Pharmacol* 143: 803–818.
- Couture R, Harrison M, Vianna RM, Cloutier F (2001). Kinin receptors in pain and inflammation. *Eur J Pharmacol* 429: 161–176.
- Cruden NL, Newby DE (2008). Therapeutic potential of icatibant (HOE-140, JE-049). *Expert Opin Pharmacother* 9: 2383–2390.
- Doggrell SA (2006). Bradykinin B2 receptors as a target in diabetic nephropathy. *Curr Opin Investig Drugs* 7: 251–255.
- Duchene J, Ahluwalia A (2009). The kinin B(1) receptor and inflammation: new therapeutic target for cardiovascular disease. *Curr Opin Pharmacol* 9: 125–131.
- Fortin JP, Marceau FO (2006). Advances in the development of bradykinin ligands. *Curr Top Med Chem* 6: 1353–1363.
- Leeb-Lundberg LMF, Marceau F, Muller-Esterl W, Pettibone DJ, Zuraw BL (2005). International Union of Pharmacology. XLV. Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences. *Pharmacol Rev* 57: 27–77.
- Marceau F, Hess JF, Bachvarov DR (1998). The B-1 receptors for kinins. *Pharmacol Rev* 50: 357–386.
- Marceau F, Regoli D (2004). Bradykinin receptor ligands: Therapeutic perspectives. *Nature Rev Drug Discov* 3: 845–852.
- Regoli D, Allogho SN, Rizzi A, Gobeil FJ (1998). Bradykinin receptors and their antagonists. *Eur J Pharmacol* 348: 1–10.
- Rodi D, Couture R, Ongali B, Simonato M (2005). Targeting kinin receptors for the treatment of neurological diseases. *Curr Pharm Des* 11: 1313–1326.
- Thornton E, Ziebell JM, Leonard AV, Vink R (2010). Kinin receptor antagonists as potential neuroprotective agents in central nervous system injury. *Molecules* 15: 6598–6618.

## References

- Gobeil F *et al.* (1996a). *Hypertension* 28: 833–839.
- Gobeil F *et al.* (1996b). *Br J Pharmacol* 118: 289–294.
- Gobeil F *et al.* (1999). *Hypertension* 33: 823–829.
- Rizzi A *et al.* (1997). *Hypertension* 29: 951–956.
- Pruneau D *et al.* (1999). *Immunopharmacology* 43: 187–194.

# Calcitonin, amylin, CGRP and adrenomedullin

**Overview:** Calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors, see Poyner *et al.*, 2002; Hay *et al.*, 2008) are generated by the genes *CALCR* (which codes for the CT receptor (CTR), ENSG00000064989) and *CALCRL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR, ENSG0000004948). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying protein), which are single TM domain proteins of *ca.* 130 amino acids, identified as a family of three members; RAMP1 (ENSG00000132329), RAMP2 (ENSG00000131477) and RAMP3 (ENSG00000122679). There are splice variants of CTR; these in turn produce variants of the AMY receptor (see Poyner *et al.*, 2002). The endogenous agonists are the peptides CT,  $\alpha$ CGRP (formerly known as CGRP-I),  $\beta$ CGRP (formerly known as CGRP-II), AMY (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), AM and AM2/Intermedin (AM2/IMD). There are species differences in peptide sequences, particularly for the CTs. CTR-stimulating peptide (CRSP) is another member of the family with selectivity for the CTR but it is not expressed in humans (Katafuchi *et al.*, 2003). BIBN4096BS (also known as olcegepant,  $pK_i$  ~10.5) and MK0974 (also known as telcagepant,  $pK_i$  ~9) are the most selective antagonists available, having a high selectivity for CGRP receptors, with a particular preference for those of primate origin.

CLR by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, AM and AM2/IMD

Nomenclature	CGRP	AM <sub>1</sub>	AM <sub>2</sub>
Composition	<i>CALCRL+RAMP1</i>	<i>CALCRL+RAMP2</i>	<i>CALCRL+RAMP3</i>
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Rank order of potency	CGRP > AM $\geq$ AM2/IMD > AMY $\geq$ salmon CT	AM > CGRP, AM2/IMD > AMY > salmon CT	AM = AM2/IMD $\geq$ CGRP > AMY > salmon CT
Selective agonists	$\alpha$ CGRP	AM	AM
Selective antagonists	BIBN4096BS (10.5, Doods <i>et al.</i> , 2000; Hay <i>et al.</i> , 2003, 2006); MK0974 (9, Salvatore <i>et al.</i> , 2008)	AM-(22–52) (7, Hay <i>et al.</i> , 2003)	–
Probes	[ <sup>125</sup> I]- $\alpha$ CGRP (0.1 nM)	[ <sup>125</sup> I]-AM (rat, 0.1–1.0 nM)	[ <sup>125</sup> I]-AM (rat, 0.1–1.0 nM)

Transfection of human CTR with any RAMP can generate receptors with a high affinity for both salmon CT and AMY and varying affinity for different antagonists (Christopoulos *et al.*, 1999; Hay *et al.*, 2005, 2006). The insert negative (and major) human CTR splice variant (hCT<sub>(a)</sub>) with RAMP1 (i.e. the AMY<sub>1(a)</sub> receptor) has a high affinity for CGRP, unlike hCT<sub>(a)</sub>-RAMP3 (i.e. AMY<sub>3(a)</sub> receptor) (Christopoulos *et al.*, 1999; Hay *et al.*, 2005). However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent (Tilakaratne *et al.*, 2000).

Nomenclature	Calcitonin (CT)	AMY <sub>1</sub>	AMY <sub>2</sub>	AMY <sub>3</sub>
Composition	<i>CALCR</i>	<i>CALCR+RAMP1</i>	<i>CALCR+RAMP2</i>	<i>CALCR+RAMP3</i>
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Rank order of potency	Salmon CT $\geq$ human CT $\geq$ AMY, CGRP > AM, AM2/IMD	AMY <sub>1(a)</sub> : Salmon CT $\geq$ AMY $\geq$ CGRP > AM2/IMD > human CT > AM	Poorly defined	AMY <sub>3(a)</sub> : Salmon CT $\geq$ AMY > CGRP > AM2/IMD > human CT > AM
Selective agonists	Human CT	AMY	AMY	AMY
Probes	[ <sup>125</sup> I]-CT (salmon, 0.1 nM), [ <sup>125</sup> I]-CT (human, 0.1–1.0 nM)	[ <sup>125</sup> I]-BH-AMY (rat, 0.1–1.0 nM)	[ <sup>125</sup> I]-BH-AMY (rat, 0.1–1.0 nM)	[ <sup>125</sup> I]-BH-AMY (rat, 0.1–1.0 nM)

The ligands described represent the best available but their selectivity is limited, apart from BIBN4096BS and MK0974. For example, AM has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM<sub>2</sub> receptors. AM2/IMD also has high affinity for the AM<sub>2</sub> receptor (Hong *et al.*, 2011). CGRP-(8–37) acts as an antagonist of CGRP ( $pK_i$  ~8) and inhibits some AM and AMY responses ( $pK_i$  ~6–7). It is inactive at CT receptors. Salmon CT-(8–32) is an antagonist at both AMY and CT receptors. AC187, a salmon CT analogue, is also an antagonist at AMY and CT receptors. Human AM-(22–52) has some selectivity towards AM receptors, but with modest potency ( $pK_i$  ~7), limiting its use (Hay *et al.*, 2003). AM-(22–52) is slightly more effective at AM<sub>1</sub> than AM<sub>2</sub> receptors but this difference is not sufficient for this peptide to be a useful discriminator of the AM receptor subtypes.

Ligand responsiveness at CTR and AMY receptors can be affected by receptor splice variation and can depend on the pathway being measured. Particularly for AMY receptors, relative potency can vary with the type and level of RAMP present and can be influenced by other factors such as G proteins (Tilakaratne *et al.*, 2000; Morfis *et al.*, 2008).

G<sub>s</sub> is a prominent route for effector coupling for CLR and CTR but other pathways (e.g. Ca<sup>2+</sup>, ERK, Akt) and G proteins can be activated (Walker *et al.*, 2010). There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, ENSG00000126522) is important for the coupling of CLR to adenylyl cyclase (Evans *et al.*, 2000).

[<sup>125</sup>I]-Salmon CT is the most common radioligand for CT receptors but it has high affinity for AMY receptors and is also poorly reversible. [<sup>125</sup>I]-Tyr<sup>0</sup>-CGRP is widely used as a radioligand for CGRP receptors.

Some early literature distinguished between *CGRP*<sub>1</sub> and *CGRP*<sub>2</sub> receptors. It is now clear that *CALCRL/RAMP1* represents the *CGRP*<sub>1</sub> subtype and is now known simply as the CGRP receptor (Hay *et al.*, 2008). The *CGRP*<sub>2</sub> receptor is considered to have arisen from the actions of CGRP at *AM<sub>2</sub>* and *AMY* receptors. This term should not be used (Hay *et al.*, 2008).

**Abbreviations:** AC187, acetyl-[Asn<sup>30</sup>,Tyr<sup>32</sup>]salmon CT; BIBN4096BS, 1-piperidinecarboxamide, *N*-(2-[[5-amino-1-(4-{4-pyridinyl}-1-piperazinyl)carbonyl]pentyl]amino]-1-[[3,5-dibromo-4-hydroxyphenyl]methyl]-2-oxoethyl)-4-(1,4-dihydro-2-oxo-3[2*H*]-quinazolinyl); MK0974, *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide

### Further Reading

- Benemei S, Nicoletti P, Capone JG, Geppetti P (2009). CGRP receptors in the control of pain and inflammation. *Curr Opin Pharmacol* **9**: 9–14.
- Gibbons C, Dackor R, Dunworth W, Fritz-Six K, Caron KM (2007). Receptor activity-modifying proteins: RAMPing up adrenomedullin signaling. *Mol Endocrinol* **21**: 783–796.
- Hay DL, Poyner DR, Quirion R (2008). International Union of Pharmacology. LXIX. Status of the calcitonin gene-related peptide subtype 2 receptor. *Pharmacol Rev* **60**: 143–145.
- Hay DL, Poyner DR, Sexton PM (2006). GPCR modulation by RAMPs. *Pharmacol Ther* **109**: 173–197.
- Hong Y, Hay DL, Quirion R, Poyner DR (2011). The pharmacology of Adrenomedullin 2/Intermedin. *Br J Pharmacol* in press.
- Ishimitsu T, Ono H, Minami J, Matsuoka H (2006). Pathophysiologic and therapeutic implications of adrenomedullin in cardiovascular disorders. *Pharmacol Ther* **111**: 909–927.
- Nikitenko LL, Fox SB, Kehoe S, Rees MC, Bicknell R (2006). Adrenomedullin and tumour angiogenesis. *Br J Cancer* **94**: 1–7.
- Poyner DR, Sexton PM, Marshall I, Smith DM, Quirion R, Born W *et al.* (2002). International Union of Pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors. *Pharmacol Rev* **54**: 233–246.
- Recober A, Russo AF (2009). Calcitonin gene-related peptide: an update on the biology. *Curr Opin Neurol* **22**: 241–246.
- Walker CS, Conner AC, Poyner DR, Hay DL (2010). Regulation of signal transduction by calcitonin gene-related peptide receptors. *Trends Pharmacol Sci* **31**: 476–483.

### References

- Christopoulos G *et al.* (1999). *Mol Pharmacol* **56**: 235–242.
- Doods H *et al.* (2000). *Br J Pharmacol* **129**: 420–423.
- Evans BN *et al.* (2000). *J Biol Chem* **275**: 31438–31443.
- Hay DL *et al.* (2003). *Br J Pharmacol* **140**: 477–486.
- Hay DL *et al.* (2005). *Mol Pharmacol* **67**: 1655–1665.
- Hay DL *et al.* (2006). *Mol Pharmacol* **70**: 1984–1991.
- Katafuchi T *et al.* (2003). *J Biol Chem* **278**: 12046–12054.
- Morfis M *et al.* (2008). *Endocrinology* **149**: 5423–5431.
- Salvatore CA *et al.* (2008). *J Pharmacol Exp Ther* **324**: 416–421.
- Tilakaratne N *et al.* (2000). *J Pharmacol Exp Ther* **294**: 61–72.

# Calcium-sensing

**Overview:** The calcium-sensing receptor (CaS, provisional nomenclature) responds to extracellular calcium and magnesium in the millimolar range and to gadolinium and some polycations in the micromolar range (Brown *et al.*, 1993). The sensitivity of CaS to primary agonists can be increased by aromatic L-amino acids (Conigrave *et al.*, 2000) and also by elevated extracellular pH (Quinn *et al.*, 2004) or decreased extracellular ionic strength (Quinn *et al.*, 1998).

Nomenclature	CaS
Other names	CaSR, CaR
Ensembl ID	ENSG00000036828
Principal transduction	G <sub>q/11</sub> , G <sub>i/o</sub> , G <sub>12/13</sub> (Ward, 2004)
Cation rank order of potency	Gd <sup>3+</sup> > Ca <sup>2+</sup> > Mg <sup>2+</sup> (Brown <i>et al.</i> , 1993)
Polyamine rank order of potency	Spermine>spermidine>putrescine (Quinn <i>et al.</i> , 1997)
Amino-acid rank order of potency	L-Phe, L-Trp, L-His>L-Ala>L-Ser, L-Pro, L-Glu>L-Asp but not L-Lys, L-Arg, L-Leu, and L-Ile (Conigrave <i>et al.</i> , 2000)
Positive allosteric modulators	NPS R568 (Nemeth <i>et al.</i> , 1998), calindol (Petrel <i>et al.</i> , 2004), cinacalcet (Nemeth <i>et al.</i> , 2004), AC265347 (Ma <i>et al.</i> , 2011)
Negative allosteric modulators	NPS 2143, NPS 89636 (Nemeth <i>et al.</i> , 2001), Calhex-231 (Petrel <i>et al.</i> , 2004), 2-benzylpyrrolidine derivatives of NPS 2143 (Yang <i>et al.</i> , 2005)

Positive allosteric modulators are termed Type II calcimimetics and can suppress parathyroid hormone (PTH) secretion (Nemeth *et al.*, 1998). Negative allosteric modulators are called calcilytics and can act to increase PTH secretion (Nemeth *et al.*, 2001).

The central role of CaS in the maintenance of extracellular calcium homeostasis is seen most clearly in patients with loss-of-function CaS mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaS null mice (Ho *et al.*, 1995; Chang *et al.*, 2008), which exhibit similar increases in PTH secretion and blood Ca<sup>2+</sup> levels. A gain-of-function mutation in the CaS gene is associated with autosomal dominant hypocalcaemia.

GPRC<sub>6</sub> (ENSG00000173612, also known as GPRC6A) is a related G<sub>q</sub>-coupled receptor which responds to basic amino acids (Wellendorph *et al.*, 2005).

**Abbreviations:** AC265347, 1-benzothiazol-2-yl-1-(2,4-dimethyl-phenyl)-ethanol; Calhex-231, (1S,2S,1'R)-N<sup>1</sup>-(4-chlorobenzoyl)-N<sup>2</sup>-[1-(1-naphthyl)ethyl]-1,2-diaminocyclohexane; calindol, (R)-2-[1-(1-naphthyl) ethylaminomethyl]-1H-indole; NPS R568, (R)-N-(3-methoxy- $\alpha$ -phenylethyl)-3-(2-chlorophenyl)-1-propylamine hydrochloride; NPS 2143, N-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine;

## Further Reading

- Brown EM (2010). Clinical utility of calcimimetics targeting the extracellular calcium-sensing receptor (CaSR). *Biochem Pharmacol* **80**: 297–307.
- Cavanaugh A, Huang Y, Breitwieser GE (2011). Behind the curtain: Cellular mechanisms for allosteric modulation of calcium sensing receptors. *Br J Pharmacol* in press.
- Khan MA, Conigrave AD (2010). Mechanisms of multimodal sensing by extracellular Ca<sup>2+</sup>-sensing receptors: a domain-based survey of requirements for binding and signalling. *Br J Pharmacol* **159**: 1039–1050.
- Magno AL, Ward BK, Ratajczak T (2011). The calcium-sensing receptor: a molecular perspective. *Endocr Rev* **32**: 3–30.
- Ward DT, Riccardi D (2011). New concepts in calcium-sensing receptor pharmacology and signalling. *Br J Pharmacol* in press.

## References

- Brown EM *et al.* (1993). *Nature* **366**: 575–580.
- Chang W *et al.* (2008). *Sci Signal* **1**: ra1.
- Conigrave AD *et al.* (2000). *Proc Natl Acad Sci U S A* **97**: 4814–4819.
- Ho C *et al.* (1995). *Nat Genet* **11**: 389–394.
- Ma JN *et al.* (2011). *J Pharmacol Exp Ther* **337**: 275–284.
- Nemeth EF *et al.* (1998). *Proc Natl Acad Sci U S A* **95**: 4040–4045.
- Nemeth EF *et al.* (2001). *J Pharmacol Exp Ther* **299**: 323–331.
- Nemeth EF *et al.* (2004). *J Pharmacol Exp Ther* **308**: 627–635.
- Petrel C *et al.* (2004). *J Biol Chem* **279**: 18990–18997.
- Quinn SJ *et al.* (1997). *Am J Physiol Cell Physiol* **273**: C1315–C1323.
- Quinn SJ *et al.* (1998). *J Biol Chem* **273**: 19579–19586.
- Quinn SJ *et al.* (2004). *J Biol Chem* **279**: 37241–37249.
- Ward DT (2004). *Cell Calcium* **35**: 217–228.
- Wellendorph P *et al.* (2005). *Mol Pharmacol* **67**: 589–597.
- Yang W *et al.* (2005). *Bioorg Med Chem Lett* **15**: 1225–1228.

# Cannabinoid

**Overview:** Cannabinoid receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Cannabinoid Receptors; see Pertwee *et al.*, 2010) are activated by endogenous ligands that include *N*-arachidonylethanolamine (anandamide), *N*-homo- $\gamma$ -linolenylethanolamine, *N*-docosatetra-7,10,13,16-enylethanolamine and 2-arachidonoylglycerol. Potency determinations of endogenous agonists at these receptors are complicated by the possibility of differential susceptibility to enzymatic conversion (see Alexander and Kendall, 2007).

Nomenclature	CB <sub>1</sub>	CB <sub>2</sub>
Ensembl ID	ENSG00000118432	ENSG00000188822
Principal transduction	G <sub>ij/o</sub>	G <sub>ij/o</sub>
Selective agonists	ACEA (Hillard <i>et al.</i> , 1999), ACPA (Hillard <i>et al.</i> , 1999), methanandamide (Khanolkar <i>et al.</i> , 1996), O-1812 (Di Marzo <i>et al.</i> , 2001)	HU308 (Hanus <i>et al.</i> , 1999), JWH133 (Huffman <i>et al.</i> , 1999; Pertwee, 2000), L759633 (Ross <i>et al.</i> , 1999), L759656 (Ross <i>et al.</i> , 1999), AM1241 (Ibrahim <i>et al.</i> , 2003)
Selective antagonists	AM251 (8.1, Lan <i>et al.</i> , 1999a), AM281 (7.9, Lan <i>et al.</i> , 1999b), rimonabant (7.9, Showalter <i>et al.</i> , 1996), LY320135 (6.9, Felder <i>et al.</i> , 1998)	SR144528 (9.2, Rinaldi-Carmona <i>et al.</i> , 1998), AM630 (7.5, Ross <i>et al.</i> , 1999)
Probes	[ <sup>3</sup> H]-rimonabant (0.6 nM, Rinaldi-Carmona <i>et al.</i> , 1996)	–

Both CB<sub>1</sub> and CB<sub>2</sub> receptors may be labelled with [<sup>3</sup>H]-CP55940 (0.6 nM; Showalter *et al.*, 1996) and [<sup>3</sup>H]-WIN55212-2 (2–12 nM; Slipetz *et al.*, 1995; Song and Bonner, 1996). Anandamide is also an agonist at vanilloid receptors (TRPV1, see Page S166) and PPARs (see Page S181 and O'Sullivan, 2007; Zygmunt *et al.*, 1999). There is evidence for an allosteric site on the CB<sub>1</sub> receptor (Price *et al.*, 2005). All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems (see Pertwee *et al.*, 2010). For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have been identified (see Pertwee *et al.*, 2010). Moreover, GPR18, GPR55 and GPR119 (see Page S69), although showing little structural similarity to CB<sub>1</sub> and CB<sub>2</sub> receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands (see Pertwee *et al.*, 2010).

**Abbreviations:** ACEA, arachidonoyl-2-chloroethylamide; ACPA, arachidonoylcyclopropylamide; AM1241, (2-iodo-5-nitro-phenyl)-[1-(1-methyl-piperidin-2-ylmethyl)-1*H*-indol-3-yl]-methanone; AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AM281, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide; AM630, 6-iodopravadoline; CP55940, (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; HU308, [4-[4-(1,1-dimethylheptyl)-2,6-dimethoxy-phenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl]-methanol; JWH133, (3-(1,1-dimethylbutyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; L759633, (6*a*,10*a*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; L759656, (6*a*,10*a*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6-dimethyl-9-methylene-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene; LY320135, (6-methoxy-2-[4-methoxyphenyl]benzo[*b*]thien-3-yl)(4-cyanophenyl)methanone; **methanandamide**, (*R*)-(+)-arachidonoyl-1'-hydroxy-2'-propylamide; O-1812, (*R*)-(20-cyano-16,16-dimethyldocosa-*cis*-5,8,11,14-tetraenyl)-1'-hydroxy-2'-propylamine; **rimonabant**, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, also known as SR141716A; SR144528, *N*-([1*S*]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; WIN55212-2, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

## Further Reading

- Alexander SPH, Kendall DA (2007). The complications of promiscuity: endocannabinoid action and metabolism. *Br J Pharmacol* **152**: 602–623.
- Bosier B, Muccioli GG, Hermans E, Lambert DM (2010). Functionally selective cannabinoid receptor signalling: Therapeutic implications and opportunities. *Biochem Pharmacol* **80**: 1–12.
- Bradshaw HB, Lee SH, McHugh D (2009). Orphan endogenous lipids and orphan GPCRs: A good match. *Prostaglandins Other Lipid Mediat* **89**: 131–134.
- Centonze D, Finazzi-Agro A, Bernardi G, Maccarrone M (2007). The endocannabinoid system in targeting inflammatory neurodegenerative diseases. *Trends Pharmacol Sci* **28**: 180–187.
- Di Marzo V, Bisogno T, De Petrocellis L (2007). Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. *Chem Biol* **14**: 741–756.
- Di Marzo V, De Petrocellis L (2006). Plant, synthetic, and endogenous cannabinoids in medicine. *Annu Rev Med* **57**: 553–574.
- Di Marzo V, Petrosino S (2007). Endocannabinoids and the regulation of their levels in health and disease. *Curr Opin Lipidol* **18**: 129–140.
- Fernandez-Ruiz J, Romero J, Velasco G, Tolon RM, Ramos JA, Guzman M (2007). Cannabinoid CB<sub>2</sub> receptor: a new target for controlling neural cell survival? *Trends Pharmacol Sci* **28**: 39–45.
- Godlewski G, Offertaler L, Wagner JA, Kunos G (2009). Receptors for acylethanolamides-GPR55 and GPR119. *Prostaglandins Other Lipid Mediat* **89**: 105–111.
- Hansen HS, Diep TA (2009). *N*-Acylethanolamines, anandamide and food intake. *Biochem Pharmacol* **78**: 553–560.
- Howell AC, Reggio PH, Childers SR, Hampson RE, Ulloa NM, Deutsch DG (2011). Endocannabinoid Tone versus Constitutive Activity of Cannabinoid Receptors. *Br J Pharmacol* in press.
- Izzo AA, Sharkey KA (2010). Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther* **126**: 21–38.
- Maccarrone M, Gasperi V, Catani MV, Diep TA, Dainese E, Hansen HS *et al.* (2010). The endocannabinoid system and its relevance for nutrition. *Annu Rev Nutr* **30**: 423–440.
- McPartland JM, Glass M, Pertwee RG (2007). Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *Br J Pharmacol* **152**: 583–593.
- O'Sullivan SE (2007). Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol* **152**: 583–593.

- Pertwee RG, Howlett AC, Abood ME, Alexander SPH, Di Marzo V, Elphick MR *et al.* (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>. *Pharmacol Rev* **62**: 588–631.
- Ross RA (2011). L- $\alpha$ -Lysophosphatidylinositol meets GPR55: a deadly relationship. *Trends Pharmacol Sci* **32**: 265–269.
- Sharir H, Abood ME (2010). Pharmacological characterization of GPR55, a putative cannabinoid receptor. *Pharmacol Ther* **126**: 301–313.
- Ueda N, Tsuboi K, Uyama T (2010). Enzymological studies on the biosynthesis of N-acylethanolamines. *Biochim Biophys Acta* **1801**: 1274–1285.

## References

- Di Marzo V *et al.* (2001). *Biochem Biophys Res Commun* **281**: 444–451.
- Felder CC *et al.* (1998). *J Pharmacol Exp Ther* **284**: 291–297.
- Hanus L *et al.* (1999). *Proc Natl Acad Sci U S A* **96**: 14228–14233.
- Hillard CJ *et al.* (1999). *J Pharmacol Exp Ther* **289**: 1427–1433.
- Huffman JW *et al.* (1999). *Bioorg Med Chem* **7**: 2905–2914.
- Ibrahim MM *et al.* (2003). *Proc Natl Acad Sci USA* **100**: 10529–10533.
- Khanolkar AD *et al.* (1996). *J Med Chem* **39**: 4515–4519.
- Lan R *et al.* (1999b). *AAPS PharmSci* **1**: article 4. DOI: 10.1208/ps010204
- Lan RX *et al.* (1999a). *J Med Chem* **42**: 769–776.
- Pertwee RG (2000). *Expert Opin Investig Drugs* **9**: 1553–1571.
- Price MR *et al.* (2005). *Mol Pharmacol* **68**: 1484–1495.
- Rinaldi-Carmona M *et al.* (1996). *Life Sci* **58**: 1239–1247.
- Rinaldi-Carmona M *et al.* (1998). *J Pharmacol Exp Ther* **284**: 644–650.
- Ross RA *et al.* (1999). *Br J Pharmacol* **126**: 665–672.
- Showalter VM *et al.* (1996). *J Pharmacol Exp Ther* **278**: 989–999.
- Slipetz DM *et al.* (1995). *Mol Pharmacol* **48**: 352–361.
- Song ZH, Bonner TI (1996). *Mol Pharmacol* **49**: 891–896.
- Zygmunt PM *et al.* (1999). *Nature* **400**: 452–457.



# Chemokine

**Overview:** Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, Murphy *et al.*, 2000; Murphy, 2002) comprise a large subfamily of GPCR activated by one or more of the chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes.

Chemokines can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as  $\beta$ -chemokines;  $n = 28$ ), CXC (also known as  $\alpha$ -chemokines;  $n = 16$ ) and CX<sub>3</sub>C ( $n = 1$ ) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines, respectively. C chemokines ( $n = 2$ ) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. Listed are those human agonists with EC<sub>50</sub> values <50 nM in either Ca<sup>2+</sup> flux or chemotaxis assays at human recombinant receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and HIV-encoded non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, and at least two, CCR5 and CXCR4, play prominent roles in pathogenesis. The tables include both standard chemokine names (Zlotnik and Yoshie, 2000) and the most commonly used synonyms. Numerical data quoted are typically pKi or pIC<sub>50</sub> values from radioligand binding to heterologously expressed receptors.

Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
Other names	CKR1, CC CK <sub>1</sub> , CC CKR1, MIP-1 $\alpha$ R, MIP-1 $\alpha$ /RANTES	CKR2, CC CK <sub>2</sub> , CC CKR2, MCP-1	CKR3, CC CK <sub>3</sub> , CC CKR3	CKR4, CC CK <sub>4</sub> , CC CKR4	CKR5, CC CK <sub>5</sub> , CC CKR <sub>5</sub> , CHEM13
Ensembl ID	ENSG00000163823	ENSG00000121807	ENSG00000183625	ENSG00000183813	ENSG00000160791
Principal transduction	G <sub>ij/o</sub>	G <sub>ij/o</sub>	G <sub>ij/o</sub>	G <sub>ij/o</sub>	G <sub>ij/o</sub>
Agonists	CCL3 (MIP-1 $\alpha$ ), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14a (HCC-1), CCL15 (HCC-2), CCL23 (MPIF-1)	CCL2 (MCP-1), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL16 (HCC-4)	CCL11 (eotaxin), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL15 (HCC-2), CCL24 (eotaxin-2), CCL26 (eotaxin-3), CCL28 (MEC)	CCL22 (MDC), CCL17 (TARC), vMIP-III	CCL3 (MIP-1 $\alpha$ ), CCL4 (MIP-1 $\beta$ ), CCL5 (RANTES), CCL8 (MCP-2), CCL11 (eotaxin), CCL14a (HCC-1), CCL16 (HCC-4), R5 HIV-1 gp120
Selective agonists	CCL15 (HCC-2), CCL23 (MPIF-1)	CCL2 (MCP-1)	CCL11 (Eotaxin), CCL24 (eotaxin-2), CCL26 (eotaxin-3),	CCL22 (MDC), CCL17 (TARC)	MIP-1 $\beta$ , R5-HIV gp120
Selective antagonists	BX471 (8.3-9), 2b-1 (8.7), UCB35625 (8.0), CP481715 (8.0), CCL4 (MIP-1 $\beta$ )	CCL11 (eotaxin), CCL26 (eotaxin-3), GSK Compound 34 (7.6)	Banyu Compound 1b (8.6), SB328437 (8.4), BMS Compound 87b (8.1), CXCL10 (IP10), CXCL9 (Mig), CXCL11 (I-TAC)	–	TAK779 (9.0), CCL7 (MCP-3), SCH C, SCH D, MRK-1, E913 (8.7), maraviroc, aplaviroc
Probes	[ <sup>125</sup> I]-MIP-1 $\alpha$ , [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-MCP-3	[ <sup>125</sup> I]-MCP-1, [ <sup>125</sup> I]-MCP-3	[ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-eotaxin, [ <sup>125</sup> I]-MCP-3	[ <sup>125</sup> I]-TARC, [ <sup>125</sup> I]-CTACK/CCL27	[ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-MCP-2, [ <sup>125</sup> I]-MIP-1 $\alpha$ , [ <sup>125</sup> I]-MIP-1 $\beta$

Nomenclature	CCR6	CCR7	CCR8	CCR9	CCR10
Other names	GPR-CY4, CKR-L3, STRL-22, DRY-6, DCR2, BN-1, GPR29	EBI-1, BLR-2	TER1, CKR-L1, GPR-CY6, ChemR1	GPR 9-6	GPR-2
Ensembl ID	ENSG00000112486	ENSG00000126353	ENSG00000179934	ENSG00000173585	ENSG00000184451
Principal transduction	G <sub>ij/o</sub>	G <sub>ij/o</sub>	G <sub>ij/o</sub>	G <sub>ij/o</sub>	G <sub>ij/o</sub>
Agonists	CCL20 (LARC), HBD2	CCL19 (ELC, MIP-3 $\beta$ ), CCL21 (SLC)	CCL1 (I-309), CCL4 (MIP-1 $\beta$ ), CCL16 (HCC-4), CCL17 (TARC), HHV8 vMIP-I	CCL25 (TECK)	CCL27 (Eskine, ALP, CTACK), CCL28 (MEC)
Selective agonists	LARC, HBD2	ELC, SLC	I-309	TECK	Eskine, MEC
Selective antagonists	–	–	MCV MC148R (vMCC-I)	–	–
Probes	[ <sup>125</sup> I]-LARC	[ <sup>125</sup> I]-ELC, [ <sup>125</sup> I]-SLC	[ <sup>125</sup> I]-I309	[ <sup>125</sup> I]-TECK	–

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6
Other names	IL8R <sub>α</sub> , IL-8 receptor type I, IL-8 receptor $\alpha$	IL8R <sub>β</sub> , IL-8 receptor type II, IL-8 receptor $\beta$	IP10/Mig R, GPR9	HUMSTSR, LESTR, fusin, HM89, LCR1	BLR-1, MDR15	STRL-33, BONZO, TYMSTR
Ensembl ID	ENSG00000163464	ENSG00000180871	ENSG00000186810	ENSG00000121966	ENSG00000160683	ENSG00000172215
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Agonists	CXCL6 (GCP-2), CXCL8 (IL-8),	CXCL1 (GRO $\alpha$ ), CXCL2 (GRO $\beta$ ), CXCL3 (GRO $\gamma$ ), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2), CXCL8 (IL-8), HCMV UL146 (vCXCL1)	CXCL9 (Mig), CXCL10 (IP10), CXCL11 (I-TAC)	CXCL12 $\alpha$ (SDF-1 $\alpha$ ), CXCL12 $\beta$ (SDF-1 $\beta$ )	CXCL13 (BLC, BCA-1)	CXCL16 (SR-PSOX)
Selective agonists	–	GRO $\alpha$ , GRO $\gamma$ , GRO $\beta$ , NAP-2, ENA78	IP10, MIG, I-TAC	SDF-1 $\alpha$ , SDF-1 $\beta$ , X4-HIV gp120	BLC	CXCL16
Selective antagonists	–	SB225002 (7.7)	eotaxin, MCP-3	AMD3100, HIV-1 Tat, T134, ALX40-4C	–	–
Probes	[ <sup>125</sup> I]-IL8	[ <sup>125</sup> I]-IL8, [ <sup>125</sup> I]-GRO $\alpha$ , [ <sup>125</sup> I]-NAP-2, [ <sup>125</sup> I]-ENA78	[ <sup>125</sup> I]-IP10, [ <sup>125</sup> I]-I-TAC/CXCL11	[ <sup>125</sup> I]-SDF-1	–	[ <sup>125</sup> I]-CXCL16

CXCR1 and CXCR2 also couple to phospholipase C when co-transfected with members of the G<sub>q/11</sub> family of G proteins. Mouse CXCR2 binds iodinated mouse KC and mouse MIP-2 with high affinity (mouse KC and MIP-2 are homologues of human GRO chemokines), but shows low affinity for human IL-8.

Nomenclature	CX <sub>3</sub> CR1	XCRI
Other names	CMKBRL1, V28	GPRS
Ensembl ID	ENSG00000168329	ENSG00000173578
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>
Agonists	CX3CL1 (Fractalkine)	XCL1 $\alpha$ and $\beta$ (Lymphotactin $\alpha$ and $\beta$ )
Selective agonists	Fractalkine	Lymphotactin
Probes	[ <sup>125</sup> I]-Fractalkine	SEAP-XCL1

Three human 7TM chemokine binding proteins have been identified that lack a known signalling function: 1) D6 (ENSG00000144648), which binds multiple CC chemokines and is expressed on lymphatic endothelial cells and placental trophoblasts; 2) a molecule previously inappropriately named CCR11 and now known as CCX CKR or the human homologue of the bovine gustatory receptor PPAR1 (ENSG00000118519, ENSG00000129048), which binds ELC, SLC and TECK; and 3) Duffy, a highly promiscuous CC and CXC chemokine binding protein expressed mainly on erythrocytes, endothelial cells and Purkinje cells. CXCR7 (former aliases: RDC1, CMKOR1 and GPR159, ENSG00000144476) binds CXCL11 and CXCL12 with high affinity, and is expressed in all four cardiac valves and by marginal zone B cells in mammals. Mice lacking this receptor undergo perinatal mortality because of valvular stenosis. Work in zebrafish has identified a role for a highly conserved CXCR7 homologue in shaping CXCL12 gradients, which guide primordial germ cell migration. Whether this is how it works in mammals, or whether there is, in addition, a signal transduction function for CXCR7 has not yet been fully resolved. Thus, the name CXCR7, though widely used in the field, has not yet been endorsed officially by IUPHAR. Specific chemokine receptors facilitate cell entry by microbes, such as *Plasmodium vivax*, HIV-1 and the poxvirus myxoma virus. Virally encoded chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ECRF3, a homologue of CXCR2 from *Herpesvirus saimiri*), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers.

The CC chemokine family (CCL1–28) includes I309 (CCL1), MCP-1 (CCL2), MIP-1 $\alpha$  (CCL3), MIP-1 $\beta$  (CCL4), RANTES (CCL5), MCP-3 (CCL7), MCP-2 (CCL8), eotaxin (CCL11), MCP-4 (CCL13), HCC-1 (CCL14), Lkn-1/HCC-2 (CCL15), TARC (CCL17), ELC (CCL19), LARC (CCL20), SLC (CCL21), MDC (CCL22), MPIF-1 (CCL23), eotaxin-2 (CCL24), TECK (CCL25), eotaxin (CCL26), eskine/CTACK (CCL27) and MEC (CCL28). The CXC chemokine family (CXCL1–16) includes GRO $\alpha$  (CXCL1), GRO $\beta$  (CXCL2), GRO $\gamma$  (CXCL3), platelet factor 4 (CXCL4), ENA78 (CXCL5), GCP-2 (CXCL6), NAP-2 (CXCL7), IL-8 (CXCL8), MIG (CXCL9), IP10 (CXCL10), I-TAC (CXCL11), SDF-1 (CXCL12), BLC (CXCL13), BRAK (CXCL14), mouse lungkine (CXCL15) and SR-PSOX (CXCL16). The CX<sub>3</sub>C chemokine (CX3CL1) is also known as fractalkine (neurotactin in the mouse). Like CXCL16, and unlike other chemokines, CX3CL1 is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (XCL1) is also known as lymphotactin. The non-chemokine family includes the cytokine domain of tyrosyl-tRNA synthetase, HBD2, HIV gp120 and HIV Tat. Two chemokine receptor antagonists have now been approved by the FDA: the CCR5 antagonist maraviroc (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and the CXCR4 antagonist AMD3100 (Plerixifor, Mozibil from Genzyme) for hematopoietic

stem cell mobilization with G-CSF in patients undergoing transplantation in the context of chemotherapy for lymphoma and multiple myeloma.

**Abbreviations:** BLC, B-lymphocyte chemokine; ELC, Epstein–Barr virus-induced receptor ligand chemokine; ENA-78, epithelial cell-derived neutrophil-activating factor-78 amino acids; GCP-2, granulocyte chemoattractant protein 2; HBD2, human  $\beta$  defensin 2; HCC, hemofiltrate CC chemokine; IL-8, interleukin 8; IP-10,  $\gamma$ -interferon-inducible protein 10; I-TAC, interferon-inducible T-cell  $\alpha$  chemoattractant; LARC, liver and activation-related chemokine (CCL20); MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mucosa expressed chemokine; MIG, monokine-induced by  $\gamma$ -interferon; MIP, macrophage inflammatory protein; MPIF-1, myeloid progenitor inhibitory factor 1; NAP-2, neutrophil-activating peptide 2; RANTES, regulated on activation normal T cell expressed and secreted; SDF, stromal cell-derived factor; SLC, secondary lymphoid tissue chemokine; SEAP, secreted alkaline phosphatase; TARC, T-cell and activation-related chemokine; TECK, thymus-expressed chemokine

### Further Reading

- Bonecchi R, Galliera E, Borroni EM, Corsi MM, Locati M, Mantovani A (2009). Chemokines and chemokine receptors: an overview. *Front Biosci* **14**: 540–551.
- Borroni EM, Mantovani A, Locati M, Bonecchi R (2010). Chemokine receptors intracellular trafficking. *Pharmacol Ther* **127**: 1–8.
- Horuk R (2009). Chemokine receptor antagonists: overcoming developmental hurdles. *Nat Rev Drug Discov* **8**: 23–33.
- Jones KL, Maguire JJ, Davenport AP (2011). Chemokine receptor CCR5: from AIDS to atherosclerosis. *Br J Pharmacol* **162**: 1453–1469.
- Koenen RR, Weber C (2010). Therapeutic targeting of chemokine interactions in atherosclerosis. *Nat Rev Drug Discov* **9**: 141–153.
- Lazennec G, Richmond A (2010). Chemokines and chemokine receptors: new insights into cancer-related inflammation. *Trends Mol Med* **16**: 133–144.
- Mellado M, Carrasco YR (2008). Imaging techniques: new insights into chemokine/chemokine receptor biology at the immune system. *Pharmacol Ther* **119**: 24–32.
- Mortier A, Van DJ, Proost P (2008). Regulation of chemokine activity by posttranslational modification. *Pharmacol Ther* **120**: 197–217.
- Murphy PM (2002). International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. *Pharmacol Rev* **54**: 227–229.
- Murphy PM, Baggiolini M, Charo IF, Hebert CA, Horuk R, Matsushima K *et al.* (2000). International Union of Pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev* **52**: 145–176.
- Pease JE (2011). Targeting chemokine receptors in allergic disease. *Biochem J* **434**: 11–24.
- Salanga CL, O'Hayre M, Handel T (2009). Modulation of chemokine receptor activity through dimerization and crosstalk. *Cell Mol Life Sci* **66**: 1370–1386.
- Sorce S, Myburgh R, Krause KH (2011). The chemokine receptor CCR5 in the central nervous system. *Prog Neurobiol* **93**: 297–311.
- Thelen M, Munoz LM, Rodriguez-Frade JM, Mellado M (2010). Chemokine receptor oligomerization: functional considerations. *Curr Opin Pharmacol* **10**: 38–43.
- Wang J, Norcross M (2008). Dimerization of chemokine receptors in living cells: key to receptor function and novel targets for therapy. *Drug Discov Today* **13**: 625–632.
- Ward SG, Marelli-Berg FM (2009). Mechanisms of chemokine and antigen-dependent T-lymphocyte navigation. *Biochem J* **418**: 13–27.
- Zlotnik A, Yoshie O (2000). Chemokines: a new classification system and their role in immunity. *Immunity* **12**: 121–127.

# Cholecystokinin

**Overview:** Cholecystokinin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on CCK receptors, Noble *et al.*, 1999) are activated by the endogenous peptides cholecystokinin (CCK)-4, CCK-8, CCK-33 and gastrin. There is evidence for species homologues of CCK<sub>2</sub> receptors distinguished by the relative affinities of the two stereoisomers of devazepide, *R*-L365260 and *S*-L365260, or by the differences in affinity of the agonist BC264 (Durieux *et al.*, 1992).

Nomenclature	CCK <sub>1</sub>	CCK <sub>2</sub>
Other names	CCK <sub>A</sub>	CCK <sub>B</sub> , CCK <sub>8</sub> /gastrin
Ensembl ID	ENSG00000163394	ENSG00000110148
Principal transduction	G <sub>q/11</sub> /G <sub>s</sub>	G <sub>s</sub>
Rank order of potency	CCK-8 >>gastrin, des-CCK-8 >CCK-4	CCK-8 ≥gastrin, des-CCK-8, CCK-4
Selective agonists	A71623, JMV180, GW5823	Desulfated CCK-8, gastrin, CCK-4, PBC264, RB400
Selective antagonists	Devazepide (9.8), T0632 (9.6), SR27897 (9.2), IQM95333 (9.2), PD140548 (7.9–8.6), lorglumide (7.2)	YM022 (10.2), L740093 (10.0), GV150013 (9.3), RP73870 (9.3), L365260 (7.5–8.7), LY262691 (7.5)
Probes	[ <sup>3</sup> H]-Devazepide (0.2 nM)	[ <sup>3</sup> H]-Propionyl-BC264 (0.15 nM), [ <sup>3</sup> H]-PD140376 (0.2 nM), [ <sup>3</sup> H]-L365260 (2 nM), [ <sup>3</sup> H]- or [ <sup>125</sup> I]-gastrin (1 nM), [ <sup>125</sup> I]-PD142308 (0.25 nM)

A mitogenic gastrin receptor, which can be radiolabelled with [<sup>125</sup>I]-gastrin-(1–17) and which appears to couple to the G<sub>s</sub> family of G proteins, has been described in human colon cancer cells (Bold *et al.*, 1994) and other cell lines (e.g. pancreatic AR42J and Swiss 3T3 fibroblasts, Seva *et al.*, 1994; Singh *et al.*, 1995).

**Abbreviations:** A71623, Boc-Trp-Lys(O-toluylaminocarbonyl)-Asp-(NMe)Phe-NH<sub>2</sub>; BC264, Tyr(SO<sub>3</sub>H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH<sub>2</sub>; GV150013, (+)-*N*-(1-[1-adamantane-1-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl)-*N'*-phenylurea; GW5823, 2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(methoxyphenyl)acetamide; IQM95333, (4*α*,5*R*)-2-benzyl-5[*N*-(*tert*-butoxycarbonyl)-*L*-Trp]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine; JMV180, Boc-Tyr(SO<sub>3</sub>H)Ahx-Gly-Trp-Ahx-Asp<sup>2</sup>phenylethyl ester; L365260, 3*R*(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-Napos;-(3-methylphenyl)urea; L740093, *N*-([3*R*]-5-[3-azabicyclo[3.2.2]nonan-3-yl]-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea; LY262691, *trans*-*N*-(4-bromophenyl)-3-oxo-4,5-diphenyl-1-pyrazolidinocarboxamide(3.3.1.1<sup>3/7</sup>); PD140376, *L*-3-([4-aminophenyl)methyl]-*N*-(*α*-methyl-*N*-[[tricyclo(3.3.1.1*D*-Trp)-*β*-Ala]; PD140548, *N*-(*α*-methyl-*N*-[[tricyclo(3.3.1.1*L*-Trp)-*D*-3-(phenylmethyl)-*β*-Ala]; PD142308, iodinated PD140548; RB400, HOOC-CH<sub>2</sub>-CO-Trp-NMe(Nle)-Asp-Phe-NH<sub>2</sub>; RP73870, ((*R*)); SR27897, 1-([2-(4-(2-chlorophenyl)thiazole-2-yl)aminocarbonyl]indolyl)acetic acid; T0632, sodium (*S*)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[[3-isoquinolyl]carbonyl]amino-6-methoxy-2-oxo-1*H*-indole)propanoate; YM022, (*R*)-1-(2,3-dihydro-1-[2'-methylphenacyl]-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea

## Further Reading

- Berna MJ, Tapia JA, Sancho V, Jensen RT (2007). Progress in developing cholecystokinin (CCK)/gastrin receptor ligands that have a therapeutic potential. *Curr Opin Pharmacol* 7: 583–592.
- Cawston EE, Miller LJ (2010). Therapeutic potential for novel drugs targeting the type 1 cholecystokinin receptor. *Br J Pharmacol* 159: 1009–1021.
- De Tullio P, Delarge J, Pirotte B (2000). Therapeutic and chemical developments of cholecystokinin receptor ligands. *Expert Opin Investig Drugs* 9: 129–146.
- Dockray GK (2009). Cholecystokinin and gut-brain signalling. *Regul Pept* 155: 6–10.
- Dufresne M, Seva C, Fourmy D (2006). Cholecystokinin and gastrin receptors. *Physiol Rev* 86: 805–847.
- Herranz R (2003). Cholecystokinin antagonists: pharmacological and therapeutic potential. *Med Res Rev* 23: 559–605.
- Inui A (2003). Neuropeptide gene polymorphisms and human behavioural disorders. *Nat Rev Drug Discov* 2: 986–998.
- Kopin AS, McBride EW, Schaffer K, Beinboen M (2000). CCK receptor polymorphisms: an illustration of emerging themes in pharmacogenomics. *Trends Pharmacol Sci* 21: 346–353.
- Lovick TA (2009) CCK as a modulator of cardiovascular function. *J Chem Neuroanat* 38: 176–184.
- Miller LJ, Gao F (2008). Structural basis of cholecystokinin receptor binding and regulation. *Pharmacol Ther* 119: 83–95.
- Moran TH (2000). Cholecystokinin and satiety: current perspectives. *Nutrition* 16: 858–865.
- Noble F, Roques BP (1999). CCK<sub>B</sub> receptor: chemistry, molecular biology, biochemistry and pharmacology. *Prog Neurobiol* 56: 1–31.
- Noble F, Wank SA, Crawley JN, Bradwejn J, Seroogy KB, Hamon M, Roques BP (1999). International Union of Pharmacology. XXI. Structure, distribution, and functions of cholecystokinin receptors. *Pharmacol Rev* 51: 745–781.
- Peter SA, D'Amato M, Beglinger C (2006). CCK1 antagonists: are they ready for clinical use? *Dig Dis* 24: 70–82.
- Raybould HE (2007). Mechanism of CCK signaling from gut to brain. *Curr Opin Pharmacol* 7: 570–574.
- Rozenfurt E, Walsh J (2001). Gastrin, CCK, signaling, and cancer. *Annu Rev Physiol* 63: 49–76.

## References

- Bold RJ *et al.* (1994). *Biochem Biophys Res Commun* 202: 1222–1226.
- Durieux C *et al.* (1992). *Mol Pharmacol* 41: 1089–1095.
- Seva C *et al.* (1994). *Science* 265: 410–412.
- Singh P. *et al.* (1995). *J Biol Chem* 270: 8429–8438.

# Corticotropin-releasing factor

**Overview:** Corticotropin-releasing factor (CRF, nomenclature as recommended by the NC-IUPHAR on Corticotropin-releasing Factor Receptors, see Hauger *et al.*, 2003) receptors are activated by the endogenous peptides CRF (also known as corticotropin-releasing hormone [CRH], a 41 amino-acid peptide, ENSG00000147571), urocortin 1 (a 40 amino-acid peptide, ENSG00000163794), urocortin 2 (a 38 amino-acid peptide, ENSG00000145040) and urocortin 3 (a 38 amino-acid peptide, ENSG00000178473). CRF<sub>1</sub> and CRF<sub>2</sub> receptors are activated non-selectively by CRF and urocortin 1. Binding to CRF receptors can be conducted using [<sup>125</sup>I]-Tyr<sup>0</sup>-CRF or [<sup>125</sup>I]-Tyr<sup>0</sup>-sauvagine with K<sub>d</sub> values of 0.1–0.4 nM. CRF<sub>1</sub> and CRF<sub>2</sub> receptors are non-selectively antagonized by  $\alpha$ -helical CRF-(9-41), D-Phe-CRF-(12-41) and astressin.

Nomenclature	CRF <sub>1</sub>	CRF <sub>2</sub>
Other names	CRF-RA, PC-CRF	CRF-RB, HM-CRF
Ensembl ID	ENSG00000120088	ENSG00000106113
Principal transduction	G <sub>s</sub>	G <sub>s</sub>
Selective agonists	–	Urocortin 2 (Reyes <i>et al.</i> , 2001), urocortin 3 (Lewis <i>et al.</i> , 2001)
Selective antagonists	CP154526 (8.3–9.0, Lundkvist <i>et al.</i> , 1996), NBI27914 (8.3–9.0, Chen <i>et al.</i> , 1996), antalarmin (8.3–9.0, Webster <i>et al.</i> , 1996), CRA1000 (8.3–9.0, Chaki <i>et al.</i> , 1999), DMP696 (8.3–9.0, He <i>et al.</i> , 2000), R121919 (8.3–9.0, Zobel <i>et al.</i> , 2000), SRA125543A (8.7–9.0, Gully <i>et al.</i> , 2002) CP376395 (7.8, Chen <i>et al.</i> , 2008)	K41498 (9.2, Lawrence <i>et al.</i> , 2002), K31440 (8.7–8.8, Ruhmann <i>et al.</i> , 2002), antisauvagine-30 (Ruhmann <i>et al.</i> , 1998)

A CRF binding protein has been identified (CRF-BP, ENSG00000145708) to which both CRF and urocortin 1 bind with high affinities, which has been suggested to bind and inactivate circulating CRF (Perkins *et al.*, 1995).

**Abbreviations:** **antalarmin**, N-butyl-N-ethyl-(2,5,6-trimethyl)-7-[2,4,6-trimethylphenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl-amine; **astressin**, cyc<sup>30–33</sup>[D-Phe<sup>12</sup>,Nle<sup>21,38</sup>,Glu<sup>30</sup>,Lys<sup>33</sup>]CRF-(12-41); **CP154526**, butyl-ethyl-(2,5-dimethyl)-7-[2,4,6-trimethylphenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine; **CRA1000**, 2-(N-[2-methylthio-4-isopropylphenyl]-N-ethyl-amino-4-[4-{3-fluorophenyl}-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine); **DMP696**, 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine; **D-Phe-CRF-(12-41)**, D-Phe<sup>12</sup>,Nle<sup>21,38</sup>, $\alpha$ MeLeu<sup>37</sup>-CRF; **K31440**, Ac-(D-Tyr<sup>11</sup>,His<sup>12</sup>,Nle<sup>17</sup>)sauvagine-(11-40); **K41498**, [D-Phe<sup>11</sup>,His<sup>12</sup>,Nle<sup>17</sup>]sauvagine-(11-40); **NBI27914**, 2-methyl-4-(N-propyl-N-cyclopropanemethylamino)-5-chloro-6-(2,4,6-trichloroanilino)pyrimidine; **R121919**, 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine; **SRA125543A**, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride

## Further Reading

- Binder EB, Nemeroff CB (2010). The CRF system, stress, depression and anxiety-insights from human genetic studies. *Mol Psychiatry* **15**: 574–588.
- Bonci A, Borgland S (2009). Role of orexin/hypocretin and CRF in the formation of drug-dependent synaptic plasticity in the mesolimbic system. *Neuropharmacology* **56** (Suppl. 1): 107–111.
- Fekete EM, Zorrilla EP (2007). Physiology, pharmacology, and therapeutic relevance of urocortins in mammals: ancient CRF paralogs. *Front Neuroendocrinol* **28**: 1–27.
- Hauger RL, Grigoriadis DE, Dallman MF, Plotsky PM, Vale WW, Dautzenberg FM (2003). International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacol Rev* **55**: 21–26.
- Kehne JH, Cain CK (2010). Therapeutic utility of non-peptidic CRF<sub>1</sub> receptor antagonists in anxiety, depression, and stress-related disorders: evidence from animal models. *Pharmacol Ther* **128**: 460–487.
- Koob GF (2010). The role of CRF and CRF-related peptides in the dark side of addiction. *Brain Res* **1314**: 3–14.
- Tache Y, Bonaz B (2007). Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. *J Clin Invest* **117**: 33–40.
- Tsatsanis C, Dermitzaki E, Venihaki M, Chatzaki E, Minas V, Gravanis A *et al.* (2007). The corticotropin-releasing factor (CRF) family of peptides as local modulators of adrenal function. *Cell Mol Life Sci* **64**: 1638–1655.
- Wise RA, Morales M (2010). A ventral tegmental CRF-glutamate-dopamine interaction in addiction. *Brain Res* **1314**: 38–43.
- Ziegler CG, Krug AW, Zouboulis CC, Bornstein SR (2007). Corticotropin releasing hormone and its function in the skin. *Horm Metab Res* **39**: 106–109.

## References

- Chaki S *et al.* (1999). *Eur J Pharmacol* **371**: 205–211.
- Chen C *et al.* (1996). *J Med Chem* **39**: 4358–4360.
- Chen YL *et al.* (2008). *J Med Chem* **51**: 1385–1392.
- Gully D *et al.* (2002). *J Pharmacol Exp Ther* **301**: 322–332.
- He L *et al.* (2000). *J Med Chem* **43**: 449–456.
- Lawrence AJ *et al.* (2002). *Br J Pharmacol* **136**: 896–904.
- Lewis K *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 7570–7575.
- Lundkvist J *et al.* (1996). *Eur J Pharmacol* **309**: 195–200.
- Perkins AV *et al.* (1995). *J Endocrinol* **146**: 395–401.
- Reyes TM *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 2843–2848.
- Ruhmann A *et al.* (1998). *Proc Natl Acad Sci U S A* **95**: 15264–15269.
- Ruhmann A *et al.* (2002). *Peptides* **23**: 453–460.
- Webster EL *et al.* (1996). *Endocrinology* **137**: 5747–5750.
- Zobel AW *et al.* (2000). *J Psychiatr Res* **34**: 171–181.

# Dopamine

**Overview:** Dopamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Dopamine Receptors, see Schwartz *et al.*, 1998) are commonly divided into D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) families, where the endogenous agonist is dopamine. Quinpirole is an agonist with selectivity for D<sub>2</sub>-like receptors.

Nomenclature	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	D <sub>5</sub>
Other names	D <sub>1A</sub>	–	–	–	D <sub>1B</sub>
Ensembl ID	ENSG00000184845	ENSG00000149295	ENSG00000151577	ENSG00000069696	ENSG00000169676
Principal transduction	G <sub>s</sub> , G <sub>olf</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>s</sub>
Selective agonists	R(+)-SKF81297, R(+)-SKF38393	Sumanriole (McCall <i>et al.</i> , 2005)	PD128907	PD168077, A412997 (Moreland <i>et al.</i> , 2005)	–
Selective antagonists	SCH23390, SKF83566, SCH39166	Raclopride, domperidone	S33084 (9.6, Millan <i>et al.</i> , 2000), nafadotride (9.5), (+)S14297 (7.9, Millan <i>et al.</i> , 1994), SB277011 (8.0, Reavill <i>et al.</i> , 2000)	L745870 (9.3), U101958 (8.9, Schlachter <i>et al.</i> , 1997), L741742 (8.5)	–
Probes	[ <sup>3</sup> H]-SCH23390 (0.2 nM), [ <sup>125</sup> I]-SCH23982 (0.7 nM)	[ <sup>3</sup> H]-Raclopride, [ <sup>3</sup> H]-spiperone	[ <sup>3</sup> H]-7-OH-DPAT, [ <sup>3</sup> H]-PD128907, [ <sup>3</sup> H]-spiperone	[ <sup>3</sup> H]-NGD941 (5 nM, Primus <i>et al.</i> , 1997), [ <sup>125</sup> I]-L750667 (1 nM, Patel <i>et al.</i> , 1996), [ <sup>3</sup> H]-spiperone	[ <sup>125</sup> I]-SCH23982 (0.8 nM) [ <sup>3</sup> H]-SCH23390 (0.5 nM)

The selectivity of many of these agents is less than two orders of magnitude. [<sup>3</sup>H]-Raclopride exhibits similar high affinity for D<sub>2</sub> and D<sub>3</sub> receptors (low affinity for D<sub>4</sub>), but has been used to label D<sub>2</sub> receptors in the presence of a D<sub>3</sub>-selective antagonist. [<sup>3</sup>H]-7-OH-DPAT has similar affinity for D<sub>2</sub> and D<sub>3</sub> receptors, but labels only D<sub>3</sub> receptors in the absence of divalent cations. The pharmacological profile of the D<sub>3</sub> receptor is similar to, yet distinct from, that of the D<sub>1</sub> receptor. The splice variants of the D<sub>2</sub> receptor are commonly termed D<sub>2S</sub> and D<sub>2L</sub> (short and long). The *DRD4* gene encoding the D<sub>4</sub> receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

**Abbreviations:** L741742, 5-(4-chlorophenyl)-4-methyl-3-(1-[2-phenethyl]piperidin-4-yl)isoxazole; L745870, 3-[[4-(4-chlorophenyl)piperazin-1-yl)methyl]-1H-pyrrolo[2,3-*b*]pyridine; L750667, iodinated L745870; NGD941, 2-phenyl-4(S)-(4-[2-pyrimidinyl]-[piperazin-1-yl]-methyl)-imidazole dimaleate; (+)-7-OH-DPAT, (+)-7-hydroxy-2-aminopropylaminotetralin; PD128907, *R*-(+)-*trans*-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3-*b*]-1,4-oxazine-9-ol; PD168077, *N*-methyl-4-(2-cyanophenyl)piperazinyl-3-methylbenzamide; (+)S14297, (+)-7-(*N,N*-dipropylamino)-5,6,7,8-tetrahydronaphtho(2,3*b*)dihydro-2,3-furane; S33084, (3*aR*,9*bS*)-*N*[4-(8-cyano-1,3*a*,4,9*b*-tetrahydro-3*H*-benzopyrano[3,4-*c*]pyrrole-2-yl)butyl] (4-phenyl)benzamide; SB277011, *trans-N*-(4-[2-[6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl]ethyl]cyclohexyl)-4-quinolininecarboxamide; SCH23390, 7-chloro-8-hydroxy-3-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; SCH23982, 8-iodo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine; SCH39166, (-)-*trans*-6,7,7*a*,8,9,13*b*-hexahydro-3-chloro-2-hydroxy-*N*-ethyl-5*H*-benzo[*d*]naphtho-(2,*b*)azepine; R(+)-SKF81297, R(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; R(+)-SKF38393, R(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; R(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; SKF83566, (-)-7-bromo-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine; U101958, 3-isopropoxy-*N*-methyl-*N*-(1-[phenylmethyl]-4-piperidinyl)-2-pyridinylamine

## Further Reading

- Beaulieu JM, Gainetdinov RR (2011). The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* 63: 182–217.
- Bjorklund A, Dunnett SB (2007). Dopamine neuron systems in the brain: an update. *Trends Neurosci* 30: 194–202.
- Bjorklund A, Dunnett SB (2007). Fifty years of dopamine research. *Trends Neurosci* 30: 185–187.
- Carlsson A, Carlsson ML (2008). Adaptive properties and heterogeneity of dopamine D<sub>2</sub> receptors – pharmacological implications. *Brain Res Rev* 58: 374–378.
- De Mei C, Ramos M, Iitaka C, Borrelli E (2009). Getting specialized: presynaptic and postsynaptic dopamine D<sub>2</sub> receptors. *Curr Opin Pharmacol* 9: 53–58.
- Giorgetti G, Piergentili A, Ruggieri S, Quaglia W (2008). Dopamine D<sub>5</sub> receptors: a challenge to medicinal chemists. *Mini Rev Med Chem* 8: 976–995.
- Hasbi A, O'Dowd BF, George SR (2010). Heteromerization of dopamine D<sub>2</sub> receptors with dopamine D<sub>1</sub> or D<sub>5</sub> receptors generates intracellular calcium signaling by different mechanisms. *Curr Opin Pharmacol* 10: 93–99.
- Hoebel BG, Avena NM, Rada P (2007). Accumbens dopamine-acetylcholine balance in approach and avoidance. *Curr Opin Pharmacol* 7: 617–627.
- Horowski R (2007). A history of dopamine agonists. From the physiology and pharmacology of dopamine to therapies for prolactinomas and Parkinson's disease – a subjective view. *J Neural Transm* 114: 127–134.
- Iversen SD, Iversen LL (2007). Dopamine: 50 years in perspective. *Trends Neurosci* 30: 188–193.
- Joyce JN, Millan MJ (2007). Dopamine D<sub>3</sub> receptor agonists for protection and repair in Parkinson's disease. *Curr Opin Pharmacol* 7: 100–105.
- Le Foll B, Gallo A, Le Strat Y, Lu L, Gorwood P (2009). Genetics of dopamine receptors and drug addiction: a comprehensive review. *Behav Pharmacol* 20: 1–17.
- Maggio R, Millan MJ (2010). Dopamine D<sub>2</sub>-D<sub>3</sub> receptor heteromers: pharmacological properties and therapeutic significance. *Curr Opin Pharmacol* 10: 100–107.

- Ohara K (2007). The n-3 polyunsaturated fatty acid/dopamine hypothesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **31**: 469–474.
- Rollo CD (2009). Dopamine and aging: intersecting facets. *Neurochem Res* **34**: 601–629.
- Rolls ET, Loh M, Deco G, Winterer G (2008). Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. *Nat Rev Neurosci* **9**: 696–709.
- Rondou P, Haegeman G, Van Craenenbroeck K (2010). The dopamine D4 receptor: biochemical and signalling properties. *Cell Mol Life Sci* **67**: 1971–1986.
- Schwartz J-C *et al.* (1998). Dopamine receptors. In: Girdlestone D (ed.). *The IUPHAR Compendium of Receptor Characterization and Classification*. IUPHAR Media: London, pp. 141–151.
- Scott L, Aperia A (2009). Interaction between N-methyl-D-aspartic acid receptors and D1 dopamine receptors: an important mechanism for brain plasticity. *Neuroscience* **158**: 62–66.
- Stanwood GD (2008). Protein-protein interactions and dopamine D2 receptor signaling: a calcium connection. *Mol Pharmacol* **74**: 317–319.
- Thomas MJ, Kalivas PW, Shaham Y (2008). Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *Br J Pharmacol* **154**: 327–342.
- Undieh AS (2010). Pharmacology of signaling induced by dopamine D<sub>1</sub>-like receptor activation. *Pharmacol Ther* **128**: 37–60.
- Wood MD, Wren PB (2008). Serotonin-dopamine interactions: implications for the design of novel therapeutic agents for psychiatric disorders. *Prog Brain Res* **172**: 213–230.

## References

- McCall RB *et al.* (2005). *J Pharmacol Exp Ther* **314**: 1248–1256.
- Millan MJ *et al.* (1994). *Eur J Pharmacol* **260**: R3–R5.
- Millan MJ *et al.* (2000). *J Pharmacol Exp Ther* **293**: 1048–1062.
- Moreland RB *et al.* (2005). *Pharmacol Biochem Behav* **82**: 140–147.
- Patel S *et al.* (1996). *Mol Pharmacol* **50**: 1658–1664.
- Primus RJ *et al.* (1997). *J Pharmacol Exp Ther* **282**: 1020–1027.
- Reavill C *et al.* (2000). *J Pharmacol Exp Ther* **294**: 1154–1165.
- Schlachter SK *et al.* (1997). *Eur J Pharmacol* **322**: 283–286.

# Endothelin

**Overview:** Endothelin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on endothelin receptors, Davenport, 2002) are activated by the endogenous 21 amino-acid peptides endothelin-1 (ET-1, ENSG00000078401), ET-2 (ENSG00000127129) and ET-3 (ENSG00000124205). Non-selective peptide (e.g. TAK044, pA<sub>2</sub> 8.4) and non-peptide (e.g. bosentan, pA<sub>2</sub> 6.0–7.2; SB209670, pA<sub>2</sub> 9.4) antagonists can block both ET<sub>A</sub> and ET<sub>B</sub> receptors. Splice variants of the ET<sub>A</sub> receptor have been identified in rat pituitary cells; one of these, ET<sub>A</sub>R-C13, appeared to show loss of function with comparable plasma membrane expression (Hatae *et al.*, 2007).

Nomenclature	ET <sub>A</sub>	ET <sub>B</sub>
Ensembl ID	ENSG00000151617	ENSG00000136160
Principal transduction	G <sub>q/11</sub> , G <sub>s</sub>	G <sub>q/11</sub> , G <sub>i/o</sub>
Potency order	ET-1, ET-2 > ET-3 (Maguire and Davenport, 1995)	ET-1, ET-2, ET-3
Selective agonists	–	[Ala <sup>1,3,11,15</sup> ]ET-1 (Molenaar <i>et al.</i> , 1992), sarafotoxin S6c (Russell and Davenport, 1996), IRL1620 (Watakabe <i>et al.</i> , 1992), BQ3020 (Russell and Davenport, 1996)
Selective antagonists	A127722 (9.2–10.5, Opgenorth <i>et al.</i> , 1996), LU135252 (8.9, Riechers <i>et al.</i> , 1996), SB234551 (8.7–9.0, Ohlstein <i>et al.</i> , 1998), PD156707 (8.2–8.5, Maguire <i>et al.</i> , 1997), FR139317 (7.3–7.9, Maguire and Davenport, 1995), BQ123 (6.9–7.4, Maguire and Davenport, 1995), ZD4054 (pIC <sub>50</sub> 8.3, Morris <i>et al.</i> , 2005), sitaxsentan (8.0, Wu <i>et al.</i> , 1997), ambrisentan (7.1, Bolli <i>et al.</i> , 2004)	BQ788 (8.4, Russell and Davenport, 1996), A192621 (8.1, von Geldern <i>et al.</i> , 1999), IRL2500 (7.2, Russell and Davenport, 1996), Ro468443 (7.1, Breu <i>et al.</i> , 1996)
Probes	[ <sup>3</sup> H]-S0139 (0.6 nM), [ <sup>3</sup> H]-BQ123 (3.2 nM, Ihara <i>et al.</i> , 1995), [ <sup>125</sup> I]-PD164333 (0.2 nM, Davenport <i>et al.</i> , 1998), [ <sup>125</sup> I]-PD151242 (0.5 nM, Davenport <i>et al.</i> , 1994)	[ <sup>125</sup> I]-IRL1620 (20 pM, Watakabe <i>et al.</i> , 1992), [ <sup>125</sup> I]-BQ3020 (0.1 nM, Molenaar <i>et al.</i> , 1992), [ <sup>125</sup> I]-[Ala <sup>1,3,11,15</sup> ]ET-1 (0.2 nM, Molenaar <i>et al.</i> , 1992)

Subtypes of the ET<sub>B</sub> receptor have been proposed, although gene disruption studies in mice suggest that the heterogeneity results from a single gene product (Mizuguchi *et al.*, 1997).

**Abbreviations:** A127722, *trans-trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-([N,N-dibutylamino]carbonylmethyl)pyrrolidine-3-carboxylate; A192621, (2*R*,3*R*,4*S*)-2-(4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-[2,6-diethylphenyl]acetamido)pyrrolidine-3-carboxylic acid; **ambrisentan**, 2-(4,6-dimethylpyrimidin-2-yl)oxy-3-methoxy-3,3-diphenylpropanoic acid; **BQ123**, *cyc*(DTrp-DAsp-Pro-D-Val-Leu); **BQ3020**, N-acetyl-Leu-Met-Asp-Lys-Glu-Ala-Val-Tyr-Phe-Ala-His-Leu-Asp-Ile-Ile-Trp; **BQ788**, *N-cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyl-D-norleucine; **FR139317**, (R)-2-([R-2-((S)-2-([1-[hexahydro-1*H*-azepinyl]carbonyl]amino)methyl]pentanoyl)amino-3-(3-[methyl-1*H*-indodolyl]propionylamino-3-(2-pyridyl))propionate; **IRL1620**, Suc[Glu<sup>9</sup>,Ala<sup>11,15</sup>]ET-1<sub>10-21</sub>; **IRL2500**, N-(3,5-dimethylbenzoyl)-N-methyl-D-(4-phenylphenyl)-Ala-Trp; **LU135252**, (+)-(S)-2-(4,6-dimethoxypyrimidin-2-yl)oxy-3-methoxy-3,3-propionic acid; **PD151242**, (N-[hexahydro-1-azepinyl]carbonyl)Leu(1-Me)-DTrp-DTyr; **PD156707**, 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate; **PD164333**, 2-benzo[1,3]dioxol-5-yl-4-(3-[2-(4-hydroxyphenyl)-ethylcarbamoyl]-propoxy)-4,5-dimethoxyphenyl-3-(4-methoxybenzoyl)-but-2-enoate; **RES7011**, *cyc*(Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp)-Trp-Phe-Phe-Asn-Tyr-Tyr-Trp; **Ro468443**, (R)-4-*tert*-butyl-N-(6-[2,3-dihydroxypropoxy]-5-[2-methoxyphenoxy]-2-[4-methoxyphenyl]-pyrimidin-4-yl)-benzenesulfonamide; **S0139**, 27-O-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricone, sodium salt; **SB209670**, (+)-1*S*,2*R*,3-*S*-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxypheyl)-5-prop-1-yloxyindane-2-carboxylate; **SB234551**, (E)-α-([1-butyl-5-[2-([2-carboxyphenyl]methoxy)-4-methoxyphenyl]-1*H*-pyrazol-4-yl]methylene)-6-methoxy-1,3-benzodioxole-5-propanoic acid; **sitaxsentan**, N-(4-chloro-3-methyl-1,2-oxazol-5-yl)-2-[2-(6-methyl-1,3-benzodioxol-5-yl)acetyl]thiophene-3-sulfonamide; **TAK044**, *cyc*(D-Asp-Asp(Php)-Asp-D-Thg-Leu-D-Trp)-4-oxobut-2-enoate; **ZD4054**, N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide

## Further Reading

- Bagnato A, Rosano L (2008). The endothelin axis in cancer. *Int J Biochem Cell Biol* **40**: 1443–1451.
- Davenport AP (2002). International Union of Pharmacology. XXIX. Update on endothelin receptor nomenclature. *Pharmacol Rev* **54**: 219–226.
- Dhaun N, Goddard J, Kohan DE, Pollock DM, Schiffrin EL, Webb DJ (2008). Role of endothelin-1 in clinical hypertension: 20 years on. *Hypertension* **52**: 452–459.
- Dhaun N, Pollock DM, Goddard J, Webb DJ (2007). Selective and mixed endothelin receptor antagonism in cardiovascular disease. *Trends Pharmacol Sci* **28**: 573–579.
- Dupuis J, Hoepfer MM (2008). Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* **31**: 407–415.
- Kawanabe Y, Nauli SM (2011). Endothelin. *Cell Mol Life Sci* **68**: 195–203.
- Khorodova A, Montmayeur JP, Strichartz G (2009). Endothelin receptors and pain. *J Pain* **10**: 4–28.
- Kirkby NS, Hadoke PW, Bagnall AJ, Webb DJ (2008). The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? *Br J Pharmacol* **153**: 1105–1119.
- Kohan DE, Rossi NF, Inscho EW, Pollock DM (2011). Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev* **91**: 1–77.
- Nguyen A, Thorin-Trescases N, Thorin E (2010). Working under pressure: coronary arteries and the endothelin system. *Am J Physiol Regul Integr Comp Physiol* **298**: R1188–R1194.
- Schneider MP, Boesen EI, Pollock DM. (2007). Contrasting actions of endothelin ET<sub>A</sub> and ET<sub>B</sub> receptors in cardiovascular disease. *Annu Rev Pharmacol Toxicol* **47**: 731–759.
- Schorlemmer A, Matter ML, Shohet RV (2008). Cardioprotective signaling by endothelin. *Trends Cardiovasc Med* **18**: 233–239.



- Thorin E, Webb DJ (2010). Endothelium-derived endothelin-1. *Pflugers Arch* **459**: 951–958.
- Viridis A, Ghiadoni L, Taddei S (2010). Human endothelial dysfunction: EDCFs. *Pflugers Arch* **459**: 1015–1023.
- Watts SW (2010). Endothelin receptors: what's new and what do we need to know? *Am J Physiol Regul Integr Comp Physiol* **298**: R254–R260.

## References

- Bolli MH *et al.* (2004). *J Med Chem* **47**: 2776–2795.
- Breu V *et al.* (1996). *FEBS Lett* **383**: 37–41.
- Davenport AP *et al.* (1994). *Br J Pharmacol* **111**: 4–6.
- Davenport AP *et al.* (1998). *Br J Pharmacol* **123**: 223–230.
- Hatae N *et al.* (2007). *Mol Endocrinol* **21**:1192–1204.
- Ihara M *et al.* (1995). *Eur J Pharmacol* **274**: 1–6.
- Maguire JJ *et al.* (1997). *J Pharmacol Exp Ther* **280**: 1102–1108.
- Maguire JJ, Davenport AP (1995). *Br J Pharmacol* **115**: 191–197.
- Mizuguchi T *et al.* (1997). *Br J Pharmacol* **120**: 1427–1430.
- Molenaar P *et al.* (1992). *Br J Pharmacol* **107**: 637–639.
- Morris CD *et al.* (2005). *Br J Cancer* **92**: 2148–2152.
- Ohlstein EH *et al.* (1998). *J Pharmacol Exp Ther* **286**: 650–656.
- Oppenorth TJ *et al.* (1996). *J Pharmacol Exp Ther* **276**: 473–481.
- Riechers H *et al.* (1996). *J Med Chem* **39**: 2123–2128.
- Russell FD, Davenport AP (1996). *Br J Pharmacol* **119**: 631–636.
- von Geldern TW *et al.* (1999). *J Med Chem* **42**: 3668–3678.
- Watakabe T *et al.* (1992). *Biochem Biophys Res Commun* **185**: 867–873.
- Wu C *et al.* (1997). *J Med Chem* **40**: 1690–1697.

# Formylpeptide

**Overview:** The formylpeptide receptors (ENSMF00510000502765, nomenclature agreed by NC-IUPHAR Subcommittee on the formyl peptide receptor family, see Ye *et al.*, 2009) respond to exogenous ligands such as the bacterial product formyl-Met-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ENSG00000135046), cathepsin G (ENSG00000100448) and spinorphin, derived from  $\beta$ -haemoglobin (ENSG00000244734).

Nomenclature	FPR1	FPR2/ALX	FPR3
Other names	Formyl peptide, fMLP, FPR	FPRL1, FPR2, FPRH2, RFP, ALX	FPRH1, FMLPY, RMLP-R-I, FPRL2
Ensembl ID	ENSG00000171051	ENSG00000171049	ENSG00000187474
Principal transduction	G <sub>ij</sub> , G <sub>z</sub>	G <sub>i</sub> (Maddox <i>et al.</i> , 1997)	–
Rank order of potency	fMLP > Cathepsin G > Annexin I (Le <i>et al.</i> , 2002; Sun <i>et al.</i> , 2004)	LXA <sub>4</sub> = ATL = ATLa2 > LTC <sub>4</sub> = LTD <sub>4</sub> >> 15-deoxy-LXA <sub>4</sub> >> fMLP (Clish <i>et al.</i> , 1999; Fiore <i>et al.</i> , 1994; Fiore and Serhan, 1995; Gronert <i>et al.</i> , 2001; Takano <i>et al.</i> , 1997)	–
Selective agonists	fMLP (Le <i>et al.</i> , 1999)	LXA <sub>4</sub> , ATL, ATLa2 (Guilford <i>et al.</i> , 2004), RvD1 (Krishnamoorthy <i>et al.</i> , 2010)	F2L (Migeotte <i>et al.</i> , 2005)
Selective antagonists	Cyclosporin H (6.3-7.0, Wenzel-Seifert and Seifert, 1993), BOC-PLPLP (6.0-6.5, Wenzel-Seifert and Seifert, 1993), spinorphin (4, Liang <i>et al.</i> , 2001)	–	–
Probes	[ <sup>3</sup> H]-fMLP	[ <sup>3</sup> H]-LXA <sub>4</sub> (0.2–1.7 nM; Fiore <i>et al.</i> , 1994; Takano <i>et al.</i> , 1997)	–

Note that the data for FPR2/ALX are also reproduced on the Leukotriene, lipoxin, oxoecosanoid and resolvin receptor pages (see Page S74).

**Abbreviations:** BOC-PLPLP, Boc-Phe-Leu-Phe-Leu-Phe; ATL, aspirin-triggered lipoxin A<sub>4</sub> [15-*epi*-LXA<sub>4</sub>, 5S,6R,15R-trihydroxyl-7E,9E,13E,11z-eicosatetraenoic acid]; ATLa2, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA<sub>4</sub>]; F2L, an acetylated 21-aa cleavage protein of haem-binding protein (ENSG00000013583); LTC<sub>4</sub>, leukotriene C<sub>4</sub>; LTD<sub>4</sub>, leukotriene D<sub>4</sub>; LXA<sub>4</sub>, lipoxin A<sub>4</sub> [5S,6R,15S-trihydroxyl-7E,9E,13E-11z-eicosatetraenoic acid]; RvD1, resolvin D1

## Further Reading

- Cattaneo F, Guerra G, Ammendola R (2010). Expression and signaling of formyl-peptide receptors in the brain. *Neurochem Res* 35: 2018–2026.
- Dufton N, Perretti M (2010). Therapeutic anti-inflammatory potential of formyl-peptide receptor agonists. *Pharmacol Ther* 127: 175–188.
- Gavins FN (2010). Are formyl peptide receptors novel targets for therapeutic intervention in ischaemia-reperfusion injury? *Trends Pharmacol Sci* 31: 266–276.
- Liberles SD, Horowitz LF, Kuang D *et al.* (2009). Formyl peptide receptors are candidate chemosensory receptors in the vomeronasal organ. *Proc Natl Acad Sci U S A* 106: 9842–9847.
- Rabiet MJ, Macari L, Dahlgren C, Boulay F (2011). N-Formyl peptide receptor 3 (FPR3) departs from the homologous FPR2/ALX receptor with regard to the major processes governing chemoattractant receptor regulation, expression at the cell surface, and phosphorylation. *J Biol Chem* 286: 26718–26731.
- Ye RD, Boulay F, Wang JM *et al.* (2009). International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev* 61: 119–161.

## References

- Clish CB *et al.* (1999). *Proc Natl Acad Sci U S A* 96: 8247–8252.
- Fiore S *et al.* (1994). *J Exp Med* 180: 253–260.
- Fiore S, Serhan CN (1995). *Biochemistry* 34: 16678–16686.
- Gronert K *et al.* (2001). *Am J Pathol* 158: 3–9.
- Guilford WJ *et al.* (2004). *J Med Chem* 47: 2157–2165.
- Krishnamoorthy S *et al.* (2010). *Proc Natl Acad Sci U S A* 107: 1660–1665.
- Le Y *et al.* (1999). *J Immunol* 163: 6777–6784.
- Le Y *et al.* (2002). *Trends Immunol* 23: 541–548.
- Liang TS *et al.* (2001). *J Immunol* 167: 6609–6614.
- Maddox JF *et al.* (1997). *J Biol Chem* 272: 6972–6978.
- Migeotte I *et al.* (2005). *J Exp Med* 201: 83–93.
- Sun R *et al.* (2004). *J Immunol* 173: 428–436.
- Takano T *et al.* (1997). *J Exp Med* 185: 1693–1704.
- Wenzel-Seifert K, Seifert R (1993). *J Immunol* 150: 4591–4599.

# Free fatty acid

**Overview:** Free fatty acid receptors (FFA, nomenclature as agreed by NC-IUPHAR Subcommittee on free fatty acid receptors, Stoddart *et al.*, 2008) are activated by free fatty acids. Long chain saturated and unsaturated fatty acids (C16:0, C18:0, C18:1, C18:2, C18:3,n-6, C20:4, C20:5,n-3, C22:6,n-3, Briscoe *et al.*, 2003; Itoh *et al.*, 2003; Kotarsky *et al.*, 2003) activate FFA<sub>1</sub> receptors, while short chain fatty acids (C2, C3, C4 and C5) activate FFA<sub>2</sub> (Brown *et al.*, 2003; Le Poul *et al.*, 2003; Nilsson *et al.*, 2003) and FFA<sub>3</sub> (Brown *et al.*, 2003; Le Poul *et al.*, 2003) receptors. In addition, thiazolidinedione PPAR $\gamma$  agonists such as rosiglitazone activate FFA<sub>1</sub> (pEC<sub>50</sub> 5.2; Kotarsky *et al.*, 2003; Stoddart *et al.*, 2007; Smith *et al.*, 2009) and small molecule allosteric modulators, such as 4-CMTB, have recently been characterised for FFA<sub>2</sub> (Lee *et al.*, 2008; Smith *et al.*, 2011).

Nomenclature	FFA <sub>1</sub>	FFA <sub>2</sub>	FFA <sub>3</sub>
Other names	GPR40 (Sawzdargo <i>et al.</i> , 1997)	GPR43 (Sawzdargo <i>et al.</i> , 1997)	GPR41 (Sawzdargo <i>et al.</i> , 1997). LSSIG (Senga <i>et al.</i> , 2003)
Ensembl ID	ENSG00000126266	ENSG00000126262	ENSG00000185897
Principal transduction	G <sub>q/11</sub> (Briscoe <i>et al.</i> , 2003; Itoh <i>et al.</i> , 2003; Stoddart <i>et al.</i> , 2007)	G <sub>q/11</sub> , G <sub>i/o</sub> (Brown <i>et al.</i> , 2003; Le Poul <i>et al.</i> , 2003; Nilsson <i>et al.</i> , 2003)	G <sub>i/o</sub> (Brown <i>et al.</i> , 2003; Le Poul <i>et al.</i> , 2003; Stoddart <i>et al.</i> , 2007)
Selective agonists	Linoleic acid (Briscoe <i>et al.</i> , 2003; Itoh <i>et al.</i> , 2003), TUG424 (pEC <sub>50</sub> 7.5, Christiansen <i>et al.</i> , 2008), GW9508 (pEC <sub>50</sub> 7.3; Briscoe <i>et al.</i> , 2006; Sum <i>et al.</i> , 2007), Cpd B (pEC <sub>50</sub> 6.1; Tan <i>et al.</i> , 2008)	(S)-2-(4-chlorophenyl)-N-(5-fluorothiazol-2-yl)-3-methylbutanamide (pEC <sub>50</sub> 6.4 Lee <i>et al.</i> , 2008)	–
Selective antagonists	GW1100 (Briscoe <i>et al.</i> , 2006; Stoddart <i>et al.</i> , 2007)	–	–

GW1100 is also an oxytocin receptor antagonist (Briscoe *et al.*, 2006).

GPR42 (ENSG00000126251) was originally described as a pseudogene within the family (ENSFM00250000002583), but the discovery of several polymorphisms suggests that some versions of GPR42 may be functional (Liaw and Connolly, 2009). GPR120 (ENSG00000186188) and GPR84 (ENSG00000139572) are structurally-unrelated G protein-coupled receptors. GPR120 is activated by unsaturated long chain free fatty acids (Gotoh *et al.*, 2007; Hirasawa *et al.*, 2005; Katsuma *et al.*, 2005) and GW9508 (pEC<sub>50</sub> 5.7; Briscoe *et al.*, 2006), while GPR84 was found to respond to medium chain fatty acids (Wang *et al.*, 2006).

**Abbreviations:** C16:0, palmitic acid; C18:0, stearic acid; C18:1, oleic acid; C18:2, linoleic acid; C18:3,n-6,  $\gamma$ -linolenic acid; C2, acetic acid; C20:4, arachidonic acid; C20:5,n-3, 5z,8z,11z,14z,17z-eicosapentaenoic acid, EPA; C22:6,n-3, 4z,7z,10z,13z,16z,19z-docosahexaenoic acid, DHA; C3, propionic acid; C4, butyric acid; C5, valeric acid; 4-CMTB, 4-chloro- $\alpha$ -(1-methylethyl)-N-2-thiazolylbenzeneacetamide; Cpd B, 3-chloro-5-trifluoromethyl-pyridin-2-yl-methoxy(4-(3-methylphenyl)methyl-1,3-thiazolidinedione-2,4-dione); GW1100, ethyl 4-(5-[[2-(ethyloxy)-5-pyrimidinyl]methyl]-2-[[4-(4-fluorophenyl)methyl]thio]-4-oxo-1[4H]-pyrimidinyl]benzoate; GW9508, 3-(4-[[3-(phenyloxy)phenyl]methyl]amino]phenyl)propanoic acid; TUG424, 4-[2-(2-methylphenyl)ethynyl]-benzenepropanoic acid

## Further Reading

- Alquier T, Poytout V (2009). GPR40: good cop, bad cop? *Diabetes* **58**: 1035–1036.
- Hara T, Hirasawa A, Ichimura A, Kimura I, Tsujimoto G (2011). Free fatty acid receptors FFAR1 and GPR120 as novel therapeutic targets for metabolic disorders. *J Pharm Sci* **100**: 3594–3601.
- Ichimura A, Hirasawa A, Hara T, Tsujimoto G (2009). Free fatty acid receptors act as nutrient sensors to regulate energy homeostasis. *Prostaglandins Other Lipid Mediat* **89**: 82–88.
- Maslowski KM, Mackay CR (2011). Diet, gut microbiota and immune responses. *Nat Immunol* **12**: 5–9.
- Milligan G, Stoddart LA, Smith NJ (2009). Agonism and allostereism: the pharmacology of the free fatty acid receptors FFA<sub>2</sub> and FFA<sub>3</sub>. *Br J Pharmacol* **158**: 146–153.
- Morgan NG, Dhayal S (2009). G-protein coupled receptors mediating long chain fatty acid signalling in the pancreatic beta-cell. *Biochem Pharmacol* **78**: 1419–1427.
- Sleeth ML, Thompson EL, Ford HE, Zac-Varghese SE, Frost G (2010). Free fatty acid receptor 2 and nutrient sensing: a proposed role for fibre, fermentable carbohydrates and short-chain fatty acids in appetite regulation. *Nutr Res Rev* **23**: 135–145.
- Stoddart LA, Smith NJ, Milligan G (2008). International Union of Pharmacology. LXXI. Free fatty acid receptors FFA<sub>1</sub>, -2, and -3: pharmacology and pathophysiological functions. *Pharmacol Rev* **60**: 405–417.
- Wellendorph P, Johansen LD, Brauner-Osborne H (2009). Molecular pharmacology of promiscuous seven transmembrane receptors sensing organic nutrients. *Mol Pharmacol* **76**: 453–465.

## References

- Briscoe CP *et al.* (2003). *J Biol Chem* **278**: 11303–11311.
- Briscoe CP *et al.* (2006). *Br J Pharmacol* **148**: 619–628.
- Brown AJ *et al.* (2003). *J Biol Chem* **278**: 11312–11319.
- Christiansen E *et al.* (2008). *J Med Chem* **51**: 7061–7064.
- Gotoh C *et al.* (2007). *Biochem Biophys Res Commun* **354**: 591–597.
- Hirasawa A *et al.* (2005). *Nat Med* **11**: 90–94.
- Itoh Y *et al.* (2003). *Nature* **422**: 173–176.
- Katsuma S *et al.* (2005). *J Biol Chem* **280**: 19507–19515.
- Kotarsky K *et al.* (2003). *Pharmacol Toxicol* **93**: 249–258.
- Liaw CW and Connolly DT. (2009) *DNA Cell Biol* **28**: 555–560.

- Le Poul E *et al.* (2003). *J Biol Chem* **278**: 25481–25489.
- Lee T *et al.* (2008). *Mol Pharmacol* **74**: 1559–1609.
- Nilsson NE *et al.* (2003). *Biochem Biophys Res Commun* **303**: 1047–1052.
- Sawzdargo M *et al.* (1997). *Biochem Biophys Res Commun* **239**: 543–547.
- Senga T *et al.* (2003). *Blood* **101**: 1185–1187.
- Smith NJ *et al.* (2009) *J Biol Chem* **284**: 17527–17439.
- Smith NJ *et al.* (2011) *Mol Pharmacol* **80**: 163–173.
- Stoddart LA *et al.* (2007). *Mol Pharmacol* **71**: 994–1005.
- Sum CS *et al.* (2007). *J Biol Chem* **282**: 29248–29255.
- Tan CP *et al.* (2008) *Diabetes* **57**: 2211–2219.
- Wang J *et al.* (2006). *J Biol Chem* **281**: 34457–34464.

# Frizzled

**Overview:** Receptors of the Class Frizzled (FZD, nomenclature as agreed by the NC-IUPHAR committee on Frizzled receptors, Schulte, 2010), which also includes Smoothened (Smo, ENSG00000128602, not considered here), are GPCR originally identified in *Drosophila* (Chan *et al.*, 1992), which are highly conserved across species. FZD are activated by WNTs, which are lipidated, cysteine-rich glycoprotein hormones with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription factor  $\beta$ -catenin (ENSG00000168036) or being  $\beta$ -catenin-independent (often referred to as canonical vs non-canonical WNT/FZD signaling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors (LRP 5, ENSG00000162337 and LRP6, ENSG00000070018), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of  $\beta$ -catenin.  $\beta$ -Catenin, in turn, modifies gene transcription in concert with TCF/LEF transcription factors.  $\beta$ -Catenin-independent FZD signaling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of pertussis toxin-sensitive heterotrimeric G proteins (Kilander *et al.* 2011), the elevation of intracellular calcium (Slusarski *et al.*, 1997), activation of cGMP-specific PDE6 (Ahumada *et al.*, 2002) and elevation of cAMP (Hansen *et al.*, 2009). FZD signalling can also occur through Dishevelled phosphoproteins (ENSF00000001536) to RAC-1 and JNK, as well as Rho and ROCK kinases. As with other GPCRs, members of the Frizzled family are functionally dependent on the  $\beta$ -arrestin scaffolding protein for internalization (Chen *et al.*, 2003),  $\beta$ -catenin-dependent (Bryja *et al.*, 2007) and -independent (Bryja *et al.*, 2008; Kim and Han, 2007) signalling. The pattern of cell signalling is complicated by the presence of additional ligands which can enhance (Norrin or R-spondin) or inhibit FZD function (secreted Frizzled-related proteins [sFRP], Wnt inhibitory factor [WIF], SOST or Dickkopf), as well as modulatory proteins with positive (Ryk, ENSG00000163785; ROR1, ENSG00000185483 and ROR2, ENSG00000169071, see Page S183) and negative (Kremen) regulatory features, which may also function as independent signalling proteins.

Nomenclature	Other names	Ensembl ID
FZD <sub>1</sub>	Frizzled-1	ENSG00000157240
FZD <sub>2</sub>	Frizzled-2	ENSG00000180340
FZD <sub>3</sub>	Frizzled-3	ENSG00000104290
FZD <sub>4</sub>	Frizzled-4, CD344	ENSG00000174804
FZD <sub>5</sub>	Frizzled-5	ENSG00000163251
FZD <sub>6</sub>	Frizzled-6	ENSG00000164930
FZD <sub>7</sub>	Frizzled-7	ENSG00000155760
FZD <sub>8</sub>	Frizzled-8	ENSG00000177283
FZD <sub>9</sub>	Frizzled-9, CD349	ENSG00000188763
FZD <sub>10</sub>	Frizzled-10, CD350	ENSG00000111432

There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships (see Kikuchi *et al.*, 2009).

## Ligands associated with FZD signalling

WNTs: WNT1 (ENSG00000125084), WNT2 (ENSG00000105989, also known as Int-1-related protein), WNT2B (ENSG00000134245, also known as WNT-13), WNT3 (ENSG00000108379), WNT3A (ENSG00000154342), WNT4 (ENSG00000162552), WNT5A (ENSG00000114251), WNT5B (ENSG00000111186), WNT6 (ENSG00000115596), WNT7A (ENSG00000154764), WNT7B (ENSG00000188064), WNT8A (ENSG00000061492), WNT8B (ENSG00000075290), WNT9A (ENSG00000143816, also known as WNT-14), WNT9B (ENSG00000158955, also known as WNT-15 or WNT-14b), WNT10A (ENSG00000135925), WNT10B (ENSG00000169884, also known as WNT-12), WNT11 (ENSG00000085741) and WNT16 (ENSG000000002745).

*Extracellular proteins that interact with FZDs:* Norrin (ENSG00000124479), R-spondin 1 (ENSG00000169218), R-spondin 2 (ENSG00000147655), R-spondin 3 (ENSG00000146374), R-spondin 4 (ENSG00000101282), sFRP 1 (ENSG00000104332), sFRP 2 (ENSG00000145423), sFRP 3 (ENSG00000162998), sFRP 4 (ENSG00000106483), sFRP 5 (ENSG00000120057),

*Extracellular proteins that interact with WNTs or LRPs:* Dickkopf 1 (ENSG00000104901), WIF 1 (ENSG00000156076), SOST (ENSG00000167941), Kremen 1 (ENSG00000183762) and Kremen 2 (ENSG00000131650)

**Abbreviations:** FZD, Frizzled; TCF/LEF, T cell factor/lymphoid enhancer binding factor

## Further Reading

- Angers S, Moon RT (2009). Proximal events in Wnt signal transduction. *Nat Rev Mol Cell Biol* 10: 468–477.
- Blankestijn WM, van de Schans VA, ter Horst P, Smits JF (2008). The Wnt/frizzled/GSK-3 $\beta$  pathway: a novel therapeutic target for cardiac hypertrophy. *Trends Pharmacol Sci* 29: 175–180.
- Chien AJ, Moon RT (2007). WNTs and WNT receptors as therapeutic tools and targets in human disease processes. *Front Biosci* 12: 448–457.
- Egger-Adam D, Katanaev VL (2008). Trimeric G protein-dependent signaling by Frizzled receptors in animal development. *Front Biosci* 13: 4740–4755.
- Jin T, Fantus IG, Sun J (2008). Wnt and beyond Wnt: multiple mechanisms control the transcriptional property of  $\beta$ -catenin. *Cell Signal* 20: 1697–1704.
- Kikuchi A, Yamamoto H, Kishida S (2007). Multiplicity of the interactions of Wnt proteins and their receptors. *Cell Signal* 19: 659–671.

- Kikuchi A, Yamamoto H, Sato A (2009). Selective activation mechanisms of Wnt signaling pathways. *Trends Cell Biol* **19**: 119–129.
- Luo J, Chen J, Deng ZL, Luo X, Song WX, Sharff KA *et al.* (2007). Wnt signaling and human diseases: what are the therapeutic implications? *Lab Invest* **87**: 97–103.
- Maiese K, Li F, Chong ZZ, Shang YC (2008). The Wnt signaling pathway: aging gracefully as a protectionist? *Pharmacol Ther* **118**: 58–81.
- Salinas PC, Zou Y (2008). Wnt signaling in neural circuit assembly. *Annu Rev Neurosci* **31**: 339–358.
- Schulte G (2010). International Union of Basic and Clinical Pharmacology. LXXX. The class frizzled receptors. *Pharmacol Rev* **62**: 632–667.
- Schulte G, Bryja V (2007). The frizzled family of unconventional G-protein-coupled receptors. *Trends Pharmacol Sci* **28**: 518–525.
- Schulte G, Schambony A, Bryja V (2010).  $\beta$ -Arrestins – scaffolds and signalling elements essential for WNT/Frizzled signalling pathways? *Br J Pharmacol* **159**: 1051–1058.
- Seifert JR, Mlodzik M (2007). Frizzled/PCP signalling: a conserved mechanism regulating cell polarity and directed motility. *Nat Rev Genet* **8**: 126–138.
- Speese SD, Budnik V (2007). Wnts: up-and-coming at the synapse. *Trends Neurosci* **30**: 268–275.
- Staal FJ, Luis TC, Tiemessen MM (2008). WNT signalling in the immune system: WNT is spreading its wings. *Nat Rev Immunol* **8**: 581–593.
- van de Schans VA, Smits JF, Blankesteyn WM (2008). The Wnt/frizzled pathway in cardiovascular development and disease: friend or foe? *Eur J Pharmacol* **585**: 338–345.

## References

- Ahumada A *et al.* (2002). *Science* **298**: 2006–2010.
- Bryja V *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 6690–6695.
- Bryja V *et al.* (2008). *EMBO Rep* **9**: 1244–1250.
- Chan SD *et al.* (1992). *J Biol Chem* **267**: 25202–25207.
- Chen W *et al.* (2003). *Science* **301**: 1394–1397.
- Hansen C *et al.* (2009). *J Biol Chem* **284**: 2513–2526.
- Kilander MBC *et al.* (2011). *Cell Signal* **23**:550–554.
- Kim GH, Han JK (2007). *EMBO J* **26**: 2513–2526.
- Slusarski DC *et al.* (1997). *Nature* **390**: 410–413.

# GABA<sub>B</sub>

**Overview:** Functional GABA<sub>B</sub> receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA<sub>B</sub> receptors, Bowery *et al.*, 2002; see also Pin *et al.*, 2007) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub> (Bowery *et al.*, 2002; Pin *et al.*, 2004; Emson, 2007; Pin *et al.*, 2007; Ulrich and Bettler, 2007). GABA<sub>B</sub> receptors are widespread in the CNS and regulate both pre- and post-synaptic activity. The GABA<sub>B1</sub> subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10-100-fold less than for the native receptor. The GABA<sub>B1</sub> subunit when expressed alone is not transported to the cell membrane and is non-functional. Co-expression of GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits allows transport of GABA<sub>B1</sub> to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca<sup>2+</sup> channels (Ca<sub>v</sub>2.1, Ca<sub>v</sub>2.2), or inwardly rectifying potassium channels (Kir3) (Bowery and Enna, 2000; Bowery *et al.*, 2002; Bettler *et al.*, 2004). The GABA<sub>B2</sub> subunit also determines the rate of internalisation of the dimeric GABA<sub>B</sub> receptor (Hannan *et al.*, 2011). The GABA<sub>B1</sub> subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA<sub>B2</sub> subunit mediates G-protein coupled signalling (Bowery *et al.*, 2002, Pin *et al.*, 2004). The two subunits interact by direct allosteric coupling (Monnier *et al.*, 2011) such that GABA<sub>B2</sub> increases the affinity of GABA<sub>B1</sub> for agonists and reciprocally GABA<sub>B1</sub> facilitates the coupling of GABA<sub>B2</sub> to G proteins (Pin *et al.*, 2004; Kubo and Tateyama, 2005). GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between  $\alpha$ -helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the GABA<sub>B1</sub> subunit but other domains of the proteins also contribute to their heteromerization (Bettler *et al.*, 2004; Pin *et al.*, 2004). Recent evidence indicates that higher order assemblies of GABA<sub>B</sub> receptor comprising dimers of heterodimers occur in recombinant expression systems and *in vivo* and that such complexes exhibit negative functional cooperativity between heterodimers (Pin *et al.*, 2009; Comps-Agrar *et al.*, 2011). Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA<sub>B2</sub> subunit to impart altered signalling kinetics and agonist potency to the receptor complex (Bartoi *et al.*, 2010; Schwenk *et al.*, 2010 and reviewed by Pinard *et al.*, 2010). Four isoforms of the human GABA<sub>B1</sub> subunit have been cloned. The predominant GABA<sub>B1(a)</sub> and GABA<sub>B1(b)</sub> isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA<sub>B1(a)</sub>-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA<sub>B1(b)</sub>-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition (Vigot *et al.*, 2006; Pérez-Garci *et al.*, 2006). Isoforms generated by alternative splicing are GABA<sub>B1(c)</sub> that differs in the ECD, and GABA<sub>B1(e)</sub>, which is a truncated protein that can heterodimerize with the GABA<sub>B2</sub> subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors (Bowery *et al.*, 2002). Additional GABA<sub>B1</sub> subunit isoforms have been described in rodents and humans (Lee *et al.*, 2010 and reviewed by Bettler *et al.*, 2004).

Nomenclature	GABA <sub>B</sub>
Ensembl ID	GABA <sub>B1</sub> ENSG00000237051; GABA <sub>B2</sub> ENSG00000136928
Principal transduction	G <sub>i/o</sub>
Selective agonists	3-APPA (CGP27492, 5 nM), 3-APMPA (CGP35024, 16 nM), (R)-(-)-baclofen (32 nM), CGP44532 (45 nM)
Selective antagonists	CGP62349 (2.0 nM), CGP55845A (6 nM), SCH50911 (3 $\mu$ M), 2-hydroxy-s(-)-saclofen (11 $\mu$ M), CGP35348 (27 $\mu$ M)
Probes (K <sub>D</sub> )	[ <sup>3</sup> H](R)-(-)-baclofen, [ <sup>3</sup> H]CGP54626 (1.5 nM; Bittiger <i>et al.</i> , 1992), [ <sup>3</sup> H]CGP62349 (0.9 nM, Keir <i>et al.</i> , 1999), [ <sup>125</sup> I]CGP64213 (1 nM, Galvez <i>et al.</i> , 2000), [ <sup>125</sup> I]CGP71872 (K <sub>i</sub> = 0.5 nM, Belley <i>et al.</i> , 1999)

Potencies of agonists and antagonists listed in the table, quantified as IC<sub>50</sub> values for the inhibition of [<sup>3</sup>H]CGP27492 binding to rat cerebral cortex membranes, are from Froestl and Mickel (1997), Bowery *et al.* (2002) and Froestl (2011). Radioligand K<sub>D</sub> values relate to binding to rat brain membranes. CGP71872 is a photoaffinity ligand for the GABA<sub>B1</sub> subunit (Belley *et al.*, 1999). CGP27492, CGP35024 and CGP44532 act as antagonists at human GABA<sub>A</sub>  $\rho$ 1 receptors, with potencies in the low micromolar range (Froestl, 2011). In addition to the ligands listed in the table, Ca<sup>2+</sup> binds to the VTM of the GABA<sub>B1</sub> subunit to act as a positive allosteric modulator of GABA (Galvez *et al.*, 2000). In cerebellar Purkinje neurones, the interaction of Ca<sup>2+</sup> with the GABA<sub>B</sub> receptor enhances the activity of mGlu<sub>1</sub> through functional cross-talk involving G-protein G $\beta\gamma$  subunits (Tabata *et al.*, 2004; Rives *et al.*, 2009). Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF177 and (+)-BFFF (Bettler *et al.*, 2004; Binet *et al.*, 2004; Adams and Lawrence, 2007; Froestl, 2011). The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA<sub>B2</sub> subunit (Pin *et al.*, 2004; Dupuis *et al.*, 2006). In the presence of CPG7930, or GS39783, CGP35348 and 2-hydroxy-saclofen behave as partial agonists (Froestl, 2011). Knock-out of the GABA<sub>B1</sub> subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA<sub>B1</sub><sup>-/-</sup> BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but not familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety (Enna and Bowery, 2004; Vacher *et al.*, 2006). A similar phenotype has been found for GABA<sub>B2</sub><sup>-/-</sup> BALB/c mice (Gassmann *et al.*, 2004).

**Abbreviations:** 3-APMPA (CGP35024), 3-amino-propyl-(P-methyl)-phosphinic acid; 3-APPA (CGP27492), 3-amino-propyl-phosphinic acid; (+)-BFFF, (-)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one; BHF177, (1R,2R,4S)-bicyclo[2.2.1]hept-2-yl]-2-methyl-5-[4-(trifluoromethyl)phenyl]-4-pyrimidinamine; CGP7930, 2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; CGP35348, p-(3-aminopropyl)-P-diethoxymethylphosphinic acid; CGP44532, 3-amino-2-hydroxypropylmethylphosphinic acid; CGP54626, [S-(R,R)]-[3-[[1-(3,4-dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl)phosphinic acid; CGP55845A, 3-[-1-(S)-(3,4-dichlorophenyl)-ethyl]amino-2(S)-hydroxypropyl-(P-benzyl)-phosphinic acid; CGP62349, [3-[1-R-[[3-(methoxyphenylmethyl)hydroxyphosphinyl]-2(S)-hydroxypropyl]amino]ethyl]-benzoic acid; CGP64213, [3-[-(R)-[[3-5N-[1-[2-[[3-iodo-4-hydroxyphenyl]ethyl]carboxamido]pentyl]hydroxyphosphinyl]-2(S)-hydroxy-propyl]amino]ethyl-benzoic acid; CGP71872, 3-(1-(R)-3-((5-(4-azido-2-hydroxy-5-iodobenzoylamino)pentyl)hydroxyphosphoryl)-2-(S)-hydroxypropylamino)ethyl)benzoic acid; GS39783, N,N'-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; SCH50911, (+)-(2S)-5,5-dimethyl-2-morpholineacetic acid; VTM, Venus flytrap module

### Further Reading

- Benke D (2010). Mechanisms of GABA<sub>B</sub> receptor exocytosis, endocytosis, and degradation. *Adv Pharmacol* **58**: 93–111.
- Bettler B, Kaupmann K, Mosbacher J, Gassmann M (2004). Molecular structure and physiological functions of GABA<sub>B</sub> receptors. *Physiol Rev* **84**: 835–367.
- Bowery, N.G. (2000). Pharmacology of GABA<sub>B</sub> receptors. In: Möhler H (ed.). *Handbook of Experimental Pharmacology, Pharmacology of GABA and Glycine Neurotransmission*, Vol. 150. Springer: Berlin, pp 311–328.
- Bowery NG (2006). GABA<sub>B</sub> receptor: a site of therapeutic benefit. *Curr Opin Pharmacol* **6**: 37–43.
- Bowery NG, Enna SJ (2000).  $\gamma$ -Aminobutyric acid<sub>B</sub> receptors: first of the functional metabotropic heterodimers. *J Pharmacol Exp Ther* **292**: 2–7.
- Bowery NG, Bettler B, Froestl W, Gallagher JP, Marshall F, Raiteri M *et al.* (2002). International Union of Pharmacology XXXIII. Mammalian  $\gamma$ -aminobutyric acid<sub>B</sub> receptors: structure and function. *Pharmacol Rev* **54**: 247–264.
- Emson PC (2007). GABA<sub>B</sub> receptors: structure and function. *Prog Brain Res* **160**: 43–57.
- Enna SJ, Bowery NG (2004). GABA<sub>B</sub> receptor alterations as indicators of physiological and pharmacological function. *Biochem Pharmacol* **68**: 1541–1548.
- Froestl W (2011). An historical perspective on GABAergic drugs. *Future Med Chem* **3**: 163–175.
- Froestl W, Mickel SW (1997). Chemistry of GABA<sub>B</sub> modulators. In: Enna SJ, Bowery NG (eds). *The GABA Receptors*. Humana Press: Totowa, pp. 271–296.
- Kornau HC (2006). GABA<sub>B</sub> receptors and synaptic modulation. *Cell Tissue Res* **326**: 517–533.
- Kubo Y, Tateyama M (2005). Towards a view of functioning dimeric metabotropic receptors. *Curr Opin Neurobiol* **15**: 289–295.
- Lehmann A, Jensen JM, Boeckstaens GE (2010). GABA<sub>B</sub> receptor agonism as a novel therapeutic modality in the treatment of gastroesophageal reflux disease. *Adv Pharmacol* **58**: 287–313.
- Marshall FH, Foord SM (2010). Heterodimerization of the GABA<sub>B</sub> receptor-implications for GPCR signaling and drug discovery. *Adv Pharmacol* **58**: 63–91.
- Padgett CL, Slesinger PA (2010). GABA<sub>B</sub> receptor coupling to G-proteins and ion channels. *Adv Pharmacol* **58**: 123–147.
- Pin J-P, Kniazeff J, Binet V, Liu J, Maurel D, Galvez T *et al.* (2004). Activation mechanism of the heterodimeric GABA<sub>B</sub> receptor. *Biochem Pharmacol* **68**: 1565–1572.
- Pin J-P, Comps-Agrar L, Maurel D, Monnier C, Rives ML, Trinquet E *et al.* (2009). G-protein-coupled receptor oligomers: two or more for what? Lessons from mGlu and GABA<sub>B</sub> receptors. *J Physiol* **587**: 5337–5544.
- Pin J-P, Neubig R, Bouvier M, Devi L, Filizola M, Javitch JA *et al.* (2007). International Union of Basic and Clinical Pharmacology. LXVII. Recommendations for the recognition and nomenclature of G protein-coupled receptor heteromultimers. *Pharmacol Rev* **59**: 5–13.
- Pinard A, Seddik R, Bettler B. (2010). GABA<sub>B</sub> receptors: physiological functions and mechanisms of diversity. *Adv Pharmacol* **58**: 231–255.
- Rondard P, Goudet C, Kniazeff J, Pin J-P, Prézeau L (2011). The complexity of their activation mechanism opens new possibilities for the modulation of mGlu and GABA<sub>B</sub> class C G protein-coupled receptors. *Neuropharmacology* **60**: 82–92.
- Ulrich D, Bettler B (2007). GABA<sub>B</sub> receptors: synaptic functions and mechanisms of diversity. *Curr Opin Neurobiol* **17**: 298–303.

### References

- Adams CL, Lawrence AJ (2007). *CNS Drug Rev* **13**: 308–316.
- Bartoi T *et al.* (2010). *J Biol Chem* **285**: 20625–20633.
- Belley M *et al.* (1999). *Bioorg Med Chem* **7**: 2697–2704.
- Binet V *et al.* (2004). *J Biol Chem* **279**: 29085–29091.
- Bittiger H *et al.* (1992). *Pharmacol Commun* **2**: 23.
- Comps-Agrar L *et al.* (2011). *EMBO J* (doi:10.1038/emboj.2011.143).
- Dupuis DS *et al.* (2006). *Mol Pharmacol* **70**: 2027–2036.
- Galvez T *et al.* (2000). *Mol Pharmacol* **57**: 419–426.
- Gassmann M *et al.* (2004). *J Neurosci* **42**: 6086–6097.
- Keir MJ *et al.* (1999). *Brain Res Mol Brain Res* **71**: 279–289.
- Lee C *et al.* (2010). *PLoS ONE* **5**: e14044.
- Monnier C *et al.* (2011). *EMBO J* **30**: 32–42.
- Pérez-Garci E *et al.* (2006). *Neuron* **50**: 603–616.
- Rives ML *et al.* (2009). *EMBO J* **28**: 2195–2208.
- Schwenk J *et al.* (2010). *Nature* **465**: 231–235.
- Tabata T *et al.* (2004). *Proc Natl Acad Sci USA* **101**: 16952–16957.
- Vacher CM *et al.* (2006). *J Neurochem* **97**: 979–991.
- Vigot R *et al.* (2006). *Neuron* **50**: 589–601.



# Galanin

**Overview:** Galanin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous peptides galanin (ENSG0000069482) and galanin-like peptide (GALP, ENSG0000197487). Human galanin is a 30 amino-acid non-amidated peptide (Evans and Shine, 1991); in other species, it is 29 amino acids long and C-terminally amidated. Amino acids 1–14 of galanin are highly conserved in mammals, birds, reptiles, amphibia and fish. Shorter peptide species (e.g. human galanin-1–19, (Bersani *et al.*, 1991a) and porcine galanin-5–29 (Sillard *et al.*, 1992)) and N-terminally extended forms (e.g. N-terminally seven and nine residue elongated forms of porcine galanin (Bersani *et al.*, 1991b; Sillard *et al.*, 1992)) have been reported.

Nomenclature	GAL <sub>1</sub>	GAL <sub>2</sub>	GAL <sub>3</sub>
Other names	Galanin-1 receptor, GALR1	Galanin-2 receptor, GALR2	Galanin-3 receptor, GALR3
Ensembl ID	ENSG00000166573	ENSG00000182687	ENSG00000128310
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub> , G <sub>q/11</sub>	G <sub>i/o</sub>
Rank order of potency	Galanin>GALP (Ohtaki <i>et al.</i> , 1999)	GALP≥galanin (Ohtaki <i>et al.</i> , 1999)	GALP>galanin (Lang <i>et al.</i> , 2005)
Selective agonists	–	Galanin-(2–29) (Fathi <i>et al.</i> , 1997; Wang <i>et al.</i> , 1997), D-Trp <sup>2</sup> -galanin-(1–29) (Smith <i>et al.</i> , 1997)	–
Selective antagonists	2,3-Dihydro-dithiin-1,4-dithiin-1,1,4,4-tetroxide (Scott <i>et al.</i> , 2000)	M871 (7.9, Sollenberg <i>et al.</i> , 2006)	–

Galanin-(1–11) is a high-affinity agonist at GAL<sub>1</sub>/GAL<sub>2</sub> (pK<sub>i</sub> 9) and galanin-(2–11) is selective for GAL<sub>2</sub> and GAL<sub>3</sub> compared to GAL<sub>1</sub> (Lu *et al.*, 2005). [<sup>125</sup>I]-[Tyr<sup>26</sup>]galanin binds to all three subtypes with K<sub>d</sub> values ranging from 0.05 to 1 nM (Skofitsch *et al.*, 1986; Smith *et al.*, 1997;1998; Wang *et al.*, 1997; Fitzgerald *et al.*, 1998). Porcine galanin-(3–29) does not bind to cloned GAL<sub>1</sub>, GAL<sub>2</sub> or GAL<sub>3</sub> receptors, but a receptor that is functionally activated by porcine galanin-(3–29) has been reported in pituitary and gastric smooth muscle cells (Wynick *et al.*, 1993; Gu *et al.*, 1995). Additional galanin receptor subtypes are also suggested from studies with chimeric peptides (e.g. M15, M35 and M40), which act as antagonists in functional assays in the cardiovascular system (Ulman *et al.*, 1993), spinal cord (Wiesenfeld-Hallin *et al.*, 1992), locus coeruleus, hippocampus (Bartfai *et al.*, 1991) and hypothalamus (Leibowitz and Kim, 1992; Bartfai *et al.*, 1993), but exhibit agonist activity at some peripheral sites (Bartfai *et al.*, 1993; Gu *et al.*, 1995). The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL<sub>1</sub> receptors expressed endogenously in Bowes human melanoma cells (Ohtaki *et al.*, 1999), and at heterologously expressed recombinant GAL<sub>1</sub>, GAL<sub>2</sub> and GAL<sub>3</sub> receptors (Smith *et al.*, 1997; Fitzgerald *et al.*, 1998; Smith *et al.*, 1998).

**Abbreviations:** C7, galanin-(1–13)-spantide; M15, galanin-(1–13)-substance P-5–11 amide, also known as galantide; M32, galanin-(1–13)-neuropeptide Y amide-(25–36) amide; M35, galanin-(1–13)-bradykinin-(2–9) amide; M40, galanin-(1–13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-Leu-Ala amide; M871, galanin-(2–13)-Glu-His-(Pro)<sub>3</sub>-(Ala-Leu)<sub>2</sub>-Ala-amide

## Further Reading

- Bauer JW, Lang R, Jakab M, Kofler B (2008). Galanin family of peptides in skin function. *Cell Mol Life Sci* 65: 1820–1825.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288.
- Hökfelt T (ed.) (2010) Galanin. In: *Experientia Supplementum*, Vol. 102. Springer AG: Basel.
- Lang R, Gundlach AL, Kofler B (2007). The galanin peptide family: receptor pharmacology, pleiotropic biological actions, and implications in health and disease. *Pharmacol Ther* 115: 177–207.
- Lang R, Kofler B (2011) The galanin peptide family in inflammation. *Neuropeptides* 45: 1–8.
- Lawrence C, Fraley GS (2011). Galanin-like peptide (GALP) is a hypothalamic regulator of energy homeostasis and reproduction. *Front Neuroendocrinol* 32: 1–9.
- Man PS, Lawrence CB (2008). Galanin-like peptide: a role in the homeostatic regulation of energy balance? *Neuropharmacology* 55: 1–7.
- Mitsukawa K, Lu X, Bartfai T (2008). Galanin, galanin receptors and drug targets. *Cell Mol Life Sci* 65: 1796–1805.
- Moreno E, Vaz SH, Cai NS, Ferrada C, Quiroz C, Barodia SK, Kabbani N, Canela EI, McCormick PJ, Lluís C, Franco R, Ribeiro J, Sebastião AM, Ferré S (2011) Dopamine-galanin receptor heteromers modulate cholinergic neurotransmission in the rat ventral hippocampus. *J Neurosci* 31: 7412–7423.
- Ogren SO, Kuteeva E, Elvander-Tottie E, Hökfelt T (2010). Neuropeptides in learning and memory processes with focus on galanin. *Eur J Pharmacol* 626: 9–17.
- Wraith DC, Pope R, Butzkueven H, Holder H, Vanderplank P, Lowrey P, Day MJ, Gundlach AL, Kilpatrick TJ, Scolding N, Wynick D (2009) A role for galanin in human and experimental inflammatory demyelination. *Proc Natl Acad Sci USA* 106: 15466–15471.

## References

- Bartfai T *et al.* (1991). *Proc Natl Acad Sci U S A* 88: 10961–10965.
- Bartfai T *et al.* (1993). *Proc Natl Acad Sci U S A* 90: 11287–11291.
- Bersani M *et al.* (1991a). *FEBS Lett* 283: 189–194.
- Bersani M *et al.* (1991b). *Endocrinology* 129: 2693–2698.
- Evans HF, Shine J (1991). *Endocrinol* 129: 1682–1684.
- Fathi Z *et al.* (1997). *Mol Brain Res* 51: 49–59.
- Fitzgerald LW *et al.* (1998). *J Pharmacol Exp Ther* 287: 448–456.
- Gu ZF *et al.* (1995). *J Pharmacol Exp Ther* 272: 371–378.
- Lang R *et al.* (2005). *Neuropeptides* 39: 179–184.
- Leibowitz SF, Kim T (1992). *Brain Res* 599: 148–152.
- Lu X *et al.* (2005). *Neuropeptides* 39: 165–167.

- Ohtaki T *et al.* (1999). *J Biol Chem* **274**: 37041–37045.
- Scott MK *et al.* (2000). *Bioorg Med Chem* **8**: 1383–1391.
- Sillard R *et al.* (1992). *Peptides* **13**: 1055–1060.
- Skofitsch G *et al.* (1986). *Peptides* **7**: 1029–1042.
- Smith KE *et al.* (1997). *J Biol Chem* **272**: 24612–24616.
- Smith KE *et al.* (1998). *J Biol Chem* **273**: 23321–23326.
- Sollenberg UE *et al.* (2006). *Int J Pept Res Ther* **12**: 115–119.
- Ulman LG *et al.* (1993). *J Physiol* **464**: 491–499.
- Wang S *et al.* (1997). *Mol Pharmacol* **52**: 337–343.
- Wiesenfeld-Hallin Z *et al.* (1992). *Proc Natl Acad Sci U S A* **89**: 3334–3337.
- Wynick D *et al.* (1993). *Proc Natl Acad Sci U S A* **90**: 4231–4235.

# Ghrelin

**Overview:** Ghrelin receptors (see Davenport *et al.*, 2005) are activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (ENSG00000157017). The human gene encoding the precursor peptide has 83% sequence homology to rat prepro-ghrelin, although the mature peptides from rat and human differ by only two amino acids (Matsumoto *et al.*, 2001). Alternative splicing results in the formation of a second peptide, des-Gln<sup>14</sup>-ghrelin with equipotent biological activity (Hosoda *et al.*, 2000). A unique post-translational modification (octanoylation of Ser<sup>3</sup>, catalysed by ghrelin O-acyltransferase [MBOAT4, ENSG00000177669], Yang *et al.*, 2008) occurs in both peptides, essential for full activity in binding to the ghrelin receptors in the hypothalamus and pituitary; and the release of growth hormone from the pituitary (Kojima *et al.*, 1999). Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding (Bednarek *et al.*, 2000) and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin function (Holst *et al.*, 2009). In cell systems, the ghrelin receptor is constitutively active (Holst and Schwartz, 2004), but this is abolished by a naturally occurring mutation (A204E) that results in decreased cell surface receptor expression and is associated with familial short stature (Pantel *et al.*, 2006).

Nomenclature	Ghrelin
Other names	GHS-R1a (Growth hormone secretagogue receptor type 1), growth hormone-releasing peptide receptor
Ensembl ID	ENSG00000121853
Principal transduction	G <sub>q/11</sub>
Rank order of potency	Ghrelin=des-Gln-ghrelin (Matsumoto <i>et al.</i> , 2001; Bedendi <i>et al.</i> , 2003)
Selective antagonists	YIL781 (K <sub>8</sub> 11 nM) (Esler <i>et al.</i> , 2007)
Probes	[ <sup>125</sup> I-His <sup>9</sup> ]-ghrelin (0.4 nM, Katugampola <i>et al.</i> , 2001), [ <sup>125</sup> I-Tyr <sup>4</sup> ]-ghrelin (0.5 nM, Bedendi <i>et al.</i> , 2003), [ <sup>125</sup> I]-Tyr <sup>4</sup> -des-octanoyl (0.7 nM, Bedendi <i>et al.</i> , 2003)

Des-octanoyl ghrelin has been shown to bind (as [<sup>125</sup>I]-Tyr<sup>4</sup>-des-octanoyl ghrelin) and have effects in the cardiovascular system (Bedendi *et al.*, 2003), which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified ([D-Arg<sup>1</sup>, D-Phe<sup>5</sup>, D-Trp<sup>7,9</sup>, Leu<sup>11</sup>]-substance P; pD<sub>2</sub> 8.3; Holst *et al.*, 2003). TZP101, described as a ghrelin receptor agonist (pK<sub>i</sub> 7.8 and pD<sub>2</sub> 7.5 at human recombinant ghrelin receptors), has been shown to stimulate ghrelin receptor mediated food intake and gastric emptying but not elicit release of growth hormone, or modify ghrelin stimulated growth hormone release, thus pharmacologically discriminating the orexigenic and gastrointestinal actions of ghrelin from the release of growth hormone (Fraser *et al.*, 2008).

**Abbreviations:** TZP101, (4R,7S,10R,13R)-7-cyclopropyl-13-(4-fluorobenzyl)-3-oxa-6,9,12,15-tetraaza-4,9,10-trimethyl-4,5,6,7,10,12,13,15,16,17,18-undecahydro-1,2-benzocyclooctadecene-8,11,14-trione; YIL781, 6-(4-fluorophenoxy)-3-([(3S)-1-isopropylpiperidin-3-yl]methyl)-2-methylquinazolin-4(3H)-one

## Further Reading

- Andrews ZB (2011). The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci* **34**: 31–40.
- Angelidis G, Valotassiou V, Georgoulis P (2010). Current and potential roles of ghrelin in clinical practice. *J Endocrinol Invest* **33**: 823–838.
- Briggs DI, Andrews ZB (2011). Metabolic status regulates ghrelin function on energy homeostasis. *Neuroendocrinology* **93**: 48–57.
- Cao JM, Ong H, Chen C (2006). Effects of ghrelin and synthetic GH secretagogues on the cardiovascular system. *Trends Endocrinol Metab* **17**: 13–18.
- Cummings DE (2006). Ghrelin and the short- and long-term regulation of appetite and body weight. *Physiol Behav* **89**: 71–84.
- Davenport AP, Bonner TI, Foord SM, Harmar AJ, Neubig RR, Pin JP *et al.* (2005). International Union of Pharmacology. LVI. Ghrelin receptor nomenclature, distribution, and function. *Pharmacol Rev* **57**: 541–546.
- De Smet B, Mitselos A, Depoortere I (2009). Motilin and ghrelin as prokinetic drug targets. *Pharmacol Ther* **123**: 207–223.
- De Vriese C, Perret J, Delporte C (2010). Focus on the short- and long-term effects of ghrelin on energy homeostasis. *Nutrition* **26**: 579–584.
- Dezaki K, Sone H, Yada T (2008). Ghrelin is a physiological regulator of insulin release in pancreatic islets and glucose homeostasis. *Pharmacol Ther* **118**: 239–249.
- Garcia EA, Korbonits M (2006). Ghrelin and cardiovascular health. *Curr Opin Pharmacol* **6**: 142–147.
- Granata R, Baragli A, Settanni F, Scarlatti F, Ghigo E (2010). Unraveling the role of the ghrelin gene peptides in the endocrine pancreas. *J Mol Endocrinol* **45**: 107–118.
- Hosoda H, Kojima M, Kangawa K (2006). Biological, physiological, and pharmacological aspects of ghrelin. *J Pharmacol Sci* **100**: 398–410.
- Kojima M, Kangawa K (2010). Ghrelin: more than endogenous growth hormone secretagogue. *Ann N Y Acad Sci* **1200**: 140–148.
- Leite-Moreira AF, Soares JB (2007). Physiological, pathological and potential therapeutic roles of ghrelin. *Drug Discov Today* **12**: 276–288.
- Maguire JJ, Davenport AP (2005). Regulation of vascular reactivity by established and emerging GPCRs. *Trends Pharmacol Sci* **26**: 448–454.
- Nikolopoulos D, Theocharis S, Kouraklis G (2010). Ghrelin: a potential therapeutic target for cancer. *Regul Pept* **163**: 7–17.
- Olszewski PK, Schioth HB, Levine AS (2008). Ghrelin in the CNS: from hunger to a rewarding and memorable meal? *Brain Res Rev* **58**: 160–170.
- Peeters TL (2006). Potential of ghrelin as a therapeutic approach for gastrointestinal motility disorders. *Curr Opin Pharmacol* **6**: 553–558.
- Romero A, Kirchner H, Heppner K, Pfluger PT, Tschop MH, Nogueiras R (2010). GOAT: the master switch for the ghrelin system? *Eur J Endocrinol* **163**: 1–8.
- Sanger GJ (2008). Motilin, ghrelin and related neuropeptides as targets for the treatment of GI diseases. *Drug Discov Today* **13**: 234–239.
- Seim I, Josh P, Cunningham P, Herington A, Chopin L (2011). Ghrelin axis genes, peptides and receptors: Recent findings and future challenges. *Mol Cell Endocrinol* **340**: 3–9.

## References

- Bedendi I *et al.* (2003). *Eur J Pharmacol* **476**: 87–95.
- Bednarek MA *et al.* (2000). *J Med Chem* **43**: 4370–4376.
- Esler WP *et al.* (2007). *Endocrinology* **148**: 5175–5185.
- Fraser GL *et al.* (2008). *Endocrinology* **149**: 6280–6288.
- Holst B, Schwartz TW (2004). *Trends Pharmacol Sci* **25**: 113–117.
- Holst B *et al.* (2009). *Mol Pharmacol* **75**: 44–59.
- Pantel J *et al.* (2006). *J Clin Invest* **116**: 760–768.
- Holst B *et al.* (2003). *Mol Endocrinol* **17**: 2201–2210.
- Hosoda H *et al.* (2000). *J Biol Chem* **275**: 21995–22000.
- Katugampola SD *et al.* (2001). *Br J Pharmacol* **134**: 143–149.
- Kojima M *et al.* (1999). *Nature* **402**: 656–660.
- Matsumoto M *et al.* (2001). *Biochem Biophys Res Commun* **287**: 142–146.
- Yang J *et al.* (2008). *Cell* **132**: 387–396.

# Glucagon, glucagon-like peptide and secretin

**Overview:** The glucagon family of receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on the Glucagon receptor family, see Mayo *et al.*, 2003) are activated by the endogenous peptide (27–44 aa) hormones glucagon, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide or GIP, ENSG00000159224), growth hormone-releasing hormone (GHRH, ENSG00000118702) and secretin (ENSG0000070031). One common precursor (ENSG00000115263) generates glucagon, GLP-1 and GLP-2 peptides (Irwin, 2001).

Nomenclature	Glucagon	GLP-1	GLP-2
Ensembl ID	ENSG00000215644	ENSG00000112164	ENSG00000065325
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Selective agonists	Glucagon	GLP-1-(7-37) (Dillon <i>et al.</i> , 1993); GLP-1-(7-36)amide (Thorens <i>et al.</i> , 1993), exendin-3 (Raufman <i>et al.</i> , 1991), exendin-4 (Thorens <i>et al.</i> , 1993)	GLP-2
Selective antagonists	L168049 (Cascieri <i>et al.</i> , 1999), des-His <sup>1</sup> -[Glu <sup>9</sup> ]glucagon amide (Post <i>et al.</i> , 1993), BAY27-9955 (Petersen and Sullivan, 2001), xNNC92-1687 (Madsen <i>et al.</i> , 1998)	Exendin-(9-39) (Thorens <i>et al.</i> , 1993); T0632 (Tibaduiza <i>et al.</i> , 2001)	–
Probes	[ <sup>125</sup> I]-glucagon	[ <sup>125</sup> I]-GLP-1-(7-36) amide, [ <sup>125</sup> I]-exendin, [ <sup>125</sup> I]-exendin-(9-39), [ <sup>125</sup> I]-GLP-1-(7-37)	–

Nomenclature	GIP	GHRH	Secretin
Ensembl ID	ENSG00000010310	ENSG00000106128	ENSG00000080293
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Selective agonists	GIP	BIM28011 (Coy <i>et al.</i> , 1996)	Secretin
Selective antagonists	[Pro <sup>3</sup> ]GIP	JV-1-36 (Schally and Varga, 1999), JV-1-38 (Schally and Varga, 1999)	[(CH <sub>2</sub> NH) <sup>4,5</sup> ]secretin (Kim <i>et al.</i> , 1993)
Probes	[ <sup>125</sup> I]-GIP	[ <sup>125</sup> I]-GHRH	[ <sup>125</sup> I]-(Tyr <sup>10</sup> )secretin

The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems (Christopoulos *et al.*, 2003), although the physiological significance of this has yet to be established.

**Abbreviations:** BAY27-9955, (+)-3,5-diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl; BIM28011, [D-Ala<sup>2</sup>,Ala<sup>8,9,15,27</sup>,D-Arg<sup>29</sup>]hGHRH-(1–29)NH<sub>2</sub>; JV-1-36, [PhAc-Tyr<sup>1</sup>,D-Arg<sup>2</sup>,Phe(4-Cl)<sup>6</sup>,Arg<sup>9</sup>,Abu<sup>15</sup>,Nle<sup>27</sup>,D-Arg<sup>28</sup>,Har<sup>29</sup>]hGHRH(1–29)NH<sub>2</sub>; JV-1-38, [PhAc-Tyr<sup>1</sup>,D-Arg<sup>2</sup>,Phe(4-Cl)<sup>6</sup>,Har<sup>9</sup>,Tyr(Me)<sup>10</sup>,Abu<sup>15</sup>,Nle<sup>27</sup>,D-Arg<sup>28</sup>,Har<sup>29</sup>]hGHRH(1–29)NH<sub>2</sub>; L168049, 2-(4-pyridyl)-5-(4-chlorophenyl)-3-(5-bromo-2-propyloxyphenyl)pyrrole; NNC92-1687, 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanone; T0632, sodium (S)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[[3-isoquinolinyl]-carbonyl]amino-6-methoxy-2-oxo-1H-indole)propanoate

## Further Reading

- Authier F, Desbuquois B (2008). Glucagon receptors. *Cell Mol Life Sci* 65: 1880–1899.
- Burcelin R, Serino M, Cabou C (2009). A role for the gut-to-brain GLP-1-dependent axis in the control of metabolism. *Curr Opin Pharmacol* 9: 744–752.
- De Block CE, Van Gaal LF (2009). GLP-1 receptor agonists for type 2 diabetes. *Lancet* 374: 4–6.
- Doyle ME, Egan JM (2007). Mechanisms of action of glucagon-like peptide 1 in the pancreas. *Pharmacol Ther* 113: 546–593.
- Dube PE, Brubaker PL (2007). Frontiers in glucagon-like peptide-2: multiple actions, multiple mediators. *Am J Physiol Endocrinol Metab* 293: E460–E465.
- Frezza EE, Wachtel MS, Chiriva-Internati M (2007). The multiple faces of glucagon-like peptide-1 – obesity, appetite, and stress: what is next? A review. *Dig Dis Sci* 52: 643–649.
- Hayes MR, De Jonghe BC, Kanoski SE (2010). Role of the glucagon-like-peptide-1 receptor in the control of energy balance. *Physiol Behav* 100: 503–510.
- Holst JJ (2007). The physiology of glucagon-like peptide 1. *Physiol Rev* 87: 1409–1439.
- Holst JJ, Deacon CF, Vilsboll T, Krarup T, Madsbad S (2008). Glucagon-like peptide-1, glucose homeostasis and diabetes. *Trends Mol Med* 14: 161–168.
- Markovic D, Grammatopoulos DK (2009). Focus on the splicing of secretin GPCRs transmembrane-domain 7. *Trends Biochem Sci* 34: 443–452.
- Mayo KE, Miller LJ, Bataille D, Dalle S, Goke B, Thorens B *et al.* (2003). International Union of Pharmacology. XXXV. The glucagon receptor family. *Pharmacol Rev* 55: 167–194.
- Miller LJ, Dong M, Harikumar KG (2011). Ligand binding and activation of the secretin receptor, a prototypic family B G protein-coupled receptor. *Br J Pharmacol* in press.
- Nauck MA (2009). Unraveling the science of incretin biology. *Am J Med* 122: S3–S10.
- Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ (2011). Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia* 54: 10–18.

- Schally AV, Varga JL, Engel JB (2008). Antagonists of growth-hormone-releasing hormone: an emerging new therapy for cancer. *Nat Clin Pract Endocrinol Metab* **4**: 33–43.
- St-Pierre DH, Broglio F (2010). Secretin: Should we revisit its metabolic outcomes? *J Endocrinol Invest* **33**: 266–275.
- Verspohl EJ (2009). Novel therapeutics for type 2 diabetes: incretin hormone mimetics (glucagon-like peptide-1 receptor agonists) and dipeptidyl peptidase-4 inhibitors. *Pharmacol Ther* **124**: 113–138.
- Vrang N, Larsen PJ (2010). Preproglucagon derived peptides GLP-1, GLP-2 and oxyntomodulin in the CNS: role of peripherally secreted and centrally produced peptides. *Prog Neurobiol* **92**: 442–462.
- Williams DL (2009). Minireview: finding the sweet spot: peripheral versus central glucagon-like peptide 1 action in feeding and glucose homeostasis. *Endocrinology* **150**: 2997–3001.

## References

- Cascieri MA *et al.* (1999). *J Biol Chem* **274**: 8694–8697.
- Christopoulos A *et al.* (2003). *J Biol Chem* **278**: 3293–3297.
- Coy DH *et al.* (1996). *Ann N Y Acad Sci* **805**: 149–158.
- Dillon JS *et al.* (1993). *Endocrinology* **133**: 1907–1910.
- Irwin DM (2001). *Regul Pept* **98**: 1–12.
- Kim CD *et al.* (1993). *Am J Physiol Gastrointest Liver Physiol* **265**: G805–G810.
- Madsen P *et al.* (1998). *J Med Chem* **41**: 5150–5157.
- Petersen KF, Sullivan JT (2001). *Diabetologia* **44**: 2018–2024.
- Post SR *et al.* (1993). *Proc Natl Acad Sci U S A* **90**: 1662–1666.
- Raufman JP *et al.* (1991). *J Biol Chem* **266**: 2897–2902.
- Schally AV, Varga JL (1999). *Trends Endocrinol Metab* **10**: 383–391.
- Thorens B *et al.* (1993). *Diabetes* **42**: 1678–1682.
- Tibaduiza EC *et al.* (2001). *J Biol Chem* **276**: 37787–37793.

# Glutamate, metabotropic

**Overview:** Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors, Schoepp *et al.*, 2000) are activated by the endogenous ligands L-glutamate, L-aspartate, L-serine-O-phosphate (LSOP), N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are 1S,3R-ACPD and L-CCG-I, which show limited selectivity for Group II receptors. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu<sub>2</sub> and mGlu<sub>3</sub> at low nanomolar concentrations, mGlu<sub>8</sub> at high nanomolar concentrations, and mGlu<sub>1</sub>, mGlu<sub>4</sub>, mGlu<sub>5</sub> and mGlu<sub>7</sub> in the micromolar range (Kingston *et al.*, 1998). Three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G-protein effector coupling: Group I (mGlu<sub>1</sub> and mGlu<sub>3</sub>); Group II (mGlu<sub>2</sub> and mGlu<sub>3</sub>) and Group III (mGlu<sub>4</sub>, mGlu<sub>6</sub>, mGlu<sub>7</sub> and mGlu<sub>8</sub>) (see Further Reading). Group I mGlu receptors may be activated by DHPG and 3HPG (Brabet *et al.*, 1995), and antagonized by (S)-hexylhomobiotenic acid (Madsen *et al.*, 2005). Group II mGlu receptors may be activated by LY389795 (Monn *et al.*, 1999), LY379268 (Monn *et al.*, 1999), LY354740 (Schoepp *et al.*, 1997; Wu *et al.*, 1998), DCG-IV and 2R,4R-APDC (Schoepp *et al.*, 1996), and antagonised by EGLU (4.3, Jane *et al.*, 1996) and LY307452 (Escribano *et al.*, 1998; Wermuth *et al.*, 1996). Group III mGlu receptors may be activated by (RS)PPG (Gasparini *et al.*, 1999a).

In addition to orthosteric ligands that interact with the glutamate recognition site directly, allosteric modulators have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Nomenclature	mGlu <sub>1</sub>	mGlu <sub>2</sub>	mGlu <sub>3</sub>	mGlu <sub>4</sub>
Other names	mGluR <sub>1</sub>	mGluR <sub>2</sub>	mGluR <sub>3</sub>	mGluR <sub>4</sub>
Ensembl ID	ENSG00000152822	ENSG00000164082	ENSG00000198822	ENSG00000124493
Principal transduction	G <sub>q/11</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Selective agonists	–	–	NAAG (Wroblewska <i>et al.</i> , 1997)	L-AP4, LSOP (Wu <i>et al.</i> , 1998)
Selective positive allosteric modulators	Ro01-6128, Ro67-4853, Ro67-7476 (Knoflach <i>et al.</i> , 2001)	LY487379 (Johnson <i>et al.</i> , 2003), CBiPES (Johnson <i>et al.</i> , 2005), BINA (Bonnefous <i>et al.</i> , 2005b)	–	(-)-PHCCC (Maj <i>et al.</i> , 2003), SIB1893, MPEP (Mathiesen <i>et al.</i> , 2003), VU0155041 (Niswender <i>et al.</i> , 2008), VU0361737 (Engers <i>et al.</i> , 2009)
Selective competitive antagonists	3-MATIDA (Moroni <i>et al.</i> , 2002), AIDA (Moroni <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999), LY367385 (Clark <i>et al.</i> , 1997), (S)-TBPG (Costantino <i>et al.</i> , 2001)	PCCG-4 (Pellicciari <i>et al.</i> , 1996)	–	MAP4
Selective negative allosteric modulators	CPCCOEt (Litschig <i>et al.</i> , 1999), BAY36-7620 (Carroll <i>et al.</i> , 2001), LY456236 (Li <i>et al.</i> , 2002), 3,5-DMPPP (Micheli <i>et al.</i> , 2003), EM-TBPC (Malherbe <i>et al.</i> , 2003), JNJ16259685 (Lavreysen <i>et al.</i> , 2004), A841720 (8.0, Zheng <i>et al.</i> , 2005)	Ro64-5229 (Kolczewski <i>et al.</i> , 1999)	–	–

The activity of NAAG as an agonist at mGlu<sub>3</sub> receptors was questioned on the basis of contamination with glutamate (Chopra *et al.*, 2009; Fricker *et al.*, 2009), but this has been refuted (Neale, 2011).

Nomenclature	mGlu <sub>5</sub>	mGlu <sub>6</sub>	mGlu <sub>7</sub>	mGlu <sub>8</sub>
Other names	mGluR <sub>5</sub>	mGluR <sub>6</sub>	mGluR <sub>7</sub>	mGluR <sub>8</sub>
Ensembl ID	ENSG00000168959	ENSG00000113262	ENSG00000196277	ENSG00000179603
Principal transduction	G <sub>q/11</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Selective agonists	CHPG (Doherty <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999)	Homo-AMPA (Bräuner-Osborne <i>et al.</i> , 1996), 1-benzyl-APDC (Tuckmantel <i>et al.</i> , 1997)	LSOP (Wu <i>et al.</i> , 1998), L-AP4	LSOP (Wu <i>et al.</i> , 1998), L-AP4, (S)-3,4-DCPG (Thomas <i>et al.</i> , 2001)

Nomenclature	mGlu <sub>5</sub>	mGlu <sub>6</sub>	mGlu <sub>7</sub>	mGlu <sub>8</sub>
Selective positive allosteric modulators	DFB (O'Brien <i>et al.</i> , 2003), CPPHA (O'Brien <i>et al.</i> , 2004), CDPPB (Kinney <i>et al.</i> , 2005), VU1545 (de Paulis <i>et al.</i> , 2006)	–	AMN082 (Mitsukawa <i>et al.</i> , 2005)	–
Selective competitive antagonists	ACDPP (6.5, Bonnefous <i>et al.</i> , 2005a)	MAP4, THPG (Thoreson <i>et al.</i> , 1997)	–	MPPG (Wu <i>et al.</i> , 1998)
Selective negative allosteric modulators	SIB1757 (Varney <i>et al.</i> , 1999), SIB1893 (Varney <i>et al.</i> , 1999), MPEP (Gasparini <i>et al.</i> , 1999b), MTEP (Brodkin <i>et al.</i> , 2002), fenobam (Porter <i>et al.</i> , 2005), YM298198 (Kohara <i>et al.</i> , 2005)	–	MMPIP (Suzuki <i>et al.</i> , 2007)	–

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [<sup>3</sup>H]-R214127 (Lavreysen *et al.*, 2003) and [<sup>3</sup>H]-YM298198 (Kohara *et al.*, 2005) at mGlu<sub>1</sub> receptors and [<sup>3</sup>H]-methoxyMPEP (Gasparini *et al.*, 2002) and [<sup>3</sup>H]-methoxymethyl-MTEP (Anderson *et al.*, 2002) at mGlu<sub>5</sub> receptors. Although a number of radioligands have been used to examine binding using native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (e.g. human *versus* rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(S)-(+)-CBPG is an antagonist at mGlu<sub>1</sub>, but is an agonist (albeit of reduced efficacy) at mGlu<sub>5</sub> receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors (Uyama *et al.*, 1997). A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomoinbotenic acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but resistant to LY341495 (Chung *et al.*, 1997). There are also reports of a distinct metabotropic glutamate receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification (Klein *et al.*, 1997; Pellegrini-Giampietro *et al.*, 1996).

**Abbreviations:** A841720, 3-(azepan-1-yl)-9-(dimethylamino)-[1]benzothio[3,2-d]pyrimidin-4-one; ACDPP, 3-amino-6-chloro-5-dimethylamino-*N*-2-pyridinylpyrazinecarboxamide hydrochloride; 1S,3R-ACPD, 1-aminocyclopentane-1S,3R-dicarboxylate; AIDA, 1-aminoindan-1,5(RS)-dicarboxylic acid; also known as UPF523; AMN082, *N,N'*-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride; L-AP4, *S*-2-amino-4-phosphonobutyrate; 2R,4R-APDC, aminopyrrolidine-2R,4R-dicarboxylate; also known as LY314593; BAY 36-7620, (3a*S*,6a*S*)-6a-naphthalen-2-ylmethyl-5-methylidene-hexahydro-1-cyclopenta[*c*]furan-1-one; BINA, 3'-([2-cyclopentyl-2,3-dihydro-6,7-dimethyl-1-oxo-1*H*-inden-5-yl]oxy)methyl)-(1,1'-biphenyl)-4-carboxylic acid, also known as biphenyl indanone A; CBiPES, *N*-[4'-cyano-biphenyl-3-yl]-*N*-(3-pyridinylmethyl)-ethanesulphonamide hydrochloride; (S)-(+)-CBPG, (s)-(-)-2-(3*R*-carboxybicyclo[1.1.1]pentyl)glycine; L-CCG-I, (2*S*,3*S*,4*S*)- $\alpha$ -(carboxycyclopropyl)glycine; CDPPB, 3-cyano-*N*-(1,3-diphenyl-1*H*-[pyrazol-5-yl]benzamide; CHPG, 2-chloro-5-hydroxyphenylglycine; CPCCOEt, cyclopropan[*b*]chromen-1*a*-carboxylate; 4CPG, 4-carboxyphenylglycine; CPPHA, *N*-[4-chloro-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]phenyl]-2-hydroxybenzamide; DCG-IV, (2*S*,1'*R*,2'*R*,3'*R*)-2-(2,3-dicarboxycyclopropyl)glycine; (S)-3,4-DCPG, (S)-3,4-dicarboxylphenylglycine; DFB, 3,3'-difluorobenzaldazine; DHPG, *S*-3,5-dihydroxyphenylglycine; DMPPP, 3,5-dimethyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-tri-methyl-propyl) ester; EGLU, (s)- $\alpha$ -ethylglutamate; EM-TBPC, (1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydrobenzo[*d*]azepin-3-yl)-1,6-dihydropyrimidine-5-carbonitrile; fenobam, *N*-(3-chlorophenyl)-*N'*-(4,5-dihydro-1-methyl-4-oxo-1-*H*-imidazole-2-yl)-urea; 3HPG, 3-hydroxyphenylglycine; [<sup>11</sup>C]-JNJ-16567083, (3-ethyl-2-[<sup>11</sup>C]methyl-6-quinolinyl)(*cis*-4-methoxycyclohexyl) methanone; JNJ16259685, (3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolinyl-7-yl)(*cis*-4-methoxycyclohexyl)methanone; LY307452, 2*S*,4*S*-2-amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioic acid; LY341495, 2*S*,2*S*-2-amino-2-(1*S*,2*S*-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propanoic acid; LY354740, (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate; LY367385, (+)-2-methyl-4-carboxyphenylglycine; LY379268, (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; LY389795, (-)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; LY393675,  $\alpha$ -substituted-cyclobutylglycine; LY456066, (2-[4-(indan-2-ylamino)-5,6,7,8-tetrahydro-quinazolin-2-ylsulfanyl]-ethanol, hydrochloride; LY456236, [(4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine hydrochloride; LY487379, 2,2,2-trifluoro-*N*-[4-(2-methoxyphenoxy)phenyl]-*N*-(3-pyridinylmethyl)-ethanesulphonamide; 3-MATIDA,  $\alpha$ -amino-5-carboxy-3-methyl-2-thiopheneacetic acid; MAP4, (S)-2-methyl-2-amino-4-phosphonobutanoate; methoxy-MPEP, 2-methyl-6-((3-methoxyphenyl)ethynyl)-pyridine; methoxy-PEPy, 3-methoxy-5-(pyridin-2-yl-ethynyl)-pyridine; MMPIP, 6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-*c*]pyridin-4(5*H*)-one hydrochloride; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MPPG, (RS)- $\alpha$ -methyl-4-phosphonophenylglycine; MTEP, 3-[[2-methyl-1,3-thiazol-4-yl]ethynyl]pyridine; methoxymethyl-MTEP, 3-(methoxymethyl)-5-[[2-methyl-1,3-thiazol-4-yl]ethynyl]pyridine; NAAG, *N*-acetylaspartylglutamate, also known as spaglumic acid; PCCG-4, (2*S*,1'*S*,2'*S*,3'*R*)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine; PHCCC, *N*-phenyl-7-(hydroxylimino)cyclopropan[*b*]chromen-1*a*-carboxamide; (RS)PPG, (R,S)-4-phosphonophenylglycine; R214127, 1-(3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-phenyl-1-ethanone; Ro01-6128, diphenylacetyl-carbamic acid ethyl ester; Ro62-5229, (Z)-1-[2-cycloheptyloxy-2-(2,6-dichlorophenyl)ethenyl]-1*H*-1,2,4-triazole; Ro67-4853, (9*H*-xanthene-9-carbonyl)-carbamic acid butyl ester; Ro67-7476, (S)-2-(4-fluorophenyl)-1-(toluene-4-sulphonyl)-pyrrolidine; SIB1757, 6-methyl-2-(phenylazo)-3-pyrindol; SIB1893, ([phenylazo]-3-pyrindole)-2-methyl-6-(2-phenylethenyl)pyridine; S-TBPG, 2-(3'-(1*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine; THPG, (RS)-3,4,5-trihydroxyphenylglycine; VU1545, *N*-[1-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]-4-nitrobenzamide; VU0155041, *cis*-2-[[[(3,5-dichlorophenyl)amino]carbonyl]cyclohexanecarboxylic acid; VU0361737, *N*-(4-chloro-3-methoxyphenyl)-2-pyridinecarboxamide; YM298198, 6-[[[(2-methoxyethyl)amino]methyl]-*N*-methyl-*N*-neopentylthio[3,2-*a*]benzimidazole-2-carboxamide



## Further Reading

- Anwyl R (2009). Metabotropic glutamate receptor-dependent long-term potentiation. *Neuropharmacology* 56: 735–740.
- Bird MK, Lawrence AJ (2009). The promiscuous mGlu5 receptor – a range of partners for therapeutic possibilities? *Trends Pharmacol Sci* 30: 617–623.
- Chaki S (2010). Group II metabotropic glutamate receptor agonists as a potential drug for schizophrenia. *Eur J Pharmacol* 639: 59–66.
- Chiechio S, Copani A, Zammataro M, Battaglia G, Gereau RW, Nicoletti F (2010). Transcriptional regulation of type-2 metabotropic glutamate receptors: an epigenetic path to novel treatments for chronic pain. *Trends Pharmacol Sci* 31: 153–160.
- Conn PJ, Lindsley CW, Jones CK (2009). Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. *Trends Pharmacol Sci* 30: 25–31.
- D’Antoni S, Berretta A, Bonaccorso CM, Bruno V, Aronica E, Nicoletti F *et al.* (2008). Metabotropic glutamate receptors in glial cells. *Neurochem Res* 33: 2436–2443.
- Durand D, Pampillo M, Caruso C, Lasaga M (2008). Role of metabotropic glutamate receptors in the control of neuroendocrine function. *Neuropharmacology* 55: 577–583.
- Duty S (2010). Therapeutic potential of targeting group III metabotropic glutamate receptors in the treatment of Parkinson’s disease. *Br J Pharmacol* 161: 271–287.
- Gladding CM, Fitzjohn SM, Molnar E (2009). Metabotropic glutamate receptor-mediated long-term depression: molecular mechanisms. *Pharmacol Rev* 61: 395–412.
- Goudet C, Magnaghi V, Landry M, Nagy F, Gereau RW, Pin JP (2009). Metabotropic receptors for glutamate and GABA in pain. *Brain Res Rev* 60: 43–56.
- Julio-Pieper M, Flor PJ, Dinan TG, Cryan JF (2011). Exciting times beyond the brain: metabotropic glutamate receptors in peripheral and non-neural tissues. *Pharmacol Rev* 63: 35–58.
- Kim CH, Lee J, Lee JY, Roche KW (2008). Metabotropic glutamate receptors: phosphorylation and receptor signaling. *J Neurosci Res* 86: 1–10.
- Krivoy A, Fischel T, Weizman A (2008). The possible involvement of metabotropic glutamate receptors in schizophrenia. *Eur Neuropsychopharmacol* 18: 395–405.
- Marek GJ (2010). Metabotropic glutamate2/3 (mGlu2/3) receptors, schizophrenia and cognition. *Eur J Pharmacol* 639: 81–90.
- Moreno JL, Sealton SC, Gonzalez-Maeso J (2009). Group II metabotropic glutamate receptors and schizophrenia. *Cell Mol Life Sci* 66: 3777–3785.
- Moussawi K, Kalivas PW (2010). Group II metabotropic glutamate receptors (mGlu2/3) in drug addiction. *Eur J Pharmacol* 639: 115–122.
- Nicoletti F, Bockaert J, Collingridge GL, Conn PJ, Ferraguti F, Schoepp DD *et al.* (2011). Metabotropic glutamate receptors: From the workbench to the bedside. *Neuropharmacology* 60: 1017–1041.
- Niswender CM, Conn PJ (2010). Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* 50: 295–322.
- O’Connor RM, Finger BC, Flor PJ, Cryan JF (2010). Metabotropic glutamate receptor 7: at the interface of cognition and emotion. *Eur J Pharmacol* 639: 123–131.
- Olive MF (2010). Cognitive effects of group I metabotropic glutamate receptor ligands in the context of drug addiction. *Eur J Pharmacol* 639: 47–58.
- Pilc A, Chaki S, Nowak G, Witkin JM (2008). Mood disorders: regulation by metabotropic glutamate receptors. *Biochem Pharmacol* 75: 997–1006.
- Robichaud AJ, Engers DW, Lindsley CW, Hopkins CR (2011). Recent progress on the identification of metabotropic glutamate 4 receptor ligands and their potential utility as CNS therapeutics. *ACS Chemical Neuroscience* in press.
- Schoepp DD, Alexander SP, Beart P, Conn PJ, Lodge D, Nakanishi S *et al.* (2000). Metabotropic glutamate receptors. In: Watson SP, Girdlestone D (eds). *IUPHAR Compendium of Receptor Characterization and Classification*, 2nd edn. IUPHAR Press: London, pp. 195–208.
- Shin SS, Martino JJ, Chen S (2008). Metabotropic glutamate receptors (mGlu) and cellular transformation. *Neuropharmacology* 55: 396–402.
- Simonyi A, Schachtman TR, Christoffersen GR (2010). Metabotropic glutamate receptor subtype 5 antagonism in learning and memory. *Eur J Pharmacol* 639: 17–25.
- Tang FR, Bradford HF, Ling EA (2009). Metabotropic glutamate receptors in the control of neuronal activity and as targets for development of anti-epileptogenic drugs. *Curr Med Chem* 16: 2189–2204.
- Wieronska JM, Pilc A (2009). Metabotropic glutamate receptors in the tripartite synapse as a target for new psychotropic drugs. *Neurochem Int* 55: 85–97.
- Wood MR, Hopkins CR, Brogan JT, Conn PJ, Lindsley CW (2011). ‘Molecular switches’ on mGluR allosteric ligands that modulate modes of pharmacology. *Biochemistry* 50: 2403–2410.

## References

- Anderson JJ *et al.* (2002). *J Pharmacol Exp Ther* 303: 1044–1051.
- Bonnefous C *et al.* (2005a). *Bioorg Med Chem Lett* 15: 1197–1200.
- Bonnefous C *et al.* (2005b). *Bioorg Med Chem Lett* 15: 4354–4358.
- Brabet I *et al.* (1995). *Neuropharmacology* 34: 895–903.
- Bräuner-Osborne H *et al.* (1996). *J Med Chem* 39: 3188–3194.
- Brodtkin J *et al.* (2002). *Eur J Neurosci* 16: 2241–2244.
- Carroll FY *et al.* (2001). *Mol Pharmacol* 59: 965–973.
- Chopra M *et al.* (2009). *J Pharmacol Exp Ther* 330: 212–219.
- Chung DS *et al.* (1997). *J Pharmacol Exp Ther* 283: 742–749.
- Clark BP *et al.* (1997). *Bioorg Med Chem Lett* 7: 2777–2780.
- Costantino G *et al.* (2001). *Bioorg Med Chem* 9: 221–227.
- de Paulis T *et al.* (2006). *J Med Chem* 49: 3332–3344.
- Doherty AJ *et al.* (1997). *Neuropharmacology* 36: 265–267.
- Engers DW *et al.* (2009). *J Med Chem* 52: 4115–4118.
- Escribano A *et al.* (1998). *Bioorg Med Chem Lett* 8: 765–770.
- Fricker AC *et al.* (2009). *Neuropharmacology* 56: 1060–1067.
- Gasparini F *et al.* (1999a). *J Pharmacol Exp Ther* 289: 1678–1687.
- Gasparini F *et al.* (1999b). *Neuropharmacology* 38: 1493–1503.
- Gasparini F *et al.* (2002). *Bioorg Med Chem Lett* 12: 407–409.
- Jane DE *et al.* (1996). *Neuropharmacology* 35: 1029–1035.
- Johnson MP *et al.* (2003). *J Med Chem* 46: 3189–3192.
- Johnson MP *et al.* (2005). *Psychopharmacology* 179: 271–283.
- Kingston AE *et al.* (1998). *Neuropharmacology* 37: 1–12.
- Kinney GG *et al.* (2005). *J Pharmacol Exp Ther* 313: 199–206.
- Klein J *et al.* (1997). *Neuropharmacology* 36: 305–311.
- Knoflach F *et al.* (2001). *Proc Natl Acad Sci U S A* 98: 13402–13407.
- Kohara A *et al.* (2005). *J Pharmacol Exp Ther* 315: 163–169.
- Kolczewski S *et al.* (1999). *Bioorg Med Chem Lett* 9: 2173–2176.
- Lavreysen H *et al.* (2003). *Mol Pharmacol* 63: 1082–1093.
- Lavreysen H *et al.* (2004). *Neuropharmacology* 47: 961–972.
- Li L *et al.* (2002). *Neuropharmacology* 43: 295.
- Litschig S *et al.* (1999). *Mol Pharmacol* 55: 453–461.
- Madsen U *et al.* (2005). *Neuropharmacology* 49 Suppl 1: 114–119.
- Maj M *et al.* (2003). *Neuropharmacology* 45: 895–906.
- Malherbe P *et al.* (2003). *J Biol Chem* 278: 8340–8347.
- Mannaioni G *et al.* (1999). *Neuropharmacology* 38: 917–926.
- Mathiesen JM *et al.* (2003). *Br J Pharmacol* 138: 1026–1030.
- Micheli F *et al.* (2003). *Bioorg Med Chem* 11: 171–183.
- Mitsukawa K *et al.* (2005). *Proc Natl Acad Sci U S A* 102: 18712–18717.
- Monn JA *et al.* (1999). *J Med Chem* 42: 1027–1040.

- Moroni F *et al.* (1997). *J Pharmacol Exp Ther* **281**: 721–729.
- Moroni F *et al.* (2002). *Neuropharmacology* **42**: 741–751.
- Neale JH (2011). *J Neurochem* in press.
- Niswender CM *et al.* (2008). *Mol Pharmacol* **74**: 1345–1358.
- O'Brien JA *et al.* (2003). *Mol Pharmacol* **64**: 731–740.
- O'Brien JA *et al.* (2004). *J Pharmacol Exp Ther* **309**: 568–577.
- Pellegrini-Giampietro DE *et al.* (1996). *Br J Pharmacol* **118**: 1035–1043.
- Pellicciari R *et al.* (1996). *J Med Chem* **39**: 2259–2269.
- Porter RH *et al.* (2005). *J Pharmacol Exp Ther* **315**: 711–721.
- Schoepp DD *et al.* (1996). *Neuropharmacology* **35**: 1661–1672.
- Suzuki G *et al.* (2007). *J Pharmacol Exp Ther* **323**: 147–156.
- Schoepp DD *et al.* (1997). *Neuropharmacology* **36**: 1–11.
- Thomas NK *et al.* (2001). *Neuropharmacology* **40**: 311–318.
- Thoreson WB *et al.* (1997). *Neuropharmacology* **36**: 13–20.
- Tuckmantel W *et al.* (1997). *Bioorg Med Chem Lett* **7**: 601–606.
- Uyama Y *et al.* (1997). *Brain Res* **752**: 327–330.
- Varney MA *et al.* (1999). *J Pharmacol Exp Ther* **290**: 170–181.
- Wermuth CG *et al.* (1996). *J Med Chem* **39**: 814–816.
- Wroblewska B *et al.* (1997). *J Neurochem* **69**: 174–181.
- Wu S *et al.* (1998). *Mol Brain Res* **53**: 88–97.
- Zheng GZ *et al.* (2005). *J Med Chem* **48**: 7374–7388.

# Glycoprotein hormone

**Overview:** Glycoprotein hormone receptors (provisional nomenclature) are activated by a heterodimeric glycoprotein made up of a common  $\alpha$  chain (116 amino-acid ENSG00000135346), with a unique  $\beta$  chain that confers the biological specificity to FSH (follicle-stimulating hormone, follitropin, 129 amino-acid, ENSG00000131808), LH (luteinizing hormone, lutropin, 141 amino-acid ENSG00000104826), CG (choriogonadotropin, chorionic gonadotropin, 165 amino-acid, ENSG00000104818/ENSG00000104827) or TSH (thyrotropin, thyroid-stimulating hormone, 138 amino-acid ENSG00000134200). There is binding cross-reactivity across the endogenous agonists for each of the glycoprotein hormone receptors. The deglycosylated hormones appear to exhibit reduced efficacy at these receptors (Sairam, 1989).

Nomenclature	FSH	LH	TSH
Ensembl ID	ENSG00000170820	ENSG00000168546	ENSG00000146013
Principal transduction	G <sub>s</sub>	G <sub>s</sub> , G <sub>q/11</sub> and G <sub>i</sub>	All four families of G proteins can be activated by this receptor
Selective agonists	FSH	LH, CG	TSH
Probes	[ <sup>125</sup> I]-FSH	[ <sup>125</sup> I]-LH, [ <sup>125</sup> I]-CG	[ <sup>125</sup> I]-TSH

Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Grave's disease (e.g. Rapoport *et al.*, 1998). Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders (Aittomaki *et al.*, 1995; Beau *et al.*, 1998; Gromoll *et al.*, 1996; Touraine *et al.*, 1999). Loss-of-function mutations of the LH receptor are associated with Leydig cell hypoplasia and gain-of-function mutations are associated with male-limited gonadotropin-independent precocious puberty (e.g. Latronico and Segaloff, 1999; Shenker, 2002) and Leydig cell tumours (Liu *et al.*, 1999). Mutations of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas (Parma *et al.*, 1993) and congenital hyperthyroidism (Kopp *et al.*, 1995). TSH receptor loss-of-function mutations are associated with thyrotropin resistance (Sunthornthepvarakul *et al.*, 1995). The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein (Quintana *et al.*, 1994).

## Further Reading

- Chiamolera MI, Wondisford FE (2009). Thyrotropin-releasing hormone and the thyroid hormone feedback mechanism. *Endocrinology* **150**: 1091–1096.
- George JW, Dille EA, Heckert LL (2011). Current concepts of follicle-stimulating hormone receptor gene regulation. *Biol Reprod* **84**: 7–17.
- Hermann BP, Heckert LL (2007). Transcriptional regulation of the FSH receptor: new perspectives. *Mol Cell Endocrinol* **260–262**: 100–108.
- Kleinau G, Krause G (2009). Thyrotropin and homologous glycoprotein hormone receptors: structural and functional aspects of extracellular signaling mechanisms. *Endocr Rev* **30**: 133–151.
- Mueller S, Jaeschke H, Gunther R, Paschke R (2010). The hinge region: an important receptor component for GPCR function. *Trends Endocrinol Metab* **21**: 111–122.
- Piersma D, Verhoef-Post M, Berns EM, Themmen AP (2007). LH receptor gene mutations and polymorphisms: an overview. *Mol Cell Endocrinol* **260–262**: 282–286.
- Puett D, Angelova K, da Costa MR, Warrenfeltz SW, Fanelli F (2010). The luteinizing hormone receptor: insights into structure-function relationships and hormone-receptor-mediated changes in gene expression in ovarian cancer cells. *Mol Cell Endocrinol* **329**: 47–55.
- Rao CV, Lei ZM (2007). The past, present and future of nongonadal LH/hCG actions in reproductive biology and medicine. *Mol Cell Endocrinol* **269**: 2–8.
- Ziecik AJ, Kaczmarek MM, Blitek A, Kowalczyk AE, Li X, Rahman NA (2007). Novel biological and possible applicable roles of LH/hCG receptor. *Mol Cell Endocrinol* **269**: 51–60.

## References

- Aittomaki K *et al.* (1995). *Cell* **82**: 959–968.
- Beau I *et al.* (1998). *J Clin Invest* **102**: 1352–1359.
- Gromoll J *et al.* (1996). *J Clin Endocrinol Metab* **81**: 1367–1370.
- Kopp P *et al.* (1995). *N Engl J Med* **332**: 150–154.
- Latronico AC, Segaloff DL (1999). *Am J Hum Genet* **65**: 949–958.
- Liu G *et al.* (1999). *N Engl J Med* **341**: 1731–1736.
- Parma J *et al.* (1993). *Nature* **365**: 649–651.
- Quintana J *et al.* (1994). *J Biol Chem* **269**: 8772–8779.
- Rapoport B *et al.* (1998). *Endocr Rev* **19**: 673–716.
- Sairam MR (1989). *FASEB J* **3**: 1915–1926.
- Shenker A (2002). *Receptors Channels* **8**: 3–18.
- Sunthornthepvarakul T *et al.* (1995). *N Engl J Med* **332**: 155–160.
- Touraine P *et al.* (1999). *Mol Endocrinol* **13**: 1844–1854.

# Gonadotropin-releasing hormone (GnRH)

**Overview:** GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors (provisional nomenclature, also called Type I and Type II, respectively) have been cloned from numerous species (most of which express two or three types of GnRH receptor) and grouped phylogenetically (Silver *et al.*, 2005). Gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH<sub>2</sub>, also known as luteinising hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin, ENSG00000147437) designated GnRH I, to distinguish it from related peptides, such as GnRH II (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH<sub>2</sub>, also known as chicken GnRH-II, ENSG00000180290). Receptors for all three ligands exist in amphibians but only GnRH I and GnRH II (and their cognate receptors) have been found in mammals (Sealfon *et al.*, 1997; Millar, 2005). GnRH<sub>1</sub> receptors are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I and all lack the C-terminal tails found in other GPCR. GnRH<sub>2</sub> receptors all possess C-terminal tails and (where tested) are selective for GnRH II (over GnRH I). An alternative phylogenetic classification (see Millar *et al.*, 2004) divided these receptors into three classes and includes both GnRH I-selective mammalian and GnRH II-selective non-mammalian receptors as GnRH<sub>1</sub> receptors. Although thousands of peptide analogues of GnRH I have been synthesised and several (agonists and antagonists) are used therapeutically (Kiesel *et al.*, 2002), the potency of most of these peptides at GnRH<sub>2</sub> receptors is unknown.

Nomenclature	GnRH <sub>1</sub>	GnRH <sub>2</sub>
Other names	Type I GnRHR, LHRH receptor, GnRH I receptor	Type II GnRHR
Ensembl ID	ENSG00000109163	ENSG00000211451
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	GnRH I > GnRH II	GnRH II > GnRH I
Selective agonists	Triptorelin, buserelin, leuprorelin, nafarelin, histrelin, goserelin	–
Selective antagonists	Antide (9.0, Neill, 2002), cetrorelix (8.8, Neill, 2002), ganirelix, abarelix	Trptorelix-1 (Maiti <i>et al.</i> , 2003)
Probes	[ <sup>125</sup> I]-GnRH I, [ <sup>125</sup> I]-buserelin	[ <sup>125</sup> I]-GnRH II

GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors couple primarily to G<sub>q/11</sub> (Grosse *et al.*, 2000) but coupling to G<sub>s</sub> and G<sub>i</sub> is evident in some systems (Krsmanovic *et al.*, 2003). GnRH<sub>2</sub> receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases (see Caunt *et al.*, 2004). There is increasing evidence for expression of GnRH receptors on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues (Limonta *et al.*, 2003; Harrison *et al.*, 2004; Schally and Nagy, 2004; Cheng and Leung, 2005). In some human cancer cell models GnRH II is more potent than GnRH I, implying mediation by GnRH<sub>2</sub> receptors (Grundker *et al.*, 2002). However, GnRH<sub>2</sub> receptors that are expressed by some primates are probably not expressed in humans because the human *GNRHR2* gene contains a frame shift and internal stop codon (Morgan *et al.*, 2003). The possibility remains that this gene generates GnRH<sub>2</sub> receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (see Neill *et al.*, 2004). Alternatively, there is evidence for multiple active GnRH receptor conformations (Caunt *et al.*, 2004; Maudsley *et al.*, 2004; Millar *et al.*, 2004) raising the possibility that GnRH<sub>1</sub> receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand specificity) than effects on G<sub>q/11</sub> in pituitary cells (Maudsley *et al.*, 2004). Loss-of-function mutations in the GnRH<sub>1</sub> receptor and deficiency of GnRH I are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' GnRH<sub>1</sub> receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists (Leanos-Miranda *et al.*, 2003). GnRH receptor signalling may be dependent upon receptor oligomerisation (Conn *et al.*, 1982; Kroeger *et al.*, 2001).

## Further Reading

- Bliss SP, Navratil AM, Xie J, Roberson MS (2010). GnRH signaling, the gonadotrope and endocrine control of fertility. *Front Neuroendocrinol* **31**: 322–340.
- Bouligand J, Ghervan C, Trabado S, Brailly-Tabard S, Guiochon-Mantel A, Young J (2010). Genetics defects in GNRH1: a paradigm of hypothalamic congenital gonadotropin deficiency. *Brain Res* **1364**: 3–9.
- Ciechanowska M, Lapot M, Mateusiak K, Przekop F (2010). Neuroendocrine regulation of GnRH release and expression of GnRH and GnRH receptor genes in the hypothalamus-pituitary unit in different physiological states. *Reprod Biol* **10**: 85–124.
- Colledge WH (2009). Kisspeptins and GnRH neuronal signalling. *Trends Endocrinol Metab* **20**: 115–121.
- Finch AR, Sedgley KR, Armstrong SP, Caunt CJ, McArdle CA (2010). Trafficking and signalling of gonadotrophin-releasing hormone receptors: an automated imaging approach. *Br J Pharmacol* **159**: 751–760.
- Gardner S, Stavrou E, Rischitor PE, Faccenda E, Pawson AJ (2010). Targeting mediators of Wnt signalling pathways by GnRH in gonadotropes. *J Mol Endocrinol* **44**: 195–201.
- Huhtaniemi I, White R, McArdle CA, Persson BE (2009). Will GnRH antagonists improve prostate cancer treatment? *Trends Endocrinol Metab* **20**: 43–50.
- Millar RP, Lu ZL, Pawson AJ, Flanagan CA, Morgan K, Maudsley SR (2004). Gonadotropin-releasing hormone receptors. *Endocr Rev* **25**: 235–275.
- Millar RP (2005). GnRHs and GnRH receptors. *Anim Reprod Sci* **88**: 5–28.
- Navratil AM, Bliss SP, Roberson MS (2010). Membrane rafts and GnRH receptor signaling. *Brain Res* **1364**: 53–61.
- Silveira LF, Trarbach EB, Latronico AC (2010). Genetics basis for GnRH-dependent pubertal disorders in humans. *Mol Cell Endocrinol* **324**: 30–38.

## References

- Caunt CJ *et al.* (2004). *Endocrinology* **145**: 3594–3602.
- Cheng CK, Leung PC (2005). *Endocr Rev* **26**: 283–306.
- Conn PM *et al.* (1982). *Endocrinology* **111**: 335–337.
- Grosse R *et al.* (2000). *J Biol Chem* **275**: 9193–9200.
- Grundker C *et al.* (2002). *Am J Obstet Gynecol* **187**: 528–537.
- Harrison GS *et al.* (2004). *Endocr Relat Cancer* **11**: 725–748.
- Kiesel LA *et al.* (2002). *Clin Endocrinol* **56**: 677–687.
- Kroeger KM *et al.* (2001). *J Biol Chem* **276**: 12736–12743.

- Krsmanovic LZ *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 2969–2974.
- Leanos-Miranda A *et al.* (2003). *J Clin Endocrinol Metab* **88**: 3360–3367.
- Limonta P *et al.* (2003). *Front Neuroendocrinol* **24**: 279–295.
- Maiti K *et al.* (2003). *Mol Cells* **16**: 173–179.
- Maudsley S *et al.* (2004). *Cancer Res* **64**: 7533–7544.
- Morgan K *et al.* (2003). *Endocrinology* **144**: 423–436.
- Neill JD (2002). *Endocrinology* **143**: 737–743.
- Neill JD *et al.* (2004). *Trends Endocrinol Metab* **15**: 383–392.
- Schally AV, Nagy A (2004). *Trends Endocrinol Metab* **15**: 300–310.
- Sealfon SC *et al.* (1997). *Endocr Rev* **18**: 180–205.
- Silver MR *et al.* (2005). *Endocrinology* **146**: 3351–3361.

# G protein-coupled estrogen (GPER)

**Overview:** The G protein-coupled estrogen receptor (GPER, provisional nomenclature) was identified following observations of oestrogen-evoked cyclic AMP signalling in breast cancer cells (Aronica *et al.*, 1994), dependent on the expression of an orphan GPCR GPR30 (Owman *et al.*, 1996; Carmeci *et al.*, 1997). There are observations of both cell-surface and intracellular localization of GPER (Revankar *et al.*, 2005; Thomas *et al.*, 2005).

Nomenclature	GPER
Other names	GPR30, IL8-related receptor DRY12, flow-induced endothelial G-protein coupled receptor, GPCR-BR
Ensembl ID	ENSG00000164850
Principal transduction	G <sub>s</sub> (Filardo <i>et al.</i> , 2000), G <sub>i/o</sub> (Revankar <i>et al.</i> , 2005)
Selective agonists	G1 (Bologa <i>et al.</i> , 2006)
Selective antagonists	G15 (Dennis <i>et al.</i> , 2009)
Probes	[ <sup>3</sup> H]-Oestrogen (Revankar <i>et al.</i> , 2005; Thomas <i>et al.</i> , 2005)

Antagonists at the nuclear oestrogen receptor, such as ICI182780 and tamoxifen (Filardo *et al.*, 2000), as well as the flavonoid 'phytoestrogens' genistein and quercetin (Maggiolini *et al.*, 2004), are agonists at GPER receptors.

**Abbreviations:** G1, 1-(4-[6-bromo-benzo[1,3]dioxol-5-yl]-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)ethanone; G15, 4-(6-bromo-benzo[1,3]dioxol-5-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline; ICI182780, 7 $\alpha$ -(9-[[4,4,5,5,5-pentafluoropentyl]sulphonyl]nonyl)estra-1,3,5(10)-triene-3,17 $\beta$ -diol

## Further Reading

- Nilsson BO, Olde B, Leeb-Lundberg LM (2011). G protein-coupled estrogen receptor 1 (GPER1)/GPR30: a new player in cardiovascular and metabolic estrogenic signaling. *Br J Pharmacol* **163**: 1131–1139.
- Olde B, Leeb-Lundberg LMF (2009). GPR30/GPER1: searching for a role in estrogen physiology. *Trends Endocrinol Metab* **20**: 409–416.
- Prossnitz ER, Arterburn JB, Smith HO, Oprea TI, Sklar LA, Hathaway HJ (2008). Estrogen signaling through the transmembrane G protein-coupled receptor GPR30. *Annu Rev Physiol* **70**: 165–190.
- Prossnitz ER, Barton M (2009). Signaling, physiological functions and clinical relevance of the G protein-coupled estrogen receptor GPER. *Prostaglandins Other Lipid Mediat* **89**: 89–97.
- Prossnitz ER, Maggiolini M (2009). Mechanisms of estrogen signaling and gene expression via GPR30. *Mol Cell Endocrinol* **308**: 32–38.
- Prossnitz ER, Sklar LA, Oprea TI, Arterburn JB (2008). GPR30: a novel therapeutic target in estrogen-related disease. *Trends Pharmacol Sci* **29**: 116–123.
- Smith HO, Arias-Pulido H, Kuo DY *et al.* (2009). GPR30 predicts poor survival for ovarian cancer. *Gynecol Oncol* **114**: 465–471.

## References

- Aronica SM *et al.* (1994). *Proc Natl Acad Sci U S A* **91**: 8517–8521.
- Bologa CG *et al.* (2006). *Nat Chem Biol* **2**: 207–212.
- Carmeci C *et al.* (1997). *Genomics* **45**: 607–617.
- Dennis MK *et al.* (2009). *Nat Chem Biol* **5**: 421–427.
- Filardo EJ *et al.* (2000). *Mol Endocrinol* **14**: 1649–1660.
- Maggiolini M *et al.* (2004). *J Biol Chem* **279**: 27008–27016.
- Owman C *et al.* (1996). *Biochem Biophys Res Commun* **228**: 285–292.
- Revankar CM *et al.* (2005). *Science* **307**: 1625–1630.
- Thomas P *et al.* (2005). *Endocrinology* **146**: 624–632.

# GPR18, GPR55 and GPR119

**Overview:** GPR18, GPR55 and GPR119 (provisional nomenclature), although showing little structural similarity to CB<sub>1</sub> and CB<sub>2</sub> receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands (see Pertwee *et al.*, 2010).

Nomenclature	GPR18	GPR55	GPR119
Other names	–	–	SNORF25
Ensembl ID	ENSG00000125245	ENSG00000135898	ENSG00000147262
Principal transduction	G <sub>i/o</sub> (Kohno <i>et al.</i> , 2006)	G <sub>12/13</sub> (Ryberg <i>et al.</i> , 2007)	G <sub>s</sub> (Ning <i>et al.</i> , 2008; Overton <i>et al.</i> , 2006)
Putative endogenous agonists	<i>N</i> -Arachidonoylglycine (Kohno <i>et al.</i> , 2006)	Lysophosphatidylinositol (Oka <i>et al.</i> , 2007), 2-arachidonoylglycerolphosphoinositol (Oka <i>et al.</i> , 2009)	<i>N</i> -Oleylethanolamine > <i>N</i> -palmitoylethanolamine > <i>N</i> -stearoylethanolamine (anandamide is ineffective, Overton <i>et al.</i> , 2006)
Synthetic agonists	–	AM251 (Henstridge <i>et al.</i> , 2009; Kapur <i>et al.</i> , 2009)	PSN375963, PSN632408 (Overton <i>et al.</i> , 2006), AS1269574 (Yoshida <i>et al.</i> , 2010)

GPR18 failed to respond to a variety of lipid-derived agents in an *in vitro* screen (Yin *et al.*, 2009), but has recently been reported to be activated by Δ<sup>9</sup>-tetrahydrocannabinol (McHugh *et al.*, 2011). GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB<sub>1</sub> receptor antagonists/inverse agonists (see Pertwee *et al.*, 2010). Lysophosphatidylinositol has been reported to act at other sites (Bondarenko *et al.*, 2011). Oleoyl-lysophosphatidylcholine has also been suggested to act, at least in part, through GPR119 (Ning *et al.*, 2008). Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with OEA-mediated responses suggests additional mechanisms of action (Ning *et al.*, 2008).

**Abbreviations:** AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AS1269574, 2-([2-(4-bromophenyl)-6-methyl-4-pyrimidinyl]amino)ethanol; PSN375963, 4-(5-[4-butylcyclohexyl]-1,2,4-oxadiazol-3-yl)pyridine; PSN632408, 4-([3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]methoxy)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester; rimonabant, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, also known as SR141716A

## Further Reading

- Bradshaw HB, Lee SH, McHugh D (2009). Orphan endogenous lipids and orphan GPCRs: a good match. *Prostaglandins Other Lipid Mediat* **89**: 131–134.
- Godlewski G, Offertaler L, Wagner JA, Kunos G (2009). Receptors for acylethanolamides-GPR55 and GPR119. *Prostaglandins Other Lipid Mediat* **89**: 105–111.
- Hansen HS, Diep TA (2009). *N*-Acylethanolamines, anandamide and food intake. *Biochem Pharmacol* **78**: 553–560.
- Pertwee RG, Howlett AC, Abood ME, Alexander SPH, Di Marzo V, Elphick MR *et al.* (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>. *Pharmacol Rev* **62**: 588–631.
- Ross RA (2011). L-α-Lysophosphatidylinositol meets GPR55: a deadly relationship. *Trends Pharmacol Sci* **32**: 265–269.
- Sharir H, Abood ME (2010). Pharmacological characterization of GPR55, a putative cannabinoid receptor. *Pharmacol Ther* **126**: 301–313.

## References

- Bondarenko AI *et al.* (2011). *Pflugers Arch* **461**: 177–189.
- Henstridge CM *et al.* (2009). *FASEB J* **23**: 183–193.
- Kapur A *et al.* (2009). *J Biol Chem* **284**: 29817–29827.
- Kohno M *et al.* (2006). *Biochem Biophys Res Commun* **347**: 827–832.
- McHugh D *et al.* (2011). *Br J Pharmacol* in press.
- Ning Y *et al.* (2008). *Br J Pharmacol* **155**: 1056–1065.
- Oka S *et al.* (2007). *Biochem Biophys Res Commun* **362**: 928–934.
- Oka S *et al.* (2009). *J Biochem* **145**: 13–20.
- Overton HA *et al.* (2006). *Cell Metab* **3**: 167–175.
- Ryberg E *et al.* (2007). *Br J Pharmacol* **152**: 1092–1101.
- Yin H *et al.* (2009). *J Biol Chem* **284**: 12328–12338.
- Yoshida S *et al.* (2010). *Biochem Biophys Res Commun* **400**: 437–441.

# Histamine

**Overview:** Histamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Histamine Receptors, see Hill *et al.*, 1997) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues (see Hill *et al.*, 1997).

Nomenclature	H <sub>1</sub>	H <sub>2</sub>	H <sub>3</sub>	H <sub>4</sub>
Ensembl ID	ENSG00000196639	ENSG00000168546	ENSG00000146013	ENSG00000134489
Principal transduction	G <sub>q/11</sub>	G <sub>s</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Selective agonists	Histaprofiden, N <sup>ε</sup> -methylhistaprofiden	Amthamine	Methimepip (Kitbunnadaj <i>et al.</i> , 2005), immethridine (Kitbunnadaj <i>et al.</i> , 2004)	Clobenpropit, 4-methylhistamine, VUF8430 (Lim <i>et al.</i> , 2006)
Selective antagonists	Triprolidine (9.9), mepyramine (9.1)	Tiotidine (7.8), ranitidine (7.1)	Clobenpropit (9.9), iodophenpropit (9.6), A331440 (8.5, Hancock <i>et al.</i> , 2004), thioperamide (8.4)	JNJ7777120 (8.1)
Probes	[ <sup>3</sup> H]-Mepyramine (1 nM), [ <sup>11</sup> C]-Mepyramine, [ <sup>11</sup> C]-doxepin	[ <sup>3</sup> H]-Tiotidine (15 nM), [ <sup>125</sup> I]-iodoaminopotentidine (0.3 nM)	[ <sup>3</sup> H]-R-α-Methylhistamine (0.5 nM), [ <sup>3</sup> H]-N <sup>ε</sup> -methylhistamine (2 nM), [ <sup>125</sup> I]-iodophenpropit (0.6 nM), [ <sup>125</sup> I]-iodoproxyfan (0.06 nM)	[ <sup>3</sup> H]-JNJ7777120 (3.6 nM)

Histaprofiden and N<sup>ε</sup>-methylhistaprofiden are reduced efficacy agonists. The H<sub>4</sub> receptor appears to exhibit broadly similar pharmacology to the H<sub>3</sub> receptor for imidazole-containing ligands, although R-α-methylhistamine and N-α-methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Liu *et al.*, 2001; Nguyen *et al.*, 2001; Zhu *et al.*, 2001). Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H<sub>4</sub> receptor (Lim *et al.*, 2005). [<sup>3</sup>H]-Histamine has been used to label the H<sub>4</sub> receptor in heterologous expression systems.

## Further Reading

- Gemkow MJ, Davenport AJ, Harich S, Ellenbroek BA, Cesura A, Hallett D (2009). The histamine H<sub>3</sub> receptor as a therapeutic drug target for CNS disorders. *Drug Discov Today* 14: 509–515.
- Haas HL, Sergeeva OA, Selbach O (2008). Histamine in the nervous system. *Physiol Rev* 88: 1183–1241.
- Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM *et al.* (1997). International Union of Pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev* 49: 253–278.
- Leurs R, Chazot PL, Shenton FC, Lim HD, de Esch IJ (2009). Molecular and biochemical pharmacology of the histamine H<sub>4</sub> receptor. *Br J Pharmacol* 157: 14–23.
- Panula P, Nuutinen S (2011). Histamine and H<sub>3</sub> receptor in alcohol-related behaviors. *J Pharmacol Exp Ther* 336: 9–16.
- Passani MB, Blandina P, Torrealba F (2011). The histamine H<sub>3</sub> receptor and eating behavior. *J Pharmacol Exp Ther* 336: 24–29.
- Thurmond RL, Gelfand EW, Dunford PJ (2008). The role of histamine H<sub>1</sub> and H<sub>4</sub> receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* 7: 41–53.
- Yanai K, Tashiro M (2007). The physiological and pathophysiological roles of neuronal histamine: An insight from human positron emission tomography studies. *Pharmacol Ther* 113: 1–15.
- Zampeli E, Tiligada E (2009). The role of histamine H<sub>4</sub> receptor in immune and inflammatory disorders. *Br J Pharmacol* 157: 24–33.
- Zhang M, Thurmond RL, Dunford PJ (2007). The histamine H<sub>4</sub> receptor: a novel modulator of inflammatory and immune disorders. *Pharmacol Ther* 113: 594–606.

## References

- Hancock AA *et al.* (2004). *Eur J Pharmacol* 487: 183–197.
- Kitbunnadaj R *et al.* (2004). *J Med Chem* 47: 2414–2417.
- Kitbunnadaj R *et al.* (2005). *Bioorg Med Chem* 13: 6309–6323.
- Lim HD *et al.* (2005). *J Pharmacol Exp Ther* 314: 1310–1321.
- Lim HD *et al.* (2006). *J Med Chem* 49: 6650–6651.
- Liu C *et al.* (2001). *Mol Pharmacol* 59: 420–426.
- Nakamura T *et al.* (2000). *Biochem Biophys Res Commun* 279: 615–620.
- Nguyen T *et al.* (2001). *Mol Pharmacol* 59: 427–433.
- Oda T *et al.* (2000). *J Biol Chem* 275: 36781–36786.
- Zhu Y *et al.* (2001). *Mol Pharmacol* 59: 434–441.



# Hydroxycarboxylic acid family

**Overview:** The hydroxycarboxylic acid family of receptors (ENSM00500000271913, nomenclature as agreed by NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors, see Offermanns *et al.*, 2011) respond to organic acids, including the endogenous short chain fatty acids, butyrate and lactate, as well as the lipid lowering agents nicotinic acid (niacin), acipimox and acifran (Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003). These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA<sub>2</sub> receptors only (Tunaru *et al.*, 2003; Wise *et al.*, 2003).

Nomenclature	HCA <sub>1</sub>	HCA <sub>2</sub>	HCA <sub>3</sub>
Other names	GPR81, GPR104	GPR109A, Niacin receptor 1, HM74A, Nic1, Puma-G,	GPR109B, Low affinity nicotinic acid receptor, HM74, Nic2
Ensembl ID	ENSG00000196917	ENSG00000182782	ENSG00000255398
Principal transduction	G <sub>i/o</sub> (Ge <i>et al.</i> , 2008)	G <sub>i/o</sub> (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003; Tunaru <i>et al.</i> , 2003)	G <sub>i/o</sub> (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003)
Selective agonists	Lactate (Cai <i>et al.</i> , 2008; Liu <i>et al.</i> , 2009)	Nicotinic acid (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003; Tunaru <i>et al.</i> , 2003), acipimox (Wise <i>et al.</i> , 2003), 3-hydroxybutyrate (Taggart <i>et al.</i> , 2005)	3-Hydroxyoctanoic acid (Ahmed <i>et al.</i> , 2009), IBC293 (Semple <i>et al.</i> , 2006)
Probes	–	[ <sup>3</sup> H]-Nicotinic acid (Soga <i>et al.</i> , 2003)	–

Further closely-related GPCR include the 5-oxoecicosanoid receptor (ENSG00000162881, see Page S74) and GPR31 (ENSG00000120436).

**Abbreviations:** IBC293, 1-(1-methylethyl)-1H-benzotriazole-5-carboxylic acid

## Further Reading

- Boatman PD, Richman JG, Semple G (2008). Nicotinic acid receptor agonists. *J Med Chem* **51**: 7653–7662.
- Chapman MJ, Redfern JS, McGovern ME, Giral P (2010). Niacin and fibrates in atherogenic dyslipidemia: Pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* **126**: 314–345.
- Gille A, Bodor ET, Ahmed K, Offermanns S (2008). Nicotinic acid: pharmacological effects and mechanisms of action. *Annu Rev Pharmacol Toxicol* **48**: 79–106.
- Guyton JR (2007). Niacin in cardiovascular prevention: mechanisms, efficacy, and safety. *Curr Opin Lipidol* **18**: 415–420.
- Offermanns S, Colletti SL, Lovenberg TW, Semple G, Wise A, IJzerman AP (2011). International Union of Basic and Clinical Pharmacology. LXXXII: nomenclature and classification of hydroxy-carboxylic acid receptors (GPR81, GPR109A, and GPR109B). *Pharmacol Rev* **63**: 269–290.
- Soudijn W, van Wijngaarden I, IJzerman AP (2007). Nicotinic acid receptor subtypes and their ligands. *Med Res Rev* **27**: 417–433.
- Vosper H (2009). Niacin: a re-emerging pharmaceutical for the treatment of dyslipidaemia. *Br J Pharmacol* **158**: 429–441.

## References

- Ahmed K *et al.* (2009). *J Biol Chem* **284**: 21928–21933.
- Cai TQ *et al.* (2008). *Biochem Biophys Res Commun* **377**: 987–991.
- Ge H *et al.* (2008). *J Lipid Res* **49**: 797–803.
- Liu C *et al.* (2009). *J Biol Chem* **284**: 2811–2822.
- Semple G *et al.* (2006). *J Med Chem* **49**: 1227–1230.
- Soga T *et al.* (2003). *Biochem Biophys Res Commun* **303**: 364–369.
- Taggart AK *et al.* (2005). *J Biol Chem* **280**: 26649–26652.
- Tunaru S *et al.* (2003). *Nat Med* **9**: 352–355.
- Wise A *et al.* (2003). *J Biol Chem* **278**: 9869–9874.

# KISS1, neuropeptide FF, prolactin-releasing peptide and QRFP

**Overview:** KISS1 (nomenclature agreed by NC-IUPHAR committee on kisspeptin receptors (Kirby *et al.*, 2010), neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) respond to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. Kisspeptin-54 (KP54, originally named metastin), KP13 and KP10 are biologically-active peptides cleaved from the *KISS1* gene product (ENSG00000170498), while a single propeptide precursor (ENSG00000139574) generates the octapeptides NPFF (FLFQPQRF-NH<sub>2</sub>, neuropeptide FF or F-8-F-amide) and NPSF (SLAAPQRF-NH<sub>2</sub>, neuropeptide SF) and the octadecapeptide NPAF (AGEGLSSPFWSLAAPQRF-NH<sub>2</sub>, neuropeptide AF or A-18-F-amide). NPFF and NPAF were originally isolated from bovine brain (Yang *et al.*, 1985). The precursor (ENSG00000071677) for PrRP generates 31 and 20-amino-acid versions. QRFP (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from ENSG00000188710, and is also known as P518 or 26RFa. RFRP is an RFamide-related peptide (Hinuma *et al.*, 2000) derived from a FMRFamide-related peptide precursor (ENSG00000105954), which is cleaved to generate neuropeptide NPSF (Neuropeptide RFRP-1), neuropeptide RFRP-2 and neuropeptide NPVF (neuropeptide RFRP-3).

Nomenclature	KISS1	NPFF1	NPFF2	PrRP	QRFP
Other names	hOT7T175 (Ohtaki <i>et al.</i> , 2001), GPR54, metastin, hypogonadotropin	Neuropeptide FF 1, GPR147 (Bonini <i>et al.</i> , 2000), OT7T022	Neuropeptide FF 2, GPR74 (Bonini <i>et al.</i> , 2000), HLWAR77	Prolactin-releasing peptide, GPR10 (Hinuma <i>et al.</i> , 1998), hGR3, UHR-1	SP9155 (Jiang <i>et al.</i> , 2003), AQ27 (Fukusumi <i>et al.</i> , 2003), P518
Ensembl ID	ENSG00000116014	ENSG00000148734	ENSG00000056291	ENSG00000119973	ENSG00000186867
Principal transduction	G <sub>q/11</sub> (Kotani <i>et al.</i> , 2001; Muir <i>et al.</i> , 2001)	G <sub>q/11</sub>	G <sub>i/o</sub> (Mollereau <i>et al.</i> , 2005)	G <sub>q/11</sub> (Langmead <i>et al.</i> , 2000)	G <sub>q/11</sub> , G <sub>i/o</sub> (Fukusumi <i>et al.</i> , 2003)
Potency order	–	FMRF, NPFF > NPAF > NPSF, QRFP, PrP31 (Gouardères <i>et al.</i> , 2007)	NPAF, NPFF > PrP31 > FMRF, QRFP > NPSF (Gouardères <i>et al.</i> , 2007)	PrRP20, PrRP31 (Langmead <i>et al.</i> , 2000)	–
Selective agonists	KP54, KP13, KP10 (Kotani <i>et al.</i> , 2001; Ohtaki <i>et al.</i> , 2001), 4-fluorobenzoyl-FGLRW-NH <sub>2</sub> (Tomita <i>et al.</i> , 2008), [dY] <sup>1</sup> KP-10 (Curtis <i>et al.</i> , 2010)	NPFF, NPVF	NPFF, dNPA (Roussin <i>et al.</i> , 2005), AC263093 (Lameh <i>et al.</i> , 2010)	PrRP	QRFP
Selective antagonists	Peptide 234 (Roseweir <i>et al.</i> , 2009)	AC262620, AC262970 (Lameh <i>et al.</i> , 2010)	–	Neuropeptide Y (Lagerstrom <i>et al.</i> , 2005)	–
Probes	[ <sup>125</sup> I]-KP10 (Kotani <i>et al.</i> , 2001), [ <sup>125</sup> I]KP14 (Mead <i>et al.</i> , 2007), [ <sup>125</sup> I]-Tyr <sup>45</sup> -KP15 (Ohtaki <i>et al.</i> , 2001)	[ <sup>125</sup> I]-NPFF, [ <sup>125</sup> I]-YVP (Gouardères <i>et al.</i> , 2002), [ <sup>3</sup> H]-NPVF (Talmont <i>et al.</i> , 2009)	[ <sup>125</sup> I]-NPFF, [ <sup>125</sup> I]-EYF (Gouardères <i>et al.</i> , 2002), [ <sup>3</sup> H]-EYF (Talmont <i>et al.</i> , 2009)	[ <sup>125</sup> I]-PrRP20 (Langmead <i>et al.</i> , 2000), [ <sup>125</sup> I]-PrRP31 (Ellacott <i>et al.</i> , 2005)	[ <sup>125</sup> I]-QRFP (Takayasu <i>et al.</i> , 2006)

An orphan receptor GPR83 (ENSG00000123901) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors. The antagonist RF9 is selective for NPFF receptors, but does not distinguish between the NPFF1 and NPFF2 subtypes ( $pK_i$  7.1 and 7.2, respectively, Simonin *et al.*, 2006).

**Abbreviations:** dNPA, D-Asn-Pro-(N-Me)Ala-Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH<sub>2</sub>; NPVF, Val-Pro-Asn-Leu-Pro-Gln-Arg-Phe-NH<sub>2</sub>; Peptide 234, ac[(D)-A]NWNGFG[9D]-W]RF; RF9, adamantylcarbonyl-arginyl-phenylalaninamide; AC262620, AC262970, AC263093

## Further Reading

- Colledge WH (2009). Kisspeptins and GnRH neuronal signalling. *Trends Endocrinol Metab* 20: 115–121.
- Fukusumi S, Fujii R, Hinuma S (2006). Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. *Peptides* 27: 1073–1086.
- Hameed S, Jayasena CN, Dhillo WS (2011). Kisspeptin and fertility. *J Endocrinol* 208: 97–105.
- Jayasena CN, Dhillo WS, Bloom SR (2009). Kisspeptins and the control of gonadotropin secretion in humans. *Peptides* 30: 76–82.
- Kirby HR, Maguire JJ, Colledge WH, Davenport AP (2010). International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. *Pharmacol Rev* 62: 565–578.
- Mead EJ, Maguire JJ, Kuc RE, Davenport AP (2007). Kisspeptins: a multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. *Br J Pharmacol* 151: 1143–1153.
- Millar RP, Roseweir AK, Tello JA, Anderson RA, George JT, Morgan K *et al.* (2010). Kisspeptin antagonists: unraveling the role of kisspeptin in reproductive physiology. *Brain Res* 1364: 81–89.
- Mouldous L, Mollereau C, Zajac JM (2010). Opioid-modulating properties of the neuropeptide FF system. *Biofactors* 36: 423–429.

- Oakley AE, Clifton DK, Steiner RA (2009). Kisspeptin signaling in the brain. *Endocr Rev* **30**: 713–743.
- Samson WK, Taylor MM (2006). Prolactin releasing peptide (PrRP): an endogenous regulator of cell growth. *Peptides* **27**: 1099–1103.
- Seminara SB (2006). Mechanisms of disease: the first kiss—a crucial role for kisspeptin-1 and its receptor, G-protein-coupled receptor 54, in puberty and reproduction. *Nat Clin Pract Endocrinol Metab* **2**: 328–334.
- Takayanagi Y, Onaka T (2010). Roles of prolactin-releasing peptide and RFamide related peptides in the control of stress and food intake. *FEBS J* **277**: 4998–5005.
- Tena-Sempere M (2010). Kisspeptin signaling in the brain: recent developments and future challenges. *Mol Cell Endocrinol* **314**: 164–169.
- Vyas N, Mollereau C, Cheve G, McCurdy CR (2006). Structure-activity relationships of neuropeptide FF and related peptidic and non-peptidic derivatives. *Peptides* **27**: 990–996.
- Yang HY, Tao T, Iadarola MJ (2008). Modulatory role of neuropeptide FF system in nociception and opiate analgesia. *Neuropeptides* **42**: 1–18.

## References

- Bonini JA *et al.* (2000). *J Biol Chem* **275**: 39324–39331.
- Curtis AE *et al.* (2010). *Am J Physiol Endocrinol Metab* **298**: E296–E303.
- Ellacott KL *et al.* (2005). *Peptides* **26**: 675–681.
- Fukusumi S *et al.* (2003). *J Biol Chem* **278**: 46387–46395.
- Gouardères C *et al.* (2002). *Neuroscience* **115**: 349–361.
- Gouardères C *et al.* (2007). *Neuropharmacology* **52**: 376–386.
- Hinuma S *et al.* (1998). *Nature* **393**: 272–276.
- Hinuma S *et al.* (2000). *Nat Cell Biol* **2**: 703–708.
- Jiang Y *et al.* (2003). *J Biol Chem* **278**: 27652–27657.
- Kotani M *et al.* (2001). *J Biol Chem* **276**: 34631–34636.
- Lagerstrom MC *et al.* (2005). *Genomics* **85**: 688–703.
- Lameh J *et al.* (2010). *J Pharmacol Exp Ther* **334**: 244–254.
- Langmead CJ *et al.* (2000). *Br J Pharmacol* **131**: 683–688.
- Mead EJ *et al.* (2007). *Endocrinology* **148**: 140–147.
- Mollereau C *et al.* (2005). *Mol Pharmacol* **67**: 965–975.
- Muir A *et al.* (2001). *J Biol Chem* **276**: 28969–28975.
- Ohtaki T *et al.* (2001). *Nature* **411**: 613–617.
- Roseweir AK *et al.* (2009). *J Neurosci* **29**: 3920–3929.
- Roussin A *et al.* (2005). *Biochem Biophys Res Commun* **336**: 197–203.
- Simonin F *et al.* (2006). *Proc Natl Acad Sci U S A* **103**: 466–471.
- Takayasu S *et al.* (2006). *Proc Natl Acad Sci U S A* **103**: 7438–7443.
- Talmont F *et al.* (2009). *Neurochem Int* **55**: 815–819.
- Tomita K *et al.* (2008). *Biopolymers* **90**: 503–511.
- Yang HY *et al.* (1985). *Proc Natl Acad Sci U S A* **82**: 7757–7761.

# Leukotriene, lipoxin, oxoeicosanoid and resolvin

**Overview:** Leukotriene receptors (nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors, Brink *et al.*, 2003) are activated by the endogenous ligands leukotriene (LT) B<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>, 12R-HETE and 12S-HETE. CysLT<sub>1</sub> and CysLT<sub>2</sub> are co-expressed by most myeloid cells. However, the function of CysLT<sub>2</sub> remains unclear. CysLT<sub>2</sub> has been demonstrated to exert a suppressive influence on CysLT<sub>1</sub> expression, suggesting an autoregulatory function which is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking CysLT<sub>2</sub> receptors (Jiang *et al.*, 2007).

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-S-transferase/LTC<sub>4</sub> synthase,  $\gamma$ -glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ , Lin *et al.*, 1999) and the FPR2/ALX lipoxin receptor (Fiore *et al.*, 1994), complicating the interpretation of radioligand binding and functional studies (e.g. LTC<sub>4</sub> is rapidly converted in many systems to LTD<sub>4</sub>). Metabolic inhibitors (e.g. serine–borate complex) reduce this problem but can also have non-specific effects.

Nomenclature	BLT <sub>1</sub>	BLT <sub>2</sub>	CysLT <sub>1</sub>	CysLT <sub>2</sub>
Other names	LTB <sub>4</sub>	–	HG55, HMTMF81, LTD <sub>4</sub>	HPN321, LTC <sub>4</sub>
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000173198	ENSG00000152207
Principal transduction	G <sub>q/11</sub> , G <sub>i/o</sub>	G <sub>q/11</sub> , G <sub>i/o</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	LTB <sub>4</sub> > 20-hydroxy-LTB <sub>4</sub> >> 12R-HETE (Yokomizo <i>et al.</i> , 2001)	LTB <sub>4</sub> > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE = 5S-HETE > 20-hydroxy-LTB <sub>4</sub> (Yokomizo <i>et al.</i> , 2001)	LTD <sub>4</sub> > LTC <sub>4</sub> > LTE <sub>4</sub> (Sarau <i>et al.</i> , 1999)	LTC <sub>4</sub> = LTD <sub>4</sub> >> LTE <sub>4</sub> (Nothacker <i>et al.</i> , 2000)
Selective agonists	–	12S-HETE	–	BAYu9773
Selective antagonists	CP105696 (pIC <sub>50</sub> 7.2), U75302 (pIC <sub>50</sub> 6.9)	LY255283 (pIC <sub>50</sub> 6.0)	Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3)	–
Probes	[ <sup>3</sup> H]-LTB <sub>4</sub> (0.2–0.7 nM), [ <sup>3</sup> H]-CGS23131 (13 nM)	[ <sup>3</sup> H]-LTB <sub>4</sub> (0.2–23 nM)	[ <sup>3</sup> H]-LTD <sub>4</sub> , [ <sup>3</sup> H]-ICI198615	[ <sup>3</sup> H]-LTD <sub>4</sub>

BAYu9773 is an antagonist at CysLT<sub>1</sub> (6.8–7.7) and a reduced efficacy agonist at CysLT<sub>2</sub> receptors. The CysLT<sub>1</sub> and CysLT<sub>2</sub> receptors also respond to uracil nucleotides (Mellor *et al.*, 2001; 2003). GPR17 has been described as a ‘dualistic’ receptor responding to both uracil nucleotides and cysteinyl leukotrienes, responses which may be inhibited by antagonists of either P2 or CysLT receptors (Ciana *et al.*, 2006).

Lipoxin A<sub>4</sub> receptors (FPR2/ALX, nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors; Ye *et al.*, 2009) are activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A<sub>4</sub> (LXA<sub>4</sub>) and 15-epi-LXA<sub>4</sub> (aspirin-triggered lipoxin A<sub>4</sub>, ATL). The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide (Chiang *et al.*, 2000) as well as annexin 1 (ANXA1) and its N-terminal peptides (Perretti *et al.*, 2002). In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the FPR2/ALX receptor (Resnati *et al.*, 2002). Furthermore, FPR2/ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A (Su *et al.*, 1999; Sodin-Semrl *et al.*, 2004).

Oxoeicosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoeicosanoid Receptors; Brink *et al.*, 2004) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-EETE the most potent agonist identified for this receptor.

Nomenclature	FPR2/ALX	OXE
Other names	FPRL1, FPR2, FPRH2, RFP, ALX	TG1019 (Hosoi <i>et al.</i> , 2002), R527 (Jones <i>et al.</i> , 2003), hGPCR48 (Koike <i>et al.</i> , 2006)
Ensembl ID	ENSG00000171049	ENSG00000162881
Principal transduction	G <sub>i</sub> (Maddox <i>et al.</i> , 1997)	G <sub>i/o</sub> (O’Flaherty <i>et al.</i> , 2000; Hosoi <i>et al.</i> , 2002; Jones <i>et al.</i> , 2003; Hosoi <i>et al.</i> , 2005)
Rank order of potency	LXA <sub>4</sub> = ATL = ATLa2 > LTC <sub>4</sub> = LTD <sub>4</sub> >> 15-deoxy-LXA <sub>4</sub> >> fMLP (Clish <i>et al.</i> , 1999; Fiore <i>et al.</i> , 1994; Fiore and Serhan, 1995; Gronert <i>et al.</i> , 2001; Takano <i>et al.</i> , 1997)	5-Oxo-EETE, 5-oxo-C20:3 >> 5s-HpETE > 5s-HETE (Hosoi <i>et al.</i> , 2002; Jones <i>et al.</i> , 2003, Patel <i>et al.</i> , 2008)
Selective agonists	LXA <sub>4</sub> , ATL, ATLa2 (Guilford <i>et al.</i> , 2004), RvD1 (Krishnamoorthy <i>et al.</i> , 2010)	5-Oxo-EETE
Probes	[ <sup>3</sup> H]-LXA <sub>4</sub> (0.2–1.7 nM; Fiore <i>et al.</i> , 1994; Takano <i>et al.</i> , 1997)	[ <sup>3</sup> H]-5-oxo-EETE (3.8 nM, O’Flaherty <i>et al.</i> , 1998)

Note that the data for FPR2/ALX are also reproduced on the Formylpeptide receptor pages (see Page S48). A receptor selective for LXB<sub>4</sub> has been suggested from functional studies (Maddox and Serhan, 1996; Romano *et al.*, 1996; Ariel *et al.*, 2003). Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as DHA and EPA, acted as receptor antagonists (Hosoi *et al.*, 2002).

Resolvin receptors (provisional nomenclature) are activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is the result of sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase (Arita *et al.*, 2005a,b). In addition, 2 GPCRs for resolvin D1 (RvD1) have been identified, FPR2/ALX, the lipoxin A<sub>4</sub> receptor, and GPR32, an orphan receptor (Krishnamoorthy *et al.*, 2010).

Nomenclature	RvE1	RvD1
Other names	ChemR23, chemokine receptor-like 1, DEZ	GPR32
Ensembl ID	ENSG00000174600	ENSG00000142511
Principal transduction	Not yet established	Not yet established
Rank order of potency	RvE1 > chemerin C-terminal peptide > 18R-HEPE > EPA (Arita <i>et al.</i> , 2005a,b)	RvD1 > LXA <sub>4</sub>
Selective agonists	RvE1	RvD1, LXA <sub>4</sub>
Probes	[ <sup>3</sup> H]-RvE1 (11 nM, Arita <i>et al.</i> , 2005a)	[ <sup>3</sup> H]-RvD1 (0.2 nM, Krishnamoorthy <i>et al.</i> , 2010)

**Abbreviations:** 12R-HETE, 12R-hydroxyeicosa-5Z,8Z,10E,14Z-tetraenoic acid; 18R-HEPE, 18R-hydroxyeicosapentaenoic acid; 5s-HETE, 5s-hydroxy-6E,8Z,11Z,14Z-eicosatetraenoic acid; 5s-HpETE, 5s-hydroperoxy-6E,8Z,11Z,14Z-eicosatetraenoic acid; 5-oxo-C20:3, 5-oxo-6E,8Z,11Z-eicosatrienoic acid; 5-oxo-ETE, 5-oxo-6E,8Z,11Z,14Z-eicosatetraenoic acid; ANXA1, annexin 1; ATL, aspirin-triggered lipoxin A<sub>4</sub> [15-*epi*-LXA<sub>4</sub>, 5s,6R,15R-trihydroxyl-7E,9E,13E,11Z-eicosatetraenoic acid]; ATLa2, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA<sub>4</sub>]; BAYu9773, 6(R)-(4'-carboxyphenyl-thio)-5(S)-hydroxy-7E,11Z,14Z-eicosatetraenoic acid; CGS23131, (E)-5-(3-carboxybenzoyl)-2-([6-(4-methoxyphenyl)-5-hexenyl]oxy)benzene propanoic acid; also known as LY223982; CP105696, (+)-1-(3S,4R)-[3-(4-phenylbenzyl)-4-hydroxy-chroman-7-yl]cyclopentane carboxylic acid; DHA, 4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoic acid; EPA, 5Z,8Z,11Z,14Z,17Z-eicosapentaenoic acid; ICI198615, (1-[2-methoxy-4-([phenylsulfonfylamino]carbonyl)phenyl]methyl)-1H-indazol-6-yl)carbamoyl cyclopentyl ester; LTC<sub>4</sub>, leukotriene C<sub>4</sub>; LTD<sub>4</sub>, leukotriene D<sub>4</sub>; LXA<sub>4</sub>, lipoxin A<sub>4</sub> [5S,6R,15S-trihydroxyl-7E,9E,13E-11Z-eicosatetraenoic acid]; LY255283, 1-(5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)-heptyl]-oxy]-phenyl)-ethanone; OXE, oxoecosanoid; RvE1, resolvin E1 or 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-EPA; SR2640, 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid; U75302, 6-(6-(3-hydroxy-1E,5Z-undecadien-1-yl)-2-pyridinyl)-1,5-hexanediol

## Further Reading

- Ariel A, Serhan CN (2007). Resolvins and protectins in the termination program of acute inflammation. *Trends Immunol* 28: 176–183.
- Baker N, O'Meara SJ, Scannell M, Maderna P, Godson C (2009). Lipoxin A<sub>4</sub>: anti-inflammatory and anti-angiogenic impact on endothelial cells. *J Immunol* 182: 3819–3826.
- Brink C, Dahlen SE, Drazen J, Evans JF, Nicosia S *et al.* (2003). International Union of Pharmacology. XXXVII. Nomenclature for Leukotriene and Lipoxin Receptors. *Pharmacol Rev* 55: 195–227.
- Brink C, Dahlen SE, Drazen J, Evans JF, Hay DWP, Rovati GE *et al.* (2004). International Union of Pharmacology XLIV. Nomenclature for the oxoecosanoid receptor. *Pharmacol Rev* 56: 149–157.
- Grant GE, Rokach J, Powell WS (2009). 5-Oxo-ETE and the OXE receptor. *Prostaglandins Other Lipid Mediat* 89: 98–104.
- Kohli P, Levy BD (2009). Resolvins and protectins: mediating solutions to inflammation. *Br J Pharmacol* 158: 960–971.
- Ryan A, Godson C (2010). Lipoxins: regulators of resolution. *Curr Opin Pharmacol* 10: 166–172.
- Serhan CN, Chiang N (2008). Endogenous pro-resolving and anti-inflammatory lipid mediators: a new pharmacologic genus. *Br J Pharmacol* 153 Suppl 1: S200–S215.
- Serhan CN, Chiang N, Van Dyke TE (2008). Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 8: 349–361.
- Serhan CN, Yacoubian S, Yang R (2008). Anti-inflammatory and proresolving lipid mediators. *Annu Rev Pathol* 3: 279–312.
- Uddin M, Levy BD (2011). Resolvins: Natural agonists for resolution of pulmonary inflammation. *Prog Lipid Res* 50: 75–88.
- Xu ZZ, Ji RR (2011). Resolvins are potent analgesics for arthritic pain. *Br J Pharmacol* in press.
- Ye RD, Boulay F, Wang JM *et al.* (2009). International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev* 61: 119–161.

## References

- Ariel A *et al.* (2003). *J Immunol* 170: 6266–6272.
- Arita M *et al.* (2005a). *J Exp Med* 201: 713–722.
- Arita M *et al.* (2005b). *J Immunol* 178: 3912–3917.
- Chiang N *et al.* (2000). *J Exp Med* 191: 1197–1208.
- Ciana P *et al.* (2006). *EMBO J* 25: 4615–4627.
- Clish CB *et al.* (1999). *Proc Natl Acad Sci U S A* 96: 8247–8252.
- Fiore S *et al.* (1994). *J Exp Med* 180: 253–260.
- Fiore S, Serhan CN (1995). *Biochemistry* 34: 16678–16686.
- Gronert K *et al.* (2001). *Am J Pathol* 158: 3–9.
- Guilford WJ *et al.* (2004). *J Med Chem* 47: 2157–2165.
- Hosoi T *et al.* (2002). *J Biol Chem* 277: 31459–31465.
- Hosoi T *et al.* (2005). *Biochem Biophys Res Commun* 334: 987–995.
- Jiang Y *et al.* (2007). *Blood* 110: 3263–3270.
- Jones CE *et al.* (2003). *Mol Pharmacol* 63: 471–477.
- Koike D *et al.* (2006). *J Biochem (Tokyo)* 139: 543–549.
- Krishnamoorthy S *et al.* (2010). *Proc Natl Acad Sci U S A* 107: 1660–1665.
- Lin Q *et al.* (1999). *Biochemistry* 38: 185–190.
- Maddox JF *et al.* (1997). *J Biol Chem* 272: 6972–6978.
- Maddox JF, Serhan CN (1996). *J Exp Med* 183: 137–146.
- Mellor EA *et al.* (2001). *Proc Natl Acad Sci U S A* 98: 7964–7969.
- Mellor EA *et al.* (2003). *Proc Natl Acad Sci U S A* 100: 11589–11593.
- Nothacker HP *et al.* (2000). *Mol Pharmacol* 58: 1601–1608.
- O'Flaherty JT *et al.* (1998). *J Biol Chem* 273: 32535–32541.
- O'Flaherty JT *et al.* (2000). *J Immunol* 164: 3345–3352.
- Patel P *et al.* (2008). *J Pharmacol Exp Ther* 325: 698–707.
- Perretti M *et al.* (2002). *Nat Med* 8: 1296–1302.
- Resnati M *et al.* (2002). *Proc Natl Acad Sci U S A* 99: 1359–1364.
- Romano M *et al.* (1996). *J Immunol* 157: 2149–2154.
- Sarau HM *et al.* (1999). *Mol Pharmacol* 56: 657–663.
- Sodin-Semrl S *et al.* (2004). *Int J Immunopathol Pharmacol* 17: 145–156.
- Su SB *et al.* (1999). *J Exp Med* 189: 395–402.
- Takano T *et al.* (1997). *J Exp Med* 185: 1693–1704.
- Yokomizo T *et al.* (2001). *J Biol Chem* 276: 12454–12459.

# Lysophosphatidic acid

**Overview:** Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid Receptors; Chun *et al.*, 2010) are activated by the endogenous lipid derivative LPA. Originally identified as members of the endothelial differentiation gene (*edg*) family along with sphingosine 1-phosphate receptors, the gene names have been updated to *LPAR1*, etc. to reflect the receptor function of these proteins. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Radioligand binding has been conducted in heterologous expression systems using [<sup>3</sup>H]-LPA (e.g. Fukushima *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding, and therefore the relationship between recombinant and endogenously expressed receptors is unclear. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. LPA has also been described to be an agonist at PPAR $\gamma$  receptors (McIntyre *et al.*, 2003), although the physiological significance of this observation remains unclear (Simon *et al.*, 2005).

Nomenclature	LPA <sub>1</sub>	LPA <sub>2</sub>	LPA <sub>3</sub>	LPA <sub>4</sub>	LPA <sub>5</sub>	LPA <sub>6</sub>
Other names	VZG-1, Edg2, <i>lp</i> <sub>A1</sub>	Edg4, <i>lp</i> <sub>A2</sub>	Edg7, <i>lp</i> <sub>A3</sub>	p2y9, gpr23	GPR92	P2y5, P2RY5
Ensembl ID	ENSG00000198121	ENSG00000064547	ENSG00000171517	ENSG00000147145	ENSG00000184574	ENSG00000139679
Principal transduction	G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>12/13</sub>	G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>12/13</sub>	G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>s</sub>	G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>s</sub> , G <sub>12/13</sub> (Lee <i>et al.</i> , 2007)	G <sub>q</sub> , G <sub>12/13</sub> (Kotarsky <i>et al.</i> , 2006; Lee <i>et al.</i> , 2006)	G <sub>12/13</sub> (Yanagida <i>et al.</i> , 2009; Kimura <i>et al.</i> , 2011)
Selective agonists	–	FAP10, FAP12 (Virag <i>et al.</i> , 2003)	OMPT (Hasegawa <i>et al.</i> , 2003)	–	–	–
Selective antagonists	Ki16425 (Ohta <i>et al.</i> , 2003), AM966 (Swaney <i>et al.</i> , 2010)	–	DGPP 8:0 (Ohta <i>et al.</i> , 2003)	–	–	–

FAP12, VPC12249 and VPC32179 have antagonist activity at LPA<sub>1</sub> and LPA<sub>3</sub> receptors (Bagga *et al.*, 2004; Okusa *et al.*, 2003; Virag *et al.*, 2003). The selectivity of these antagonists is less than two orders of magnitude. None of the currently available chemical tools have validated specificity *in vivo*.

**Abbreviations:** AM966, (4'-[4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl]-biphenyl-4-yl)-acetic acid; DGPP 8:0, dioctanoylglycerol pyrophosphate; FAP10, decanol phosphate; FAP12, dodecanol phosphate; Ki16425, 3-(4-[4-[(1-[2-chlorophenyl]ethoxy)carbonylamino]-3-methyl-5-isoxazolyl]benzylsulfanyl)propanoic acid; OMPT, 1-oleoyl-2-O-methyl-rac-glycerophosphothionate; VPC12249, (s)-phosphoric acid mono-[3-(4-benzyloxy-phenyl)-2-octadec-9-enoylamino-propyl] ester; VPC32179, (R)-phosphoric acid mono-[2-octadec-9-enoylamino-3-[4-(pyridin-2-ylmethoxy)-phenyl]-propyl] ester

## Further Reading

- Aoki J, Inoue A, Okudaira S (2008). Two pathways for lysophosphatidic acid production. *Biochim Biophys Acta* **1781**: 513–518.
- Choi JW, Herr DR, Noguchi K, Yung YC, Lee CW, Mutoh T, Lin ME, Teo ST, Park KE, Mosley AN, Chun J (2010). LPA receptors: subtypes and biological actions. *Annu Rev Pharmacol Toxicol*, **50**: 157–186.
- Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH (2010). International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* **62**: 579–587.
- Georas SN (2009). Lysophosphatidic acid and autotaxin: emerging roles in innate and adaptive immunity. *Immunol Res* **45**: 229–238.
- Hama K, Aoki J (2010). LPA<sub>3</sub>, a unique G protein-coupled receptor for lysophosphatidic acid. *Prog Lipid Res* **49**: 335–342.
- Ishii S, Noguchi K, Yanagida K (2009). Non-Edg family lysophosphatidic acid (LPA) receptors. *Prostaglandins Other Lipid Mediat* **89**: 57–65.
- Lin ME, Herr DR, Chun J (2010). Lysophosphatidic acid (LPA) receptors: signaling properties and disease relevance. *Prostaglandins Other Lipid Mediat* **91**: 130–138.
- Meyer Zu Heringdorf D, Jakobs KH (2007). Lysophospholipid receptors: Signalling, pharmacology and regulation by lysophospholipid metabolism. *Biochim Biophys Acta* **1768**: 923–940.
- Mutoh T, Chun J (2008). Lysophospholipid activation of G protein-coupled receptors. *Subcell Biochem* **49**: 269–297.
- Noguchi K, Herr D, Mutoh T, Chun J (2009). Lysophosphatidic acid (LPA) and its receptors. *Curr Opin Pharmacol* **9**: 15–23.
- Pyne NJ, Pyne S (2008). Sphingosine 1-phosphate, lysophosphatidic acid and growth factor signaling and termination. *Biochim Biophys Acta* **1781**: 467–476.
- Shimizu T (2009). Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu Rev Pharmacol Toxicol* **49**: 123–150.
- Sun W, Yang J (2010). Molecular basis of lysophosphatidic acid-induced NF- $\kappa$ B activation. *Cell Signal* **22**: 1799–1803.
- Swaney JS, Chapman C, Correa LD, Stebbins KJ, Bunday RA, Prodanovich PC *et al.* (2010). A novel, orally active LPA<sub>1</sub> receptor antagonist inhibits lung fibrosis in the mouse bleomycin model. *Br J Pharmacol* **160**: 1699–1713.
- Tigy G (2010). Aiming drug discovery at lysophosphatidic acid targets. *Br J Pharmacol* **161**: 241–270.

**References**

- Bagga S *et al.* (2004). *Blood* **104**: 4080–4087.
- Fukushima N *et al.* (1998). *Proc Natl Acad Sci U S A* **95**: 6151–6156.
- Hasegawa Y *et al.* (2003). *J Biol Chem* **278**: 11962–11969.
- Kimura T *et al.* (2011). *Cardiovasc Res* **92**: 149–158.
- Kotarsky K *et al.* (2006). *J Pharmacol Exp Ther* **318**: 619–628.
- Lee CW *et al.* (2006). *J Biol Chem* **281**: 23589–23597.
- Lee CW *et al.* (2007). *J Biol Chem* **282**: 4310–4317.
- McIntyre TM *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 131–136.
- Ohta H *et al.* (2003). *Mol Pharmacol* **64**: 994–1005.
- Okusa MD *et al.* (2003). *Am J Physiol Renal Physiol* **285**: F565–F574.
- Simon MF *et al.* (2005). *J Biol Chem* **280**: 14656–14662.
- Virag T *et al.* (2003). *Mol Pharmacol* **63**: 1032–1042.
- Yanagida K *et al.* (2009). *J Biol Chem* **284**: 17731–17741.

# Melanin-concentrating hormone

**Overview:** Melanin-concentrating hormone (MCH) receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRQV) generated from a precursor (ENSG00000183395), which also produces neuropeptides EI and GE.

Nomenclature	MCH <sub>1</sub>	MCH <sub>2</sub>
Other names	SLC-1, GPR24	SLT, GPRv17
Ensembl ID	ENSG00000128285	ENSG00000152034
Principal transduction	G <sub>q/11</sub> , G <sub>i/o</sub>	G <sub>q/11</sub> (Hill <i>et al.</i> , 2001; Mori <i>et al.</i> , 2001; Rodriguez <i>et al.</i> , 2001)
Rank order of potency	Human MCH > salmon MCH	Human MCH = salmon MCH (Hill <i>et al.</i> , 2001)
Selective antagonists	SNAP7941 (9.2, Borowsky <i>et al.</i> , 2002), GW803430 (9, Gehlert <i>et al.</i> , 2009), ATC0175 (pIC <sub>50</sub> 7.9-8.2, Chaki <i>et al.</i> , 2005), T226296 (7.5, Takekawa <i>et al.</i> , 2002)	–
Probes	[ <sup>3</sup> H]-MCH (Burgaud <i>et al.</i> , 1997), [Phe <sup>13</sup> , [ <sup>125</sup> I]-Tyr <sup>19</sup> ]MCH (Burgaud <i>et al.</i> , 1997), [ <sup>125</sup> I]-S36057 (0.04 nM, Audinot <i>et al.</i> , 2001)	–

The MCH<sub>2</sub> receptor appears to be a non-functional pseudogene in rodents (Tan *et al.*, 2002).

**Abbreviations:** ATC0175, N-(cis-4-[[4-(dimethylamino)quinazolin-2-yl]amino]cyclohexyl)-3,4-difluorobenzamide hydrochloride; GW803430, 6-(4-chlorophenyl)-3-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]thieno[3,2-d]pyrimidin-4-one; S36057, 3-iodo-tyr-(8-amino-3,6-dioxo-octanoyl)MCH-(6-17); SNAP7941, (+)-methyl(4S)-3-([3-(4-[3-(acetylamino)phenyl]-1-piperidinyl)propyl]amino)carbonyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate hydrochloride; T226296, (-)-N-[6-(dimethylamino)-methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide

## Further Reading

- Chung S, Parks GS, Lee C, Civelli O (2011). Recent updates on the melanin-concentrating hormone (MCH) and its receptor system: lessons from MCH1R antagonists. *J Mol Neurosci* 43: 115–121.
- Chung S, Saito Y, Civelli O (2009). MCH receptors/gene structure-in vivo expression. *Peptides* 30: 1985–1989.
- Eberle AN, Mild G, Zumsteg U (2010). Cellular models for the study of the pharmacology and signaling of melanin-concentrating hormone receptors. *J Recept Signal Transduct Res* 30: 385–402.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288.
- Gao XB (2009). Electrophysiological effects of MCH on neurons in the hypothalamus. *Peptides* 30: 2025–2030.
- Kemp EH, Weetman AP (2009). Melanin-concentrating hormone and melanin-concentrating hormone receptors in mammalian skin physiology. *Peptides* 30: 2071–2075.
- Lakaye B, Coumans B, Harray S, Grisar T (2009). Melanin-concentrating hormone and immune function. *Peptides* 30: 2076–2080.
- Luthin DR (2007). Anti-obesity effects of small molecule melanin-concentrating hormone receptor 1 (MCHR1) antagonists. *Life Sci* 81: 423–440.
- Pissios P (2009). Animals models of MCH function and what they can tell us about its role in energy balance. *Peptides* 30: 2040–2044.
- Pissios P, Bradley RL, Maratos-Flier E (2006). Expanding the scales: The multiple roles of MCH in regulating energy balance and other biological functions. *Endocr Rev* 27: 606–620.
- Rokosz LL, Hobbs DW (2006). Biological examination of melanin concentrating hormone receptor 1: multi-tasking from the hypothalamus. *Drug News Perspect* 19: 273–286.
- Saito Y, Nagasaki H (2008). The melanin-concentrating hormone system and its physiological functions. *Results Probl Cell Differ* 46: 159–179.
- Shimazaki T, Yoshimizu T, Chaki S (2006). Melanin-concentrating hormone MCH1 receptor antagonists: a potential new approach to the treatment of depression and anxiety disorders. *CNS Drugs* 20: 801–811.

## References

- Audinot V *et al.* (2001). *Br J Pharmacol* 133: 371–378.
- Borowsky B *et al.* (2002). *Nat Med* 8: 825–830.
- Burgaud JL *et al.* (1997). *Biochem Biophys Res Commun* 241: 622–629.
- Chaki S *et al.* (2005). *J Pharmacol Exp Ther* 313: 831–839.
- Gehlert DR *et al.* (2009). *J Pharmacol Exp Ther* 329: 429–438.
- Hill J *et al.* (2001). *J Biol Chem* 276: 20125–20129.
- Mori M *et al.* (2001). *Biochem Biophys Res Commun* 283: 1013–1018.
- Rodriguez M *et al.* (2001). *Mol Pharmacol* 60: 632–639.
- Takekawa S *et al.* (2002). *Eur J Pharmacol* 438: 129–135.
- Tan CP *et al.* (2002). *Genomics* 79: 785–792.



# Melanocortin

**Overview:** Melanocortin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by members of the melanocortin family (MSH –  $\alpha$ ,  $\beta$ , and  $\gamma$  forms –  $\delta$  form is not found in mammals) and adrenocorticotrophin (ACTH). Endogenous antagonists include agouti and agouti-related protein (AGRP).

Nomenclature	MC <sub>1</sub>	MC <sub>2</sub>	MC <sub>3</sub>	MC <sub>4</sub>	MC <sub>5</sub>
Other names	–	ACTH	–	–	–
Ensembl ID	ENSG00000258839	ENSG00000185231	ENSG00000124089	ENSG00000166603	ENSG00000176136
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Rank order of potency	$\alpha$ -MSH > $\beta$ -MSH $\geq$ ACTH, $\gamma$ -MSH	ACTH	$\gamma$ -MSH, $\beta$ -MSH $\geq$ ACTH, $\alpha$ -MSH	$\beta$ -MSH $\geq$ $\alpha$ -MSH, ACTH > $\gamma$ -MSH	$\alpha$ -MSH $\geq$ $\beta$ -MSH $\geq$ ACTH > $\gamma$ -MSH
Selective agonists	–	–	D-Trp <sup>8</sup> - $\gamma$ -MSH (Grieco <i>et al.</i> , 2000)	THIQ (Van der Ploeg <i>et al.</i> , 2002), MK0493 (Krishna <i>et al.</i> , 2009)	–
Selective antagonists	–	–	–	HS014 (8.5, Schiöth <i>et al.</i> , 1998), MBP10 (Bednarek <i>et al.</i> , 2001)	–
Probes	[ <sup>125</sup> I]-NDP-MSH	[ <sup>125</sup> I]-ACTH-(1–24)	[ <sup>125</sup> I]-NDP-MSH, [ <sup>125</sup> I]-SHU9119	[ <sup>125</sup> I]-NDP-MSH, [ <sup>125</sup> I]-SHU9119	[ <sup>125</sup> I]-NDP-MSH

Polymorphisms of the MC<sub>1</sub> receptor have been linked to variations in skin pigmentation. Defects of the MC<sub>2</sub> receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC<sub>4</sub> receptor have been linked to obesity (Chagnon *et al.*, 1997; Farooqi and O'Rahilly, 2008).

**Abbreviations:** **HS014**, *cyc*(S–S)-(Ac-Cys<sup>11</sup>,D-Nal<sup>14</sup>,Cys<sup>18</sup>,Asp-NH<sub>2</sub>) $\beta$ -MSH-(11-22); **MBP10**, cyclo(6 $\beta$ →10 $\epsilon$ )(succinyl(6)-D-(2')Nal<sup>7</sup>-Arg<sup>8</sup>-Trp<sup>9</sup>-Lys<sup>10</sup>)-NH<sub>2</sub>; **MK0493**, N-1-(2-[1-(tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl)-5-chlorophenyl]ethyl)acetamide; **NDP-MSH**, [Nle<sup>4</sup>,d-Phe<sup>7</sup>] $\alpha$ -MSH; **SHU9119**, Ac-Nle-Asp-His-d-Nal<sup>2</sup>-Arg-Trp-Lys-NH<sub>2</sub>; **THIQ**, N-([3R]-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl)-(1R)-1-(4-chlorobenzyl)-2-(4-cyclohexyl-4-[1H-1,2,4-triazol-1-ylmethyl]piperidin-1-yl)-2-oxoethylamine

## Further Reading

- Breit A, Buch TR, Boekhoff I, Solinski HJ, Damm E, Gudermann T (2011). Alternative G protein coupling and biased agonism: new insights into melanocortin-4 receptor signalling. *Mol Cell Endocrinol* **331**: 232–240.
- Catania A (2007). The melanocortin system in leukocyte biology. *J Leukoc Biol* **81**: 383–392.
- Cooray SN, Clark AJ (2011). Melanocortin receptors and their accessory proteins. *Mol Cell Endocrinol* **331**: 215–221.
- Ducrest AL, Keller L, Roulin A (2008). Pleiotropy in the melanocortin system, coloration and behavioural syndromes. *Trends Ecol Evol* **23**: 502–510.
- Farooqi IS, O'Rahilly S (2008). Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat Clin Pract Endocrinol Metab* **4**: 569–577.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288.
- Greenfield JR (2011). Melanocortin signalling and the regulation of blood pressure in human obesity. *J Neuroendocrinol* **23**: 186–193.
- Mountjoy KG (2010). Functions for pro-opiomelanocortin-derived peptides in obesity and diabetes. *Biochem J* **428**: 305–324.
- Wikberg JE, Mutulis F (2008). Targeting melanocortin receptors: an approach to treat weight disorders and sexual dysfunction. *Nat Rev Drug Discov* **7**: 307–323.

## References

- Bednarek MA *et al.* (2001). *J Med Chem* **44**: 3665–3672.
- Chagnon YC *et al.* (1997). *Mol Med* **3**: 663–673.
- Grieco P *et al.* (2000). *J Med Chem* **43**: 4998–5002.
- Farooqi IS, O'Rahilly S (2008). *Nat Clin Pract Endocrinol Metab* **4**: 569–577.
- Krishna R *et al.* (2009). *Clin Pharmacol Ther* **86**: 659–666.
- Schiöth HB *et al.* (1998). *Br J Pharmacol* **124**: 75–82.
- Van Der Ploeg LH *et al.* (2002). *Proc Natl Acad Sci U S A* **99**: 11381–11386.

# Melatonin

**Overview:** Melatonin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on melatonin receptors, Dubocovich *et al.*, 2010) are activated by the endogenous ligands melatonin and *N*-acetylserotonin.

Nomenclature	MT <sub>1</sub>	MT <sub>2</sub>
Other names	MEL <sub>1A</sub> , ML <sub>1A</sub> , Mel <sub>1a</sub>	MEL <sub>1B</sub> , ML <sub>1B</sub> , Mel <sub>1b</sub>
Ensembl ID	ENSG00000168412	ENSG00000134640
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>
Selective agonists	–	IKK7 (Sugden <i>et al.</i> , 1999), 5-methoxyluzindole (Dubocovich <i>et al.</i> , 1997)
Selective antagonists	–	K185 (9.3, Sugden <i>et al.</i> , 1999), 4P-PDOT (8.8, Dubocovich <i>et al.</i> , 1997), DH97 (8.0, Teh and Sugden, 1998)
Probes	2-Iodo-[ <sup>125</sup> I]-melatonin (Dubocovich <i>et al.</i> , 1997), [ <sup>3</sup> H]-melatonin (Browning <i>et al.</i> , 2000)	2-Iodo-[ <sup>125</sup> I]-melatonin (Dubocovich <i>et al.</i> , 1997), [ <sup>3</sup> H]-melatonin (Browning <i>et al.</i> , 2000)

Melatonin, 2-iodo-melatonin, S20098, GR196429, LY156735 and TAK375 (Kato *et al.*, 2005) are nonselective agonists for MT<sub>1</sub> and MT<sub>2</sub> receptors. (-)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT<sub>1</sub> receptors (Ting *et al.*, 1999). Luzindole is an MT<sub>1</sub>/MT<sub>2</sub> melatonin receptor-selective competitive antagonist with some selectivity for the MT<sub>2</sub> receptor (Dubocovich *et al.*, 1998). MT<sub>1</sub>/MT<sub>2</sub> heterodimers present different pharmacological profiles from MT<sub>1</sub> and MT<sub>2</sub> receptors (Ayoub *et al.*, 2004).

The MT<sub>3</sub> binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML<sub>2</sub> receptor, binds selectively 2-iodo-[<sup>125</sup>I]-5MCA-NAT (Molinari *et al.*, 1996). Pharmacological investigations of MT<sub>3</sub> binding sites have primarily been conducted in hamster tissues. At this site, *N*-acetylserotonin (Eison and Mullins, 1993; Popova and Dubocovich, 1995; Molinari *et al.*, 1996; Lucchelli *et al.*, 1997) and 5MCA-NAT (Popova and Dubocovich, 1995) appear to function as agonists, while prazosin (Lucchelli *et al.*, 1997) functions as an antagonist. A suggested physiological function of the MT<sub>3</sub> receptor is in the control of intraocular pressure in rabbits (Pintor *et al.*, 2003). The MT<sub>3</sub> binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (ENSG00000124588, Nosjean *et al.*, 2000; 2001). *Xenopus* melanophores and chick brain express a distinct receptor (x420, P49219; c346, P49288, initially termed Mel<sub>1c</sub>) coupled to the G<sub>i/o</sub> family of G proteins, for which GPR50 has recently been suggested to be a mammalian counterpart (see Dufourny *et al.*, 2008) although melatonin does not bind to GPR50 receptors.

**Abbreviations:** 4P-PDOT, 4-phenyl-2-propionamidotetraline; AMMTC, *N*-acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole; DH97, 2-benzyl-*N*-pentanoyltryptamine; GR196429, *N*-(2-[2,3,7,8-tetrahydro-1*H*-furo(2,3-*g*)indol-1-yl]ethyl)acetamide; IKK7, *N*-butanoyl-2-(2-methoxy-6*H*-isoindolo [2,1-*a*]indol-11-yl)ethanamine; K185, *N*-butanoyl-2-(5,6,7-trihydro-11-methoxybenzo[3,4]cyclohept[2,1-*a*]indol-13-yl)ethanamine; LY156735, β-methyl-6-chloromelatonin; 5MCA-NAT, 5-methoxy-carbonylamino-*N*-acetyltryptamine; S20098, *N*-(2-[7-methoxy-1-naphthalenyl]ethyl)acetamide; TAK375, (S)-*N*-[2(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide

## Further Reading

- Alarma-Estrany P, Pintor J (2007). Melatonin receptors in the eye: location, second messengers and role in ocular physiology. *Pharmacol Ther* **113**: 507–522.
- Ambroz-Tututi M, Rocha-Gonzalez HI, Cruz SL, Granados-Soto V (2009). Melatonin: a hormone that modulates pain. *Life Sci* **84**: 489–498.
- de Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ (2010). Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. *Nat Rev Drug Discov* **9**: 628–642.
- Dubocovich ML, Delagrangre P, Krause DN, Sugden D, Cardinali DP, Olcese J (2010). International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacol Rev* **62**: 343–380.
- Dufourny L, Levasseur A, Migaud M, Callebaut I, Pontarotti P, Malpoux B *et al.* (2008). GPR50 is the mammalian ortholog of Mel<sub>1c</sub>: evidence of rapid evolution in mammals. *BMC Evol Biol* **8**: 105.
- Falcon J, Besseau L, Sauzet S, Boeuf G (2007). Melatonin effects on the hypothalamo-pituitary axis in fish. *Trends Endocrinol Metab* **18**: 81–88.
- Hardeland R (2008). Melatonin, hormone of darkness and more: occurrence, control mechanisms, actions and bioactive metabolites. *Cell Mol Life Sci* **65**: 2001–2018.
- Jockers R, Maurice P, Boutin JA, Delagrangre P (2008). Melatonin receptors, heterodimerization, signal transduction and binding sites: what's new? *Br J Pharmacol* **154**: 1182–1195.
- Luchetti F, Canonico B, Betti M, Arcangeletti M, Pilolli F, Piroddi M *et al.* (2010). Melatonin signaling and cell protection function. *FASEB J* **24**: 3603–3624.
- Reiter RJ, Tan DX, Fuentes-Broto L (2010). Melatonin: a multitasking molecule. *Prog Brain Res* **181**: 127–151.
- Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R (2008). Melatonin in the skin: synthesis, metabolism and functions. *Trends Endocrinol Metab* **19**: 17–24.
- Srinivasan V, Pandi-Perumal SR, Spence DW, Moscovitch A, Trakht I, Brown GM *et al.* (2010). Potential use of melatonergic drugs in analgesia: mechanisms of action. *Brain Res Bull* **81**: 362–371.

## References

- Ayoub MA *et al.* (2004). *Mol Pharmacol* **66**: 312–321.
- Browning C *et al.* (2000). *Br J Pharmacol* **129**: 877–886.
- Dubocovich ML *et al.* (1997). *Naunyn-Schmiedeberg's Arch Pharmacol* **355**: 365–375.

- Dubocovich ML *et al.* (1998). *FASEB J* **12**: 1211–1220.
- Eison AS, Mullins UL (1993). *Life Sci* **53**: L393–L398.
- Kato K *et al.* (2005). *Neuropharmacology* **48**: 301–310.
- Lucchelli A *et al.* (1997). *Br J Pharmacol* **121**: 1775–1781.
- Molinari EJ *et al.* (1996). *Eur J Pharmacol* **301**: 159–168.
- Nosjean O *et al.* (2000). *J Biol Chem* **275**: 31311–31317.
- Nosjean O *et al.* (2001). *Biochem Pharmacol* **61**: 1369–1379.
- Pintor J *et al.* (2003). *Br J Pharmacol* **138**: 831–836.
- Popova JS, Dubocovich ML (1995). *J Neurochem* **64**: 130–138.
- Sugden D *et al.* (1999). *Reprod Nutr Dev* **39**: 335–344.
- Teh MT, Sugden D (1998). *Naunyn-Schmiedeberg's Arch Pharmacol* **358**: 522–528.
- Ting KN *et al.* (1999). *Br J Pharmacol* **127**: 987–995.

# Motilin

**Overview:** Motilin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by a 22 amino-acid peptide derived from a precursor (ENSG0000096395), which also generates motilin-associated peptide. These receptors are suggested to be responsible for the gastrointestinal prokinetic effects of motilides (particular macrolide antibiotics) as well as small molecule receptor agonists.

Nomenclature	Motilin
Other names	MTLR1 (Feighner <i>et al.</i> , 1999), GPR38 (Mckee <i>et al.</i> , 1997)
Ensembl ID	ENSG00000102539
Principal transduction	G <sub>q/11</sub> (Depoortere and Peeters, 1995; Feighner <i>et al.</i> , 1999)
Rank order of potency	Motilin > ABT229, mitemcinal > erythromycin (Clark <i>et al.</i> , 1999) = GSK962040 (Sanger <i>et al.</i> , 2009)
Selective agonists	ABT229 (Lartey <i>et al.</i> , 1995), mitemcinal (Koga <i>et al.</i> , 1994; Takanashi <i>et al.</i> , 2007), GSK962040 (Sanger <i>et al.</i> , 2009)
Selective antagonists	MA2029 (pA <sub>2</sub> 9.2, Sudo <i>et al.</i> , 2008), GM109 (Takanashi <i>et al.</i> , 1995; pA <sub>2</sub> 7.2-7.5 Clark <i>et al.</i> , 1999)
Probes	[ <sup>125</sup> I]-Motilin (0.1 nM, Feighner <i>et al.</i> , 1999)

In rodents, the gene encoding the motilin precursor appears to be absent, while the receptor appears to be a pseudogene. Functions of motilin are not usually detected in rodents, although brain and other responses to motilin have been reported; the mechanism of action is obscure (see Sanger *et al.*, 2011).

**Abbreviations:** **ABT229**, 8,9-anhydro-4"-deoxy-3'-N-desmethyl-3'-N-ethylerythromycin B 6,9-hemiacetal; **GM109**, phe-cyclo[Lys-Tyr(3-tBu)-β-Ala].trifluoroacetate; **GSK962040**, N-(3-fluorophenyl)-1-[(4-[(3S)-3-methyl-1-piperazinyl]methyl)phenyl]acetyl]-4-piperidinamine; **MA2029**, (S)-N-[(S)-2-(3-tert-butyl-4-hydroxy-phenyl)-1-ethylcarbamoyl-ethyl]-3-methyl-2-[methyl-(S)-2-methylamino-3-phenyl-propionyl]-amino]-butyramide hydrochloride; **mitemcinal**, de(N-methyl)-11-deoxy-N-isopropyl-12-O-methyl-11-oxo-8,9-anhydroerythromycin A 6,9-hemiacetal fumaric acid, also known as GM611

## Further Reading

- Ceddia RB (2011). Motilin beyond gut motility: A novel role in the regulation of adipose tissue metabolism. *Am J Physiol Endocrinol Metab* in press.
- De Smet B, Mitselos A, Depoortere I (2009). Motilin and ghrelin as prokinetic drug targets. *Pharmacol Ther* **123**: 207–223.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288.
- Sanger GJ (2008). Motilin, ghrelin and related neuropeptides as targets for the treatment of GI diseases. *Drug Discov Today* **13**: 234–239.
- Sanger GJ, Holbrook JD, Andrews PL (2011). The translational value of rodent gastrointestinal functions: a cautionary tale. *Trends Pharmacol Sci* **32**: 402–409.
- Takeshita E, Matsuura B, Dong M, Miller LJ, Matsui H, Onji M (2006). Molecular characterization and distribution of motilin family receptors in the human gastrointestinal tract. *J Gastroenterol* **41**: 223–230.

## References

- Clark MJ *et al.* (1999). *Clin Exp Pharmacol Physiol* **26**: 242–245.
- Depoortere I, Peeters TL (1995). *Regul Pept* **55**: 227–235.
- Feighner SD *et al.* (1999). *Science* **284**: 2184–2188.
- Koga H *et al.* (1994). *Bioorg Med Chem Lett* **4**: 1347–1352.
- Lartey PA *et al.* (1995). *J Med Chem* **38**: 1793–1798.
- McKee KK *et al.* (1997). *Genomics* **46**: 426–434.
- Sanger GJ *et al.* (2009). *Neurogastroenterol Motil* **21**: 657–1.
- Sudo H *et al.* (2008). *Eur J Pharmacol* **581**: 296–305.
- Takanashi H *et al.* (1995). *J Pharmacol Exp Ther* **273**: 624–628.
- Takanashi H *et al.* (2007). *Pharmacology* **79**: 137–148.

# Neuromedin U

**Overview:** Neuromedin U receptors (provisional nomenclature) are activated by the endogenous 25 amino acid peptide neuromedin U (NMU), a peptide originally isolated from pig spinal cord (Minamino *et al.*, 1985). In humans, NMU appears to be the sole product of a precursor (ENSG00000109255) showing a broad tissue distribution, but which is expressed at highest levels in the upper gastrointestinal tract, CNS, bone marrow and fetal liver. Much shorter versions of NMU are found in some species, but not human, and are derived at least in some instances from the proteolytic cleavage of the longer NMU. Despite species differences in NMU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity. Neuromedin S (NMS) has also been identified as an endogenous agonist (Mori *et al.*, 2005). NMS is a 36 amino-acid product of a precursor protein derived from a single gene (ENSG00000204640) and contains an amidated C-terminal heptapeptide identical to NMU. NMS appears to activate NMU receptors with equivalent potency to NMU.

Nomenclature	NMU1	NMU2
Other names	GPR66, FM3, SNORF62 (Fujii <i>et al.</i> , 2000; Hedrick <i>et al.</i> , 2000; Hosoya <i>et al.</i> , 2000; Howard <i>et al.</i> , 2000; Kojima <i>et al.</i> , 2000; Raddatz <i>et al.</i> , 2000; Szekeres <i>et al.</i> , 2000)	FM4, TGR1, SNORF72 (Hosoya <i>et al.</i> , 2000; Howard <i>et al.</i> , 2000; Raddatz <i>et al.</i> , 2000; Shan <i>et al.</i> , 2000)
Ensembl ID	ENSG00000171596	ENSG00000132911
Principal transduction	G <sub>q/11</sub> (Hedrick <i>et al.</i> , 2000; Brighton <i>et al.</i> , 2004a)	G <sub>q/11</sub> (Hosoya <i>et al.</i> , 2000; Brighton <i>et al.</i> , 2004a)
Antagonists	–	R-PSOP (Liu <i>et al.</i> , 2009)

NMU1 and NMU2 couple predominantly to G<sub>q/11</sub> although there is evidence of good coupling to G<sub>i/o</sub> (see Hosoya *et al.*, 2000; Brighton *et al.*, 2004a; Hsu and Luo, 2007). NMU1 and NMU2 can be labelled with [<sup>125</sup>I]-NMU and [<sup>125</sup>I]-NMS (of various species, e.g. Meng *et al.*, 2008); BODIPY<sup>®</sup> TMR-NMU or Cy3B-NMU-8 (Brighton *et al.*, 2004a). A range of radiolabelled (<sup>125</sup>I-), fluorescently labelled (e.g. Cy3, Cy5, rhodamine and FAM) and biotin labelled versions of NMU and NMS are now commercially available.

**Abbreviations:** NMS, neuromedin S; NMU, neuromedin U; R-PSOP, (R)-5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

## Further Reading

- Brighton PJ, Szekeres PG, Willars GB (2004b). Neuromedin U and its receptors: structure, function, and physiological roles. *Pharmacol Rev* 56: 231–248.
- Budhiraja S, Chugh A (2009). Neuromedin U: physiology, pharmacology and therapeutic potential. *Fundam Clin Pharmacol* 23: 149–157.
- Mitchell JD, Maguire JJ, Davenport AP (2009). Emerging pharmacology and physiology of neuromedin U and the structurally related peptide neuromedin S. *Br J Pharmacol* 158: 87–103.
- Novak CM (2009). Neuromedin S and U. *Endocrinology* 150: 2985–2987.

## References

- Brighton PJ *et al.* (2004a). *Mol Pharmacol* 66: 1544–1556.
- Fujii R *et al.* (2000). *J Biol Chem* 275: 21068–21074.
- Hedrick JA *et al.* (2000). *Mol Pharmacol* 58: 870–875.
- Hosoya M *et al.* (2000). *J Biol Chem* 275: 29528–29532.
- Howard AD *et al.* (2000). *Nature* 406: 70–74.
- Hsu S-H and Luo C-W (2007) *Am J Physiol Endocrinol Metab* 293: E1021–E1029.
- Kojima M *et al.* (2000) *Biochem Biophys Res Commun* 276: 435–438.
- Liu JJ *et al.* (2009) *J Pharmacol Exptl Therap* 330: 268–275.
- Meng T *et al.* (2008) *Acta Pharmacol Sin* 29: 517–527.
- Minamino N *et al.* (1985). *Biochem Biophys Res Commun* 130: 1078–1085.
- Mori K *et al.* (2005). *EMBO J* 24: 325–335.
- Raddatz R *et al.* (2000). *J Biol Chem* 275: 32452–32459.
- Shan L *et al.* (2000). *J Biol Chem* 275: 39482–39486.
- Szekeres PG *et al.* (2000). *J Biol Chem* 275: 20247–20250.

# Neuropeptide S

**Overview:** The neuropeptide S receptor (NPS, provisional nomenclature, see Foord *et al.*, 2005) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (ENSG00000214285).

Nomenclature	NPS
Other names	GPRA, GPR154, vasopressin receptor-related receptor 1, PGR14
Ensembl ID	ENSG00000187258
Principal transduction	G <sub>s</sub> , G <sub>q/11</sub> (Gupte <i>et al.</i> , 2004; Vendelin <i>et al.</i> , 2005)
Selective agonists	NPS
Probes	[ <sup>125</sup> I-Tyr <sup>10</sup> ]-NPS

Polymorphisms in the NPS receptor have been suggested to be associated with asthma (Vendelin *et al.*, 2005) and irritable bowel syndrome (D'Amato *et al.*, 2007).

## Further Reading

- Dal Ben D, Antonini I, Buccioni M, Lambertucci C, Marucci G, Thomas A *et al.* (2011). Neuropeptide S receptor: recent updates on nonpeptide antagonist discovery. *Chem Med Chem* **6**: 1163–1171.
- Dal Ben D, Antonini I, Buccioni M, Lambertucci C, Marucci G, Vittori S *et al.* (2010). Molecular modeling studies on the human neuropeptide S receptor and its antagonists. *Chem Med Chem* **5**: 371–383.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288.
- Guerrini R, Salvadori S, Rizzi A, Regoli D, Calo' G (2010). Neurobiology, pharmacology, and medicinal chemistry of neuropeptide S and its receptor. *Med Res Rev* **30**: 751–777.
- Pape HC, Jungling K, Seidenbecher T, Lesting J, Reinscheid RK (2010). Neuropeptide S: a transmitter system in the brain regulating fear and anxiety. *Neuropharmacology* **58**: 29–34.
- Reinscheid RK (2008). Neuropeptide S: anatomy, pharmacology, genetics and physiological functions. *Results Probl Cell Differ* **46**: 145–158.

## References

- D'Amato M *et al.* (2007). *Gastroenterology* **133**: 808–817.
- Gupte J *et al.* (2004). *Proc Natl Acad Sci U S A* **101**: 1508–1513.
- Vendelin J *et al.* (2005). *Am J Respir Cell Mol Biol* **33**: 262–270.

# Neuropeptide Y

**Overview:** Neuropeptide Y (NPY) receptors (nomenclature agreed by NC-IUPHAR on Neuropeptide Y Receptors, see Michel *et al.*, 1998) are activated by the endogenous peptides NPY, NPY-(3-36), peptide YY (PYY), PYY-(3-36) and pancreatic polypeptide (PP). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine receptor (originally named LESTR, Loetscher *et al.*, 1994). The y6 receptor is a functional gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated non-functional gene (Gregor *et al.*, 1996). Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the relative potency of PP is greater at the rat Y<sub>4</sub> receptor than at the human receptor (Eriksson *et al.*, 1998). In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [<sup>125</sup>I]-PYY or [<sup>125</sup>I]-NPY can be used to label Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>5</sub> and Y<sub>6</sub> subtypes non-selectively, while [<sup>125</sup>I]-[cPP(1-7),NPY(19-23),Ala<sup>31</sup>,Aib<sup>32</sup>,Gln<sup>34</sup>]hPP may be used to label Y<sub>5</sub> receptors preferentially.

Nomenclature	Y <sub>1</sub>	Y <sub>2</sub>	Y <sub>4</sub>	Y <sub>5</sub>	Y <sub>6</sub>
Other names	–	–	PP <sub>1</sub>	–	Y <sub>5</sub> , PP <sub>2</sub> , Y <sub>28</sub>
Ensembl ID	ENSG00000164128	ENSG00000185149	ENSG00000204174	ENSG00000164129	ENSG00000226306
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Rank order of potency	NPY ≥ PYY >> PP	NPY ≥ PYY >> PP	PP > NPY = PYY	NPY ≥ PYY ≥ PP	NPY = PYY > PP
Selective agonists	[Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY, [Pro <sup>34</sup> ]NPY, [Leu <sup>31</sup> ,Pro <sup>34</sup> ]PYY, [Pro <sup>34</sup> ]PYY	NPY-(3-36), PYY-(3-36)	PP	[Ala <sup>31</sup> ,Aib <sup>32</sup> ]NPY (Cabrele <i>et al.</i> , 2000)	–
Selective antagonists	BIBO3304 (9.5, Wieland <i>et al.</i> , 1998), BIBP3226 (8.2, Gerald <i>et al.</i> , 1996)	BIIE0246 (8.5, Doods <i>et al.</i> , 1999), JNJ5207787 (Bonaventure <i>et al.</i> , 2004)	–	L152804 (7.6, Kanatani <i>et al.</i> , 2000)	–
Probes	[ <sup>125</sup> I]-[Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY, [ <sup>3</sup> H]-BIBP3226 (2.1 nM)	[ <sup>125</sup> I]-PYY-(3-36)	[ <sup>125</sup> I]-PP	[ <sup>125</sup> I]-[cPP(1-7),NPY(19-23), Ala <sup>31</sup> ,Aib <sup>32</sup> ,Gln <sup>34</sup> ]hPP (Dumont <i>et al.</i> , 2004)	–

The Y<sub>1</sub> agonists indicated are selective relative to Y<sub>2</sub> receptors. BIBP3226 is selective relative to Y<sub>2</sub>, Y<sub>4</sub> and Y<sub>5</sub> receptors (Gerald *et al.*, 1996). NPY-(13-36) is Y<sub>2</sub> selective relative to Y<sub>1</sub> and Y<sub>5</sub> receptors. PYY-(3-36) is Y<sub>2</sub> selective relative to Y<sub>1</sub> receptors.

**Abbreviations:** **BIBO3304:** (R)-N-([4-{aminocarbonylaminoethyl}-phenyl]methyl)-N<sup>2</sup>-(diphenylacetyl)-argininamide trifluoroacetate; **BIBP3226:** R-N<sup>2</sup>-(diphenylacetyl)-N-(4-hydroxyphenyl)methyl-argininamide; **BIIE0246:** (S)-N<sup>2</sup>-([1-[2-(4-[(R,S)-5,11-dihydro-6(6H)-oxodibenz[b,e]azepin-11-yl]-1-piperazinyl)-2-oxoethyl]cyclopentyl]acetyl)-N-(2-[1,2-dihydro-3,5(4H)-dioxo-1,2-diphenyl-3H-1,2,4-triazol-4-yl]ethyl)-argininamide; **JNJ5207787,** N-(1-acetyl-2,3-dihydro-1H-indol-6-yl)-3-(3-cyano-phenyl)-N-[1-(2-cyclopentylethyl)piperidin-4-yl]acrylamide; **L152804:** 2-(3,3-dimethyl-1-oxo-4H-1H-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione

## Further Reading

- Brothers SP, Wahlestedt C (2010). Therapeutic potential of neuropeptide Y (NPY) receptor ligands. *EMBO Mol Med* 2: 429–439.
- Lunniss GE, Barnes AA, Barton N *et al.* (2009). The identification and optimisation of novel and selective diamide neuropeptide Y Y2 receptor antagonists. *Bioorg Med Chem Lett* 19: 4022–4025.
- Michel MC, Beck-Sickingler A, Cox H, Doods HN, Herzog H, Larhammar D, Quirion R, Schwartz T, Westfall T (1998). International Union of Pharmacology XVI. Recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors. *Pharmacol Rev* 50: 143–150.
- Nguyen AD, Herzog H, Sainsbury A (2011). Neuropeptide Y and peptide YY: important regulators of energy metabolism. *Curr Opin Endocrinol Diabetes Obes* 18: 56–60.
- Tough IR, Holliday ND, Cox HM (2006) Y<sub>4</sub> receptors mediate the inhibitory responses of pancreatic polypeptide in human and mouse colon mucosa. *J Pharmacol Exp Ther* 319: 20–30.

## References

- Bonaventure P *et al.* (2004). *J Pharmacol Exp Ther* 308: 1130–1137.
- Cabrele C *et al.* (2000). *J Biol Chem* 275: 36043–36048.
- Doods H *et al.* (1999). *Eur J Pharmacol* 384: R3–R5.
- Dumont Y *et al.* (2004). *Neuropeptides* 38: 163–174.
- Eriksson H *et al.* (1998). *Regul Pept* 75-76: 29–37.
- Gerald C *et al.* (1996). *Nature* 382: 168–171.
- Gregor P *et al.* (1996). *J Biol Chem* 271: 27776–27781.
- Kanatani A *et al.* (2000). *Biochem Biophys Res Commun* 272: 169–173.
- Loetscher M *et al.* (1994). *J Biol Chem* 269: 232–237.
- Wieland HA *et al.* (1998). *Br J Pharmacol* 125: 549–555.

# Neuropeptides B and W

**Overview:** The neuropeptide BW receptor 1 (NPBW1, provisional nomenclature) is activated by two 23-amino-acid peptides, neuropeptide W (NPW-23) and neuropeptide B (NPB-23) (Shimomura *et al.*, 2002; Fujii *et al.*, 2002). C-terminally extended forms of the peptides (NPW-30 and NPB-29) also activate NPBW1 (Brezillon *et al.*, 2003). Unique to both forms of NPB is the N-terminal bromination of the first tryptophan residue. des-Br-NPB-23 and des-Br-NPB-29 were not found to be major components of bovine hypothalamic tissue extracts. The NPBW2 receptor is activated by the short and C-terminal extended forms of NPB and NPW (Brezillon *et al.*, 2003).

Nomenclature	NPBW1	NPBW2
Other names	GPR7	GPR8
Ensembl ID	ENSG00000183729	ENSG00000125522
Principal transduction	G <sub>i/o</sub> (Mazzocchi <i>et al.</i> , 2005)	G <sub>i/o</sub> (Mazzocchi <i>et al.</i> , 2005)
Rank order of potency	NPB-29 > NPB-23 > NPW-23 > NPW-30 (Brezillon <i>et al.</i> , 2003)	NPW-23 > NPW-30 > NPB-29 > NPB-23 (Brezillon <i>et al.</i> , 2003)
Selective agonists	Ava-3, Ava-5 (Kanesaka <i>et al.</i> , 2007)	–
Probes	[ <sup>125</sup> I]-NPW-23 (0.44 nM, Singh <i>et al.</i> , 2004)	[ <sup>125</sup> I]-NPW-23

Potency measurements were conducted with heterologously-expressed receptors with a range of 0.14–0.57 nM (NPBW1) and 0.98–21 nM (NPBW2).

**Abbreviations:** Ava3, TrpTyrLysAvaAvaAvaGlyArgAlaAlaGlyLeuLeuSerGlyLeu-NH<sub>2</sub>; Ava5, TrpTyrLysAvaAvaAvaAvaAvaAvaGlyArgAlaAlaGlyLeuLeuSerGlyLeu-NH<sub>2</sub>

## Further Reading

Lee DK, George SR, O'Dowd BF (2003). Continued discovery of ligands for G protein-coupled receptors. *Life Sci* **74**: 293–297.  
 Hondo M, Ishii M, Sakurai T (2008). The NPB/NPW neuropeptide system and its role in regulating energy homeostasis, pain, and emotion. *Results Probl Cell Differ* **46**: 239–256.  
 Singh G, Davenport AP (2006). Neuropeptide B and W: neurotransmitters in an emerging G-protein-coupled receptor system. *Br J Pharmacol* **148**: 1033–1041.

## References

- Brezillon S *et al.* (2003). *J Biol Chem* **278**: 776–783.  
 Fujii R *et al.* (2002). *J Biol Chem* **277**: 34010–34016.  
 Kanesaka M *et al.* (2007). *J Peptide Sci* **13**:379–385.  
 Mazzocchi G *et al.* (2005). *J Clin Endocrinol Metab* **90**: 3466–3471.  
 Shimomura Y *et al.* (2002). *J Biol Chem* **277**: 35826–35832.  
 Singh G *et al.* (2004). *Brain Res* **1017**: 222–226.  
 Singh G, Davenport AP (2006). *Br J Pharmacol* **148**: 1033–1041.



# Neurotensin

**Overview:** Neurotensin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (ENSG00000133636), which also generates neuromedin N, an agonist at the NTS<sub>2</sub> receptor. A nonpeptide antagonist, SR142948A, shows high affinity (pK<sub>i</sub>~9) at both NTS<sub>1</sub> and NTS<sub>2</sub> receptors (Gully *et al.*, 1997). [<sup>3</sup>H]-Neurotensin and [<sup>125</sup>I]-neurotensin may be used to label NTS<sub>1</sub> and NTS<sub>2</sub> receptors at 0.1–0.3 and 3–5 nM concentrations, respectively.

Nomenclature	NTS <sub>1</sub>	NTS <sub>2</sub>
Other names	High-affinity neurotensin receptor, NTRH, NTR-1, NT <sub>1</sub>	Low-affinity neurotensin receptor, NTRL, NTR-1, NT <sub>2</sub>
Ensembl ID	ENSG00000101188	ENSG00000169006
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	Neurotensin > neuromedin N (Hermans <i>et al.</i> , 1997)	Neurotensin = neuromedin N (Mazella <i>et al.</i> , 1996)
Selective agonists	JMV449 (Souaze <i>et al.</i> , 1997)	Levocobastine (Mazella <i>et al.</i> , 1996)
Selective antagonists	SR48692 (7.5–8.2; Gully <i>et al.</i> , 1997)	–
Probes	[ <sup>3</sup> H]-SR48692 (3.4 nM; Labbe-Jullie <i>et al.</i> , 1995)	–

Neurotensin appears to be a low-efficacy agonist at the NTS<sub>2</sub> receptor (Vita *et al.*, 1998), while the NTS<sub>1</sub> receptor antagonist SR48692 is an agonist at NTS<sub>2</sub> receptors (Vita *et al.*, 1998). An additional protein, provisionally termed NTS3 (also known as NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation (Nielsen *et al.*, 1999). It has been reported to interact with the NTS<sub>1</sub> receptor (Martin *et al.*, 2002) and has been implicated in hormone trafficking and/or neurotensin uptake.

**Abbreviations:** **JMV449**, *H*-Lysψ (CH<sub>2</sub>NH)-Lys-Pro-Tyr-Ile-Leu; **SR142948A**, 2-([5-[2,6-dimethoxyphenyl]-1-[4-(*N*-[3-dimethylaminopropyl]-*N*-methylcarbamoyl)-2-isopropylphenyl]-1*H*-pyrazole-3-carbonyl]amino)adamantane-2-carboxylic acid hydrochloride; **SR48692**, 2-([1-[7-chloro-4-quinoliny]-5-[2,6-dimethoxyphenyl]pyrazol-3-yl]carboxylamino)tricyclo(3.3.1.1.[3.7])decan-2-carboxylic acid

## Further Reading

- Antonelli T, Fuxe K, Tomasini MC, Mazzoni E, Agnati LF, Tanganelli S *et al.* (2007). Neurotensin receptor mechanisms and its modulation of glutamate transmission in the brain: relevance for neurodegenerative diseases and their treatment. *Prog Neurobiol* **83**: 92–109.
- Boules M, Shaw A, Fredrickson P, Richelson E (2007). Neurotensin agonists: potential in the treatment of schizophrenia. *CNS Drugs* **21**: 13–23.
- Ferraro L, Tomasini MC, Mazza R, Fuxe K, Fournier J, Tanganelli S *et al.* (2008). Neurotensin receptors as modulators of glutamatergic transmission. *Brain Res Rev* **58**: 365–373.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288.
- Hwang JI, Kim DK, Kwon HB, Vaudry H, Seong JY (2009). Phylogenetic history, pharmacological features, and signal transduction of neurotensin receptors in vertebrates. *Ann N Y Acad Sci* **1163**: 169–178.

## References

- Gully D *et al.* (1997). *J Pharmacol Exp Ther* **280**: 802–812.
- Hermans E *et al.* (1997). *Br J Pharmacol* **121**: 1817–1823.
- Labbe-Jullie C *et al.* (1995). *Mol Pharmacol* **47**: 1050–1056.
- Martin S *et al.* (2002). *Gastroenterology* **123**: 1135–1143.
- Mazella J *et al.* (1996). *J Neurosci* **16**: 5613–5620.
- Nielsen MS *et al.* (1999). *J Biol Chem* **274**: 8832–8836.
- Souaze F *et al.* (1997). *J Biol Chem* **272**: 10087–10094.
- Vita N *et al.* (1998). *Eur J Pharmacol* **360**: 265–272.

# Opioid and opioid-like

**Overview:** Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (met), [Leu]enkephalin (leu),  $\beta$ -endorphin ( $\beta$ -end),  $\alpha$ -neo-dynorphin, dynorphin A (dynA), dynorphin B (dynB), Big dynorphin (Big dyn), nociceptin/orphanin FQ (N/OFQ), and possibly endomorphin -1 and -2. The Greek letter names for the opioid receptors,  $\mu$ ,  $\delta$ , and  $\kappa$ , are well established and IUPHAR considers these names most appropriate (Foord *et al.*, 2005). The human N/OFQ receptor is considered 'opioid-related' rather than opioid because while it exhibits a high degree of structural homology with the conventional opioid receptors (Mollereau *et al.*, 1994), it displays a distinct pharmacology.

Nomenclature	Delta opioid receptor	Kappa opioid receptor	Mu opioid receptor	N/OFQ receptor
Preferred abbreviation	$\delta$	$\kappa$	$\mu$	NOP
Other names	OP <sub>1</sub> , DOP, DOR	OP <sub>2</sub> , KOP, KOR	OP <sub>3</sub> , MOP, MOR	ORL1, OP <sub>4</sub>
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>
Rank order of potency	$\beta$ -End = leu = met > dynA	Big dyn > dynA >> $\beta$ -end > leu > met	$\beta$ -End > met $\geq$ leu $\geq$ dynA	N/OFQ >> dynA
Selective agonists	DPDPE (Mosberg <i>et al.</i> , 1983), DSBULET (Delay-Goyet <i>et al.</i> , 1988), [DAla <sup>2</sup> ]deltorphin I or II (Erspamer <i>et al.</i> , 1989), SNC80 (Bilsky <i>et al.</i> , 1995)	U69593 (Lahti <i>et al.</i> , 1985), CI977 (Hunter <i>et al.</i> , 1990), Salvinorin A (Roth <i>et al.</i> , 2002)	Endomorphin-1 and -2 (Zadina <i>et al.</i> , 1997), morphine (Goldstein and Naidu, 1989), DAMGO (Handa <i>et al.</i> , 1981), sufentanil (Yeadon and Kitchen, 1988), PL017 (Costa <i>et al.</i> , 1992)	N/OFQ, N/OFQ-(1-13)-NH <sub>2</sub> (Guerrini <i>et al.</i> , 1997), Ro646198 (Jenck <i>et al.</i> , 2000), UFP-112 (Rizzi <i>et al.</i> , 2007)
Selective antagonists	Naltrindole (Portoghese <i>et al.</i> , 1988), naltriben (Sofuoglu <i>et al.</i> , 1991)	Nor-binaltorphimine (Portoghese <i>et al.</i> , 1987), GNTI (Stevens <i>et al.</i> , 2000)	CTAP (Pelton <i>et al.</i> , 1986)	J113397 (8.3, Kawamoto <i>et al.</i> , 1999), SB612111 (9.5, Zaratin <i>et al.</i> , 2004), UFP101 (7.2, Calo' <i>et al.</i> , 2002)
Probes	[ <sup>3</sup> H]-DPDPE (Goldstein and Naidu, 1989), [ <sup>3</sup> H]-naltrindole (Yamamura <i>et al.</i> , 1992), [ <sup>3</sup> H]-deltorphin II (Gomes <i>et al.</i> , 2000), [ <sup>3</sup> H]-naltriben (Lever and Scheffel, 1998)	[ <sup>3</sup> H]-U69593 (Lahti <i>et al.</i> , 1985), [ <sup>3</sup> H]-CI977 (Simonin <i>et al.</i> , 2001)	[ <sup>3</sup> H]-DAMGO (Goldstein and Naidu, 1989), [ <sup>3</sup> H]-PL017 (Hawkins <i>et al.</i> , 1987)	[ <sup>3</sup> H]-N/OFQ (Dooley and Houghten, 1996), [ <sup>3</sup> H]-Leu-N/OFQ, [ <sup>125</sup> I]-Tyr <sup>14</sup> -N/OFQ

Subtypes of  $\mu$  ( $\mu$ 1,  $\mu$ 2),  $\delta$  ( $\delta$ 1,  $\delta$ 2) and  $\kappa$  ( $\kappa$ 1,  $\kappa$ 2,  $\kappa$ 3) receptor have been proposed based primarily on binding studies with poorly selective ligands or results from *in vivo* studies. Only three naloxone-sensitive opioid receptors have been cloned, and while the  $\mu$ -receptor in particular may be subject to extensive alternative splicing, these putative isoforms have not been definitively correlated with any of the proposed subtypes. A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (ENSG00000060491) and termed an opioid growth factor receptor. Opioid receptor subtypes may reflect hetero-dimerization of opioid receptors with each other or with other GPCR, and while there is increasing evidence for heterodimers in native cells, the consequences of this heterodimerization for signalling remains largely unknown. For  $\mu$ -opioid receptors at least, dimerization does not seem to be required for signalling (Kuszk *et al.*, 2009).

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human  $\mu$ -receptors (see Oertel *et al.*, 2009) and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists (Bruchas *et al.*, 2007). As ever, the mechanisms underlying the acute and long term regulation of opioid receptor function are the subject of intense investigation and debate.

**Abbreviations:** CI977, (5R)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-(-)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro[4,5]dec-8-yl)-4-benzofuranacetamide hydrochloride; CTAP, D-Phe-cyc[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-NH<sub>2</sub>; DAMGO, Tyr-DAla-Gly-[NMePhe]-NH(CH<sub>2</sub>)<sub>2</sub>; DPDPE, cyc[DPen<sup>2</sup>, DPen<sup>3</sup>]enkephalin; DSBULET, Tyr-D-Ser(OtBu)-Gly-Phe-Leu-Thr; GNTI, 5'-guanidinyl-17-(cyclopropylmethyl)-6,7-dehydro-4,5 $\alpha$ -epoxy-3,14-dihydroxy-6,7-2',3'-indolomorphinan; ICI174864, N,N-diallyl-Tyr-Aib-Phe-Leu-OH (Aib is aminoisobutyric acid); J113397, 1-[(3*r*,4*r*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one; PL017, [N-MePhe<sup>3</sup>,DPro<sup>4</sup>]morphiceptin; Ro646198, (1*S*,3*aS*)-8-(2,3,3*a*,4,5,6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one; SB612111, (-)-*cis*-1-methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol; SNC80, (+)-4-[( $\alpha$ R)- $\alpha$ -(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide; U69593, 5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ -( $\alpha$ )-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro(4,5)dec-8-yl)benzene acetamide; UFP101, [Nphe<sup>1</sup>,Arg<sup>14</sup>,Lys<sup>15</sup>]nociceptin-NH<sub>2</sub>; UFP-112, [(pF)Phe<sup>4</sup>Aib<sup>7</sup>Arg<sup>14</sup>Lys<sup>15</sup>]N/OFQ-NH<sub>2</sub>

## Further Reading

Armstead WM (2011). Nociceptin/orphanin phenylalanine glutamine (FQ) receptor and cardiovascular disease. *Cardiovasc Ther* 29: 23–28.  
Ballantyne JC, Laforge KS (2007). Opioid dependence and addiction during opioid treatment of chronic pain. *Pain* 129: 235–255.  
Bruchas MR, Land BB, Chavkin C (2010). The dynorphin/ $\kappa$  opioid system as a modulator of stress-induced and pro-addictive behaviors. *Brain Res* 1314: 44–55.

- Brujnzeel AW (2009).  $\kappa$ -Opioid receptor signaling and brain reward function. *Brain Res Rev* **62**: 127–146.
- Bushlin I, Rozenfeld R, Devi LA (2010). Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Curr Opin Pharmacol* **10**: 80–86.
- Cahill CM, Holdridge SV, Morinville A (2007). Trafficking of  $\delta$ -opioid receptors and other G-protein-coupled receptors: implications for pain and analgesia. *Trends Pharmacol Sci* **28**: 23–31.
- Carlezon WA, Jr., Beguin C, Knoll AT, Cohen BM (2009).  $\kappa$ -opioid ligands in the study and treatment of mood disorders. *Pharmacol Ther* **123**: 334–343.
- DeHaven-Hudkins DL, DeHaven RN, Little PJ, Techner LM (2008). The involvement of the  $\mu$ -opioid receptor in gastrointestinal pathophysiology: therapeutic opportunities for antagonism at this receptor. *Pharmacol Ther* **117**: 162–187.
- Doll C, Konietzko J, Poll F, Koch T, Hollt V, Schulz S (2011). Agonist-selective patterns of  $\mu$ -opioid receptor phosphorylation revealed by phosphosite-specific antibodies. *Br J Pharmacol* **164**: 298–307.
- Fichna J, Janecka A, Costentin J, Do Rego JC (2007). The endomorphin system and its evolving neurophysiological role. *Pharmacol Rev* **59**: 88–123.
- Gomes I, IJzerman AP, Ye K, Maillet EL, Devi LA (2011). G protein-coupled receptor heteromerization: a role in allosteric modulation of ligand binding. *Mol Pharmacol* **79**: 1044–1052.
- Henriksen G, Willoch F (2008). Imaging of opioid receptors in the central nervous system. *Brain* **131**: 1171–1196.
- Kieffer BL, Evans CJ (2009). Opioid receptors: from binding sites to visible molecules in vivo. *Neuropharmacology* **56** (Suppl 1): 205–212.
- Koch T, Hollt V (2008). Role of receptor internalization in opioid tolerance and dependence. *Pharmacol Ther* **117**: 199–206.
- Lambert DG (2008). The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential. *Nat Rev Drug Discov* **7**: 694–710.
- Morgan MM, Christie MJ (2011). Analysis of opioid efficacy, tolerance, addiction, and dependence from cell culture to human. *Br J Pharmacol* **164**: 1322–1334.
- Oertel BG, Kettner M, Scholich K, Renne C, Roskam B, Geisslinger G *et al.* (2009). A common human micro-opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain. *J Biol Chem* **284**: 6530–6535.
- Pineyro G, Archer-Lahlou E (2007). Ligand-specific receptor states: implications for opiate receptor signalling and regulation. *Cell Signal* **19**: 8–19.
- Pradhan AA, Walwyn W, Nozaki C, Filliol D, Erbs E, Matifas A *et al.* (2010). Ligand-directed trafficking of the delta-opioid receptor in vivo: two paths toward analgesic tolerance. *J Neurosci* **30**: 16459–16468.
- Schwarzer C (2009). 30 years of dynorphins – new insights on their functions in neuropsychiatric diseases. *Pharmacol Ther* **123**: 353–370.
- Shippenberg TS (2009). The dynorphin/ $\kappa$  opioid receptor system: a new target for the treatment of addiction and affective disorders? *Neuropsychopharmacology* **34**: 247.
- Somogyi AA, Barratt DT, Collier JK (2007). Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**: 429–444.
- Terenius L, Johansson B (2010). The opioid systems – panacea and nemesis. *Biochem Biophys Res Commun* **396**: 140–142.
- van Rijn RM, Whistler JL, Waldhoer M (2010). Opioid-receptor-heteromer-specific trafficking and pharmacology. *Curr Opin Pharmacol* **10**: 73–79.
- Watkins LR, Hutchinson MR, Rice KC, Maier SF (2009). The ‘toll’ of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. *Trends Pharmacol Sci* **30**: 581–591.
- Zollner C, Stein C (2007). Opioids. *Handb Exp Pharmacol* **31–63**.

## References

- Bilsky EJ *et al.* (1995). *J Pharmacol Exp Ther* **273**: 359–366.
- Bruchas MR *et al.* (2007). *J Biol Chem* **282**: 29803–29811.
- Calo' G *et al.* (2002). *Br J Pharmacol* **136**: 303–311.
- Costa EM *et al.* (1992). *Life Sci* **50**: 73–81.
- Delay-Goyet P *et al.* (1988). *J Biol Chem* **263**: 4124–4130.
- Dooley CT, Houghten RA (1996). *Life Sci* **59**: L23–L29.
- Erspamer V *et al.* (1989). *Proc Natl Acad Sci U S A* **86**: 5188–5192.
- Foord SM *et al.* (2005). *Pharmacol Rev* **57**: 279–288.
- Goldstein A, Naidu A (1989). *Mol Pharmacol* **36**: 265–272.
- Gomes I *et al.* (2000). *J Neurosci* **20**: RC110.
- Guerrini R *et al.* (1997). *J Med Chem* **40**: 1789–1793.
- Handa BK *et al.* (1981). *Eur J Pharmacol* **70**: 531–540.
- Hawkins KN (1987). *Eur J Pharmacol* **133**: 351–352.
- Hunter JC *et al.* (1990). *Br J Pharmacol* **101**: 183–189.
- Jenck F *et al.* (2000). *Proc Natl Acad Sci U S A* **97**: 4938–4943.
- Kawamoto H *et al.* (1999). *J Med Chem* **42**: 5061–5063.
- Kuszak AJ *et al.* (2009). *J Biol Chem* **284**: 26732–26741.
- Lahti RA *et al.* (1985). *Eur J Pharmacol* **109**: 281–284.
- Lever JR, Scheffel U (1998). *Eur J Pharmacol* **350**: 335–344.
- Mollereau C *et al.* (1994). *FEBS Lett* **341**: 33–38.
- Mosberg HI *et al.* (1983). *Proc Natl Acad Sci U S A* **80**: 5871–5874.
- Pelton JT *et al.* (1986). *J Med Chem* **29**: 2370–2375.
- Portoghese PS *et al.* (1987). *J Med Chem* **30**: 1991–1994.
- Portoghese PS *et al.* (1988). *Eur J Pharmacol* **146**: 185–186.
- Rizzi A *et al.* (2007). *Peptides* **28**: 1240–1251.
- Roth BL *et al.* (2002). *Proc Natl Acad Sci U S A* **99**: 11934–11939.
- Simonin F *et al.* (2001). *Eur J Pharmacol* **414**: 189–195.
- Sofuoglu M *et al.* (1991). *J Pharmacol Exp Ther* **257**: 676–680.
- Stevens WC *et al.* (2000). *J Med Chem* **43**: 2759–2769.
- Yamamura MS *et al.* (1992). *Life Sci* **50**: L119–L124.
- Yeadon M, Kitchen I (1988). *Neuropharmacology* **27**: 345–348.
- Zadina JE *et al.* (1997). *Nature* **386**: 499–502.
- Zaratin PF *et al.* (2004). *J Pharmacol Exp Ther* **308**: 454–461.

# Orexin

**Overview:** Orexin receptors (provisional nomenclature) are activated by the endogenous polypeptides orexin-A and orexin-B (also known as hypocretin-1 and -2; 33 and 28 aa) derived from a common precursor, preproorexin or orexin precursor (ENSG00000161610), by proteolytic cleavage (Sakurai *et al.*, 1998). Binding to both receptors may be accomplished with [<sup>125</sup>I]-orexin A (Holmqvist *et al.*, 2001).

Nomenclature	OX <sub>1</sub>	OX <sub>2</sub>
Other names	Hypocretin receptor type 1	Hypocretin receptor type 2
Ensembl ID	ENSG00000121764	ENSG00000137252
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	Orexin-A > orexin-B	Orexin-A = orexin-B
Selective agonists	–	[Ala <sup>11</sup> ,D-Leu <sup>15</sup> ]orexin-B (Asahi <i>et al.</i> , 2003)
Selective antagonists	SB408124 (7.5, Langmead <i>et al.</i> , 2004), SB334867A (7.2–7.3, Porter <i>et al.</i> , 2001)	EMPA (8.6–9.0, Malherbe <i>et al.</i> , 2009), JNJ10397049 (7.9–8.3, McAtee <i>et al.</i> , 2004), compound 29 (7.4; Hirose <i>et al.</i> , 2003)

The primary coupling of orexin receptors to G<sub>q/11</sub> proteins is rather speculative and based on the strong activation of phospholipase C. Coupling of both receptors to G<sub>i/o</sub> and G<sub>s</sub> has also been reported (Kukkonen and Åkerman, 2005; Ramanjaneya *et al.*, 2009); for most cellular responses observed, the G protein pathway is unknown. The rank order of endogenous agonist potency may depend on the cellular signal transduction machinery. The synthetic [Ala<sup>11</sup>,D-Leu<sup>15</sup>]orexin-B may show poor OX<sub>2</sub> receptor selectivity (Putula *et al.*, 2011).

Loss-of-function mutations in the gene encoding the OX<sub>2</sub> receptor underlie canine hereditary narcolepsy (Lin *et al.*, 1999).

**Abbreviations:** **compound 29**, N-acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline; **EMPA**, N-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulphonyl)-amino]-N-pyridin-3-ylmethyl-acetamide; **JNJ10397049**, 1-(2,4-dibromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; **SB334867A**, 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl-urea hydrochloride; **SB408124**, 1-(6,8-difluoro-2-methyl-quinolin-4-yl)-3-(4-dimethylamino-phenyl)-urea

## Further Reading

- Boss C, Brisbare-Roch C, Jenck F (2009). Biomedical application of orexin/hypocretin receptor ligands in neuroscience. *J Med Chem* **52**: 891–903.
- Coleman PJ, Renger JJ (2010). Orexin receptor antagonists: a review of promising compounds patented since 2006. *Expert Opin Ther Pat* **20**: 307–324.
- Heinonen MV, Purhonen AK, Makela KA, Herzig KH (2008). Functions of orexins in peripheral tissues. *Acta Physiol (Oxf)* **192**: 471–485.
- Nishino S (2007). The hypothalamic peptidergic system, hypocretin/orexin and vigilance control. *Neuropeptides* **41**: 117–133.
- Sakurai T (2007). The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nat Rev Neurosci* **8**: 171–181.
- Scammell TE, Winrow CJ (2011). Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol* **51**: 243–266.
- Sharf R, Sarhan M, Dileone RJ (2010). Role of orexin/hypocretin in dependence and addiction. *Brain Res* **1314**: 130–138.
- Tsujino N, Sakurai T (2009). Orexin/Hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. *Pharmacol Rev* **61**: 162–176.

## References

- Asahi S *et al.* (2003). *Bioorg Med Chem Lett* **13**: 111–113.
- Hirose M *et al.* (2003). *Bioorg Med Chem Lett* **13**: 4497–4499.
- Holmqvist T *et al.* (2001). *Neurosci Lett* **305**: 177–180.
- Kukkonen JP, Åkerman KE (2005). In: *Hypocretins. Integrators of Physiological Signals*. Springer Verlag: pp. 221–231.
- Langmead CJ *et al.* (2004). *Br J Pharmacol* **141**: 340–346.
- Lin L *et al.* (1999). *Cell* **98**: 365–376.
- Malherbe P *et al.* (2009). *Br J Pharmacol* **156**: 1326–1341.
- McAtee LC *et al.* (2004). *Bioorg Med Chem Lett* **14**: 4225–4229.
- Porter RA *et al.* (2001). *Bioorg Med Chem Lett* **11**: 1907–1910.
- Putula J *et al.* (2011). *Neurosci Lett* **494**: 57–60.
- Ramanjaneya M *et al.* (2009). *J Endocrinol* **202**: 249–261.
- Sakurai T *et al.* (1998). *Cell* **92**: 573–585.

# P2Y

**Overview:** P2Y receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, Abbracchio *et al.*, 2003; 2006) are activated by the endogenous ligands ATP, ADP, UTP, UDP and UDP-glucose. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established and so it might be appropriate to use wording such as 'UTP-preferring (or ATP-, etc.) P2Y receptor' or 'P2Y<sub>1</sub>-like', etc., until further, as yet undefined, corroborative criteria can be applied.

Nomenclature	P2Y <sub>1</sub>	P2Y <sub>2</sub>	P2Y <sub>4</sub>	P2Y <sub>6</sub>
Ensembl ID	ENSG00000169860	ENSG00000175591	ENSG00000186912	ENSG00000171631
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	ADP > ATP	UTP = ATP	UTP > ATP (at rat recombinant receptors, UTP = ATP)	UDP >> UTP > ATP
Selective agonists	2-MeSADP, ADPβS, MRS2365 (Bourdon <i>et al.</i> , 2006)	UTPγS (Lazarowski <i>et al.</i> , 1996), Ap <sub>4</sub> A (Castro <i>et al.</i> , 1992), 2-thioUTP (El-Tayeb <i>et al.</i> , 2006), MRS2768 (Ko <i>et al.</i> , 2008)	UTPγS (Lazarowski <i>et al.</i> , 1996), MRS4062 (Maruoka <i>et al.</i> , 2011)	UDP, 3-phenacylUDP (PSB0474, El-Tayeb <i>et al.</i> , 2006), 5-iodoUDP (Besada <i>et al.</i> , 2006)
Selective antagonists	MRS2500 (8.8, Kim <i>et al.</i> , 2003), MRS2279 (8.0, Waldo <i>et al.</i> , 2002), MRS2179 (7.0, Boyer <i>et al.</i> , 1996), PIT (6.8, Gao <i>et al.</i> , 2004)	–	ATP (6.2, Kennedy <i>et al.</i> , 2000)	MRS2578 (pIC <sub>50</sub> 7.4, Mamedova <i>et al.</i> , 2004)
Probes	[ <sup>3</sup> H]-MRS2279 (8 nM, Waldo <i>et al.</i> , 2002), [ <sup>35</sup> S]-ADPβS, [ <sup>35</sup> S]-ATPαS, [ <sup>35</sup> S]-dATPαS	–	–	–

Nomenclature	P2Y <sub>11</sub>	P2Y <sub>12</sub>	P2Y <sub>13</sub>	P2Y <sub>14</sub>
Other names	–	P2Y <sub>ADP</sub> , P2T	GPR86, GPR94, SP174	KIAAA00001, gpr105
Ensembl ID	ENSG00000244165	ENSG00000169313	ENSG00000181631	ENSG00000174944
Principal transduction	G <sub>s</sub> , G <sub>q/11</sub>	G <sub>i/o</sub>	G <sub>i/o</sub>	G <sub>q/11</sub>
Rank order of potency	ATP > UTP	ADP >> ATP	ADP >> ATP	UDP-glucose
Selective agonists	ARC67085 (Communi <i>et al.</i> , 1999), NAD <sup>+</sup> (Moreschi <i>et al.</i> , 2006), NAADP <sup>+</sup> (Moreschi <i>et al.</i> , 2008), NF546 (Meis <i>et al.</i> , 2010)	ADP, 2-MeSADP	–	MRS2690 (Ko <i>et al.</i> , 2007)
Selective antagonists	NF157 (Ullmann <i>et al.</i> , 2005)	ATP, ARL66096 (Humphries <i>et al.</i> , 1995)	MRS2211 (Kim <i>et al.</i> , 2005)	–

ARC69931MX shows selectivity for P2Y<sub>12</sub> and P2Y<sub>13</sub> receptors compared to other P2Y receptors (Marteau *et al.* 2003; Takasaki *et al.*, 2001). NF157 also has antagonist activity at P2X<sub>1</sub> receptors (Ullmann *et al.*, 2005). UDP has been reported to be an antagonist at the P2Y<sub>14</sub> receptor (Fricks *et al.*, 2008).

An orphan GPCR suggested to be a 'P2Y<sub>15</sub>' receptor (Inbe *et al.*, 2004) appears not to be a genuine nucleotide receptor (see Abbracchio *et al.*, 2006), but rather responds to dicarboxylic acids (He *et al.*, 2004). Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a p2y<sub>3</sub> receptor (ENSGALG00000017327), couples to the G<sub>q/11</sub> family of G proteins and shows the rank order of potency ADP > UTP > ATP = UDP (Webb *et al.*, 1996a). In addition, human sources have yielded a clone with a preliminary identification of p2y5 (ENSG00000139679) and contradictory evidence of responses to ATP (King and Townsend-Nicholson, 2000; Webb *et al.*, 1996b). This protein is now classified as LPA<sub>4</sub>, a receptor for lysophosphatidic acid (Pasternack *et al.*, 2008; Yanagida *et al.*, 2009) (see Page S76). The clone p2y7 (ENSG00000196943), originally suggested to be a P2Y receptor (Akbar *et al.*, 1996), has been shown to encode a leukotriene receptor (Yokomizo *et al.*, 1997). A P2Y receptor that was initially termed a p2y8 receptor (P79928) has been cloned from *Xenopus laevis*; it shows the rank order of potency ADPβS > ATP = UTP = GTP = CTP = TTP = ITP > ATPγS and elicits a Ca<sup>2+</sup>-dependent Cl<sup>-</sup> current in *Xenopus* oocytes (Bogdanov *et al.*, 1997). The p2y10 clone (ENSG00000078589) lacks functional data. Diadenosine polyphosphates also have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap<sub>4</sub>A > Ap<sub>5</sub>A > Ap<sub>3</sub>A, coupling via G<sub>q/11</sub> (Castro *et al.*, 1992). P2Y-like receptors have recently been described on mitochondria (Belous *et al.*, 2004). CysLT<sub>1</sub> and CysLT<sub>2</sub> leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes C<sub>4</sub> and D<sub>4</sub> (Mellor *et al.*, 2001; 2003); Human (ENSG00000144230) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes as well as UDP and UDP-glucose (Ciana *et al.*, 2006). Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and ARL69931 (Ciana *et al.*, 2006).

**Abbreviations:** ARC67085, 2-propylthio- $\beta$ -dichloromethylene-ATP; AR-C69931MX,  $N^6$ -(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)- $\beta$ -dichloromethylene-ATP, also known as cangrelor; 2-MeSADP, 2-methylthio-adenosine-5'-diphosphate; 2-MeSATP, 2-methylthio-adenosine-5'-triphosphate; ARL66096, 2-propylthio- $\beta$ -difluoromethylene ATP (previously FPL66096); ATP $\gamma$ S, adenosine 5'-(3-thio)triphosphate; MRS2179,  $N^6$ -methyl-2'-deoxyadenosine-3',5'-bisphosphate; MRS2211, pyridoxal-5'-phosphate-6-azo (2-chloro-5-nitrophenyl)-2,4-disulfonate; MRS2279, 2-chloro- $N^6$ -methyl-(*N*)-methanocarba-2'-deoxyadenosine-3',5'-bisphosphate; MRS2365, (*N*)-methanocarba-2-MeSADP; MRS2500,  $N^6$ -methyl-(*N*)-methanocarba-2'-deoxyadenosine-3',5'-bisphosphate; MRS2578,  $N,N''$ -1,4-butanediyl bis(*N'*-[3-isothiocyantophenyl]) thiourea; MRS2690, 2-thiouridine-5'-diphosphoglucose; MRS2768, uridine-5'-tetrphosphate  $\delta$ -phenyl ester; MRS4062,  $N^4$ -phenylpropoxycytidine-5'-triphosphate; NF157, 8,8'-[carbonylbis(imino-3,1-phenylenecarbonylimino(4-fluoro-3,1-phenylene)carbonylimino)]bis-1,3,5-naphthalene trisulfonic acid hexasodium salt; NF546, 4,4'-(carbonylbis(imino-3,1-phenylene-carbonylimino-3,1-(4-methyl-phenylene)-carbonylimino))-bis(1,3-xylylene- $\alpha,\alpha'$ -diphosphonic acid); PIT, 2,2'-pyridylisatogen tosylate

### Further Reading

- Abbracchio MP, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Miras-Portugal MT *et al.* (2003). Characterization of the UDP-glucose receptor (re-named here the P2Y<sub>14</sub> receptor) adds diversity to the P2Y receptor family. *Trends Pharmacol Sci* **24**: 52–55.
- Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C *et al.* (2006). International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacol Rev* **58**: 281–341.
- Burnstock G (2007). Purine and pyrimidine receptors. *Cell Mol Life Sci* **64**: 1471–1483.
- Burnstock G (2008). Purinergic signalling and disorders of the central nervous system. *Nat Rev Drug Discov* **7**: 575–590.
- Erlinge D, Burnstock G (2008). P2 receptors in cardiovascular regulation and disease. *Purinergic Signal* **4**: 1–20.
- Jacobson KA, Ivanov AA, de Castro S, Harden TK, Ko H (2009). Development of selective agonists and antagonists of P2Y receptors. *Purinergic Signal* **5**: 75–89.

### References

- Akbar GKM *et al.* (1996). *J Biol Chem* **271**: 18363–18367.
- Belous A *et al.* (2004). *J Cell Biochem* **92**: 1062–1073.
- Besada P *et al.* (2006). *J Med Chem* **49**: 5532–5543.
- Bogdanov YD *et al.* (1997). *J Biol Chem* **272**: 12583–12590.
- Bourdon DM *et al.* (2006). *J Thromb Haemost* **4**: 861–868.
- Boyer JL *et al.* (1996). *Mol Pharmacol* **50**: 1323–1329.
- Castro E *et al.* (1992). *Br J Pharmacol* **106**: 833–837.
- Ciana P *et al.* (2006). *EMBO J* **25**: 4615–4627.
- Communi D *et al.* (1999). *Br J Pharmacol* **128**: 1199–1206.
- El-Tayeb A *et al.* (2006). *J Med Chem* **49**: 7076–7087.
- Fricks IP *et al.* (2008). *J Pharmacol Exp Ther* **325**: 588–594.
- Gao ZG *et al.* (2004). *Biochem Pharmacol* **68**: 231–237.
- He W *et al.* (2004). *Nature* **429**: 188–193.
- Humphries RG *et al.* (1995). *Br J Pharmacol* **115**: 1110–1116.
- Inbe H *et al.* (2004). *J Biol Chem* **279**: 19790–19799.
- Kennedy C *et al.* (2000). *Mol Pharmacol* **57**: 926–931.
- Kim HS *et al.* (2003). *J Med Chem* **46**: 4974–4987.
- Kim YC *et al.* (2005). *Biochem Pharmacol* **70**: 266–274.
- King BF, Townsend-Nicholson A (2000). *J Auton Nerv Syst* **81**: 164–170.
- Ko H *et al.* (2007). *J Med Chem* **50**: 2030–2039.
- Ko H *et al.* (2008). *Bioorg Med Chem* **16**: 6319–6332.
- Lazarowski ER *et al.* (1996). *Br J Pharmacol* **117**: 203–209.
- Mamedova LK *et al.* (2004). *Biochem Pharmacol* **67**: 1763–1770.
- Marteau F *et al.* (2003). *Mol Pharmacol* **64**: 104–112.
- Maruoka H *et al.* (2011). *J Med Chem* **54**: 4018–4033.
- Meis S *et al.* (2010). *J Pharmacol Exp Ther* **332**: 238–247.
- Mellor EA *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 7964–7969.
- Mellor EA *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 11589–11593.
- Moreschi I *et al.* (2006). *Biochem Biophys Res Commun* **345**: 573–580.
- Moreschi I *et al.* (2008). *Cell Calcium* **43**: 344–355.
- Noguchi K *et al.* (2003). *J Biol Chem* **278**: 25600–25606.
- Pasternack SM *et al.* (2008). *Nat Genet* **40**: 329–334.
- Takasaki J *et al.* (2001). *Mol Pharmacol* **60**: 432–439.
- Ullmann H *et al.* (2005). *J Med Chem* **48**: 7040–7048.
- Waldo GL *et al.* (2002). *Mol Pharmacol* **62**: 1249–1257.
- Webb TE *et al.* (1996a). *Mol Pharmacol* **50**: 258–265.
- Webb TE *et al.* (1996b). *Biochem Biophys Res Commun* **219**: 105–110.
- Yanagida K *et al.* (2009). *J Biol Chem* **284**: 17731–17741.
- Yokomizo T *et al.* (1997). *Nature* **387**: 620–624.

# Parathyroid hormone and parathyroid hormone-related peptide

**Overview:** Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) receptors (provisional nomenclature) are activated by precursor-derived peptides: PTH (84 amino acids, ENSG00000152266), PTHrP (141 amino-acids and related peptides (PTHrP-1-36, PTHrP-38-94 and osteostatin (PTHrP-107-139) (ENSG00000087494) and TIP39 (39 amino acids, ENSG00000142538). [<sup>125</sup>I]-PTH may be used to label both PTH<sub>1</sub> and PTH<sub>2</sub> receptors.

Nomenclature	PTH <sub>1</sub>	PTH <sub>2</sub>
Other names	PTH/PTHrP, PPR	–
Ensembl ID	ENSG00000160801	ENSG00000144407
Principal transduction	G <sub>s</sub> , G <sub>q/11</sub>	G <sub>s</sub> , G <sub>q/11</sub>
Rank order of potency	PTH = PTHrP	TIP39, PTH >> PTHrP
Selective agonists	–	TIP39 (Hoare <i>et al.</i> , 2000)
Selective antagonists	–	TIP-9-39 (Jonsson <i>et al.</i> , 2001)

Although PTH is an agonist at human PTH<sub>2</sub> receptors, it fails to activate the rodent orthologues. TIP39 is a weak antagonist at PTH<sub>1</sub> receptors (Jonsson *et al.*, 2001).

**Abbreviations:** PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; TIP39, tuberoinfundibular protein of 39 residues

## Further Reading

- Datta NS, Abou-Samra AB (2009). PTH and PTHrP signaling in osteoblasts. *Cell Signal* **21**: 1245–1254.
- Dobolyi A, Palkovits M, Usdin TB (2010). The TIP39-PTH<sub>2</sub> receptor system: unique peptidergic cell groups in the brainstem and their interactions with central regulatory mechanisms. *Prog Neurobiol* **90**: 29–59.
- Gesty-Palmer D, Luttrell LM (2011). ‘Biasing’ the parathyroid hormone receptor: a novel anabolic approach to increasing bone mass? *Br J Pharmacol* **164**: 59–67.
- Guerreiro PM, Renfro JL, Power DM, Canario AV (2007). The parathyroid hormone family of peptides: structure, tissue distribution, regulation, and potential functional roles in calcium and phosphate balance in fish. *Am J Physiol Regul Integr Comp Physiol* **292**: R679–R696.
- Kraenzlin ME, Meier C (2011). Parathyroid hormone analogues in the treatment of osteoporosis. *Nat Rev Endocrinol* in press.
- Mierke DF, Mao L, Pellegrini M *et al.* (2007). Structural characterization of the parathyroid hormone receptor domains determinant for ligand binding. *Biochem Soc Trans* **35**: 721–723.
- Naveh-Manly T (2010). The play of proteins on the parathyroid hormone messenger ribonucleic acid regulates its expression. *Endocrinology* **151**: 1398–1402.
- Silva BC, Bilezikian JP (2011). New approaches to the treatment of osteoporosis. *Annu Rev Med* **62**: 307–322.
- Silver J, Naveh-Manly T (2009). Phosphate and the parathyroid. *Kidney Int* **75**: 898–905.
- Villardaga JP, Romero G, Friedman PA, Gardella TJ (2011). Molecular basis of parathyroid hormone receptor signaling and trafficking: a family B GPCR paradigm. *Cell Mol Life Sci* **68**: 1–13.

## References

- Hoare SR *et al.* (2000). *J Biol Chem* **275**: 27274–27283.
- Jonsson KB *et al.* (2001). *Endocrinology*, **142**, 704–709.

# Platelet-activating factor

**Overview:** Platelet-activating factor (PAF, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is a biologically active phospholipid mediator. PAF acts by binding to a unique G protein-coupled receptor (PAF-R) and activates multiple intracellular signaling pathways by coupling to the G<sub>q/11</sub> and G<sub>i/o</sub> families of G proteins. PAF-R is activated by PAF and its metabolically stable analogue mc-PAF. Other suggested endogenous ligands are oxidized phosphatidylcholine (Marathe *et al.*, 1999) and lysophosphatidylcholine (Ogita *et al.*, 1997). It may also be activated by bacterial lipopolysaccharide (Nakamura *et al.*, 1992).

Nomenclature	PAF-R
Ensembl ID	ENSG00000169403
Principal transduction	G <sub>q/11</sub> , G <sub>i</sub> , G <sub>o</sub>
Selective agonists	mc-PAF
Selective antagonists	CV-6209 (9.5), SR27417 (10.0), WEB2086 (8.0), L659989 (8.1), ginkgolide B (6.4)
Radioligand	[ <sup>3</sup> H]-PAF (1.6 nM, Fukunaga <i>et al.</i> , 2001)

Note that a previously recommended radioligand ([<sup>3</sup>H]-WEB2086; K<sub>d</sub> 44.6 nM) is currently unavailable.

**Abbreviations:** CV-6209, 2-(*N*-acetyl-*N*-[2-methoxy-3-octadecylcarbamoyloxypropoxycarbamoyl]aminomethyl)-1-ethylpyridinium chloride; L659989, *trans*-2-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran; mc-PAF, 1-*O*-alkyl-2-*N*-methylcarbamoyl-*sn*-glycero-3-phosphocholine; also known as (methyl)carbam(o)yl-PAF or c-PAF; SR27417, *N*-(2-dimethylaminoethyl)-*N*-(3-pyridinylmethyl)(4-[2,4,6-triisopropylphenyl]thiazol-2-yl)amine; WEB2086, 3-(4-[2-chlorophenyl]-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine-2-yl)-1-(4-morpholinyl)-1-propanone; also known as apafant

## Further Reading

- Honda Z, Ishii S, Shimizu T (2002). Platelet-activating factor receptor. *J Biochem* **1331**: 773–779.
- Ishii S, Nagase T, Shimizu T (2002). Platelet-activating factor receptor. *Prostaglandins Other Lipid Mediators* **68**: 599–609.
- Ishii S, Shimizu T (2000). Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice. *Prog Lipid Res* **39**: 41–82.
- Izumi T, Shimizu T (1995). Platelet-activating factor receptor; gene expression and signal transduction. *Biochim Biophys Acta* **1259**: 317–333.
- Kasperska-Zajac A, Brzoza Z, Rogala B (2008). Platelet-activating factor (PAF): a review of its role in asthma and clinical efficacy of PAF antagonists in the disease therapy. *Recent Pat Inflamm Allergy Drug Discov* **2**: 72–76.
- Montrucchio G, Alloatti G, Camussi G (2000). Role of platelet-activating factor in cardiovascular pathophysiology. *Physiol Rev* **80**: 1669–1699.
- MacLennan KM, Smith PF, Darlington CL (1996). Platelet-activating factor in the CNS. *Prog Neurobiol* **50**: 585–596.
- Prescott SM, Zimmerman GA, Stafforini DM, McIntyre TM (2000). Platelet-activating factor and related lipid mediators. *Annu Rev Biochem* **69**: 419–445.
- Shimizu T (2009). Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu Rev Pharmacol Toxicol* **49**: 123–150.
- Stafforini DM, McIntyre TM, Zimmerman GA, Prescott SM (2003). Platelet-activating factor, a pleiotropic mediator of physiological and pathological processes. *Crit Rev Clin Lab Sci* **40**: 643–672.
- Summers JB, Albert DH (1995). Platelet activating factor antagonists. *Adv Pharmacol* **32**: 67–168.

## References

- Fukunaga K *et al.* (2001). *J Biol Chem* **276**: 43025–43030.
- Marathe GK *et al.* (1999). *J Biol Chem* **274**: 28395–28404.
- Nakamura M *et al.* (1992). *FEBS Lett* **314**: 125–129.
- Ogita T *et al.* (1997). *Am J Physiol* **272**: H17–H24.



# Proteinase-activated

**Overview:** Proteinase-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Proteinase-activated Receptors, see Hollenberg and Compton, 2002) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmask a tethered ligand at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. Tethered ligand sequences at human PAR1–4 are SFLLRN, SLIGKV, TFRGAP and GYPGQV, respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at the PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation, thereby preventing activation by activating proteinases but not by agonist peptides. The role of such an action *in vivo* is unclear.

Nomenclature	PAR <sub>1</sub>	PAR <sub>2</sub>	PAR <sub>3</sub>	PAR <sub>4</sub>
Other names	Thrombin receptor, PAR-1, PAR <sub>1</sub>	PAR-2, PAR <sub>2</sub>	Thrombin receptor, PAR-3, PAR <sub>3</sub>	Thrombin receptor, PAR-4, PAR <sub>4</sub>
Ensembl ID	ENSG00000181104	ENSG00000164251	ENSG00000164220	ENSG00000127533
Principal transduction	G <sub>q/11</sub> /G <sub>i/o</sub> /G <sub>12/13</sub>	G <sub>q/11</sub> /G <sub>i/o</sub> /G <sub>12/13</sub>	G <sub>q/11</sub> /G <sub>i/o</sub>	G <sub>q/11</sub> /G <sub>i/o</sub>
Agonist proteases	Thrombin, activated protein C, matrix metalloproteinase 2	Trypsin, tryptase, TF/VIIa, Xa	Thrombin	Thrombin, trypsin, cathepsin G
Selective agonists	TFLLR-NH <sub>2</sub>	2-Furoyl-LIGRLO-NH <sub>2</sub> (McGuire <i>et al.</i> , 2004), SLIGRL-NH <sub>2</sub> , SLIGKV-NH <sub>2</sub>	–	AYPGKF-NH <sub>2</sub> , GYPGQV-NH <sub>2</sub> , GYPGKF-NH <sub>2</sub>
Selective antagonists	RWJ56110 (Andrade-Gordon <i>et al.</i> , 1999), SCH530348 (Chackalamannil <i>et al.</i> , 2008), E5555 (Serebruanu <i>et al.</i> , 2009)	–	–	–
Probes	[ <sup>3</sup> H]-haTRAP (Ahn <i>et al.</i> , 1997)	<i>Trans</i> -cinnamoyl-LIGRLO[N- <sup>3</sup> H]-propionyl]-NH <sub>2</sub> (Al Ani <i>et al.</i> , 1999), 2-furoyl-LIGRL[N <sup>3</sup> H]propionyl]-O-NH <sub>2</sub> and 2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH <sub>2</sub> (Hollenberg <i>et al.</i> , 2008).	–	–

TFLLR-NH<sub>2</sub> is selective relative to the PAR<sub>2</sub> receptor (Blackhart *et al.*, 1996; Kawabata *et al.*, 1999). Thrombin is inactive at the PAR<sub>2</sub> receptor.

Endogenous serine proteinases (EC 3.4.21...) active at the proteinase-activated receptors include: thrombin, generated by the action of Factor X (ENSG00000126218) on liver-derived prothrombin (ENSG00000180210); trypsin, generated by the action of enterokinase (ENSG00000154646) on pancreatic-derived trypsinogen (ENSG00000204983); tryptase, a family of enzymes ( $\alpha/\beta$  ENSG00000172236;  $\gamma$ 1 ENSG00000116176;  $\delta$ 1 ENSG00000095917) secreted from mast cells; cathepsin G (ENSG00000100448) generated from leukocytes; liver-derived protein C (ENSG00000115718) generated in plasma by thrombin and matrix metalloproteinase 1 (see Page S317).

**Abbreviations:** [<sup>3</sup>H]-haTRAP, Ala-*p*-fluoroPhe-Ala-Arg-cyclohexylAla-homoArg-[<sup>3</sup>H]-Tyr-amide; RWJ56110, ( $\alpha$ S)-N-([1S]-3-amino-1-[[[(phenylmethyl)amino]propyl]- $\alpha$ -[[[1-[2,6-dichlorophenyl]methyl]-3-[1-pyrrolidinylmethyl]-1H-indol-6-yl]amino]carbonyl]amino)-3,4-difluoro-benzenepropanamide; SCH530348 (chemical name); E5555 (chemical name)

## Further Reading

- Adams MN, Ramachandran R, Yau MK, Suen JY, Fairlie DP, Hollenberg MD *et al.* (2011). Structure, function and pathophysiology of protease activated receptors. *Pharmacol Ther* 130: 248–282.
- Garcia PS, Gulati A, Levy JH (2010). The role of thrombin and protease-activated receptors in pain mechanisms. *Thromb Haemost* 103: 1145–1151.
- Hollenberg MD, Compton SJ (2002). International Union of Pharmacology. XXVIII. Proteinase-activated receptors. *Pharmacol Rev* 54: 203–217.
- Shpacovitch V, Feld M, Bunnett NW, Steinhoff M (2007). Protease-activated receptors: novel PARTners in innate immunity. *Trends Immunol* 28: 541–550.
- Soh UJ, Dores MR, Chen B, Trejo J (2010). Signal transduction by protease-activated receptors. *Br J Pharmacol* 160: 191–203.
- Steinhoff M, Buddenkotte J, Shpacovitch V, Rattenholl A, Moormann C, Vergnolle N *et al.* (2005). Proteinase-activated receptors: transducers of proteinase-mediated signaling in inflammation and immune response. *Endocr Rev* 26: 1–43.
- Vergnolle N (2009). Protease-activated receptors as drug targets in inflammation and pain. *Pharmacol Ther* 123: 292–309.

## References

- Ahn HS *et al.* (1997). *Mol Pharmacol* 51: 350–356.
- Al Ani B *et al.* (1999). *J Pharmacol Exp Ther* 290: 753–760.
- Andrade-Gordon P *et al.* (1999). *Proc Natl Acad Sci U S A* 96: 12257–12262.

- Blackhart BD *et al.* (1996). *J Biol Chem* **271**: 16466–16471.
- Chackalamannil S *et al.* (2008). *J Med Chem* **51**: 3061–3064.
- Hollenberg MD *et al.* (2008). *J Pharmacol Exp Ther* **326**: 453–462.
- McGuire, J. J., Saifeddine, M., Triggle, C. R., Sun, K., and Hollenberg, M. D. (2004) *J Pharmacol Exp Ther* **309**, 1124–1131.
- Kawabata A *et al.* (1999). *J Pharmacol Exp Ther* **288**: 358–370.
- Serebruany, V. L., Kogushi, M., Dastros-Pitei, D., Flather, M., and Bhatt, D. L. (2009) *Thromb Haemost* **102**, 111–119.

# Prostanoid

**Overview:** Prostanoid receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors, see Coleman *et al.*, 1994) are activated by the endogenous ligands prostaglandin (PG) D<sub>2</sub> (D), PGE<sub>2</sub> (E), PGF<sub>2α</sub> (F), PGH<sub>2</sub> (H), prostacyclin [PGI<sub>2</sub> (I)] and thromboxane A<sub>2</sub> (T). Measurement of the potency of PGI<sub>2</sub> and TXA<sub>2</sub> is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

Nomenclature	DP <sub>1</sub>	DP <sub>2</sub>	FP	IP	TP
Other names	–	CRTh2, GPR44	–	–	–
Ensembl ID	ENSG00000168229	ENSG00000183134	ENSG00000122420	ENSG00000160013	ENSG00000006638
Principal transduction	G <sub>s</sub>	G <sub>i/o</sub>	G <sub>q/11</sub>	G <sub>s</sub>	G <sub>q/11</sub>
Rank order of potency	D >> E > F > I, T	D >> F, E > I, T	F > D > E > I, T	I >> D, E, F > T	T = H >> D, E, F, I
Selective agonists	L644698, BW245C, ZK118182, RS93520, SQ27986	13,14-Dihydro-15-oxo PGD <sub>2</sub> , 15R-15-methyl PGD <sub>2</sub> (Hata <i>et al.</i> , 2003; Monneret <i>et al.</i> , 2003)	Fluprostenol, latanoprost free acid, AL12180 (Sharif <i>et al.</i> , 2006)	Cicaprost, AFP07, BMY45778 (Seiler <i>et al.</i> , 1997)	U46619, STA <sub>2</sub> , I-BOP, AGN192093
Selective antagonists	BWA868C (9.3, Giles <i>et al.</i> , 1989), S5751 (8.8, Arimura <i>et al.</i> , 2001), laropiprant (10.1, Sturino <i>et al.</i> , 2007)	Ramatroban (Sugimoto <i>et al.</i> , 2003), CAY10471 (Royer <i>et al.</i> , 2007)	AS604872 (Cirillo <i>et al.</i> , 2007)	RO1138452 (8.8), RO3244794 (8.5) (Bley <i>et al.</i> , 2006)	BMS180291 (9.3–10.0), ONO-3708 (8.9), GR32191 (8.3–9.4, Lumley <i>et al.</i> , 1989), SQ29548 (8.1–9.1, Swayne <i>et al.</i> , 1988)
Probes	[ <sup>3</sup> H]-PGD <sub>2</sub> (13–34 nM)	[ <sup>3</sup> H]-PGD <sub>2</sub> (6–11 nM)	[ <sup>3</sup> H]-PGF <sub>2α</sub> (2–4 nM), [ <sup>3</sup> H]-(+)-fluprostenol (34 nM)	[ <sup>3</sup> H]-Iloprost (1–20 nM)	[ <sup>3</sup> H]-SQ29548 (5–40 nM), [ <sup>125</sup> I]-SAP (0.2–1.0 nM), [ <sup>125</sup> I]-I-BOP (0.3–5.0 nM)

Ramatroban is also a TP receptor antagonist. Cicaprost exhibits moderate EP<sub>4</sub> receptor agonist potency (Abramovitz *et al.*, 2000). Iloprost also binds to EP<sub>1</sub> receptors. The TP receptor exists in  $\alpha$  and  $\beta$  isoforms due to alternative splicing of the cytoplasmic tail (Raychowdhury *et al.*, 1994).

Nomenclature	EP <sub>1</sub>	EP <sub>2</sub>	EP <sub>3</sub>	EP <sub>4</sub>
Ensembl ID	ENSG00000160951	ENSG00000125384	ENSG00000050628	ENSG00000171522
Principal transduction	G <sub>q/11</sub>	G <sub>s</sub>	G <sub>i/o</sub>	G <sub>s</sub>
Rank order of potency	E > F, I > D, T	E > F, I > D, T	E > F, I > D, T	E > F, I > D, T
Selective agonists	17-Phenyl-PGE <sub>2</sub> , ONO-DI-004	Butaprost-free acid, CP533536 (Cameron <i>et al.</i> , 2009), ONO-AE1–259	Sulprostone, SC46275, ONO-AE-248	ONO-AE1–329, L902688 (Young <i>et al.</i> , 2004), CP734432 (Prasanna <i>et al.</i> , 2009)
Selective antagonists	ONO8711 (9.2), GW848687X (9.1, Giblin <i>et al.</i> , 2007), SC51322 (8.8)	–	L798106 (7.7), ONO-AE3-240 (8.8, Amano <i>et al.</i> , 2003)	GW627368 (9.2), ONO-AE3–208 (8.5), L161982 (8.5), BGC201531 (7.8, Maubach <i>et al.</i> , 2009), CJ042794 (8.6, Murase <i>et al.</i> , 2008), ER819762 (Chen <i>et al.</i> , 2010), MK2894 (Blouin <i>et al.</i> , 2010)
Probes	[ <sup>3</sup> H]-PGE <sub>2</sub> (1–25 nM)	[ <sup>3</sup> H]-PGE <sub>2</sub> (5–22 nM)	[ <sup>3</sup> H]-PGE <sub>2</sub> (0.3–7 nM)	[ <sup>3</sup> H]-PGE <sub>2</sub> (0.6–24 nM)

17-Phenyl-PGE<sub>2</sub> also shows agonist activity at EP<sub>3</sub> receptors. Sulprostone also has affinity for EP<sub>1</sub> receptors. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP (Liljebris *et al.*, 1995), IP (Takechi *et al.*, 1996; Wise *et al.*, 1995; Wilson *et al.*, 2011) and TP (Krauss *et al.*, 1996) receptors. mRNA for the EP<sub>1</sub> and EP<sub>3</sub> receptors undergo alternative splicing to produce two (Okuda-Ashitaka *et al.*, 1996) and at least six variants, respectively, which can interfere with signalling (Okuda-Ashitaka *et al.*, 1996) or generate complex patterns of G-protein (G<sub>i/o</sub>, G<sub>q/11</sub>, G<sub>s</sub> and G<sub>12/13</sub>) coupling (e.g. Kotani *et al.*, 1995; Negishi *et al.*, 1995). The possibility of additional receptors for the isoprostanes has been suggested (Pratico *et al.*, 1996). Receptors (prostamide F, which as yet lack a molecular correlate) that preferentially recognize PGF<sub>2α</sub>-1-ethanolamide and its analogues (e.g. bimatoprost) have been identified, together with moderate-potency antagonists (e.g. AGN 211334) (see Woodward *et al.*, 2008).

**Abbreviations:** AFP07, 7,7-difluoro-16S,20-dimethyl-18,19-didehydro-PGE<sub>2</sub>; AGN192093, (Z)-7-([1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,7 $\beta$ ]-7-[[1E,3S]-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]oct-6-yl)-5-heptenoic acid; AH23848, (1 $\alpha$ [z],2 $\beta$ ,5 $\alpha$ )-(±)-7-(5-[[1,1'-biphenyl]-4-yl]methoxy)-2-[4-morpholinyl]-3-oxocyclopentyl)-4-heptenoate; AL12180, 5,6-dihydro-4,5-didehydro-11-deoxy-11-oxa-16-(3-chlorophenoxy)- $\omega$ -tetranor-PGF<sub>2 $\alpha$</sub> ; AS604872, (2S)-3-([1,1-biphenyl]-4-ylsulphonyl-N-(R)-phenyl(2-pyridinyl)-methyl)-1,3-thiazolidine-2-carboxamide; BGC201531, (N-(4-[4-(5-methoxypyridin-2-yl)phenoxy]methyl)-5-methylfuran-2-carbonyl)-2-methylbenzenesulphonamide; BMS180291, (1S-(1 $\alpha$ ,2 $\alpha$ ,3 $\alpha$ ,4 $\alpha$ )-2-([3-[4-(pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl)benzenepropanoic acid; also known as ifetroban; BMY45778, 3-(4-[4,5-diphenyl-2-oxazolyl]-5-oxazolyl)phenoxyacetic acid; BW245C, 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin; BW848687, 6-[2-(5-chloro-2-[[2,4-difluorophenyl]methyl]oxy)phenyl]-1-cyclopenten-1-yl]-2-pyridinecarboxylic acid; BWA868C, 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)hydantoin; CAY10471, (+)-3-([4-fluorophenyl]sulfonyl)methylamino-1,2,3,4-tetrahydro-9H-carbazole-9-acetic acid; CJ042794, 4-[(1S)-1-[(5-chloro-2-[[4-fluorophenyl]oxy]phenyl]carbonyl)amino]ethyl benzoic acid; CP533536, N-(4-*t*-butylbenzyl)-pyridyl-3-yl-sulphonamidomethylphenoxyacetic acid; CP734432, 5-[3-[(2S)-2-[(3R)-3-hydroxy-4-[3-(trifluoromethyl)phenyl]butyl]-5-oxopyrrolidin-1-yl]propyl]thiophene-2-carboxylate; ER819762, (S)-1'-(3,5-dimethylbenzyl)-2-ethyl-7,9-dimethoxy-10-methyl-5,10-dihydrospiro [benzo[e]imidazo [1,5-a]azepine-1,4'-piperidin]-3(2H)-one; GR32191, [1R-[1(2),2 $\alpha$ ,3 $\beta$ ,5]]-(+)-7-[5-[[1,1'-biphenyl]-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid; GW627368, N-2-[4-[4,9-dithioxy-1-oxo-1,3-dihydro-2H-benzo[f]isindol-2-yl]phenyl]-acetyl)benzenesulphonamide; GW848687X, 6-[2-[5-chloro-2-[(2,4-difluorophenyl)methoxy]phenyl]cyclopenten-1-yl]pyridine-2-carboxylic acid; I-BOP, (1S-[1 $\alpha$ ,2 $\beta$ [5z],3 $\alpha$ [1e,3s],4 $\alpha$ ]-7-(3-[hydroxy-4-[4'-iodophenoxy]-1-butenyl]-7-oxabicyclo[2.2.1]hept-2-yl)-5-heptanoate; L161982, 5-butyl-2,4-dihydro-[[2'-[N-(5-methyl-2-thiophenecarbonyl)sulphamoyl]biphenyl-4-yl]methyl]-2-[(2-trifluoromethyl)phenyl]-1,2,4-triazol-3-one; L644698, 4-(3-[3-hydroxyoctyl]-4-oxo-2-thiazolidinyl)propyl)benzoate racemate; L798106, 5-bromo-2-methoxy-N-[3-(naphthalen-2-yl-methyl)phenyl]-acryloyl]benzenesulphonamide; L902688, 8-aza-1-decarboxy-11-deoxy-16,16-difluoro-16-phenyl- $\omega$ -tetranor-1-(5-tetrazolo) PGE<sub>2</sub>; MK2894, 4-[1-[(2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl]carbonyl)amino]cyclopropyl]benzoic acid; ONO3708, (9,11)-(11,12)-dideoxa-9 $\alpha$ ,11 $\alpha$ -dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentano-15-epi-TXA<sub>2</sub>; ONO8711, 6-[(2S,3S)-3-(4-chloro-2-methylphenylsulphonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5Z-hexenoic acid; ONO-DI-004, 17S-17,20-dimethyl-2,5-ethano-6-oxo PGE<sub>2</sub>; ONO-AE-248, 11,15-O-dimethyl-PGE<sub>2</sub>; ONO-AE1-259, 16s-9-deoxy-9 $\beta$ -chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-PGE<sub>2</sub>; ONO-AE1-329, 16-(3-methoxymethyl)phenyl- $\omega$ -tetranor-3,7-dithia-PGE<sub>2</sub>; ONO-AE3-208, 2-(2-(2-methyl-2-naphth-1-ylacetyl)amino)phenylmethyl)-benzoic acid; ONO-AE3-240, 2-(2-[3-naphth-1-yl-3-sec-butyl-propionylamino]-4-[pyrazol-1-ylmethyl]phenylmethyl)-benzoic acid; RO1138452, 4,5-dihydro-1H-imidazol-Z-yl)-[4-(4-isopropoxybenzyl)phenyl]amine; RO3244794, R-3-(4-fluorophenyl)-2-[5-(4-fluorophenyl)-benzofuran-2-ylmethoxycarbonylamino]-propionic acid; RS93520, Z-4-[(C3'S,1R,2R,3S,6R)-2C3'-cyclohexyl-3'-hydroxyprop-1-ynyl]-3-hydroxybicyclo[4.2.0]oct-7-ylidene butyrate; SAP, 7-([1R,2S,3S,5R]-6,6-dimethyl-3-benzenesulphonamino-bicyclo[3.1.1]hept-2-yl)-5z-heptenoic acid; SC46275, methyl-7-(2 $\beta$ -[6-(1-cyclopenten-1-yl)-4R-hydroxy-4-methyl-1e,5e-hexadienyl]-3 $\alpha$ -hydroxy-5-oxo-1R,1 $\alpha$ -cyclopentyl)-4z-heptenoic acid; SC51322, 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3-[furanylmethyl]-thio]-1-oxopropyl]hydrazide; SQ29548, (1S-[1 $\alpha$ ,2 $\beta$ [5z],3 $\beta$ ,4 $\beta$ ]-7-(3-[[2-(phenylamino)carbonyl]hydrazino]methyl)-7-oxabicyclo[2.2.1]hept-2-yl)-5-heptenoate; S5751, ((Z)-[1R,2R,3S,5S]-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid); SQ27986, [1S-[1B,2B(5Z),3A(1E,3S)4B]]-7-[3-(3-cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid; STA<sub>2</sub>, 11 $\alpha$ -carba-9 $\alpha$ ,11 $\beta$ -thia-Txa<sub>2</sub>; U46619, 11 $\alpha$ ,9 $\alpha$ -epoxymethano-PGH<sub>2</sub>; ZK 118182, (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-2-oxa-16,17,18,19,20-pentano-5,13-prostadienoic acid; ZK138357, (5Z)-7-([2R,4S,5S]-2-[2-chlorophenyl]-5-[[1E]-[3R,S]-3-hydroxy-3-cyclohexyl-1-propenyl]-1,3-dioxolan-4-yl)-5-heptanoic acid

## Further Reading

- Andreasson K (2010). Emerging roles of PGE<sub>2</sub> receptors in models of neurological disease. *Prostaglandins Other Lipid Mediat* **91**: 104–112.
- Coleman RA, Smith WL, Narumiya S (1994). VIII. International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. *Pharmacol Rev* **46**: 205–229.
- Feletou M, Huang Y, Vanhoutte PM (2010). Vasoconstrictor prostanoids. *Pflugers Arch* **459**: 941–950.
- Feletou M, Vanhoutte PM, Verbeuren TJ (2010). The thromboxane/endoperoxide receptor (TP): the common villain. *J Cardiovasc Pharmacol* **55**: 317–332.
- Flavahan NA (2007). Balancing prostanoid activity in the human vascular system. *Trends Pharmacol Sci* **28**: 106–110.
- Jones RL, Giembycz MA, Woodward DF (2009). Prostanoid receptor antagonists: development strategies and therapeutic applications. *Br J Pharmacol* **158**: 104–145.
- Nakahata N (2008). Thromboxane A<sub>2</sub>: Physiology/pathophysiology, cellular signal transduction and pharmacology. *Pharmacol Ther* **118**: 18–35.
- Pettipher R (2008). The roles of the prostaglandin D<sub>2</sub> receptors DP<sub>1</sub> and CRTH2 in promoting allergic responses. *Br J Pharmacol* **153**: S191–S199.
- Pettipher R, Hansel TT, Armer R (2007). Antagonism of the prostaglandin D<sub>2</sub> receptors DP<sub>1</sub> and CRTH2 as an approach to treat allergic diseases. *Nat Rev Drug Discov* **6**: 313–325.
- Schuligoi R, Sturm E, Luschnig P, Konya V, Philipose S, Sedej M *et al.* (2010). CRTH2 and D-type prostanoid receptor antagonists as novel therapeutic agents for inflammatory diseases. *Pharmacology* **85**: 372–382.
- Smyth EM, Grosser T, Wang M, Yu Y, FitzGerald GA (2009). Prostanoids in health and disease. *J Lipid Res* **50** Suppl: S423–S428.
- Sugimoto Y, Narumiya S (2007). Prostaglandin E receptors. *J Biol Chem* **282**: 11613–11617.
- Woodward DF, Jones RL, Narumiya S (2011). International Union of Basic and Clinical Pharmacology LXXXIII: classification of prostanoid receptors, updating 15 years of progress. *Pharmacol Rev* **63**: 471–538.
- Woodward DF, Liang Y, Krauss AHP (2008). Prostanoids (prostaglandin-ethanolamides) and their pharmacology. *Br J Pharmacol* **153**: 410–419.
- Yang C, Liu X, Cao Q, Liang Q, Qiu X (2011). Prostaglandin E receptors as inflammatory therapeutic targets for atherosclerosis. *Life Sci* **88**: 201–205.

## References

- Abramovitz M *et al.* (2000). *Biochim Biophys Acta* **1483**: 285–293.
- Amano H *et al.* (2003). *J Exp Med* **197**: 221–232.
- Arimura A *et al.* (2001). *J Pharmacol Exp Ther* **298**: 411–419.
- Bley KR *et al.* (2006). *Br J Pharmacol* **147**: 335–345.
- Blouin M *et al.* (2010). *J Med Chem* **53**: 2227–2238.
- Cameron KO *et al.* (2009). *Bioorg Med Chem Lett* **19**: 2075–2078.
- Chen Q *et al.* (2010). *Br J Pharmacol* **160**: 292–310.
- Cirillo R *et al.* (2007). *Am J Obstet Gynecol* **197**: 54–59.
- Giblin GM *et al.* (2007). *Bioorg Med Chem Lett* **17**: 385–389.
- Giles H *et al.* (1989). *Br J Pharmacol* **96**: 291–300.
- Hata AN *et al.* (2003). *J Pharmacol Exp Ther* **306**: 463–470.
- Kotani M *et al.* (1995). *Mol Pharmacol* **48**: 869–879.

- Krauss AH *et al.* (1996). *Br J Pharmacol* **117**: 1171–1180.
- Liljebris C *et al.* (1995). *J Med Chem* **38**: 289–304.
- Lumley P *et al.* (1989). *Br J Pharmacol* **97**: 783–794.
- Maubach KA *et al.* (2009). *Br J Pharmacol* **156**: 316–327.
- Monneret G *et al.* (2003). *J Pharmacol Exp Ther* **304**: 349–355.
- Murase A *et al.* (2008). *Life Sci* **82**: 226–232.
- Negishi M *et al.* (1995). *J Biol Chem* **270**: 16122–16127.
- Okuda-Ashitaka E *et al.* (1996). *J Biol Chem* **271**: 31255–31261.
- Prasanna G *et al.* (2009). *Exp Eye Res* **89**: 608–617.
- Pratico D *et al.* (1996). *J Biol Chem* **271**: 14916–14924.
- Raychowdhury MK *et al.* (1994). *J Biol Chem* **269**: 19256–19261.
- Royer JF *et al.* (2007). *Allergy* **62**: 1401–1409.
- Seiler SM *et al.* (1997). *Prostaglandins* **53**: 21–35.
- Sharif NA *et al.* (2006). *J Ocul Pharmacol Ther* **22**: 291–309.
- Sturino CF *et al.* (2007). *J Med Chem* **50**: 794–806.
- Sugimoto H *et al.* (2003). *J Pharmacol Exp Ther* **305**: 347–352.
- Swayne GT *et al.* (1988). *Eur J Pharmacol* **152**: 311–319.
- Takechi H *et al.* (1996). *J Biol Chem* **271**: 5901–5906.
- Wilson SM *et al.* (2011). *Mol Pharmacol* **79**: 586–595.
- Wise H *et al.* (1995). *Eur J Pharmacol* **278**: 265–269.
- Young RN *et al.* (2004). *Heterocycles* **64**: 437–446.

# Prokineticin

**Overview:** Prokineticin receptors (provisional nomenclature, see Foord *et al.*, 2005) respond to the cysteine-rich 81-86 amino-acid peptides prokineticin 1 (PROK1, also known as endocrine-gland-derived vascular endothelial growth factor, mambakine, ENSG00000143125) and prokineticin 2 (PROK2, protein Bv8 homolog, ENSG00000163421). An orthologue of PROK1 from black mamba (*Dendroaspis polylepsis*) venom, mamba intestinal toxin 1 (MIT1, Schweitz *et al.*, 1999) is a potent, non-selective agonist at prokineticin receptors (Masuda *et al.*, 2002), while Bv8, an orthologue of PROK2 from amphibians (*Bombina sp.*, Mollay *et al.*, 1999), is equipotent at recombinant PK<sub>1</sub> and PK<sub>2</sub> receptors (Negri *et al.*, 2005), and has high potency in macrophage chemotaxis assays, which are lost in PK<sub>1</sub>-null mice (Martucci *et al.*, 2006).

Nomenclature	PK <sub>1</sub>	PK <sub>2</sub>
Other names	PK-R1, GPR73 (Lin <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002), G-protein coupled receptor ZAQ (Masuda <i>et al.</i> , 2002)	PK-R2, GPR73a (Lin <i>et al.</i> , 2002), GPRg2 (Soga <i>et al.</i> , 2002), ISE (Masuda <i>et al.</i> , 2002)
Ensembl ID	ENSG00000169618	ENSG00000101292
Principal transduction	G <sub>q/11</sub> (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002)	G <sub>q/11</sub> (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002)
Rank order of potency	PROK2 ≥ PROK1 (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002)	PROK2 ≥ PROK1 (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002)

**Abbreviations:** PROK1, prokineticin 1; PROK2, prokineticin 2

## Further Reading

- Abreu AP, Kaiser UB, Latronico AC (2010). The role of prokineticins in the pathogenesis of hypogonadotropic hypogonadism. *Neuroendocrinology* **91**: 283–290.
- Balasubramanian R, Plummer L, Sidis Y, Pitteloud N, Cecilia M, Zhou QY *et al.* (2011). The puzzles of the prokineticin 2 pathway in human reproduction. *Mol Cell Endocrinol* **346**: 44–50.
- Catalano RD, Lannagan TR, Gorowiec M, Denison FC, Norman JE, Jabbour HN (2010). Prokineticins: novel mediators of inflammatory and contractile pathways at parturition? *Mol Hum Reprod* **16**: 311–319.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288.
- Maldonado-Perez D, Evans J, Denison F, Millar RP, Jabbour HN (2007). Potential roles of the prokineticins in reproduction. *Trends Endocrinol Metab* **18**: 66–72.
- Monnier J, Samson M (2010). Prokineticins in angiogenesis and cancer. *Cancer Lett* **296**: 144–149.
- Nebigil CG (2009). Prokineticin receptors in cardiovascular function: foe or friend? *Trends Cardiovasc Med* **19**: 55–60.
- Negri L, Lattanzi R, Giannini E, Melchiorri P (2007). Bv8/Prokineticin proteins and their receptors. *Life Sci* **81**: 1103–1116.
- Ngan ES, Tam PK (2008). Prokineticin-signaling pathway. *Int J Biochem Cell Biol* **40**: 1679–1684.

## References

- Lin DC *et al.* (2002). *J Biol Chem* **277**: 19276–19280.
- Martucci C *et al.* (2006). *Br J Pharmacol* **147**: 225–234.
- Masuda Y *et al.* (2002). *Biochem Biophys Res Commun* **293**: 396–402.
- Mollay C *et al.* (1999). *Eur J Pharmacol* **374**: 189–196.
- Negri L *et al.* (2005). *Br J Pharmacol* **146**: 625–632.
- Schweitz H *et al.* (1999). *FEBS Lett* **461**: 183–188.
- Soga T *et al.* (2002). *Biochim Biophys Acta* **1579**: 173–179.

# Relaxin family peptide

**Overview:** Relaxin family peptide receptors (RXFP, nomenclature as recommended by the NC-IUPHAR committee on relaxin family peptide receptors, Bathgate *et al.* 2006) may be divided into two groups RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: H1 relaxin [ENSG00000107018], H2 relaxin [ENSG00000107014], H3 relaxin [also known as INSL7, ENSG00000171136], insulin-like peptide (INSL) 3 [OTTHUMG00000070952] and INSL5 [ENSG00000172410].

Species homologues of relaxin have distinct pharmacology – H2 relaxin interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 (Scott *et al.*, 2005a) and porcine relaxin may have a higher efficacy than H2 relaxin (Halls *et al.*, 2005). H3 relaxin has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (Scott *et al.*, 2005b). At least two binding sites have been identified on RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane (Halls *et al.*, 2005; Sudo *et al.*, 2003). The unique N-terminal LDLa module of RXFP1 and RXFP2 is essential for receptor signalling (Scott *et al.*, 2006).

Nomenclature	RXFP1	RXFP2
Other names	Relaxin receptor, LGR7, leucine-rich repeat-containing G-protein-coupled receptor 7, RX1	INSL3 receptor, LGR8, leucine-rich repeat-containing G-protein-coupled receptor 8, GREAT, RX2
Ensembl ID	ENSG00000171509	ENSG00000133105
Principal transduction	G <sub>s</sub> , G <sub>αoB</sub> , G <sub>α3</sub> (Halls <i>et al.</i> , 2006, 2009a; Hsu <i>et al.</i> , 2002)	G <sub>s</sub> , G <sub>αoB</sub> (Halls <i>et al.</i> , 2006; Kumagai <i>et al.</i> , 2002)
Rank order of potency	H2 relaxin > H3 relaxin >> INSL3 (Sudo <i>et al.</i> , 2003)	INSL3 > H2 relaxin >> H3 relaxin (Kumagai <i>et al.</i> , 2002; Sudo <i>et al.</i> , 2003)
Antagonists	LGR7-truncate (Scott <i>et al.</i> , 2006), B13/17K H2 relaxin (Hossain <i>et al.</i> , 2010)	INSL3 B-chain analog (Del Borgo <i>et al.</i> , 2006), (des 1-8) A-chain INSL3 analog (Bullesbach and Schwabe, 2005), INSL3 B chain dimer (Shabanpoor <i>et al.</i> , 2011).
Probes	[ <sup>33</sup> P]-H2 relaxin (0.2 nM; Sudo <i>et al.</i> , 2003), Europium-labelled H2 relaxin (1 nM; Hossain <i>et al.</i> , 2009)	[ <sup>33</sup> P]-H2 relaxin (1.06 nM; Sudo <i>et al.</i> , 2003), [ <sup>125</sup> I]-INSL3 (0.1 nM; Muda <i>et al.</i> , 2005), Europium-labelled INSL3 (0.9 nM; Shabanpoor <i>et al.</i> , 2008)

Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism (Ferlin *et al.*, 2003). Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, none of which bind relaxin family peptides (Muda *et al.*, 2005). Splice variants of RXFP1 encoding the N-terminal LDLa module act as antagonists of RXFP1 signalling (Scott *et al.*, 2005b; 2006). cAMP elevation appears to be a major signalling pathway for RXFP1 and RXFP2 (Hsu *et al.*, 2000; Hsu *et al.*, 2002) but RXFP1 also activates MAP kinases, nitric oxide signalling and interacts with tyrosine kinases and glucocorticoid receptors (Halls *et al.*, 2007). RXFP1 signalling involves lipid rafts, residues in the C-terminus of the receptor and activation of phosphatidylinositol-3-kinase (Halls *et al.*, 2009a). More recent studies provide evidence that RXFP1 is pre-assembled in signalosomes with other signalling proteins including G<sub>αs</sub>, G<sub>βγ</sub> and adenylyl cyclase 2 that display constitutive activity and are exquisitely sensitive to sub-picomolar concentrations of relaxin (Halls and Cooper, 2010). The cAMP signalling pattern is highly dependent on the cell type in which RXFP1 is expressed (Halls *et al.*, 2009b).

Nomenclature	RXFP3	RXFP4
Other names	Relaxin 3 receptor, GPCR135, somatostatin and angiotensin-like peptide receptor SALPR, RX3	INSL5 receptor, GPCR142, GPR100, relaxin 3 receptor 2, RX4
Ensembl ID	ENSG00000182631	ENSG00000173080
Principal transduction	G <sub>i/o</sub> (Matsumoto <i>et al.</i> , 2000; Van der Westhuizen <i>et al.</i> , 2007)	G <sub>i/o</sub> (Liu <i>et al.</i> , 2003b)
Rank order of potency	H3 relaxin > H3 relaxin B chain (Liu <i>et al.</i> , 2003a), also H2 relaxin (see below)	INSL5 = H3 relaxin > H3 relaxin B chain (Liu <i>et al.</i> , 2003b; 2005a)
Antagonists	INSL5 (Liu <i>et al.</i> , 2005a), R3(BΔ23-27)R/I5 chimeric peptide (Kuei <i>et al.</i> , 2007), R3 B1-22R (Haugaard-Kedström <i>et al.</i> , 2011)	R3(BΔ23-27)R/I5 chimeric peptide (Kuei <i>et al.</i> , 2007)
Probes	[ <sup>125</sup> I]-H3 relaxin (0.3 nM; Liu <i>et al.</i> , 2003a), [ <sup>125</sup> I]-H3-B/INSL5 A chimera (0.5 nM; Liu <i>et al.</i> , 2005b), Europium-labelled H3-B/INSL5 A chimera (5 nM; Haugaard-Kedstrom <i>et al.</i> , 2011)	[ <sup>125</sup> I]-H3 relaxin (0.2 nM; Liu <i>et al.</i> , 2003b), [ <sup>125</sup> I]-H3-B/INSL5 A chimera (1.2 nM; Liu <i>et al.</i> , 2005b), Europium-labelled INSL5 (5 nM; Haugaard-Kedstrom <i>et al.</i> , 2011)

H3 relaxin acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 is an agonist at RXFP4 and an antagonist at RXFP3. Unlike RXFP1 and RXFP2 both RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino-acids at the N-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes (Wilkinson *et al.*, 2005). Recent studies suggest that H2 relaxin also interacts with RXFP3 to cause a pattern of activation of signalling pathways that are a subset of those activated by H3 relaxin. The two patterns of signaling observed in several cell types expressing RXFP3 are strong inhibition of forskolin-stimulated cAMP accumulation, ERK1/2 activation and nuclear factor NFκ-B reporter gene activation with H3 relaxin, and weaker activity with H2 relaxin, porcine relaxin, or insulin-like peptide

(INSL) 3 and a strong stimulation of activator protein (AP)-1 reporter genes with H2 relaxin, and weaker activation with H3 or porcine relaxin (Van der Westhuizen *et al.*, 2010). Two distinct ligand binding sites were also identified on RXFP3-expressing cells using two different radioligands. <sup>125</sup>I-INSL5 A-chain/relaxin-3 B-chain chimera binds with high affinity with competition by H3 relaxin or a H3 relaxin B-chain peptide, whereas <sup>125</sup>I-H2 relaxin binding is competed for by H2 relaxin, H3 relaxin, or INSL3 and weakly by porcine relaxin. Thus at RXFP3, H2 relaxin is a biased ligand compared to the cognate ligand H3 relaxin.

**Abbreviations:** H2 relaxin, human gene 2 relaxin; H3 relaxin, human gene 3 relaxin; INSL3, insulin-like peptide 3; INSL5, insulin-like peptide 5

### Further Reading

- Bathgate RA, Ivell R, Sanborn BM, Sherwood OD, Summers RJ (2006). International Union of Pharmacology LVII: Recommendations for the nomenclature of receptors for relaxin family peptides. *Pharmacol Rev* **58**: 7–31.
- Callander GE, Bathgate RA (2010). Relaxin family peptide systems and the central nervous system. *Cell Mol Life Sci* **67**: 2327–2341.
- Chan LJ, Hossain MA, Samuel CS, Separovic F, Wade JD (2011). The relaxin peptide family – structure, function and clinical applications. *Protein Pept Lett* **18**: 220–229.
- Du XJ, Bathgate RA, Samuel CS, Dart AM, Summers RJ (2010). Cardiovascular effects of relaxin: from basic science to clinical therapy. *Nat Rev Cardiol* **7**: 48–58.
- Grossman J, Frishman WH (2010). Relaxin: a new approach for the treatment of acute congestive heart failure. *Cardiol Rev* **18**: 305–312.
- Halls ML, van der Westhuizen ET, Bathgate RA, Summers RJ (2007). Relaxin family peptide receptors – former orphans reunite with their parent ligands to activate multiple signalling pathways. *Br J Pharmacol* **150**: 677–691.
- Hoffmann FG, Opazo JC (2011). Evolution of the relaxin/insulin-like gene family in placental mammals: implications for its early evolution. *J Mol Evol* **72**: 72–79.
- Ivell R, Kotula-Balak M, Glynn D, Heng K, Anand-Ivell R (2011). Relaxin family peptides in the male reproductive system – a critical appraisal. *Mol Hum Reprod* **17**: 71–84.
- Kong RC, Shilling PJ, Lobb DK, Gooley PR, Bathgate RA (2010). Membrane receptors: structure and function of the relaxin family peptide receptors. *Mol Cell Endocrinol* **320**: 1–15.
- van der Westhuizen ET, Halls ML, Samuel CS *et al.* (2008). Relaxin family peptide receptors – from orphans to therapeutic targets. *Drug Discov Today* **13**: 640–651.
- van der Westhuizen ET, Summers RJ, Halls ML, Bathgate RA, Sexton PM (2007). Relaxin receptors – new drug targets for multiple disease states. *Curr Drug Targets* **8**: 91–104.

### References

- Bullesbach EE, Schwabe C (2005). *J Biol Chem* **280**: 14586–14590.
- Del Borgo MP *et al.* (2006). *J Biol Chem* **281**: 13068–13074.
- Ferlin A *et al.* (2003). *J Clin Endocrinol Metab* **88**: 4273–4279.
- Halls ML *et al.* (2005). *J Pharmacol Exp Ther* **313**: 677–687.
- Halls ML *et al.* (2006). *Mol Pharmacol* **70**, 214–226.
- Halls ML *et al.* (2009a). *Mol Pharmacol* **75**, 415–428.
- Halls ML *et al.* (2009b). *Ann N Y Acad Sci* **1160**: 108–111.
- Halls ML, Cooper DM (2010). *EMBO J*, **29**: 2772–2787.
- Haugaard-Kedström LM *et al.* (2011). *JACS* **133**: 4965–4974.
- Hossain MA *et al.* (2009). *Org Biomol Chem* **7**: 1547–1553.
- Hossain MA *et al.* (2010). *Amino acids* **39**: 409–416.
- Hsu SY *et al.* (2000). *Mol Endocrinol* **14**: 1257–1271.
- Hsu SY *et al.* (2002). *Science* **295**: 671–674.
- Kuei C *et al.* (2007) *J Biol Chem* **282**: 25425–25435.
- Kumagai J *et al.* (2002). *J Biol Chem* **277**: 31283–31286.
- Liu C *et al.* (2003a). *J Biol Chem* **278**: 50754–50764.
- Liu C *et al.* (2003b). *J Biol Chem* **278**: 50765–50770.
- Liu C *et al.* (2005a). *J Biol Chem* **280**: 292–300.
- Liu C *et al.* (2005b). *Mol Pharmacol* **67**: 231–240.
- Matsumoto M *et al.* (2000). *Gene* **248**: 183–189.
- Muda M *et al.* (2005). *Mol Hum Reprod* **11**: 591–600.
- Scott DJ *et al.* (2005a). *Ann N Y Acad Sci* **1041**: 8–12.
- Scott DJ *et al.* (2005b). *Ann N Y Acad Sci* **1041**: 13–16.
- Scott DJ *et al.* (2006). *J Biol Chem* **281**: 34942–34954.
- Shabanpoor F *et al.* (2011). *Biopolymers* **96**: 81–87.
- Sudo S *et al.* (2003). *J Biol Chem* **278**: 7855–7862.
- Van der Westhuizen ET *et al.* (2007) *Mol Pharmacol* **71**, 1618–1629.
- Van der Westhuizen ET *et al.* (2010) *Mol Pharmacol* **77**, 759–772.
- Wilkinson TN *et al.* (2005) *BMC Evol Biol* **5**, 14.



# Somatostatin

**Overview:** Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (sst1–sst5; nomenclature approved by the NC-IUPHAR Subcommittee on Somatostatin Receptors, see Hoyer *et al.*, 2000). Activation of these receptors produces a wide range of physiological effects throughout the body including inhibiting the secretion of many hormones. The relationship of the cloned receptors to endogenously expressed receptors is not yet well established in some cases. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14) and somatostatin-28 (SRIF-28). Cortistatin (CST-14) has also been suggested to be an endogenous ligand for somatostatin receptors (Delecea *et al.*, 1996).

Nomenclature	sst <sub>1</sub>	sst <sub>2</sub>	sst <sub>3</sub>	sst <sub>4</sub>	sst <sub>5</sub>
Alternative names	SSTR1, SRIF <sub>2A</sub> , SRIF <sub>2A</sub>	SSTR2, SRIF <sub>1</sub> , SRIF <sub>1A</sub>	SSTR3, SRIF <sub>1</sub> , SRIF <sub>1C</sub>	SSTR4, SRIF <sub>2</sub> , SRIF <sub>2B</sub>	SSTR5, SRIF <sub>1</sub> , SRIF <sub>1B</sub>
Ensembl ID	ENSG00000139874	ENSG00000180616	ENSG00000183473	ENSG00000132671	ENSG00000162009
Principal transduction	G <sub>i</sub>	G <sub>i</sub>	G <sub>i</sub>	G <sub>i</sub>	G <sub>i</sub>
Selective agonists	des-Ala <sup>1,2,5</sup> -[DTrp <sup>8</sup> , lamp <sup>9</sup> ]SRIF, L797591	Octreotide, seglitide, BIM23027, L054522	L796778	NNC269100, L803087	BIM23268, BIM23052, L817818
Selective antagonists	SRA880	Cyanamid 154806 (7.7–8.0)	NVP ACQ090	–	BIM23627 (7.1)
Probes	–	[ <sup>125</sup> I]-[Tyr <sup>3</sup> ]octreotide (0.13 nM) [ <sup>125</sup> I]-BIM23027	–	–	[ <sup>125</sup> I]-[Tyr <sup>3</sup> ]octreotide (0.23 nM)

[<sup>125</sup>I]-[Tyr<sup>11</sup>]SRIF-14, [<sup>125</sup>I]-LTT-SRIF-28, [<sup>125</sup>I]-CGP23996 and [<sup>125</sup>I]-[Tyr<sup>10</sup>]CST-14 may be used to label somatostatin receptors nonselectively; BIM23052 is said to be selective in rat but not human receptor (Patel and Srikant, 1994). A number of nonpeptide subtype-selective agonists have been synthesised (see Rohrer *et al.*, 1998).

**Abbreviations:** **BIM23027**, *cyc*(N-Me-Ala-Tyr-D-Trp-Lys-Abu-Phe); **BIM23052**, DPhe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>; **BIM23056**, DPhe-Phe-Tyr-D-Trp-Lys-Val-Phe-dNal-NH<sub>2</sub>; **BIM23268**, *cyc*(Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys)-NH<sub>2</sub>; **CGP23996**, *cyc*(Asn-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser); **Cyanamid 154806**, Ac-(4-NO<sub>2</sub>-Phe)-*cyc*(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)-D-Tyr-NH<sub>2</sub>; **L797591**, (2R)-N-(6-amino-2,2,4-trimethylhexyl)-3-(1-naphthyl)-2-(((2-phenylethyl)2-pyridin-2-ylethyl)amino)carbonylamino)propanamide; **L054522**, tert-butyl (bS)-b-methyl-N[[4-(2-oxo-2,3,-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl]-D-tryptophyl-L-lysinate; **L796778**, methyl (2S)-6-amino-2-(((2R)-2-(((1S)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl)amino)carbonylamino)hexanoyl)amino)hexanoate; **L803087**, methyl (2S)-5-[[amino(imino)methyl]amino]-2-[[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino]pentanoate; **L817818**, (2R)-2-aminopropyl N2-[[2-(2-naphthyl)-1H-benzo[g]indo-3-yl]acetyl]-L-lysinate; **LTT-SRIF-28**, [Leu<sup>8</sup>,DTrp<sup>22</sup>,DTyr<sup>25</sup>]SRIF-28; **NNC269100**, 1-[3-[N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino]propyl]-3-[3-(<sup>1</sup>H-imidazol-1-yl)propyl]thiourea

## Further Reading

- Crider AM, Witt KA (2007). Somatostatin sst4 ligands: chemistry and pharmacology. *Mini Rev Med Chem* 7: 213–220.
- Csaba Z, Dournaud P (2001). Cellular biology of somatostatin receptors. *Neuropeptides* 35: 1–23.
- Dasgupta P (2004). Somatostatin analogues: multiple roles in cellular proliferation, neoplasia, and angiogenesis. *Pharmacol Ther* 102: 61–85.
- Duran-Prado M, Malagon MM, Gracia-Navarro F, Castano JP (2008). Dimerization of G protein-coupled receptors: new avenues for somatostatin receptor signalling, control and functioning. *Mol Cell Endocrinol* 286: 63–68.
- Hannon JP, Nunn C, Stolz B, Bruns C, Weckbecker G, Lewis I *et al.* (2002). Drug design at peptide receptors – somatostatin receptor ligands. *J Mol Neurosci* 18: 15–27.
- Hofland LJ, Feelders RA, de Herder WW, Lamberts SW (2010). Pituitary tumours: the sst/D2 receptors as molecular targets. *Mol Cell Endocrinol* 326: 89–98.
- Hoyer D, Epelbaum J, Feniuk W, Humphrey PPA, Meyerhof W, O'Carroll AM *et al.* (2000). Somatostatin receptors. In: Watson SP, Girdlestone D (eds). *The IUPHAR Compendium of Receptor Characterization and Classification*, 2nd edn. IUPHAR Media: London, pp. 354–364.
- Lahlou H, Guillermet J, Hortala M, Vernejoul F, Pyronnet S, Bousquet C, Susini C (2004). Molecular signalling of somatostatin receptors. *Ann N Y Acad Sci* 1014: 121–131.
- Moller LN, Stidsen CE, Hartmann B, Holst JJ (2003). Somatostatin receptors. *Biochim Biophys Acta* 1616: 1–84.
- Olias G, Viollet C, Kusserow H, Epelbaum J, Meyerhof W (2004). Regulation and function of somatostatin receptors. *J Neurochem* 89: 1057–1091.
- Patel YC (1999). Somatostatin and its receptor family. *Front Neuroendocrinology* 20: 157–198.
- Patel YC, Greenwood MT, Panetta R, Demchyshyn L, Niznik H, Srikant CB (1995). The somatostatin receptor family. *Life Sci* 57: 1249–1265.
- Rashid AJ, O'Dowd BF, George SR (2004). Minireview: Diversity and complexity of signaling through peptidergic G protein-coupled receptors. *Endocrinology* 145: 2645–2652.
- Siehler S, Nunn C, Hannon J, Feuerbach D, Hoyer D (2008). Pharmacological profile of somatostatin and cortistatin receptors. *Mol Cell Endocrinol* 286: 26–34.
- Van der Hoeck J, Hofland LJ, Lamberts SW (2005). Novel subtype specific and universal somatostatin analogues: clinical potential and pitfalls. *Curr Pharm Des* 11: 1573–1592.
- Van Op den Bosch J, Adriaensen D, Van Nassauw L, Timmermans JP (2009). The role(s) of somatostatin, structurally related peptides and somatostatin receptors in the gastrointestinal tract: a review. *Regul Pept* 156: 1–8.
- Weckbecker G, Lewis I, Albert R, Schmid HA, Hoyer D, Bruns C (2003). Opportunities in somatostatin research: Biological, chemical and therapeutic aspects. *Nat Rev Drug Discov* 2: 999–1017.
- Zatelli MC, degli Uberti E (2009). The significance of new somatostatin analogs as therapeutic agents. *Curr Opin Investig Drugs* 10: 1025–1031.

**References**

- Delecea L *et al.* (1996). *Nature* **381**: 242–245.  
Patel YC, Srikant CB (1994). *Endocrinology* **135**: 2814–2817.  
Rohrer SP *et al.* (1998). *Science* **282**: 737–740.

# Sphingosine 1-phosphate

**Overview:** Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid receptors; see Chun *et al.*, 2010) are activated by the endogenous lipid derivatives S1P and sphingosylphosphorylcholine (SPC). Originally identified as members of the endothelial differentiation gene (*edg*) family along with lysophosphatidic acid receptors, the gene names have recently been updated to *S1PR1*, etc. to reflect the receptor function of these proteins. S1P has also been described to act at intracellular sites (see Takabe *et al.*, 2008), although most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [<sup>32</sup>P]-S1P (e.g. Okamoto *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding. Targeted deletion of several S1P receptors and key enzymes involved in S1P biosynthesis or degradation has clarified signalling pathways and physiological roles.

Nomenclature	S1P <sub>1</sub>	S1P <sub>2</sub>	S1P <sub>3</sub>	S1P <sub>4</sub>	S1P <sub>5</sub>
Other names	<i>edg1</i> , <i>lp<sub>B1</sub></i>	<i>edg5</i> , <i>lp<sub>B2</sub></i> , AGR16, H218	<i>edg3</i> , <i>lp<sub>B3</sub></i>	<i>edg6</i> , <i>lp<sub>C1</sub></i>	<i>edg8</i> , <i>lp<sub>B4</sub></i> , NRG-1
Ensembl ID	ENSG00000170989	ENSG00000175898	ENSG00000186354	ENSG00000125910	ENSG00000180739
Principal transduction	G <sub>i/o</sub>	G <sub>q</sub> , G <sub>12/13</sub> , G <sub>s</sub>	G <sub>q</sub> , G <sub>i/o</sub> , G <sub>s</sub>	G <sub>i/o</sub> , G <sub>12/13</sub> , G <sub>s</sub>	G <sub>i/o</sub> , G <sub>12/13</sub>
Rank order of potency	S1P > dihydro-S1P > SPC (Okamoto <i>et al.</i> , 1998, Ancellin and Hla, 1999)	S1P > dihydro-S1P > SPC (Okamoto <i>et al.</i> , 1998, Ancellin and Hla, 1999)	S1P > dihydro-S1P > SPC (Okamoto <i>et al.</i> , 1998)	S1P > dihydro-S1P > SPC (Van Brocklyn <i>et al.</i> , 2000)	S1P > dihydro-S1P > SPC (Im <i>et al.</i> , 2000)
Selective agonists	SEW2871 (Sanna <i>et al.</i> , 2004), AUY954 (Pan <i>et al.</i> , 2006)	–	–	–	–
Selective antagonists	W146 (Sanna <i>et al.</i> , 2006)	JTE013 (Osada <i>et al.</i> , 2002)	–	–	–

The immunomodulator fingolimod (FTY720) may be phosphorylated *in vivo* (Albert *et al.*, 2005) to generate a relatively potent agonist with activity at S1P<sub>1</sub>, S1P<sub>3</sub>, S1P<sub>4</sub> and S1P<sub>5</sub> receptors (Brinkmann *et al.*, 2002; Mandala *et al.*, 2002). VPC23019 and VPC44116 have antagonist activity at S1P<sub>1</sub> and S1P<sub>3</sub> receptors (see Marsolais and Rosen, 2009). This compound has received world-wide approval as the first oral therapy for relapsing forms of Multiple Sclerosis, with a novel mechanism of action (Cohen and Chun, 2011; Choi *et al.*, 2011).

**Abbreviations:** AUY954, an aminocarboxylate analog of fingolimod; JTE013, pyrazolopyridine analog; SEW2871, 5-(4-phenyl-5-trifluoromethylthiophen-2-yl)-3-(3-trifluoromethylphenyl)-(1,2,4)-oxadiazole; S1P, sphingosine 1-phosphate; VPC23019, (*R*)-phosphoric acid mono-[2-amino-2-(3-octyl-phenylcarbamoyl)-ethyl] ester; VPC44116, [3-amino-3-(3-octylphenylcarbamoyl)propyl]-phosphonic acid; W146, (*R*)-3-amino-(3-hexylphenylamino)-4-oxobutylphosphonic acid

## Further Reading

- Aktas O, Kury P, Kieseier B, Hartung HP (2010). Fingolimod is a potential novel therapy for multiple sclerosis. *Nat Rev Neurol* 6: 373–382.
- Bartke N, Hannun YA (2009). Bioactive sphingolipids: metabolism and function. *J Lipid Res* 50: S91–S96.
- Chi H (2011). Sphingosine-1-phosphate and immune regulation: trafficking and beyond. *Trends Pharmacol Sci* 32: 16–24.
- Choi JW, Lee CW, Chun J (2008). Biological roles of lysophospholipid receptors revealed by genetic null mice: an update. *Biochim Biophys Acta* 1781: 531–539.
- Choi JW, Gardell SE, Herr DR, Rivera R, Lee CW, Noguchi K *et al.* (2011). FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc Natl Acad Sci U S A* 108: 751–756.
- Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH (2010). International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid Receptor Nomenclature. *Pharmacol Rev* 62: 579–587.
- Cohen JA, Chun J (2011). Mechanisms of fingolimod's efficacy and adverse effects in multiple sclerosis. *Ann Neurol* 69: 759–777.
- Hla T, Brinkmann V (2011). Sphingosine 1-phosphate (S1P): Physiology and the effects of S1P receptor modulation. *Neurology* 76: S3–S8.
- Hla T, Venkataraman K, Michaud J (2008). The vascular S1P gradient-cellular sources and biological significance. *Biochim Biophys Acta* 1781: 477–482.
- Huwiler A, Pfeilschifter J (2009). Lipids as targets for novel anti-inflammatory therapies. *Pharmacol Ther* 124: 96–112.
- Igarashi J, Michel T (2009). Sphingosine-1-phosphate and modulation of vascular tone. *Cardiovasc Res* 82: 212–220.
- Ishii S, Noguchi K, Yanagida K (2009). Non-Edg family lysophosphatidic acid (LPA) receptors. *Prostaglandins Other Lipid Mediat* 89: 57–65.
- Kim RH, Takabe K, Milstien S, Spiegel S (2009). Export and functions of sphingosine-1-phosphate. *Biochim Biophys Acta* 1791: 692–696.
- Levkau B (2008). Sphingosine-1-phosphate in the regulation of vascular tone: a finely tuned integration system of S1P sources, receptors, and vascular responsiveness. *Circ Res* 103: 231–233.
- Marsolais D, Rosen H (2009). Chemical modulators of sphingosine-1-phosphate receptors as barrier-oriented therapeutic molecules. *Nat Rev Drug Discov* 8: 297–307.
- Means CK, Brown JH (2009). Sphingosine-1-phosphate receptor signalling in the heart. *Cardiovasc Res* 82: 193–200.
- Meyer Zu Heringdorf D, Jakobs KH (2007). Lysophospholipid receptors: Signalling, pharmacology and regulation by lysophospholipid metabolism. *Biochim Biophys Acta* 1768: 923–940.
- Milstien S, Gude D, Spiegel S (2007). Sphingosine 1-phosphate in neural signalling and function. *Acta Paediatr Suppl* 96: 40–43.
- Nixon GF (2009). Sphingolipids in inflammation: pathological implications and potential therapeutic targets. *Br J Pharmacol* 158: 982–993.
- Pappu R, Schwab SR, Cornelissen I, Pereira JP, Regard JB, Xu Y *et al.* (2007). Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. *Science* 316: 295–298.

- Pyne NJ, Long JS, Lee SC, Loveridge C, Gillies L, Pyne S (2009). New aspects of sphingosine 1-phosphate signaling in mammalian cells. *Adv Enzyme Regul* **49**: 214–221.
- Pyne NJ, Pyne S (2010). Sphingosine 1-phosphate and cancer. *Nat Rev Cancer* **10**: 489–503.
- Pyne S, Pyne NJ (2011). Translational aspects of sphingosine 1-phosphate biology. *Trends Mol Med*.
- Rosen H, Gonzalez-Cabrera P, Marsolais D, Cahalan S, Don AS, Sanna MG (2008). Modulating tone: the overture of S1P receptor immunotherapeutics. *Immunol Rev* **223**: 221–235.
- Rosen H, Gonzalez-Cabrera PJ, Sanna MG, Brown S (2009). Sphingosine 1-Phosphate Receptor Signaling. *Annu Rev Biochem* **78**: 743–768.
- Shimizu T (2009). Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu Rev Pharmacol Toxicol* **49**: 123–150.
- Spiegel S, Milstien S (2011). The outs and the ins of sphingosine-1-phosphate in immunity. *Nat Rev Immunol* **11**: 403–415.
- Takabe K, Paugh SW, Milstien S, Spiegel S (2008). ‘Inside-out’ signaling of sphingosine-1-phosphate: therapeutic targets. *Pharmacol Rev* **60**: 181–195.

## References

- Albert R *et al.* (2005). *J Med Chem* **48**: 5373–5377.
- Ancellin N, Hla T (1999). *J Biol Chem* **274**: 18997–19002.
- Brinkmann V *et al.* (2002). *J Biol Chem* **277**: 21453–21457.
- Im DS *et al.* (2000). *J Biol Chem* **275**: 14281–14286.
- Mandala S *et al.* (2002). *Science* **296**: 346–349.
- Okamoto H *et al.* (1998). *J Biol Chem* **273**: 27104–27110.
- Osada M *et al.* (2002). *Biochem Biophys Res Commun* **299**: 483–487.
- Pan S *et al.* (2006). *Chem Biol* **13**: 1227–1234.
- Sanna MG *et al.* (2004). *J Biol Chem* **279**: 13839–13848.
- Sanna MG *et al.* (2006). *Nat Chem Biol* **2**: 434–441.
- van Brocklyn JR *et al.* (2000). *Blood* **95**: 2624–2629.

# Tachykinin

**Overview:** Tachykinin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous peptides substance P (SP), neurokinin A (NKA; previously known as substance K, neurokinin  $\alpha$ , neuromedin L), neurokinin B (NKB; previously known as neurokinin  $\beta$ , neuromedin K), neuropeptide K and neuropeptide  $\gamma$  (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in pharmacology exist for all three receptors, in particular with nonpeptide ligands.

Nomenclature	NK <sub>1</sub>	NK <sub>2</sub>	NK <sub>3</sub>
Other names	Substance P	Substance K	Neurokinin B, neuromedin K
Ensembl ID	ENSG00000115353	ENSG00000075073	ENSG00000169836
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>q/11</sub>
Rank order of potency	SP > NKA > NKB	NKA > NKB >> SP	NKB > NKA > SP
Selective agonists	SP methylester, [Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP, [Pro <sup>9</sup> ]SP, septide	[ $\beta$ -Ala <sup>8</sup> ]NKA-(4-10), [Lys <sup>5</sup> ,Me-Leu <sup>9</sup> ,Mle <sup>10</sup> ]NKA-(4-10), GR64349	Senktide, [MePhe <sup>7</sup> ]NKB
Selective antagonists	Aprepitant (10.7; Hale <i>et al.</i> , 1998), SR140333 (9.5), LY303870 (9.4), CP99994 (9.3), RP67580 (7.6)	GR94800 (9.6), GR159897 (9.5), MEN10627 (9.2), SR48968 (9.0), MEN11420 (8.6; Catalioto <i>et al.</i> , 1998)	SR142802 (9.2), SB223412 (9.0, Sarau <i>et al.</i> , 1997), PD157672 (7.8)
Probes	[ <sup>3</sup> H]- or [ <sup>125</sup> I]-SP, [ <sup>3</sup> H]- or [ <sup>125</sup> I]-BH-[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP, [ <sup>125</sup> I]-L703606 (0.3 nM), [ <sup>18</sup> F]-SPA-RQ	[ <sup>3</sup> H]-SR48968 (0.5 nM), [ <sup>3</sup> H]-GR100679, [ <sup>125</sup> I]-NKA	[ <sup>3</sup> H]-Senktide, [ <sup>125</sup> I]-[MePhe <sup>7</sup> ]NKB, [ <sup>3</sup> H]-SR142801 (0.13 nM)

The NK<sub>1</sub> receptor has also been described to couple to other G proteins (Roush and Kwatra, 1998). The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to SP on the NK<sub>1</sub> receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK<sub>3</sub> receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells (Donaldson *et al.*, 1996; Krause *et al.*, 1997).

**Abbreviations:** Aprepitant, 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (also known as Emend); CP99994, (+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine; [<sup>18</sup>F]-SPA-RQ, ([<sup>18</sup>F]-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl)[(2S,3S)-2-phenyl-piperidin-3-yl]-amine; GR100679, cyclohexylcarbonyl-Gly-Ala-DTrp-Phe-NMe<sub>2</sub>; GR159897, (R)-1-(2-[5-fluoro-1H-indol-3-yl]ethyl)-4-methoxy-4([phenylsulfanyl]methyl)piperidine; GR64349, Lys-Asp-Ser-Phe-Val-Gly-(R- $\gamma$ -lactam); GR94800, N- $\alpha$ -benzoyl-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH<sub>2</sub>; L-703606, cis-2(diphenylmethyl)-N-([2-iodophenyl]methyl)-1-azabicyclo[2.2.2]octan-3-amide; L-742694, 2(s)-([3,5-bis(trifluoromethyl)benzyl]-oxy)-3(S)-phenyl-4-([3-oxo-1,2,4-triazol-5-yl]methyl)morpholine; LY303870, (R)-1-(N-[2-methoxybenzyl]acetylamino)-3-(1H-indol-3-yl)-2-(N-[2-{4-(piperidin-1-yl)piperidin-1-yl}acetyl]amino)propane; also known as lanepitant; MEN10627, cyc(2 $\beta$ -5 $\beta$ )(Met-Asp-Trp-Phe-Dap-Leu); MEN11420, cyc(2 $\beta$ -5 $\beta$ )[Asn(2-AcNH- $\beta$ -D-Glc)-Asp-Trp-Phe-Dap-Leu]; also known as nepadutant; PD157672, Boc-(s)Phe-(R) $\alpha$ MePheNH(CH<sub>2</sub>)<sub>7</sub>NHCONH<sub>2</sub>; RP67580, 3 $\alpha$ R,7 $\alpha$ R-(1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone; SB223412, (s)-(-)-N-( $\alpha$ -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide; SR140333, (s)-1-(2-[3-{3,4-dichlorophenyl}-1-[3-isopropoxyphenylacetyl]piperidin-3-yl]ethyl)-4-phenyl-1-azoniabicyclo(2.2.2)octane chloride; SR142801, (s)-(-)-N-(1-[3-{1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl}propyl]-4-phenylpiperidin-4-yl)-N-methylacetamide; SR48968, (s)-N-methyl-N-(4-acetyl-amino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide; also known as saredutant

## Further Reading

- Commons KG (2010). Neuronal pathways linking substance P to drug addiction and stress. *Brain Res* 1314: 175–182.
- Diemunsch P, Joshi GP, Brichant JF (2009). Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. *Br J Anaesth* 103: 7–13.
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288.
- Jones S, Gibbins JM (2008). The neurokinin 1 receptor: a potential new target for anti-platelet therapy? *Curr Opin Pharmacol* 8: 114–119.
- Rance NE, Krajewski SJ, Smith MA, Cholanian M, Dacks PA (2010). Neurokinin B and the hypothalamic regulation of reproduction. *Brain Res* 1364: 116–128.
- Tuluc F, Lai JP, Kilpatrick LE, Evans DL, Douglas SD (2009). Neurokinin 1 receptor isoforms and the control of innate immunity. *Trends Immunol* 30: 271–276.

## References

- Catalioto RM *et al.* (1998). *Br J Pharmacol* 123: 81–91.
- Donaldson LF *et al.* (1996). *Biochem J* 320: 1–5.
- Hale JJ *et al.* (1998). *J Med Chem* 41: 4607–4614.
- Krause JE *et al.* (1997). *Proc Natl Acad Sci U S A* 94: 310–315.
- Roush ED, Kwatra MM (1998). *FEBS Lett* 428: 291–294.
- Sarau HM *et al.* (1997). *J Pharmacol Exp Ther* 281: 1303–1311.

# Trace amine-associated

**Overview:** Trace amine-associated receptors (nomenclature as agreed by NC-IUPHAR for trace amine receptors, see Maguire *et al.*, 2009) were initially discovered as a result of a search for novel 5-HT receptors (Borowsky *et al.*, 2001), where 15 mammalian orthologues were identified and divided into two families. Emerging evidence suggests that TA<sub>1</sub> is a modulator of monoaminergic activity in the brain (Xie and Miller, 2009) with TA<sub>1</sub> and dopamine D<sub>2</sub> receptors shown to form constitutive heterodimers when co-expressed (Espinoza *et al.*, 2011).

Nomenclature	TA <sub>1</sub>	TA <sub>2</sub>
Other names	TAA1, TaR-1, BO111	TAA2, GPR58
Ensembl ID	ENSG00000146399	ENSG00000146378
Principal transduction	G <sub>s</sub>	G <sub>s</sub>
Potency order	Tyramine ≥ PEA > octopamine = dopamine (Borowsky <i>et al.</i> , 2001)	PEA > tryptamine (Borowsky <i>et al.</i> , 2001)
Probes	[ <sup>3</sup> H]-Tyramine (20 nM, Borowsky <i>et al.</i> , 2001)	–

TAAR3 (BO107, ENSMUSG00000069708, ENSRNOG00000025982), in some individuals, and TAAR4 (ENSMUSG00000069707, ENSRNOG00000029877) are pseudogenes in man, although functional in rodents. The signalling characteristics and pharmacology of TAA<sub>5</sub> (PNR, Putative Neurotransmitter Receptor, ENSG00000135569), TAA<sub>6</sub> (Trace amine receptor 4, TaR-4, ENSG00000146383), TAA<sub>8</sub> (Trace amine receptor 5, GPR102, ENSG00000146385) and TAA<sub>9</sub> (trace amine associated receptor 9, ENSG00000237110) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have been shown to have affinity for rodent cloned trace amine receptors, including TA<sub>1</sub> (Scanlan *et al.*, 2004). An antagonist EPPTB has recently been described that has a pK<sub>i</sub> of 9.1 at the mouse TA<sub>1</sub> but less than 5.3 for human TA<sub>1</sub> (Stalder *et al.*, 2011).

**Abbreviations:** EPPTB, N-(3-ethoxyphenyl)-4-pyrrolidin-1-yl-3-trifluoromethylbenzamide; PEA, 2-phenylethylamine

## Further Reading

- Burchett SA, Hicks TP (2006). The mysterious trace amines: protean neuromodulators of synaptic transmission in mammalian brain. *Prog Neurobiol* **79**: 223–246.
- Grandy DK (2007). Trace amine-associated receptor 1-Family archetype or iconoclast? *Pharmacol Ther* **116**: 355–390.
- Maguire JJ, Parker WA, Foord SM, Bonner TI, Neubig RR, Davenport AP (2009). International Union of Pharmacology. LXXII. Recommendations for trace amine receptor nomenclature. *Pharmacol Rev* **61**: 1–8.
- Miller GM (2011). The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. *J Neurochem* **116**: 164–176.
- Sotnikova TD, Caron MG, Gainetdinov RR (2009). Trace amine-associated receptors as emerging therapeutic targets. *Mol Pharmacol* **76**: 229–235.
- Zucchi R, Chiellini G, Scanlan TS, Grandy DK (2006). Trace amine-associated receptors and their ligands. *Br J Pharmacol* **149**: 967–978.

## References

- Borowsky B *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 8966–8971.
- Scanlan TS *et al.* (2004). *Nat Med* **10**: 638–642.
- Espinoza S *et al.* (2011). *Mol Pharmacol* **80**: 416–425.
- Stalder H *et al.* (2011). *Bioorg Med Chem Lett* **21**: 1227–1231.
- Xie Z, Miller GM (2009). *Biochem Pharmacol* **78**: 1095–1104.

# TRH

**Overview:** Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) are activated by the endogenous tripeptide TRH (pGlu-His-ProNH<sub>2</sub>). TRH and TRH analogues fail to distinguish TRH<sub>1</sub> and TRH<sub>2</sub> receptors (Sun *et al.*, 2003). [<sup>3</sup>H]-TRH is able to label both TRH<sub>1</sub> and TRH<sub>2</sub> receptors with *K<sub>d</sub>* values of 13 and 9 nM, respectively.

Nomenclature	TRH <sub>1</sub>	TRH <sub>2</sub>
Other names	TRH receptor, thyroliberin	–
Ensembl ID	ENSG00000174417	ENSMUSG00000039079, ENSRNOG00000012789
Principal transduction	G <sub>q</sub>	G <sub>q</sub>
Selective antagonists	Midazolam (Drummond <i>et al.</i> , 1989), chlordiazepoxide (Straub <i>et al.</i> , 1990), diazepam	–

The human orthologue of the rodent TRH<sub>2</sub> receptor has yet to be identified.

**Abbreviations:** MeTRH, pGlu-[N<sup>ε</sup>-methyl]His-ProNH<sub>2</sub>

## Further Reading

- Bilek R, Bicikova M, Safarik L (2011). TRH-like peptides. *Physiol Res* **60**: 207–215.
- Chiamolera MI, Wondisford FE (2009). Thyrotropin-releasing hormone and the thyroid hormone feedback mechanism. *Endocrinology* **150**: 1091–1096.
- Engel S, Gershengorn MC (2007). Thyrotropin-releasing hormone and its receptors – a hypothesis for binding and receptor activation. *Pharmacol Ther* **113**: 410–419.
- Gaspar E, Hardenbicker C, Bodo E, Wenzel B, Ramot Y, Funk W *et al.* (2010). Thyrotropin releasing hormone (TRH): a new player in human hair-growth control. *FASEB J* **24**: 393–403.
- Kamath J, Yarbrough GG, Prange AJ, Winokur A (2009). The thyrotropin-releasing hormone (TRH)-immune system homeostatic hypothesis. *Pharmacol Ther* **121**: 20–28.
- Kleinau G, Krause G (2009). Thyrotropin and homologous glycoprotein hormone receptors: structural and functional aspects of extracellular signaling mechanisms. *Endocr Rev* **30**: 133–151.

## References

- Drummond AH *et al.* (1989). *Ann N Y Acad Sci* **553**: 197–204.
- Straub RE *et al.* (1990). *Proc Natl Acad Sci U S A* **87**: 9514–9518.
- Sun Y *et al.* (2003). *J Mol Endocrinol* **30**: 87–97.

# Urotensin-II

**Overview:** The urotensin-II (U-II) receptor (UT, nomenclature as agreed by NC-IUPHAR, see Foord *et al.*, 2005, Douglas and Ohlstein, 2000) is activated by the endogenous dodecapeptide U-II, originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish (Bern *et al.*, 1985). Several structural forms of U-II exist in fish and amphibians. The Goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* (Coulouarn *et al.*, 1998; Liu *et al.*, 1999; Mori *et al.*, 1999; Nothacker *et al.*, 1999). Human U-II (derived from ENSG00000049247), an 11-amino-acid peptide (Coulouarn *et al.*, 1998), retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding (Kinney *et al.*, 2002; Brkovic *et al.*, 2003). This sequence is also conserved in the deduced amino-acid sequence of rat (14 amino-acids) and mouse (14 amino-acids) U-II, although the N-terminal is more divergent from the human sequence (Coulouarn *et al.*, 1999). A second endogenous ligand for UT has been discovered in rat (Sugo and Mori, 2008). The urotensin II-related peptide (URP) an octapeptide, is derived from a different gene, but shares the C-terminal sequence (CFWKYCV) common to U-II from other species. Identical sequences to rat URP are predicted for the mature mouse and human peptides.

Nomenclature	UT
Other names	GPR14, SENR, UR-IIR
Ensembl ID	ENSG00000181408
Principal transduction	G <sub>q/11</sub>
Selective agonists	[Pen <sup>5</sup> ]U-II-(4-11), U-II-(4-11), U-II (Grieco <i>et al.</i> , 2002), AC7954 (Lehmann <i>et al.</i> , 2005), FL104 and analogues (Lehmann <i>et al.</i> , 2006; 2007)
Selective antagonists	Urantide (8.3, Patacchini <i>et al.</i> , 2003), SB706375 (7.5-8.0, Douglas <i>et al.</i> , 2005), palosuran (pIC <sub>50</sub> 7.1, Clozel <i>et al.</i> , 2004), SB611812 (6.6, Rakowski <i>et al.</i> , 2005)
Probes	[ <sup>25</sup> I]-hU-II (0.24 nM, Maguire <i>et al.</i> , 2000)

In human vasculature, human U-II elicits both vasoconstrictor (pD<sub>2</sub> 9.3–10.1, Maguire *et al.*, 2000) and vasodilator (pIC<sub>50</sub> 10.3–10.4, Stirrat *et al.*, 2001) responses.

**Abbreviations:** [Pen<sup>5</sup>]U-II-(4-11), [pencillamine, β,β-dimethylcysteine]<sup>5</sup>U-II-(4-11); AC7954, 3-(4-chlorophenyl)-3-(2-dimethyl-aminoethyl)-isochroman-1-one HCl; FL104, (+)N-(1-[4-chlorophenyl]-3-dimethylaminopropyl)-4-phenylbenzamide oxalate; palosuran, 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulphate, also known as ACT058362; SB611812, 2,6-dichloro-N-(4-chloro-3-[[2-(dimethylamino)ethyl]oxy]phenyl)-4-(trifluoromethyl)benzenesulfonamide; SB706375, 2-bromo-4,5-dimethoxy-N-[3-(R)-1-methyl-pyrrolidin-3-yloxy]-4-trifluoromethyl-phenyl]-benzenesulphonamide HCl; urantide, [Pen<sup>5</sup>,DTrp<sup>7</sup>,Orn<sup>8</sup>]hU-II(4-11)

## Further Reading

- Desai N, Sajjad J, Frishman WH (2008). Urotensin II: a new pharmacologic target in the treatment of cardiovascular disease. *Cardiol Rev* 16: 142–153.
- Douglas SA, Ohlstein EH (2000). Urotensin receptors. In: *The IUPHAR Receptor Compendium of Receptor Characterization and Classification*. IUPHAR Media Ltd: London, pp. 365–372.
- Foord SM, Bonner TI, Neubig RR *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288.
- Guidolin D, Albertin G, Ribatti D (2010). Urotensin-II as an angiogenic factor. *Peptides* 31: 1219–1224.
- Hunt BD, Ng LL, Lambert DG (2010). A rat brain atlas of urotensin-II receptor expression and a review of central urotensin-II effects. *Naunyn Schmiedebergs Arch Pharmacol* 382: 1–31.
- Leprince J, Chatenet D, Dubessy C, Fournier A, Pfeiffer B, Scalbert E *et al.* (2008). Structure-activity relationships of urotensin II and URP. *Peptides* 29: 658–673.
- Lescot E, Bureau R, Rault S (2008). Nonpeptide Urotensin-II receptor agonists and antagonists: review and structure-activity relationships. *Peptides* 29: 680–690.
- Maryanoff BE, Kinney WA (2010). Urotensin-II receptor modulators as potential drugs. *J Med Chem* 53: 2695–2708.
- Ong KL, Wong LY, Cheung BM (2008). The role of urotensin II in the metabolic syndrome. *Peptides* 29: 859–867.
- Proulx CD, Holleran BJ, Lavigne P *et al.* (2008). Biological properties and functional determinants of the urotensin II receptor. *Peptides* 29: 691–699.
- Ross B, McKendry K, Giaid A (2010). Role of urotensin II in health and disease. *Am J Physiol Regul Integr Comp Physiol* 298: R1156–R1172.
- Vaudry H, Do Rego JC, Le Mevel JC, Chatenet D, Tostivint H, Fournier A *et al.* (2010). Urotensin II, from fish to human. *Ann N Y Acad Sci* 1200: 53–66.

## References

- Bern HA *et al.* (1985). *Recent Prog Horm Res* 41: 533–552.
- Brkovic A *et al.* (2003). *J Pharmacol Exp Ther* 306: 1200–1209.
- Clozel M *et al.* (2004). *J Pharmacol Exp Ther* 311: 204–212.
- Coulouarn Y *et al.* (1998). *Proc Natl Acad Sci U S A* 95: 15803–15808.
- Coulouarn Y *et al.* (1999). *FEBS Lett* 457: 28–32.
- Douglas SA *et al.* (2005). *Br J Pharmacol* 145: 620–635.
- Grieco P *et al.* (2002). *J Med Chem* 45: 4391–4394.
- Kinney WA *et al.* (2002). *Angew Chem Int Ed Engl* 41: 2940–2944.
- Lehmann F *et al.* (2005). *Bioorg Med Chem* 13: 3057–3068.
- Lehmann F *et al.* (2006). *J Med Chem* 49:2232–2240.
- Lehmann F *et al.* (2007). *Eur J Med Chem*, 42:276–285.
- Liu Q *et al.* (1999). *Biochem Biophys Res Commun* 266: 174–178.
- Maguire JJ *et al.* (2000). *Br J Pharmacol* 131: 441–446.
- Mori M *et al.* (1999). *Biochem Biophys Res Commun* 265: 123–129.
- Nothacker HP *et al.* (1999). *Nat Cell Biol* 1: 383–385.
- Patacchini R *et al.* (2003). *Br J Pharmacol* 140: 1155–1158.
- Rakowski E *et al.* (2005). *J Mol Cell Cardiol* 39: 785–791.
- Stirrat A *et al.* (2001). *Am J Physiol Heart Circ Physiol* 280: H925–H928.
- Sugo T, Mori M (2008). *Peptides* 29: 809–812.



# Vasopressin & oxytocin

**Overview:** Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytocin receptors) are activated by the endogenous cyclic nonapeptides AVP and OT. These peptides are derived from precursors (ENSG00000101200 and ENSG00000101405, respectively), which also produce neurophysins.

Nomenclature	V <sub>1A</sub>	V <sub>1B</sub>	V <sub>2</sub>	OT
Ensembl ID	ENSG00000166148	ENSG00000198049	ENSG00000126895	ENSG00000180914
Principal transduction	G <sub>q/11</sub>	G <sub>q/11</sub>	G <sub>s</sub>	G <sub>q/11</sub> , G <sub>i/o</sub>
Rank order of potency	AVP > OT	AVP > OT	AVP > OT	OT ≥ AVP
Selective agonists	F180, [Phe <sup>2</sup> ,Orn <sup>8</sup> ]VT	d[D-3-Pal <sup>2</sup> ]VP, d[Cha <sup>4</sup> ]AVP (Derick <i>et al.</i> , 2002), d[Leu <sup>4</sup> ,Lys <sup>8</sup> ]VP (Pena <i>et al.</i> , 2007)	d[Val <sup>4</sup> ,DArg <sup>8</sup> ]VP, OPC51803, VNA932	[Thr <sup>4</sup> ,Gly <sup>7</sup> ]OT (Elands <i>et al.</i> , 1988)
Selective antagonists	d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> , Arg <sup>8</sup> ]VP (9.0), SR49059 (8.9), YM087 (8.2)	SSR149415 (8.4; Griebel <i>et al.</i> , 2002; Serradeil-Le Gal <i>et al.</i> , 2002)	VPA985 (8.9, Albright <i>et al.</i> , 1998), d(CH <sub>2</sub> ) <sub>5</sub> [D-Ile <sup>2</sup> , Ile <sup>4</sup> ]AVP (8.4), SR121463A (8.4; Serradeil-Le Gal <i>et al.</i> , 1996), OPC31260 (7.6; Yamamura <i>et al.</i> , 1992), YM087 (8.96)	SSR126768A (9.3; Serradeil-Le Gal <i>et al.</i> , 2004) desGlyNH <sub>2</sub> -d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> , Thr <sup>4</sup> ,Orn <sup>8</sup> ] OT (8.5), L372662 (8.4),
Probes	[ <sup>3</sup> H]-AVP, [ <sup>3</sup> H]-SR49059 (1.5 nM), [ <sup>3</sup> H]-d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> , Arg <sup>8</sup> ]AVP (1.1 nM), [ <sup>125</sup> I]-HO-Phaa,D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-NH <sub>2</sub> (50 pM)	[ <sup>3</sup> H]-AVP, [ <sup>3</sup> H]-SSR149415 (1 nM; Serradeil-Le Gal <i>et al.</i> 2007)	[ <sup>3</sup> H]-AVP, [ <sup>3</sup> H]-desGly-NH <sub>2</sub> [D-Ile <sup>2</sup> ,Ile <sup>4</sup> ]AVP (2.8 nM), [ <sup>3</sup> H]-d[D-Arg <sup>8</sup> ]AVP (0.8 nM), [ <sup>3</sup> H]-SR121463A (4.1 nM)	[ <sup>3</sup> H]-OT, [ <sup>35</sup> S]-Non Peptide OT Antagonist (42 pM; Lemaire <i>et al.</i> , 2002), [ <sup>125</sup> I]-d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> , Thr <sup>4</sup> ,Orn <sup>8</sup> , Tyr-NH <sub>2</sub> <sup>9</sup> ]OVT (90 pM), [ <sup>111</sup> In]-DOTA-dLVT (4.5 nM; Chini <i>et al.</i> , 2003)

The V<sub>2</sub> receptor exhibits marked species differences, such that many ligands (d(CH<sub>2</sub>)<sub>5</sub>[D-Ile<sup>2</sup>,Ile<sup>4</sup>]VP and [<sup>3</sup>H]-desGly-NH<sub>2</sub>[D-Ile<sup>2</sup>,Ile<sup>4</sup>]VP) exhibit low affinity at human V<sub>2</sub> receptors (Ala *et al.*, 1997). Similarly, [<sup>3</sup>H]-d[D-Arg<sup>8</sup>]VP is V<sub>2</sub> selective in the rat, not in the human (Saito *et al.*, 1997). The gene encoding the V<sub>2</sub> receptor is polymorphic in man, underlying nephrogenic diabetes insipidus (Bichet, 1998). YM087 display high affinity for both human V<sub>1a</sub> and V<sub>2</sub> receptors (Tahara *et al.*, 1998). d[Cha<sup>4</sup>]AVP is selective only for the human and bovine V<sub>1b</sub> receptors (Derick *et al.*, 2002), while d[Leu<sup>4</sup>,Lys<sup>8</sup>]VP has high affinity for the rat V<sub>1b</sub> receptor (Pena *et al.*, 2007).

**Abbreviations:** F180, Hmp-Phe-Ile-Hgn-Asn-Cys-Pro-Dab(Abu)-Gly-NH<sub>2</sub>; [<sup>111</sup>In]-DOTA-dLVT, [<sup>111</sup>In]-DOTA-Lys<sup>8</sup>-deamino-vasotocin; L372662, 1-(1-[4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl]piperidin-4-yl)-1,4-dihydrobenz[d][1,3]oxazin-2-one; OPC31260, 5-dimethylamino-1-(4-[2-methylbenzoylamino]benzoyl)-2,3,4,5-tetrahydro-1H-benzazepine; OPC51803, (5*r*)-2-(1-[2-chloro-4-[1-pyrrolidinyl]benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepin-5-yl)-N-isopropylacetamide; [<sup>35</sup>S]-non-peptide OT antagonist, [<sup>35</sup>S]-(1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyloxy)phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1H)-quinolinone); SR121463A, 1-(4-Boc-2-methoxybenzenesulfonyl)-5-ethoxy-3-spiro-(4-[2-morpholinoethoxy]cyclohexane)indol-2-one fumarate; equatorial isomer; SR49059, (2*s*)-1-([2*r*,3*s*]-[5-chloro-3-(chlorophenyl)-1-[3,4-dimethoxysulfonyl]-3-hydroxy]-2,3-dihydro-1H-indole-2-carbonyl)-pyrrolidine-2-carboxamide; SSR149415, (2*S*,4*R*)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide; SSR126768A, 4-chloro-3-[(3*R*)-(+)-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-N-ethyl-N-(3-pyridylmethyl)-benzamide, hydrochloride; VNA932, (2-chloro-4-[3-methyl-pyrazol-1-yl]-phenyl)-(5*H*,11*H*)-pyrrolo(2,1-*c*)(1,4)benzodiazepin-10-yl-methanone; VPA985, 5-fluoro-2-methyl-N-(4-[5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl]-3-chlorophenyl)benzamide; YM087, (4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepin-6-yl) carbonyl]-2-phenylbenzanilide monohydrochloride)

## Further Reading

- Gimpl G, Reitz J, Brauer S, Trossen C (2008). Oxytocin receptors: ligand binding, signalling and cholesterol dependence. *Prog Brain Res* 170: 193–204.
- Lee HJ, Macbeth AH, Pagani JH, Young WS, III (2009). Oxytocin: the great facilitator of life. *Prog Neurobiol* 88: 127–151.
- Manning M, Stoev S, Chini B *et al.* (2008). Peptide and non-peptide agonists and antagonists for the vasopressin and oxytocin V<sub>1a</sub>, V<sub>1b</sub>, V<sub>2</sub> and OT receptors: research tools and potential therapeutic agents. *Prog Brain Res* 170: 473–512.
- McGregor IS, Callaghan PD, Hunt GE (2008). From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use? *Br J Pharmacol* 154: 358–368.
- Oghlakan G, Klapholz M (2009). Vasopressin and vasopressin receptor antagonists in heart failure. *Cardiol Rev* 17: 10–15.

Roper J, O'Carroll AM, Young W, III, Lolait S (2011). The vasopressin Avpr1b receptor: molecular and pharmacological studies. *Stress* **14**: 98–115.

Veeraveedu PT, Palaniyandi SS, Yamaguchi K, Komai Y, Thandavarayan RA, Sukumaran V *et al.* (2010). Arginine vasopressin receptor antagonists (vaptans): pharmacological tools and potential therapeutic agents. *Drug Discov Today* **15**: 826–841.

## References

- Ala Y *et al.* (1997). *Eur J Pharmacol* **331**: 285–293.
- Albright JD *et al.* (1998). *J Med Chem* **41**: 2442–2444.
- Bichet DG (1998). *Am J Med* **105**: 431–442.
- Chini B *et al.* (2003). *Br J Cancer* **89**: 930–936.
- Derick S *et al.* (2002). *Endocrinology* **143**: 4655–4664.
- Elands J *et al.* (1988). *Am J Physiol Endocrinol Metab* **254**: E31–E38.
- Griebel G *et al.* (2002). *Proc Natl Acad Sci U S A* **99**: 6370–6375.
- Lemaire W *et al.* (2002). *Eur J Pharmacol* **450**: 19–28.
- Pena A *et al.* (2007). *Endocrinology* **148**: 4136–4146.
- Saito M *et al.* (1997). *Biochem Pharmacol* **53**: 1711–1717.
- Serradeil-Le Gal C *et al.* (1996). *J Clin Invest* **98**: 2729–2738.
- Serradeil-Le Gal C *et al.* (2002). *J Pharmacol Exp Ther* **300**: 1122–1130.
- Serradeil-Le Gal C *et al.* (2004). *J Pharmacol Exp Ther* **309**: 414–424.
- Serradeil-Le Gal C *et al.* (2007). *Am J Physiol Regul Integr Comp Physiol* **293**: R938–R949.
- Tahara A *et al.* (1998). *Naunyn-Schmiedeberg's Arch Pharmacol* **357**: 63–69.
- Yamamura Y *et al.* (1992). *Br J Pharmacol* **105**: 787–791.

# VIP & PACAP

**Overview:** Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors, Harmar *et al.*, 1998) are activated by the endogenous peptides VIP, PACAP-38, PACAP-27, peptide histidine isoleucineamide (PHI), peptide histidine methionineamide (PHM) and peptide histidine valine (PHV). 'PACAP type II receptors' (VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors) display comparable affinity for PACAP and VIP, whereas PACAP-27 and PACAP-38 are >100 fold more potent than VIP as agonists of most isoforms of the PAC<sub>1</sub> receptor. However, one splice variant of the human PAC<sub>1</sub> receptor has been reported to respond to PACAP-38, PACAP-27 and VIP with comparable affinity (Dautzenberg *et al.*, 1999). PG99-465 (Moreno *et al.*, 2000) has been used as a selective VPAC<sub>2</sub> receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC<sub>1</sub> and PAC<sub>1</sub> receptors (Dickson *et al.*, 2006). The selective PAC<sub>1</sub> receptor agonist maxadilan, was extracted from the salivary glands of sand flies (*Lutzomyia longipalpis*) and has no sequence homology to VIP or PACAP (Moro and Lerner, 1997). Two deletion variants of maxadilan, M65 (Uchida *et al.*, 1998) and max.d.4 (Moro *et al.*, 1999) have been reported to be PAC<sub>1</sub> receptor antagonists, but these peptides have not been extensively characterised.

Nomenclature	VPAC <sub>1</sub>	VPAC <sub>2</sub>	PAC <sub>1</sub>
Other names	VIP <sub>1</sub> /PACAP, VIP, VIP <sub>1</sub> , PACAP type II, PVR2	VIP <sub>2</sub> /PACAP, VIP <sub>2</sub> , PACAP <sub>3</sub> , PVR2	PACAP, PACAP type I, PVR1
Ensembl ID	ENSG00000114812	ENSG00000106018	ENSG00000078549
Principal transduction	G <sub>s</sub>	G <sub>s</sub>	G <sub>s</sub>
Rank order of potency	VIP, PACAP-27, PACAP-38 >> GHRH, PHI, secretin	VIP, PACAP-38, PACAP-27 > PHI >> GHRH, secretin	PACAP-27, PACAP-38 >> VIP
Selective agonists	[Ala <sup>11,22,28</sup> ]VIP, [Lys <sup>15</sup> ,Arg <sup>16</sup> ,Leu <sup>27</sup> ]VIP(1-7)/GRF(8-27)-NH <sub>2</sub>	Ro251553 (Gourlet <i>et al.</i> , 1997a, 1997b) Ro251392 (Xia <i>et al.</i> , 1997)	Maxadilan (Moro and Lerner, 1997)
Selective antagonists	PG97-269 (Gourlet <i>et al.</i> , 1997a)	–	–
Probes	[ <sup>125</sup> I]-VIP, [ <sup>125</sup> I]-PACAP-27	[ <sup>125</sup> I]-VIP, [ <sup>125</sup> I]-PACAP-27	[ <sup>125</sup> I]-PACAP-27

**Abbreviations:** PG97-269, [Ac-His<sup>1</sup>,D-Phe<sup>2</sup>,Lys<sup>15</sup>,Arg<sup>16</sup>]VIP(3-7)/GRF(8-27)-NH<sub>2</sub>; Ro251392, Ac-His<sup>1</sup>[Glu<sup>8</sup>,OCH<sub>3</sub>-Tyr<sup>10</sup>,Lys<sup>12</sup>,Nle<sup>17</sup>,Ala<sup>19</sup>,Asp<sup>25</sup>,Leu<sup>26</sup>,Lys<sup>27,28</sup>]VIP (*cyclo* 21–25); Ro251553, Ac-His<sup>1</sup>[Glu<sup>8</sup>,Lys<sup>12</sup>,Nle<sup>17</sup>,Ala<sup>19</sup>,Asp<sup>25</sup>,Leu<sup>26</sup>,Lys<sup>27,28</sup>,Gly<sup>29,30</sup>,Thr<sup>31</sup>]VIP-NH<sub>2</sub> (*cyclo* 21–25)

## Further Reading

- Couvineau A, Ceraudo E, Tan YV, Laburthe M (2010). VPAC1 receptor binding site: contribution of photoaffinity labeling approach. *Neuropeptides* **44**: 127–132.
- Gonzalez-Rey E, Varela N, Chorny A, Delgado M (2007). Therapeutical approaches of vasoactive intestinal peptide as a pleiotropic immunomodulator. *Curr Pharm Des* **13**: 1113–1139.
- Dickson L, Finlayson K (2009). VPAC and PAC receptors: from ligands to function. *Pharmacol Ther* **121**: 294–316.
- Groneberg DA, Rabe KF, Fischer A (2006). Novel concepts of neuropeptide-based drug therapy: vasoactive intestinal polypeptide and its receptors. *Eur J Pharmacol* **533**: 182–194.
- Harmar AJ, Arimura A, Gozes I, Journot L, Laburthe M, Pisegna JR *et al.* (1998). International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. *Pharmacol Rev* **50**: 265–270.
- Hill JM (2007). Vasoactive intestinal peptide in neurodevelopmental disorders: therapeutic potential. *Curr Pharm Des* **13**: 1079–1089.
- Laburthe M, Couvineau A, Tan V (2007). Class II G protein-coupled receptors for VIP and PACAP: structure, models of activation and pharmacology. *Peptides* **28**: 1631–1639.
- Moody TW, Ito T, Osefo N, Jensen RT (2011). VIP and PACAP: recent insights into their functions/roles in physiology and disease from molecular and genetic studies. *Curr Opin Endocrinol Diabetes Obes* **18**: 61–67.
- Nakata M, Yada T (2007). PACAP in the glucose and energy homeostasis: physiological role and therapeutic potential. *Curr Pharm Des* **13**: 1105–1112.
- Schytz HW, Olesen J, Ashina M (2010). The PACAP receptor: a novel target for migraine treatment. *Neurotherapeutics* **7**: 191–196.
- Vaudry D, Falluel-Morel A, Bourgault S, Basille M, Burel D *et al.* (2009) Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. *Pharmacol Rev* **61**: 283–357.

## References

- Dautzenberg FM *et al.* (1999). *J Neuroendocrinol* **11**: 941–949.
- Dickson L *et al.* (2006). *Neuropharmacology* **51**: 1086–1098.
- Gourlet P *et al.* (1997a). *Peptides* **18**: 1539–1545.
- Gourlet P *et al.* (1997b). *Peptides* **18**: 403–408.
- Moreno D *et al.* (2000) *Peptides* **21**: 1543–1549.
- Moro O, Lerner EA (1997). *J Biol Chem* **272**: 966–970.
- Moro O *et al.* (1999). *J Biol Chem* **274**: 23103–23110.
- Uchida D *et al.* (1998). *Ann N Y Acad Sci* **865**: 253–258.
- Xia M *et al.* (1997). *J Pharmacol Exp Ther* **281**: 629–633.



# LIGAND-GATED ION CHANNELS

Ligand-gated ion channels (LGICs) are integral membrane proteins that contain a pore which allows the regulated flow of selected ions across the plasma membrane. Ion flux is passive and driven by the electrochemical gradient for the permeant ions. The channels are opened, or gated, by the binding of a neurotransmitter to an orthosteric site(s) that triggers a conformational change that results in the conducting state. Modulation of gating can occur by the binding of endogenous, or exogenous, modulators to allosteric sites. LGICs mediate fast synaptic transmission, on a millisecond time scale, in the nervous system and at the somatic neuromuscular junction. Such transmission involves the release of a neurotransmitter from a pre-synaptic neurone and the subsequent activation of post-synaptically located receptors that mediate a rapid, phasic, electrical signal (the excitatory, or inhibitory, post-synaptic potential). However, in addition to their traditional role in phasic neurotransmission, it is now established that some LGICs mediate a tonic form of neuronal regulation that results from the activation of extra-synaptic receptors by ambient levels of neurotransmitter. The expression of some LGICs by non-excitatory cells is suggestive of additional functions.

By convention, the LGICs comprise the excitatory, cation-selective, nicotinic acetylcholine (Millar and Gotti, 2009; Changeux, 2010), 5-HT<sub>3</sub> (Barnes *et al.*, 2009; Walstab *et al.*, 2010), ionotropic glutamate (Lodge, 2009; Traynelis *et al.*, 2010) and P2X receptors (Jarvis and Khakh, 2009; Surprenant and North, 2009) and the inhibitory, anion-selective, GABA<sub>A</sub> (Olsen and Sieghart, 2008; Belelli *et al.*, 2009) and glycine receptors (Lynch, 2009; Yevenes and Zeilhofer, 2011). The nicotinic acetylcholine, 5-HT<sub>3</sub>, GABA<sub>A</sub> and glycine receptors (and an additional zinc-activated channel) are pentameric structures and are frequently referred to as the Cys-loop receptors due to the presence of a defining loop of residues formed by a disulphide bond in the extracellular domain of their constituent subunits (Miller and Smart, 2010; Thompson *et al.*, 2010). However, the prokaryotic ancestors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in the literature (Hilf and Dutzler, 2009). The ionotropic glutamate and P2X receptors are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinatorial diversity results, within each class of LGIC, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs thus present attractive targets for new therapeutic agents with improved discrimination between receptor isoforms and a reduced propensity for off-target effects. The development of novel, faster screening techniques for compounds acting on LGICs (Dunlop *et al.*, 2008) will greatly aid in the development of such agents.

## Further Reading

- Barnes NM, Hales TG, Lummis SCR, Peters JA (2009). The 5-HT<sub>3</sub> receptor – the relationship between structure and function. *Neuropharmacology* **56**: 273–284.
- Belelli D, Harrison NL, Maguire J, Macdonald RL, Walker MC, Cope DW (2009). Extrasynaptic GABA<sub>A</sub> receptors: form, pharmacology, and function. *J Neurosci* **29**: 12757–12763.
- Changeux J-P (2010). Allosteric receptors: from electric organ to cognition. *Annu Rev Pharmacol Toxicol* **50**: 1–38.
- Dunlop J, Bowlby M, Peri R, Vasilyev D, Arias R (2008). High-throughput electrophysiology: an emerging paradigm for ion channel screening and physiology. *Nat Rev Drug Discov* **7**: 358–368.
- Hilf RJ, Dutzler R (2009). A prokaryotic perspective on pentameric ligand-gated ion channel structure. *Curr Opin Struct Biol* **19**: 418–424.
- Jarvis MF, Khakh BS (2009). ATP-gated P2X cation-channels. *Neuropharmacology* **56**: 230–236.
- Lodge D (2009). The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature. *Neuropharmacology* **56**: 6–21.
- Lynch JW (2009). Native glycine receptors and their physiological roles. *Neuropharmacology* **56**: 303–309.
- Millar NS, Gotti C (2009). Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology* **56**: 237–246.
- Miller PS, Smart TG (2010). Binding, activation and modulation of Cys-loop receptors. *Trends Pharmacol Sci* **31**: 161–174.
- Olsen RW, Sieghart W (2009). International Union of Pharmacology. LXX. Subtypes of  $\gamma$ -aminobutyric acid<sub>A</sub> receptors: classification on the basis of subunit composition, pharmacology, and function. Update. *Pharmacol Rev* **60**: 243–260.
- Surprenant A, North RA (2009). Signaling at purinergic P2X receptors. *Annu Rev Physiol* **71**: 333–359.
- Thompson AJ, Lester HA, Lummis SCR (2010). The structural basis of function in Cys-loop receptors. *Q Rev Biophys* **43**: 449–499.
- Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK *et al.* (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev* **62**: 405–496.
- Walstab J, Rappold G, Niesler B (2010). 5-HT<sub>3</sub> receptors: role in disease and target of drugs. *Pharmacol Ther* **128**: 146–169.
- Yevenes GE, Zeilhofer HU (2011). Allosteric modulation of glycine receptors. *Br J Pharmacol* **164**: 224–236.

# 5-HT<sub>3</sub> (5-Hydroxytryptamine<sub>3</sub>)

**Overview:** The 5-HT<sub>3</sub> receptor [nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-hydroxytryptamine (serotonin) receptors (Hoyer *et al.*, 1994; see also Peters *et al.*, 2010)] is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, GABA<sub>A</sub> and strychnine-sensitive glycine receptors. The receptor exists as a pentamer of 4TM subunits that form an intrinsic cation selective channel (Barnes *et al.*, 2009). Five human 5-HT<sub>3</sub> receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT<sub>3A</sub> and hetero-oligomeric assemblies of 5-HT<sub>3A</sub> and 5-HT<sub>3B</sub> subunits have been characterised in detail. The 5-HT<sub>3C</sub> (ENSG00000178084), 5-HT<sub>3D</sub> (ENSG00000186090) and 5-HT<sub>3E</sub> (ENSG00000186038) subunits (Karnovsky *et al.*, 2003; Niesler *et al.*, 2003), like the 5-HT<sub>3B</sub> subunit, do not form functional homomers, but are reported to assemble with the 5-HT<sub>3A</sub> subunit to influence its functional expression rather than pharmacological profile (Niesler *et al.*, 2007; Holbrook *et al.*, 2009; Walstab *et al.*, 2010a). 5-HT<sub>3A</sub>, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT<sub>3A</sub> receptor (Walstab *et al.*, 2010a). The co-expression of 5-HT<sub>3A</sub> and 5-HT<sub>3C-E</sub> subunits has been demonstrated in human colon (Kapeller *et al.*, 2011). A recombinant hetero-oligomeric 5-HT<sub>3AB</sub> receptor has been reported to contain two copies of the 5-HT<sub>3A</sub> subunit and three copies of the 5-HT<sub>3B</sub> subunit in the order B-B-A-B-A (Barrera *et al.*, 2005), but this is inconsistent with recent reports which show at least one A-A interface (Lochner and Lummis, 2010; Thompson *et al.*, 2011b). The 5-HT<sub>3B</sub> subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT<sub>3AB</sub> versus homo-oligomeric 5-HT<sub>3A</sub> recombinant receptors (Davies *et al.*, 1999; Dubin *et al.*, 1999; Hanna *et al.*, 2000; Kelley *et al.*, 2003; Stewart *et al.*, 2003; Peters *et al.*, 2005; Jensen *et al.*, 2008), influences the potency of channel blockers, but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists (Brady *et al.*, 2001; but see Dubin *et al.*, 1999; Das and Dillon, 2003; Deeb *et al.*, 2009) which may be explained by the orthosteric binding site residing at an interface formed between 5-HT<sub>3A</sub> subunits (Lochner and Lummis, 2010; Thompson *et al.*, 2011b). However, 5-HT<sub>3A</sub> and 5-HT<sub>3AB</sub> receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles (Solt *et al.*, 2005; Rüsç *et al.*, 2007; Hu and Peoples, 2008). The potential diversity of 5-HT<sub>3</sub> receptors is increased by alternative splicing of the genes *HTR3A* and *E* (Hope *et al.*, 1993; Bruss *et al.*, 2000; Niesler *et al.*, 2007, 2008; Niesler 2011). In addition, the use of tissue-specific promoters driving expression from different transcriptional start sites has been reported for the *HTR3A*, *HTR3B*, *HTR3D* and *HTR3E* genes, which could result in 5-HT<sub>3</sub> subunits harbouring different N-termini (Tzvetkov *et al.*, 2007; Jensen *et al.*, 2008; Niesler, 2011). To date, inclusion of the 5-HT<sub>3A</sub> subunit appears imperative for 5-HT<sub>3</sub> receptor function.

Nomenclature	5-HT <sub>3</sub>
Former names	M
Ensembl ID	5-HT3A ENSG00000166736, 5-HT3B ENSG00000149305
Selective agonists (pEC <sub>50</sub> )	SR57227A (6.4), 3-chlorophenyl-biguanide (5.4–5.8), 2-methyl-5-HT (5.5–5.6), 1-phenylbiguanide (4.1)
Selective antagonists (pK <sub>i</sub> )	(S)-Zacopride (9.0), granisetron (8.6–8.8), tropisetron (8.5–8.8), ondansetron (7.8–8.3)
Channel blockers (pIC <sub>50</sub> )	TMB-8 (5.4), diltiazem (4.1–4.8), picrotoxinin (4.9 + 5-HT <sub>3B</sub> = 4.2), bilobalide (3.3 + 5-HT <sub>3B</sub> = 2.5); ginkgolide B (3.1 + 5-HT <sub>3B</sub> > 3.0)
Radioligands (K <sub>d</sub> )	[ <sup>3</sup> H]Ramosetron (0.15 nM), [ <sup>3</sup> H]granisetron (1.2 nM), [ <sup>3</sup> H](S)-zacopride (2.0 nM), [ <sup>3</sup> H]GR65630 (2.6 nM), [ <sup>3</sup> H]LY278584 (3 nM)
Functional characteristics	γ = 0.4–0.8 pS [+ 5-HT <sub>3B</sub> , γ = 16 pS]; inwardly rectifying current [+ 5-HT <sub>3B</sub> , rectification reduced]; n <sub>H</sub> 2–3 [+ 5-HT <sub>3B</sub> 1–2]; relative permeability to divalent cations reduced by co-expression of the 5-HT <sub>3B</sub> subunit

Quantitative data in the table refer to homo-oligomeric assemblies of the human 5-HT<sub>3A</sub> subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT<sub>3B</sub> subunit are indicated in parenthesis. Methadone, although not a selective antagonist, displays multimodal and subunit-dependent antagonism of 5-HT<sub>3</sub> receptors (Deeb *et al.*, 2009). Similarly, TMB-8, diltiazem, picrotoxin, bilobalide and ginkgolide B are not selective for 5-HT<sub>3</sub> receptors (*e.g.* Thompson *et al.*, 2011a). The anti-malarial drugs mefloquine and quinine exert a modestly more potent block of 5-HT<sub>3A</sub> versus 5-HT<sub>3AB</sub> receptor-mediated responses (Thompson and Lummis, 2008). Varenicline, known better as a partial agonist of nicotinic acetylcholine α4β2 receptors, is also an agonist of the 5-HT<sub>3A</sub> receptor (Lummis *et al.*, 2011). Human (Belelli *et al.*, 1995; Miyake *et al.*, 1995), rat (Isenberg *et al.*, 1993), mouse (Maricq *et al.*, 1991), guinea-pig (Lankiewicz *et al.*, 1998) ferret (Mochizuki *et al.*, 2000) and canine (Jensen *et al.*, 2006) orthologues of the 5-HT<sub>3A</sub> receptor subunit have been cloned that exhibit intraspecies variations in receptor pharmacology. Notably, most ligands display significantly reduced affinities at the guinea-pig 5-HT<sub>3</sub> receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT<sub>3</sub> receptors are subject to allosteric modulation by extracellular divalent cations, alcohols, several general anaesthetics and 5-hydroxy- and halide-substituted indoles (see reviews by Parker *et al.*, 1996; Thompson and Lummis, 2006, 2007; Walstab *et al.*, 2010b).

**Abbreviations:** GR65630, 3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propanone; LY278584, 1-methyl-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1H-indazole-3-carboxamide; SR57227A, 4-amino-(6-chloro-2-pyridyl)-1 piperidine hydrochloride, TMB-8, 8-(diethylamino)octyl-3,4,5-trimethoxybenzoate

## Further Reading

- Barnes NM, Hales TG, Lummis SCR, Peters JA (2009). The 5-HT<sub>3</sub> receptor – the relationship between structure and function. *Neuropharmacology* 56: 273–284.
- Chameau P, Van Hooft JA (2006). Serotonin 5-HT<sub>3</sub> receptors in the central nervous system. *Cell Tissue Res* 326: 573–581.
- Costall B, Naylor RJ (2004). 5-HT<sub>3</sub> receptors. *Curr Drug Targets CNS Neurol Disord* 3: 27–37.
- Engleman EA, Rodd ZA, Bell RL, Murphy JM (2008). The role of 5-HT<sub>3</sub> receptors in drug abuse and as a target for pharmacotherapy. *CNS Neurol Disord Drug Targets* 7: 454–467.
- Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ *et al.* (1994). International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev*: 46, 157–203.

- Jensen AA, Davies PA, Bräuner-Osborne H, Krzywkowski K (2008). 3B but which 3B? And that's just one of the questions: the heterogeneity of human 5-HT<sub>3</sub> receptors. *Trends Pharmacol Sci* **29**: 437–444.
- Machu TK (2011). Therapeutics of 5-HT<sub>3</sub> receptor antagonists: current uses and future directions. *Pharmacol Ther* **130**: 338–347.
- Modica MN, Pittalà V, Romeo G, Salerno L, Siracusa MA (2010). Serotonin 5-HT<sub>3</sub> and 5-HT<sub>4</sub> ligands: an update of medicinal chemistry research in the last few years. *Curr Med Chem* **17**: 334–362.
- Niesler B (2011). 5-HT<sub>3</sub> receptors: potential of individual isoforms for personalised therapy. *Curr Opin Pharmacol* **11**: 81–86.
- Niesler B, Kapeller J, Hammer C, Rappold G (2008). Serotonin type 3 receptor genes: *HTR3A, B, C, D, E*. *Pharmacogenomics* **9**: 501–514.
- Parker RM, Bentley KR, Barnes NM (1996). Allosteric modulation of 5-HT<sub>3</sub> receptors: focus on alcohols and anaesthetic agents. *Trends Pharmacol Sci* **17**: 95–99.
- Peters JA, Hales TG, Lambert JJ (2005). Molecular determinants of single channel conductance and ion selectivity in the Cys-loop transmitter-gated ion channels: insights from the 5-HT<sub>3</sub> receptor. *Trends Pharmacol Sci* **26**: 587–594.
- Peters JA, Barnes NM, Hales TG, Lummis SCR (2010). 5-HT<sub>3</sub> receptors, introductory chapter. IUPHAR database (IUPHAR-DB), <http://www.iuphar-db.org/IC/FamilyIntroductionForward?familyId=2>
- Thompson AJ, Lummis SCR (2006). 5-HT<sub>3</sub> receptors. *Curr Pharm Des* **12**: 3615–3630.
- Thompson AJ, Lummis SCR (2007). The 5-HT<sub>3</sub> receptor as a therapeutic target. *Expert Opin Ther Targets* **11**: 527–540.
- Thompson AJ, Lester HA, Lummis SCR (2010). The structural basis of function in Cys-loop receptors. *Q Rev Biophys* **43**: 449–499.
- Walstab J, Rappold G, Niesler B (2010b). 5-HT<sub>3</sub> receptors: role in disease and target of drugs. *Pharmacol Ther* **128**: 146–169.
- Yaakob N, Malone DT, Exintaris B, Irving HR (2011). Heterogeneity amongst 5-HT<sub>3</sub> receptor subunits: is this significant? *Curr Mol Med* **11**: 57–68.

## References

- Barrera NP *et al.* (2005). *Proc Natl Acad Sci U S A* **102**: 12595–12600.
- Belelli D *et al.* (1995). *Mol Pharmacol* **48**: 1054–1062.
- Brady CA *et al.* (2001). *Neuropharmacology* **41**: 282–284.
- Bruss M *et al.* (2000). *Naunyn Schmiedebergs Arch Pharmacol* **362**: 392–401.
- Das P, Dillon GH (2003). *Brain Res Mol Brain Res* **119**: 207–212.
- Davies PA *et al.* (1999). *Nature* **397**: 359–363.
- Deeb TZ *et al.* (2009). *Mol Pharmacol* **75**: 908–917.
- Dubin A *et al.* (1999). *J Biol Chem* **274**: 30799–30810.
- Hanna MC *et al.* (2000). *J Neurochem* **75**: 240–247.
- Hope AG *et al.* (1993). *Eur J Pharmacol* **245**: 187–192.
- Holbrook JD *et al.* (2009). *J Neurochem* **108**: 384–396.
- Hu XQ, Peoples RW (2008). *J Biol Chem* **283**: 6826–6831.
- Isenberg KE *et al.* (1993). *Neuroreport* **18**: 121–124.
- Jensen TN *et al.* (2006). *Eur J Pharmacol* **538**: 23–31.
- Kapeller J *et al.* (2011). *J Comp Neurol* **519**: 420–432.
- Karnovsky AM *et al.* (2003). *Gene* **319**: 137–148.
- Kelley SP *et al.* (2003). *Nature* **424**: 321–324.
- Lankiewicz S *et al.* (1998). *Mol Pharmacol* **53**: 202–212.
- Lochner M, Lummis SCR (2010). *Biophys J* **98**: 1494–1502.
- Lummis SCR *et al.* (2011). *J Pharmacol Exp Ther* **339**: 125–131.
- Maricq AV *et al.* (1991). *Science* **254**: 432–437.
- Miyake A *et al.* (1995). *Mol Pharmacol* **48**: 407–416.
- Mochizuki S *et al.* (2000). *Eur J Pharmacol* **399**: 97–106.
- Niesler B *et al.* (2003). *Gene* **310**: 101–111.
- Niesler B *et al.* (2007). *Mol Pharmacol* **72**: 8–17.
- Rüsch D *et al.* (2007). *J Pharmacol Exp Ther* **321**: 1069–1074.
- Solt K *et al.* (2005). *J Pharmacol Exp Ther* **315**: 771–776.
- Stewart A *et al.* (2003). *Neuropharmacology* **44**: 214–223.
- Thompson AJ, Lummis SCR (2008). *Br J Pharmacol* **153**: 1686–1696.
- Thompson AJ *et al.* (2011a). *Neuropharmacology* **60**: 488–495.
- Thompson AJ *et al.* (2011b). *J Physiol* **589**: 4243–4257.
- Tzvetkov MV *et al.* (2007). *Gene* **386**: 52–62.
- Walstab J *et al.* (2010a) *J Biol Chem* **285**: 26956–26965.

# Acetylcholine (nicotinic)

**Overview:** Nicotinic acetylcholine receptors are members of the Cys-loop family of transmitter-gated ion channels that includes the GABA<sub>A</sub>, strychnine-sensitive glycine and 5-HT<sub>3</sub> receptors (Sine and Engel, 2006; Albuquerque *et al.*, 2009; Millar and Gotti, 2009; Taly *et al.*, 2009, Wu and Lukas, 2011). All nicotinic receptors are pentamers in which each of the five subunits contains four  $\alpha$ -helical transmembrane domains. Genes (Ensembl family ID ENSF00000000049) encoding a total of 17 subunits ( $\alpha$ 1-10,  $\beta$ 1-4,  $\gamma$ ,  $\delta$  and  $\epsilon$ ) have been identified (Kalamida *et al.*, 2007). All subunits with the exception of  $\alpha$ 8 (present in avian species) have been identified in mammals. All  $\alpha$  subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named  $\alpha$  lack these residues (Millar and Gotti, 2009). The orthosteric ligand binding site is formed by residues within at least three peptide domains on the  $\alpha$  subunit (principal component), and three on the adjacent subunit (complementary component). nAChRs contain several allosteric modulatory sites. One such site, for positive allosteric modulators (PAMs) and allosteric agonists, has been proposed to reside within an intrasubunit cavity between the four transmembrane domains (Young *et al.*, 2008; Gill *et al.*, 2011; see also Hibbs and Gouaux, 2011). The high resolution crystal structure of the molluscan acetylcholine binding protein, a structural homologue of the extracellular binding domain of a nicotinic receptor pentamer, in complex with several nicotinic receptor ligands (*e.g.*, Celie *et al.*, 2004) and the crystal structure of the extracellular domain of the  $\alpha$ 1 subunit bound to  $\alpha$ -bungarotoxin at 1.94 Å resolution (Dellisanti *et al.*, 2007), has revealed the orthosteric binding site in detail (reviewed Sine and Engel, 2006; Kalamida *et al.*, 2007; Changeux and Taly, 2008; Rucktooa *et al.*, 2009). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry ( $\alpha$ 1)<sub>2</sub> $\beta$ 1 $\delta$  $\epsilon$ , whereas an extrajunctional ( $\alpha$ 1)<sub>2</sub> $\beta$ 1 $\gamma$  $\delta$  receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of  $\alpha$ (2-6) and  $\beta$ (2-4) subunits. For  $\alpha$ 2,  $\alpha$ 3,  $\alpha$ 4 and  $\beta$ 2 and  $\beta$ 4 subunits, pairwise combinations of  $\alpha$  and  $\beta$  (*e.g.*,  $\alpha$ 3 $\beta$ 4,  $\alpha$ 4 $\beta$ 2) are sufficient to form a functional receptor *in vitro*, but far more complex isoforms may exist *in vivo* (reviewed by Gotti *et al.*, 2006, 2009, Millar and Gotti, 2009). There is strong evidence that the pairwise assembly of some  $\alpha$  and  $\beta$  subunits can occur with variable stoichiometry [*e.g.*, ( $\alpha$ 4)<sub>2</sub>( $\beta$ 2)<sub>2</sub>, or ( $\alpha$ 4)<sub>3</sub>( $\beta$ 2)<sub>2</sub>] which influences the biophysical and pharmacological properties of the receptor (Millar and Gotti, 2009).  $\alpha$ 5 and  $\beta$ 3 subunits lack function when expressed alone, or pairwise, but participate in the formation of functional hetero-oligomeric receptors when expressed as a third subunit with another  $\alpha$  and  $\beta$  pair [*e.g.*,  $\alpha$ 4 $\alpha$ 5 $\alpha$  $\beta$ 2,  $\alpha$ 4 $\alpha$  $\beta$ 2 $\beta$ 3,  $\alpha$ 5 $\alpha$ 6 $\beta$ 2, see Millar and Gotti (2009) for further examples]. The  $\alpha$ 6 subunit can form a functional receptor when co-expressed with  $\beta$ 4 *in vitro*, but more efficient expression ensues from incorporation of a third partner, such as  $\beta$ 3 (Yang *et al.*, 2009). The  $\alpha$ 7,  $\alpha$ 8, and  $\alpha$ 9 subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (*e.g.*,  $\alpha$ 7 $\beta$ 2 and  $\alpha$ 9 $\alpha$ 10). For functional expression of the  $\alpha$ 10 subunit, co-assembly with  $\alpha$ 9 is necessary. The latter, along with the  $\alpha$ 10 subunit, appears to be largely confined to cochlear and vestibular hair cells. Comprehensive listings of nicotinic receptor subunit combinations identified from recombinant expression systems, or *in vivo*, are given in Millar and Gotti (2009). In addition, numerous proteins interact with nicotinic ACh receptors modifying their assembly, trafficking to and from the cell surface, and activation by ACh (reviewed by Millar, 2008; Araud *et al.*, 2010; Jones *et al.*, 2010).

The nicotinic receptor subcommittee of NC-IUPHAR has recommended a nomenclature and classification scheme for nicotinic acetylcholine (nACh) receptors based on the subunit composition of known, naturally- and/or heterologously-expressed nACh receptor subtypes (Lukas *et al.*, 1999). Headings for this table reflect abbreviations designating nACh receptor subtypes based on the predominant  $\alpha$  subunit contained in that receptor subtype. An asterisk following the indicated  $\alpha$  subunit denotes that other subunits are known to, or may, assemble with the indicated  $\alpha$  subunit to form the designated nACh receptor subtype(s). Where subunit stoichiometries within a specific nACh receptor subtype are known, numbers of a particular subunit larger than 1 are indicated by a subscript following the subunit (enclosed in parentheses – see also Collingridge *et al.*, 2009).

Nomenclature	$\alpha$ 1*	$\alpha$ 2*	$\alpha$ 3*
Previous names	Muscle-type, muscle	–	Autonomic, ganglionic
Selective agonists	Succinylcholine (selective for ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\gamma$ $\delta$ )	–	–
Positive allosteric modulators	–	LY-2087101 (Broad <i>et al.</i> , 2006, also potentiates $\alpha$ 4 $\beta$ 2 and $\alpha$ 4 $\beta$ 4)	–
Selective antagonists	Waglerin-1 (selective for ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\delta$ $\epsilon$ ), $\alpha$ -bungarotoxin, $\alpha$ -conotoxin GI, $\alpha$ -conotoxin MI, pancuronium	–	$\alpha$ 3 $\beta$ 2: $\alpha$ -conotoxin MII (also blocks $\alpha$ 6-containing), $\alpha$ -conotoxin-GIC, $\alpha$ -conotoxin PnIA, $\alpha$ -conotoxin TxIA $\alpha$ 3 $\beta$ 4: $\alpha$ -conotoxin AulB
Commonly used antagonists	( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\gamma$ $\delta$ and ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\delta$ $\epsilon$ : $\alpha$ -bungarotoxin, > pancuronium > vecuronium > rocuronium > (+)-Tc (IC <sub>50</sub> = 43–82 nM)	$\alpha$ 2 $\beta$ 2: DH $\beta$ E ( $K_B$ = 0.9 $\mu$ M), (+)-Tc ( $K_B$ = 1.4 $\mu$ M) $\alpha$ 2 $\beta$ 4: DH $\beta$ E ( $K_B$ = 3.6 $\mu$ M), (+)-Tc ( $K_B$ = 4.2 $\mu$ M)	$\alpha$ 3 $\beta$ 2: DH $\beta$ E ( $K_B$ = 1.6 $\mu$ M, IC <sub>50</sub> = 2.0 $\mu$ M), (+)-Tc ( $K_B$ = 2.4 $\mu$ M) $\alpha$ 3 $\beta$ 4: DH $\beta$ E ( $K_B$ = 19 $\mu$ M, IC <sub>50</sub> = 26 $\mu$ M), (+)-Tc ( $K_B$ = 2.2 $\mu$ M)
Channel blockers	( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\delta$ $\epsilon$ and ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\gamma$ $\delta$ : gallamine (IC <sub>50</sub> ~ 1 $\mu$ M) $\alpha$ (1) <sub>2</sub> $\beta$ 1 $\delta$ $\epsilon$ : mecamylamine (IC <sub>50</sub> ~ 1.5 $\mu$ M)	mecamylamine, hexamethonium	$\alpha$ 3 $\beta$ 2: mecamylamine (IC <sub>50</sub> = 7.6 $\mu$ M), hexamethonium $\alpha$ 3 $\beta$ 4: mecamylamine (IC <sub>50</sub> = 0.39 $\mu$ M), hexamethonium
Radioligands ( $K_D$ )	[ <sup>3</sup> H]/[ <sup>125</sup> I]- $\alpha$ -bungarotoxin	[ <sup>3</sup> H]/[ <sup>125</sup> I]-epibatidine (h $\alpha$ 2 $\beta$ 4, 42 pM; r $\alpha$ 2 $\beta$ 2, 10–21 pM; r $\alpha$ 2 $\beta$ 4, 84–87 pM), [ <sup>3</sup> H]-cytisine	[ <sup>3</sup> H]/[ <sup>125</sup> I]-epibatidine (h $\alpha$ 3 $\beta$ 2, 7 pM; h $\alpha$ 3 $\beta$ 4, 230 pM; r $\alpha$ 3 $\beta$ 2, 14–34 pM, r $\alpha$ 3 $\beta$ 4, 290–304 pM), [ <sup>3</sup> H]-cytisine
Functional characteristics	$\alpha$ (1) <sub>2</sub> $\beta$ $\gamma$ $\delta$ : P <sub>Ca</sub> /P <sub>Na</sub> = 0.16–0.2, P <sub>i</sub> = 2.1–2.9%; $\alpha$ (1) <sub>2</sub> $\beta$ $\delta$ $\epsilon$ : P <sub>Ca</sub> /P <sub>Na</sub> = 0.65–1.38, P <sub>i</sub> = 4.1–7.2%	$\alpha$ 2 $\beta$ 2: P <sub>Ca</sub> /P <sub>Na</sub> ~ 1.5	$\alpha$ 3 $\beta$ 2: P <sub>Ca</sub> /P <sub>Na</sub> = 1.5; $\alpha$ 3 $\beta$ 4: P <sub>Ca</sub> /P <sub>Na</sub> = 0.78–1.1, P <sub>i</sub> = 2.7–4.6%



Nomenclature	$\alpha 4^*$	$\alpha 6^*$	$\alpha 7^*$
Previous names	Neuronal, $\alpha$ -bungarotoxin-insensitive	–	Neuronal, $\alpha$ -bungarotoxin-sensitive
Selective agonists	$\alpha 4\beta 2$ : TC-2559 (Chen <i>et al.</i> , 2003), TC-2403 (RJR-2403, Papke <i>et al.</i> , 2000)	–	( $\alpha 7$ ): PNU-282987 (Bodnar <i>et al.</i> , 2005), PHA-543613 (Wishka <i>et al.</i> , 2006); PHA-709829 (Acker <i>et al.</i> , 2008), A-582941 (Bitner <i>et al.</i> , 2007, TC-5619 (Hauser <i>et al.</i> , 2009)
Allosteric agonists	–	–	4BP-TQS (Gill <i>et al.</i> , 2011)
Positive allosteric modulators	$\alpha 4\beta 2$ and $\alpha 4\beta 4$ : LY-2087101 (Broad <i>et al.</i> , 2006, also potentiates $\alpha 2^*$ ), NS9283 (Lee <i>et al.</i> , 2011)	–	( $\alpha 7$ ): Type 1: LY-2087101 (Broad <i>et al.</i> , 2006), NS1738 (Timmermann <i>et al.</i> , 2007; also blocks $\alpha 3\beta 4$ and $\alpha 4\beta 2$ ) ( $\alpha 7$ ): Type 2: PNU-120596 (Hurst <i>et al.</i> , 2005), A-867744 (Malysz <i>et al.</i> , 2009; also blocks $\alpha 3\beta 4$ and $\alpha 4\beta 2$ ) ( $\alpha 7$ ): Type 1/2 intermediate: JNJ1930942 (Dinklo <i>et al.</i> , 2011)
Selective antagonists	–	$\alpha 6/\alpha 3\beta 2\beta 3$ chimera: $\alpha$ -conotoxin PIA $\alpha 6\beta 2\beta 3$ : $\alpha$ -conotoxin MII [H9A, L15A] $\alpha 6\beta 2^*$ : $\alpha$ -conotoxin MII (also blocks $\alpha 3\beta 2$ )	( $\alpha 7$ ): $\alpha$ -bungarotoxin, methyllycaconitine, $\alpha$ -conotoxin Iml, $\alpha$ -conotoxin ArIB
Commonly used antagonists	$\alpha 4\beta 2$ : DH $\beta$ E ( $K_B = 0.1 \mu\text{M}$ ; $\text{IC}_{50} = 0.08\text{--}0.9 \mu\text{M}$ ), (+)-Tc ( $K_B = 3.2 \mu\text{M}$ , $\text{IC}_{50} = 34 \mu\text{M}$ ) $\alpha 4\beta 4$ : DH $\beta$ E ( $K_B = 0.01 \mu\text{M}$ , $\text{IC}_{50} = 0.19\text{--}1.2 \mu\text{M}$ ), (+)-Tc ( $K_B = 0.2 \mu\text{M}$ , $\text{IC}_{50} = 50 \mu\text{M}$ )	$\alpha 6/\alpha 3\beta 2\beta 3$ chimera: DH $\beta$ E ( $\text{IC}_{50} = 1.1 \mu\text{M}$ )	( $\alpha 7$ ): DH $\beta$ E ( $\text{IC}_{50} = 8\text{--}20 \mu\text{M}$ ) ( $\alpha 7$ ): (+)-Tc ( $\text{IC}_{50} = 3.1 \mu\text{M}$ )
Channel blockers	$\alpha 4\beta 2$ : mecamylamine ( $\text{IC}_{50} = 3.6\text{--}4.1 \mu\text{M}$ ), hexamethonium ( $\text{IC}_{50} = 6.8\text{--}29 \mu\text{M}$ ) $\alpha 4\beta 4$ : mecamylamine ( $\text{IC}_{50} = 0.33\text{--}4.9 \mu\text{M}$ ), hexamethonium ( $\text{IC}_{50} = 91 \mu\text{M}$ )	$\alpha 6/\alpha 3\beta 2\beta 3$ chimera: mecamylamine ( $\text{IC}_{50} = 11 \mu\text{M}$ ), hexamethonium	( $\alpha 7$ ): mecamylamine ( $\text{IC}_{50} = 15.6 \mu\text{M}$ )
Radioligands ( $K_d$ )	[ $^3\text{H}$ ]/[ $^{125}\text{I}$ ]-epibatidine (h $\alpha 4\beta 2$ , 10–33 pM; h $\alpha 4\beta 4$ , 187 pM; r $\alpha 4\beta 2$ , 30–46 pM; r $\alpha 4\beta 4$ , 85–94 pM), [ $^3\text{H}$ ]-cytisine (h $\alpha 4\beta 2$ , 430–630 pM; r $\alpha 4\beta 2$ , 100 pM; h $\alpha 4\beta 4$ 100 pM), [ $^3\text{H}$ ]-nicotine (r $\alpha 4\beta 2$ , 400 pM)	[ $^3\text{H}$ ]-epibatidine (native $\alpha 6\beta 4^*$ , 35 pM), [ $^{125}\text{I}$ ]- $\alpha$ -conotoxin MII	[ $^3\text{H}$ ]-epibatidine ((h $\alpha 7$ ) <sub>s</sub> , 0.6 pM) [ $^3\text{H}$ ]/[ $^{125}\text{I}$ ]- $\alpha$ -bungarotoxin ((h $\alpha 7$ ) <sub>s</sub> , 0.7–5 nM), [ $^3\text{H}$ ]-methyllycaconitine (native r $\alpha 7^*$ , 1.9 nM), [ $^3\text{H}$ ]-A-585539 (native h $\alpha 7$ , 70 pM; Anderson <i>et al.</i> , 2008), [ $^3\text{H}$ ]AZ11637326 (h $\alpha 7$ ) <sub>s</sub> , 230 pM; Gordon <i>et al.</i> , 2010)
Functional characteristics	$\alpha 4\beta 2$ : $P_{\text{Ca}}/P_{\text{Na}} = 1.65$ , $P_i = 2.6\text{--}2.9\%$ ; $\alpha 4\beta 4$ : $P_i = 1.5\text{--}3.0 \%$	–	$P_{\text{Ca}}/P_{\text{Na}} = 6.6\text{--}20$ , $P_i = 8.8\text{--}11.4\%$

Nomenclature	$\alpha 8^*$ (avian)	$\alpha 9^*$
Previous names	Neuronal, $\alpha$ -bungarotoxin-sensitive	–
Selective agonists	–	–
Selective antagonists	–	( $\alpha 9$ ): $\alpha$ -bungarotoxin, strychnine, nicotine, muscarine $\alpha 9\alpha 10$ : $\alpha$ -conotoxin RgIA, $\alpha$ -bungarotoxin, strychnine, nicotine, muscarine
Commonly used antagonists	( $\alpha 8$ ): $\alpha$ -bungarotoxin > atropine $\geq$ (+)-Tc $\geq$ strychnine	( $\alpha 9$ ): $\alpha$ -bungarotoxin > methyllycaconitine > strychnine ~ tropisetron > (+)-Tc $\alpha 9\alpha 10$ : $\alpha$ -bungarotoxin > tropisetron = strychnine > (+)-Tc
Channel blockers	–	–
Radioligands ( $K_d$ )	[ $^3\text{H}$ ]-epibatidine (( $\alpha 8$ ) <sub>s</sub> , 0.2 nM) [ $^3\text{H}$ ]/[ $^{125}\text{I}$ ]- $\alpha$ -bungarotoxin (native $\alpha 8^*$ , 5.5 nM)	[ $^3\text{H}$ ]-methyllycaconitine (h $\alpha 9\alpha 10$ , 7.5 nM) [ $^3\text{H}$ ]/[ $^{125}\text{I}$ ]- $\alpha$ -bungarotoxin
Functional characteristics	–	( $\alpha 9$ ): $P_{\text{Ca}}/P_{\text{Na}} = 9$ ; $\alpha 9\alpha 10$ : $P_{\text{Ca}}/P_{\text{Na}} = 9$ , $P_i = 22\%$

Commonly used agonists of nicotinic acetylcholine receptors that display limited discrimination in functional assays between receptor subtypes include A-85380, cytisine, DMPP, epibatidine, nicotine and the natural transmitter, ACh. A summary of their profile across differing receptors is provided in Gotti *et al.* (2006) and quantitative data across numerous assay systems are summarised in Jensen *et al.* (2005). Quantitative data presented in the table for commonly used antagonists and channel blockers for human receptors studied under voltage-clamp are from Buisson *et al.*, 1996, Chavez-Noriaga *et al.*, (1997), Papke *et al.* (2001, 2008), Paul *et al.* (2002) and Wu *et al.* (2006). Type I PAMs increase peak agonist-evoked responses but have little, or no, effect on the rate of desensitization of  $\alpha 7$  nicotinic ACh receptors whereas type II PAMs also cause a large reduction in desensitization (reviewed by Williams *et al.*, 2011).

**Abbreviations:** 4BP-TQS, 4-(4-bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide; A-582941, 2-methyl-5-(6-phenyl-pyridazin-3-yl)-octahydro-pyrrolo[3,4-c]pyrrole; A-585539, (1S,4S)-2,2-dimethyl-5-(6-phenylpyridazin-3-yl)-5-aza-2-azabicyclo[2.2.1]heptane; A-867744, 4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide; ABT-594, (R)-5-(2-azetidylmethoxy)-2-chloropyridine; ACh, acetylcholine; AZ11637326, (5'-(2-fluoro[3,4,5(-3)H3]phenyl)-spiro[1-azabicyclo [2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine, DH $\beta$ E, dihydro- $\beta$ -erythroidine; DMPP, 1,1-dimethyl-4-phenylpiperazinium; JNJ-1930942, 2-[[4-fluoro-3-(trifluoromethyl)phenyl]amino]-4-(4-pyridinyl)-5-thiazolemethanol; LY-2087101, see Broad *et al.* (2006) for structure; NS1738, 1-(5-chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-urea; NS9283, 3-(3-(pyridine-3-yl)-1,2,4-oxadiazol-5-yl)benzoxazole; PHA-543613, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide; PHA-709829, N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide; PNU-120596, 1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea; PNU-282987 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride; PSAB-OPP, (R)-(-)-5'phenylspiro[1-azabicyclo[2.2.2] octane-3,2'-(3'H)furo[2,3-b]pyridine; TC-2403 (RJR-12403), (E)-N-methyl-4-(3-pyridinyl)-3-butene-1-amine; TC-2559, (E)-N-methyl-4-[3-(5-ethoxypyridinyl)]-3-buten-1-amine; TC-5619, N-[2-(pyridin-3-ylmethyl)-1-azabicyclo[2.2.2]oct-3-yl]-1-benzofuran-2-carboxamide; (+)-Tc, (+)-tubocurarine

### Further Reading

- Albuquerque EX, Pereira EF, Alkondon M, Rogers SW (2009). Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev* 89: 73–120.
- Araud T, Wonnacott S, Bertrand D (2010). Associated proteins: the universal toolbox controlling ligand gated ion channel function. *Biochem Pharmacol* 80: 160–169.
- Arneric SP, Holladay M, Williams M (2007). Neuronal nicotinic receptors: a perspective on two decades of drug discovery research. *Biochem Pharmacol* 74: 1092–1101.
- Arias HR (2010). Positive and negative modulation of nicotinic receptors. *Adv Protein Chem Struct Biol* 80: 153–203.
- Balfour DJK (2009). The neuronal pathways mediating the behavioral and addictive properties of nicotine. *Handb Exp Pharmacol* 192: 209–233.
- Benowitz NL (2009). Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol* 49: 57–71.
- Champniaux N, Changeux J-P (2004). Knockout and knockin mice to investigate the role of nicotinic receptors in the central nervous system. *Prog Brain Res* 145: 235–251.
- Changeux JP, Taly A (2008). Nicotinic receptors, allosteric proteins and medicine. *Trends Mol Med* 14: 93–102.
- Collingridge GL, Olsen RW, Peters J, Spedding M (2009). A nomenclature for ligand-gated ion channels. *Neuropharmacology* 56: 2–5.
- Dajas-Bailador F, Wonnacott S (2004). Nicotinic acetylcholine receptors and the regulation of neuronal signalling. *Trends Pharmacol Sci* 25: 317–324.
- D'hoedt D, Bertrand D (2009). Nicotinic acetylcholine receptors: an overview on drug discovery. *Expert Opin Ther Targets* 13: 395–411.
- Faghih R, Gopalakrishnan M, Briggs CA (2008). Allosteric modulators of the  $\alpha 7$  nicotinic acetylcholine receptor. *J Med Chem* 51: 701–712.
- Fucile S (2004). Ca<sup>2+</sup>-permeability of nicotinic acetylcholine receptors. *Cell Calcium* 35: 1–8.
- Gotti C, Zoli M, Clementi F (2006). Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol Sci* 27: 482–491.
- Gotti C, Clementi F, Fornari A, Gaimarri A, Guiducci S, Manfredi I *et al.* (2009). Structural and functional diversity of native brain neuronal nicotinic receptors. *Biochem Pharmacol* 78: 703–711.
- Hogg RC, Bertrand D (2004). Nicotinic acetylcholine receptors as drug targets. *Curr Drug Targets CNS Neurol Disord* 3: 123–130.
- Hogg RC, Raggabass M, Bertrand D (2003). Nicotinic acetylcholine receptors: from structure to brain function. *Rev Physiol Biochem Pharmacol* 147: 1–46.
- Jensen AA, Frøland B, Liljefors T, Krogsgaard-Larsen P (2005). Neuronal nicotinic acetylcholine receptors: structural revelations, target identifications, and therapeutic inspirations. *J Med Chem* 48: 4705–4745.
- Jones AK, Buckingham SD, Sattelle DB (2010). Proteins interacting with nicotinic acetylcholine receptors: expanding functional and therapeutic horizons. *Trends Pharmacol Sci* 31: 455–462.
- Kalamida D, Poulas K, Avramopoulou V, Fostieri E, Lagoumintzis G, Lazaridis K *et al.* (2007). Muscle and neuronal nicotinic acetylcholine receptors. Structure, function and pathogenicity. *FEBS J* 274: 3799–3845.
- Letchworth SR, Whiteaker P (2011). Progress and challenges in the study of  $\alpha 6$ -containing nicotinic acetylcholine receptors. *Biochem Pharmacol* 82: 862–872.
- Lukas RJ, Changeux J-P, Le Novère N, Albuquerque EX, Balfour DJ, Berg DK *et al.* (1999). International Union of Pharmacology. XX. Current status of the nomenclature for nicotinic acetylcholine receptors and their subunits. *Pharmacol Rev* 51: 397–401.
- Millar NS (2008). RIC-3: a nicotinic acetylcholine receptor chaperone. *Br J Pharmacol* 153 (Suppl. 1): S177–S183.
- Millar NS, Gotti C (2009). Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology* 56: 237–246.
- Millar NS, Harkness PC (2008). Assembly and trafficking of nicotinic acetylcholine receptors. *Mol Membr Biol* 25: 279–292.
- Miwa JM, Freedman R, Lester HA (2011). Neural systems governed by nicotinic acetylcholine receptors: emerging hypotheses. *Neuron* 70: 20–33.
- Olivera BM, Quirk M, Vincler M, MacIntosh JM (2008). Subtype-selective conopeptides targeted to nicotinic receptors. *Channels (Austin)* 2: 143–152.
- Pandya A, Yakel JL (2011). Allosteric modulators of the  $\alpha 4\beta 2$  subtype of neuronal nicotinic acetylcholine receptors. *Biochem Pharmacol* 82: 862–872.
- Romanelli MN, Gratteri P, Guandalini L, Martini E, Bonaccini C, Gualtieri F (2007). Central nicotinic receptors: structure, function, ligands, and therapeutic potential. *ChemMedChem* 2: 746–767.
- Rucktooa P, Smit AB, Sixma TK (2009). Insight in nAChR subtype selectivity from AChBP crystal structures. *Biochem Pharmacol* 78: 777–787.
- Sharma G, Vijayaraghavan S (2008). Nicotinic receptors containing the  $\alpha 7$  subunit: a model for rational drug design. *Curr Med Chem* 15: 2921–2932.
- Steinlein OK, Bertrand D (2008). Neuronal nicotinic acetylcholine receptors: from the genetic analysis to neurological diseases. *Biochem Pharmacol* 76: 1175–1183.
- Sine SM, Engel AG (2006). Recent advances in Cys-loop receptor structure and function. *Nature* 440: 448–455.
- Taly A, Corringer PJ, Guedin D, Lestage P, Changeux JP (2009). Nicotinic receptors: allosteric transitions and therapeutic targets in the nervous system. *Nat Rev Drug Discov* 8: 733–750.
- Tsetlin V, Hucho F (2009). Nicotinic acetylcholine receptors at atomic resolution. *Curr Opin Pharmacol* 9: 306–310.
- Tsetlin V, Utkin Y, Kasheverov I (2009). Polypeptide and peptide toxins, magnifying lenses for binding sites in nicotinic acetylcholine receptors. *Biochem Pharmacol* 78: 720–731.
- Tsetlin V, Kuzmin D, Kasheverov I (2011). Assembly of nicotinic and other Cys-loop receptors. *J Neurochem* 116: 734–741.
- Unwin N (2005). Refined structure of the nicotinic acetylcholine receptor at 4 Å resolution. *J Mol Biol* 346: 967–989.
- Williams DK, Wang J, Papke RL (2011). Positive allosteric modulators as an approach to nicotinic acetylcholine receptor-targeted therapeutics: advantages and limitations. *Biochem Pharmacol* 82: 915–930.

- Yang KC, Jin GZ, Wu J (2009). Mysterious  $\alpha 6$ -containing nAChRs: function, pharmacology, and pathophysiology. *Acta Pharmacol Sin* 30: 740–751.
- Wu J, Lukas RJ (2011). Naturally expressed nicotinic acetylcholine receptor subtypes. *Biochem Pharmacol* 82: 800–807.
- Zouridakis M, Zisimopoulou P, Poulas K, Tzartos SJ (2009). Recent advances in understanding the structure of nicotinic acetylcholine receptors. *IUBMB Life* 61: 407–423.

## References

- Acker BA *et al.* (2008). *Bioorg Med Chem Lett* 18: 3611–3625.
- Anderson DJ *et al.* (2008). *J Pharmacol Exp Ther* 324: 179–187.
- Bitner RS *et al.* (2007). *J Neurosci* 27: 10578–10587.
- Bodnar AL *et al.* (2005). *J Med Chem* 48: 905–908.
- Broad LM *et al.* (2006). *J Pharmacol Exp Ther* 318: 1108–1117.
- Buisson B *et al.* (1996). *J Neurosci* 16: 7880–7891.
- Celie PH *et al.* (2004). *Neuron* 25: 907–914.
- Chavez-Noriaga LE *et al.* (1997). *J Pharmacol Exp Ther* 280: 346–356.
- Chen Y *et al.* (2003). *Neuropharmacology* 45: 334–344.
- Dellisanti CD *et al.* (2007). *Nat Neurosci* 10: 953–962.
- Dinklo T *et al.* (2011). *J Pharmacol Exp Ther* 336: 560–574.
- Gill JK *et al.* (2011). *Proc Natl Acad Sci U S A* 108: 5867–5872.
- Gordon JC *et al.* (2010). *Eur J Pharmacol* 645: 63–69.
- Hauser TA *et al.* (2009). *Biochem Pharmacol* 78: 803–812.
- Hibbs RE, Gouaux E (2011). *Nature* 474: 54–60.
- Hurst RS *et al.* (2005). *J Neurosci* 25: 4396–4405.
- Lee CH *et al.* (2011). *Biochem Pharmacol* 82: 959–966.
- Malysz J *et al.* (2009). *J Pharmacol Exp Ther* 330: 257–267.
- Papke RL *et al.* (2000). *J Neurochem* 75: 204–216.
- Papke RL *et al.* (2001). *J Pharmacol Exp Ther* 297: 646–656.
- Papke RL *et al.* (2008). *Neuropharmacology* 54: 1189–1200.
- Paul M *et al.* (2002). *Anesth Analg* 94: 597–603.
- Timmermann DB *et al.* (2007). *J Pharmacol Exp Ther* 323: 294–307.
- Wishka DG *et al.* (2006). *J Med Chem* 49: 4425–4436.
- Wu J *et al.* (2006). *J Physiol* 576: 103–118.
- Young GT *et al.* (2008). *Proc Natl Acad Sci U S A* 105: 14686–14691.

# GABA<sub>A</sub> (γ-aminobutyric acid)

**Overview:** The GABA<sub>A</sub> receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT<sub>3</sub> and strychnine-sensitive glycine receptors. GABA<sub>A</sub> receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed 'GABA<sub>A</sub>, slow' (Campogna and Pearce, 2011). GABA<sub>A</sub> receptors exist as pentamers of 4TM subunits that form an intrinsic anion selective channel. Sequences of six α, three β, three γ, one δ, three ρ, one ε, one π and one θ GABA<sub>A</sub> receptor subunits (Ensembl gene family ID ENSF00000000053) have been reported in mammals (Korpi *et al.*, 2002; Whiting, 2003; Sieghart, 2006; Olsen and Sieghart, 2008, 2009). The π-subunit is restricted to reproductive tissue. Alternatively spliced versions of many subunits exist (e.g. α4- and α6- (both not functional) α5-, β2-, β3- and γ2), along with RNA editing of the α3 subunit (Daniel and Ohman, 2009). The three ρ-subunits, (ρ1-3) function as either homo- or hetero-oligomeric assemblies (Zhang *et al.*, 2001; Chebib, 2004). Receptors formed from ρ-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed GABA<sub>C</sub> receptors (Zhang *et al.*, 2001), but they are classified as GABA<sub>A</sub> receptors by NC-IUPHAR on the basis of structural and functional criteria (Barnard *et al.*, 1998; Olsen and Sieghart, 2008, 2009).

Many GABA<sub>A</sub> receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α.2β.1γ (Korpi *et al.*, 2002, Olsen and Sieghart, 2008). It is thought that the majority of GABA<sub>A</sub> receptors harbour a single type of α- and β-subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of GABA<sub>A</sub> receptors in the CNS, followed by the α2β3γ2 and α3β3γ2 isoforms. Receptors that incorporate the α4- α5- or α6-subunit, or the β1-, γ1-, γ3-, δ-, ε- and θ-subunits, are less numerous, but they may nonetheless serve important functions. For example, extrasynaptically located receptors that contain α6- and δ-subunits in cerebellar granule cells, or an α4- and δ-subunit in dentate gyrus granule cells and thalamic neurones, mediate a tonic current that is important for neuronal excitability in response to ambient concentrations of GABA (see Mody and Pearce, 2004; Semyanov *et al.*, 2004; Farrant and Nusser, 2005; Belelli *et al.*, 2009). GABA binding occurs at the β+/α- subunit interface and the homologous γ+/α- subunits interface creates the benzodiazepine site. A second site for benzodiazepine binding has recently been postulated to occur at the α+/β- interface (Ramerstorfer *et al.*, 2011; reviewed by Sigel and Lüscher, 2011). The particular α- and γ-subunit isoforms exhibit marked effects on recognition and/or efficacy at the benzodiazepine site. Thus, receptors incorporating either α4- or α6-subunits are not recognised by 'classical' benzodiazepines, such as flunitrazepam (but see You *et al.*, 2010). The trafficking, cell surface expression, internalisation and function of GABA<sub>A</sub> receptors and their subunits are discussed in detail in several recent reviews (Chen and Olsen, 2007; Jacob *et al.*, 2008; Lüscher *et al.*, 2011; Vithlani *et al.*, 2011) but one point worthy of note is that receptors incorporating the γ2 subunit (except when associated with α5) cluster at the postsynaptic membrane (but may distribute dynamically between synaptic and extrasynaptic locations), whereas those incorporating the δ subunit appear to be exclusively extrasynaptic.

NC-IUPHAR (Barnard *et al.* 1998; Olsen and Sieghart, 2008) class GABA<sub>A</sub> receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native GABA<sub>A</sub> receptors are classed as conclusively identified (*i.e.*, α1β2γ2, α1βγ2, α3βγ2, α4βγ2, α4βδ, α4β3δ, α5βγ2, α6βγ2, α6β2δ, α6β3δ and ρ) with further receptor isoforms occurring with high probability, or only tentatively (Olsen and Sieghart, 2008, 2009). It is beyond the scope of this Guide to discuss the pharmacology of individual GABA<sub>A</sub> receptor isoforms in detail; such information can be gleaned in the reviews by Barnard *et al.* (1998), Frolund *et al.* (2002), Korpi *et al.* (2002), Krosgaard-Larsen *et al.* (2002), Johnston (2005), Sieghart (2006), Möhler (2007), Olsen and Sieghart (2008, 2009) and Attack (2008, 2010). Agents that discriminate between α-subunit isoforms are noted in the table and additional agents that demonstrate selectivity between receptor isoforms, for example *via* β-subunit selectivity, are indicated in the text below. The distinctive agonist and antagonist pharmacology of ρ receptors is summarised in the table and additional aspects are reviewed by Zhang *et al.* (2001), Chebib (2004), Johnston *et al.* (2010) and Ng *et al.* (2011).

Nomenclature	GABA <sub>A</sub>
Ensembl Gene family ID	ENSF00000000053
Selective agonists (GABA site)	Muscimol (partial agonist at ρ subunits), isoguvacine (partial agonist at ρ subunits), THIP (gaboxadol; δ subunit preferring, antagonist at ρ subunits), piperidine-4-sulphonic acid (low efficacy at α4 and α6 subunits, antagonist at ρ subunits), isonipectic acid (α4 and α6 subunit selective <i>via</i> relatively high efficacy, antagonist at ρ subunits), (±)- <i>cis</i> -2-CAMP (ρ subunit selective), 5-MeIAA (ρ subunit selective)
Selective antagonists (GABA site)	Bicuculline (not active at ρ subunits), gabazine (SR95531; weakly active on ρ subunits), TPMPA (ρ subunit selective), <i>cis</i> - and <i>trans</i> -3-ACPBPA (ρ subunit selective), Aza-THIP (ρ subunit selective)
Selective agonists (positive allosteric modulators) (benzodiazepine site)	Diazepam (not α4- or α6-subunits), flunitrazepam (not α4- or α6-subunits), bretazenil (including α4- and α6-subunits, zolpidem, zaleplon and indiplon (α1 subunit selective <i>via</i> high affinity), ocinaplon (α1 subunit selective as essentially a full agonist <i>versus</i> partial agonist at α2, α3 and α5 subunit-containing receptors), L838417 (α2, α3 and α5 subunit selective as a partial agonist <i>versus</i> antagonist at α1-subunit-containing receptors), Ro154513 (selective for α4- and α6-subunit-containing receptors as an agonist <i>versus</i> inverse agonist at α1-, α2-, α3- and α5-subunit-containing receptors), TP003 (selective for α3-subunit-containing receptors as a high efficacy partial agonist <i>versus</i> essentially antagonist activity at α1- α2- and α5-subunit-containing receptors), TPA023 (selective for α2- and α3-subunit-containing receptors as a low efficacy partial agonist <i>versus</i> essentially antagonist activity at α1- and α5-subunit-containing receptors)
Selective antagonists (neutral allosteric modulators) (benzodiazepine site)	Flumazenil (low affinity for α4- or α6-subunits and partial agonist), ZK93426, L838417 (α1 subunit selective <i>via</i> antagonist activity <i>versus</i> partial agonist at α2-, α3- and α5-subunit subunit containing receptors)
Inverse agonists (negative allosteric modulators) (benzodiazepine site)	DMCM, Ro194603, α3IA (α3 selective <i>via</i> higher affinity and greater inverse agonist activity <i>versus</i> α1, α2 and α5-subunit containing receptors), L655708, RY024 (α5 selective <i>via</i> high affinity), α5IA, MRK016 (α5 selective <i>versus</i> α1, α2 and α3-subunit containing receptors <i>via</i> greater inverse agonist efficacy), Ro4938581 (α5 selective <i>versus</i> α1, α2 and α3-subunit containing receptors <i>via</i> higher affinity and greater inverse agonist activity)

Nomenclature	GABA <sub>A</sub>
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (potentiation), tetrahydrodeoxycorticosterone (potentiation), Zn <sup>2+</sup> (potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ- or γ-subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively, Krishek <i>et al.</i> , 1998), extracellular protons (subunit dependent activity, Krishek <i>et al.</i> , 1996)
Channel blockers	Picrotoxin, TBPS
Probes	
GABA site	[ <sup>3</sup> H]Muscimol, [ <sup>3</sup> H]gabazine (SR95531)
benzodiazepine site	[ <sup>3</sup> H]Flunitrazepam (not α4- or α6-subunit), [ <sup>3</sup> H]zolpidem (α1-subunit selective), [ <sup>3</sup> H]L655708 (α5-subunit selective), [ <sup>3</sup> H]RY80 (α5-subunit selective), [ <sup>3</sup> H]Ro154513 [selectively labels α4- and α6-subunit-containing receptors in the presence of a saturating concentration of a 'classical' benzodiazepine ( <i>e.g.</i> , diazepam)], [ <sup>3</sup> H]CGS8216, [ <sup>11</sup> C]flumazenil (PET ligand with low affinity for α4- or α6-subunits), [ <sup>18</sup> F]fluoroethylflumazenil (PET ligand)
Anion channel	[ <sup>35</sup> S]TBPS

The potency and efficacy of many GABA agonists varies between receptor GABA<sub>A</sub> receptor isoforms (Frolund *et al.*, 2002; Krosggaard-Larsen *et al.*, 2002). For example, THIP (gaboxadol) is a partial agonist at receptors with the subunit composition α4β3γ2, but elicits currents in excess of those evoked by GABA at the α4β3δ receptor where GABA itself is a low efficacy agonist (Brown *et al.*, 2002; Bianchi and MacDonald, 2003). The antagonists bicuculline and gabazine differ in their ability to suppress spontaneous openings of the GABA<sub>A</sub> receptor, the former being more effective (Thompson *et al.* 1999). The presence of the γ subunit within the heterotrimeric complex reduces the potency and efficacy of agonists (Stórustovu and Ebert, 2006). The GABA<sub>A</sub> receptor contains distinct allosteric sites that bind barbiturates and endogenous (*e.g.*, 5α-pregnan-3α-ol-20-one) and synthetic (*e.g.*, alphaxalone) neuroactive steroids in a diastereo- or enantio-selective manner (see Belelli and Lambert 2005; Herd *et al.*, 2007; Hosie *et al.*, 2007; Veleiro and Burton, 2009). Picrotoxinin and TBPS act at an allosteric site within the chloride channel pore to negatively regulate channel activity; negative allosteric regulation by γ-butyrolactone derivatives also involves the picrotoxinin site, whereas positive allosteric regulation by such compounds is proposed to occur at a distinct locus. Many intravenous (*e.g.*, etomidate, propofol) and inhalational (*e.g.*, halothane, isoflurane) anaesthetics and alcohols also exert a regulatory influence upon GABA<sub>A</sub> receptor activity (Bonin and Orser, 2008; Olsen and Li, 2011). Specific amino acid residues within GABA<sub>A</sub> receptor α- and β-subunits that influence allosteric regulation by anaesthetic and non-anaesthetic compounds have been identified (Hemmings *et al.*, 2005; Hosie *et al.*, 2007). Photoaffinity labelling of distinct amino acid residues within purified GABA<sub>A</sub> receptors by the etomidate derivative, [<sup>3</sup>H]-azietomidate, has also been demonstrated (Li *et al.*, 2006) and this binding subject to positive allosteric regulation by anaesthetic steroids (Li *et al.*, 2009). An array of natural products including flavonoid and terpenoid compounds exert varied actions at GABA<sub>A</sub> receptors (reviewed in detail by Johnston, 2005).

In addition to the agents listed in the table, modulators of GABA<sub>A</sub> receptor activity that exhibit subunit dependent activity include: salicylidene salicylhydrazide [negative allosteric modulator selective for β1- versus β2-, or β3-subunit-containing receptors (Thompson *et al.*, 2004)]; fragrant dioxane derivatives [positive allosteric modulators selective for β1- versus β2-, or β3-subunit-containing receptors (Sergeeva *et al.*, 2010)]; loreclezole, etomidate, tracazolate mefenamic acid, etifoxine, stiripentol, valerinic acid amide [positive allosteric modulators with selectivity for β2/β3- over β1-subunit-containing receptors, see Korpi *et al.* (2002), Fisher (2009), Khom *et al.*, (2010)]; tracazolate [intrinsic efficacy, *i.e.*, potentiation, or inhibition, is dependent upon the identity of the γ1-3-, δ-, or ε-subunit co-assembled with α1- and β1-subunits (Thompson *et al.*, 2002)]; amiloride [selective blockade of receptors containing an α6-subunit (Fisher, 2002)]; furosemide [selective blockade of receptors containing an α6-subunit co-assembled with β2/β3-, but not β1-subunit (see Korpi *et al.* (2002))]; La<sup>3+</sup> [potentiates responses mediated by α1β3γ2L receptors, weakly inhibits α6β3γ2L receptors, and strongly blocks α6β3δ and α4β3δ receptors (Saxena *et al.*, 1997, Brown *et al.*, 2002)]; ethanol [selectively potentiates responses mediated by α4β3δ and α6β3δ receptors versus receptors in which β2 replaces β3, or γ replaces δ (Wallner *et al.*, 2006, but see also Korpi *et al.*, 2007)]; DS1 and DS2 [selectively potentiate responses mediated by δ-subunit-containing receptors (Wafford *et al.*, 2009)]. It should be noted that the apparent selectivity of some positive allosteric modulators (*e.g.*, neurosteroids such as 5α-pregnan-3α-ol-20-one for δ-subunit-containing receptors (*e.g.*, α1β3δ) may be a consequence of the unusually low efficacy of GABA at this receptor isoform (Bianchi and MacDonald, 2003; Belelli *et al.*, 2009).

**Abbreviations:** 3-ACPBPBA, 3-amino-cyclopentenylbutylphosphonic acid; 5-Me-IAA, 5-methyl-1H-imidazole-4-acetic acid; (±)-*cis*-2-CAMP, (±)-*cis*-2-aminomethylcyclopropane carboxylic acid; α3IA, 6-(4-pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1H-pyridin-2-one; α5IA, 3-(5-methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methoxy]-1,2,4-triazolo[3,4-*a*]phthalazine; CACA, *cis*-aminocrotonic acid; CGS8216, 2-phenylpyrazolo[4,3-*c*]quinolin-3(5)-one; DMCM, methy-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate; DS1, 4-chloro-N-[6,8-dibromo-2-(2-thienyl)imidazo[1,2-*a*]pyridine-3-yl benzamide; DS2, 4-chloro-N-[2-(2-thienyl)imidazo[1,2-*a*]pyridine-3-yl benzamide; L655708, ethyl(s)-(11,12,13,13a-tetrahydro-7-methoxy-9-oxo)-imidazo[1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-1-carboxylate; L838417, 7-*tert*-butyl-3-(2,5-difluoro-phenyl)-6-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)-[1,2,4]triazolo[4,3-*b*]pyridazine; MRK016, 3-*tert*-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1H-1,2,4-triazol-5-ylmethoxy)-pyrazolo[1,5-*d*]-[1,2,4]triazine; Ro154513, ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-*a*][1,4] benzodiazepine-3-carboxylate; Ro194603, imidazo[1,5-*a*]1,4-thienodiazepinone; Ro4938581, 3-bromo-10-difluoromethyl-9H-imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine; SR95531, 2-(3'-carboxy-2'-propyl)-3-amino-6-*p*-methoxyphenylpyridazinium bromide; TBPS, *tert*-butylbicycloposphorothionate; TP003, 4,2'-difluoro-5-[8-fluoro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-*a*]pyridine-3-yl]biphenyl-2-carbonitrile; TPA023, 7-(1,1-dimethylethyl)-6-(2-ethyl-2H-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine; TPMPA, (1,2,5,6-tetrahydropyridine-4-yl)methylphosphonic acid; RY024, *tert*-butyl-8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazol[1,5-*a*][1,4]benzodiazepine-3-carboxylate; RY80, ethyl-8-acetylene-5, 6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate; ZK93423, 6-benzyloxy-4-methoxymethyl-β-carboline-3-carboxylate ethyl ester; ZK93426, 5-isopropyl-4-methyl-β-carboline-3-carboxylate ethyl ester

#### Further Reading

Atack JR (2008). GABA<sub>A</sub> receptor subtype-selective efficacy: TPA023, an α2/α3 selective non-sedating anxiolytic and α5IA, an α5 selective cognition enhancer. *CNS Neurosci Ther* 14: 25–35.

Atack JR (2010). GABA<sub>A</sub> receptor α2/α3 subtype-selective modulators as potential nonsedating anxiolytics. *Curr Top Behav Neurosci* 2: 331–360.

- Barnard EA, Skolnick P, Olsen RW, Mohler H, Sieghart W, Biggio G *et al.* (1998). International Union of Pharmacology. XV. Subtypes of γ-aminobutyric acid<sub>A</sub> receptors: classification on the basis of subunit structure and receptor function *Pharmacol Rev* **50**: 291–313.
- Belelli D, Lambert JJ (2005). Neurosteroids: endogenous regulators of the GABA<sub>A</sub> receptor. *Nat Rev Neurosci* **6**: 565–575.
- Belelli D, Harrison NL, Maguire J, Macdonald RL, Walker MC, Cope DW (2009). Extrasynaptic GABA<sub>A</sub> receptors: form, pharmacology, and function. *J Neurosci* **29**: 12757–12763.
- Bonin RP, Orser BA (2008). GABA<sub>A</sub> receptor subtypes underlying general anesthesia. *Pharmacol Biochem Behav* **90**: 105–112.
- Bowery NG, Smart TG (2006). GABA and glycine as neurotransmitters: a brief history. *Br J Pharmacol* **147** (Suppl. 1): S109–S119.
- Capogna M, Pearce RA (2011). GABA<sub>A</sub> slow: causes and consequences. *Trends Neurosci* **34**: 101–112.
- Chebib M (2004). GABA<sub>C</sub> receptor ion channels. *Clin Exp Pharmacol Physiol* **31**: 800–804.
- Daniel C, Ohman M (2009). RNA editing and its impact on GABA<sub>A</sub> receptor function. *Biochem Soc Trans* **37**: 1399–1403.
- Chen ZW, Olsen RW (2007). GABA<sub>A</sub> receptor associated proteins: a key factor regulating GABA<sub>A</sub> receptor function. *J Neurochem* **100**: 279–294.
- D'Hulst C, Atack JR, Kooy RF (2009). The complexity of the GABA<sub>A</sub> receptor shapes unique pharmacological properties. *Drug Discov Today* **14**: 866–875.
- Farrant M, Nusser Z. (2005). Variations on an inhibitory theme: phasic and tonic activation of GABA<sub>A</sub> receptors. *Nat Rev Neurosci* **6**: 215–229.
- Farrant M, Kaila K (2007). The cellular, molecular and ionic basis of GABA<sub>A</sub> receptor signalling. *Prog Brain Res* **160**: 59–87.
- Frolund B, Ebert B, Kristiansen U, Liljefors T, Krosgaard-Larsen P (2002). GABA<sub>A</sub> receptor ligands and their therapeutic potentials. *Curr Top Med Chem* **2**: 817–832.
- Galanopoulou AS (2010). Mutations affecting GABAergic signaling in seizures and epilepsy. *Pflugers Arch* **460**: 505–523.
- Hanchar HJ, Wallner M, Olsen RW (2004). Alcohol effects on γ-aminobutyric acid type A receptors: are extrasynaptic receptors the answer? *Life Sci* **76**: 1–8.
- Hemmings HC, Akabas MH, Goldstein PA, Trudell JR, Orser BA, Harrison NL (2005). Emerging molecular mechanisms of general anesthetic action. *Trends Pharmacol Sci* **26**: 503–510.
- Herd MB, Belelli D, Lambert JJ (2007). Neurosteroid modulation of synaptic and extrasynaptic GABA<sub>A</sub> receptors. *Pharmacol Ther* **116**: 20–34.
- Hosie AM, Wilkins ME, Smart TG (2007). Neurosteroid binding sites on GABA<sub>A</sub> receptors. *Pharmacol Ther* **116**: 7–19.
- Jacob TC, Moss SJ, Jurd R (2008). GABA<sub>A</sub> receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat Rev Neurosci* **9**: 331–343.
- Johnston GA (2005). GABA<sub>A</sub> receptor channel pharmacology. *Curr Pharm Des* **11**: 1867–1885.
- Johnston GA, Chebib M, Hanrahan JR, Mewett KN (2010). Neurochemicals for the investigation of GABA<sub>C</sub> receptors. *Neurochem Res* **35**: 1970–1977.
- Korpi ER, Grunder G, Luddens H (2002). Drug interactions at GABA<sub>A</sub> receptors. *Prog Neurobiol* **67**: 113–159.
- Korpi ER, Debus F, Linden AM, Malecot C, Leppa E, Vekovischeva O *et al.* (2007). Does ethanol act preferentially via selected brain GABA<sub>A</sub> receptor subtypes? The current evidence is ambiguous. *Alcohol* **41**: 163–176.
- Krosgaard-Larsen P, Frolund B, Liljefors T (2002). Specific GABA<sub>A</sub> agonists and partial agonists. *Chem Rec* **2**: 419–430.
- Lüscher B, Fuchs T, Kilpatrick CL (2011). GABA<sub>A</sub> receptor trafficking-mediated plasticity of inhibitory synapses. *Neuron* **70**: 385–409.
- Mody I, Pearce RA (2004). Diversity of inhibitory neurotransmission through GABA<sub>A</sub> receptors. *Trends Neurosci* **27**: 569–575.
- Möhler H (2006). GABA<sub>A</sub> receptors in central nervous system disease: anxiety, epilepsy, and insomnia. *J Recept Signal Transduct Res* **26**: 731–740.
- Möhler H (2007). Molecular regulation of cognitive functions and developmental plasticity: impact of GABA<sub>A</sub> receptors. *J Neurochem* **102**: 1–12.
- Möhler H, Fritschy JM, Vogt K, Crestani F, Rudolph U (2005). Pathophysiology and pharmacology of GABA<sub>A</sub> receptors. *Handb Exp Pharmacol* **169**: 225–247.
- Munro G, Ahring PK, Mirza NR (2009). Developing analgesics by enhancing spinal inhibition after injury: GABA<sub>A</sub> receptor subtypes as novel targets. *Trends Pharmacol Sci* **30**: 453–459.
- Ng CK, Kim HL, Gavande N, Yamamoto I, Kumar RJ, Mewett KN *et al.* (2011). Medicinal chemistry of ρ GABA<sub>C</sub> receptors. *Future Med Chem* **3**: 197–209.
- Nutt DJ, Stahl SM (2010). Searching for perfect sleep: the continuing evolution of GABA<sub>A</sub> receptor modulators as hypnotics. *J Psychopharmacol* **24**: 1601–1612.
- Olsen RW, Li GD (2011). GABA<sub>A</sub> receptors as molecular targets of general anesthetics: identification of binding sites provides clues to allosteric modulation. *Can J Anaesth* **58**: 206–215.
- Olsen RW, Sieghart W (2008). IUPHAR, LXX. Subtypes of γ-aminobutyric acid<sub>A</sub> receptors: classification on the basis of subunit composition, pharmacology, and function. Update. *Pharmacol Rev* **60**: 243–260.
- Olsen RW, Sieghart W (2009). GABA<sub>A</sub> receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology* **56**: 141–148.
- Olsen RW, Chang CS, Li G, Hanchar HJ, Wallner M (2004). Fishing for allosteric sites on GABA<sub>A</sub> receptors. *Biochem Pharmacol* **68**: 1675–1684.
- Rudolph U, Möhler H (2004). Analysis of GABA<sub>A</sub> receptor function and dissection of the pharmacology of benzodiazepines and general anesthetics through mouse genetics. *Annu Rev Pharmacol Toxicol* **44**: 475–498.
- Rudolph U, Möhler H (2006). GABA-based therapeutic approaches: GABA<sub>A</sub> receptor subtype functions. *Curr Opin Pharmacol* **6**: 18–23.
- Semyanov A, Walker MC, Kullmann DM, Silver RA (2004). Tonically active GABA<sub>A</sub> receptors: modulating gain and maintaining the tone. *Trends Neurosci* **27**: 263–269.
- Sieghart W (2006). Structure, pharmacology, and function of GABA<sub>A</sub> receptor subtypes. *Adv Pharmacol* **54**: 231–263.
- Sigel E, Lüscher BP (2011). A closer look at the high affinity benzodiazepine binding site on GABA<sub>A</sub> receptors. *Curr Top Med Chem* **11**: 241–246.
- Tan KR, Rudolph U, Lüscher C (2011). Hooked on benzodiazepines: GABA<sub>A</sub> receptor subtypes and addiction. *Trends Neurosci* **34**: 188–197.
- Veleiro AS, Burton G (2009). Structure-activity relationships of neuroactive steroids acting on the GABA<sub>A</sub> receptor. *Curr Med Chem* **16**: 455–472.
- Vithlani M, Terunuma M, Moss SJ (2011). The dynamic modulation of GABA<sub>A</sub> receptor trafficking and its role in regulating the plasticity of inhibitory synapses. *Physiol Rev* **91**: 1009–1022.
- Wallner M, Hanchar HJ, Olsen RW (2006). Low dose acute alcohol effects on GABA<sub>A</sub> receptor subtypes. *Pharmacol Ther* **112**: 513–528.
- Whiting PJ (2003). The GABA<sub>A</sub> receptor gene family: new opportunities for drug development. *Curr Opin Drug Discov Devel* **6**: 648–657.
- Zeller A, Jurd R, Lambert S, Arras M, Drexler B, Grashoff C *et al.* (2008). Inhibitory ligand-gated ion channels as substrates for general anesthetic actions. *Handb Exp Pharmacol* **182**: 31–51.
- Zhang D, Pan ZH, Awobuluyi M, Lipton SA (2001). Structure and function of GABA<sub>C</sub> receptors: a comparison of native versus recombinant receptors. *Trends Pharmacol Sci* **22**: 121–132.

## References

- Bianchi MT, MacDonald RL (2003). *J Neurosci* **23**: 10934–10943.
- Brown N *et al.* (2002). *Br J Pharmacol* **136**: 965–974.
- Fisher JL (2002). *Mol Pharmacol* **61**: 1322–1328.
- Fisher JL (2009). *Neuropharmacology* **56**: 190–197.

- Khom S *et al.* (2010). *Br J Pharmacol* **161**: 65–78.
- Krishek BJ *et al.* (1996). *J Physiol* **492**: 431–443.
- Krishek BJ *et al.* (1998). *J Physiol* **507**: 639–652.
- Li GD *et al.* (2006). *J Neurosci* **26**: 11599–11605.
- Li GD *et al.* (2009). *J Biol Chem* **284**: 11771–11775.
- Ramerstorfer J *et al.* (2011). *J Neurosci* **31**: 870–877.
- Saxena NC *et al.* (1997). *Mol Pharmacol* **51**: 328–335.
- Sergeeva OA *et al.* (2010). *J Biol Chem* **285**: 23985–23993.
- Stórustovu SI, Ebert B (2006). *J Pharmacol Exp Ther* **316**: 3151–3159.
- Thompson SA *et al.* (1999). *Br J Pharmacol* **127**: 1349–1358.
- Thompson SA. *et al.* (2002). *Mol Pharmacol* **61**: 861–869.
- Thompson SA *et al.* (2004). *Br J Pharmacol* **142**: 97–106.
- Wafford KA *et al.* (2009). *Neuropharmacology* **56**: 182–189.
- You H *et al.* (2010). *Neuropharmacology* **59**: 527–533.

# Glutamate (ionotropic)

**Overview:** The ionotropic glutamate receptors comprise members of the NMDA (*N*-methyl-D-aspartate), AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptor classes, named originally according to their preferred, synthetic, agonist (Dingledine *et al.*, 1999; Lodge, 2009; Traynelis *et al.*, 2010). Receptor heterogeneity within each class arises from the homo-oligomeric, or hetero-oligomeric, assembly of distinct subunits into cation-selective tetramers. Each subunit of the tetrameric complex comprises an extracellular amino terminal domain (ATD), an extracellular ligand binding domain (LBD), a transmembrane domain (TMD) composed of three membrane spans (M1, M3 and M4) with a channel lining re-entrant 'p-loop' (M2) located between M1 and M3 and an intracellular carboxy-terminal domain (CTD) (see Mayer, 2006; Kaczor and Matosiuk, 2010; Nakagawa, 2010; Traynelis *et al.*, 2010). The X-ray structure of a homomeric ionotropic glutamate receptor (GluA2 – see below) has recently been solved at 3.6Å resolution (Sobolevsky *et al.*, 2009) and although providing the most complete structural information current available may not be representative of the subunit arrangement of, for example, the heteromeric NMDA receptors (Karakas *et al.*, 2011). It is beyond the scope of this supplement to discuss the pharmacology of individual ionotropic glutamate receptor isoforms in detail; such information can be gleaned from Dingledine *et al.* (1999), Jane *et al.* (2000), Cull-Candy and Leszkiewicz (2004), Kew and Kemp (2005), Erreger *et al.* (2007), Paoletti and Neyton (2007), Chen *et al.* (2008), Jane *et al.* (2009) and Traynelis *et al.* (2010). Agents that discriminate between subunit isoforms are, where appropriate, noted in the tables and additional compounds that distinguish between receptor isoforms are indicated in the text below.

The classification of glutamate receptor subunits has been recently been re-addressed by NC-IUPHAR (Collingridge *et al.*, 2009). The scheme developed recommends a revised nomenclature for ionotropic glutamate receptor subunits that is adopted here.

**NMDA receptors:** NMDA receptors assemble as obligate heteromers that may be drawn from GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B subunits. Alternative splicing can generate eight isoforms of GluN1 with differing pharmacological properties. Various splice variants of GluN2B, 2C, 2D and GluN3A have also been reported. Activation of NMDA receptors containing GluN1 and GluN2 subunits requires the binding of two agonists, glutamate to the S1 and S2 regions of the GluN2 subunit and glycine to S1 and S2 regions of the GluN1 subunit (Erreger *et al.* 2004; Chen and Wyllie, 2006). The minimal requirement for efficient functional expression of NMDA receptors *in vitro* is a di-heteromeric assembly of GluN1 and at least one GluN2 subunit variant, as a dimer of heterodimers arrangement in the extracellular domain (Furukawa *et al.*, 2005; Mayer, 2006; Karakas *et al.*, 2011). However, more complex tri-heteromeric assemblies, incorporating multiple subtypes of GluN2 subunit, or GluN3 subunits, can be generated *in vitro* and occur *in vivo*. The NMDA receptor channel commonly has a high relative permeability to Ca<sup>2+</sup> and is blocked, in a voltage-dependent manner, by Mg<sup>2+</sup> such that at resting potentials the response is substantially inhibited.

Nomenclature	NMDA
Ensembl Gene family ID	ENSF00000000436
Selective agonists (glutamate site)	NMDA (GluN2D > GluN2C > GluN2B > GluN2A), L-aspartate (GluN2D = GluN2B > GluN2C = GluN2A), D-aspartate (GluN2D > GluN2C = GluN2B > GluN2A), (RS)-(tetrazol-5-yl)glycine (GluN2D > GluN2C = GluN2B > GluN2A), homoquinolinic acid (GluN2B $\cong$ GluN2A $\cong$ GluN2D > GluN2C; partial agonist at GluN2A and GluN2C)
Selective antagonists (glutamate site)	D-AP5, CGS19755 (selfotel), CGP37849, LY233053, D-CCPene (GluN2A = GluN2B > GluN2C = GluN2D), UBP141 (GluN2D > GluN2D > GluN2A > GluN2A, Morley <i>et al.</i> , 2005), NVP-AAM077 (GluN2A > GluN2B (human), Auberson <i>et al.</i> 2002; but weakly selective for rat GluN2A versus GluN2B Feng <i>et al.</i> , 2004; Frizelle <i>et al.</i> , 2006; Neyton and Paoletti, 2006), conantokin-G (GluN2B > GluN2D = GluN2C = GluN2A)
Selective agonists (glycine site)	Glycine (GluN2D > GluN2C > GluN2B > GluN2A), D-serine (GluN2D > GluN2C > GluN2B > GluN2A), (+)-HA966 (partial agonist, GluN2B > GluN2A)
Selective antagonists (glycine site)	5,7-Dichlorokynureate, L689560, L701324, GV196771A
Channel blockers	Mg <sup>2+</sup> (GluN2A = GluN2B > GluN2C = GluN2D), (+)-MK801, ketamine, phencyclidine, memantine (GluN2C $\cong$ GluN2D $\cong$ GluN2B > GluN2A), amantadine (GluN2C = GluN2D $\cong$ GluN2B $\cong$ GluN2A), N <sup>1</sup> -dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D)
Probes	
Glutamate site	[ <sup>3</sup> H]CPP, [ <sup>3</sup> H]CGS19755, [ <sup>3</sup> H]CGP39653
Glycine site	[ <sup>3</sup> H]Glycine, [ <sup>3</sup> H]L689560, [ <sup>3</sup> H]MDL105519, [ <sup>3</sup> H]CGP61594 (photoaffinity ligand)
Cation channel	[ <sup>3</sup> H]-MK801 (dizocilpine)

Potency orders unreferenced in the table are from Kuner and Schoepfer (1996), Dravid *et al.* (2007), Erreger *et al.* (2007), Paoletti and Neyton (2007), Chen *et al.* (2008) and Traynelis *et al.* (2010). In addition to the glutamate and glycine binding sites documented in the table, physiologically important inhibitory modulatory sites exist for Mg<sup>2+</sup>, Zn<sup>2+</sup>, and protons (see Dingledine *et al.*, 1999; Cull-Candy and Leszkiewicz, 2004; Traynelis *et al.*, 2010). Voltage-independent inhibition by Zn<sup>2+</sup> binding with high affinity within the ATD is highly subunit selective (GluN2A >> GluN2B > GluN2C  $\cong$  GluN2D; Paoletti and Neyton, 2007, Traynelis *et al.*, 2010). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner (Malayev *et al.*, 2002, Horak *et al.*, 2006). Tonic proton blockade of NMDA receptor function is alleviated by polyamines and the inclusion of exon 5 within GluN1 subunit splice variants, whereas the non-competitive antagonists ifenprodil and CP101606 (traxoprodil) increase the fraction of receptors blocked by protons at ambient concentration. Inclusion of exon 5 also abolishes potentiation by polyamines and inhibition by Zn<sup>2+</sup> that occurs through binding in the ATD (Traynelis *et al.*, 1998). Ifenprodil, CP101606, haloperidol, felbamate and Ro84304 discriminate between recombinant NMDA receptors assembled from GluN1 and either GluN2A, or GluN2B, subunits by acting as selective, non-competitive, antagonists of hetero-oligomers incorporating GluN2B through a binding site at the ATD GluN1/GluN2B subunit interface (Karakas *et al.*, 2011). LY233536 is a competitive antagonist that also displays selectivity for GluN2B over GluN2A subunit-containing receptors. Similarly, CGP61594 is a photoaffinity label that interacts selectively with receptors incorporating GluN2B versus GluN2A, GluN2D and, to a lesser extent, GluN2C subunits. In addition to influencing the pharmacological profile of the NMDA receptor, the identity of the GluN2 subunit co-assembled with GluN1 is an



important determinant of biophysical properties that include sensitivity to block by  $Mg^{2+}$ , single-channel conductance and maximal open probability and channel deactivation time (Cull-Candy and Leszkiewicz, 2004; Erreger *et al.*, 2004; Gielen *et al.*, 2009). Incorporation of the GluN3A subunit into tri-heteromers containing GluN1 and GluN2 subunits is associated with decreased single-channel conductance, reduced permeability to  $Ca^{2+}$  and decreased susceptibility to block by  $Mg^{2+}$  (Cavara and Hollmann, 2008; Henson *et al.*, 2010). Reduced permeability to  $Ca^{2+}$  has also been observed following the inclusion of GluN3B in tri-heteromers. The expression of GluN3A, or GluN3B, with GluN1 alone forms, in *Xenopus laevis* oocytes, a cation channel with unique properties that include activation by glycine (but not NMDA), lack of permeation by  $Ca^{2+}$  and resistance to blockade by  $Mg^{2+}$  and NMDA receptor antagonists (Chatterton *et al.*, 2002). The function of heteromers composed of GluN1 and GluN3A is enhanced by  $Zn^{2+}$ , or glycine site antagonists, binding to the GluN1 subunit (Madry *et al.*, 2008).  $Zn^{2+}$  also directly activates such complexes. The co-expression of GluN1, GluN3A and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts (Smothers and Woodward, 2007).

**AMPA and Kainate receptors:** AMPA receptors assemble as homomers, or heteromers, that may be drawn from GluA1, GluA2, GluA3 and GluA4 subunits. Transmembrane AMPA receptor regulatory proteins (TARPs) of class I (*i.e.*  $\gamma 2$ ,  $\gamma 3$ ,  $\gamma 4$  and  $\gamma 8$ ) act, with variable stoichiometry, as auxiliary subunits to AMPA receptors and influence their trafficking, single channel conductance gating and pharmacology (reviewed by Esteban, 2008; Milstein and Nicoll, 2008; Tomita, 2010; Jackson and Nicoll, 2011). Functional kainate receptors can be expressed as homomers of GluK1, GluK2 or GluK3 subunits. GluK1-3 subunits are also capable of assembling into heterotetramers (*e.g.* GluK1/K2; see Lerma, 2006; Pinheiro and Mulle, 2006; Perrais *et al.*, 2010). Two additional kainate receptor subunits, GluK4 and GluK5, when expressed individually, form high affinity binding sites for kainate, but lack function, but can form heteromers when expressed with GluK1-3 subunits (*e.g.* GluK2/K5; reviewed by Pinheiro and Mulle, 2006; Jane *et al.*, 2009; Perrais *et al.*, 2010). Kainate receptors may also exhibit 'metabotropic' functions (Lerma, 2006; Rodriguez-Morino and Sihra, 2007). As found for AMPA receptors, kainate receptors are modulated by auxiliary subunits (Neto proteins, see Perrais *et al.*, 2010; Lerma, 2011). An important function difference between AMPA and kainate receptors is that the latter require extracellular  $Na^+$  and  $Cl^-$  for their activation (Bowie, 2010; Plested, 2011). RNA encoding the GluA2 subunit undergoes extensive RNA editing in which the codon encoding a p-loop glutamine residue (Q) is converted to one encoding arginine (R). This Q/R site strongly influences the biophysical properties of the receptor. Recombinant AMPA receptors lacking RNA edited GluA2 subunits are: (1) permeable to  $Ca^{2+}$ ; (2) blocked by intracellular polyamines at depolarized potentials causing inward rectification (the latter being reduced by TARPs); (3) blocked by extracellular argitoxin and Joro spider toxins and (4) demonstrate higher channel conductances than receptors containing the edited form of GluA2 (Seeburg and Hartner, 2003; Isaac *et al.*, 2007). GluK1 and GluK2, but not other kainate receptor subunits, are similarly edited and broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GluK1, or GluK2, subunit (Lerma, 2006; Perrais *et al.*, 2010). Native AMPA and kainate receptors displaying differential channel conductances,  $Ca^{2+}$  permeabilities and sensitivity to block by intracellular polyamines have been identified (Cull-Candy *et al.*, 2006; Isaac *et al.*, 2007; Liu and Zukin, 2007). GluA1-4 can exist as two variants generated by alternative splicing (termed 'flip' and 'flop') that differ in their desensitization kinetics and their desensitization in the presence of cyclothiazide which stabilises the non-desensitized state. TARPs also stabilise the non-desensitized conformation of AMPA receptors and facilitate the action of cyclothiazide (Milstein and Nicoll, 2008). Splice variants of GluK1-3 also exist which affects their trafficking (Lerma, 2006; Perrais *et al.*, 2010).

Nomenclature	AMPA	Kainate
Ensembl Gene family ID	ENSF00000000118	ENSF00000000118
Selective agonists	AMPA, (S)-5-fluorowillardiine	ATPA, (S)-4-AHCP, 8-deoxy-neodysiherbaine, (S)-5-iodowillardiine, LY339434 (all selective for receptors containing a GluK1 subunit), (2S,4R)-4-methylglutamate (SYM2081), dysiherbaine, domoic acid (inactive at GluK3), kainate (low potency at GluK3)
Selective antagonists	NBQX, ATPO, LY293558, GYKI53655/LY300168 (active isomer GYKI53784/LY303070) (noncompetitive)	UBP302, UBP310, ACET, LY382884, LY466195 (all selective for receptors containing a GluK1 subunit), NS3763 (non-competitive, GluK1 selective), MSVIII-19 (GluK1 selective), 2,4-epi-neodysiherbaine (GluK1 and GluK2 selective)
Positive modulators	Pyrrolidinones (piracetam, aniracetam), benzothiadiazides (cyclothiazide, S18986, IDRA-21), benzylpiperidines (CX-516 (BDP-12), CX-546), biarylpropylsulfonamides (LY392098, LY404187 and LY503430)	Concanavalin A (GluK1 and GluK2, not GluK3)
Channel blockers	Intracellular polyamines, extracellular argitoxin, extracellular Joro toxin, (selective for channels lacking GluA2)	Intracellular polyamines (subtype selective; GluK3 >> GluK2)
Probes ( $K_d$ )	[ $^3H$ ]AMPA, [ $^3H$ ]CNQX	[ $^3H$ ]Kainate, [ $^3H$ ](2S,4R)-4-methylglutamate, [ $^3H$ ]UBP310 (GluK1, 21 nM, GluK3, 0.56 $\mu$ M, Atlason <i>et al.</i> , 2010)

All AMPA receptors are additionally activated by kainate (and domoate) with relatively low potency, ( $EC_{50} \sim 100 \mu M$ ). Inclusion of TARPs within the receptor complex increases the potency and maximal effect of kainate (Milstein and Nicoll, 2008; Jackson and Nicoll, 2011). AMPA is weak partial agonist at GluK1 and at heteromeric assemblies of GluK1/GluK2, GluK1/GluK5 and GluK2/GluK5 (Jane *et al.*, 2009). Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. LY293558 also has kainate (GluK1) receptor activity as has GYKI53655 (GluK3 and GluK2/GluK3) (Jane *et al.*, 2009). ATPO is a potent competitive antagonist of AMPA receptors, has a weaker antagonist action at kainate receptors comprising GluK1 subunits, but is devoid of activity at kainate receptors formed from GluK2 or GluK2/GluK5 subunits. The pharmacological activity of ATPO resides with the (S)-enantiomer. ACET and UBP310 may block GluK3, in addition to GluK1 (Perrais *et al.*, 2009; Atlason *et al.*, 2010). (2S,4R)-4-methylglutamate (SYM2081) is equipotent in activating (and desensitising) GluK1

and GluK2 receptor isoforms and, *via* the induction of desensitisation at low concentrations, has been used as a functional antagonist of kainate receptors. Both (2S,4R)-4-methylglutamate and LY339434 have agonist activity at NMDA receptors. (2S,4R)-4-methylglutamate is also an inhibitor of the glutamate transporters EAAT1 and EAAT2.

**Delta subunits:** GluD1 and GluD2 comprise, on the basis of sequence homology, an 'orphan' class of ionotropic glutamate receptor subunit. They do not form a functional receptor when expressed solely, or in combination with other ionotropic glutamate receptor subunits, in transfected cells (Yuzaki, 2003). However, GluD2 subunits bind D-serine and glycine and GluD2 subunits carrying the mutation A654T form a spontaneously open channel that is closed by D-serine (Naur *et al.*, 2007).

**Abbreviations:** (S)-4-AHCP, (S)-2-amino-3-(3-hydroxy-7,8-dihydro-6H-cyclohepta[d]isoxazol-4-yl)propionic acid; ACET, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; AMPA, (RS)- $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; APTA, (RS)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propionic acid; ATPO, (RS)-2-amino-3-(3-[5-*tert*-butyl-3-(phosphonomethoxy)-4-isoxazolyl]propionic acid; CGP37849, (RS)-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid; CGP39653, (RS)-(E)-2-amino-4-propyl-5-phosphono-3-pentenoic acid; CGS19755, ( $\pm$ )-*cis*-4-phosphonomethylpiperidine-2-carboxylic acid; CGP 61594, ( $\pm$ )-*trans*-4-[2-(4-azidophenyl)-acetylaminol]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid; CNQX, 6-cyano-7-nitroquinoline-2,3-dione; CP101606, (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; CPP, (R)-3-(2-carboxypiperazine-4-yl)propyl-1-phosphonic acid; CX-516; 1-(quinoxalin-6-yl-carbonyl)piperidine; CX-546, 1-(1,4-benzodioxan-6-ylcarbonyl)piperidine; d-AP5, (R)-2-amino-5-phosphonopentanoate; d-CCPene, (R)-(E)-3-(2-carboxypiperazine-4-yl)propenyl-1-phosphonic acid; GV196771A, E-4,6-dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidenedimethyl)-1H-indole-2-carboxylic acid; GYKI53655, ( $\pm$ )-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5H-2,3-benzodiazepine; also known as LY300168; GYKI53784, (-)-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5H-2,3-benzodiazepine, also known as LY303070; HA966, 3-amino-1-hydroxypyrrolidin-2-one; IDRA-21, 7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-5,5-dioxide; L689560, *trans*-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline; L701324, 7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(H)quinolone; LY233053, ( $\pm$ )-*cis*-4-[(2H-tetrazol-5-yl)methyl]piperidine-2-carboxylic acid; LY233536, ( $\pm$ )-6-(1H-tetrazol-5-ylmethyl)decahydroisoquinoline-3-carboxylic acid; LY293558, (3S,4aR,6R,8aR)-6-[2-(1H-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid; LY339434, (2S,4R,6E)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid; LY382884, (3S,4aR,6S,8aR)-6-[(4-carboxyphenyl)methyl-1,2,3,4,4a,5,6,7,8a-decahydroisoquinoline-3-carboxyethyl]-hexahydro-furo-[3,2-*b*]pyran-2-carboxylic acid; LY392098, propane-2-sulfonic acid [2-(4-thiophen-3-yl-phenyl)propyl]amide; LY404187, propane-2-sulfonic acid [2-(4'-cyanobiphenyl-4-yl)propyl]amide; LY466195, (3S,4aR,6S,8aR)-6-[(2S)-2-carboxy-4,4-difluoro-1-pyrrolidinyl]-methyl]decahydro-3-isoquinolinecarboxylic acid; LY503430, (R)-4'-[1-fluoro-1-methyl-2-(propane-2-sulfonylamino)ethyl]biphenyl-4-carboxylic acid methylamide; MDL105519, (E)-3-(2-phenyl-2-carboxyethyl)-4,6-dichloro-1H-indole-2-carboxylic acid; MSVIII-19, (2R,3aR,7aR)-2-[(2S)-2-amino-2-carboxyethyl]-hexahydro-furo-[3,2-*b*]pyran-2-carboxylic acid; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoline; NS3763, 5-carboxy-2,4-di-benzamidobenzoic acid; NVP-AAM077, (R)-[(S)-1-(4-bromophenyl)ethylamino]-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl)methyl]phosphonic acid; Ro8-4304, 4-3-[4-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-hydroxypropoxybenzamide; S18986, (S)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide; UBP141, (2R\*,3S\*)-1-(phenanthrenyl-3-carbonyl)piperazine-2,3-dicarboxylic acid; UBP302, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl)pyrimidine-2,4-dione, UBP310, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxythiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione

## Further Reading

- Bowie D (2008). Ionotropic glutamate receptors & CNS disorders. *CNS Neurol Disord Drug Targets* 7: 129–143.
- Bowie D (2010). Ion dependent gating of kainate receptors. *J Physiol* 588: 67–81.
- Cavara NA, Hollmann M (2008). Shuffling the deck anew: how NR3 tweaks NMDA receptor function. *Mol Neurobiol* 38: 16–26.
- Chen PD, Wyllie DJ (2006). Pharmacological insights obtained from structure-function studies of ionotropic glutamate receptors. *Br J Pharmacol* 147: 839–853.
- Collingridge GL, Olsen RW, Peters JA, Spedding M (2009). A nomenclature for ligand-gated ion channels. *Neuropharmacology* 56: 2–5.
- Contractor A, Mulle C, Swanson GT (2010). Kainate receptors coming of age: milestones of two decades of research. *Trends Neurosci* 34: 154–163.
- Cull-Candy SG, Leszkiewicz DN (2004). Role of distinct NMDA receptor subtypes at central synapses. *Sci STKE* 255: re16.
- Cull-Candy SG, Kelly L, Farrant M (2006). Regulation of Ca<sup>2+</sup>-permeable AMPA receptors: synaptic plasticity and beyond. *Curr Opin Neurobiol* 16: 288–297.
- Dingledine R, Borges K, Bowie D, Traynelis SF (1999). The glutamate receptor ion channels. *Pharmacol Rev* 51: 7–61.
- Esteban JA (2008). Intracellular machinery for the transport of AMPA receptors. *Br J Pharmacol* 153 (Suppl. 1): S35–S43.
- Erreger K, Chen PE, Wyllie DJ, Traynelis SF (2004). Glutamate receptor gating. *Crit Rev Neurobiol* 16: 187–224.
- Hall BJ, Ghosh A (2008). [http://www.ncbi.nlm.nih.gov/pubmed/18201773?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18201773?ordinalpos=25&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum) Regulation of AMPA receptor recruitment at developing synapses. *Trends Neurosci* 31: 82–89.
- Hardingham GE, Bading H (2010). Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat Rev Neurosci* 11: 682–696.
- Isaac JTR, Ashby MC, McBain CJ (2007). The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. *Neuron* 54: 859–871.
- Hansen KB, Yuan H, Traynelis SF (2007). Structural aspects of AMPA receptor activation, desensitization and deactivation. *Curr Opin Neurobiol* 17: 281–288.
- Henson MA, Roberts AC, Pérez-Otaño I, Philpot BD (2010). Influence of the NR3A subunit on NMDA receptor functions. *Prog Neurobiol* 91: 23–37.
- Jackson AC, Nicoll RA (2011). The expanding social network of ionotropic glutamate receptors: TARPs and other transmembrane auxiliary subunits. *Neuron* 70: 178–199.
- Jane DE, Tse H-W, Skifter DA, Christie JM, Monaghan DT (2000). Glutamate receptor ion channels: activators and inhibitors In: Endo M, Kurachi Y, Mishina M (eds). *Handbook of Experimental Pharmacology, Pharmacology of Ionic Channel Function: Activators and Inhibitors*, Vol. 147. Springer: Berlin. pp. 415–478.
- Jane DE, Lodge D, Collingridge GL (2009). Kainate receptors: pharmacology, function and therapeutic potential. *Neuropharmacology* 56: 90–113.
- Kaczor AA, Matosiuk D (2010). Molecular structure of ionotropic glutamate receptors. *Curr Med Chem* 17: 2608–2635.
- Kessels HW, Malinow R (2009). Synaptic AMPA receptor plasticity and behavior. *Neuron* 61: 340–350.
- Kew JN, Kemp JA (2005). Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology* 179: 4–29.
- Kloda A, Martinac B, Adams DJ (2007). Polymodal regulation of NMDA receptor channels. *Channels (Austin)* 1: 334–343.
- Jerma J (2006). Kainate receptor physiology. *Curr Opin Pharmacol* 6: 89–97.

- Lerma J (2011). Net(o) excitement for kainate receptors. *Nat Neurosci* **14**: 808–810.
- Liu SJ, Zukin RS (2007). Ca<sup>2+</sup>-permeable AMPA receptors in synaptic plasticity and neuronal death. *Trends Neurosci* **30**: 126–134.
- Lodge D (2009). The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature. *Neuropharmacology* **56**: 6–21.
- Low CM, Wee KS (2010). New insights into the not-so-new NR3 subunits of N-methyl-D-aspartate receptor: localization, structure, and function. *Mol Pharmacol* **78**: 1–11.
- Mayer ML (2006). Glutamate receptors at atomic resolution. *Nature* **440**: 456–462.
- Mellor IR (2010). The AMPA receptor as a therapeutic target: current perspectives and emerging possibilities. *Future Med Chem* **2**: 877–891.
- Milstein AD, Nicoll RA (2008). [http://www.ncbi.nlm.nih.gov/pubmed/18514334?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18514334?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum) Regulation of AMPA receptor gating and pharmacology by TARP auxiliary subunits. *Trends Pharmacol Sci* **29**: 333–339.
- Monaghan DT, Jane DE (2009). Pharmacology of NMDA Receptors. In: Van Dongen AM (ed.). *Biology of the NMDA Receptor*. Chapter 12. CRC Press: Boca Raton.
- Mony L, Kew JN, Gunthorpe MJ, Paoletti P (2009). Allosteric modulators of NR2B-containing NMDA receptors: molecular mechanisms and therapeutic potential. *Br J Pharmacol* **157**: 1301–1317.
- Nakagawa T (2010). The biochemistry, ultrastructure, and subunit assembly mechanism of AMPA receptors. *Mol Neurobiol* **42**: 161–184.
- O'Neill MJ, Witkin JM (2007). AMPA receptor potentiators: application for depression and Parkinson's disease. *Curr Drug Targets* **8**: 603–620.
- O'Neill MJ, Bleakman D, Zimmerman DM, Nisenbaum ES (2004). AMPA receptor potentiators for the treatment of CNS disorders. *Curr Drug Targets CNS Neurol Disord* **3**: 181–194.
- Paoletti P, Neyton J (2007). NMDA receptor subunits: function and pharmacology. *Curr Opin Pharmacol* **7**: 39–47.
- Paoletti P, Vergnano AM, Barbour B, Casado M (2009). Zinc at glutamatergic synapses. *Neuroscience* **158**: 126–136.
- Perrais D, Veran J, Mulle C (2010). Gating and permeation of kainate receptors: differences unveiled. *Trends Pharmacol Sci* **31**: 516–522.
- Pinheiro P, Mulle C (2006). Kainate receptors. *Cell Tissue Res* **326**: 457–482.
- Planells-Cases R, Lerma J, Ferrer-Montiel A (2006). Pharmacological intervention at ionotropic glutamate receptor complexes. *Curr Pharm Des* **12**: 3583–3596.
- Plested AJ (2011). Kainate receptor modulation by sodium and chloride. *Adv Exp Med Biol* **717**: 93–113.
- Prorok M, Castellino FJ (2007). The molecular basis of conantokin antagonism of NMDA receptor function. *Curr Drug Targets* **8**: 633–642.
- Rodriguez-Morino A, Sihra TS (2007). Kainate receptors with a metabotropic modus operandi. *Trends Neurosci* **30**: 630–637.
- Seeburg PH, Hartner J (2003). Regulation of ion channel/neurotransmitter receptor function by RNA editing. *Curr Opin Neurobiol* **13**: 279–283.
- Stawski P, Janovjak H, Trauner D (2010). Pharmacology of ionotropic glutamate receptors: a structural perspective. *Bioorg Med Chem* **18**: 7759–7772.
- Stephenson FA, Cousins SL, Kenny AV (2008). Assembly and forward trafficking of NMDA receptors. *Mol Membr Biol* **25**: 311–320.
- Swanson GT, Sakai R (2009). Ligands for ionotropic glutamate receptors. *Prog Mol Subcell Biol* **46**: 123–157.
- Tomita, S. (2010). Regulation of ionotropic glutamate receptors by their auxiliary subunits. *Physiology (Bethesda)* **25**: 41–49.
- Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK *et al.* (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev* **62**: 405–496.
- Ward SE, Bax BD, Harries M (2010). Challenges for and current status of research into positive modulators of AMPA receptors. *Br J Pharmacol* **160**: 181–190.
- Waxman EA, Lynch DR (2005). N-methyl-D-aspartate receptor subtypes: multiple roles in excitotoxicity and neurological disease. *Neuroscientist* **11**: 37–49.
- Yuzaki M (2003). The delta2 glutamate receptor: 10 years later. *Neurosci Res* **46**: 11–22.

## References

- Atlason PT *et al.* (2010). *Mol Pharmacol* **78**: 1036–1045.
- Auberson YP *et al.* (2002). *Bioorg Med Chem Lett* **12**: 1099–1102.
- Chatterton JE *et al.* (2002). *Nature* **415**: 793–798.
- Chen PE *et al.* (2008). *J Physiol* **586**: 227–245.
- Dravid SM *et al.* (2007). *J Physiol* **581**: 107–128.
- Erreger K *et al.* (2007). *Mol Pharmacol* **72**: 907–920.
- Feng B *et al.* (2004). *Br J Pharmacol* **141**: 508–516.
- Frizelle PA *et al.* (2006). *Mol Pharmacol* **70**: 1022–1032.
- Furukawa H *et al.* (2005). *Nature* **438**: 185–192.
- Gielen M *et al.* (2009). *Nature* **459**: 703–707.
- Horak M *et al.* (2006). *Neuroscience* **137**: 93–102.
- Karakas E *et al.* (2011). *Nature* **475**: 249–253.
- Kuner T, Schoepfer R (1996). *J Neurosci* **16**: 3549–3558.
- Madry C *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 12563–12568.
- Malayev A *et al.* (2002). *Br J Pharmacol* **135**: 901–909.
- Morley RM *et al.* (2005). *J Med Chem* **48**: 2627–2637.
- Naur P *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 14116–11421.
- Neyton J, Paoletti P (2006). *J Neurosci* **26**: 1331–1333.
- Perrais D *et al.* (2009). *Neuropharmacology* **56**: 131–140.
- Smothers CT, Woodward JJ (2007). *J Pharmacol Exp Ther* **322**: 739–748.
- Sobolevsky AI *et al.* (2009). *Nature* **462**: 745–756.
- Traynelis SF *et al.* (1998). *J Neurosci* **18**: 6163–6175.

# Glycine

**Overview:** The inhibitory glycine receptor [nomenclature as agreed by the NC-IUPHAR sub-committee on glycine receptors (Lynch, 2009a)] is a member of the Cys-loop superfamily of transmitter-gated ion channels that includes the GABA<sub>A</sub>, nicotinic acetylcholine and 5-HT<sub>3</sub> receptors (Lynch 2009b). The receptor is expressed either as a homo-pentamer of  $\alpha$  subunits, or a complex now thought to harbour 2 $\alpha$  and 3 $\beta$  subunits (Grudzinska *et al.*, 2005; Betz and Laube, 2006), that contain an intrinsic anion channel. Four differentially expressed isoforms of the  $\alpha$ -subunit ( $\alpha 1$ - $\alpha 4$ ) and one variant of the  $\beta$ -subunit ( $\beta 1$ , ENSG00000109738) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for  $\alpha 1$  ( $\alpha 1^{\text{INS}}$  and  $\alpha 1^{\text{del}}$ ),  $\alpha 2$  ( $\alpha 2A$  and  $\alpha 2B$ ),  $\alpha 3$  ( $\alpha 3S$  and  $\alpha 3L$ ) and  $\beta$  ( $\beta \Delta 7$ ) subunits and by mRNA editing of the  $\alpha 2$  and  $\alpha 3$  subunit (Meier *et al.*, 2005; Oertel *et al.*, 2007; Eichler *et al.*, 2008). Both  $\alpha 2$  splicing and  $\alpha 3$  mRNA editing can produce subunits (*i.e.*,  $\alpha 2B$  and  $\alpha 3P185L$ ) with enhanced agonist sensitivity. Predominantly, the mature form of the receptor contains  $\alpha 1$  (or  $\alpha 3$ ) and  $\beta$  subunits while the immature form is mostly composed of only  $\alpha 2$  subunits. RNA transcripts encoding the  $\alpha 4$ -subunit have not been detected in adult humans. The N-terminal domain of the  $\alpha$ -subunit contains both the agonist and strychnine binding sites that consist of several discontinuous regions of amino acids. Inclusion of the  $\beta$ -subunit in the pentameric glycine receptor contributes to agonist binding, reduces single channel conductance and alters pharmacology. The  $\beta$ -subunit also anchors the receptor, *via* an amphipathic sequence within the large intracellular loop region, to gephyrin. The latter is a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse (see Moss and Smart, 2001; Kirsch, 2006; Kneussel and Loeblich, 2007). G-protein  $\beta\gamma$  subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop (Yevens *et al.*, 2003; 2006). Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors (Pitt *et al.*, 2008). Intracellular Ca<sup>2+</sup> appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation (Fucile *et al.*, 2000).

Nomenclature	$\alpha 1$	$\alpha 2$	$\alpha 3$
Ensembl ID	ENSG00000145888	ENSG00000101958	ENSG00000145451
Selective agonists (potency order)	Glycine > $\beta$ -alanine > taurine	Glycine > $\beta$ -alanine > taurine	Glycine > $\beta$ -alanine > taurine
Selective antagonists and modulators with subunit selectivity	Strychnine, PMBA, bilobalide (IC <sub>50</sub> = 20 $\mu$ M + $\beta$ = 204 $\mu$ M), pregnenolone sulphate ( $K_i$ = 1.9 $\mu$ M; + $\beta$ = 2.7 $\mu$ M), tropisetron ( $K_i$ = 84 $\mu$ M), colchicine (IC <sub>50</sub> = 324 $\mu$ M), nifedepine (IC <sub>50</sub> = 3.3 $\mu$ M + $\beta$ = 1.2 $\mu$ M), ginkgolide X (IC <sub>50</sub> = 0.76 $\mu$ M + $\beta$ > 300 $\mu$ M), HU308 (weak inhibition)	Strychnine, PMBA, bilobalide (8 $\mu$ M + $\beta$ = 50 $\mu$ M), pregnenolone sulphate ( $K_i$ = 5.5 $\mu$ M; + $\beta$ = 10.1 $\mu$ M), tropisetron ( $K_i$ = 13 $\mu$ M + $\beta$ = 5.4 $\mu$ M), colchicine (IC <sub>50</sub> = 64 $\mu$ M), DCKA (IC <sub>50</sub> = 188 $\mu$ M), ginkgolide X (IC <sub>50</sub> = 2.8 $\mu$ M + $\beta$ > 300 $\mu$ M), HU210 (90 nM), HU308 (1.1 $\mu$ M), WIN55,212-2 (220 nM)	Strychnine, nifedepine (IC <sub>50</sub> = 29.2 $\mu$ M + $\beta$ = 11.4 $\mu$ M), HU210 (50 nM), HU 308 (97 nM), WIN55212-2 (97 nM), (12E,20Z,18S)-8-hydroxyvariabilin (IC <sub>50</sub> = 7.0 $\mu$ M)
Selective potentiators (EC <sub>50</sub> )	HU210 (270 nM), anandamide (38 nM), $\Delta^9$ -tetrahydrocannabinol (~3 $\mu$ M, ~1500% potentiation)	$\Delta^9$ -tetrahydrocannabinol (~1 $\mu$ M, ~230% potentiation)	$\Delta^9$ -tetrahydrocannabinol (~5 $\mu$ M, ~1500% potentiation)
Endogenous potentiators (EC <sub>50</sub> )	Zn <sup>2+</sup> (37 nM) (not affected by $\beta$ )	Zn <sup>2+</sup> (540 nM) (not affected by $\beta$ )	
Endogenous inhibitors (IC <sub>50</sub> )	Zn <sup>2+</sup> (15 $\mu$ M; + $\beta$ = 13 $\mu$ M), Cu <sup>2+</sup> (4-15 $\mu$ M) (not affected by $\beta$ ), H <sup>+</sup>	Zn <sup>2+</sup> (360 $\mu$ M; + $\beta$ = 180 $\mu$ M), Cu <sup>2+</sup> (17 $\mu$ M)	Zn <sup>2+</sup> (150 $\mu$ M), Cu <sup>2+</sup> (9 $\mu$ M)
Channel blockers (IC <sub>50</sub> )	cyanotriphenylborate (1.3 $\mu$ M + $\beta$ = 2.8 $\mu$ M), picrotoxin (6.3 $\mu$ M + $\beta$ = 219 $\mu$ M), picrotoxinin (5.1 $\mu$ M + $\beta$ = 27 $\mu$ M), picrotin (5.2 $\mu$ M + $\beta$ = 27 $\mu$ M), ginkgolide B (0.6-8.0 $\mu$ M + $\beta$ = 0.18-2.5 $\mu$ M),	cyanotriphenylborate (>>20 $\mu$ M; + $\beta$ = 7.5 $\mu$ M), picrotoxin (2.3 $\mu$ M + $\beta$ = 29.7 $\mu$ M), picrotoxinin (0.41 $\mu$ M), picrotin (13.1 $\mu$ M), ginkgolide B (3.7-11.4 $\mu$ M + $\beta$ = 0.14-0.8 $\mu$ M)	picrotoxin (+ $\beta$ weakens block), picrotoxinin (0.43 $\mu$ M + $\beta$ = 8.9 $\mu$ M), picrotin (6.0 $\mu$ M + $\beta$ = 24 $\mu$ M), ginkgolide B (1.8 $\mu$ M + $\beta$ = 0.55 $\mu$ M)
Probes	[ <sup>3</sup> H]strychnine	[ <sup>3</sup> H]strychnine	[ <sup>3</sup> H]strychnine
Functional characteristics	$\gamma$ = 86 pS (main state) (+ $\beta$ = 44 pS)	$\gamma$ = 111 pS (main state) (+ $\beta$ = 54 pS)	$\gamma$ = 105 pS (main state) (+ $\beta$ = 48)

Data in the table refer to homo-oligomeric assemblies of the  $\alpha$ -subunit, significant changes introduced by co-expression of the  $\beta 1$  subunit are indicated in parenthesis. Not all glycine receptor ligands are listed within the table, but some that may be useful in distinguishing between glycine receptor isoforms are indicated (see Lynch (2009a) for a more comprehensive listing). Pregnenolone sulphate, tropisetron and colchicine, for example, although not selective antagonists of glycine receptors, are included for this purpose. Strychnine is a potent and selective competitive glycine receptor antagonist with affinities in the range 5-15 nM. RUS135 demonstrates comparable potency, but additionally blocks GABA<sub>A</sub> receptors. There are conflicting reports concerning the ability of cannabinoids to inhibit (Lozovaya *et al.*, 2005), or potentiate and at high concentrations activate (Hejazi *et al.*, 2006; Yang *et al.*, 2008; Ahrens *et al.*, 2009; Demir *et al.*, 2009; Xiong *et al.*, 2011) glycine receptors. Nonetheless, cannabinoid analogues may hold promise in distinguishing between glycine receptor subtypes (Yang *et al.*, 2008). In addition, potentiation of glycine receptor activity by cannabinoids has been claimed to contribute to cannabis-induced analgesia relying on Ser296/307 ( $\alpha 1/\alpha 3$ ) in M3 (Xiong *et al.*, 2011). Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and GABA<sub>A</sub> receptors. Picrotoxin acts as an allosteric inhibitor that appears to bind within the pore, and shows strong selectivity towards homomeric receptors. While its components, picrotoxinin and picrotin, have equal potencies at  $\alpha 1$  receptors, their potencies at  $\alpha 2$  and  $\alpha 3$  receptors differ modestly and may allow some distinction between different receptor types (Yang *et al.*, 2007). Binding of picrotoxin within the pore has recently been demonstrated in the crystal structure of the related *C. elegans* GluCl Cys-loop receptor (Hibbs and Gouaux, 2011) In addition to the

compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (comprehensively reviewed by Laube *et al.*, 2002; Lynch, 2004; Webb and Lynch, 2007; Yevenes and Zeilhofer, 2011).  $Zn^{2+}$  acts through distinct binding sites of high- and low-affinity to allosterically enhance channel function at low (<10  $\mu M$ ) concentrations and inhibits responses at higher concentrations in a subunit selective manner (Miller *et al.*, 2005). The effect of  $Zn^{2+}$  is somewhat mimicked by  $Ni^{2+}$ . Endogenous  $Zn^{2+}$  is essential for normal glycinergic neurotransmission mediated by  $\alpha 1$  subunit-containing receptors (Hirzel *et al.*, 2006). Elevation of intracellular  $Ca^{2+}$  produces fast potentiation of glycine receptor-mediated responses. Dideoxyforskolin (4  $\mu M$ ) and tamoxifen (0.2–5  $\mu M$ ) both potentiate responses to low glycine concentrations (15  $\mu M$ ), but act as inhibitors at higher glycine concentrations (100  $\mu M$ ). Additional modulatory agents that enhance glycine receptor function include inhalational, and several intravenous general anaesthetics (*e.g.* minaxolone, propofol and pentobarbitone) and certain neurosteroids. Ethanol and higher order *n*-alcohols also enhance glycine receptor function although whether this occurs by a direct allosteric action at the receptor (Mascia *et al.*, 2000), or through G-protein  $\beta\gamma$  subunits (Yevenes *et al.*, 2010) is debated. Recent crystal structures of the bacterial homologue, GLIC, have identified transmembrane binding pockets for both anaesthetics (Nury *et al.*, 2011) and alcohols (Howard *et al.*, 2011). Solvents inhaled as drugs of abuse (*e.g.* toluene, 1-1-1-trichloroethane) may act at sites that overlap with those recognising alcohols and volatile anaesthetics to produce potentiation of glycine receptor function. The function of glycine receptors formed as homomeric complexes of  $\alpha 1$  or  $\alpha 2$  subunits, or hetero-oligomers of  $\alpha 1/\beta$  or  $\alpha 2/\beta$  subunits, is differentially affected by the 5-HT<sub>3</sub> receptor antagonist tropisetron (ICS 205-930) which may evoke potentiation (which may occur within the femtomolar range at the homomeric glycine  $\alpha 1$  receptor), or inhibition, depending upon the subunit composition of the receptor and the concentrations of the modulator and glycine employed. Potentiation and inhibition by tropeines involves different binding modes (Maksay *et al.*, 2009). Additional tropeines, including atropine, modulate glycine receptor activity.

**Abbreviations:** DCKA, dichlorokynurenic acid, HU210, (6aR,10aR)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol; HU308, [(1R,2R,5R)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl]-6,6-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]methanol; PMBA, 3-[2'-phosphonomethyl[1,1'-biphenyl]-3-yl]alanine; RU5135, 3 $\alpha$ -hydroxy-16-imino-5 $\beta$ -17-azaandrostan-11-one, WIN55212-2, (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

### Further Reading

- Betz H, Laube B (2006). Glycine receptors: recent insights into their structural organization and functional diversity. *J Neurochem* 97: 1600–1610.
- Bowery NG, Smart TG (2006). GABA and glycine as neurotransmitters: a brief history. *Br J Pharmacol* 47 (Suppl. 1): S109–S119.
- Callister RJ, Graham BA (2010). Early history of glycine receptor biology in mammalian spinal cord circuits. *Front Mol Neurosci* 3: 13.
- Cascio M (2004). Structure and function of the glycine receptor and related nicotinic receptors. *J Biol Chem* 279: 19383–19386.
- Colquhoun D, Sivilotti LG (2004). Function and structure in glycine receptors and some of their relatives. *Trends Neurosci* 27: 337–344.
- Dumoulin A, Triller A, Kneussel M (2010). Cellular transport and membrane dynamics of the glycine receptor. *Front Mol Neurosci* 2: 28.
- Gilbert DF, Islam R, Lynagh T, Lynch JW, Webb TI (2009). High Throughput Techniques for Discovering New Glycine Receptor Modulators and their Binding Sites. *Front Mol Neurosci* 2: 17.
- Harvey RJ, Topf M, Harvey K, Rees MI (2008). The genetics of hyperekplexia: more than startle! *Trends Genet* 24: 439–447.
- Harvey VL, Caley A, Müller UC, Harvey RJ, Dickenson AH (2009). A selective role for  $\alpha 3$  subunit glycine receptors in inflammatory pain. *Front Mol Neurosci* 2: 14.
- Hernandes MS, Troncone LR (2009). Glycine as a neurotransmitter in the forebrain: a short review. *J Neural Transm* 116: 1551–1560.
- Kirsch J (2006). Glycinergic transmission. *Cell Tissue Res* 326, 535–540.
- Kneussel M, Loeblich S (2007). Trafficking and synaptic anchoring of ionotropic inhibitory neurotransmitter receptors. *Biol Cell* 99: 297–309.
- Laube B, Maksay G, Schemm R, Betz H (2002). Modulation of glycine receptor function: a novel approach for therapeutic intervention at inhibitory synapses. *Trends Pharmacol Sci* 23: 519–527.
- Legendre P (2001). The glycinergic inhibitory synapse *Cell Mol Life Sci* 58: 760–793.
- Lewis T M, Schofield PR (1999). Structure-function relationships for the human glycine receptor: insights from hyperekplexia mutations. *Ann NY Acad Sci* 868: 681–684.
- Lobo IA, Harris RA (2005). Sites of alcohol and volatile anesthetic action on glycine receptors. *Int Rev Neurobiol* 65: 53–87.
- Lynch JW (2004). Molecular structure and function of the glycine receptor chloride channel. *Physiol Rev* 84: 1051–1095.
- Lynch JW (2009a). Glycine receptors, introductory chapter. IUPHAR database (IUPHAR-DB), <http://www.iuphar-db.org/IC/FamilyIntroduction> Forward?familyId=9
- Lynch JW (2009b) Native glycine receptor subtypes and their physiological roles. *Neuropharmacology* 56: 303–309.
- Lynch JW, Callister RJ.(2006). Glycine receptors: a new therapeutic target in pain pathways. *Curr Opin Investig Drugs* 7: 48–53.
- Moss SJ, Smart TG (2001). Constructing inhibitory synapses. *Nature Neurosci Rev* 2: 240–250.
- Perkins DI, Trudell JR, Crawford DK, Alkana RL, Davies DL (2010). Molecular targets and mechanisms for ethanol action in glycine receptors. *Pharmacol Ther* 127: 53–65.
- Sivilotti LG (2010). What single-channel analysis tells us of the activation mechanism of ligand-gated channels: the case of the glycine receptor. *J Physiol* 588: 45–58.
- Webb TI, Lynch JW (2007). Molecular pharmacology of the glycine receptor chloride channel. *Curr Pharm Des* 13: 2350–2367.
- Xu TL, Gong N (2010). Glycine and glycine receptor signaling in hippocampal neurons: diversity, function and regulation. *Prog Neurobiol* 91: 349–361.
- Yevenes GE, Zeilhofer HU (2011). Allosteric modulation of glycine receptors. *Br J Pharmacol* 164: 224–236.

### References

- Ahrens J *et al.* (2009). *Pharmacology* 83: 217–222.
- Demir R *et al.*(2009). *Pharmacology* 83: 270–274.
- Eichler SA *et al.* (2008). *J Cell Mol Biol Med* 12: 2848–2866.
- Fucile S *et al.* (2000). *Neuron* 28: 571–583.
- Grudzinska J *et al.* (2005). *Neuron* 45: 727–739.
- Hejazi N *et al.* (2006). *Mol Pharmacol* 69: 991–997.
- Hibbs RE, Gouaux E (2011). *Nature* 474: 54–60.
- Hirzel K *et al.* (2006). *Neuron* 52: 679–690.
- Howard RJ *et al.* (2011). *Proc Natl Acad Sci U S A* 108: 12149–12154.
- Lozovaya N *et al.* (2005). *J Neurosci* 25: 7499–7506.
- Maksay G *et al.* (2009). *J Neurochem* 109: 1725–1732.
- Mascia MP *et al.* (2000). *Proc Natl Acad Sci U S A* 97: 9305–9310.
- Meier JC *et al.* (2005). *Nat Neurosci* 8: 736–744.
- Miller PS *et al.* (2005). *J Physiol (Lond)* 566: 657–670.
- Nury H *et al.* (2011). *Nature* 469: 428–431.
- Oertel J *et al.* (2007). *J Biol Chem* 282: 2798–2807.

- Pitt SJ *et al.* (2008). *J Neurosci* **28**: 11454–11467.  
Xiong W *et al.* (2011). *Nat Chem Biol* **7**: 296–303.  
Yang Z *et al.* (2007). *J Neurochem* **103**: 580–589.  
Yang Z *et al.* (2008). *Biochem Pharmacol* **76**: 1014–1023.
- Yevenes GE *et al.* (2003). *Nat Neurosci* **6**: 819–824.  
Yevenes GE *et al.* (2006). *J Biol Chem* **281**: 39300–39307.  
Yevenes GE *et al.* (2010). *J Biol Chem* **285**: 30203–30213.

# P2X

**Overview:** P2X receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2X Receptors, Collingridge *et al.*, 2009; Khakh *et al.*, 2001) are ligand-gated ion channels with a trimeric topology (Jiang *et al.*, 2003; Kawate *et al.*, 2009; Nicke *et al.*, 1998), gating primarily Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup>, exceptionally Cl<sup>-</sup> with two putative TM domains, where the endogenous ligand is ATP. The Nomenclature Subcommittee has recommended that for P2X receptors, structural criteria should be the initial criteria for nomenclature where possible. The P2X receptor nomenclature recommended below reflects the newly accepted format for ligand-gated ion channels (see Collingridge *et al.*, 2009). Functional P2X receptors exist as polymeric transmitter-gated channels; the native receptors may occur as either homopolymers (e.g. P2X1 in smooth muscle) or heteropolymers (e.g. P2X2:P2X3 in the nodose ganglion and P2X1:P2X5 in mouse cortical astrocytes, Lalo *et al.*, 2008). P2X2, P2X4 and P2X7 receptors have been shown to form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes (see Surprenant and North, 2009). The hemi-channel pannexin-1 has been implicated in the pore formation induced by P2X7 (Pelegrin and Surprenant, 2009), but not P2X2 (Chaumont and Khakh, 2008), receptor activation.

Nomenclature	P2X1	P2X2	P2X3	P2X4
Ensembl ID	ENSG00000108405	ENSG00000187848	ENSG00000109991	ENSG00000135124
Potent agonists	L-βγ-meATP, αβ-meATP, BzATP	–	αβ-meATP, BzATP	–
Potent antagonists	TNP-ATP (pIC <sub>50</sub> 8.9, Virginio <i>et al.</i> , 1998), Ip <sub>s</sub> I (pIC <sub>50</sub> 8.5), NF023 (pIC <sub>50</sub> 6.7); NF449 (pIC <sub>50</sub> 6.3, Kassack <i>et al.</i> , 2004)	–	TNP-ATP (pIC <sub>50</sub> 8.9, Virginio <i>et al.</i> , 1998), AF353 (pIC <sub>50</sub> 8.0, Gever <i>et al.</i> , 2010), A317491 (7.5, Jarvis <i>et al.</i> , 2002), RO3 (pIC <sub>50</sub> 7.5, Ford <i>et al.</i> , 2006)	–

A317491 and RO3 also block the P2X2:P2X3 heteromultimer (Jarvis *et al.*, 2002; Ford *et al.*, 2006). NF449, A317491 and RO3 are more than 10-fold selective for P2X1 and P2X3 receptors, respectively.

Nomenclature	P2X5	P2X6	P2X7
Other names	–	–	P <sub>2z</sub>
Ensembl ID	ENSG00000083454	ENSG00000099957	ENSG00000089041
Potent antagonists	–	–	Brilliant Blue G (pIC <sub>50</sub> 8.0, Jiang <i>et al.</i> , 2000), A804598 (pIC <sub>50</sub> 8.0), A839977 (pIC <sub>50</sub> 7.7, Donnelly-Roberts and Jarvis, 2007; Donnelly-Roberts <i>et al.</i> , 2009, Honore <i>et al.</i> , 2009), decavanadate (pA <sub>2</sub> 7.4, Michel <i>et al.</i> , 2006a), KN62 (Gargett and Wiley, 1997), A740003 (pIC <sub>50</sub> 7.4), A438079 (pIC <sub>50</sub> 6.9, Donnelly-Roberts and Jarvis, 2007)

Agonists listed show selectivity within recombinant P2X receptors of *ca.* one order of magnitude. A804598, A839977, A740003 and A438079 are at least 10-fold selective for P2X7 receptors and show similar affinity across human and rodent receptors (Donnelly-Roberts and Jarvis, 2007, Donnelly-Roberts *et al.*, 2009; Honore *et al.*, 2009).

Several P2X receptors (particularly P2X1 and P2X3) may be inhibited by desensitisation using stable agonists (e.g. αβ-meATP); suramin and PPADS are non-selective antagonists at r & hP2X1–3,5 and hP2X4, but not rP2X4,6,7 (Buell *et al.*, 1996), and can also inhibit ATPase activity (Crack *et al.*, 1994). Ip<sub>s</sub>I is inactive at rP2X2, an antagonist at rP2X3 (pIC<sub>50</sub> 5.6) and enhances agonist responses at rP2X4 (King *et al.*, 1999). Antagonist potency of NF023 at recombinant P2X2, P2X3 and P2X5 is two orders of magnitude lower than that at P2X1 receptors (Soto *et al.*, 1999). The P2X7 receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN62 and chelerythrine (Shemon *et al.*, 2004), while the p38 MAP kinase inhibitor SB202190 and the cyclic imide AZ11645373 show a species-dependent non-competitive action (Donnelly-Roberts *et al.*, 2004; Michel *et al.*, 2006b; Stokes *et al.*, 2006; Michel, 2009). The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit P2X1 and P2X3 containing channels (King *et al.*, 2005). Some recombinant P2X receptors expressed to high density bind [<sup>35</sup>S]-ATPγS and [<sup>3</sup>H]-αβ-meATP, although the latter can also bind to 5'-nucleotidase (Michel *et al.*, 1995). [<sup>3</sup>H]-A317491 and [<sup>3</sup>H]-A804598 have been used as high affinity antagonist radioligands for P2X3 (and P2X2/3) and P2X7 receptors, respectively (Donnelly-Roberts *et al.*, 2009).

**Abbreviations:** αβ-meATP, αβ-methylene-adenosine 5'-triphosphate; βγ-meATP, βγ-methylene-adenosine 5'-triphosphate; A317491, 5-([3-phenoxybenzyl]((1S)-1,2,3,4-tetrahydro-1-naphthalenyl)amino)carbonyl)-1,2,4-benzenetricarboxylic acid; A438079, 3-(5-(2,3-dichlorophenyl)-1H-tetrazol-1-yl) methyl pyridine; A740003, (N-(1-([cyanoinimino](5-quinolinylamino) methyl)amino)-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide; A839977, 1-(2,3-dichlorophenyl)-N-[2-(pyridin-2-yloxy)benzyl]-1H-tetrazol-5-amine; A804598, (S)-1-(1-(4-bromophenyl)ethyl)-2-cyano-3-(quinoline-5-yl)guanidine; AF353, (5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine; ATPγS, adenosine 5'-(3-thio)triphosphate; AZ11645373, 3-[1-[4-(3-nitrophenyl)phenoxy]-4-pyridin-4-ylbutan-2-yl]-1,3-thiazolidine-2,4-dione; Ip<sub>s</sub>I, diinosine-5',5''-pentaphosphate; KN62, 1-(N,O-bis[5-isoquinolinesulphonyl]-N-methyl-L-tyrosyl)-4-phenylpiperazine; NF023, 8,8'-(carbonylbis[imino-3,1-phenylene carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid; NF449, 4,4',4''-(carbonylbis[imino-5,1,3-benzenetriyl-bis(carbonylimino)])tetrakisbenzene-1,3-disulfonic acid octasodium salt; PPADS, pyridoxal phosphate-6-azophenyl-2',4'-disulphonate; RO3, 5-(methyl[2-methylethyl-4,5-dimethoxyphenyl]-2,4-pyridinediamine); SB202190, 4-[4-(4-fluorophenyl)-5-pyridin-4-yl]-1H-imidazol-2-yl]phenol; TNP-ATP, 2',3'-O-(2,4,6-trinitrophenyl)-ATP

## Further Reading

Burnstock G (2008). Purinergic signalling and disorders of the central nervous system. *Nat Rev Drug Discov* 7: 575–590.  
 Browne LE, Jiang LH, North RA (2010). New structure enlivens interest in P2X receptors. *Trends Pharmacol Sci* 31: 229–237.

- Browne LE, Cao L, Broomhead HE, Bragg L, Wilkinson WJ, North RA (2011). P2X receptor channels show threefold symmetry in ionic charge selectivity and unitary conductance. *Nat Neurosci* **14**: 17–18.
- Collingridge GL, Olsen RW, Peters J, Spedding M (2009). A nomenclature for ligand-gated ion channels. *Neuropharmacology*, **56**: 2–5.
- Donnelly-Roberts D, McGaraughty S, Shieh CC, Honore P, Jarvis MF (2008). Painful purinergic receptors. *J Pharmacol Exp Ther* **324**: 409–415.
- Evans RJ (2010). Structural interpretation of P2X receptor mutagenesis studies on drug action. *Br J Pharmacol* **161**: 961–971.
- Guile SD, Alcaraz L, Birkinshaw TN, Bowers KC, Ebden MR, Furber M *et al.* (2009). Antagonists of the P2X<sub>7</sub> receptor. From lead identification to drug development. *J Med Chem* **52**: 3123–3141.
- Hu H, Hoylaerts MF (2010). The P2X<sub>1</sub> ion channel in platelet function. *Platelets* **21**: 153–166.
- Jarvis MF (2010). The neural-glia purinergic receptor ensemble in chronic pain states. *Trends Neurosci* **33**: 48–57.
- Jarvis MF, Khakh BS (2009). ATP-gated P2X cation-channels. *Neuropharmacology* **56**: 208–215.
- Khakh BS, Burnstock G, Kennedy C, King BF, North RA, Séguéla P *et al.* (2001). International Union of Pharmacology. XXIV. Current status of the nomenclature and properties of P2X receptors and their subunits. *Pharmacol Rev* **53**: 107–118.
- Pankratov Y, Lalo U, Krishtal OA, Verkhratsky A (2009). P2X receptors and synaptic plasticity. *Neuroscience* **158**: 137–148.
- Skaper SD, Debetto P, Giusti P (2010). The P2X<sub>7</sub> purinergic receptor: from physiology to neurological disorders. *FASEB J* **24**: 337–345.
- Surprenant A, North RA (2009). Signaling at Purinergic P2X receptors. *Annu Rev Physiol*, **71**: 333–359.
- Young MT (2010). P2X receptors: dawn of the post-structure era. *Trends Biochem Sci* **35**: 83–90.
- Zemkova H, Balik A, Jindrichova M, Vavra V (2008). Molecular structure of purinergic P2X receptors and their expression in the hypothalamus and pituitary. *Physiol Res* **57** (Suppl. 3): S23–S38.

## References

- Buell G *et al.* (1996). *EMBO J* **15**: 55–62.
- Chaumont S, Khakh BS (2008). *Proc Natl Acad Sci U S A*, **105**: 12063–12068.
- Crack BE *et al.* (1994). *Br J Pharmacol* **113**: 1432–1438.
- Donnelly-Roberts DL *et al.* (2004). *J Pharmacol Exp Ther* **308**: 1053–1061.
- Donnelly-Roberts DL *et al.* (2009). *Br J Pharmacol*, **157**: 1203–1214.
- Donnelly-Roberts DL, Jarvis MF (2007). *Br J Pharmacol* **151**: 571–579.
- Ford APDW *et al.* (2006). *Br J Pharmacol* **147**: S132–S143.
- Gargett CE, Wiley JS (1997). *Br J Pharmacol* **120**: 1483–1490.
- Gever JR *et al.* (2010). *Br J Pharmacol* **160**: 1387–1398.
- Honore P *et al.*, (2009). *Behav Brain Res* **204**: 77–81.
- Jarvis MF *et al.* (2002). *Proc Natl Acad Sci USA* **99**: 17179–17184.
- Jiang LH *et al.* (2000). *Mol Pharmacol* **58**: 82–88.
- Jiang LH *et al.* (2003). *J Neurosci* **23**: 8903–8910.
- Kassack MU *et al.* (2004). *Eur J Med Chem* **39**: 345–357.
- Kawate T *et al.* (2009). *Nature*, **460**: 592–598.
- King BF *et al.* (1999). *Br J Pharmacol* **128**: 981–988.
- King BF *et al.* (2005). *Br J Pharmacol* **145**: 313–322.
- Lalo U *et al.* (2008). *J Neurosci*, **28**: 5473–5480.
- Michel AD (2009). *Br J Pharmacol*, **156**: 1312–1325.
- Michel AD *et al.* (1995). *Br J Pharmacol* **115**: 767–774.
- Michel AD *et al.* (2006a). *Eur J Pharmacol* **534**: 19–29.
- Michel AD *et al.* (2006b). *Br J Pharmacol* **149**: 948–957.
- Nicke A *et al.* (1998). *EMBO J* **17**: 3016–3028.
- Pelegrin P, Surprenant A (2009). *Purinergic Signal* **5**: 129–137.
- Shemon AN *et al.* (2004). *Br J Pharmacol* **142**: 1015–1019.
- Soto F *et al.* (1999). *Neuropharmacology* **38**: 141–149.
- Stokes L *et al.* (2006). *Br J Pharmacol*, **149**: 880–887.
- Virginio C *et al.* (1998). *Mol Pharmacol* **53**: 969–973.



# ZAC (Zinc-activated channel)

**Overview:** The zinc-activated channel [ZAC, nomenclature as agreed by the NC-IUPHAR Subcommittee for the zinc activated channel (Hales and Peters (2010))] is a member of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT<sub>3</sub>, GABA<sub>A</sub> and strychnine-sensitive glycine receptors (Davies *et al.*, 2003; Houtani *et al.*, 2005). The channel is likely to exist as a homopentamer of 4TM subunits that form an intrinsic cation selective channel displaying constitutive activity that can be blocked by (+)-tubocurarine (Davies *et al.*, 2003). ZAC is present in the human, chimpanzee, dog, cow and opossum genomes, but is functionally absent from mouse, or rat, genomes (Davies *et al.*, 2003; Houtani *et al.*, 2005).

Nomenclature	ZAC
Other names	L2
Ensembl ID	ENSG00000186919
Selective agonists (pEC <sub>50</sub> )	Zn <sup>2+</sup> (3.3 )
Selective antagonists (pIC <sub>50</sub> )	(+)-Tubocurarine (5.2)
Functional characteristics	Outwardly rectifying current (both constitutive and evoked by Zn <sup>2+</sup> )

Although tabulated as an antagonist, it is possible that (+)-tubocurarine acts as a channel blocker.

## References

- Davies PA *et al.* (2003). *J Biol Chem* **278**: 712–717.  
Hales TG, Peters JA (2010). ZAC. IUPHAR database (IUPHAR-DB), <http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=587>  
Houtani T *et al.* (2005). *Biochem Biophys Res Commun* **335**: 277–285.



# ION CHANNELS

**Overview:** Ion channels are pore-forming proteins that allow the flow of ions across membranes, either plasma membranes or the membranes of intracellular organelles (Hille, 2001). Many ion channels (such as most Na, K Ca and some Cl channels) are gated by voltage but others (such as certain K and Cl channels, TRP channels, ryanodine receptors and IP<sub>3</sub> receptors) are relatively voltage-insensitive and are gated by second messengers and other intracellular and/or extracellular mediators. As such, there is some blurring of the boundaries between 'ion channels' and 'ligand-gated channels' which are compiled separately in this guide.

Resolution of ion channel structures, beginning with K channels (Doyle *et al.*, 1998) then Cl channels (Dutzler *et al.*, 2002) and most recently Na channels (Payandeh *et al.*, 2011) has greatly improved understanding of the structural basis behind ion channel function. Many ion channels (e.g., K, Na, Ca, HCN and TRP channels) share several structural similarities. These channels are thought to have evolved from a common ancestor and have been classified together as the 'voltage-gated-like (VGL) ion channel chanome' (see Yu *et al.*, 2005). Other ion channels, however, such as Cl channels, aquaporins and connexins, have completely different structural properties to the VGL channels, having evolved quite separately.

Currently, ion channels (including ligand-gated ion channels) represent the second largest target for existing drugs after G protein-coupled receptors (Overington *et al.*, 2006). However, the advent of novel, faster screening techniques for compounds acting on ion channels (Dunlop *et al.*, 2008) suggests that these proteins represent promising targets for the development of additional, novel therapeutic agents in the near future.

## Further Reading

- Doyle D, Morais Cabral J, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait B, MacKinnon R (1998). The structure of the potassium channel: molecular basis of potassium conduction and selectivity. *Science* **280**: 69–77.
- Dunlop J, Bowlby M, Peri R, Vasilyev D, Arias R (2008). High-throughput electrophysiology: an emerging paradigm for ion channel screening and physiology. *Nat Rev Drug Discov* **7**: 358–368.
- Dutzler R, Campbell EB, Cadene M, Chait B, MacKinnon R (2002). X-ray structure of a ClC chloride channel at 3.0Å reveals the molecular basis of ion selectivity. *Nature* **415**: 287–294.
- Hille B (2001). *Ion Channel of Excitable Membranes*. 3rd edn. Sinauer Associates: Sunderland MA.
- Overington JP, Al-Lazikani B, Hopkins AL (2006). How many drug targets are there? *Nat Rev Drug Discov* **5**: 993–996.
- Payandeh J, Scheuer T, Zheng N, Catterall WA (2011). The crystal structure of a voltage-gated sodium channel. *Nature* **475**: 353–358.
- Yu FH, Yarov-Yarovoy V, Gutman GA, Catterall WA (2005). Overview of molecular relationships in the voltage-gated ion channel superfamily. *Pharmacol Rev* **57**: 387–295.

# Acid-sensing (proton-gated) ion channels (ASICs)

**Overview:** Acid-sensing ion channels (ASICs, provisional nomenclature; see Wemmie *et al.*, 2006; Lingueglia, 2007) are members of a Na<sup>+</sup> channel superfamily that includes the epithelial Na<sup>+</sup> channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabditis elegans*, channels in *Drosophila melanogaster* and 'orphan' channels that include BLINaC (Sakai *et al.*, 1999) and INaC (Schaefer *et al.* 2000). ASIC subunits contain two TM domains and assemble as homo- or hetero-trimers (Jasti *et al.*, 2007; Gonzales *et al.*, 2009) to form proton-gated, voltage-insensitive, Na<sup>+</sup> permeable, channels (reviewed by Gründer and Chen (2010)). Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASIC $\alpha$ , BNaC2 $\alpha$ ) (Waldmann *et al.* 1997a), ASIC1b (ASIC $\beta$ , BNaC2 $\beta$ ) (Chen *et al.*, 1998) and ASIC1b2 (ASIC $\beta$ 2) (Ugawa *et al.*, 2001); note that ASIC1a is also permeable to Ca<sup>2+</sup>] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1 $\alpha$ , BNC1a) (Price *et al.*, 1996; Waldmann *et al.*, 1996; Garcia-Anoveros *et al.*, 1997) and ASIC2b (MDEG2, BNaC1 $\beta$ ); (Lingueglia *et al.*, 1997)] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H<sup>+</sup>-gated currents. A third member, ASIC3 (DRASIC, TNaC1) (Waldmann *et al.*, 1997b), has been identified. A fourth mammalian member of the family (ASIC4/SPASIC) does not support a proton-gated channel in heterologous expression systems and is reported to down regulate the expression of ASIC1a and ASIC3 (Akopian *et al.* 2000; Grunder *et al.*, 2000; Donier *et al.*, 2008). ASIC channels are primarily expressed in central and peripheral neurons including nociceptors where they participate in neuronal sensitivity to acidosis. They have also been detected in taste receptor cells (ASIC1-3), photoreceptors and retinal cells (ASIC1-3), cochlear hair cells (ASIC1b), testis (hASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC1a and -3), urothelial cells, adipose cells (ASIC3), vascular smooth muscle cells (ASIC1-3), immune cells (ASIC1,-3 and -4) and bone (ASIC1-3). The activation of ASIC1a within the central nervous system contributes to neuronal injury caused by focal ischemia (Xiong *et al.*, 2007) and to axonal degeneration in autoimmune inflammation in a mouse model of multiple sclerosis (Friese *et al.*, 2007). However, activation of ASIC1a can terminate seizures (Ziemann *et al.*, 2008). Peripheral ASIC3-containing channels play a role in post-operative pain (Deval *et al.*, 2011). Further proposed roles for centrally and peripherally located ASICs are reviewed in Wemmie *et al.* (2006) and Lingueglia (2007). The relationship of the cloned ASICs to endogenously expressed proton-gated ion channels is becoming established (Escoubas *et al.*, 2000; Sutherland *et al.*, 2001; Wemmie *et al.*, 2002, 2003, 2006; Diochot *et al.*, 2004, 2007; Lingueglia *et al.*, 2006; Lingueglia, 2007; Hattori *et al.*, 2009). Heterologously expressed heteromultimers form ion channels with altered kinetics, ion selectivity and sensitivity to blockers that resemble some of the native proton activated currents recorded from neurones (Lingueglia *et al.*, 1997; Babinski *et al.*, 2000, Escoubas *et al.*, 2000, Baron *et al.*, 2008).

Nomenclature	ASIC1	ASIC2	ASIC3
Other names	ASIC; BNaC2	BNC1; BNaC1; MDEG	DRASIC, TNaC1
Ensembl ID	ENSG00000110881	ENSG00000108684	ENSG00000213199
Endogenous activators	Extracellular H <sup>+</sup> (ASIC1a, pEC <sub>50</sub> ~ 6.2–6.8; ASIC1b, pEC <sub>50</sub> ~ 5.1–6.2)	Extracellular H <sup>+</sup> (pEC <sub>50</sub> ~ 4.1–5.0)	Extracellular H <sup>+</sup> (transient component pEC <sub>50</sub> ~ 6.2–6.7) (sustained component pEC <sub>50</sub> ~ 3.5–4.3), agmatine (EC <sub>50</sub> ~ 9.8 mM @ pH 7.4, aracaine (EC <sub>50</sub> ~ 1.2 mM @ pH 7.4), GMQ (largely non-desensitizing; pEC <sub>50</sub> ~ 3.0 @ pH 7.4)
Blockers (IC <sub>50</sub> )	ASIC1a: Psalmotoxin 1 (PcTx1) (0.9 nM), Zn <sup>2+</sup> (~7 nM), A-317567 (~2 μM), Pb <sup>2+</sup> (~4 μM), Ni <sup>2+</sup> (~0.6 mM), amiloride (10 μM), EIPA, benzamil (10 μM), nafamostat (~13 μM), diarylamidines (~3 μM), ibuprofen/ flurbiprofen (350 μM) ASIC1b: Amiloride (21–23 μM); Pb <sup>2+</sup> (~1.5 μM), diarylamidines	Amiloride (28 μM), A-317567 (~30 μM), nafamostat (~70 μM), Cd <sup>2+</sup> (~1 mM), diarylamidines	APETx2 (63 nM) (transient component only), nafamostat (2.5 ~ μM) (transient component), amiloride (16–63 μM) (transient component only – sustained component enhanced by 200 μM amiloride @ pH 4), A-317567 (~10 μM), aspirin/diclofenac (92 μM – sustained component), salicylic acid (260 μM – sustained component), Gd <sup>3+</sup> (40 μM), Zn <sup>2+</sup> (61 μM), diarylamidines
Functional characteristics	ASIC1a: $\gamma$ ~14pS; P <sub>Na</sub> /P <sub>K</sub> = 5–13, P <sub>Na</sub> /P <sub>Ca</sub> = 2.5; rapid activation rate (5.8–13.7 ms) rapid inactivation rate (1.2–4 s) @ pH 6.0, slow recovery (5.3–13 s) @ pH 7.4 ASIC1b: $\gamma$ ~ 19 pS; P <sub>Na</sub> /P <sub>K</sub> = 14.0; P <sub>Na</sub> >> P <sub>Ca</sub> ; rapid activation rate (9.9 ms); rapid inactivation rate (0.9–1.7 s) @ pH 6.0, slow recovery (4.4–7.7 s) @ pH 7.4	$\gamma$ ~10.4–13.4 pS; P <sub>Na</sub> /P <sub>K</sub> = 10, P <sub>Na</sub> /P <sub>Ca</sub> = 20; rapid activation rate, moderate inactivation rate (3.3–5.5 s) @ pH 5	$\gamma$ ~ 13–15 pS; biphasic response consisting of rapidly inactivating transient and sustained components; very rapid activation (<5 ms) and inactivation (0.4 s); fast recovery (0.4–0.6 s) @ pH 7.4, transient component partially inactivated at pH 7.2
Probes	[ <sup>125</sup> I]-PcTx1 (ASIC1a K <sub>D</sub> = 213 pM)	–	–

Psalmotoxin 1 (PcTx1) inhibits ASIC1a by modifying activation and desensitization by H<sup>+</sup>, but promotes ASIC1b opening. PcTx1 has little effect upon ASIC2a, ASIC3, or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 (Escoubas *et al.*, 2000; Diochot *et al.*, 2007) but does block ASIC1a expressed as a heteromultimer with ASIC2b (Sherwood *et al.*, 2011). Spermine, which apparently competes with PcTx1 for binding to ASIC1a, selectively enhances the function of the channel (Duan *et al.*, 2011). Blockade of ASIC1a by PcTx1 activates the endogenous enkephalin pathway and has very potent analgesic effects in rodents (Mazzuca *et al.*, 2007). APETx2 most potently blocks homomeric ASIC3 channels, but also ASIC2b+ASIC3, ASIC1b+ASIC3, and ASIC1a+ASIC3 heteromeric channels with IC<sub>50</sub> values of 117 nM, 900 nM and 2 μM, respectively. APETx2 has no effect on ASIC1a, ASIC1b, ASIC2a, or ASIC2a+ASIC3 (Diochot *et al.*, 2004; 2007). IC<sub>50</sub> values for A-317567 are inferred from blockade of ASIC channels native to dorsal root ganglion neurones (Dube *et al.*, 2005). The pEC<sub>50</sub> values for proton activation of ASIC channels are influenced by numerous factors including extracellular di- and poly-valent ions, Zn<sup>2+</sup>, protein kinase C and serine proteases (reviewed by Lingueglia *et al.*, 2006). Rapid acidification is required for activation of ASIC1 and ASIC3 due to fast inactivation/desensitization.

pEC<sub>50</sub> values for H<sup>+</sup>-activation of either transient, or sustained, currents mediated by ASIC3 vary in the literature and may reflect species and/or methodological differences (Waldmann *et al.*, 1997b; de Weille *et al.*, 1998; Babinski *et al.*, 1999). The transient and sustained current components mediated by rASIC3 are selective for Na<sup>+</sup> (Waldmann *et al.*, 1997b); for hASIC3 the transient component is Na<sup>+</sup> selective (P<sub>Na</sub>/P<sub>K</sub> > 10) whereas the sustained current appears non-selective (P<sub>Na</sub>/P<sub>K</sub> = 1.6) (de Weille *et al.*, 1998; Babinski *et al.*, 1999). The reducing agents dithiothreitol (DTT) and glutathione (GSH) increase ASIC1a currents expressed in CHO cells and ASIC-like currents in sensory ganglia and central neurons (Andrey *et al.*, 2005; Chu *et al.*, 2006) whereas oxidation, through the formation of intersubunit disulphide bonds, reduces currents mediated by ASIC1a (Zha *et al.*, 2009). ASIC1a is also irreversibly modulated by extracellular serine proteases, such as trypsin, through proteolytic cleavage (Vukicevic *et al.*, 2006). Non-steroidal anti-inflammatory drugs (NSAIDs) are direct blockers of ASIC currents at therapeutic concentrations (reviewed by Voilley, 2004). Extracellular Zn<sup>2+</sup> potentiates proton activation of homomeric and heteromeric channels incorporating ASIC2a, but not homomeric ASIC1a or ASIC3 channels (Baron *et al.*, 2001). However, removal of contaminating Zn<sup>2+</sup> by chelation reveals a high affinity block of homomeric ASIC1a and heteromeric ASIC1a+ASIC2 channels by Zn<sup>2+</sup> indicating complex biphasic actions of the divalent (Chu *et al.*, 2004). Nitric oxide potentiates submaximal currents activated by H<sup>+</sup> mediated by ASIC1a, ASIC1b, ASIC2a and ASIC3 (Cadiou *et al.*, 2007). Ammonium activates ASIC channels (most likely ASIC1a) in midbrain dopaminergic neurones: that may be relevant to neuronal disorders associated with hyperammonemia (Pidoplichko and Dani, 2006). The positive modulation of homomeric, heteromeric and native ASIC channels by the peptide FMRFamide and related substances, such as neuropeptides FF and SF, is reviewed in detail by Lingueglia *et al.* (2006). Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes, enhance ASIC currents (Mamet *et al.*, 2002), and in the case of arachidonic acid directly activate the channel (Smith *et al.*, 2007; Deval *et al.*, 2008). The sustained current component mediated by ASIC3 is potentiated by hypertonic solutions in a manner that is synergistic with the effect of arachidonic acid (Deval *et al.*, 2008). Selective activation of ASIC3 by GMQ at a site separate from the proton binding site is potentiated by mild acidosis and reduced extracellular Ca<sup>2+</sup> (Yu *et al.*, 2010).

**Abbreviations:** A-317567 C-[6-[2-(1-Isopropyl-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-cyclopropyl]-naphthalen-2-yl]-methanedi-amine, EIPA, ethylisopropylamiloride; GMQ, 2-guanidine-4-methylquinazoline; FMRFamide, Phe-Met-Arg-Phe-amide; Neuropeptide FF, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-amide; Neuropeptide SF, Ser-Leu-Ala-Pro-Gln-Arg-Phe-amide

### Further Reading

- Chen X, Orser BA, MacDonald JF (2010). Design and screening of ASIC inhibitors based on aromatic diamidines for combating neurological disorders. *Eur J Pharmacol* 648: 15–23.
- Deval E, Gasull X, Noël J, Salinas M, Baron A, Diochot S, Lingueglia E (2010). Acid-sensing ion channels (ASICs): pharmacology and implication in pain. *Pharmacol Ther* 128: 549–558.
- Diochot S, Salinas M, Baron A, Escoubas P, Lazdunski M (2007). Peptides inhibitors of acid-sensing ion channels. *Toxicol* 49: 271–284.
- Dubé GR, Elagoz A, Mangat H (2009). Acid sensing ion channels and acid nociception. *Curr Pharm Des* 15: 1750–1766.
- Gründer S, Chen X (2010). Structure, function, and pharmacology of acid-sensing ion channels (ASICs): focus on ASIC1a. *Int J Physiol Pathophysiol Pharmacol* 2: 73–94.
- Lingueglia E (2007). Acid-sensing ion channels in sensory perception. *J Biol Chem* 282: 17325–17329.
- Lingueglia E, Deval E, Lazdunski M (2006). FMRFamide-gated sodium channel and ASIC channels: a new class of ionotropic receptors for FMRFamide and related peptides. *Peptides* 27: 1138–1152.
- Kress M, Waldmann R (2006). Acid sensing ionic channels. *Curr Top Membr* 57: 241–276.
- Krishtal O (2003). The ASICs: signaling molecules? Modulators? *Trends Neurosci* 26: 477–483.
- Noel, J., Salinas, M., Baron, A., Diochot, S., Deval, E., Lingueglia, E. (2010). Current perspectives on acid-sensing ion channels: new advances and therapeutic implications. *Expert Rev Clin Pharmacol* 3, 331–346.
- Reeh PW, Kress M (2001). Molecular physiology of proton transduction in nociceptors. *Curr Opin Pharmacol* 1: 45–51.
- Sluka KA, Winter OC, Wemmie JA (2009). Acid-sensing ion channels: a new target for pain and CNS diseases. *Curr Opin Drug Discov Devel* 12: 693–704.
- Voilley N (2004). Acid-sensing ion channels (ASICs): new targets for the analgesic effects of non-steroid anti-inflammatory drugs (NSAIDs). *Curr Drug Targets Inflamm Allerg* 3: 71–79.
- Waldmann R, Lazdunski M (1998). H<sup>+</sup>-gated cation channels: neuronal acid sensors in the NaC/DEG family of ion channels *Curr Opin Neurobiol* 8: 418–424.
- Waldmann R (2001). Proton-gated cation channels-neuronal acid sensors in the central and peripheral nervous system. *Adv Exp Med Biol* 502: 293–304.
- Wemmie JA, Price MP, Welsh MJ (2006). Acid-sensing ion channels: advances, questions and therapeutic opportunities. *Trends Neurosci* 29: 578–586.
- Xiong ZG, Chu XP, Simon RP (2007). Acid sensing ion channels—novel therapeutic targets for ischemic brain injury. *Front Biosci* 12: 1376–1386.
- Xiong ZG, Pignataro G, Li M, Chang SY, Simon RP (2008). Acid-sensing ion channels as pharmacological targets for neurodegenerative diseases. *Curr Opin Pharmacol* 8: 25–32.
- Xu TL, Duan B (2009). Calcium-permeable acid-sensing ion channel in nociceptive plasticity: a new target for pain control. *Prog Neurobiol* 87: 171–180.
- Xu TL, Xiong ZG (2007). Dynamic regulation of acid-sensing ion channels by extracellular and intracellular modulators. *Curr Med Chem* 14:1753–1763.

### References

- Akopian AN *et al.* (2000). *Neuroreport* 11: 2217–2222.
- Andrey F *et al.* (2005). *Biochim Biophys Acta* 1745: 1–6.
- Babinski K *et al.* (1999). *J Neurochem* 72: 51–57.
- Babinski K *et al.* (2000). *J Biol Chem* 37: 28519–28525.
- Baron A *et al.* (2001). *J Biol Chem* 276: 35361–35367.
- Baron A *et al.* (2008). *J Neurosci* 28:1498–1508.
- Cadiou H *et al.* (2007). *J Neurosci* 27: 13251–13260.
- Chen C-C *et al.* (1998). *Proc Natl Acad Sci U S A* 95: 10240–10245.
- Chu X-P *et al.* (2004). *J Neurosci* 24: 8678–8689.
- Chu X-P *et al.* (2006). *J Neurosci* 26: 5329–5339.
- Deval E *et al.* (2008). *EMBO J* 27: 3047–3055.
- Deval E *et al.* (2011). *J Neurosci* 31: 6059–6066.
- Diochot S *et al.* (2004). *EMBO J* 23: 1516–1525.
- Donier E *et al.* (2008). *Eur J Neurosci* 28: 74–86.
- Duan B *et al.* (2011). *J Neurosci* 31: 2101–2112.
- Dube GR *et al.* (2005). *Pain* 117: 88–96.

- Escoubas P *et al.* (2000). *J Biol Chem* **275**: 25116–25121.
- Friese MA *et al.* (2007). *Nat Med* **13**: 1483–1489.
- Garcia-Anoveros J *et al.* (1997). *Proc Natl Acad Sci U S A* **94**: 1459–1464.
- Gonzales EB *et al.* (2009). *Nature* **460**: 599–604.
- Grunder S *et al.* (2000). *Neuroreport* **11**: 1607–1611.
- Hattori T *et al.* (2009). *Circ Res* **105**: 279–286.
- Jasti J *et al.* (2007). *Nature* **449**: 316–323.
- Lingueglia E *et al.* (1997). *J Biol Chem* **272**: 29778–29783.
- Mamet J *et al.* (2002). *J Neurosci* **22**: 10662–10670.
- Mazucca M *et al.* (2007). *Nat Neurosci* **10**: 943–945.
- Pidoplichko VI, Dani JA (2006). *Proc Natl Acad Sci U S A* **103**: 11376–11380.
- Price MP *et al.* (1996). *J Biol Chem* **271**: 7879–7882.
- Sakai H *et al.* (1999). *J Physiol (Lond)* **519**: 323–333.
- Schaefer L *et al.* (2000). *FEBS Lett* **471**: 205–210.
- Sherwood TW *et al.* (2011). *J Neurosci* **31**: 9723–9734.
- Smith ES *et al.* (2007). *Neuroscience* **145**: 686–698.
- Sutherland SP *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 711–716.
- Ugawa S *et al.* (2001). *Neuroreport* **12**: 2865–2869.
- Vukicevic M *et al.* (2006). *J Biol Chem* **281**: 714–722.
- Waldmann R *et al.* (1996). *J Biol Chem* **271**: 10433–10436.
- Waldmann R *et al.* (1997a). *Nature* **386**: 173–177.
- Waldmann R *et al.* (1997b). *J Biol Chem* **272**: 20975–20978.
- de Weille JR *et al.* (1998). *FEBS Lett* **433**: 257–260.
- Wemmie JA *et al.* (2002). *Neuron* **34**: 463–477.
- Wemmie JA *et al.* (2003). *J Neurosci* **23**: 5496–5502.
- Yu Y *et al.* (2010). *Neuron* **68**: 61–72.
- Zha XM *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 3573–3578.
- Ziemann AE *et al.* (2008). *Nat Neurosci* **11**: 816–822.

# Aquaporins

**Overview:** Aquaporins and aquaglyceroporins are membrane channels that allow the permeation of water and certain other small solutes across the cell membrane. Since the isolation and cloning of the first aquaporin (AQP1) (Preston *et al.*, 1992), 12 additional members of the family have been identified, although little is known about the functional properties of two of these (AQP11 (ENSG00000178301) and AQP12 (ENSG00000184945)). The other 11 aquaporins can be divided into two families (aquaporins and aquaglyceroporins) depending on whether they are permeable to glycerol (King *et al.*, 2004). One or more members of this family of proteins have been found to be expressed in almost all tissues of the body. Individual AQP subunits have six transmembrane domains with an inverted symmetry between the first three and last three domains (Castle, 2005). Functional AQPs exist as tetramers but, unusually, each subunit contains a separate pore, so each channel has four pores.

Nomenclature	AQP0	AQP1	AQP2	AQP3
Ensembl ID	ENSG00000135517	ENSG00000240583	ENSG00000167580	ENSG00000165272
Activators	–	cGMP	–	–
Inhibitors	Hg <sup>2+</sup>	Hg <sup>2+</sup> , TEA, Ag <sup>+</sup>	Hg <sup>2+</sup>	Hg <sup>2+</sup> , acid pH
Permeability	Water (low)	Water (high)	Water (high)	Water (high), glycerol

Nomenclature	AQP4	AQP5	AQP6	AQP7
Ensembl ID	ENSG00000171885	ENSG00000161798	ENSG00000086159	ENSG00000165269
Activators	–	–	Acid pH	–
Inhibitors	PKC activation	Hg <sup>2+</sup>	Hg <sup>2+</sup>	Hg <sup>2+</sup>
Permeability	Water (high)	Water (high)	Water (low), anions	Water (high), glycerol

Nomenclature	AQP8	AQP9	AQP10
Ensembl ID	ENSG00000103375	ENSG00000103569	ENSG00000143595
Activators	–	–	–
Inhibitors	Hg <sup>2+</sup>	Hg <sup>2+</sup> , phloretin	Hg <sup>2+</sup>
Permeability	Water (high)	Water (low), glycerol	Water (low), glycerol

AQP6 is an intracellular channel permeable to anions as well as water (Yasui *et al.* 1999).

## Further Reading

- Agre P (2006). The aquaporin water channels. *Proc Am Thoroc Soc* 3: 5–13.
- Agre P, King LS, Yasui M, Guggino WB, Ottersen OP, Fujiyoshi Y *et al.* (2002). Aquaporin water channels: from atomic structure to clinical medicine. *J Physiol* 542: 3–16.
- Amiry-Moghaddam M, Ottersen OP (2003). The molecular basis of water transport in the brain. *Nat Rev Neurosci* 4: 991–1001.
- Carbrey JM, Agre P (2009). Discovery of the aquaporins and development of the field. *Handb Exp Pharmacol* 190: 3–28.
- Castle NA (2005). Aquaporins as targets for drug discovery. *Drug Discov Today* 10: 485–493.
- De Groot BL, Grubmuller H (2005). The dynamics and energetics of water permeation and proton exclusion in aquaporins. *Curr Opin Struct Biol* 15: 176–183.
- Frigeri A, Nicchia GP, Svelto M (2007). Aquaporins as targets for drug discovery. *Curr Pharm Des* 13: 2421–2427.
- Ishibashi K, Hara S, Kondo S (2009). Aquaporin water channels in mammals. *Clin Exp Nephrol* 13: 107–117.
- Jeyaseelan K, Sreeramian S, Armugam A, Wintour EM (2006). Aquaporins: a promising target for drug development. *Expert Opin Ther Targets* 10: 889–909.
- Kimelberg HK (2004). Water homeostasis in the brain: basic concepts. *Neuroscience* 129: 851–860.
- King KL, Kozono D, Agre P (2004). From structure to disease: the evolving tale of aquaporin biology. *Nat Rev Mol Cell Biol* 5: 687–698.
- Rojek A, Praetorius J, Frokiaer J, Nielsen S, Fenton RA (2008). A current view of the mammalian aquaglyceroporins. *Annu Rev Physiol* 70: 301–327.
- Takeda T, Taguchi D (2009). Aquaporins as potential drug targets for Meniere's disease and its related diseases. *Handb Exp Pharmacol* 190: 17–184.
- Verkman AS (2009). Aquaporins: translating bench research to human disease. *J Exp Biol* 212: 1707–1715.
- Wang F, Feng XC, Li YM, Yang H, Ma TH (2006). Aquaporins as potential drug targets. *Acta Pharmacol Sin* 27: 395–401.

## References

- Preston GM *et al* (1992). *Science* 256: 385–387.
- Yasui M *et al* (1999). *Nature* 402: 184–187.

# Calcium (voltage-gated)

**Overview:** Calcium (Ca<sup>2+</sup>) channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for Ca<sup>2+</sup> channels was proposed by Ertel *et al.* (2000) and approved by the NC-IUPHAR subcommittee on Ca<sup>2+</sup> channels (Catterall *et al.*, 2005). Ca<sup>2+</sup> channels form hetero-oligomeric complexes. The  $\alpha 1$  subunit is pore-forming and provides the extracellular binding site(s) for practically all agonists and antagonists. The 10 cloned  $\alpha$ -subunits can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type, Ca<sub>v</sub>1.x) channels; (2) the high-voltage activated dihydropyridine-insensitive (Ca<sub>v</sub>2.x) channels and (3) the low-voltage-activated (T-type, Ca<sub>v</sub>3.x) channels. Each  $\alpha 1$  subunit has four homologous repeats (I–IV), each repeat having six transmembrane domains and a pore-forming region between transmembrane domains S5 and S6. Gating is thought to be associated with the membrane-spanning S4 segment, which contains highly conserved positive charges. Many of the  $\alpha 1$ -subunit genes give rise to alternatively spliced products. At least for high-voltage activated channels, it is likely that native channels comprise co-assemblies of  $\alpha 1$ ,  $\beta$  and  $\alpha 2$ – $\delta$  subunits. The  $\gamma$  subunits have not been proven to associate with channels other than  $\alpha 1$ s. The  $\alpha 2$ – $\delta 1$  and  $\alpha 2$ – $\delta 2$  subunits bind gabapentin and pregabalin.

Nomenclature	Ca <sub>v</sub> 1.1	Ca <sub>v</sub> 1.2	Ca <sub>v</sub> 1.3	Ca <sub>v</sub> 1.4	Ca <sub>v</sub> 2.1
Alternative names	L-type, $\alpha_{1S}$ , skeletal muscle L	L-type, $\alpha_{1C}$ , cardiac or smooth muscle L	L-type, $\alpha_{1D}$	L-type, $\alpha_{1F}$	P-type, Q-type, $\alpha_{1a}$
Ensembl ID	ENSG00000081248	ENSG00000151067	ENSG00000157388	ENSG00000102001	ENSG00000141837
Activators	(-)-(S)-BayK8644 SZ(+)-(S)-202-791 FPL64176	(-)-(S)-BayK8644 SZ(+)-(S)-202-791 FPL64176	(-)-(S)-BayK8644	(-)-(S)-BayK8644	
Blockers	dihydropyridine antagonists, e.g. nifedipine, diltiazem, verapamil, calciseptine	dihydropyridine antagonists, e.g. nifedipine diltiazem, verapamil, calciseptine	Less sensitive to dihydropyridine antagonists verapamil	Less sensitive to dihydropyridine antagonists	$\omega$ -Agatoxin IVA (P: IC <sub>50</sub> ~ 1 nM) (Q: IC <sub>50</sub> ~ 90 nM) $\omega$ -Agatoxin IVB, $\omega$ -Conotoxin, MVIIC
Functional characteristics	High voltage-activated, slow inactivation	High voltage-activated, slow inactivation (Ca <sup>2+</sup> dependent)	Low-moderate voltage-activated, slow inactivation (Ca <sup>2+</sup> dependent)	Moderate voltage-activated, slow inactivation (Ca <sup>2+</sup> independent)	Moderate voltage-activated, moderate inactivation

Nomenclature	Ca <sub>v</sub> 2.2	Ca <sub>v</sub> 2.3	Ca <sub>v</sub> 3.1	Ca <sub>v</sub> 3.2	Ca <sub>v</sub> 3.3
Alternative names	N-type, $\alpha_{1B}$	R-type, $\alpha_{1E}$	T-type, $\alpha_{1G}$	T-type, $\alpha_{1H}$	T-type, $\alpha_{1I}$
Ensembl ID	ENSG00000148408	ENSG00000198216	ENSG00000006283	ENSG00000196557	ENSG00000100346
Blockers	$\omega$ -Conotoxin GVIA, $\omega$ -Conotoxin MVIIC	SNX482 (may not be completely specific), high Ni <sup>2+</sup>	Mibefradil, low sens. to Ni <sup>2+</sup> , kurtoxin, SB-209712	Mibefradil, high sens. to Ni <sup>2+</sup> , kurtoxin, SB-209712	Mibefradil, low sens. to Ni <sup>2+</sup> , kurtoxin, SB-209712
Functional characteristics	High voltage-activated, moderate inactivation	Moderate voltage-activated, fast inactivation	Low voltage-activated, fast inactivation	Low voltage-activated, fast inactivation	Low voltage-activated, moderate inactivation

In many cell types, P and Q current components cannot be adequately separated and many researchers in the field have adopted the terminology 'P/Q-type' current when referring to either component. Ziconotide (a synthetic peptide equivalent to  $\omega$ -conotoxin) has been approved for the treatment of chronic pain (Williams *et al.*, 2008).

**Abbreviations:** FPL64176, 2,5-dimethyl-4-[2(phenylmethyl)benzoyl]-H-pyrrole-3-carboxylate; SB-209712, (1,6-bis{1-[4-(3-phenylpropyl)piperidinyl]}hexane); (-)-(S)-BAYK8664, (-)-(S)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate; SNX482, 41 amino acid peptide-(GVDKAGCRYMFGGCSVNDCCPRLGCHSLFSYCAWDLTFSD); SZ(+)-(S)-202-791, isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate

## Further Reading

- Bauer CS, Tran-Van-Minh A, Kadurin I, Dolphin AC (2010). A new look at calcium channel  $\alpha 2\delta$  subunits. *Curr Opin Neurobiol* 20: 563–571.
- Belardetti F, Zamponi GW (2008). Linking calcium-channel isoforms to potential therapies. *Curr Opin Investig Drugs* 9: 707–715.
- Buraei Z, Yang J (2010). The  $\beta$  subunit of voltage-gated Ca<sup>2+</sup> channels. *Physiol Rev* 90: 1461–1506.
- Catterall WA (2000). Structure and regulation of voltage-gated Ca<sup>2+</sup> channels. *Ann Rev Cell Dev Biol* 16: 521–555.
- Catterall WA (2011). Voltage-gated calcium channels. *Cold Spring Harb Perspect Biol* 3: a003947.
- Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J (2005). International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacol Rev* 57: 411–425.
- Catterall, WA, Dib-Hajj S, Meisler MH, Pietrobon D (2008). Inherited neuronal ion channelopathies: new windows on complex neurological diseases. *J Neurosci* 28: 11768–11777.
- Davies A, Hendrich J, Van Minh AT, Wratten J, Douglas L, Dolphin AC (2007). Functional biology of the alpha(2)delta subunits of voltage-gated calcium channels. *Trends Pharmacol Sci* 28: 220–228.
- Dolphin AC (2003). G protein modulation of voltage-gated calcium channels. *Pharmacol Rev* 55: 607–627.



- Dolphin AC (2009). Calcium channel diversity: multiple roles of calcium channel subunits. *Curr Opin Neurobiol* **19**: 237–244.
- Elmslie KS (2004). Calcium channel blockers in the treatment of disease. *J Neurosci Res* **75**: 733–741.
- Ertel EA, Campbell KP, Harpold MM, Hofmann F, Mori Y, Perez-Reyes E *et al.* (2000). Nomenclature of voltage-gated calcium channels. *Neuron* **25**: 533–535.
- Gao L (2010). An update on peptide drugs for voltage-gated calcium channels. *Recent Pat CNS Drug Discov* **5**: 14–22.
- Han TS, Teichert RW, Olivera BM, Bulaj G (2008). Conus venoms – a rich source of peptide-based therapeutics. *Curr Pharm Des* **14**: 2462–2479.
- Hofmann F, Lacinova L, Klugbauer N (1999). Voltage-dependent calcium channels; from structure to function. *Rev Physiol Biochem Pharmacol* **139**: 35–87.
- Kochegarov AA (2003). Pharmacological modulators of voltage-gated calcium channels and their therapeutic application. *Cell Calcium* **33**: 145–162.
- Lewis RJ, Garcia ML (2003). Therapeutic potential of venom peptides. *Nat Rev Drug Discov* **2**: 790–802.
- Lory P, Chemin J (2007). Towards the discovery of novel T-type calcium channel blockers. *Expert Opin Ther Targets* **11**: 717–722.
- Nelson MT, Todorovic SM, Perez-Reyes E (2006). The role of T-type calcium channels in epilepsy and pain. *Curr Pharm Des* **12**: 2189–2197.
- Perez-Reyes E (2003). Molecular physiology of low-voltage-activated T-type calcium channels. *Physiol Rev* **83**: 117–161.
- Pexton T, Moeller-Bertram T, Schilling JM, Wallace MS (2011). Targeting voltage-gated calcium channels for the treatment of neuropathic pain: a review of drug development. *Expert Opin Investig Drugs* **20**: 1277–1284.
- Taylor CP, Anelotti T, Fauman E (2007). Pharmacology and mechanism of action of pregabalin; the calcium channel alpha2-delta subunit as a target for antiepileptic drug discovery. *Epilepsy Res* **73**: 137–150.
- Terlau H, Olivera BM (2004). Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol Rev* **84**: 41–68.
- Triggler DJ (2006). L-type calcium channels. *Curr Pharm Des* **12**: 443–457.
- Triggler DJ (2007). Calcium channel antagonists: clinical uses – past, present and future. *Biochem Pharmacol* **74**: 1–9.
- Trimmer JS, Rhodes KJ (2004). Localisation of voltage-gated ion channels in mammalian brain. *Ann Rev Physiol* **66**: 477–519.
- Williams JA, Day M, Heavner JE (2008). Ziconotide: an update and review. *Expert Opin Pharmacother* **9**: 1575–1583.
- Yamamoto T, Takahara A (2009). Recent updates of N-type calcium channel blockers with therapeutic potential for neuropathic pain and stroke. *Curr Top Med Chem* **9**: 377–395.
- Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004**: re15.
- Zamponi GW, Lewis RJ, Todorovic SM, Arneric SP, Snutch TP (2009). Role of voltage-gated calcium channels in ascending pain pathways. *Brain Res Rev* **60**: 84–89.

# CatSper channels

**Overview:** CatSper channels (CatSper1-4; nomenclature as agreed by NC-IUPHAR, Clapham and Garbers, 2005) are putative 6TM, voltage-gated, calcium permeant channels that are presumed to assemble as a tetramer of  $\alpha$ -like subunits and mediate the current  $I_{\text{CatSper}}$ . In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca<sub>v</sub>) (Ren *et al.*, 2001). CatSper1 (Ren *et al.*, 2001), CatSper2 (Quill *et al.*, 2001) and CatSper3 and 4 (Lobley *et al.*, 2003; Lin *et al.*, 2005; Qi *et al.*, 2007), in common with a recently identified putative 2TM auxiliary CatSper $\beta$  protein (Liu *et al.*, 2007) and two putative 1TM associated CatSper $\gamma$  and CatSper $\delta$  proteins (Wang *et al.*, 2009; Chung *et al.*, 2011), are restricted to the testis and localised to the principle piece of sperm tail.

Nomenclature	CatSper1	CatSper2	CatSper3	CatSper4
Ensembl ID	ENSG00000175294	ENSG00000166762	ENSG00000152705	ENSG00000188782
Activators	Constitutively active, weakly facilitated by membrane depolarisation, strongly augmented by intracellular alkalinisation. In human, but not mouse, spermatozoa progesterone (EC <sub>50</sub> ~ 8 nM) also potentiates the CatSper current ( $I_{\text{CatSper}}$ ).	–	–	–
Blockers	Cd <sup>2+</sup> (200 $\mu$ M), Ni <sup>2+</sup> (300 $\mu$ M), ruthenium red (10 $\mu$ M), NNC55-0396 (2–10 $\mu$ M), HC-056456 (20 $\mu$ M), mibefradil (30 $\mu$ M)	–	–	–
Functional characteristics	Calcium selective ion channel (Ba <sup>2+</sup> >Ca <sup>2+</sup> >>Mg <sup>2+</sup> >>Na <sup>+</sup> ); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalinization shifts the voltage-dependence of activation towards negative potentials [ $V_{1/2}$ @ pH 6.0 = +87 mV (mouse); $V_{1/2}$ @ pH 7.5 = +11 mV (mouse) or pH 7.4 = + 85 mV (human)]	Required for $I_{\text{CatSper}}$	Required for $I_{\text{CatSper}}$	Required for $I_{\text{CatSper}}$

CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems (Ren *et al.*, 2001; Quill *et al.*, 2001). The properties of CatSper1 tabulated above are derived from whole cell voltage-clamp recordings comparing currents endogenous to spermatozoa isolated from the *corpus epididymis* of wild-type and *Catsper1*<sup>(-/-)</sup> mice (Kirichok *et al.*, 2006) and also mature human sperm (Lishko *et al.*, 2011; Strünker *et al.*, 2011).  $I_{\text{CatSper}}$  is also undetectable in the spermatozoa of *Catsper2*<sup>(-/-)</sup>, *Catsper3*<sup>(-/-)</sup>, or *Catsper4*<sup>(-/-)</sup> mice and CatSper 1 associates with CatSper 2, 3, or 4 in heterologous expression systems (Qi *et al.*, 2007). Moreover, targeted disruption of *Catsper1*, 2, 3, or 4 genes results in an identical phenotype in which spermatozoa fail to exhibit the hyperactive movement (whip-like flagellar beats) necessary for penetration of the egg *cumulus* and *zona pellucida* and subsequent fertilization. Such disruptions are associated with a deficit in alkalinization and depolarization-evoked Ca<sup>2+</sup> entry into spermatozoa (Carlson *et al.*, 2003, 2005; Qi *et al.*, 2007). Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSper1-4 (Qi *et al.*, 2007) in association with the auxiliary subunits ( $\beta$ ,  $\gamma$ ,  $\delta$ ) that are also essential for function (Chung *et al.*, 2011). CatSper channels are required for the increase in intracellular Ca<sup>2+</sup> concentration in sperm evoked by egg *zona pellucida* glycoproteins (Xia and Ren, 2009). The driving force for Ca<sup>2+</sup> entry is principally determined by a mildly outwardly rectifying K<sup>+</sup> channel (KSper) that, like CatSper, is activated by intracellular alkalinization (Navarro *et al.*, 2007). Mouse KSper is encoded by *mSlo3*, a protein detected only in testis (Navarro *et al.*, 2007; Martinez-Lopez *et al.*, 2009; Zeng *et al.*, 2011). In human sperm, such alkalinization may result from the activation of H<sub>v</sub>1, a proton channel (Lishko and Kirichok, 2010). Mutations in CatSper are associated with syndromic and non-syndromic male infertility (Hildebrand *et al.*, 2010). In human ejaculated spermatozoa, progesterone (<50 nM) potentiates the CatSper current by a non-genomic mechanism and acts synergistically with intracellular alkalinisation (Lishko *et al.*, 2011; Strünker *et al.*, 2011). In addition, certain prostaglandins (e.g. PGF<sub>1 $\alpha$</sub> , PGE<sub>1</sub>) also potentiate CatSper mediated currents (Lishko *et al.*, 2011; Strünker *et al.*, 2011).

**Abbreviations:** HC-056456, (3,4-bis(2-thienylcarbonyl)-1,2,5-oxadiazole-2-ium-2-olate); NNC55-0396, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl cyclopropanecarboxylate

## Further Reading

- Clapham DE, Garbers DL (2005). International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol Rev* 57: 451–454.
- Hildebrand MS, Avenarius MR, Fellous M, Zhang Y, Meyer NC, Auer J *et al.* (2010). Genetic male infertility and mutation of CATSPER ion channels. *Eur J Hum Genet* 18: 1178–1184.
- Kirichok Y, Lishko PV (2011). Rediscovering Sperm Ion Channels with the Patch-Clamp Technique. *Mol Hum Reprod* 17: 478–499.
- Lishko PV, Kirichok Y (2010). The role of Hv1 and CatSper channels in sperm activation. *J Physiol* 588: 4667–4672.
- Navarro B, Kirichok Y, Chung JJ, Clapham DE (2008). Ion channels that control fertility in mammalian spermatozoa. *Int J Dev Biol* 52:607–613.
- Publicover SJ, Giojalas LC, Teves ME, de Oliveira GS, Garcia AA, Barratt CL *et al.* (2008). Ca<sup>2+</sup> signalling in the control of motility and guidance in mammalian sperm. *Front Biosci* 13: 5623–5637.
- Quill TA, Wang D, Garbers DL (2006). Insights into sperm cell motility through sNHE and the CatSper. *Mol Cell Endocrinol* 250: 84–92.
- Ren D, Xia J (2010). Calcium signaling through CatSper channels in mammalian fertilization. *Physiology (Bethesda)* 25: 165–175.
- Suarez SS (2008). Control of hyperactivation in sperm. *Hum Reprod Update* 14: 647–657.
- Zhang D, Gopalakrishnan M (2005). Sperm ion channels: molecular targets for the next generation of contraceptive medicines? *J Androl* 26: 643–653.

**References**

- Carlson AE *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 14864–14868.
- Carlson AE *et al.* (2005). *J Biol Chem* **280**: 32238–32244.
- Chung J-J *et al.* (2011). *Nat Commun* **2**: 153.
- Kirichok Y *et al.* (2006). *Nature* **439**: 737–740.
- Lin J-L *et al.* (2005). *Biol Reprod* **73**: 1235–1242.
- Liu J *et al.* (2007). *J Biol Chem* **282**: 18945–18952.
- Lishko PV *et al.* (2011). *Nature* **471**: 387–391.
- Lobley A *et al.* (2003). *Reprod Biol Endocrinol* **1**: 53.
- Martinez-Lopez P *et al.* (2009). *Biochem Biophys Res Commun* **381**: 204–209.
- Navarro B *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 7688–7692.
- Qi H *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 1219–1223.
- Quill TA *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 12527–12531.
- Ren D *et al.* (2001). *Nature* **413**: 603–609.
- Strünker T *et al.*, (2011). *Nature* **471**, 382–386.
- Wang H *et al.* (2009). *Biol Reprod* **81**: 539–544.
- Xia J, Ren D (2009). *Biol Reprod* **80**: 1092–1098.
- Zeng XH *et al.* (2011). *Proc Natl Acad Sci U S A* **108**: 5879–5884.

# Chloride channels

**Overview:** Chloride channels are a functionally and structurally diverse group of anion selective channels involved in processes including the regulation of the excitability of neurones, skeletal, cardiac and smooth muscle, cell volume regulation, transepithelial salt transport, the acidification of internal and extracellular compartments, the cell cycle and apoptosis (reviewed by Duran *et al.*, 2010). Excluding the transmitter-gated GABA<sub>A</sub> and glycine receptors (see separate tables), well characterised chloride channels can be classified as certain members of the voltage-sensitive CIC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels (Verkman and Galiotta, 2009). No official recommendation exists regarding the classification of chloride channels. Functional chloride channels that have been cloned from, or characterised within, mammalian tissues are listed with the exception of several classes of intracellular channels (*e.g.* CLIC) that are reviewed by Edwards and Kahl (2010).

**CIC-family:** The mammalian CIC family (reviewed by Chen, 2005; Dutzler, 2007; Jentsch, 2008; Accardi and Picollo, 2010; Duran *et al.*, 2010) contains 9 members that fall, on the basis of sequence homology, into three groups; CIC-1, CIC-2, hCIC-Ka (rCIC-K1) and hCIC-Kb (rCIC-K2); CIC-3 to CIC-5, and CIC-6 and -7. CIC-1 and CIC-2 are plasma membrane chloride channels. CIC-Ka and CIC-Kb are also plasma membrane channels (largely expressed in the kidney and inner ear) when associated with barttin (ENSG00000162399), a 320 amino acid 2TM protein (Estévez *et al.*, 2001). The localisation of the remaining members of the CIC family is likely to be predominantly intracellular *in vivo*, although they may traffic to the plasma membrane in overexpression systems. Numerous recent reports indicate that CIC-4, CIC-5, CIC-6 and CIC-7 (and by inference CIC-3) function as Cl<sup>-</sup>/H<sup>+</sup> antiporters (secondary active transport), rather than classical Cl<sup>-</sup> channels (Picollo and Pusch, 2005; Scheel *et al.*, 2005; Graves *et al.*, 2008; Neagoe *et al.*, 2010; Leisle *et al.*, 2011; reviewed by Pusch *et al.*, 2006 and Accardi and Picollo, 2010). Novarino *et al.* (2010) recently reported that the activity of CIC-5 as a Cl<sup>-</sup>/H<sup>+</sup> exchanger is important for renal endocytosis. Alternative splicing increases the structural diversity within the CIC family. The crystal structure of two bacterial CIC proteins has been described by Dutzler *et al.* (2002) and a eukaryotic CIC transporter (CmCLC) has recently been described at 3.5 Å resolution (Feng *et al.*, 2010). Each CIC subunit, with a complex topology of 18 intramembrane segments, contributes a single pore to a dimeric 'double-barrelled' CIC channel that contains two independently-gated pores, confirming the predictions of previous functional and structural investigations (reviewed by Chen, 2005; Pusch *et al.*, 2006; Dutzler, 2007; Jentsch, 2008). As found for CIC-4, CIC-5, CIC-6 and CIC-7, the prokaryotic CIC homologue (CIC-ec1) and CmCLC function as H<sup>+</sup>/Cl<sup>-</sup> antiporters, rather than as ion channels (Accardi and Miller, 2004; Feng *et al.*, 2010). The generation of monomers from dimeric CIC-ec1 has firmly established that each CIC subunit is a functional unit for transport and that cross-subunit interaction is not required for Cl<sup>-</sup>/H<sup>+</sup> exchange in CIC transporters (Robertson *et al.*, 2010).

Nomenclature	CIC-1	CIC-2	CIC-Ka	CIC-Kb
Other names	skeletal muscle Cl <sup>-</sup> channel	–	CIC-K1 (rodent)	CIC-K2 (rodent)
Ensembl ID	ENSG00000186544	ENSG00000114859	ENSG00000186510	ENSG00000184908
Activators	Constitutively active	Arachidonic acid, amidation, acid-activated omeprazole, lubiprostone (SPI-0211)	Constitutively active (when co-expressed with barttin) Niflumic acid (10–1000 µM)	Constitutively active (when co-expressed with barttin) Niflumic acid (10–1000 µM)
Blockers	S(-)CPP, S(-)CPB, 9-AC, Cd <sup>2+</sup> , Zn <sup>2+</sup> , niflumic acid, fenofibric acid	GaTx2 (apparent K <sub>D</sub> = 15 pM at -100 mV), NPPB, DPC, Cd <sup>2+</sup> , Zn <sup>2+</sup>	3-phenyl-CPP, DIDS, benzofuran derivatives, niflumic acid (>1 mM)	3-phenyl-CPP, DIDS, benzofuran derivatives
Functional characteristics	γ = 1–1.5 pS; voltage-activated (depolarization) (by fast gating of single protopores and a slower common gate allowing both pores to open simultaneously); inwardly rectifying; incomplete deactivation upon repolarization, ATP binding to cytoplasmic cystathionine β-synthetase related (CBS) domains inhibits CIC-1 (by closure of the common gate), depending on its redox status	γ = 2–3 pS; voltage-activated by membrane hyperpolarization by fast protopore and slow cooperative gating; channels only open negative to E <sub>Cl</sub> resulting in steady-state inward rectification; voltage-dependence modulated by permeant anions; activated by cell swelling, PKA, and weak extracellular acidosis; potentiated by SGK1; inhibited by phosphorylation by p34(cdc2)/cyclin B; cell surface expression and activity increased by association with Hsp90	γ = 26 pS; linear current-voltage relationship except at very negative potentials; no time dependence; inhibited by extracellular protons (pK = 7.1); potentiated by extracellular Ca <sup>2+</sup>	Bidirectional rectification; no time dependence; inhibited by extracellular protons; potentiated by extracellular Ca <sup>2+</sup>

Nomenclature	CIC-3	CIC-4	CIC-5
Ensembl ID	ENSG00000109572	ENSG00000073464	ENSG00000171365
Activators	–	–	–
Blockers	Phloretin (30 $\mu$ M); insensitive to DIDS and NPPB and tamoxifen (10 $\mu$ M)	Zn <sup>2+</sup> (50 $\mu$ M), Cd <sup>2+</sup> (68 $\mu$ M) (IC <sub>50</sub> values; Osteen and Mindell, 2008)	Insensitive to DIDS 1 mM), DPC (1 mM), 9-AC (2 mM), NPPB (0.5 mM), niflumic acid (1 mM)
Functional characteristics	Cl <sup>-</sup> /H <sup>+</sup> antiporter (Matsuda <i>et al.</i> , 2008); pronounced outward rectification; slow activation, fast deactivation; activity enhanced by CaM kinase II; inhibited by intracellular Ins(3,4,5,6)P <sub>4</sub> and extracellular acidosis	Cl <sup>-</sup> /H <sup>+</sup> antiporter (2Cl <sup>-</sup> :1H <sup>+</sup> ) Picollo and Pusch, 2005; Scheel <i>et al.</i> , 2005; Alekov and Fahlke, 2009); extreme outward rectification; voltage-dependent gating with midpoint of activation at +73 mV (Orhan <i>et al.</i> , 2011); rapid activation and deactivation; inhibited by extracellular acidosis; non-hydrolytic nucleotide binding required for full activity	Cl <sup>-</sup> /H <sup>+</sup> antiporter (2Cl <sup>-</sup> :1H <sup>+</sup> ) (Picollo and Pusch, 2005; Scheel <i>et al.</i> , 2005; Zifarelli and Pusch, 2009; Smith and Lippiat, 2010); extreme outward rectification; voltage-dependent gating with midpoint of activation of 116.0 mV; rapid activation and deactivation; potentiated and inhibited by intracellular and extracellular acidosis, respectively; ATP binding to cytoplasmic cystathionine $\beta$ -synthetase related (CBS) domains activates CIC-5

Nomenclature	CIC-6	CIC-7
Ensembl ID	ENSG00000011021	ENSG00000103249
Activators	–	Active when co-expressed with Ostm1
Blockers	DIDS (1 mM)	DIDS (40 $\mu$ M), NS5818 (52 $\mu$ M); NPPB (156 $\mu$ M) (IC <sub>50</sub> values; Schulz <i>et al.</i> , 2010)
Functional characteristics	Cl <sup>-</sup> /H <sup>+</sup> antiporter (2Cl <sup>-</sup> :1H <sup>+</sup> ) (Neagoe <i>et al.</i> , 2010); outward rectification, rapid activation and deactivation	Cl <sup>-</sup> /H <sup>+</sup> antiporter (2Cl <sup>-</sup> :1H <sup>+</sup> ) (Graves <i>et al.</i> , 2008; Schulz <i>et al.</i> , 2010; Leisle <i>et al.</i> , 2011); strong outward rectification; voltage-dependent gating with a threshold more positive than ~ + 20 mV; very slow activation and deactivation

CIC channels display the permeability sequence Cl<sup>-</sup> > Br<sup>-</sup> > I<sup>-</sup> (at physiological pH). CIC-1 has significant opening probability at resting membrane potential, accounting for 75% of the membrane conductance at rest in skeletal muscle, and is important for stabilization of the membrane potential. S(-)CPP, 9-AC and niflumic acid act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials (Liantonio *et al.*, 2007 and reviewed by Pusch *et al.*, 2002). Inhibition of CIC-2 by the peptide GaTx2, from *Leiurus quinquestratus herbareus venom*, is likely to occur through inhibition of channel gating, rather than direct open channel blockade (Thompson *et al.*, 2009). Although CIC-2 can be activated by cell swelling, it does not correspond to the VRAC channel (see below). Alternative potential physiological functions for CIC-2 are reviewed by Planells-Cases and Jentsch (2009). Functional expression of human CIC-Ka and CIC-Kb requires the presence of barttin (Estévez *et al.*, 2001; Scholl *et al.*, 2006; reviewed by Fahlke and Fischer, 2010). The properties of CIC-Ka/barttin and CIC-Kb/barttin tabulated are those observed in mammalian expression systems: in oocytes the channels display time- and voltage-dependent gating. The rodent homologue (CIC-K1) of CIC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin which increases both channel opening probability in the physiological range of potentials (Estévez *et al.*, 2001; Scholl *et al.*, 2006; Fischer *et al.*, 2010; reviewed by Fahlke and Fischer, 2010). CIC-Ka is approximately 5 to 6-fold more sensitive to block by 3-phenyl-CPP and DIDS than CIC-Kb, while newly synthesized benzofuran derivatives showed the same blocking affinity (<10  $\mu$ M) on both CLC-K isoforms (Liantonio *et al.* 2008). The biophysical and pharmacological properties of CIC-3, and the relationship of the protein to the endogenous volume-regulated anion channel(s) VRAC (see Guan *et al.*, 2006; Alekov and Fahlke, 2008) are controversial and further complicated by the possibility that CIC-3 may function as both a Cl<sup>-</sup>/H<sup>+</sup> exchanger and an ion channel (Picollo and Pusch, 2005; Wang *et al.*, 2006; Alekov and Fahlke, 2008). The functional properties tabulated are those most consistent with the close structural relationship between CIC-3, CIC-4 and CIC-5. Activation of heterologously expressed CIC-3 by cell swelling in response to hypotonic solutions is disputed, as are many other aspects of its regulation. Dependent upon the predominant extracellular anion (*e.g.* SCN<sup>-</sup> versus Cl<sup>-</sup>), CIC-4 can operate in two transport modes: a slippage mode in which behaves as an ion channel and an exchanger mode in which unitary transport rate is 10-fold lower (Alekov and Fahlke, 2009). Similar findings have been made for CIC-5 (Zdebek *et al.* 2008). CIC-7 associates with a  $\beta$  subunit, Ostm1, which increases the stability of the former (Lange *et al.*, 2006) and is essential for its function (Leisle *et al.*, 2011).

**CFTR:** CFTR, a 12TM, ABC transporter-type protein (see Page S214), is a cAMP-regulated epithelial cell membrane Cl<sup>-</sup> channel involved in normal fluid transport across various epithelia. Of the 1700 mutations identified in CFTR, the most common is the deletion mutant  $\Delta$ F508 (a class 2 mutation) which results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis (reviewed by Cuthbert, 2011). Channels carrying the  $\Delta$ F508 mutation that do traffic to the plasma membrane demonstrate gating defects. Thus, pharmacological restoration the function of the  $\Delta$ F508 mutant would require a compound that embodies 'corrector' (*i.e.* facilitates folding and trafficking to the cell surface) and 'potentiator' (*i.e.* promotes opening of channels at the cell surface) activities (see Cuthbert, 2011). In addition to acting as an anion channel *per se*, CFTR may act as a regulator of several other conductances including inhibition of the epithelial Na channel (ENaC), calcium activated chloride channels (CaCC) and volume regulated anion channel (VRAC), activation of the outwardly rectifying chloride channel (ORCC), and enhancement of the sulphonylurea sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed by Nilius and Droogmans, 2003). CFTR also regulates TRPV4, which provides the Ca<sup>2+</sup> signal for regulatory volume decrease in airway epithelia (Arniges *et al.*, 2004). The activities of CFTR and the chloride-bicarbonate exchangers SLC26A3 (DRA) and SLC26A6 (PAT1) are mutually enhanced by a physical association between the regulatory (R) domain of CFTR and the STAS domain of the SCL26 transporters, an effect facilitated by PKA-mediated phosphorylation of the R domain of CFTR (Ko *et al.*, 2004).

Nomenclature	CFTR
Other names	ABCC7
Ensembl ID	ENSG00000001626
Potentiators	VX-770, flavones (e.g. UCCF-339, UCCF-029, apigenin, genistein), benzimidazolones (e.g. UCCF-853, NS004), benzoquinolines (e.g. CBIQ), 1,4-dihydropyridines (e.g. felopidine, nimodipine), capsaicin, phenylglycines (e.g. 2-[(2-1 <i>H</i> -indol-3-yl-acetyl)-methylamino]- <i>N</i> -(4-isopropylphenyl)-2-phenylacetamide), sulfonamides (e.g. 6-(ethylphenylsulfamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid cycloheptylamide)
Blockers	GaTx-1, GlyH-101 (extracellular application causes channel block), CFTR <sub>inh</sub> -172 (intracellular application prolongs mean closed time), malonic acid hydrazide conjugates (see Verkman and Galletta, 2009), glibenclamide (non-selective)
Functional characteristics	$\gamma = 6-10$ pS; permeability sequence = $\text{Br}^- \geq \text{Cl}^- > \text{I}^- > \text{F}^-$ , ( $P_{\text{I}}/P_{\text{Cl}} = 0.1-0.85$ ); slight outward rectification; phosphorylation necessary for activation by ATP binding at binding nucleotide binding domains (NBD)1 and 2; positively regulated by PKC and PKGII (tissue specific); regulated by several interacting proteins including syntaxin 1A, Munc18 and PDZ domain proteins such as NHERF (EBP50) and CAP70

In addition to the agents listed in the table, the novel small molecule, ataluren, induces translational read through of nonsense mutations in CFTR (reviewed by Sloane and Rowe, 2010). Corrector compounds that aid the folding of  $\Delta F508$ CFTR to increase the amount of protein expressed and potentially delivered to the cell surface include VX-532 (which is also a potentiator), VRT-325, KM11060, Corr-3a and Corr-4a (see Verkman and Galletta (2009) for details and structures of Corr-3a and Corr-4a). Inhibition of CFTR by intracellular application of the peptide GaTx1, from *Leiurus quinquestriatus herbareus venom*, occurs preferentially for the closed state of the channel (Fuller *et al.*, 2007). CFTR contains two cytoplasmic nucleotide binding domains (NBDs) that bind ATP. A single open-closing cycle is hypothesised to involve, in sequence: binding of ATP at the N-terminal NBD1, ATP binding to the C-terminal NBD2 leading to the formation of an intramolecular NBD1-NBD2 dimer associated with the open state, and subsequent ATP hydrolysis at NBD2 facilitating dissociation of the dimer and channel closing, and the initiation of a new gating cycle (Aleksandrov *et al.*, 2007; Muallem and Vergani, 2009). Phosphorylation by PKA at sites within a cytoplasmic regulatory (R) domain facilitates the interaction of the two NBD domains. PKC (and PKGII within intestinal epithelial cells *via* guanylin-stimulated cGMP formation) positively regulate CFTR activity.

**Calcium activated chloride channel:** Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and non-excitable cells where they perform diverse functions (Hartzell *et al.*, 2005). The molecular nature of CaCC has been uncertain with both *CLCA*, *TWEETY* and *BEST* genes having been considered as likely candidates (Loewen and Forsyth, 2005; Hartzell *et al.*, 2008; Duran *et al.*, 2010). It is now accepted that *CLCA* expression products are unlikely to form channels *per se* and probably function as cell adhesion proteins, or are secreted (Patel *et al.*, 2009). Similarly, *TWEETY* gene products do not recapitulate the properties of endogenous CaCC. The bestrophins encoded by genes *BEST1-4* have a topology more consistent with ion channels (see Hartzell *et al.*, 2008) and form chloride channels that are activated by physiological concentrations of  $\text{Ca}^{2+}$ , but whether such activation is direct is not known (Hartzell *et al.*, 2008). However, currents generated by bestrophin over-expression do not resemble native CaCC currents. The evidence for and against bestrophin proteins forming CaCC is critically reviewed by Duran *et al.* (2010). Recently, a new gene family, TMEM16 (anoctamin) consisting of 10 members (TMEM16A-K; anoctamin 1–10) has been identified and there is firm evidence that some of these members form chloride channels (Duran and Hartzell, 2011; Kunzelmann *et al.*, 2011). TMEM16A (anoctamin 1; Ano 1) produces  $\text{Ca}^{2+}$ -activated  $\text{Cl}^-$  currents with kinetics similar to native CaCC currents recorded from different cell types (Caputo *et al.*, 2008; Schroeder *et al.*, 2008; Yang *et al.*, 2008; Rock *et al.*, 2009). Knockdown of TMEM16A greatly reduces currents mediated by calcium-activated chloride channels in submandibular gland cells (Yang *et al.*, 2008) and smooth muscle cells from pulmonary artery (Manoury *et al.*, 2010). In TMEM16A<sup>(-/-)</sup> mice secretion of  $\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  secretion by several epithelia is reduced (Ousingsawat *et al.*, 2009; Rock *et al.*, 2009). Alternative splicing regulates the voltage- and  $\text{Ca}^{2+}$ -dependence of TMEM16A and such processing may be tissue-specific manner and thus contribute to functional diversity (Ferrera *et al.*, 2009). There are also reports that TMEM16B (anoctamin 2; Ano 2) supports CaCC activity (e.g. Pifferi *et al.*, 2009) and in TMEM16B<sup>(-/-)</sup> mice Ca-activated  $\text{Cl}^-$  currents in the main olfactory epithelium (MOE) and in the vomeronasal organ are virtually absent (Billig *et al.*, 2011).

Nomenclature	CaCC
Other names	$\text{Ca}^{2+}$ -activated $\text{Cl}^-$ channel
Activators	intracellular $\text{Ca}^{2+}$
Blockers	niflumic acid, flufenamic acid, DCDPC, DIDS, SITS, NPPB, A-9-C, Ins(3,4,5,6)P <sub>4</sub> , mibefradil, fluoxetine, tannic acid
Functional characteristics	$\gamma = 0.5-5$ pS; permeability sequence, $\text{SCN}^- > \text{NO}_3^- > \text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$ ; relative permeability of $\text{SCN}^-:\text{Cl}^- \sim 8$ , $\text{I}^-:\text{Cl}^- \sim 3$ , aspartate: $\text{Cl}^- \sim 0.15$ , outward rectification (decreased by increasing $[\text{Ca}^{2+}]_i$ ); sensitivity to activation by $[\text{Ca}^{2+}]_i$ decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[\text{Ca}^{2+}]_i$ ); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status

Blockade of  $\text{I}_{\text{Cl}(\text{Ca})}$  by niflumic acid, DIDS and 9-AC is voltage-dependent whereas block by NPPB is voltage-independent (Hartzell *et al.*, 2005). Extracellular niflumic acid; DCDPC and A-9-C (but not DIDS) exert a complex effect upon  $\text{I}_{\text{Cl}(\text{Ca})}$  in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon  $[\text{Ca}^{2+}]_i$  (see Leblanc *et al.*, 2005 for summary). Considerable crossover in pharmacology with large conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels also exists (see Greenwood and Leblanc, 2007 for overview). Two novel compounds, CaCC<sub>inh</sub>-A01 and CaCC<sub>inh</sub>-B01 have recently been identified as blockers of calcium-activated chloride channels in T84 human intestinal epithelial cells (see De La Fuente *et al.* (2008) for structures). Significantly, other novel compounds totally block currents mediated by TMEM16A, but have only a modest effect upon total current mediated by CaCC native to T84 cells or human bronchial epithelial cells, suggesting that TMEM16A is not the predominant CaCC in such cells (Namkung *et al.*, 2011). CaMKII modulates CaCC in a tissue dependent manner (reviewed by Hartzell *et al.*, 2005; Leblanc *et al.*, 2005). CaMKII inhibitors block activation of  $\text{I}_{\text{Cl}(\text{Ca})}$  in T<sub>84</sub> cells but have no effect in parotid acinar cells. In tracheal and arterial smooth muscle cells, but not portal vein myocytes, inhibition of CaMKII reduces inactivation of  $\text{I}_{\text{Cl}(\text{Ca})}$ . Intracellular Ins(3,4,5,6)P<sub>4</sub> may act as an endogenous negative regulator of CaCC channels activated by  $\text{Ca}^{2+}$ , or CaMKII. Smooth muscle CaCC are also regulated positively by  $\text{Ca}^{2+}$ -dependent phosphatase, calcineurin (see Leblanc *et al.*, 2005 for summary).

**Maxi chloride channel:** Maxi Cl<sup>-</sup> channels are high conductance, anion selective, channels initially characterised in skeletal muscle and subsequently found in many cell types including neurones, glia, cardiac muscle, lymphocytes, secreting and absorbing epithelia, macula densa cells of the kidney and human placenta syncytiotrophoblasts (Sabirov and Okada, 2009). The physiological significance of the maxi Cl<sup>-</sup> channel is uncertain, but roles in cell volume regulation and apoptosis have been claimed. Evidence suggests a role for maxi Cl<sup>-</sup> channels as a conductive pathway in the swelling-induced release of ATP from mouse mammary C127i cells that may be important for autocrine and paracrine signalling by purines (Sabirov *et al.*, 2001; Dutta *et al.*, 2002). A similar channel mediates ATP release from macula densa cells within the thick ascending of the loop of Henle in response to changes in luminal NaCl concentration (Bell *et al.*, 2003). A family of human high conductance Cl<sup>-</sup> channels (TTYH1-3) that resemble Maxi Cl<sup>-</sup> channels has been cloned (Suzuki and Mizuno, 2004), but alternatively, Maxi Cl<sup>-</sup> channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane (Bahamonde *et al.*, 2003; Okada *et al.*, 2004).

Nomenclature	Maxi Cl <sup>-</sup>
Other names	High conductance anion channel, volume- and voltage-dependent ATP-conductive large conductance (VDAcL) anion channel
Activators	G-protein-coupled receptors, cytosolic GTPγS, extracellular triphenylethylene anti-oestrogens (tamoxifen, toremifene), extracellular chlorpromazine and triflupromazine, cell swelling
Blockers	SITS, DIDS, NPPB, DPC, intracellular arachidonic acid, extracellular Zn <sup>2+</sup> and Gd <sup>3+</sup>
Functional characteristics	γ = 280–430 pS (main state); permeability sequence, I > Br > Cl > F > gluconate (P <sub>Cl</sub> /P <sub>Cl</sub> = -1.5); ATP is a voltage dependent permeant blocker of single channel activity (P <sub>ATP</sub> /P <sub>Cl</sub> = 0.08–0.1); channel activity increased by patch-excision; channel opening probability (at steady-state) maximal within approximately ± 20 mV of 0 mV, opening probability decreased at more negative and (commonly) positive potentials yielding a bell-shaped curve; channel conductance and opening probability regulated by annexin 6

Differing ionic conditions may contribute to variable estimates of γ reported in the literature. Inhibition by arachidonic acid (and cis-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down ( $K_d = 4\text{--}5\ \mu\text{M}$ ) and a reduction of γ ( $K_d = 13\text{--}14\ \mu\text{M}$ ). Blockade of channel activity by SITS, DIDS, Gd<sup>3+</sup> and arachidonic acid is paralleled by decreased swelling-induced release of ATP (Sabirov *et al.*, 2001; Dutta *et al.*, 2002). Channel activation by anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with 17β-oestradiol, dibutryl cAMP, or intracellular dialysis with GDPβS (Diaz *et al.*, 2001). Activation by tamoxifen is suppressed by low concentrations of okadaic acid, suggesting that a dephosphorylation event by protein phosphatase PP2A occurs in the activation pathway (Diaz *et al.*, 2001). In contrast, 17β-estradiol and tamoxifen appear to directly inhibit the maxi Cl<sup>-</sup> channel of human placenta reconstituted into giant liposomes and recorded in excised patches (Riquelme, 2009).

**Volume regulated chloride channels:** Volume activated chloride channels (also termed VSOAC, volume-sensitive organic osmolyte/anion channel; VRC, volume regulated channel and VSOR, volume expansion-sensing outwardly rectifying anion channel) participate in regulatory volume decrease (RVD) in response to cell swelling. VRAC may also be important for several other processes including the regulation of membrane excitability, transcellular Cl<sup>-</sup> transport, angiogenesis, cell proliferation, necrosis, apoptosis, glutamate release from astrocytes, insulin release from pancreatic β cells and resistance to the anti-cancer drug, cisplatin (reviewed by Nilius and Droogmans, 2003; Mulligan and MacVicar, 2006; Okada *et al.*, 2009; Best *et al.*, 2010). VRAC may not be a single entity, but may instead represent a number of different channels that are expressed to a variable extent in different tissues and are differentially activated by cell swelling. In addition to ClC-3 expression products (see above) several former VRAC candidates including MDRI P-glycoprotein, Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews by Nilius and Droogmans, 2003; Sardini *et al.*, 2003).

Nomenclature	VRAC (volume regulated anion channel), VSOAC (volume-sensitive organic osmolyte/anion channel), VRC (volume regulated channel), VSOR (volume expansion-sensing outwardly rectifying anion channel)
Activators	cell swelling; low intracellular ionic strength; GTPγS
Blockers	NS3728, DCPIB, clomiphene, nafoxidine, mefloquine, tamoxifen, gossypol, arachidonic acid, mibefradil, NPPB, quinine, quinidine, chromones, NDGA, A-9-C, DIDS, 1,9-dideoxyforskolin, oxalonic acid (diBA-(5)-C4), carbenoxolone, IAA-94, extracellular nucleotides, nucleoside analogues, intracellular Mg <sup>2+</sup>
Functional characteristics	γ = 10–20 pS (negative potentials), 50–90 pS (positive potentials); permeability sequence SCN > I > NO <sub>3</sub> <sup>-</sup> > Br <sup>-</sup> > Cl <sup>-</sup> > F <sup>-</sup> > gluconate; outward rectification due to voltage dependence of γ; inactivates at positive potentials in many, but not all, cell types; time dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free Mg <sup>2+</sup> concentration; swelling induced activation of several intracellular signalling cascades may be permissive of, but not essential to, the activation of VRAC including: the Rho-Rho kinase-MLCK; Ras-Raf-MEK-ERK; PIK3-NOX-H <sub>2</sub> O <sub>2</sub> and Src-PLCγ-Ca <sup>2+</sup> pathways; regulation by PKCα required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of β1-integrin

In addition to conducting monovalent anions, in many cell types the activation of VRAC by a hypotonic stimulus can allow the efflux of organic osmolytes such as amino acids and polyols that may contribute to RVD.

**Other chloride channels:** In addition to some intracellular chloride channels that are not considered here, plasma membrane channels other than those listed have been functionally described. Many cells and tissues contain outwardly rectifying chloride channels (ORCC) that may correspond to VRAC active under isotonic conditions. A cAMP-activated Cl<sup>-</sup> channel that does not correspond to CFTR has been described in intestinal Paneth cells (Tsumura *et al.*, 1998). A Cl channel activated by cGMP with a dependence on raised intracellular Ca<sup>2+</sup> has been recorded in various vascular smooth muscle cells types, which has a pharmacology and biophysical characteristics very different from the 'conventional'

CaCC (see Matchkov *et al.*, 2004; Piper and Large, 2004). It has been proposed that bestrophin-3 is an essential component of the cGMP-activated channel (Matchkov *et al.*, 2008). A proton-activated, outwardly rectifying anion channel has also been described (Lambert and Oberwinkler, 2005).

**Abbreviations:** A-9-C, anthracene-9-carboxylic acid; CBIQ, 4-chlorobenzo[F]isoquinoline; CFTR<sub>inh-172</sub>, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; S-(-)CPP, S-(-)-2-(4-chlorophenoxy)propionic acid; S-(-)CPB, S-(-)-2-(4-chlorophenoxy)butyric acid; DCPIB, 4-(2-butyl-6,7-dichloro-2-cyclopentyl-indan-1-on-5-yl) oxybutyric acid; diBA-(5)-C4, bis-(1,3-dibutylbarbituric acid)pentamethine oxanol; DIDS, 4,4'-diisothiocyanostilbene-2,2'-disulphonic acid; DNDS, 4,4'-dinitrostilbene-2,2'-disulphonic acid; GlyH-101, N-(2-naphthalenyl)-[(3,5-dibromo-2,4-dihydroxyphenyl)methylene]glycine hydrazide; IAA-94, indanyloxyacetic acid 94; NDGA, nordihydroguaiaretic acid; DPC, diphenylamine carboxylic acid; DPDPC, dichloro-diphenylamine 2-carboxylic acid; KM11060, 7-chloro-4-[4-[(4-chlorophenyl)sulfonyl]piperazino]quinoline; NPA, N-phenylanthracilic acid; NPPB, 5-nitro-2-(3-phenylpropylamino)benzoic acid; NS004, 5-trifluoromethyl-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benzimidazole-2-one; NS3728, N-[3,5-bis(trifluoromethyl)-phenyl]-N'[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]urea; NS5818, N-(3,5-dichloro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea; SITS, 4'-isothiocyanostilbene-2,2'-disulphonic acid; UCCF-029, 2-(4-pyridinium)benzo[h]4H-chromen-4-one bisulfate; UCCF-180, 3-(3-butynyl)-5-methoxy-1-phenylpyrazole-4-carbaldehyde; UCCF-853, 1-(3-chlorophenyl)-5-trifluoromethyl-3-hydroxybenzimidazol-2-one, VRT-325, 4-cyclohexyloxy-2-[1-[4-(4-methoxy-benzenesulfonyl)piperazin-1-yl]ethyl]quinazoline VX-532, 4-methyl-2-(5-phenyl-1H-pyrazol-3-yl)-phenol; VX-770, N-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

### Further Reading

- Accardi A, Picollo A (2010). CLC channels and transporters: proteins with borderline personalities. *Biochim Biophys Acta* **1798**: 1457–1464.
- Alekov AK, Fahlke C (2008). Anion channels: regulation of ClC-3 by an orphan second messenger. *Curr Biol* **18**: R1061–1064.
- Aleksandrov AA, Aleksandrov LA, Riordan JR (2007). CFTR (ABCC7) is a hydrolyzable-ligand-gated channel. *Pflugers Arch* **453**: 693–702.
- Amaral MD, Kunzelmann K (2007). Molecular targeting of CFTR as a therapeutic approach to cystic fibrosis. *Trends Pharmacol Sci* **28**: 334–341.
- Aromataris EC, Rychkov GY (2006). ClC-1 chloride channel: matching its properties to a role in skeletal muscle. *Clin Exp Pharmacol Physiol* **33**: 1118–1123.
- Ashlock MA, Olson ER (2011). Therapeutics development for cystic fibrosis: a successful model for a multisystem genetic disease. *Annu Rev Med* **62**: 107–125.
- Babini E, Pusch MA (2004). Two-holed story: structural secrets about ClC proteins become unraveled? *Physiology (Bethesda)* **19**: 293–299.
- Best L, Brown PD, Sener A, Malaisse W (2010). Electrical activity in pancreatic islet cells. The VRAC hypothesis. *Islets* **2**: 59–64.
- Chen T-Y (2005). Structure and function of CLC channels. *Annu Rev Physiol* **67**: 809–839.
- Chen T-Y, Hwang TC (2008). CLC-0 and CFTR: chloride channels evolved from transporters. *Physiol Rev* **88**: 351–387.
- Cuthbert AW (2011). New horizons in the treatment of cystic fibrosis. *Br J Pharmacol* **163**: 173–183.
- Duan D (2009). Phenomics of cardiac chloride channels: the systematic study of chloride channel function in the heart. *J Physiol* **587**: 2163–2177.
- Duan DD (2011). The ClC-3 chloride channels in cardiovascular disease. *Acta Pharmacol Sin* **32**: 675–684.
- Duran C, Hartzell HC (2011). Physiological roles and diseases of tmem16/anoctamin proteins: are they all chloride channels? *Acta Pharmacol Sin* **32**: 685–692.
- Duran C, Thompson CH, Xiao Q, Hartzell HC (2010). Chloride channels: often enigmatic, rarely predictable. *Annu Rev Physiol* **72**: 95–121.
- Dutzler R (2007). A structural perspective on ClC channel and transporter function. *FEBS Lett* **581**: 2839–2844.
- Edwards JC, Kahl CR (2010). Chloride channels of intracellular membranes. *FEBS Lett* **584**: 2102–2111.
- Fahlke Ch (2001). Ion permeation and selectivity in ClC-type chloride channels. *Am J Physiol* **280**: F748–F757.
- Fahlke Ch, Fischer M (2010). Physiology and pathophysiology of ClC-K/barttin channels. *Front Physiol* **1**: 155.
- Ferrera L, Caputo A, Galiotta LJ (2010). TMEM16A protein: a new identity for Ca<sup>2+</sup>-dependent Cl<sup>-</sup> channels. *Physiology (Bethesda)* **25**: 357–363.
- Gadsby DC, Vergani P, Csanady L (2006). The ABC protein turned chloride channel whose failure causes cystic fibrosis. *Nature* **440**: 477–483.
- Galiotta LJ (2009). The TMEM16 protein family: a new class of chloride channels? *Biophys J* **97**: 3047–3053.
- Greenwood IA, Leblanc N (2007). Overlapping pharmacology of Ca<sup>2+</sup>-activated Cl<sup>-</sup> and K<sup>+</sup> channels. *Trends Pharmacol Sci* **28**: 1–5.
- Guan Y-Y, Wang G-L, Zhou J-G (2006). The ClC-3 Cl<sup>-</sup> channel in cell volume regulation, proliferation and apoptosis in vascular smooth muscle cells. *Trends Pharmacol Sci* **27**: 290–296.
- Jentsch TJ (2008). ClC chloride channels and transporters: from genes to protein structure, pathology and physiology. *Crit Rev Biochem Mol Biol* **43**: 3–36.
- Kirk KL, Wang W (2011). A unified view of cystic fibrosis transmembrane conductance regulator (CFTR) gating: combining the allostereism of a ligand-gated channel with the enzymatic activity of an ATP-binding cassette (ABC) transporter. *J Biol Chem* **286**: 12813–12819.
- Kunzelmann K, Tian Y, Martins JR, Faria D, Kongsuphol P, Ousingawat J *et al.* (2011). Anoctamins. *Pflugers Arch* **479**: 479–487.
- Hartzell C, Putzier I, Arreola J (2005). Calcium-activated chloride channels. *Annu Rev Physiol* **67**: 719–758.
- Hartzell HC, Qu Z, Yu K, Xiao Q, Chien LT (2008). Molecular physiology of bestrophins: multifunctional membrane proteins linked to best disease and other retinopathies. *Physiol Rev* **88**: 639–672.
- Krämer BK, Bergler T, Stoelcker B, Waldeger S (2008). Mechanisms of Disease: the kidney-specific chloride channels ClCKa and ClCKb, the Barttin subunit, and their clinical relevance. *Nat Clin Pract Nephrol* **4**: 38–46.
- Leblanc N, Ledoux J, Saleh S, Sanguinetti A, Angermann J, O'Driscoll K *et al.* (2005). Regulation of calcium-activated chloride channels in smooth muscle cells: a complex picture is emerging. *Can J Physiol Pharmacol* **83**: 541–556.
- Loewen ME, Forsyth GW (2005). Structure and function of CLCA proteins. *Physiol Rev* **85**: 1061–1092.
- Muallem D, Vergani P (2009). Review. ATP hydrolysis-driven gating in cystic fibrosis transmembrane conductance regulator. *Philos Trans R Soc Lond B Biol Sci* **364**: 247–255.
- Mulligan SJ, MacVicar BA (2006). VRACs CARVe a path for novel mechanisms of communication in the CNS. *Sci STKE* **357**: pe42.
- Nilius B, Droogmans G (2003). Amazing chloride channels: an overview. *Acta Physiol Scand* **177**: 119–147.
- Noy E, Senderowitz H (2011). Combating cystic fibrosis: in search for CF transmembrane conductance regulator (CFTR) modulators. *ChemMed-Chem* **6**: 243–251.
- Okada Y (2006). Cell-volume sensitive chloride channels: phenotypic properties and molecular identity. *Contrib Nephrol* **152**: 9–24.
- Okada Y, Sato K, Numata T (2009). Pathophysiology and puzzles of the volume-sensitive outwardly rectifying anion channel. *J Physiol* **587**: 2141–2145.
- Patel AC, Brett TJ, Holtzman MJ (2009). The role of CLCA proteins in inflammatory airway disease. *Annu Rev Physiol* **71**: 425–449.



- Plans V, Rickheit G, Jentsch TJ (2009). Physiological roles of CLC Cl<sup>-</sup>/H<sup>+</sup> exchangers in renal proximal tubules. *Pflügers Arch* **458**: 23–37.
- Planells-Cases R, Jentsch TJ (2009). Chloride channelopathies. *Biochim Biophys Acta* **1792**: 173–189.
- Puljak L, Kilic G (2006). Emerging roles of chloride channels in human diseases. *Biochim Biophys Acta* **1762**: 404–413.
- Pusch M, Accardi A, Liantonio A, Guida P, Traverso S, Camerino DC *et al.* (2002). Mechanisms of block of muscle type CLC chloride channels. *Mol Membr Biol* **19**: 285–292.
- Pusch M, Zifarelli G, Murgia AR, Picollo A, Babini E (2006). Channel or transporter? The CLC saga continues. *Exp Physiol* **91**: 149–152.
- Riquelme G (2009). Placental chloride channels: a review. *Placenta* **30**: 659–669.
- Riordan JR (2005). Assembly of functional CFTR chloride channels. *Annu Rev Physiol* **67**: 701–718.
- Sabirov RZ, Okada Y (2009). The maxi-anion channel: a classical channel playing novel roles through an unidentified molecular entity. *J Physiol Sci* **59**: 3–21.
- Sardini A, Amey JS, Weylandt KH, Nobles M, Valverde MA, Higgins CF (2003). Cell volume regulation and swelling-activated chloride channels. *Biochim Biophys Acta* **1618**: 153–162.
- Sloane PA, Rowe SM (2010). Cystic fibrosis transmembrane conductance regulator protein repair as a therapeutic strategy in cystic fibrosis. *Curr Opin Pulm Med* **16**: 591–597.
- Suzuki M, Mizuno A (2004). A novel human Cl<sup>-</sup> channel family related to *Drosophila* flightless locus. *J Biol Chem* **279**: 22461–22468.
- Verkman AS, Galiotta LJ (2009). Chloride channels as drug targets. *Nat Rev Drug Discov* **8**: 153–171.

## References

- Accardi A, Miller C (2004). *Nature* **427**: 803–807.
- Alekov AK, Fahlke C (2009). *J Gen Physiol* **133**: 485–496.
- Arniges M *et al.* (2004). *J Biol Chem* **279**: 54062–54068.
- Bahamonde MI *et al.* (2003). *J Biol Chem* **278**: 33284–33289.
- Bell PD *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 4322–4327.
- Billig GM *et al.* (2011). *Nat Neurosci* **14**: 763–769.
- Caputo A *et al.* (2008). *Science* **322**: 590–594.
- De La Fuente R *et al.* (2008). *Mol Pharmacol* **73**: 558–568.
- Diaz M *et al.* (2001). *J Physiol* **536**: 79–88.
- Dutta AK *et al.* (2002). *J Physiol* **542**: 803–816.
- Dutzler R *et al.* (2002). *Nature* **415**: 287–294.
- Estévez R *et al.* (2001). *Nature* **414**: 558–561.
- Feng L *et al.* (2010). *Science* **330**: 635–641.
- Ferrera L *et al.* (2009). *J Biol Chem* **284**: 33360–33368.
- Fischer M *et al.* (2010). *J Am Soc Nephrol* **21**: 1281–1289.
- Fuller MD *et al.* (2007). *J Biol Chem* **282**: 37545–37555.
- Graves AR *et al.* (2008). *Nature* **453**: 788–792.
- Ko SBH *et al.* (2004). *Nat Cell Biol* **6**: 343–350.
- Lambert S, Oberwinkler J (2005). *J Physiol* **576**: 191–213.
- Lange PF *et al.* (2006). *Nature* **440**: 220–223.
- Leisle L *et al.* (2011). *EMBO J* **30**: 2140–2152.
- Liantonio A *et al.* (2007). *Br J Pharmacol* **150**: 235–247.
- Liantonio A *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 1369–1373.
- Matchkov VV *et al.* (2004). *J Gen Physiol* **123**: 121–134.
- Matchkov VV *et al.* (2008). *Circ Res* **103**: 864–872.
- Matsuda JJ *et al.* (2008). *Am J Physiol Cell Physiol* **294**: 251–262.
- Manoury B *et al.* (2010). *J Physiol* **588**: 2305–2314.
- Namkung W *et al.* (2011). *J Biol Chem* **286**: 2365–2374.
- Novarino G *et al.* (2010). *Science* **328**: 1398–1401.
- Neagoe I *et al.* (2010). *J Biol Chem* **285**: 21689–21697.
- Okada SF *et al.* (2004). *J Gen Physiol* **124**: 513–526.
- Orhan G *et al.* (2011). *Biophys J* **100**: 1233–1241.
- Osteen JD, Mindell JA (2008). *Biophys J* **95**: 4668–4675.
- Ousingsawat J *et al.* (2009). *J Biol Chem* **284**: 28698–28703.
- Picollo A, Pusch M (2005). *Nature* **436**: 420–423.
- Pifferi S *et al.* (2009). *Pflügers Arch* **458**: 1023–1038.
- Piper AS, Large WA (2004). *J Physiol* **555**: 397–408.
- Robertson JL *et al.* (2010). *Nature* **468**: 844–847.
- Rock JR *et al.* (2009). *J Biol Chem* **284**: 14875–14880.
- Sabirov RZ *et al.* (2001). *J Gen Physiol* **118**: 251–266.
- Scheel O *et al.* (2005). *Nature* **436**: 424–427.
- Scholl U *et al.* (2006). *Proc Natl Acad Sci U S A* **103**: 11411–11416.
- Schulz P *et al.* (2010). *PLoS ONE* **5**: e12585.
- Schroeder BC *et al.* (2008). *Cell* **134**: 1019–1029.
- Smith AJ, Lippiat JD (2010). *FASEB J* **24**: 3696–3705.
- Thompson CH *et al.* (2009). *J Biol Chem* **284**: 26051–26062.
- Tsumura T *et al.* (1998). *J Physiol* **512**: 765–777.
- Yang YD *et al.* (2008). *Nature* **455**: 1210–1215.
- Zdebik AA *et al.* (2008). *J Biol Chem* **283**: 4219–4227.
- Zifarelli G, Pusch M (2009). *EMBO J* **28**: 175–182.

# Connexins and pannexins

**Overview:** Gap junctions are essential for many physiological processes including cardiac and smooth muscle contraction, regulation of neuronal excitability and epithelial electrolyte transport (see Evans and Martin 2002, Bruzzone *et al.*, 2003, Connors and Long 2004). Gap junction channels allow the passive diffusion of molecules of up to 1,000 Daltons which can include nutrients, metabolites and second messengers (such as IP<sub>3</sub>) as well as cations and anions. 21 connexin genes (Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62) and 3 pannexin genes (Px1, Px2, Px3) which are structurally related to the invertebrate innexin genes) code for gap junction proteins in humans. Each connexin gap junction comprises 2 hemichannels or 'connexons' which are themselves formed from 6 connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells (see Herve *et al.*, 2007). Connexins have a common topology, with four  $\alpha$ -helical transmembrane domains, two extracellular loops, a cytoplasmic loop, and N- and C-termini located on the cytoplasmic membrane face. In mice, the most abundant connexins in electrical synapses in the brain seem to be Cx36, Cx45 and Cx57 (Sohl *et al.*, 2005). Mutations in connexin genes are associated with the occurrence of a number of pathologies, such as peripheral neuropathies, cardiovascular diseases and hereditary deafness. The pannexin genes Px1 and Px2 are widely expressed in the mammalian brain (Vogt *et al.*, 2005). Like the connexins, at least some of the pannexins can form hemichannels (Bruzzone *et al.*, 2003, Pelegrin and Surprenant, 2007).

	Connexins	Pannexins
Nomenclature	Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62	Px1, Px2, Px3
Ensembl ID	ENSG00000159248 (Cx36)*	ENSG00000110218 (Px1) ENSG00000073150 (Px2) ENSG00000154143 (Px3)
Inhibitors	carbenoxolone flufenamic acid octanol raising external calcium	carbenoxolone little block by flufenamic acid unaffected by raising external calcium

Connexins are most commonly named according to their molecular weights, so, for example, Cx23 is the connexin protein of 23 kDa. This can cause confusion when comparing between species – for example, the mouse connexin Cx57 is orthologous to the human connexin Cx62. No natural toxin or specific inhibitor of junctional channels has been identified yet however two compounds often used experimentally to block connexins are carbenoxolone and flufenamic acid (Salameh and Dhein, 2005). At least some pannexin hemichannels are more sensitive to carbenoxolone than connexins but much less sensitive to flufenamic acid (Bruzzone *et al.*, 2005). It has been suggested that 2-aminoethoxydiphenyl borate (2-APB) may be a more effective blocker of some connexin channel subtypes (Cx26, Cx30, Cx36, Cx40, Cx45, Cx50) compared to others (Cx32, Cx43, Cx46, Bai *et al.*, 2006).

\*Due to space constraints, the Ensembl ID for only Cx36 is given. Ensembl information for the other connexins can be found from links therein.

## Further Reading

- Bennett MV, Zukin RS (2004). Electrical coupling and neuronal synchronization in the mammalian brain. *Neuron* **41**: 495–511.
- Connors BW, Long MA (2004). Electrical synapses in the mammalian brain. *Ann Rev Neurosci* **27**: 393–418.
- Cruciani V, Mikalsen SO (2006). The vertebrate connexin family. *Cell Mol Life Sci* **63**: 1125–1140.
- Evans WH, Martin PEM (2002). Gap junctions: structure and function. *Mol Memb Biol* **19**: 121–136.
- Evans WH, De Vuyst E, Leybaert L (2006). The gap junction cellular internet: connexin hemichannels enter the signalling limelight. *Biochem J* **397**: 1–14.
- Goodenough DA, Paul DL (2009). Gap Junctions. *Cold Spring Harb Perspect Biol* **1**: a002576.
- Herve JC, Sarrouilhe D (2005). Connexin-made channels as pharmacological targets. *Curr Pharm Des* **11**: 1941–1958.
- Herve JC, Phelan P, Bruzzone R, White TW (2005). Connexins, innexins and pannexins: bridging the communication gap. *Biochem Biophys Acta* **1719**: 3–5.
- Homuzdi SG, Filippov MA, Mitropoulou G, Monyer H, Bruzzone R (2004). Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks. *Biochem Biophys Acta* **1662**: 113–137.
- Kandouz M, Batist G (2010). Gap junctions and connexins as therapeutic targets in cancer. *Expert Opin Ther Targets* **14**: 681–692.
- Kumar NM, Gilula NB (1996). The gap junction communication channel. *Cell* **84**: 381–388.
- MacVicar BA, Thompson RJ (2010). Non-junction functions of pannexin-1 channels. *Trends Neurosci* **33**: 93–102.
- Mese G, Richard G, White TW (2007). Gap junctions: basic structure and function. *J Invest Dermatol* **127**: 2516–2524.
- Salameh A, Dhein S (2005). Pharmacology of gap junctions: new pharmacological targets for treatment of arrhythmia, seizure and cancer? *Biochem Biophys Acta* **1719**: 36–58.
- Shestopalov VI, Panchin Y (2008). Pannexins and gap junction protein diversity. *Cell Mol Life Sci* **65**: 376–394.
- Sohl G, Maxeiner S, Willecke K (2005). Expression and functions of neuronal gap junctions. *Nature Rev Neurosci* **6**: 191–200.
- Spray DC, Dermietzel R (1996). *Neuroscience Intelligence Unit: Gap Junctions in the Nervous System*. Springer: New York.
- Yen MR, Saier MH (2007). Gap junctional proteins of animals: the innexin/pannexin superfamily. *Prog Biophys Mol Biol* **94**: 5–14.
- Zoidl G, Dermietzel R (2010). Gap junctions in inherited human disease. *Pflugers Arch* **460**: 451–466.

## References

- Bai D *et al.* (2006). *J Pharmacol Exp Ther* **319**: 1452–1458.
- Bruzzone R *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 13644–13649.
- Bruzzone R *et al.* (2005). *J Neurochem* **92**: 1033–1043.
- Herve JC *et al.* (2007). *Prog Biophys Mol Biol* **94**: 29–65.
- Pelegrin P, Surprenant A (2007). *J Biol Chem* **282**: 2386–2394.
- Vogt A *et al.* (2005). *Brain Res Mol Brain Res* **141**: 113–120.

# Cyclic nucleotide-gated channels

**Overview:** Cyclic nucleotide-gated (CNG) channels are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. A standardised nomenclature for CNG channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al.*, 2005).

CNG channels are voltage-independent cation channels formed as tetramers. Each subunit has 6TM, with the pore-forming domain between TM5 and TM6. CNG channels were first found in rod photoreceptors (Fesenko *et al.*, 1985; Kaupp *et al.*, 1989), where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cGMP level. This results in a closure of CNG channels and a reduced 'dark current'. Similar channels were found in the cilia of olfactory neurons (Nakamura and Gold, 1987) and the pineal gland (Dryer and Henderson, 1991). The cyclic nucleotides bind to a domain in the C terminus of the subunit protein: other channels directly binding cyclic nucleotides include HCN, eag and certain plant potassium channels.

Nomenclature	CNGA1	CNGA2	CNGA3
Other names	CNG1, CNG $\alpha$ 1, RCNC1	CNG2, CNG $\alpha$ 3, OCNC1	CNG3, CNG $\alpha$ 2, CCNC1
Ensembl ID	ENSG00000198515	ENSG00000183862	ENSG00000144191
Activators	Intracellular cyclic nucleotides: cGMP (EC <sub>50</sub> $\approx$ 30 $\mu$ M) >> cAMP	Intracellular cyclic nucleotides: cGMP $\approx$ cAMP (EC <sub>50</sub> $\approx$ 1 $\mu$ M)	Intracellular cyclic nucleotides: cGMP (EC <sub>50</sub> $\approx$ 30 $\mu$ M) >> cAMP
Inhibitors	L- <i>cis</i> diltiazem	–	L- <i>cis</i> diltiazem
Functional characteristics	$\gamma$ = 25–30 pS $P_{Ca}/P_{Na}$ = 3.1	$\gamma$ = 35 pS $P_{Ca}/P_{Na}$ = 6.8	$\gamma$ = 40 pS $P_{Ca}/P_{Na}$ = 10.9

CNGA1, CNGA2 and CNGA3 express functional channels as homomers. Three additional subunits CNGA4 (ENSG00000132259), CNGB1 (ENSG00000070729) and CNGB3 (ENSG00000170289) do not, and are referred to as auxiliary subunits. The subunit composition of the native channels is believed to be as follows. Rod: CNGA1<sub>3</sub>/CNGB1<sub>a</sub>; Cone: CNGA3<sub>2</sub>/CNGB3<sub>2</sub>; Olfactory neurons: CNGA2<sub>2</sub>/CNGA4/CNGB1<sub>b</sub> (Weitz *et al.*, 2002; Zheng *et al.*, 2002; Zhong *et al.*, 2002; Peng *et al.*, 2004; Zheng and Zagotta, 2004).

## Further Reading

Biel M, Michalakakis S (2009). Cyclic nucleotide-gated channels. *Handb Exp Pharmacol* **191**: 111–136.  
 Bradley J, Reisert J, Frings S (2005). Regulation of cyclic nucleotide-gated channels. *Curr Opin Neurobiol* **15**: 343–349.  
 Brown RL, Strassmaier T, Brady JD, Karpen JW (2006). The pharmacology of cyclic nucleotide-gated channels: emerging from the darkness. *Curr Pharm Des* **12**: 3597–3613.  
 Craven KB, Zagotta WN (2006). CNG and HCN channels: two peas, one pod. *Annu Rev Physiol* **68**: 375–401.  
 Cukkemane A, Seifert R, Kaupp UB (2011). Cooperative and uncooperative cyclic-nucleotide-gated ion channels. *Trends Biochem Sci* **36**: 55–64.  
 Hofmann F, Biel M, Kaup UB (2005). International Union of Pharmacology. LI. Nomenclature and structure-function relationships of cyclic nucleotide-regulated channels. *Pharmacol Rev* **57**: 455–462.  
 Kaupp UB, Seifert R (2002). Cyclic nucleotide-gated ion channels. *Physiol Rev* **82**: 769–824.  
 Matulef K, Zagotta WN (2003). Cyclic nucleotide-gated ion channels. *Annu Rev Cell Dev Biol* **19**: 23–44.  
 Mazzolini M, Marchesi A, Giorgetti A, Torre V (2010). Gating in CNGA1 channels. *Pflugers Arch* **459**: 547–555.  
 Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004**: re15.

## References

Dryer SE, Henderson D (1991). *Nature* **353**: 756–758.  
 Fesenko EE *et al.* (1985). *Nature* **313**: 310–313.  
 Kaupp UB *et al.* (1989). *Nature* **342**: 762–766.  
 Nakamura T, Gold GH (1987). *Nature* **325**: 442–444.  
 Peng CH *et al.* (2004). *Neuron* **42**: 401–410.  
 Weitz D *et al.* (2002). *Neuron* **36**: 881–889.  
 Zheng J, Zagotta WN (2004). *Neuron* **42**: 411–421.  
 Zheng J *et al.* (2002). *Neuron* **36**: 891–896.  
 Zhong H *et al.* (2002). *Nature* **420**: 193–198.

# Epithelial sodium channels (ENaC)

**Overview:** The epithelial sodium channels (ENaC) mediates sodium reabsorption in the aldosterone-sensitive distal part of the nephron and the collecting duct of the kidney. ENaC is found on other tight epithelial tissues such as the airways, distal colon and exocrine glands. ENaC activity is tightly regulated in the kidney by aldosterone, angiotensin II, vasopressin, insulin and glucocorticoids; this fine regulation of ENaC is essential to maintain sodium balance between daily intake and urinary excretion of sodium, circulating volume and blood pressure. ENaC expression is also vital for clearance of foetal lung fluid, and to maintain air-surface-liquid. (Hummler *et al.*, 1996; Loffing and Korbmacher, 2009). Sodium reabsorption is suppressed by the 'potassium-sparing' diuretics amiloride and triamterene. ENaC is a heteromultimeric channel made of homologous  $\alpha$ ,  $\beta$  and  $\gamma$  subunits. The primary structure of  $\alpha$ ENaC subunit was identified by expression cloning (Canessa *et al.*, 1993);  $\beta$  and  $\gamma$ ENaC were identified by functional complementation of the  $\alpha$  subunit (Canessa *et al.*, 1994). Each ENaC subunit contains 2 TM  $\alpha$  helices connected by a large extracellular loop and short cytoplasmic amino- and carboxy-termini. The stoichiometry of the epithelial sodium channel in the kidney and related epithelia is, by homology with the structurally related channel ASIC1a, thought to be a heterotrimer of 1 $\alpha$ :1 $\beta$ :1 $\gamma$  subunits (Gonzales *et al.*, 2009).

Nomenclature	Epithelial sodium channel (ENaC)
Ensembl ID	Human $\alpha$ subunit, ENSG00000111319; human $\beta$ subunit, ENSG00000168447; human $\gamma$ subunit, ENSG00000166828; human $\delta$ subunit, ENSG00000162572
Activators (EC <sub>50</sub> )	S3969 (1.2 $\mu$ M) (Lu <i>et al.</i> , 2008)
Blockers (IC <sub>50</sub> )	Amiloride (100-200 nM), benzamil (~10 nM), triamterene (~5 $\mu$ M) (Canessa <i>et al.</i> , 1994; Kellenberger <i>et al.</i> , 2003), P552-02 (7.6 nM; Hirsch <i>et al.</i> , 2008)
Functional characteristics	$\gamma \approx 4-5$ pS, $P_{Na}/P_K > 20$ ; tonically open at rest; expression and ion flux regulated by circulating aldosterone-mediated changes in gene transcription. The action of aldosterone, which occurs in 'early' (1.5–3 h) and 'late' (6–24 hr) phases is competitively antagonised by spironolactone, its active metabolites and eplerenone. Glucocorticoids are important functional regulators in lung/airways and this control is potentiated by thyroid hormone; but the mechanism underlying such potentiation is unclear (Barker <i>et al.</i> , 1990; Sayegh, <i>et al.</i> , 1999; Richard <i>et al.</i> , 2004). The density of channels in the apical membrane, and hence $G_{Na}$ , can be controlled <i>via</i> both serum and glucocorticoid-regulated kinases (SGK1, 2 and 3) (Debonneville <i>et al.</i> , 2001; Friedrich <i>et al.</i> , 2003) and <i>via</i> cAMP/PKA (Morris and Schafer, 2002); and these protein kinases appear to act by inactivating Nedd-4/2, a ubiquitin ligase that normally targets the ENaC channel complex for internalization and degradation (Debonneville <i>et al.</i> , 2001, Boarse <i>et al.</i> 2011). ENaC is constitutively activated by soluble and membrane-bound serine proteases, such as furin, prostatic (CAP1), plasmin and elastase (Planes and Caughey, 2007; Rotin and Schild, 2008; Kleyman <i>et al.</i> , 2009; Rossier and Stutts, 2009; Kitamura and Tomita, 2010). The activation of ENaC by proteases is blocked by a protein, SPLUNC1, secreted by the airways and which binds specifically to ENaC to prevent its cleavage (Garcia-Caballero <i>et al.</i> , 2009). Pharmacological inhibitors of proteases ( <i>e.g.</i> camostat acting upon prostatic) reduce the activity of ENaC (Maekawa <i>et al.</i> , 2009). Phosphatidylinositides such as Ptlins(4,5)P <sub>2</sub> and Ptlins(3,4,5)P <sub>3</sub> stabilise channel gating probably by binding to the $\beta$ and $\gamma$ ENaC subunits, respectively (Ma <i>et al.</i> , 2007; Pochynyuk <i>et al.</i> , 2008), whilst C terminal phosphorylation of $\beta$ and $\gamma$ -ENaC by ERK1/2 has been reported to inhibit the withdrawal of the channel complex from the apical membrane (Yang <i>et al.</i> , 2006). This effect may contribute to the cAMP-mediated increase in sodium conductance.

Data in the table refer to the  $\alpha\beta\gamma$  heteromer. There are several human diseases resulting from mutations in ENaC subunits. Liddle's syndrome (including features of salt-sensitive hypertension and hypokalemia), is associated with gain of function mutations in the  $\beta$  and  $\gamma$  subunits leading to defective ENaC ubiquitylation and increased stability of active ENaC at the cell surface (Staub *et al.*, 1996; Rotin and Schild, 2008; Schild, 2010). Enzymes that deubiquitylate ENaC increase its function *in vivo*. Pseudohypoaldosteronism type 1 (PHA-1) can occur through either mutations in the gene encoding the mineralocorticoid receptor, or loss of function mutations in genes encoding ENaC subunits (see Bonny and Hummler, 2000). Regulation of ENaC by phosphoinositides may underlie insulin-evoked renal Na<sup>+</sup> retention that can complicate the clinical management of type 2 diabetes using insulin-sensitizing thiazolidinedione drugs (Guan *et al.* 2005).

**Abbreviations:** P552-02, N-(3,5-diamino-6-chloropyrazine-2-carbonyl)-N'-4-[4-(2,3-dihydroxypropoxy)phenyl]butyl-guanidine methanesulfonate; S3969, N-(2-hydroxyethyl)-4-methyl-2-(4-methyl-1H-indol-3-ylthio)pentanamide

## Further Reading

- Bhalla V, Hallows KR (2008). Mechanisms of ENaC Regulation and Clinical Implications. *J Am Soc Nephrol* **19**: 1845–1854.
- Bonny O, Hummler E (2000). Dysfunction of epithelial sodium transport: from human to mouse. *Kidney Int* **57**: 1313–1318.
- Bubien JK (2010). Epithelial Na<sup>+</sup> channel (ENaC), hormones, and hypertension. *J Biol Chem* **285**: 23527–23531.
- Butterworth MB (2010). Regulation of the epithelial sodium channel (ENaC) by membrane trafficking. *Biochim Biophys Acta* **1802**: 1166–1177.
- Hamm LL, Feng Z, Hering-Smith KS (2010). Regulation of sodium transport by ENaC in the kidney. *Curr Opin Nephrol Hypertens* **19**: 98–105.
- Hummler E, Vallon V (2005). Lessons from mouse mutants of epithelial sodium channel and its regulatory proteins. *J Am Soc Nephrol* **16**: 3160–3166.
- Kellenberger S, Schild L. (2002). Epithelial sodium channel/degnerin family of ion channels: a variety of functions for a shared structure. *Physiol Rev* **82**: 735–767.
- Kitamura K, Tomita K (2010). Regulation of renal sodium handling through the interaction between serine proteases and serine protease inhibitors. *Clin Exp Nephrol* **14**: 405–410.
- Kleyman TR, Carattino MD, Hughey RP (2009). ENaC at the cutting edge: regulation of epithelial sodium channels by proteases. *J Biol Chem* **284**: 20447–20451.
- Loffing J, Korbmacher C (2009). Regulated sodium transport in the renal connecting tubule (CNT) *via* the epithelial sodium channel (ENaC). *Pflugers Arch* **458**: 111–135.

- Ma HP, Chou CF, Wei SP, Eaton DC (2007). Regulation of the epithelial sodium channel by phosphatidylinositides: experiments, implications, and speculations. *Pflugers Arch* **455**: 169–180.
- Planes C, Caughey GH (2007). Regulation of the epithelial Na<sup>+</sup> channel by peptidases. *Curr Top Dev Biol* **78**: 23–46.
- Pochynyuk O, Bugaj V, Stockand JD (2008). Physiologic regulation of the epithelial sodium channel by phosphatidylinositides. *Curr Opin Nephrol Hypertens* **17**: 533–540.
- Rossier BC, Stutts MJ (2009). Activation of the epithelial sodium channel (ENaC) by serine proteases. *Annu Rev Physiol* **71**: 361–379.
- Rossier BC, Pradervand S, Schild L, Hummler E (2002). Epithelial sodium channel and the control of sodium balance: interaction between genetic and environmental factors. *Annu Rev Physiol* **64**: 877–897.
- Rotin D, Schild L (2008). ENaC and its regulatory proteins as drug targets for blood pressure control. *Curr Drug Targets* **9**: 709–716.
- Schild L (2004). The epithelial sodium channel: from molecule to disease. *Rev Physiol Biochem Pharmacol* **151**: 93–107.
- Schild L (2010). The epithelial sodium channel and the control of sodium balance. *Biochim Biophys Acta* **1802**: 1159–1165.

## References

- Barker PM *et al.* (1990). *J Physiol* **424**: 473–485.
- Boarse NA *et al.* (2011). *Nature Commun* **2**: 287.
- Canessa CM *et al.* (1993). *Nature* **361**: 467–470.
- Canessa CM *et al.* (1994). *Nature* **367**: 463–466.
- Debonneville C *et al.* (2001). *EMBO J* **20**: 7052–7059.
- Friedrich B *et al.* (2003). *Pflugers Arch* **445**: 693–696.
- Garcia-Caballero A *et al.* (2009). *Proc Natl Acad Sci USA* **106**:11412–11417.
- Gonzales EB *et al.* (2009). *Nature* **460**: 599–604.
- Guan Y *et al.* (2005). *Nature Med* **11**: 861–866.
- Hirsch AJ *et al.* (2008). *J Pharmacol Exp Ther* **325**: 77–88.
- Hummler E *et al.* (1996). *Nature Genet* **12**: 325–328.
- Kellenberger S *et al.* (2003). *Mol Pharmacol* **64**: 848–856.
- Lu M *et al.* (2008). *J Biol Chem* **283**: 11981–11994.
- Maekawa A *et al.* (2009). *J Hypertens* **27**: 181–189.
- Morris RG, Schafer JA (2002). *J Gen Physiol* **120**: 71–85.
- Richard K *et al.* (2004). *FEBS Lett* **576**: 339–342.
- Sayegh R *et al.* (1999). *J Biol Chem* **274**: 12431–12437.
- Staub O *et al.* (1996). *EMBO J* **15**: 2371–2380.
- Yang L-M *et al.* (2006). *J Biol Chem* **281**: 9859–9868.

# Hyperpolarisation-activated, cyclic nucleotide-gated (HCN)

**Overview:** The hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarisation at voltages negative to  $-50$  mV. The cyclic nucleotides cAMP and cGMP directly activate the channels and shift the activation curves of HCN channels to more positive voltages, thereby enhancing channel activity. HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons (DiFrancesco, 1993; Pape, 1996). In native cells, these currents have a variety of names, such as  $I_h$ ,  $I_q$  and  $I_i$ . The four known HCN channels have six transmembrane domains and form tetramers. It is believed that the channels can form heteromers with each other, as has been shown for HCN1 and HCN4 (Altomare *et al.*, 2003). A standardised nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al.*, 2005).

Nomenclature	HCN1	HCN2	HCN3	HCN4
Ensembl ID	ENSG00000164588	ENSG00000099822	ENSG00000143630	ENSG00000138622
Activators	cAMP > cGMP (both weak)	cAMP > cGMP	–	cAMP > cGMP
Inhibitors	Cs <sup>+</sup> , ZD7288, ivabradine	Cs <sup>+</sup> , ZD7288, ivabradine	Cs <sup>+</sup> , ZD7288, ivabradine	Cs <sup>+</sup> , ZD7288, ivabradine

HCN channels are permeable to both Na<sup>+</sup> and K<sup>+</sup> ions, with a Na<sup>+</sup>/K<sup>+</sup> permeability ratio of about 0.2. Functionally, they differ from each other in terms of time constant of activation with HCN1 the fastest, HCN4 the slowest and HCN2 and HCN3 intermediate. The compounds ZD7288 (BoSmith *et al.*, 1993) and ivabradine (Bucchi *et al.*, 2002) have proven useful in identifying and studying functional HCN channels in native cells. Zatebradine and cilobradine are also useful blocking agents.

**Abbreviations:** **Ivabradine (S16257-2)**, (3-(3-(((7S)-3,4-dimethoxybicyclo [4,2,0] octa-1,3,5-trien-7-yl) methyl) methylamino) propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride; **ZD7288**, [4-(N-ethyl-N-phenyl-amino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride

## Further Reading

- Baruscotti M, Bottelli G, Milanese R, DiFrancesco JC, DiFrancesco D (2010). HCN-related channelopathies. *Pflugers Arch* **460**: 405–415.
- Baruscotti M, Bucchi A, DiFrancesco D (2005). Physiology and pharmacology of the cardiac pacemaker ('funny') current. *Pharmacol Ther* **107**: 59–79.
- Biel M, Michalakakis S (2009). Cyclic nucleotide-gated channels. *Handb Exp Pharmacol* **191**: 111–136.
- Biel M, Ludwig A, Zong X, Hofmann F (1999). Hyperpolarisation-activated cation channels: a multi-gene family. *Rev Physiol Biochem Pharmacol* **136**: 165–181.
- Biel M, Schneider A, Wahl C (2002). Cardiac HCN channels: structure, function and modulation. *Trends Cardiovasc Med* **12**: 206–213.
- Biel M, Wahl-Schott C, Michalakakis S, Zong X (2009). Hyperpolarization-activated cation channels: from genes to function. *Physiol Rev* **89**: 847–885.
- Bois P, Guinamard R, Chemaly AE, Faivre JF, Bescond J (2007). Molecular regulation and pharmacology of pacemaker channels. *Curr Pharm Des* **13**: 2338–2349.
- Craven KB, Zagotta WN (2006). CNG and HCN channels: two peas, one pod. *Annu Rev Physiol* **68**: 375–401.
- DiFrancesco D (1993). Pacemaker mechanisms in cardiac tissue. *Ann Rev Physiol* **55**: 455–472.
- DiFrancesco D. (2010). The role of the funny current in pacemaker activity. *Circ Res* **106**: 434–446.
- DiFrancesco D, Camm JA (2004). Heart rate lowering by specific and selective *I<sub>f</sub>* current inhibition with ivabradine – a new therapeutic perspective in cardiovascular disease. *Drugs* **64**: 1757–1765.
- Dunlop J, Vasilyev D, Lu P, Cummons T, Bowlby MR (2009). Hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels and pain. *Curr Pharm Des* **15**: 1767–1772.
- Hofmann F, Biel M, Kaupp UB (2005). International Union of Pharmacology. LI. Nomenclature and structure-function relationships of cyclic nucleotide-regulated channels. *Pharmacol Rev* **57**: 455–462.
- Kaupp UB, Seifert R (2001). Molecular diversity of pacemaker ion channels. *Ann Rev Physiol* **63**: 235–257.
- Maher MP, Wu NT, Guo HQ, Dubin AE, Chaplan SR, Wickenden AD (2009). HCN channels as targets for drug discovery. *Comb Chem High Throughout Screen* **12**: 64–72.
- Meldrum BS, Rogawski MA (2007). Molecular targets for antiepileptic drug development. *Neurotherapeutics* **4**: 18–61.
- Pape HC (1996). Queer current and pacemaker: the hyperpolarisation-activated cation current in neurons. *Ann Rev Physiol* **58**: 299–327.
- Tardiff JC (2008). Ivabradine: I(f) inhibition in the management of stable angina pectoris and other cardiovascular diseases. *Drugs Today* **44**: 171–181.
- Wahl-Schott C, Biel M (2009). HCN channels: structure, cellular regulation and physiological function. *Cell Mol Life Sci* **66**: 470–494.
- Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004**: re15.

## References

- Altomare C *et al.* (2003). *J Physiol* **549**: 347–359.
- Bosmith RE *et al.* (1993). *Br J Pharmacol* **110**: 343–349.
- Bucchi A *et al.* (2002). *J Gen Physiol* **120**: 1–13.

# IP<sub>3</sub> receptor

**Overview:** The inositol 1,4,5-trisphosphate receptors (IP<sub>3</sub>R) are ligand-gated Ca<sup>2+</sup>-release channels on intracellular Ca<sup>2+</sup> store sites (such as the endoplasmic reticulum). They are responsible for the mobilization of intracellular Ca<sup>2+</sup> stores and play an important role in intracellular Ca<sup>2+</sup> signalling in a wide variety of cell types. Three different gene products (types I–III) have been isolated, which assemble as large tetrameric structures. IP<sub>3</sub>R<sub>s</sub> are closely associated with certain proteins: calmodulin and FKBP (and calcineurin via FKBP). They are phosphorylated by PKA, PKC, PKG and CaMKII.

Nomenclature	IP <sub>3</sub> R1	IP <sub>3</sub> R2	IP <sub>3</sub> R3
Other names	INSP3R1	INSP3R2	INSP3R3
Ensembl ID	ENSG00000150995	ENSG00000123104	ENSG00000096433
Endogenous activators	Ins(1,4,5)P <sub>3</sub> (nM – μM), cytosolic Ca <sup>2+</sup> (<750 μM), cytosolic ATP (<mM)	Ins(1,4,5)P <sub>3</sub> (nM–μM), cytosolic Ca <sup>2+</sup> (nM)	Ins(1,4,5)P <sub>3</sub> (nM–μM), cytosolic Ca <sup>2+</sup> (nM)
Pharmacological activators	InsP <sub>3</sub> analogues including Ins(2,4,5)P <sub>3</sub> , adenophostin A (nM)	InsP <sub>3</sub> analogues including Ins(2,4,5)P <sub>3</sub> , adenophostin A (nM)	–
Antagonists	Xestospongins C (μM), caffeine (mM), phosphatidylinositol 4,5-bisphosphate (μM), heparin (μg/ml), decavanadate (μM), calmodulin at high cytosolic Ca <sup>2+</sup>	Heparin (μg/ml), decavanadate (μM)	Heparin (μg/ml), decavanadate (μM)
Functional characteristics	Ca <sup>2+</sup> : (P <sub>Ba</sub> /P <sub>K</sub> ~6) single-channel conductance ~70 pS (50 mM Ca <sup>2+</sup> )	Ca <sup>2+</sup> : single-channel conductance ~70 pS (50 mM Ca <sup>2+</sup> ), ~390 pS (220 mM Cs <sup>+</sup> )	Ca <sup>2+</sup> : single-channel conductance ~88 pS (55 mM Ba <sup>2+</sup> )

The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect.

**Abbreviations:** FKBP, FK506-binding protein

## Further Reading

- Balla T (2009). Regulation of Ca<sup>2+</sup> entry by inositol lipids in mammalian cells by multiple mechanisms. *Cell Calcium* **45**: 527–534.
- Berridge MJ, Lipp P, Bootman MD (2000). The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1**: 11–21.
- Bolton TB (2006). Calcium events in smooth muscles and their interstitial cells: physiological roles of sparks. *J Physiol* **570**: 5–11.
- Bootman MD, Berridge MJ, Roderick HL (2002). Calcium signalling: more messengers, more channels, more complexity. *Curr Biol* **12**: R563–R565.
- Bosanac I, Michikawa T, Mikoshiba K, Ikura M (2004). Structural insights into the regulatory mechanism of IP<sub>3</sub> receptor. *Biochim Biophys Acta* **1742**: 89–102.
- Bultynck G, Sienaert I, Parys JB, Callewaert G, De Smedt H, Boens N *et al.* (2003). Pharmacology of inositol trisphosphate receptors. *Pflugers Arch* **445**: 629–642.
- Choe CU, Ehrlich BE (2006). The inositol 1,4,5-trisphosphate receptor (IP3R) and its regulators: sometimes good and sometimes bad team work. *Sci STKE* **2006**: re15.
- Foskett JK (2010). Inositol trisphosphate receptor Ca<sup>2+</sup> release channels in neurological diseases. *Pflugers Arch* **460**: 481–494.
- Foskett JK, White C, Cheung KH, Mak DO (2007). Inositol trisphosphate receptor Ca<sup>2+</sup> release channels. *Physiol Rev* **87**: 593–658.
- Mikoshiba K (2007). IP<sub>3</sub> receptor/Ca<sup>2+</sup> channel from discovery to new signaling concepts. *J Neurochem* **102**: 1426–1446.
- Mikoshiba K (2007). The IP<sub>3</sub> receptor/Ca<sup>2+</sup> channel and its cellular function. *Biochem Soc Symp* **74**: 9–22.
- Nahorski SR (2006). Pharmacology of intracellular signalling pathways. *Br J Pharmacol* **147** (Suppl. 1): S38–S45.
- Patel S, Joseph SK, Thomas AP (1999). Molecular properties of inositol 1,4,5-trisphosphate receptors. *Cell Calcium* **25**: 247–264.
- Patterson RL, Boehning D, Snyder SH (2004). Inositol 1,4,5-trisphosphate receptors as signal integrators. *Annu Rev Biochem* **73**: 437–465.
- Taylor CW, Traynor D (1995). Calcium and inositol trisphosphate receptors. *J Membr Biol* **145**: 109–118.
- Taylor CW, Tovey SC (2010). IP<sub>3</sub> receptors: toward understanding their activation. *Cold Spring Harb Perspect Biol* **2**: a004010.
- Verkhatsky A (2005). Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. *Physiol Rev* **85**: 201–279.
- Vermassen E, Parys JB, Mauger J-P (2004). Subcellular distribution of the inositol 1,4,5-trisphosphate receptors: functional relevance and molecular determinants. *Biol Cell* **96**: 3–17.

# Potassium

**Overview:** Potassium channels are fundamental regulators of excitability. They control the frequency and the shape of action potential waveform, the secretion of hormones and neurotransmitters and cell membrane potential. Their activity may be regulated by voltage, calcium and neurotransmitters (and the signalling pathways they stimulate). They consist of a primary pore-forming  $\alpha$  subunit often associated with auxiliary regulatory subunits. Since there are over 70 different genes encoding K channels  $\alpha$  subunits in the human genome, it is beyond the scope of this guide to treat each subunit individually. Instead, channels have been grouped into families and subfamilies based on their structural and functional properties. The three main families are the 2TM (two transmembrane domain), 4TM and 6TM families. A standardised nomenclature for potassium channels has been proposed by the NC-IUPHAR subcommittees on potassium channels (see Goldstein *et al.*, 2005; Gutman *et al.*, 2005; Kubo *et al.*, 2005; Wei *et al.*, 2005).

## The 2TM family of K channels

The 2TM domain family of K channels are also known as the inward-rectifier K channel family. This family includes the strong inward-rectifier K channels ( $K_{IR2.x}$ ), the G-protein-activated inward-rectifier K channels ( $K_{IR3.x}$ ) and the ATP-sensitive K channels ( $K_{IR6.x}$ , which combine with sulphonylurea receptors (SUR)). The pore-forming  $\alpha$  subunits form tetramers, and heteromeric channels may be formed within subfamilies (e.g.  $K_{IR3.2}$  with  $K_{IR3.3}$ ).

Subfamily group	$K_{IR1.x}$	$K_{IR2.x}$	$K_{IR3.x}$	$K_{IR4.x}$
Subtypes	$K_{IR1.1}$ (ROMK1)	$K_{IR2.1-2.4}$ (IRK1-4)	$K_{IR3.1-3.4}$ (GIRK1-4)	$K_{IR4.1-4.2}$
Ensembl ID*	ENSG00000151704 ( $K_{IR1.1}$ )	ENSG00000123700 ( $K_{IR2.1}$ )	ENSG00000162989 ( $K_{IR3.1}$ )	ENSG00000177807 ( $K_{IR4.1}$ )
Activators	–	–	PIP <sub>2</sub> , G $\beta$ $\gamma$	–
Inhibitors	–	[Mg <sup>2+</sup> ] <sub>i</sub> , polyamines (internal)	–	–
Functional characteristic	Inward-rectifier current	IK <sub>1</sub> in heart, 'strong' inward-rectifier current	G-protein-activated inward-rectifier current	Inward-rectifier current

Subfamily Group	$K_{IR5.x}$	$K_{IR6.x}$	$K_{IR7.x}$
Subtypes	$K_{IR5.1}$	$K_{IR6.1-6.2}$ ( $K_{ATP}$ )	$K_{IR7.1}$
Ensembl ID*	ENSG00000153822 ( $K_{IR5.1}$ )	ENSG00000121361 ( $K_{IR6.1}$ )	ENSG00000115474 ( $K_{IR7.1}$ )
Activators	–	Minoxidil, cromakalim, diazoxide, nicorandil	–
Inhibitors	–	Tolbutamide, glibenclamide	–
Functional characteristic	Inward-rectifier current	ATP-sensitive, inward-rectifier current	Inward-rectifier current
Associated subunits	–	SUR1, SUR2A, SUR2B	–

\*Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein or at the following link: <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=74>.

## The 4TM family of K channels

The 4TM family of K channels are thought to underlie many leak currents in native cells. They are open at all voltages and regulated by a wide array of neurotransmitters and biochemical mediators. The primary pore-forming  $\alpha$  subunit contains two pore domains (indeed, they are often referred to as two-pore domain K channels or K2P) and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (e.g.  $K_{2P3.1}$  with  $K_{2P9.1}$ ). There is no current, clear, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies (see Goldstein *et al.*, 2005). The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

Subfamily group	'TWIK'	'TREK'	'TASK'	'TALK'	'THIK'	'TRESK'
Subtypes	$K_{2P1.1}$ (TWIK1) $K_{2P6.1}$ (TWIK2) $K_{2P7.1}$ (KNCK7)	$K_{2P2.1}$ (TREK1) $K_{2P10.1}$ (TREK2) $K_{2P4.1}$ (TRAAK)	$K_{2P3.1}$ (TASK1) $K_{2P9.1}$ (TASK3) $K_{2P15.1}$ (TASK5)	$K_{2P16.1}$ (TALK1) $K_{2P5.1}$ (TASK2) $K_{2P17.1}$ (TASK4)	$K_{2P13.1}$ (THIK1) $K_{2P12.1}$ (THIK2)	$K_{2P18.1}$ (TRESK1)
Ensembl ID*	ENSG00000135750 ( $K_{2P1.1}$ )	ENSG00000082482 ( $K_{2P2.1}$ )	ENSG00000171303 ( $K_{2P3.1}$ )	ENSG00000164626 ( $K_{2P5.1}$ )	ENSG00000152315 ( $K_{2P13.1}$ )	ENSG00000186795 ( $K_{2P18.1}$ )



Subfamily group	'TWIK'	'TREK'	'TASK'	'TALK'	'THIK'	'TRESK'
Activators	–	Halothane (not TRAAK), riluzole, stretch, heat, arachidonic acid, acid pH <sub>i</sub>	Halothane, alkaline pH <sub>o</sub> (K <sub>2P</sub> 3.1)	Alkaline pH <sub>o</sub>	–	–
Inhibitors	Acid pH <sub>i</sub>	–	Anandamide (K <sub>2P</sub> 3.1, K <sub>2P</sub> 9.1) ruthenium red (K <sub>2P</sub> 9.1) acid pH <sub>o</sub>	–	Halothane	Arachidonic acid
Functional characteristic	Background current	Background current	Background current	Background current	Background current	Background current

The K<sub>2P</sub>7.1, K<sub>2P</sub>15.1 and K<sub>2P</sub>12.1 subtypes, when expressed in isolation, are nonfunctional. All 4TM channels are insensitive to the classical potassium channel blockers TEA and 4-AP, but are blocked to varying degrees by Ba<sup>2+</sup> ions.

\*Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein or at the following link: <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=79>.

### The 6TM family of K channels

The 6TM family of K channels comprises the voltage-gated K<sub>v</sub> subfamilies, the KCNQ subfamily the EAG subfamily (which includes hERG channels), the Ca<sup>2+</sup>-activated Slo subfamily (actually with 7TM) and the Ca<sup>2+</sup>-activated SK subfamily. As for the 2TM family, the pore-forming  $\alpha$  subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. K<sub>v</sub>1.1 with K<sub>v</sub>1.2; KCNQ2 with KCNQ3).

Subfamily group	K <sub>v</sub> 1.x	K <sub>v</sub> 2.x	K <sub>v</sub> 3.x	K <sub>v</sub> 4.x
Subtypes	K <sub>v</sub> 1.1 – K <sub>v</sub> 1.8 Shaker-related	K <sub>v</sub> 2.1–2.2 Shab-related	K <sub>v</sub> 3.1–3.4 Shal-related	K <sub>v</sub> 4.1–4.3 Shaw-related
Ensembl ID*	ENSG00000111262 (K <sub>v</sub> 1.1)	ENSG00000158445 (K <sub>v</sub> 2.1)	ENSG00000129159 (K <sub>v</sub> 3.1)	ENSG00000102057 (K <sub>v</sub> 4.1)
Inhibitors	TEA potent (1.1), TEA moderate (1.3, 1.6), 4-AP potent (1.4), $\alpha$ -dendrotoxin (1.1, 1.2, 1.6), margatoxin (1.1, 1.2, 1.3), noxiustoxin (1.2, 1.3)	TEA moderate	TEA potent, 4-AP potent (3.1, 3.2), BDS-1 (3.4)	–
Functional characteristics	K <sub>v</sub> (1.1–1.3, 1.5–1.8), K <sub>A</sub> (1.4)	K <sub>v</sub> (2.1)	K <sub>v</sub> (3.1, 3.2), K <sub>A</sub> (3.3, 3.4)	K <sub>A</sub>
Associated subunits	K <sub>v</sub> $\beta$ <sub>1</sub> , K <sub>v</sub> $\beta$ <sub>2</sub>	K <sub>v</sub> 5.1, K <sub>v</sub> 6.1–6.4, K <sub>v</sub> 8.1–8.2, K <sub>v</sub> 9.1–9.3	MiRP2 (K <sub>v</sub> 3.4)	KChIP, KChAP

Subfamily group	K <sub>v</sub> 7.x ('KCNQ')	K <sub>v</sub> 10.x, K <sub>v</sub> 11.x, K <sub>v</sub> 12.x ('EAG')	K <sub>Ca</sub> 1.x, K <sub>Ca</sub> 4.x, K <sub>Ca</sub> 5.x ('Slo')	K <sub>Ca</sub> 2.x, K <sub>Ca</sub> 3.x ('SK')
Subtypes	K <sub>v</sub> 7.1–7.5 (KCNQ1-5)	K <sub>v</sub> 10.1–10.2 (eag1–2) K <sub>v</sub> 11.1–11.3 (erg1-3, hERG 1–3) K <sub>v</sub> 12.1–12.3 (elk1-3)	K <sub>Ca</sub> 1.1, K <sub>Ca</sub> 4.1–4.2, K <sub>Ca</sub> 5.1 Slo (BK), Slack, Slick	K <sub>Ca</sub> 2.1–2.3 (SK1–SK3) K <sub>Ca</sub> 3.1 (SK4, IK)
Ensembl ID*	ENSG00000053918 (K <sub>v</sub> 7.1)	ENSG00000143473 (K <sub>v</sub> 10.1)	ENSG00000156113 (K <sub>Ca</sub> 1.1)	ENSG00000105642 (K <sub>Ca</sub> 2.1)
Activators	Retigabine (K <sub>v</sub> 7.2,–5)	–	NS004, NS1619	–
Inhibitors	TEA (K <sub>v</sub> 7.2, 7.4), XE991 (K <sub>v</sub> 7.1, 7.2, 7.4, 7.5), linopirdine	E-4031 (K <sub>v</sub> 11.1), astemizole (K <sub>v</sub> 11.1), terfenadine (K <sub>v</sub> 11.1)	TEA, charybdotoxin, iberiotoxin	Charybdotoxin (K <sub>Ca</sub> 3.1), apamin (K <sub>Ca</sub> 2.1–2.3)
Functional characteristic	K <sub>v</sub> 7.1 – cardiac I <sub>Ks</sub> K <sub>v</sub> 7.2/7.3–M current	K <sub>v</sub> 11.1 – cardiac I <sub>Kr</sub>	Maxi K <sub>Ca</sub> K <sub>Na</sub> (slack & slick)	SK <sub>Ca</sub> (K <sub>Ca</sub> 2.1–2.3) I <sub>KCa</sub> (K <sub>Ca</sub> 3.1)
Associated subunits	minK, MiRP2 (K <sub>v</sub> 7.1)	minK, MiRP1 (erg1)	–	–

\*Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein or at the following links: <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=81> or <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=69>

**Abbreviations:** 4-AP, 4-aminopyridine; BDS-1, blood depressing substance 1; E4031, 1-(2-(6-methyl-2-pyridyl)ethyl)-4-(4-methylsulphonyl aminobenzoyl)piperidine; NS004, 1-(2-hydroxy-5-chlorophenyl)-5-trifluoromethyl-2-benzimidazolone; NS1619, 1-(2'-hydroxy-5'-trifluoromethylphenyl)-5-trifluoro-methyl-2(3H)benzimidazolone; PIP<sub>2</sub>, phosphatidylinositol 4,5, bisphosphate; TEA, tetraethylammonium; XE991, 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracene

### Further Reading

- Aguilar-Bryan L, Clement JP, Gonzalez G, Kunjilwar K, Babenko A, Bryan J (1998). Toward understanding the assembly and structure of K<sub>ATP</sub> channels. *Physiol Rev* 78: 227–245.
- Ahern CA, Kobertz WR (2009). Chemical tools for K(+) channel biology. *Biochemistry* 48: 517–526.
- Ashcroft FM, Gribble FM (1998). Correlating structure and function in ATP-sensitive K<sup>+</sup> channels. *Trends Neurosci* 21: 288–294.
- Bauer CK, Schwartz JR (2001). Physiology of EAG channels. *J Membr Biol* 182: 1–15.
- Bayliss DA, Barrett PQ (2008). Emerging roles for two-pore-domain potassium channels and their potential therapeutic impact. *Trends Pharmacol Sci* 29: 566–575.
- Bean BP (2007). The action potential in mammalian central neurons. *Nat Rev Neurosci* 8: 451–465.
- Bezánilla F (2000). The voltage sensor in voltage-dependent ion channels. *Physiol Rev* 80: 555–592.
- Dalby-Brown W, Hansen HH, Korsgaard MP, Mirza N, Olesen SP (2006). K(v) channels: function, pharmacology and channel modulators. *Curr Top Med Chem* 6: 999–1023.
- Enyedi P, Czirják G (2010). Molecular background of leak K<sup>+</sup> currents: two-pore domain potassium channels. *Physiol Rev* 90: 559–605.
- Goldstein SAN, Bayliss DA, Kim D, Lesage F, Plant LD, Rajan S (2005). International Union of Pharmacology. LV. Nomenclature and molecular relationships of Two-P potassium channels. *Pharmacol Rev* 57: 527–540.
- Goldstein SAN, Bockenhauer D, O'Kelly I, Zilberberg N (2001). Potassium leak channels and the KCNK family of two-P domain subunits. *Nat Rev Neurosci* 2: 175–184.
- Gutman GA, Chandy KG, Grissmer S, Lazdunski M, McKinnon D, Pardo LA *et al.* (2005). International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev* 57: 473–508.
- Hancox JC, McPate MJ, El Harchi A, Zhang YH (2008). The hERG potassium channel and hERG screening for drug-induced torsades de pointes. *Pharmacol Ther* 119: 118–132.
- Hansen JB (2006). Towards selective Kir6.2/SUR1 potassium channel openers, medicinal chemistry and therapeutic perspectives. *Curr Med Chem* 13: 26–376.
- Honore E (2007). The neuronal background K2P channels: focus on TREK1. *Nature Rev Neurosci* 8: 251–261.
- Jenkinson DH (2006). Potassium channels- multiplicity and challenges. *Br J Pharmacol* 147 (Suppl. 1): S63–S71.
- Judge SI, Bever CT Jr (2006). Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. *Pharmacol Ther* 111: 224–259.
- Kaczorowski GJ, Garcia ML (1999). Pharmacology of voltage-gated and calcium-activated potassium channels. *Curr Opin Chem Biol* 3: 448–458.
- Kannankeril P, Roden DM, Darbar D (2010). Drug-Induced Long QT Syndrome *Pharmacol Rev* 62: 760–781.
- Kobayashi T, Ikeda K (2006). G protein-activated inwardly-rectifying potassium channels as potential therapeutic targets. *Curr Pharm Des* 12: 4513–4523.
- Kubo Y, Adelman JP, Clapham DE, Jan LY, Karschin A, Kurachi Y *et al.* (2005). International Union of Pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. *Pharmacol Rev* 57: 509–526.
- Lawson K, McKay NG (2006). Modulation of potassium channels as a therapeutic approach. *Curr Pharm Des* 12: 459–470.
- Lesage F (2003). Pharmacology of neuronal background potassium channels. *Neuropharmacology* 44: 1–7.
- Lewis RJ, Garcia ML (2003). Therapeutic potential of venom peptides. *Nat Rev Drug Discov* 2: 790–802.
- Lüscher C, Slesinger PA (2010). Emerging roles for G protein-gated inwardly rectifying potassium (GIRK) channels in health and disease. *Nat Rev Neurosci* 11: 301–315.
- Mannhold R (2006). Structure-activity relationships of K<sub>ATP</sub> channel openers. *Curr Top Med Chem* 6: 1031–1047.
- Mathie A, Veale EL (2007). Therapeutic potential of neuronal two pore domain potassium channel modulators. *Curr Opin Invest Drugs* 8: 555–562.
- Miller C (2003). A charged view of voltage-gated ion channels. *Nat Struct Biol* 10: 422–424.
- Nardi A, Olesen SP (2008). BK channel modulators: a comprehensive review. *Curr Med Chem* 15: 1126–1146.
- Nichols CG, Lopatin AN (1997). Inwardly rectifying potassium channels. *Annu Rev Physiol* 59: 171–191.
- Pongs O, Schwarz JR (2010). Ancillary subunits associated with voltage-dependent K<sup>+</sup> channels. *Physiol Rev* 90: 755–796.
- Reimann F, Ashcroft FM (1999). Inwardly rectifying potassium channels. *Curr Opin Cell Biol* 11: 503–508.
- Robbins J (2001). KCNQ potassium channels: physiology, pathophysiology and pharmacology. *Pharmacol Ther* 90: 1–19.
- Salkoff L, Butler A, Ferreira G, Santi C, Wei A (2006). High-conductance potassium channels of the SLO family. *Nature Rev Neurosci* 7: 921–931.
- Sanguinetti MC (2000). Maximal function of minimal K<sup>+</sup> channel subunits. *Trends Pharmacol Sci* 21: 199–201.
- Seino S, Miki T (2003). Physiological and pathophysiological roles of ATP-sensitive K<sup>+</sup> channels. *Prog Biophys Mol Biol* 81: 133–176.
- Stanfield PR, Nakajima S, Nakajima Y (2002). Constitutively active and G-protein coupled inward rectifier K<sup>+</sup> channels: Kir2.0 and Kir3.0. *Rev Physiol Biochem Pharmacol* 145: 47–179.
- Stocker M (2004). Ca<sup>2+</sup>-activated K<sup>+</sup> channels: molecular determinants and function of the SK family. *Nat Rev Neurosci* 5: 758–770.
- Takeda M, Tsuboi Y, Kitagawa J, Nakagawa K, Iwata K, Matsumoto S (2011). Potassium channels as a potential therapeutic target for trigeminal neuropathic and inflammatory pain. *Mol Pain* 7: 5.
- Trimmer JS, Rhodes KJ (2004). Localisation of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* 66: 477–519.
- Wang H, Tang Y, Wang L, Long CL, Zhang YL (2007). ATP-sensitive potassium channel openers and 2,3-dimethyl-2-butylamine derivatives. *Curr Med Chem* 14: 133–155.
- Weatherall KL, Goodchild SJ, Jane DE, Marrion NV (2010). Small conductance calcium-activated potassium channels: from structure to function. *Prog Neurobiol* 91: 242–255.
- Wei AD, Gutman GA, Aldrich R, Chandy KG, Grissmer S, Wulff H (2005). International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated channels. *Pharmacol Rev* 57: 463–472.
- Wickenden AD, McNaughton-Smith G (2009). Kv7 channels as targets for the treatment of pain. *Curr Pharm Des* 15: 1773–1798.
- Witchel HJ (2007). The hERG potassium channel as a therapeutic target. *Expert Opin Ther Targets* 11: 321–336.
- Wulff H, Castle NA, Pardo LA (2009). Voltage-gated potassium channels as therapeutic targets. *Nat Rev Drug Discov* 8: 982–1001.
- Yellen G (2002). The voltage-gated potassium channels and their relatives. *Nature* 419: 35–42.
- Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* 2004: re15.

# Voltage-gated proton channel

**Overview:** The voltage-gated proton channel (provisionally denoted H<sub>v</sub>1) is a putative 4TM proton-selective channel gated by membrane depolarization and which is sensitive to the transmembrane pH gradient (Ramsey *et al.*, 2006; Sasaki *et al.*, 2006; DeCoursey, 2008a,b; Capasso *et al.*, 2011). The structure of H<sub>v</sub>1 is homologous to the voltage sensing domain (VSD) of the superfamily of voltage-gated ion channels (*i.e.* segments S1 to S4) and contains no discernable pore region (Ramsey *et al.*, 2006; Sasaki *et al.*, 2006). Proton flux through H<sub>v</sub>1 is instead most likely mediated by a water wire completed in a crevice of the protein when the voltage-sensing S4 helix moves in response to a change in transmembrane potential (Ramsey *et al.*, 2010; Wood *et al.*, 2011). H<sub>v</sub>1 expresses largely as a dimer mediated by intracellular C-terminal coiled-coil interactions (Li *et al.*, 2010) but individual promoters nonetheless support gated H<sup>+</sup> flux *via* separate conduction pathways (Koch *et al.*, 2008; Lee *et al.*, 2008; Tombola *et al.*, 2008; Petheo *et al.*, 2010). Within dimeric structures, the two protomers do not function independently, but display co-operative interactions during gating resulting in increased voltage sensitivity, but slower activation, of the dimeric, *versus* monomeric, complexes (Gonzalez *et al.*, 2010; Tombola *et al.*, 2010).

Nomenclature	H <sub>v</sub> 1
Other names	Voltage-gated proton channel 1 (HVCN1), Voltage-sensor only protein (VSOP)
Ensembl ID	ENSG00000122986
Activators	–
Blockers (IC <sub>50</sub> )	Zn <sup>2+</sup> (≈0.5–2.0 μM), Cd <sup>2+</sup> (≈10 μM)
Functional characteristics	Activated by membrane depolarization mediating macroscopic currents with time-, voltage- and pH-dependence; outwardly rectifying; voltage dependent kinetics with relatively slow current activation sensitive to extracellular pH and temperature, relatively fast deactivation; voltage threshold for current activation determined by pH gradient (ΔpH = pH <sub>o</sub> -pH <sub>i</sub> ) across the membrane

The voltage threshold ( $V_{\text{thr}}$ ) for activation of H<sub>v</sub>1 is not fixed but is set by the pH gradient across the membrane such that  $V_{\text{thr}}$  is positive to the Nernst potential for H<sup>+</sup>, which ensures that only outwardly directed flux of H<sup>+</sup> occurs under physiological conditions (DeCoursey, 2008a,b; Capasso *et al.*, 2011). Phosphorylation of H<sub>v</sub>1 within the N-terminal domain by PKC enhances the gating of the channel (Musset *et al.*, 2010a). Tabulated IC<sub>50</sub> values for Zn<sup>2+</sup> and Cd<sup>2+</sup> are for heterologously expressed human and mouse H<sub>v</sub>1 (Ramsey *et al.*, 2006; Sasaki *et al.*, 2006). Zn<sup>2+</sup> is not a conventional pore blocker, but is coordinated by two, or more, external protonation sites involving histamine residues (Ramsey *et al.*, 2006). Zn<sup>2+</sup> binding may occur at the dimer interface between pairs of histamine residues from both monomers where it may interfere with channel opening (Musset *et al.*, 2010b). Mouse knockout studies demonstrate that H<sub>v</sub>1 participates in charge compensation in granulocytes during the respiratory burst of NADPH oxidase-dependent reactive oxygen species production that assists in the clearance of bacterial pathogens (Ramsey *et al.*, 2009). Additional physiological functions of H<sub>v</sub>1 are reviewed by Capasso *et al.* (2011).

## Further Reading

Capasso M, DeCoursey TE, Dyer MJ (2011). pH regulation and beyond: unanticipated functions for the voltage-gated proton channel, HVCN1. *Trends Cell Biol* **21**: 20–28.  
 DeCoursey TE (2008a). Voltage-gated proton channels. *Cell Mol Life Sci* **65**: 2554–2573.  
 DeCoursey TE (2008b). Voltage-gated proton channels: what's next? *J Physiol* **586**: 5305–5324.  
 DeCoursey TE, Cherny VV (2007). Pharmacology of voltage-gated proton channels. *Curr Pharm Des* **13**: 2400–2420.  
 Tombola F, Ulbrich MH, Isacoff EY (2009). Architecture and gating of H<sub>v</sub>1 proton channels. *J Physiol* **587**: 5325–5329.

## References

- Gonzalez C *et al.* (2010). *Nat Struct Mol Biol* **17**: 51–56.  
 Koch HP *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 9111–9116.  
 Lee S-Y *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 7692–7695.  
 Li SJ *et al.* (2010). *J Biol Chem* **285**: 12047–12054.  
 Musset B *et al.* (2010a). *J Biol Chem* **285**: 5117–5121.  
 Musset B *et al.* (2010b). *J Physiol* **588**: 1435–1449.  
 Petheo GL *et al.* (2010). *PLoS One* **5**: e14081.  
 Ramsey IS *et al.* (2006). *Nature* **440**: 1213–1216.  
 Ramsey IS *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 7642–7647.  
 Ramsey IS *et al.* (2010). *Nat Struct Mol Biol* **17**: 869–875.  
 Sasaki M *et al.* (2006). *Science* **312**: 589–592.  
 Tombola F *et al.* (2008). *Neuron* **58**: 546–556.  
 Tombola F *et al.* (2010). *Nat Struct Mol Biol* **17**: 44–50.  
 Wood ML *et al.* (2011). *Biochem. Biophys Acta*. doi: 10.1016/j.bbmem.2011.07.045

# Ryanodine receptor

**Overview:** The ryanodine receptors (RyRs) are found on intracellular Ca<sup>2+</sup> storage/release organelles. The family of RyR genes encodes three highly related Ca<sup>2+</sup> release channels: RyR1, RyR2 and RyR3, which assemble as large tetrameric structures. These RyR channels are ubiquitously expressed in many types of cells and participate in a variety of important Ca<sup>2+</sup> signaling phenomena (neurotransmission, secretion, etc.). In addition to the three mammalian isoforms described below, various nonmammalian isoforms of the ryanodine receptor have been identified and these are discussed in Sutko and Airey (1996). The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506)-binding protein, calmodulin (Yamaguchi *et al.*, 2003), triadin, calsequestrin, junctin and sorcin, and by protein kinases and phosphatases.

Nomenclature	RyR1	RyR2	RyR3
Ensembl ID	ENSG00000196218	ENSG00000198626	ENSG00000198838
Endogenous activators	Depolarisation <i>via</i> DHP receptor, cytosolic Ca <sup>2+</sup> (μM), cytosolic ATP (mM), luminal Ca <sup>2+</sup> , calmodulin at low cytosolic Ca <sup>2+</sup> , CaM kinase, PKA	Cytosolic Ca <sup>2+</sup> (μM), cytosolic ATP (mM), luminal Ca <sup>2+</sup> , CaM kinase, PKA	Cytosolic Ca <sup>2+</sup> (μM), cytosolic ATP (mM), calmodulin at low cytosolic Ca <sup>2+</sup>
Pharmacological activators	Ryanodine (nM–μM), caffeine (mM), suramin (μM)	Ryanodine (nM–μM), caffeine (mM), suramin (μM)	Ryanodine (nM–μM), caffeine (mM)
Antagonists	Cytosolic Ca <sup>2+</sup> (>100 μM), cytosolic Mg <sup>2+</sup> (mM), calmodulin at high cytosolic Ca <sup>2+</sup> , dantrolene	Cytosolic Ca <sup>2+</sup> (>1 mM), cytosolic Mg <sup>2+</sup> (mM), calmodulin at high cytosolic Ca <sup>2+</sup>	Cytosolic Ca <sup>2+</sup> (>1 mM), cytosolic Mg <sup>2+</sup> (mM), calmodulin at high cytosolic Ca <sup>2+</sup> , dantrolene
Channel blockers	Ryanodine (>100 μM), ruthenium red, procaine	Ryanodine (>100 μM), ruthenium red, procaine	Ruthenium red
Functional characteristics	Ca <sup>2+</sup> : (P <sub>Ca</sub> /P <sub>K</sub> ) single-channel conductance: ~90 pS (50 mM Ca <sup>2+</sup> ), 770 pS (200 mM K <sup>+</sup> )	Ca <sup>2+</sup> : (P <sub>Ca</sub> /P <sub>K</sub> ) single-channel conductance: ~90 pS (50 mM Ca <sup>2+</sup> ), 720 pS (210 mM K <sup>+</sup> )	Ca <sup>2+</sup> : (P <sub>Ca</sub> /P <sub>K</sub> ) single-channel conductance: ~140 pS (250 mM Ca <sup>2+</sup> ), 777 pS (250 mM K <sup>+</sup> )

The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive Ca<sup>2+</sup> release pathways. Numerous other modulators of ryanodine receptor/channel function can be found in the reviews listed below. The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect. The potential role of cyclic ADP ribose as an endogenous regulator of ryanodine receptor channels is controversial. A region of RyR likely to be involved in ion translocation and selection has been identified (Zhao *et al.*, 1999; Gao *et al.*, 2000).

## Further Reading

- Berridge M, Bootman MD, Roderick HL (2003). Calcium signalling: dynamics, homeostasis and remodelling. *Nat Rev Mol Cell Biol* 4: 517–529.
- Berridge MJ, Lipp P, Bootman MD (2000). The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* 1: 11–21.
- Betzenhauser MJ, Marks AR (2010). Ryanodine receptor channelopathies. *Pflugers Arch* 460: 467–480.
- Bouchard R, Pattarini E, Geiger JD (2003). Presence and functional significance of presynaptic ryanodine receptors. *Prog Neurobiol* 69: 391–418.
- Bolton TB (2006). Calcium events in smooth muscles and their interstitial cells: physiological roles of sparks. *J Physiol* 570: 5–11.
- Collin T, Marty A, Llano I (2005). Presynaptic calcium stores and synaptic transmission. *Curr Opin Neurobiol* 15: 275–281.
- Dulhunty AF, Beard NA, Pouliquin P, Casarotto MG (2007). Agonists and antagonists of the cardiac ryanodine receptor: potential therapeutic agents? *Parmacol Ther* 113: 247–263.
- Eisner A, Diaz ME, O'Neill SC, Trafford AW (2004). Physiology and pathological modulation of ryanodine receptor function in cardiac muscle. *Cell Calcium* 35: 583–589.
- Endo M (2009). Calcium-induced calcium release in skeletal muscle. *Physiol Rev* 89: 1153–1176.
- Fill M, Copello JA (2002). Ryanodine receptor calcium release channels. *Physiol Rev* 82: 893–922.
- Hamilton SL, Serysheva II (2009). Ryanodine receptor structure: progress and challenges. *J Biol Chem* 284: 4047–4051.
- Kushnir A, Marks AR (2010). The ryanodine receptor in cardiac physiology and disease. *Adv Pharmacol* 59: 1–30.
- Lanner JT, Georgiou DK, Joshi AD, Hamilton SL (2010). Ryanodine receptors: structure, expression, molecular details, and function in calcium release. *Cold Spring Harb Perspect Biol* 2: a003996.
- Meissner G (2004). Molecular regulation of cardiac ryanodine receptor ion channel. *Cell Calcium* 35: 621–628.
- Nahorski SR (2006). Pharmacology of intracellular signalling pathways. *Br J Pharmacol* 147 (Suppl. 1): S38–S45.
- Ross D, Sorrentino V (2002). Molecular genetics of ryanodine receptors Ca<sup>2+</sup> release channels. *Cell Calcium* 32: 307–319.
- Shoshan-Barmatz V, Ashley RH (1998). The structure, function and cellular regulation of ryanodine-sensitive Ca<sup>2+</sup>-release channels. *Int Rev Cytol* 183: 185–270.
- Sitsapasan R, Williams AJ (1998). *The Structure and Function of Ryanodine Receptors*. Imperial College Press: London.
- Sutko JL, Airey JA (1996). Ryanodine Ca<sup>2+</sup> release channels: does diversity in form equal diversity in function? *Physiol Rev* 76: 1027–1071.
- Sutko JL, Airey JA, Welch W, Ruest L (1997). The pharmacology of ryanodine and related compounds. *Pharmacol Rev* 49: 53–98.
- Taur Y, Frishman WH (2005). The cardiac ryanodine receptor (RyR2) and its role in heart disease. *Cardiol Rev* 13: 142–146.
- Verkhatsky A (2005). Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. *Physiol Rev* 85: 201–279.
- Zucchi, R, Ronca-Testoni S (1997). The sarcoplasmic reticulum Ca<sup>2+</sup> channel/ryanodine receptor: modulation by endogenous effectors, drugs and disease states. *Pharmacol Rev* 49: 1–51.

## References

- Gao L *et al.* (2000). *Biophys J* 79: 828–840.
- Yamaguchi N *et al.* (2003). *J Biol Chem* 278: 23480–23486.
- Zhao MC *et al.* (1999). *J Biol Chem* 274: 25971–25974.

# Sodium leak channel, non-selective

**Overview:** The sodium leak channel, non selective (NC-IUPHAR tentatively recommends the nomenclature  $Na_{vi}2.1$ , W.A. Catterall, personal communication) is structurally a member of the family of voltage-gated sodium channel family ( $Na_v1.1$  –  $Na_v1.9$ ) (Lee *et al.*, 1999; Yu and Catterall, 2004). In contrast to the latter,  $Na_{vi}2.1$ , is voltage-insensitive (denoted in the subscript 'vi' in the tentative nomenclature) and possesses distinctive ion selectivity and pharmacological properties.  $Na_{vi}2.1$ , which is insensitive to TTX (10  $\mu$ M), has been proposed to mediate the TTX-resistant and voltage-insensitive  $Na^+$  leak current ( $I_L$ - $Na$ ) observed in many types of neurone (Lu *et al.*, 2007). However, whether  $Na_{vi}2.1$  is constitutively active has been challenged (Swayne *et al.*, 2009).  $Na_{vi}2.1$  is widely distributed within the central nervous system and is also expressed in the heart and pancreas specifically, in rodents, within the islets of Langerhans (Lee *et al.*, 1999; Lu *et al.*, 2007).

Nomenclature	$Na_{vi}2.1$
Other names	NALCN, Nav2.1, $Na_x$ , voltage-gated channel like 1 (VGCNL1), Rb21
Ensembl ID	ENSG00000102452
Activators	Constitutively active (Lu <i>et al.</i> , 2007), or activated downstream of Src family tyrosine kinases (SFKs) (Lu <i>et al.</i> , 2009; Swayne <i>et al.</i> , 2009); positively modulated by decreased extracellular $Ca^{2+}$ concentration (Lu <i>et al.</i> , 2010)
Blockers ( $IC_{50}$ )	$Gd^{3+}$ (1.4 $\mu$ M), $Cd^{2+}$ (0.15 mM), $Co^{2+}$ (0.26 mM), verapamil (0.38 mM)
Functional characteristics	$\gamma = 27$ pS (by fluctuation analysis), $P_{Na}/P_{Cs} = 1.3$ , $P_K/P_{Cs} = 1.2$ , $P_{Ca}/P_{Cs} = 0.5$ , linear current voltage-relationship, voltage-independent and non-inactivating

In native and recombinant expression systems  $Na_{vi}2.1$  can be activated by stimulation of  $NK_1$  (in hippocampal neurones), neurotensin (in ventral tegmental area neurones) and M3 muscarinic acetylcholine receptors (in MIN6 pancreatic  $\beta$ -cells and) in a manner that is independent of signalling through G proteins (Lu *et al.*, 2009; Swayne *et al.*, 2009). Pharmacological and molecular biological evidence indicates such modulation to occur through a pathway that involves the activation of Src family tyrosine kinases. It is suggested that  $Na_{vi}2.1$  exists as a macromolecular complex with M3 receptors (Swayne *et al.*, 2009) and peptide receptors (Lu *et al.*, 2009), in the latter instance in association with the protein UNC-80, which recruits Src to the channel complex (Lu *et al.*, 2009, Wang and Ren, 2009). By contrast, stimulation of  $Na_{vi}2.1$  by decreased extracellular  $Ca^{2+}$  concentration is G-protein dependent and involves a  $Ca^{2+}$ -sensing G protein-coupled receptor and UNC80 which links  $Na_{vi}2.1$  to the protein UNC79 in the same complex (Lu *et al.*, 2010).  $Na_{vi}2.1$  null mutant mice have severe disturbances in respiratory rhythm and die within 24 hours of birth (Lu *et al.*, 2007).  $Na_{vi}2.1$  heterozygous knockout mice display increased serum sodium concentrations in comparison to wildtype littermates and a role for the channel in osmoregulation has been postulated (Sinke *et al.*, 2011).

## Further Reading

Gilon P, Rorsman P (2009). NALCN: a regulated leak channel. *EMBO Rep* 10: 963–964.  
 Swayne LA, Mezghrani A, Lory P, Nargeot, J, Monteil A (2010). The NALCN ion channel is a new actor in pancreatic  $\beta$ -cell physiology. *Islets* 2: 54–56.

## References

- Lee JH *et al.* (1999). *FEBS Lett* 445: 231–236.  
 Lu B *et al.* (2007). *Cell* 129: 371–383.  
 Lu B *et al.* (2009). *Nature* 457: 741–745.  
 Lu B *et al.* (2010). *Neuron* 68: 488–499.  
 Sinke AP *et al.* (2011). *Physiol Genomics* 43: 265–270.  
 Swayne LA *et al.* (2009). *EMBO Rep* 10: 873–880.  
 Wang H, Ren D (2009). *Channels (Austin)* 3: 161–163.  
 Yu F, Catterall WA (2004). *Sci STKE* 253: re15.

# Sodium (voltage-gated)

**Overview:** Sodium channels are voltage-gated sodium-selective ion channels present in the membrane of most excitable cells. Sodium channels comprise of one pore-forming  $\alpha$  subunit, which may be associated with either one or two  $\beta$  subunits (Isom, 2001).  $\alpha$ -Subunits consist of four homologous domains (I–IV), each containing six transmembrane segments (S1–S6) and a pore-forming loop. The positively charged fourth transmembrane segment (S4) acts as a voltage sensor and is involved in channel gating. The crystal structure of the bacterial NavAb channel has revealed a number of novel structural features compared to earlier potassium channel structures including a short selectivity filter with ion selectivity determined by interactions with glutamate side chains (Payandeh *et al.*, 2011). Interestingly, the pore region is penetrated by fatty acyl chains that extend into the central cavity which may allow the entry of small, hydrophobic pore-blocking drugs (Payandeh *et al.*, 2011). Auxiliary  $\beta$ 1,  $\beta$ 2,  $\beta$ 3 and  $\beta$ 4 subunits consist of a large extracellular N-terminal domain, a single transmembrane segment and a shorter cytoplasmic domain.

The nomenclature for sodium channels was proposed by Goldin *et al.*, (2000) and approved by the NC-IUPHAR subcommittee on sodium channels (Catterall *et al.*, 2005).

Nomenclature	Nav1.1	Nav1.2	Nav1.3	Nav1.4	Nav1.5
Alternative names	Brain type I	Brain type II	Brain type III	$\mu$ 1, SkM1	h1, SkM II, cardiac
Ensembl ID	ENSG00000144285	ENSG00000136531	ENSG00000153253	ENSG00000007314	ENSG00000183873
Activators	Veratridine, batrachotoxin	Veratridine, batrachotoxin	Veratridine, batrachotoxin	Veratridine, batrachotoxin	Veratridine, batrachotoxin
Blockers	Tetrodotoxin (10 nM), saxitoxin	Tetrodotoxin (10 nM), saxitoxin	Tetrodotoxin (2–15 nM), saxitoxin	$\mu$ -Conotoxin GIIIA, tetrodotoxin (5 nM), saxitoxin	Tetrodotoxin (2 $\mu$ M)
Functional characteristic	Fast inactivation (0.7 ms)	Fast inactivation (0.8 ms)	Fast inactivation (0.8 ms)	Fast inactivation (0.6 ms)	Fast inactivation (1 ms)

Nomenclature	Nav1.6	Nav1.7	Nav1.8	Nav1.9
Alternative names	PN4, NaCH6	PN1, NaS	SNS, PN3	NaN, SNS2
Ensembl ID	ENSG00000196876	ENSG00000169432	ENSG00000185313	ENSG00000168356
Activators	Veratridine, batrachotoxin	Veratridine, batrachotoxin	–	–
Blockers	Tetrodotoxin (6 nM), saxitoxin	Tetrodotoxin (4 nM), saxitoxin	Tetrodotoxin (60 $\mu$ M)	Tetrodotoxin (40 $\mu$ M)
Functional characteristic	Fast inactivation (1 ms)	Fast inactivation (0.5 ms)	Slow inactivation (6 ms)	Slow inactivation (16 ms)

Sodium channels are also blocked by local anaesthetic agents, antiarrhythmic drugs and antiepileptic drugs. There are two clear functional fingerprints for distinguishing different subtypes. These are sensitivity to tetrodotoxin (Nav1.5, Nav1.8 and Nav1.9 are much less sensitive to block) and rate of inactivation (Nav1.8 and particularly Nav1.9 inactivate more slowly).

## Further Reading

- Andavan GS, Lemmens-Gruber R (2011). Voltage-gated sodium channels: mutations, channelopathies and targets. *Curr Med Chem* **18**: 377–397.
- Baker MD, Wood JN (2001). Involvement of Na<sup>+</sup> channels in pain pathways. *Trends Pharmacol Sci* **22**: 27–31.
- Bean BP (2007). The action potential in mammalian central neurons. *Nat Rev Neurosci* **8**: 451–465.
- Cantrell AR, Catterall WA (2001). Neuromodulation of Na<sup>+</sup> channels: an unexpected form of cellular plasticity. *Nat Rev Neurosci* **2**: 397–407.
- Catterall WA (1995). Structure and function of voltage-gated ion channels. *Ann Rev Biochem* **64**: 493–531.
- Catterall WA (2000). From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* **26**: 13–25.
- Catterall WA, Goldin AL, Waxman SG (2005). International Union of Pharmacology. XLVII. Nomenclature and structure function relationships of voltage-gated sodium channels. *Pharmacol Rev* **57**: 397–409.
- Catterall, WA, Dib-Hajj S, Meisler MH, Pietrobon D (2008). Inherited neuronal ion channelopathies: new windows on complex neurological diseases. *J Neurosci* **28**: 11768–11777.
- Dib-Hajj SD, Cummins TR, Black JA, Waxman SG (2010). Sodium channels in normal and pathological pain. *Annu Rev Neurosci* **33**: 325–347.
- England S, de Groot MJ. (2009). Subtype-selective targeting of voltage-gated sodium channels. *Br J Pharmacol* **158**: 1413–1425.
- Fozzard HA, Hanck DA (1996). Structure and function of voltage-dependent sodium channels – comparison of brain-II and cardiac isoforms. *Physiol Rev* **76**: 887–926.
- Fozzard HA, Lee PJ, Lipkind GM (2005). Mechanism of local anesthetic drug action on voltage-gated sodium channels. *Curr Pharm Des* **11**: 2671–2686.
- George AL (2005). Inherited disorders of voltage-gated sodium channels. *J Clin Invest* **115**: 1990–1999.
- Goldin AL (2001). Resurgence of sodium channel research. *Ann Rev Physiol* **63**: 874–894.
- Han TS, Teichert RW, Olivera BM, Bulaj G (2008). Conus venoms – a rich source of peptide-based therapeutics. *Curr Pharm Des* **14**: 2462–2479.
- Isom LL (2001). Sodium channel beta subunits: anything but auxiliary. *Neuroscientist* **7**: 42–54.
- Kyle DJ, Ilyin VI (2007). Sodium channel blockers. *J Med Chem* **50**: 2583–2588.
- Lai J, Porreca F, Hunter JC, Gold MS (2004). Voltage-gated sodium channels and hyperalgesia. *Ann Rev Pharmacol Toxicol* **44**: 371–397.

- Lewis RJ, Garcia ML (2003). Therapeutic potential of venom peptides. *Nat Rev Drug Discov* 2: 790–802.
- Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M (2010). Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. *Lancet Neurol* 9: 413–424.
- Matulenko MA, Scanio MJ, Kort ME (2009). Voltage-gated sodium channel blockers for the treatment of chronic pain. *Curr Top Med Chem* 9: 362–376.
- Priest BT, Kaczorowski GJ (2007). Blocking sodium channels to treat neuropathic pain. *Expert Opin Ther Targets* 11: 291–306.
- Priestley T (2004). Voltage-gated sodium channels and pain. *Curr Drug Targets CNS Neurol Disord* 3: 441–456.
- Terlau H, Olivera BM (2004). Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol Rev* 84: 41–68.
- Trimmer JS, Rhodes KJ (2004). Localisation of voltage-gated ion channels in mammalian brain. *Ann Rev Physiol* 66: 477–519.
- Wood JN, Boorman J (2005). Voltage-gated sodium channel blockers; target validation and therapeutic potential. *Curr Top Med Chem* 5: 529–537.
- Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* 2004: re15.

## References

- Goldin AL *et al.* (2000). *Neuron* 28: 365–368.
- Payandeh J *et al.* (2011). *Nature* 475: 353–358.

# Transient receptor potential (TRP) cation channels

**Overview:** The TRP superfamily of channels (nomenclature agreed by NC-IUPHAR; Clapham *et al.*, 2005; Wu *et al.*, 2010), whose founder member is the *Drosophila* Trp channel, exists in mammals as six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with diverse modes of activation and varied permeation properties (reviewed by Owsianik *et al.*, 2006b). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and a compilation edited by Islam (2011). The established, or potential, involvement of TRP channels in disease is reviewed in Kiselyov *et al.* (2007a), Nilius *et al.* (2007) and Nilius and Owsianik (2010), together with a special edition of *Biochemica et Biophysica Acta* on the subject (Nilius, 2007). The pharmacology of most TRP channels is poorly developed (Wu *et al.*, 2010). Broad spectrum agents are listed in the tables along with more selective, or recently recognised, ligands that are flagged by the inclusion of a primary reference. Most TRP channels are regulated by phosphoinositides such as  $\text{PtdIns}(4,5)\text{P}_2$  and  $\text{Ins}(1,4,5)\text{P}_3$  although the effects reported are often complex, occasionally contradictory, and likely be dependent upon experimental conditions (reviewed by Voets and Nilius, 2007; Nilius *et al.*, 2008; Rohacs, 2009). Such regulation is generally not included in the tables.

**TRPC (canonical) family:** Members of the TRPC subfamily (reviewed by Freichel *et al.*, 2005; Putney, 2005; Ambudkar and Ong, 2007; Abramowitz and Birnbaumer, 2009; Birnbaumer, 2009; Kiselyov and Patterson, 2009; Patel *et al.*, 2010; Beech, 2011) fall into the subgroups tabulated below. TRPC2 (not tabulated) is a pseudogene in man. It is generally accepted that all TRPC channels are activated downstream of  $\text{G}_{q/11}$ -coupled receptors, or receptor tyrosine kinases (reviewed by Plant and Schaefer, 2003; Trebak *et al.*, 2007, Wu *et al.*, 2010). A comprehensive listing of G-protein coupled receptors that activate TRPC channels is given in Abramowitz and Birnbaumer (2009). Hetero-oligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in Ambudkar and Ong (2007) and Kiselyov *et al.* (2007b). TRPC channels have frequently been proposed to act as store-operated channels (SOCs) (or components of multimeric complexes that form SOC), activated by depletion of intracellular calcium stores (reviewed by Pedersen *et al.*, 2005; Ambudkar and Ong, 2007; Potier and Trebak, 2008; Salido *et al.*, 2009; Yuan *et al.*, 2009; Cheng *et al.*, 2011), but this is controversial. All members of the TRPC family are blocked by 2-APB and SKF96356 (Harteneck and Gollasch, 2011; Harteneck *et al.*, 2011). Activation of TRPC channels by lipids is discussed by Beech (2011).

**TRPC1/C4/C5 subgroup:** TRPC4/C5 may be distinguished from other TRP channels by their potentiation by micromolar concentrations of  $\text{La}^{3+}$ .

Nomenclature	TRPC1	TRPC4	TRPC5
Other names	TRP1	TRP4, CCE1	TRP5, CCE2
Ensembl ID	ENSG00000144935	ENSG00000133107	ENSG00000072315
Physical activators	Membrane stretch (likely indirect)	–	Membrane stretch (likely indirect)
Chemical activators	Activated by NO-mediated cysteine S-nitrosylation	Activated by NO-mediated cysteine S-nitrosylation, $\text{La}^{3+}$ (micromolar), potentiated by extracellular protons	NO-mediated cysteine S-nitrosylation (disputed), lysophosphatidylcholine, genesteine (independent of tyrosine kinase inhibition, Wong <i>et al.</i> , 2010), diadzein, $\text{La}^{3+}$ (micromolar), $\text{Gd}^{3+}$ (0.1 mM), $\text{Pb}^{2+}$ (5 $\mu\text{M}$ ), intracellular $\text{Ca}^{2+}$ ( $\text{EC}_{50}$ = 635 nM at negative potentials), potentiated by extracellular protons
Blockers	GsMTx-4, 2-APB, SKF96365, $\text{Gd}^{3+}$ , $\text{La}^{3+}$	ML204 ( $\text{IC}_{50}$ = 2.9 $\mu\text{M}$ , Miller <i>et al.</i> , 2011), 2-APB, SKF96365, niflumic acid, $\text{La}^{3+}$ (millimolar)	ML204 ( $\text{IC}_{50}$ $\approx$ 10 $\mu\text{M}$ , Miller <i>et al.</i> , 2011), GsMTx-4, SKF96365, 2-APB, KB-R7943, BTP2 (Pyr2), flufenamic acid, chlorpromazine, $\text{La}^{3+}$ (millimolar)
Functional characteristics	$\gamma$ = 16 pS (fluctuation analysis), conducts mono- and di-valent cations non-selectively; monovalent cation current suppressed by extracellular $\text{Ca}^{2+}$ ; non-rectifying, or mildly inwardly rectifying; non-inactivating	$\gamma$ = 30–41 pS, conducts mono- and di-valent cations non-selectively ( $\text{P}_{\text{Ca}}/\text{P}_{\text{Na}}$ = 1.1–7.7); dual (inward and outward) rectification	$\gamma$ = 41–63 pS; conducts mono- and di-valent cations non-selectively ( $\text{P}_{\text{Ca}}/\text{P}_{\text{Na}}$ = 1.8–9.5); dual rectification (inward and outward) as a homomer, outwardly rectifying when expressed with TRPC1 or TRPC4

**TRPC3/C6/C7 subgroup.** All members are activated by diacylglycerol independent of protein kinase C stimulation (Harteneck and Gollasch, 2011).

Nomenclature	TRPC3	TRPC6	TRPC7
Other names	TRP3	TRP6	TRP7
Ensembl ID	ENSG00000138741	ENSG00000137672	ENSG00000069018
Physical activators	–	Membrane stretch (likely indirect)	–



Nomenclature	TRPC3	TRPC6	TRPC7
Chemical activators	Diacylglycerols	Hyperforin (Leuner <i>et al.</i> , 2007), 2,4 diahexanoxylphloroglucinol (Leuner <i>et al.</i> , 2010), diacylglycerols, lysophosphatidylcholine, flufenamate, arachidonic acid, 20-HETE	Diacylglycerols
Blockers	Pyr3 (Kiyonaka <i>et al.</i> , 2009), 2-APB, SKF96365, ACA, KB-R7943, BTP2 (Pyr2), Gd <sup>3+</sup> , La <sup>3+</sup> , Ni <sup>2+</sup>	GsMTx-4, SKF96365, 2-APB, amiloride, ACA, KB-R7943, ML-9, La <sup>3+</sup> (IC <sub>50</sub> ≅ 6 μM), Gd <sup>3+</sup> , Cd <sup>2+</sup> , extracellular protons	SKF96365, 2-APB, amiloride, La <sup>3+</sup>
Functional characteristics	γ = 66 pS; conducts mono- and di-valent cations non-selectively (P <sub>Ca</sub> /P <sub>Na</sub> = 1.6); monovalent cation current suppressed by extracellular Ca <sup>2+</sup> ; dual (inward and outward) rectification	γ = 28-37 pS; conducts mono- and divalent cations with a preference for divalents (P <sub>Ca</sub> /P <sub>Na</sub> = 4.5–5.0); monovalent cation current suppressed by extracellular Ca <sup>2+</sup> and Mg <sup>2+</sup> , dual rectification (inward and outward), or inward rectification	γ = 25–75 pS; conducts mono and divalent cations with a preference for divalents (P <sub>Ca</sub> /P <sub>CS</sub> = 5.9); modest outward rectification (monovalent cation current recorded in the absence of extracellular divalents); monovalent cation current suppressed by extracellular Ca <sup>2+</sup> and Mg <sup>2+</sup>

**TRPM (melastatin) family:** Members of the TRPM subfamily (reviewed by Fleig and Penner, 2004; Harteneck, 2005; Pedersen *et al.*, 2005; Zholos, 2010) fall into the five subgroups tabulated below.

**TRPM1/M3 subgroup:** TRPM1 exists as five splice variants and is involved in normal melanocyte pigmentation (Oancea *et al.*, 2009) and is also a visual transduction channel in retinal ON bipolar cells (Koike *et al.*, 2010). TRPM3 (reviewed by Oberwinkler and Phillipp, 2007) exists as multiple splice variants four of which (mTRPM3α1, mTRPM3α2, hTRPM3α and hTRPM3<sub>1325</sub>) have been characterised and found to differ significantly in their biophysical properties. TRPM3 has recently been found to contribute to the detection of noxious heat (Vriens *et al.*, 2011).

Nomenclature	TRPM1	TRPM3
Other names	LTRPC1, Melastatin	LTRPC3
Ensembl ID	ENSG00000134160	ENSG00000083067
Physical activators	–	Heat (Q <sub>10</sub> = 7.2 between 15–25°C; Vriens <i>et al.</i> , 2011), hypotonic cell swelling
Chemical activators	Pregnenolone sulphate (Lambert <i>et al.</i> , 2011)	Pregnenolone sulphate (Wagner <i>et al.</i> , 2008), epipregnanolone sulphate (Majeed <i>et al.</i> , 2010), nifedipine, D-erythro-sphingosine, dihydrosphingosine
Blockers	Zn <sup>2+</sup> (IC <sub>50</sub> = 1 μM)	Rosiglitazone, troglitazone, pioglitazone (independent of PPAR-γ; Majeed <i>et al.</i> , 2011), mefenamic acid, Klose <i>et al.</i> , 2011), 2-APB, La <sup>3+</sup> , Gd <sup>3+</sup> , intracellular Mg <sup>2+</sup> , extracellular Na <sup>+</sup> (TRPM3α2 only)
Functional characteristics	Conducts mono- and di-valent cations non-selectively, dual rectification (inward and outward)	TRPM3 <sub>1235</sub> : γ = 83 pS (Na <sup>+</sup> current), 65 pS (Ca <sup>2+</sup> current); conducts mono- and di-valent cations non-selectively (P <sub>Ca</sub> /P <sub>Na</sub> = 1.6) TRPM3α1: selective for monovalent cations (P <sub>Ca</sub> /P <sub>CS</sub> = 0.1) TRPM3α2: conducts mono- and di-valent cations non-selectively (P <sub>Ca</sub> /P <sub>CS</sub> = 1–10) Outwardly rectifying (magnitude varies between splice variants)

**TRPM2:** TRPM2 functions as a sensor of redox status in cells and is also activated by heat (reviewed by Yamamoto *et al.*, 2010). Numerous splice variants of TRPM2 exist which differ in their activation mechanisms (Du *et al.*, 2009).

Nomenclature	TRPM2
Other names	(TRPC7, LTRPC2)
Ensembl ID	ENSG00000142185
Physical activators	Heat ~35°C
Chemical activators	Intracellular Ca <sup>2+</sup> via calmodulin, intracellular ADP ribose (ADPR) and cyclic ADPR (cADPR); agents producing reactive oxygen (e.g. H <sub>2</sub> O <sub>2</sub> ) and nitrogen (e.g. GEA 3162) species; potentiated by arachidonic acid
Blockers	2-APB, ACA, clotrimazole, miconazole, econazole, flufenamic acid, Zn <sup>2+</sup> , extracellular protons
Functional characteristics	γ = 52-60 pS at negative potentials, 76 pS at positive potentials; conducts mono- and di-valent cations non-selectively (P <sub>Ca</sub> /P <sub>Na</sub> = 0.6–0.7); non-rectifying; inactivation at negative potentials; activated by oxidative stress probably via PARP-1, PARP inhibitors reduce activation by oxidative stress, activation inhibited by suppression of ADPR formation by glycohydrolase inhibitors

Ca<sup>2+</sup> activates all slice variants of TRPM2, but other activators listed are effective only at the full length isoform (Du *et al.*, 2009). Inhibition of TRPM2 by clotrimazole, miconazole, econazole, flufenamic acid is largely irreversible.

**TRPM4/5 subgroup:** TRPM4 and TRPM5 are thermosensitive and have the distinction within all TRP channels of being impermeable to Ca<sup>2+</sup> (Wu *et al.*, 2010). A splice variant of TRPM4 (*i.e.* TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels (Guinamard *et al.*, 2011). TRPM4 has been shown to be an important regulator of Ca<sup>2+</sup> entry in to mast cells (Vennekens *et al.*, 2007) and dendritic cell migration (Barbet *et al.*, 2008). TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli (Liman, 2007).

Nomenclature	TRPM4	TRPM5
Other names	LTRPC4	TRP-T
Ensembl ID	ENSG00000130529	ENSG00000070985
Physical activators	Membrane depolarization ( $V_{1/2} = -20$ to $+60$ mV dependent upon conditions) in the presence of elevated [Ca <sup>2+</sup> ] <sub>i</sub> , heat ( $Q_{10} = 8.5$ @ $+25$ mV between $15$ – $25^{\circ}\text{C}$ )	Membrane depolarization ( $V_{1/2} = 0$ to $+120$ mV dependent upon conditions), heat ( $Q_{10} = 10.3$ @ $-75$ mV between $15$ and $25^{\circ}\text{C}$ )
Chemical activators	Decavanadate, whole cell current transiently activated by intracellular Ca <sup>2+</sup> ( $EC_{50}$ $0.3$ – $20$ $\mu\text{M}$ ), enhanced by BTP2	Rosiglitazone (Majeed <i>et al.</i> , 2011), transiently activated by intracellular Ca <sup>2+</sup> ( $EC_{50}$ $635$ – $840$ nM)
Blockers	Clotrimazole, 9-phenanthrol, intracellular nucleotides (ATP <sup>+</sup> , ADP, AMP, AMP-PNP – $IC_{50}$ range $1.3$ – $19$ $\mu\text{M}$ ) and adenosine ( $IC_{50}$ $630$ $\mu\text{M}$ ); intracellular spermine ( $IC_{50} = 35$ – $61$ $\mu\text{M}$ ) and flufenamic acid ( $IC_{50} = 2.8$ $\mu\text{M}$ )	Intracellular spermine ( $IC_{50} = 37$ $\mu\text{M}$ ) and flufenamic acid ( $IC_{50} = 24$ $\mu\text{M}$ ), extracellular protons ( $IC_{50} = 630$ nM), (not inhibited by ATP <sup>+</sup> )
Functional characteristics	$\gamma = 23$ pS (within the range $60$ to $+60$ mV); permeable to monovalent cations; impermeable to Ca <sup>2+</sup> ; strong outward rectification; slow activation at positive potentials, rapid deactivation at negative potentials, deactivation blocked by decavanadate	$\gamma = 15$ – $25$ pS; conducts monovalent cations selectively ( $P_{Ca}/P_{Na} = 0.05$ ); strong outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; activated and subsequently desensitized by [Ca <sup>2+</sup> ] <sub>i</sub>

TRPM4 exists as multiple splice variants: data listed are for TRPM4b. The sensitivity of TRPM4b and TRPM5 to activation by [Ca<sup>2+</sup>]<sub>i</sub> demonstrates a pronounced and time-dependent reduction following excision of inside-out membrane patches (Ullrich *et al.*, 2005). The  $V_{1/2}$  for activation of TRPM4 and TRPM5 demonstrates a pronounced negative shift with increasing temperature.

**TRPM6/M7 subgroup:** TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') and are involved in Mg<sup>2+</sup> homeostasis (reviewed by Penner and Fleig, 2007; Bates-Withers *et al.*, 2011; Runnels, 2011).

Nomenclature	TRPM6	TRPM7
Other names	–	TRP-PLIK, Chak1, MagNum, MIC
Ensembl ID	ENSG00000119121	ENSG00000092439
Physical activators	–	–
Chemical activators	Constitutively active, activated by reduction of intracellular Mg <sup>2+</sup> , potentiated by extracellular protons and 2-APB (micromolar)	Elevated cAMP and activation of PKA; potentiated by intracellular ATP; potentiated by extracellular protons, 2-APB (millimolar)
Blockers	Ruthenium red (voltage dependent block, $IC_{50} = 100$ nM at $-120$ mV), inward current mediated by monovalent cations blocked by Ca <sup>2+</sup> ( $IC_{50} = 4.8$ – $5.4$ $\mu\text{M}$ ) and Mg <sup>2+</sup> ( $IC_{50} = 1.1$ – $3.4$ $\mu\text{M}$ )	Spermine (permeant blocker), carvacrol, La <sup>3+</sup> , Mg <sup>2+</sup> , 2-APB (micromolar)
Functional characteristics	$\gamma = 40$ – $87$ pS; permeable to mono- and di-valent cations with a preference for divalents ( $\text{Mg}^{2+} > \text{Ca}^{2+}$ ; $P_{Ca}/P_{Na} = 6.9$ ), conductance sequence $\text{Zn}^{2+} > \text{Ba}^{2+} > \text{Mg}^{2+} = \text{Ca}^{2+} = \text{Mn}^{2+} > \text{Sr}^{2+} > \text{Cd}^{2+} > \text{Ni}^{2+}$ ; strong outward rectification abolished by removal of extracellular divalents, inhibited by intracellular Mg <sup>2+</sup> ( $IC_{50} = 0.5$ mM) and ATP	$\gamma = 40$ – $105$ pS at negative and positive potentials respectively; conducts mono- and di-valent cations with a preference for monovalents ( $P_{Ca}/P_{Na} = 0.34$ ); conductance sequence $\text{Ni}^{2+} > \text{Zn}^{2+} > \text{Ba}^{2+} = \text{Mg}^{2+} > \text{Ca}^{2+} = \text{Mn}^{2+} > \text{Sr}^{2+} > \text{Cd}^{2+}$ ; outward rectification, decreased by removal of extracellular divalent cations; inhibited by intracellular Mg <sup>2+</sup> , Ba <sup>2+</sup> , Sr <sup>2+</sup> , Zn <sup>2+</sup> , Mn <sup>2+</sup> and Mg.ATP (disputed); activated by and intracellular alkalization; sensitive to osmotic gradients

**TRPM8:** Is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation and participates in the thermosensation of cold temperatures (Bautista *et al.*, 2007; Colburn *et al.*, 2007; Dhaka *et al.*, 2007; reviewed by Voets *et al.* (2007), Liu and Qin (2011), Knowlton and McKemy (2011), Mälkiä *et al.* (2011).

Nomenclature	TRPM8
Other names	CMR1, TRP-p8
Ensembl ID	ENSG00000144481
Physical activators	Depolarization ( $V_{1/2} \cong +50$ mV at 15°C), cooling (<22–26°C)
Chemical Activators	WS-12, (-)-menthol (inhibited by intracellular $Ca^{2+}$ ), icilin (requires intracellular $Ca^{2+}$ as a co-factor for full agonist activity); agonist activities are temperature dependent and potentiated by cooling
Blockers	AMTB (Lashinger <i>et al.</i> , 2008), 5-benzylxytryptamine, clotrimazole, BCTC, capsaizepine, 2-APB, $La^{3+}$ , ACA, anandamide, NADA, linoleic acid, cannabinoids ( <i>e.g.</i> , cannabidiol, THC); insensitive to ruthenium red
Functional characteristics	$\gamma = 40$ –83 pS at positive potentials; conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na} = 1.0$ –3.3); pronounced outward rectification; demonstrates desensitization to chemical agonists and adaptation to a cold stimulus in the presence of $Ca^{2+}$ ; modulated by lysophospholipids and PUFAs

Activation of TRPM8 by depolarization is strongly temperature-dependent *via* a channel-closing rate that decreases with decreasing temperature. The  $V_{1/2}$  is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as menthol (Voets *et al.*, 2004) whereas antagonists produce depolarizing shifts in  $V_{1/2}$  (Mälkiä *et al.*, 2007). The  $V_{1/2}$  for the native channel is far more positive than that of heterologously expressed TRPM8 (Mälkiä *et al.*, 2007). It should be noted that menthol and structurally related compounds can elicit release of  $Ca^{2+}$  from the endoplasmic reticulum independent of activation of TRPM8 (Mahieu *et al.*, 2007). Intracellular pH modulates activation of TRPM8 by cold and icilin, but not menthol (Andersson *et al.*, 2004).

**TRPA (ankyrin) family:** TRPA1 is the sole mammalian member of this group (reviewed by Garcia-Anoveros and Nagata, 2007). In some (Story *et al.*, 2003; Bandell *et al.*, 2004, Sawada *et al.*, 2007; Karashima *et al.*, 2009), but not other (Jordt *et al.*, 2004; Nagata *et al.*, 2005), studies TRPA1 is activated by noxious cold. One study suggests that activation of TRPA1 is secondary to a cold-induced elevation of  $[Ca^{2+}]_i$  (Zurborg *et al.*, 2007), but this has been refuted (Karashima *et al.*, 2009). Additionally, TRPA1 has been proposed to be a component of a mechanosensitive transduction channel of vertebrate hair cells (Corey *et al.*, 2004; Nagata *et al.*, 2005), but TRPA1<sup>-/-</sup> mice demonstrate no impairment in hearing, or vestibular function (Bautista *et al.* 2006; Kwan *et al.*, 2006). There is consensus that TRPA1 acts as a nociceptor for environmental irritants (Baraldi *et al.*, 2010).

Nomenclature	TRPA1
Other names	ANKTM1, p120, TRPN1
Ensembl ID	ENSG00000104321
Physical activators	Cooling (<17°C) (disputed)
Chemical Activators	
Covalent	<i>e.g.</i> Isothiocyanates, cinnamaldehyde, allicin, acroline, formalin, chlorobenzylidene malononitrile
Non-covalent	<i>e.g.</i> URB597 ( $EC_{50} = 24$ $\mu$ M, Niforatus <i>et al.</i> , 2007), nicotine ( $EC_{50} \approx 20$ $\mu$ M), icilin (-)-menthol (1–100 $\mu$ M), thymol (1–100 $\mu$ M), THC, 1,4-dihydropyridines
Blockers ( $IC_{50}$ )	AP18 (3.1 $\mu$ M, Petrus <i>et al.</i> , 2007), HCO30031 (6.2 $\mu$ M, McNamara <i>et al.</i> , 2007), ruthenium red ( $IC_{50} < 1$ –3 $\mu$ M)
Functional characteristics	$\gamma = 87$ –100 pS; conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na} = 0.84$ ); outward rectification; activated by elevated intracellular $Ca^{2+}$ .

Agents activating TRPA1 in a covalent manner are thiol reactive electrophiles that bind to cysteine and lysine residues within the cytoplasmic domain of the channel (Hinman *et al.*, 2006; Macpherson *et al.*, 2007). TRPA1 is activated by a wide range of endogenous and exogenous compounds and only a few representative examples are mentioned in the table: an exhaustive listing can be found in Baraldi *et al.* (2010). In addition, TRPA1 is potently activated by intracellular zinc ( $EC_{50} = 8$  nM) (Andersson *et al.*, 2009, Hu *et al.*, 2009).

**TRPV (vanilloid) family:** Members of the TRPV family (reviewed by Vennekens *et al.*, 2008) can broadly be divided into the thermosensitive, non-selective cation channels, TRPV1–4 and the calcium selective channels TRPV5 and TRPV6.

**TRPV1–V4 subfamily:** TRPV1 is involved in the development of thermal hyperalgesia following inflammation and may contribute to the detection of noxious heat (reviewed by Pringle *et al.*, 2007; Starowicz *et al.*, 2007; Szallasi *et al.*, 2007). Numerous splice variants of TRPV1 have been described, some of which modulate the activity of TRPV1, or act in a dominant negative manner when co-expressed with TRPV1 (see Schumacher and Eilers, 2010). The pharmacology of TRPV1 channels is discussed in detail in Gunthorpe and Chizh (2009) and Vriens *et al.* (2009). TRPV2 is probably not a thermosensor in man (Park *et al.*, 2011), but has recently been implicated in innate immunity (Link *et al.*, 2010). TRPV3 and TRPV4 are both thermosensitive, with the latter also having a mechanosensing function (Eveaerts *et al.*, 2010a).

Nomenclature	TRPV1	TRPV2
Other names	VR1, vanilloid/capsaicin receptor, OTRPC1	VRL-1, OTRPC2, GRC
Ensembl ID	ENSG00000043316	ENSG00000154039
Physical activators	Depolarization ( $V_{1/2} \cong 0$ mV at 35°C), noxious heat (>43°C at pH 7.4),	Noxious heat (>53°C, rodent, not human),

Nomenclature	TRPV1	TRPV2
Chemical Activators	DkTx (irreversible), extracellular protons ( $pEC_{50} = 5.4$ at $37^{\circ}C$ ), capsaicin, resiniferatoxin, vanillotoxins, phenylacetyltrivanil, olvanil, anandamide, camphor, allicin, some eicosanoids ( <i>e.g.</i> , 12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene B <sub>4</sub> ), NADA, 2-APB, DPBA, activated by NO-mediated cysteine S-nitrosylation	Probenecid, 2-APB (rodent, not human), DPBA, cannabidiol, THC
Blockers (IC <sub>50</sub> )	Ruthenium red (0.09–0.22 $\mu$ M), 5'-iodoresiniferatoxin (3.9 nM), 6-iodo-nordihydrocapsaicin (10 nM), BCTC (6–35 nM), capsazepine (40–280 nM), A-425619 (5 nM), A-778317 (5 nM), AMG517 (0.9 nM), AMG 628 (3.7 nM), JNJ17203212 (65 nM), JYL1421 (9.2 nM), SB366791 (18 nM), SB452533, SB-705498 (3–6 nM)	Ruthenium red (0.6 $\mu$ M), SKF96365, amiloride, TRIM, La <sup>3+</sup>
Probes (K <sub>D</sub> )	[ <sup>3</sup> H]-A778317 (3.4 nM), [ <sup>3</sup> H]-resiniferatoxin, [ <sup>125</sup> I]-resiniferatoxin	–
Functional characteristics	$\gamma = 35$ pS at $-60$ mV; 77 pS at $+60$ mV, conducts mono- and di-valent cations with a selectivity for divalents ( $P_{Ca}/P_{Na} = 9.6$ ); voltage- and time- dependent outward rectification; potentiated by ethanol; activated/potentiated/upregulated by PKC stimulation; extracellular acidification facilitates activation by PKC; desensitisation inhibited by PKA; inhibited by Ca <sup>2+</sup> /calmodulin; cooling reduces vanilloid-evoked currents; may be tonically active at body temperature	Conducts mono- and di-valent cations ( $P_{Ca}/P_{Na} = 0.9-2.9$ ); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to cell surface in response to IGF-1 to induce a constitutively active conductance, translocates to the cell surface in response to membrane stretch

Nomenclature	TRPV3	TRPV4
Other names	–	VRL-2, OTRPC4, VR-OAC, TRP12
Ensembl ID	ENSG00000167723	ENSG00000111199
Physical activators	Depolarization ( $V_{1/2} \sim +80$ mV, reduced to more negative values following heat stimuli), heat ( $23^{\circ}-39^{\circ}C$ , temperature threshold reduces with repeated heat challenge)	Constitutively active, heat ( $> 24-32^{\circ}C$ ), mechanical stimuli
Chemical activators	6-tert-butyl- <i>m</i> -cresol, carvacrol, eugenol, thymol, camphor, menthol, incensole acetate, 2-APB, DPBA, NO-mediated cysteine S-nitrosylation	GSK1016790A ( $EC_{50} = 2.1$ nM, Thorneloe <i>et al.</i> , 2008), RN1747 ( $EC_{50} = 0.77$ $\mu$ M, Vincent <i>et al.</i> , 2009), bisandrographolide A, 4 $\alpha$ -PDH, 4 $\alpha$ -PDD, PMA, epoxyeicosatrienoic acids, NO-mediated cysteine S-nitrosylation
Blockers	Ruthenium red ( $<1$ $\mu$ M), DPTHF (6–10 $\mu$ M)	HC067047 ( $IC_{50} = 17$ nM, Everaerts <i>et al.</i> , 2010b), RN1734 ( $IC_{50} = 2.3$ $\mu$ M, Vincent <i>et al.</i> , 2009), ruthenium red (voltage dependent block), La <sup>3+</sup> , Gd <sup>3+</sup>
Functional characteristics	$\gamma = 197$ pS at $+40$ to $+80$ mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification; potentiated by arachidonic acid	$\gamma = -60$ pS at $-60$ mV, $-90-100$ pS at $+60$ mV; conducts mono- and di-valent cations with a preference for divalents ( $P_{Ca}/P_{Na} = 6-10$ ); dual (inward and outward) rectification; potentiated by intracellular Ca <sup>2+</sup> via Ca <sup>2+</sup> /calmodulin; inhibited by elevated intracellular Ca <sup>2+</sup> via an unknown mechanism ( $IC_{50} = 0.4$ $\mu$ M);

Activation of TRPV1 by depolarisation is strongly temperature-dependent *via* a channel opening rate that increases with increasing temperature. The  $V_{1/2}$  is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists (Voets *et al.*, 2004). The sensitivity of TRPV4 to heat, but not 4 $\alpha$ -PDD, is lost upon patch excision. TRPV4 is activated by anandamide and arachidonic acid following P450 epoxygenase-dependent metabolism to 5',6'-epoxyeicosatrienoic acid (reviewed by Nilius *et al.*, 2004). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated *via* the formation of epoxyeicosatrienoic acids. Phorbol esters bind directly to TRPV4.

**TRPV5/V6 subfamily:** Under physiological conditions, TRPV5 and TRPV6 are calcium selective channels involved in the absorption and reabsorption of calcium across intestinal and kidney tubule epithelia (reviewed by Wissenbach and Niemeyer, 2007; de Groot *et al.*, 2008).

Nomenclature	TRPV5	TRPV6
Other names	ECaC, ECaC1, CaT2, OTRPC3	ECaC2, CaT1, CaT-L
Ensembl ID	ENSG00000127412	ENSG00000165125
Activators	Constitutively active (with strong buffering of intracellular Ca <sup>2+</sup> )	Constitutively active (with strong buffering of intracellular Ca <sup>2+</sup> ), potentiated by 2-APB

Nomenclature	TRPV5	TRPV6
Blockers	Ruthenium red ( $IC_{50} = 121$ nM), econazole, miconazole, $Pb^{2+} = Cu^{2+} = Gd^{3+} > Cd^{2+} > Zn^{2+} > La^{3+} > Co^{2+} > Fe^{2+}$ ; $Mg^{2+}$	Ruthenium red ( $IC_{50} = 9$ $\mu$ M), $Cd^{2+}$ , $Mg^{2+}$ , $La^{3+}$
Functional characteristics	$\gamma = 59$ – $78$ pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ( $P_{Ca}/P_{Na} > 107$ ); voltage- and time- dependent inward rectification; inhibited by intracellular $Ca^{2+}$ promoting fast inactivation and slow downregulation; feedback inhibition by $Ca^{2+}$ reduced by calcium binding protein 80-K-H; inhibited by extracellular and intracellular acidosis; upregulated by 1,25-dihydrovitamin D3	$\gamma = 58$ – $79$ pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ( $P_{Ca}/P_{Na} > 130$ ); voltage- and time-dependent inward rectification; inhibited by intracellular $Ca^{2+}$ promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular $Mg^{2+}$ ; slow inactivation due to $Ca^{2+}$ -dependent calmodulin binding; phosphorylation by PKC inhibits $Ca^{2+}$ -calmodulin binding and slow inactivation; upregulated by 1,25-dihydroxyvitamin D3

TRPV5 preferentially conducts  $Ca^{2+}$  under physiological conditions, but in the absence of extracellular  $Ca^{2+}$ , conducts monovalent cations. Single channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution.  $Ca^{2+}$ -induced inactivation occurs at hyperpolarized potentials when  $Ca^{2+}$  is present extracellularly. Single channel events cannot be resolved (probably due to greatly reduced conductance) in the presence of extracellular divalent cations. Measurements of  $P_{Ca}/P_{Na}$  for TRPV5 and TRPV6 are dependent upon ionic conditions due to anomalous mole fraction behaviour. Blockade of TRPV5 and TRPV6 by extracellular  $Mg^{2+}$  is voltage-dependent. Intracellular  $Mg^{2+}$  also exerts a voltage dependent block that is alleviated by hyperpolarization and contributes to the time-dependent activation and deactivation of TRPV6 mediated monovalent cation currents. TRPV5 and TRPV6 differ in their kinetics of  $Ca^{2+}$ -dependent inactivation and recovery from inactivation. TRPV5 and TRPV6 function as homo- and hetero-tetramers.

**TRPML (mucolipin) family:** The TRPML family (see Qian and Noben-Trauth, 2005; Zeevi *et al.*, 2007; Puertollano and Kiselyov, 2009) consists of three mammalian members (TRPML1-3). TRPML channels are probably restricted to intracellular vesicles and mutations in the gene (*MCOLN1*) encoding TRPML1 (mucolipin-1) are the cause of the neurodegenerative disorder mucopolipidosis type IV (MLIV) in man. TRPML1 is a cation selective ion channel that is important for sorting/transport of endosomes in the late endocytotic pathway and specifically fusion between late endosome-lysosome hybrid vesicles. TRPML2 (*MCLN2*) remains to be functionally characterised in detail. TRPML3 is important for hair cell maturation, stereocilia maturation and intracellular vesicle transport. A naturally occurring gain of function mutation in TRPML3 (*i.e.* A419P) results in the varitint waddler (*Va*) mouse phenotype (reviewed by Qian and Noben-Trauth, 2005; Nilius *et al.*, 2007).

Nomenclature	TRPML1	TRPML2	TRPML3
Other names	MCLN1, mucolipin-1 (ML1)	MCLN2	
Ensembl ID	ENSG00000090674	ENSG00000153898	ENSG00000055732
Activators	TRPML1 <sup>Va</sup> : Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	TRPML2 <sup>Va</sup> : Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	TRPML3 <sup>Va</sup> : Constitutively active, current inhibited by extracellular acidification (equivalent to intralysosomal acidification) Wild type TRPML3: Activated by $Na^+$ -free extracellular (extracytosolic) solution and membrane depolarization, current inhibited by extracellular acidification (equivalent to intralysosomal acidification)
Blockers	–	–	$Gd^{3+}$
Functional characteristics	TRPML1 <sup>Va</sup> : $\gamma = 40$ pS and 76-86 pS at very negative holding potentials with $Fe^{2+}$ and monovalent cations as charge carriers, respectively; conducts $Na^+ \cong K^+ > Cs^+$ and divalent cations ( $Ba^{2+} > Mn^{2+} > Fe^{2+} > Ca^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} > Zn^{2+} > Cu^{2+}$ ) but not $Fe^{3+}$ , impermeable to protons; monovalent cation flux suppressed by divalent cations ( <i>e.g.</i> $Ca^{2+}$ , $Fe^{2+}$ ); inwardly rectifying	TRPML1 <sup>Va</sup> : Conducts $Na^+$ ; monovalent cation flux suppressed by divalent cations; inwardly rectifying	TRPML3 <sup>Va</sup> : $\gamma = 49$ pS at very negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ with maintained current in the presence of $Na^+$ , conducts $Ca^{2+}$ and $Mg^{2+}$ , but not $Fe^{2+}$ , impermeable to protons; inwardly rectifying Wild type TRPML3: $\gamma = 59$ pS at negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ and $Ca^{2+}$ ( $P_{Ca}/P_K \cong 350$ ), slowly inactivates in the continued presence of $Na^+$ within the extracellular (extracytosolic) solution; outwardly rectifying

Data in the table are for TRPML proteins mutated (*i.e.* TRPML1<sup>Va</sup>, TRPML2<sup>Va</sup> and TRPML3<sup>Va</sup>) at loci equivalent to TRPML3 A419P to allow plasma membrane expression when expressed in HEK-293 cells and subsequent characterisation by patch-clamp recording (Grimm *et al.*, 2007; Kim

*et al.*, 2007; Xu *et al.*, 2007; Dong *et al.*, 2008; Nagata *et al.*, 2008). Data for wild type TRPML3 are also tabulated (Kim *et al.*, 2007, 2008; Xu *et al.*, 2007; Nagata *et al.*, 2008). It should be noted that alternative methodologies, particularly in the case of TRPML1, have resulted in channels with differing biophysical characteristics (reviewed by Puertollano and Kiselyov, 2009).

**TRPP (polycystin) family:** The TRPP family (reviewed by Delmas *et al.*, 2004a, Delmas, 2005; Giamarchi *et al.* 2006; Witzgall, 2007; Hofherr and Kottgen, 2011) subsumes the polycystins that are divided into two structurally distinct groups, polycystic kidney disease 1-like (PKD1-like) and polycystic kidney disease 2-like (PKD2-like). Members of the PKD1-like group, in mammals, include PKD1 (reclassified as TRPP1), PDKREJ, PKD1L1, PKD1L2 and PKD1L3. The PKD2-like members comprise PKD2, PKD2L1 and PKD2L2, which have renamed TRPP2, TRPP3 and TRPP5, respectively (Moran *et al.*, 2004). PKDREJ (ENSG00000130943), PKD1L1 (ENSG00000158683), PKD1L2 (ENSMUS00000034416), PKD1L3 (ENSG00000187008) and TRPP5 (ENSG00000078795) are not listed in the table due to lack of functional data. Similarly, TRPP1 (ENSG00000008710) is also omitted because although one study (Babich *et al.*, 2004) has reported the induction of a cation conductance in CHO cells transfected with TRPP1, there is no unequivocal evidence that TRPP1 is a channel *per se* and in other studies (*e.g.* Hanaoka *et al.*, 2000, Delmas *et al.*, 2004b) TRPP1 is incapable of producing currents.

Nomenclature	TRPP2	TRPP3
Other names	Polycystin-2 (PC2), polycystic kidney disease 2 (PKD2)	Polycystic kidney disease 2-like 1 protein (PKD2L1)
Ensembl ID	ENSG00000118762	ENSG00000107593
Activators	Constitutive activity, suppressed by co-expression of TRPP1	Low constitutive activity, enhanced by membrane depolarization; changes in cell volume affect voltage-dependent gating (increased channel opening probability with cell swelling)
Blockers (IC <sub>50</sub> )	Amiloride, La <sup>3+</sup> , Gd <sup>3+</sup>	Phenamyl (0.14 μM), benzamil (1.1 μM), EIPA (10.5 μM), amiloride (143 μM), flufenamate, La <sup>3+</sup> , Gd <sup>3+</sup> ,
Functional characteristics	γ = 123–177 pS (with K <sup>+</sup> as charge carrier); P <sub>Na</sub> /P <sub>K</sub> = 0.14–1.1; conducts both mono- and di-valent cations	γ = 105–137 pS (outward conductance) 184–399 pS (inward conductance), conducts mono- and di-valent cations with a preference for divalents (P <sub>Ca</sub> /P <sub>Na</sub> = 4.0–4.3); steady state currents rectify outwardly, whereas instantaneous currents show strong inward rectification; activated and subsequently inactivated by intracellular Ca <sup>2+</sup> (human, but not mouse); inhibited by extracellular acidification and potentiated by extracellular alkalization

Data in the table are extracted from Delmas *et al.* (2004a), Dai *et al.* (2007) and Shimizu *et al.* (2009). Broadly similar single channel conductance, mono- and di-valent cation selectivity and sensitivity to blockers are observed for TRPP2 co-expressed with TRPP1 (Delmas, 2004b). Ca<sup>2+</sup>, Ba<sup>2+</sup> and Sr<sup>2+</sup> permeate TRPP3, but reduce inward currents carried by Na<sup>+</sup>. Mg<sup>2+</sup> is largely impermeant and exerts a voltage dependent inhibition that increases with hyperpolarization.

**Abbreviations:** 2-APB, 2-amino ethoxyphenylborate; 4α-PDD, 4α-phorbol 12,13-didecanoate; 4α-PDH, 4α-phorbol 12,13-dihexanoate; 5-(S)-HETE, 5-(S)-hydroxyeicosatetraenoic acid; 12-(S)-HPETE and 15-(S)-HPETE, 12- and 15-(S)-hydroperoxyeicosatetraenoic acids; 20-HETE, 20-hydroxyeicosatetraenoic acid; A-425619, 1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)urea; A-778317, 1-((R)-5-*tert*-butyl-indan-1-yl)-3-isoquinolin-5-yl-urea; ACA, *N*-(*p*-amylcinnamoyl)anthranilic acid; AMG 517, *N*-{4-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide; AMG628, (R)-*N*-(4-(6-(4-(1-(4-fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[d]thiazol-2-yl)acetamide; AMTB, *N*-(3-aminopropyl)-2-[[3-(methylphenyl) methyl]oxy]-*N*-(2-thienylmethyl)benzamide; AP18, 4-(4-chlorophenyl)-3-methyl-3-buten-2-one oxime; BCTC, *N*-(4-*tert*-butylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2*H*)-carboxamide; BTP2, 4-methyl-4'-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxanilide; DPBA, diphenylboronic anhydride; DPTHF, diphenyltetrahydrofuran; GEA3162, 1,2,3,4-oxatriazolium-5-amino-3-(3,4-dichlorophenyl)-chloride; GSK1016790A *N*-((1*S*)-1-[[4-((2*S*)-2-[[2,4-dichlorophenyl)sulfonyl]amino]-3-hydroxypropanoyl]-1-piperazinyl]carbonyl]-3-methylbutyl)-1-benzothiophene-2-carboxamide; HC030031, 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)-*N*-(4-isopropylphenyl)acetamide; HC067047, 2-methyl-1-[3-(4-morpholinyl)propyl]-5-phenyl-*N*-[3-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxamide; JYL1421; *N*-(4-*tert*-butylbenzyl)-*N'*-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea; JNJ17203212, 4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; KB-R7943, 2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiourea methanesulfonate; ML-9, 1-(5-chloronaphthalene-1-sulphonyl)homopiperazine; ML204, structure not available; NADA, *N*-arachidonoyl dopamine; PMA, phorbol 12 myristate 13-acetate; Pyr3, ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate; RN1734, 2,4-dichloro-*N*-isopropyl-*N*-(2-isopropylaminoethyl)benzenesulfonamide; RN1747, 1-(4-chloro-2-nitrophenyl)sulfonyl-4-benzylpiperazine; SB366791, *N*-(3-methoxyphenyl)-4-chlorocinnamide; SB705498, *N*-(2-bromophenyl)-*N'*-[((R)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea; SDZ249665, 1-[4-(2-aminoethoxy)-3-methoxy-benzyl]-3-(4-*tert*-butyl-benzyl)-urea; SKF96265, 1-(β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl)-1*H*-imidazole hydrochloride; THC, Δ<sup>9</sup>-tetrahydrocannabinol; TRIM, 1-(2-(trifluoromethyl)phenyl)imidazole; URB597, 3'-carbamoylbiphenyl-3-yl cyclohexylcarbamate; WS-12, 2-isopropyl-5-methyl-cyclohexanecarboxylic acid (4-methoxy-phenyl)-amide

#### Further Reading

Abramowitz J, Birnbaumer L (2009). Physiology and pathophysiology of canonical transient receptor potential channels. *FASEB J* 23: 297–328.  
 Ambudkar IS, Ong HL (2007). Organisation and function of TRPC channelosomes. *Pflügers Arch* 455: 187–200.  
 Baraldi PG, Preti D, Materazzi S, Geppetti P (2010). Transient receptor potential ankyrin 1 (TRPA1) channel as emerging target for novel analgesics and anti-inflammatory agents. *J Med Chem* 53: 5085–5107.  
 Bates-Withers C, Sah R, Clapham DE (2011). TRPM7, the Mg<sup>2+</sup> inhibited channel and kinase. *Adv Exp Med Biol* 704: 173–183.  
 Beech DJ (2011). Integration of transient receptor potential canonical channels with lipids. *Acta Physiol (Oxf)* doi: 10.1111/j.1748-1716.2011.02311.x.

- Birnbaumer L (2009). The TRPC class of ion channels: a critical review of their roles in slow, sustained increases in intracellular  $\text{Ca}^{2+}$  concentrations. *Annu Rev Pharmacol Toxicol* **49**: 395–426.
- Cheng KT, Ong HL, Liu X, Ambudkar IS (2011). Contribution of TRPC1 and Orai1 to  $\text{Ca}^{2+}$  entry activated by store depletion. *Adv Exp Med Biol* **704**: 435–449.
- Clapham DE, Montell C, Schultz G, Julius D (2005). International Union of Pharmacology. XLIII. Compendium of Voltage-gated ion channels. Transient receptor potential channels. *Pharmacol Rev* **55**: 591–596.
- Delmas P (2005). Polycystins: polymodal receptor/ion-channel cellular sensors. *Pflügers Arch* **451**: 264–276.
- Delmas P, Padilla F, Osorio N, Coste B, Raoux M, Crest M (2004a). Polycystins, calcium signaling, and human diseases. *Biochem Biophys Res Commun* **322**: 1374–1383.
- Dhaka A., Viswanath V, Patapoutian A (2006). Trp ion channels and temperature sensation. *Annu Rev Neurosci* **29**: 135–161.
- Everaerts W, Nilius B, Owsianik G (2010a). The vanilloid transient receptor potential channel TRPV4: from structure to disease. *Prog Biophys Mol Biol* **103**: 2–17.
- Fleig A, Penner R (2004). The TRPM ion channel subfamily: molecular, biophysical and functional features. *Trends Pharmacol Sci* **25**: 633–639.
- Freichel M, Vennekens R, Olausson J, Stolz S, Philipp SE, Weißgerber P *et al.* (2005). Functional role of TRPC proteins in native systems: implications from knockout and knock-down studies. *J Physiol* **567**: 59–66.
- Garcia-Anoveros J, Nagata K (2007). TRPA1. *Handb Exp Pharmacol* **179**: 347–362.
- Giamarchi A, Padilla F, Coste B, Raoux M, Crest M, Honore E *et al.* (2006). The versatile nature of the calcium-permeable cation channel TRPP2. *EMBO Rep* **7**: 787–793.
- de Groot T, Bindels RJ, Hoenderop JG (2008). TRPV5: an ingeniously controlled calcium channel. *Kidney Int* **74**: 1241–1246.
- Guinamard R, Sallé L, Simard C (2011). The non-selective monovalent cationic channels TRPM4 and TRPM5. *Adv Exp Med Biol* **704**: 147–171.
- Gunthorpe MJ, Chizh BA (2009). Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway. *Drug Discov Today* **14**: 56–67.
- Harteneck C (2005). Function and Pharmacology of TRPM cations channels. *Naunyn-Schmiedeberg's Arch Pharmacol* **371**: 307–314.
- Harteneck C, Gollasch M (2011). Pharmacological modulation of diacylglycerol-sensitive TRPC3/6/7 channels. *Curr Pharm Biotech* **12**: 35–41.
- Harteneck C, Klose C, Krautwurst D (2011). Synthetic modulators of TRP channel activity. *Adv Exp Med Biol* **704**: 87–106.
- Hofherr A, Köttgen M (2011). TRPP channels and polycystins. *Adv Exp Med Biol* **704**: 287–313.
- Islam MS (ed) (2011). Transient receptor potential channels. *Adv Exp Med Biol* **704**: 1–1095.
- Kiselyov K, Patterson RL (2009). The integrative function of TRPC channels. *Front Biosci* **14**: 45–58.
- Kiselyov K, Shin DM, Kim JY, Yuan JP, Muallem S. (2007b) TRPC channels: interacting proteins. *Handb Exp Pharmacol* **179**: 559–574.
- Kiselyov K, Soyombo A, Muallem S (2007a). TRPpathies. *J Physiol* **578**: 641–653.
- Knowlton WM, McKemy DD (2011). TRPM8: from cold to cancer, peppermint to pain. *Curr Pharm Biotechnol* **12**: 68–77.
- Koike C, Numata T, Ueda H, Mori Y, Furukawa T (2010). TRPM1: a vertebrate TRP channel responsible for retinal ON bipolar function. *Cell Calcium* **48**: 95–101.
- Liman ER (2007). TRPM5 and taste transduction. *Handb Exp Pharmacol* **179**: 287–298.
- Liu Y, Qin N (2011). TRPM8 in health and disease: cold sensing and beyond. *Adv Exp Med Biol* **704**: 185–208.
- Mälkiä A, Morenilla-Palao C, Viana F (2011). The emerging pharmacology of TRPM8 channels: hidden therapeutic potential underneath a cold surface. *Curr Pharm Biotechnol* **12**: 54–67.
- Moran MM, Xu H, Clapham DE (2004). TRP ion channels in the nervous system. *Curr Opin Neurobiol* **14**: 362–369.
- Nilius B (ed.) (2007). TRP channels in disease. *Biochem Biophys Acta* **1772**: 805–1032.
- Nilius B, Owsianik G (2010). Transient receptor potential channelopathies. *Pflügers Arch* **460**: 437–450.
- Nilius B, Voets T (2005). A TR(I)P through a world of multifunctional cation channels. *Pflügers Arch* **451**: 1–10.
- Nilius B, Vriens J, Prenen J, Droogmans G, Voets T (2004). TRPV4 calcium channel: a paradigm for gating diversity. *Am J Physiol* **286**: C195–C205.
- Nilius B, Talavera K, Owsianik G, Prenen J, Droogmans G, Voets T. (2005). Gating of TRP channels: a voltage connection? *J Physiol* **567**: 35–44.
- Nilius B, Owsianik G, Voets T, Peters JA (2007). Transient receptor potential (TRP) cation channels in disease. *Physiol Rev* **87**: 165–217.
- Nilius B, Owsianik G, Voets T (2008). Transient receptor potential channels meet phosphoinositides. *EMBO J* **27**: 2809–2816.
- Oberwinkler J, Philipp SE (2007). TRPM3. *Handb Exp Pharmacol* **179**: 253–267.
- Owsianik G, D'hoedt D, Voets T, Nilius B (2006a). Structure-function relationship of the TRP channel superfamily. *Rev Physiol Biochem Pharmacol* **156**: 61–90.
- Owsianik G, Talavera G, Voets, Nilius B (2006b). Permeation and selectivity of TRP channels. *Annu Rev Physiol* **68**: 685–717.
- Patel A, Sharif-Naeini R, Folgering JR, Bichet D, Duprat F, Honoré E (2010). Canonical TRP channels and mechanotransduction: from physiology to disease states. *Pflügers Arch* **460**: 571–581.
- Pedersen SF, Owsianik G, Nilius B (2005). TRP Channels: an overview. *Cell Calcium* **38**: 233–252.
- Penner R, Fleig A (2007). The  $\text{Mg}^{2+}$  and  $\text{Mg}^{2+}$ -nucleotide-regulated channel-kinase TRPM7. *Handb Exp Pharmacol* **179**: 313–328.
- Plant TD, Schaefer M. (2003). TRPC4 and TRPC5: receptor-operated  $\text{Ca}^{2+}$ -permeable non-selective cation channels. *Cell Calcium* **33**: 441–450.
- Potier M, Trebak M (2008). New developments in the signalling mechanisms of the store-operated calcium entry pathway. *Pflügers Arch* **457**: 405–415.
- Pringle SC, Matta JA, Ahern GP (2007). Capsaicin receptor: TRPV1 a promiscuous TRP channel. *Handb Exp Pharmacol* **179**: 153–169.
- Puertollano R, Kiselyov K (2009). TRPMLs: in sickness and in health. *Am J Physiol Renal Physiol* **296**: F1245–F1254.
- Putney JW (2005). Physiological mechanisms of TRPC activation. *Pflügers Arch* **451**: 29–34.
- Qian F, Noben-Trauth K (2005). Cellular and molecular function of mucopolipins (TRPML) and polycystin 2 (TRPP2). *Pflügers Arch* **451**: 277–285.
- Ramsey IS, Delling M, Clapham DE (2006). An introduction to TRP channels. *Annu Rev Physiol* **68**: 619–647.
- Rohacs T (2009). Phosphoinositide regulation of non-canonical transient receptor potential channels. *Cell Calcium* **45**: 554–565.
- Runnels LW (2011). TRPM6 and TRPM7: a Mul-TRP-PLIK-cation of channel functions. *Curr Pharm Biotechnol* **12**: 42–53.
- Salido GM, Sage SO, Rosado, JA (2009). TRPC channels and store-operated  $\text{Ca}^{2+}$  entry. *Biochim Biophys Acta* **1793**: 223–230.
- Schumacher MA, Eilers H (2010). TRPV1 splice variants: structure and function. *Front Biosci* **15**: 872–882.
- Starowicz K, Nigam S, Di Marzo V (2007). Biochemistry and pharmacology of endovanilloids. *Pharmacol Ther* **114**: 13–33.
- Szallasi A, Cortright DN, Blum CA, Eid SR (2007). The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. *Nat Rev Drug Discov* **6**: 357–372.
- Trebak M, Lemonnier L, Smyth JT, Vazquez G, Putney JW Jr (2007). Phospholipase C-coupled receptors and activation of TRPC channels. *Handb Exp Pharmacol* **179**: 593–614.
- Vay L, Gu C, McNaughton PA (2011). The thermo-TRP ion channel family: properties and therapeutic implications. *Br J Pharmacol* doi: 10.1111/j.1476-5381.2011.01601.x.
- Venkatachalam K, Montell C (2007). TRP channels. *Annu Rev Biochem* **76**: 387–417.
- Vennekens R, Nilius B (2007). Insights into TRPM4 function, regulation and physiological role. *Handb Exp Pharmacol* **179**: 269–285.

- Vennekens R, Owsianik G, Nilius B (2008). Vanilloid transient receptor potential cation channels: an overview. *Curr Pharm Des* **14**: 18–31.
- Vincent F, Duncton MA (2011). TRPV4 Agonists and Antagonists. *Curr Top Med Chem* **11**: 2216–2226.
- Voets T, Nilius B (2007). Modulation of TRPs by PIPs. *J Physiol* **582**: 939–944.
- Voets T, Owsianik G, Nilius B (2007). TRPM8. *Handb Exp Pharmacol* **179**: 329–344.
- Voets T, Talavera K, Owsianik G, Nilius B (2005). Sensing with TRP channels. *Nature Chem Biol* **2**: 85–92.
- Vriens J, Appendino G, Nilius B (2009). Pharmacology of vanilloid transient receptor potential cation channels. *Mol Pharmacol* **75**: 162–1279.
- Wissenbach U, Niemeier BA (2007). TRPV6. *Handb Exp Pharmacol* **179**: 221–234.
- Witzgall R (2007). TRPP2 channel regulation. *Handb Exp Pharmacol* **179**: 363–375.
- Wu LJ, Sweet TB, Clapham DE (2010). International Union of Basic and Clinical Pharmacology. LXXXVI. Current progress in the mammalian TRP ion channel family. *Pharmacol Rev* **62**: 381–404.
- Yamamoto S, Takahashi N, Mori Y (2010). Chemical physiology of oxidative stress-activated TRPM2 and TRPC5 channels. *Prog Biophys Mol Biol* **103**: 18–27.
- Yuan JP, Kim MS, Zeng W, Shin DM, Huang G, Worley PF, Muallem S (2009). TRPC channels as STIM1-regulated SOCs. *Channels (Austin)* **3**: 221–225.
- Zeevi DA, Frumkin A, Bach G (2007). TRPML and lysosomal function. *Biochim Biophys Acta* **1772**: 851–858.
- Zholos A (2010). Pharmacology of transient receptor potential melastatin channels in the vasculature. *Br J Pharmacol* **159**: 1559–1571.

## References

- Andersson DA *et al.* (2004). *J Neurosci* **24**: 5364–5369.
- Andersson DA *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 8374–8379.
- Babich V *et al.* (2004). *J Biol Chem* **279**: 25582–25589.
- Bandell M *et al.* (2004). *Neuron* **41**: 849–857.
- Barbet G *et al.* (2008). *Nat Immunol* **9**: 1148–1156.
- Bautista DM *et al.* (2006). *Cell* **124**: 1269–1282.
- Bautista DM *et al.* (2007). *Nature* **448**: 204–208.
- Colburn RW *et al.* (2007). *Neuron* **54**: 379–386.
- Corey DP *et al.* (2004). *Nature* **432**: 723–730.
- Dai XQ *et al.* (2007). *Mol Pharmacol* **72**: 1576–1585.
- Delmas P *et al.* (2004b). *FASEB J* **18**: 740–742.
- Dhaka A *et al.* (2007). *Neuron* **54**: 371–378.
- Dong X-P *et al.* (2008). *Nature* **455**: 992–997.
- Du J *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 7239–7244.
- Everaerts W *et al.* (2010b). *Proc Natl Acad Sci U S A* **107**: 19084–19089.
- Grimm C *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 19583–19588.
- Hanaoka K *et al.* (2000). *Nature* **408**: 990–994.
- Hinman A *et al.* (2006). *Proc Natl Acad Sci U S A* **103**: 19564–19568.
- Hu H *et al.* (2009). *Nat Chem Biol* **5**: 183–190.
- Jordt SE *et al.* (2004). *Nature* **427**: 260–265.
- Karashima Y *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 1273–1278.
- Kim HJ *et al.* (2007). *J Biol Chem* **282**: 36138–36142.
- Kim HJ *et al.* (2008). *EMBO J* **27**: 1197–1205.
- Kiyonaka S *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 5400–5405.
- Klose C *et al.* (2011). *Br J Pharmacol* **162**: 1757–1769.
- Kwan KY *et al.* (2006). *Neuron* **50**: 277–289.
- Lambert S *et al.* (2011). *J Biol Chem* **286**: 122221–112233.
- Lashinger ES *et al.* (2008). *Am J Physiol* **295**: F803–F810.
- Leuner K *et al.* (2007). *FASEB J* **21**: 4101–4111.
- Leuner K *et al.* (2010). *Mol Pharmacol* **77**: 368–377.
- Link TM *et al.* (2010). *Nat Immunol* **11**: 232–239.
- Macpherson LJ *et al.* (2007). *Nature* **445**: 541–545.
- Mahieu F *et al.* (2007). *J Biol Chem* **282**: 3325–3336.
- Majeed Y *et al.* (2010). *Br J Pharmacol* **161**: 430–441.
- Majeed Y *et al.* (2011). *Mol Pharmacol* **79**: 1023–1030.
- Mälkiä A *et al.* (2007). *J Physiol* **581**: 155–174.
- McNamara CR *et al.* (2007). *Proc Natl Acad Sci USA* **104**: 13525–13530.
- Miller M *et al.* (2011). *J Biol Chem* **286**: 33436–33446.
- Nagata K *et al.* (2005). *J Neurosci* **25**: 4052–4061.
- Nagata K *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 353–358.
- Niforatus W *et al.* (2007). *Mol Pharmacol* **71**: 1209–1216.
- Oancea E *et al.* (2009). *Sci Signal* **2**: ra21.
- Park U *et al.* (2011). *J Neurosci* **31**: 11425–11436.
- Petrus P *et al.* (2007). *Mol Pain* **3**: 40.
- Sawada Y *et al.* (2007). *Brain Res* **1160**: 39–46.
- Shimizu T *et al.* (2009). *Pflügers Arch* **457**: 795–807.
- Story GM *et al.* (2003). *Cell* **112**: 819–829.
- Thorneloe KS *et al.* (2008). *J Pharmacol Exp Ther* **326**: 432–442.
- Ullrich ND *et al.* (2005). *Cell Calcium* **37**: 267–278.
- Vennekens R *et al.* (2007). *Nat Immunol* **8**: 312–320.
- Vincent F *et al.* (2009). *Biochem Biophys Res Commun* **389**: 490–494.
- Voets T *et al.* (2004). *Nature* **430**: 748–754.
- Vriens J *et al.* (2011). *Neuron* **70**: 482–494.
- Wagner TF *et al.* (2008). *Nat Cell Biol* **10**: 1421–1430.
- Wong CO *et al.* (2010). *Br J Pharmacol* **159**: 1486–1496.
- Xu H *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 18321–18326.
- Zurberg S *et al.* (2007). *Nat Neurosci* **10**: 277–279.



# NUCLEAR RECEPTORS

**Overview:** Nuclear receptors are specialised transcription factors with commonalities of sequence and structure, which bind as homo- or heterodimers to specific consensus sequences of DNA (response elements) in the promoter region of particular target genes. They regulate (either promoting or repressing) transcription of these target genes in response to a variety of endogenous ligands. Endogenous agonists are hydrophobic entities which, when bound to the receptor promote conformational changes in the receptor to allow recruitment (or dissociation) of protein partners, generating a large multiprotein complex.

Two major subclasses of nuclear receptors with identified endogenous agonists can be identified: steroid and non-steroid hormone receptors. Steroid hormone receptors function typically as dimeric entities and are thought to be resident outside the nucleus in the unliganded state in a complex with chaperone proteins, which are liberated upon agonist binding. Migration to the nucleus and interaction with other regulators of gene transcription, including RNA polymerase, acetyltransferases and deacetylases, allows gene transcription to be regulated. Non-steroid hormone receptors typically exhibit a greater distribution in the nucleus in the unliganded state and interact with other nuclear receptors to form heterodimers, as well as with other regulators of gene transcription, leading to changes in gene transcription upon agonist binding.

Selectivity of gene regulation is brought about through interaction of nuclear receptors with particular consensus sequences of DNA, which are arranged typically as repeats or inverted palindromes to allow accumulation of multiple transcription factors in the promoter regions of genes.

## Further Reading

Germain P, Staels B, Dacquet C, Spedding M, Laudet V (2006). Overview of nomenclature of nuclear receptors. *Pharmacol Rev* 58: 685–704.

# Orphan nuclear receptors

In man, 48 nuclear receptors have been identified from sequence analysis of the genome (see Benoit *et al.*, 2006; Germain *et al.*, 2006), only half of which have been 'assigned' a ligand by Nomenclature Committees of NC-IUPHAR. 19 families of nuclear receptors have been identified, allowing a systematic nomenclature of the format NRXYZ, where NR represents nuclear receptor, X the subfamily (1, 2, 3, 4, 5, 6 or 0), Y the group (A, B, C, D, E, H or I) and Z the individual member.

## Preliminary pairings

Listed below are a number of putative nuclear receptors identified by NC-IUPHAR, for which only preliminary evidence for an endogenous ligand has been published.

Common nomenclature	Systematic nomenclature	Other names	Ensembl ID	Putative endogenous ligand	Comment
Rev-erb $\alpha$	NR1D1	EAR1, hRev	ENSG00000126368	Haem (Raghuram <i>et al.</i> , 2007; Yin <i>et al.</i> , 2007)	A synthetic agonist, GSK4112, has been described (Grant <i>et al.</i> , 2010)
Rev-erb $\beta$	NR1D2	EAR1 $\beta$ , RVR, BD73	ENSG00000174738	Haem (Raghuram <i>et al.</i> , 2007; Yin <i>et al.</i> , 2007)	A synthetic agonist, GSK4112, has been described (Grant <i>et al.</i> , 2010)
HNF4 $\alpha$	NR2A1	Hepatocyte nuclear factor 4- $\alpha$ , MODY1, TCF14	ENSG00000101076	Linoleic acid (Yuan <i>et al.</i> , 2009)	–
TR4	NR2C2	Testicular receptor 4, TAK1	ENSG00000177463	Retinol, retinoic acid (Zhou <i>et al.</i> , 2011)	Forms a heterodimer with TR2 (Young <i>et al.</i> , 1998)

## Orphan nuclear receptors

Common nomenclature	Systematic nomenclature	Other names	Ensembl ID	Comments
HNF4 $\gamma$	NR2A2	Hepatocyte nuclear factor 4- $\gamma$	ENSG00000164749	–
TR2	NR2C1	Testicular receptor 2	ENSG00000120798	Forms a heterodimer with TR4 (Young <i>et al.</i> , 1998); gene disruption appears without effect on testicular development or function (Shyr <i>et al.</i> , 2002)
TLX	NR2E1	Tailless homolog, TLL	ENSG00000112333	Gene disruption is associated with abnormal brain development (Monaghan <i>et al.</i> , 1997; Land and Monaghan, 2003)
PNR	NR2E3	Photoreceptor-specific nuclear receptor, retina-specific nuclear receptor	ENSG00000031544	–
COUP-TFI	NR2F1	COUP $\alpha$ , EAR3, SVP44	ENSG00000175745	Gene disruption is perinatally lethal (Qiu <i>et al.</i> , 1997)
COUP-TFII	NR2F2	COUP $\beta$ , ARP1, SVP40	ENSG00000185551	Gene disruption is embryonically lethal (Pereira <i>et al.</i> , 1999)
EAR2	NR2F6	V-erb-related gene	ENSG00000160113	Gene disruption impairs CNS development (Warnecke <i>et al.</i> , 2005)

Common nomenclature	Systematic nomenclature	Other names	Ensembl ID	Comments
ERR $\alpha$	NR3B1	ESRL1, estrogen-related receptor $\alpha$ , estrogen receptor-like 1	ENSG00000173153	Activated by some dietary flavonoids (Suetsugi <i>et al.</i> , 2003); activated by the synthetic agonist GSK4716 (Zuercher <i>et al.</i> , 2005) and blocked by XCT790 (Willy <i>et al.</i> , 2004)
ERR $\beta$	NR3B2	ESRL2, estrogen-related receptor $\beta$ , estrogen receptor-like 2	ENSG00000119715	May be activated by DY131 (Yu and Forman, 2005)
ERR $\gamma$	NR3B3	ESRL3, estrogen-related receptor $\gamma$ , estrogen receptor-like 3	ENSG00000196482	May be activated by DY131 (Yu and Forman, 2005)
Nur77	NR4A1	Nerve growth factor 1B, NGFI-B, NAK1, ST59, TR3, HMR	ENSG00000123358	An exogenous agonist, cytosporone B, has been described (Zhan <i>et al.</i> , 2008), although structural analysis and molecular modelling has not identified a ligand binding site (Baker <i>et al.</i> , 2003; Flaig <i>et al.</i> , 2005; Wang <i>et al.</i> , 2003)
NURR1	NR4A2	Immediate-early response protein NOT, transcriptionally-inducible nuclear receptor, TINUR, RNR-1	ENSG00000153234	–
NOR1	NR4A3	Neuron-derived orphan receptor, mitogen-induced nuclear orphan receptor	ENSG00000119508	–
SF1	NR5A1	Steroidogenic factor 1, adrenal 4-binding protein, steroid hormone receptor Ad4BP, Fushi tarazu factor homolog 1	ENSG00000136931	Reported to be inhibited by AC45594 (Del Tredici <i>et al.</i> , 2008) and SID7969543 (Madoux <i>et al.</i> , 2008)
LRH-1	NR5A2	Liver receptor homolog 1, $\alpha$ 1-fetoprotein transcription factor, hepatocytic transcription factor, B1-binding factor, CYP7A promoter-binding factor	ENSG00000116833	–
GCNF	NR6A1	Germ cell nuclear factor, retinoid receptor-related testis-specific receptor, RTR	ENSG00000148200	–
DAX-1	NR0B1	AHCH	ENSG00000169297	–
SHP	NR0B2	Small heterodimer partner	ENSG00000131910	–

**Abbreviations:** AC45594, 4-heptoxyphenol; DY131, N-(4-(diethylaminobenzylidene)-N'-(4-hydroxybenzoyl)-hydrazine; GSK4112, 1,1-dimethylethyl-N-[(4-chlorophenyl)methyl]-N-[(5-nitro-2-thienyl)methyl]glycinate, also known as SR6452; GSK4716, 4-hydroxy-2-[(1E)-[4-(1-methylethyl)phenyl]methylene]hydrazide; SID7969543, ethyl 2-[2-[2-(2,3-dihydro-1,4-benzodioxin-7-ylamino)-2-oxoethyl]-1-oxoisquinolin-5-yl]oxypropanoate; XCT790, (E)-3-[4-[[2,4-bis(trifluoromethyl)phenyl]methoxy]-3-methoxyphenyl]-2-cyano-N-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]prop-2-enamide

#### Further Reading

- Benoit G, Cooney A, Giguere V, Ingraham H, Lazar M, Muscat G *et al.* (2006). International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol Rev* 58: 798–836.
- Chanda D, Park JH, Choi HS (2008). Molecular basis of endocrine regulation by orphan nuclear receptor Small Heterodimer Partner. *Endocr J* 55: 253–268.
- Deblois G, Giguere V (2011). Functional and physiological genomics of estrogen-related receptors (ERRs) in health and disease. *Biochim Biophys Acta* 1812: 1032–1040.
- Duez H, Staels B (2009). Rev-erb- $\alpha$ : an integrator of circadian rhythms and metabolism. *J Appl Physiol* 107: 1972–1980.

- Duez H, Staels B (2010). Nuclear receptors linking circadian rhythms and cardiometabolic control. *Arterioscler Thromb Vasc Biol* **30**: 1529–1534.
- El-Khairi R, Martinez-Aguayo A, Ferraz-de-Souza B, Lin L, Achermann JC (2011). Role of DAX-1 (NR0B1) and steroidogenic factor-1 (NR5A1) in human adrenal function. *Endocr Dev* **20**: 38–46.
- Fernandez-Marcos PJ, Auwerx J, Schoonjans K (2011). Emerging actions of the nuclear receptor LRH-1 in the gut. *Biochim Biophys Acta (BBA) Mol Basis Dis* **1812**: 947–955.
- Germain P, Staels B, Dacquet C, Spedding M, Laudet V (2006). Overview of nomenclature of nuclear receptors. *Pharmacol Rev* **58**: 685–704.
- Gui H, Li ML, Tsai CC (2011). A tale of tailless. *Dev Neurosci* **33**: 1–13.
- Huang P, Chandra V, Rastinejad F (2010). Structural overview of the nuclear receptor superfamily: insights into physiology and therapeutics. *Annu Rev Physiol* **72**: 247–272.
- Hwang-Verslues WW, Sladek FM (2010). HNF4 $\alpha$  – role in drug metabolism and potential drug target? *Curr Opin Pharmacol* **10**: 698–705.
- Lin FJ, Qin J, Tang K, Tsai SY, Tsai MJ (2011). Coup d'Etat: an Orphan Takes Control. *Endocr Rev* **32**: 404–421.
- Mlynarczuk J, Rekawiecki R (2010). The role of the orphan receptor SF-1 in the development and function of the ovary. *Reprod Biol* **10**: 177–193.
- Pearen MA, Muscat GE (2010). Nuclear hormone receptor 4A signaling: implications for metabolic disease. *Mol Endocrinol* **24**: 1891–1903.
- Phelan CA, Gampe RT, Jr., Lambert MH, Parks DJ, Montana V, Bynum J et al. (2010). Structure of Rev-erb $\alpha$  bound to N-CoR reveals a unique mechanism of nuclear receptor-co-repressor interaction. *Nat Struct Mol Biol* **17**: 808–814.
- Schimmer BP, White PC (2010). Steroidogenic factor 1: its roles in differentiation, development, and disease. *Mol Endocrinol* **24**: 1322–1337.
- Sladek FM (2011). What are nuclear receptor ligands? *Mol Cell Endocrinol* **334**: 3–13.
- Yin L, Wu N, Lazar MA (2010). Nuclear receptor Rev-erb $\alpha$ : a heme receptor that coordinates circadian rhythm and metabolism. *Nucl Recept Signal* **8**: e001.
- Zhang Y, Hagedorn CH, Wang L (2011). Role of nuclear receptor SHP in metabolism and cancer. *Biochim Biophys Acta (BBA) Mol Basis Dis* **1812**: 893–908.
- Zhao Y, Bruemmer D (2010). NR4A orphan nuclear receptors: transcriptional regulators of gene expression in metabolism and vascular biology. *Arterioscler Thromb Vasc Biol* **30**: 1535–1541.

## References

- Baker KD et al. (2003). *Cell* **113**: 731–742.
- Del Tredici AL et al. (2008). *Mol Pharmacol* **73**: 900–908.
- Flaig R et al. (2005). *J Biol Chem* **280**: 19250–19258.
- Grant D et al. (2010). *ACS Chem Biol* **5**: 925–932.
- Land PW, Monaghan AP (2003). *Cereb Cortex* **13**: 921–931.
- Madoux F et al. (2008). *Mol Pharmacol* **73**: 1776–1784.
- Monaghan AP et al. (1997). *Nature* **390**: 515–517.
- Pereira FA et al. (1999). *Genes Dev* **13**: 1037–1049.
- Qiu Y et al. (1997). *Genes Dev* **11**: 1925–1937.
- Raghuram S et al. (2007). *Nat Struct Mol Biol* **14**: 1207–1213.
- Shyr CR et al. (2002). *Mol Cell Biol* **22**: 4661–4666.
- Suetsugi M et al. (2003). *Mol Cancer Res* **1**: 981–991.
- Wang Z et al. (2003). *Nature* **423**: 555–560.
- Warnecke M et al. (2005). *Genes Dev* **19**: 614–625.
- Willy PJ et al. (2004). *Proc Natl Acad Sci U S A* **101**: 8912–8917.
- Yin L et al. (2007). *Science* **318**: 1786–1789.
- Young WJ et al. (1998). *J Biol Chem* **273**: 20877–20885.
- Yu DD, Forman BM (2005). *Bioorg Med Chem Lett* **15**: 1311–1313.
- Yuan X et al. (2009). *PLoS ONE* **4**: e5609.
- Zhan Y et al. (2008). *Nat Chem Biol* **4**: 548–556.
- Zhou XE et al. (2011). *J Biol Chem* **286**: 2877–2885.
- Zuercher WJ et al. (2005). *J Med Chem* **48**: 3107–3109.

# Liver X and farnesoid X

**Overview:** Liver X and farnesoid X receptors (LXR and FXR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Moore *et al.*, 2006) are members of a steroid analogue-activated nuclear receptor subfamily (ENSF0000000720), which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXRs include hydroxycholesterols (OHC), while FXRs appear to be activated by bile acids.

Nomenclature	LXR $\alpha$	LXR $\beta$	FXR $\alpha$	FXR $\beta$
Systematic nomenclature	NR1H3	NR1H2	NR1H4	NR1H5
Other names	Oxysterols receptor $\alpha$	Oxysterols receptor $\beta$ , ubiquitously expressed nuclear receptor	Bile acid receptor	Lanosterol receptor
Ensembl ID	ENSG00000025434	ENSG00000131408	ENSG00000012504	ENSMUSG00000048938 (pseudogene in man)
Potency order	20s-OHC, 22R-OHC, 24s-OHC > 25-OHC, 27-OHC (Lehmann <i>et al.</i> , 1997)	20s-OHC, 22R-OHC, 24s-OHC > 25-OHC, 27-OHC (Lehmann <i>et al.</i> , 1997)	Chenodeoxycholate > lithocholate, deoxycholate (Makishima <i>et al.</i> , 1999; Parks <i>et al.</i> , 1999)	–
Selective agonists	–	–	ECDCA (Pellicciari <i>et al.</i> , 2002), fexaramine (Downes <i>et al.</i> , 2003), GW4064 (Maloney <i>et al.</i> , 2000)	Lanosterol (Otte <i>et al.</i> , 2003)
Selective antagonists	–	–	Guggulsterone (Urizar <i>et al.</i> , 2002)	–

TO901317 (Repa *et al.*, 2000) and GW3965 (Collins *et al.*, 2002) are synthetic agonists acting at both LXR $\alpha$  and LXR $\beta$  with less than 10-fold selectivity.

**Abbreviations:** ECDCA, 6 $\alpha$ -ethyl-chenodeoxycholate, also known as INT747; **guggulsterone**, *trans*-4,17(20)-pregnadiene-3,16-dione; **GW3965**, 3-(3-[N-(2-chloro-3-trifluoromethylbenzyl)-[2,2-diphenylethyl]amino]propyloxy)phenylacetic acid hydrochloride; **GW4064**, 3-[(E)-2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-propan-2-yl-1,2-oxazol-4-yl]methoxy]phenyl]ethenyl]benzoic acid; **OHC**, hydroxycholesterol; **TO901317**, N-(2,2,2-trifluoroethyl)-N-(4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl)-benzenesulfonamide

## Further Reading

- Beltowski J, Semczuk A (2010). Liver X receptor (LXR) and the reproductive system – a potential novel target for therapeutic intervention. *Pharmacol Rep* 62: 15–27.
- Calkin AC, Tontonoz P (2010). Liver X receptor signaling pathways and atherosclerosis. *Arterioscler Thromb Vasc Biol* 30: 1513–1518.
- Cariou B, Staels B (2007). FXR: a promising target for the metabolic syndrome? *Trends Pharmacol Sci* 28: 236–243.
- Chen WD, Wang YD, Meng Z, Zhang L, Huang W (2011). Nuclear bile acid receptor FXR in the hepatic regeneration. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 888–892.
- Claudel T, Zollner G, Wagner M, Trauner M (2011). Role of nuclear receptors for bile acid metabolism, bile secretion, cholestasis, and gallstone disease. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 867–878.
- El-Hajjaji FZ, Oumeddour A, Pommier AJC, Ouvrier A, Viennois E, Dufour J *et al.* (2011). Liver X receptors, lipids and their reproductive secrets in the male. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 974–981.
- Faulds MH, Zhao C, Dahlman-Wright K (2010). Molecular biology and functional genomics of liver X receptors (LXR) in relationship to metabolic diseases. *Curr Opin Pharmacol* 10: 692–697.
- Fievet C, Staels B (2009). Liver X receptor modulators: effects on lipid metabolism and potential use in the treatment of atherosclerosis. *Biochem Pharmacol* 77: 1316–1327.
- Fiorucci S, Mencarelli A, Palladino G, Cipriani S (2009). Bile-acid-activated receptors: targeting TGR5 and farnesoid-X-receptor in lipid and glucose disorders. *Trends Pharmacol Sci* 30: 570–580.
- Fiorucci S, Cipriani S, Baldelli F, Mencarelli A (2010). Bile acid-activated receptors in the treatment of dyslipidemia and related disorders. *Prog Lipid Res* 49: 171–185.
- Gabbi C, Warner M, Gustafsson JA (2009). Liver X receptor beta: emerging roles in physiology and diseases. *Mol Endocrinol* 23: 129–136.
- Gadaleta RM, van Mil SW, Oldenburg B, Siersema PD, Klomp LW, van Erpecum KJ (2010). Bile acids and their nuclear receptor FXR: relevance for hepatobiliary and gastrointestinal disease. *Biochim Biophys Acta* 1801: 683–692.
- Gardmo C, Tamburro A, Modica S, Moschetta A (2011). Proteomics for the discovery of nuclear bile acid receptor FXR targets. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 836–841.
- González N, Castrillo A (2011). Liver X receptors as regulators of macrophage inflammatory and metabolic pathways. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 982–994.
- Hageman J, Herrema H, Groen AK, Kuipers F (2010). A role of the bile salt receptor FXR in atherosclerosis. *Arterioscler Thromb Vasc Biol* 30: 1519–1528.
- Kemper JK (2011). Regulation of FXR transcriptional activity in health and disease: emerging roles of FXR cofactors and post-translational modifications. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 842–850.
- Kuipers F, Stroeve JH, Caron S, Staels B (2007). Bile acids, farnesoid X receptor, atherosclerosis and metabolic control. *Curr Opin Lipidol* 18: 289–297.
- Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B (2009). Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev* 89: 147–191.
- Mencarelli A, Fiorucci S (2010). FXR an emerging therapeutic target for the treatment of atherosclerosis. *J Cell Mol Med* 14: 79–92.

- Moore DD, Kato S, Xie W, Mangelsdorf DJ, Schmidt DR, Xiao R *et al.* (2006). International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnene X receptor, farnesoid X receptor  $\alpha$ , farnesoid X receptor  $\beta$ , liver X receptor  $\alpha$ , liver X receptor  $\beta$ , and vitamin D receptor. *Pharmacol Rev* **58**: 742–759.
- Schmuth M, Jiang YJ, Dubrac S, Elias PM, Feingold KR (2008). Thematic review series: skin lipids. Peroxisome proliferator-activated receptors and liver X receptors in epidermal biology. *J Lipid Res* **49**: 499–509.
- Wang YD, Chen WD, Moore DD, Huang W (2008). FXR: a metabolic regulator and cell protector. *Cell Res* **18**: 1087–1095.
- Zhang Y, Edwards PA (2008). FXR signaling in metabolic disease. *FEBS Lett* **582**: 10–18.
- Zollner G, Trauner M (2009). Nuclear receptors as therapeutic targets in cholestatic liver diseases. *Br J Pharmacol* **156**: 7–27.

## References

- Collins JL *et al.* (2002). *J Med Chem* **45**: 1963–1966.
- Downes M *et al.* (2003). *Mol Cell* **11**: 1079–1092.
- Lehmann JM *et al.* (1997). *J Biol Chem* **272**: 3137–3140.
- Makishima M *et al.* (1999). *Science* **284**: 1362–1365.
- Maloney PR *et al.* (2000). *J Med Chem* **43**: 2971–2974.
- Otte K *et al.* (2003). *Mol Cell Biol* **23**: 864–872.
- Parks DJ *et al.* (1999). *Science* **284**: 1365–1368.
- Pellicciari R *et al.* (2002). *J Med Chem* **45**: 3569–3572.
- Repa JJ *et al.* (2000). *Science* **289**: 1524–1529.
- Urizar NL *et al.* (2002). *Science* **296**: 1703–1706.

# Peroxisome proliferator-activated

**Overview:** Peroxisome proliferator-activated receptors (PPARs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Michalik *et al.*, 2006) are nuclear hormone receptors of the NR1C family, with diverse roles regulating lipid homeostasis, cellular differentiation, proliferation and the immune response. PPARs have many potential endogenous agonists (see Michalik *et al.*, 2006), including 15-deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub>, prostacyclin, many fatty acids and their oxidation products, lysophosphatidic acid (McIntyre *et al.*, 2003), 13-HODE, 15-HETE, Paz-PC, azelaoyl-PAF, and leukotriene B<sub>4</sub>. These receptors also bind hypolipidaemic drugs (PPAR $\alpha$ ) and anti-diabetic thiazolidinediones (PPAR $\gamma$ ), as well as many non-steroidal anti-inflammatory drugs, such as sulindac and indomethacin. Once activated by a ligand, the receptor forms a heterodimer with members of the retinoid X receptor family and can act as a transcription factor. Although radioligand binding assays have been described for all three receptors, the radioligands are not commercially available. Commonly, receptor occupancy studies are conducted using fluorescent ligands and truncated forms of the receptor limited to the ligand binding domain.

Nomenclature	PPAR $\alpha$	PPAR $\beta$	PPAR $\gamma$
Systematic nomenclature	NR1C1	NR1C2	NR1C3
Other names	–	PPAR $\delta$ , NUC1, FAAR	–
Ensembl ID	ENSG00000100406	ENSG00000112033	ENSG00000132170
Selective agonists	GW7647, WY14643, clofibrate, fenofibrate, ciprofibrate, gemfibrozil	L165041, GW501516, GW0742	Rosiglitazone, ciglitazone, troglitazone, pioglitazone, CDDO, GW1929
Selective antagonists	GW6471 (Xu <i>et al.</i> , 2002)	GSK0660 (Shearer <i>et al.</i> , 2008)	GW9662 (Huang <i>et al.</i> , 1999), CDDO-Me (Wang <i>et al.</i> , 2000), diclofenac (6.2, Adamson <i>et al.</i> , 2002), BADGE (4.0, Wright <i>et al.</i> , 2000), T0070907 (Lee <i>et al.</i> , 2002)

As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. Bishop-Bailey, 2000; Rocchi *et al.*, 2001; Nakamura *et al.*, 2002). Agonists with mixed activity at PPAR $\alpha$  and PPAR $\gamma$  have also been described (e.g. Doebber *et al.*, 2004; Guo *et al.*, 2004; Xu *et al.*, 2004).

**Abbreviations:** 13-HODE, 13-hydroxyoctadecadienoic acid; 15-HETE, 15-hydroxyeicosatetraenoic acid; azelaoyl-PAF, 1-O-hexadecyl-2-O-(9-carboxyoctanoyl)-sn-glycerol-3-phosphocholine; BADGE, bisphenol A diglycidyl ether; CDDO, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid; CDDO-Me, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid methyl ester; GSK0660, ; GW1929, (2S)-([2-benzoylphenyl]amino)-3-(4-[2-[2-methylpyridin-2-ylamino]ethoxy]phenyl)propionic acid; GW501516, 2-methyl-4-[[[4-methyl-2-[4-trifluoromethylphenyl]-1,3-thiazol-5-yl)methyl]sulfanyl]phenoxy]acetic acid; GW7647, 2-[[4-[2-[[[cyclohexylamino]carbonyl][4-cyclohexylbutyl]amino]ethyl]phenyl]thio]-2-methylpropanoic acid; GW9662, 2-chloro-5-nitro-N-phenylbenzamide; L165041, (4-[3-[4-acetyl-3-hydroxy-2-propylphenoxy]propoxy]phenoxy)acetic acid; Paz-PC, 1-palmitoyl-2-azelaoyl-sn-glycerol-3-phosphocholine; T0070907, 2-chloro-5-nitro-N-(4-pyridyl)benzamide; WY14643, N-(3-[2-quinolinylmethoxy]phenyl)-trifluoromethanesulphonamide

## Further Reading

- Belvisi MG, Mitchell JA (2009). Targeting PPAR receptors in the airway for the treatment of inflammatory lung disease. *Br J Pharmacol* **158**: 994–1003.
- Chaturvedi RK, Beal MF (2008). PPAR: a therapeutic target in Parkinson's disease. *J Neurochem* **106**: 506–518.
- Christodoulides C, Vidal-Puig A (2010). PPARs and adipocyte function. *Mol Cell Endocrinol* **318**: 61–68.
- Ehrenborg E, Krook A (2009). Regulation of skeletal muscle physiology and metabolism by peroxisome proliferator-activated receptor delta. *Pharmacol Rev* **61**: 373–393.
- Hiukka A, Maranghi M, Matikainen N, Taskinen MR (2010). PPAR $\alpha$ : an emerging therapeutic target in diabetic microvascular damage. *Nat Rev Endocrinol* **6**: 454–463.
- Itoh T, Yamamoto K (2008). Peroxisome proliferator activated receptor gamma and oxidized docosahexaenoic acids as new class of ligand. *Naunyn Schmiedeberg Arch Pharmacol* **377**: 541–547.
- Kawai M, Rosen CJ (2010). PPAR $\gamma$ : a circadian transcription factor in adipogenesis and osteogenesis. *Nat Rev Endocrinol* **6**: 629–636.
- Kawai M, Sousa KM, MacDougald OA, Rosen CJ (2010). The many facets of PPAR $\gamma$ : novel insights for the skeleton. *Am J Physiol Endocrinol Metab* **299**: E3–E9.
- Lockyer P, Schisler JC, Patterson C, Willis MS (2010). Won't get fooled again: the nonmetabolic roles of peroxisome proliferator-activated receptors (PPARs) in the heart. *Mol Endocrinol* **24**: 1111–1119.
- Michalik L, Wahli W (2008). PPARs mediate lipid signaling in inflammation and cancer. *PPAR Res*, **2008**: 134059.
- Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CK, Gonzalez FJ *et al.* (2006). International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacol Rev* **58**: 726–741.
- Reilly SM, Lee CH (2008). PPAR  $\delta$  as a therapeutic target in metabolic disease. *FEBS Lett* **582**: 26–31.
- Robinson E, Grieve DJ (2009). Significance of peroxisome proliferator-activated receptors in the cardiovascular system in health and disease. *Pharmacol Ther*, **122**: 246–263.
- Varga T, Czimmerer Z, Nagy L (2011). PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. *Biochim Biophys Acta (BBA) Mol Basis Dis* **1812**: 1007–1022.
- Villacorta L, Schopfer FJ, Zhang J, Freeman BA, Chen YE (2009). PPAR $\gamma$  and its ligands: therapeutic implications in cardiovascular disease. *Clin Sci*, **116**: 205–218.
- Wan Y (2010). PPAR $\gamma$  in bone homeostasis. *Trends Endocrinol Metab* **21**: 722–728.
- Wang N, Yin R, Liu Y, Mao G, Xi F (2011). Role of Peroxisome Proliferator-Activated Receptor-gamma in Atherosclerosis. *Circ J* **75**: 528–535.
- Youssef J, Badr M (2011). Peroxisome Proliferator-Activated Receptors and Cancer Challenges and Opportunities. *Br J Pharmacol* **164**: 68–82.

Yu S, Reddy JK (2007). Transcription coactivators for peroxisome proliferator-activated receptors. *Biochim Biophys Acta* **1771**: 936–951.

Ziouzenkova O, Plutzky J (2008). Retinoid metabolism and nuclear receptor responses: new insights into coordinated regulation of the PPAR-RXR complex. *FEBS Lett* **582**: 32–38.

## References

- Adamson DJ *et al.* (2002). *Mol Pharmacol* **61**: 7–12.
- Bishop-Bailey D (2000). *Br J Pharmacol* **129**: 823–833.
- Doebber TW *et al.* (2004). *Biochem Biophys Res Commun* **318**: 323–328.
- Guo Q *et al.* (2004). *Endocrinology* **145**: 1640–1648.
- Huang JT *et al.* (1999). *Nature* **400**: 378–382.
- Lee G *et al.* (2002). *J Biol Chem* **277**: 19649–19657.
- McIntyre TM *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 131–136.
- Nakamuta M *et al.* (2002). *Cell Biol Int* **26**: 235–241.
- Rocchi S *et al.* (2001). *Mol Cell* **8**: 737–747.
- Shearer BG *et al.* (2008). *Mol Endocrinol* **22**: 523–529.
- Wang Y *et al.* (2000). *Mol Endocrinol* **14**: 1550–1556.
- Wright HM *et al.* (2000). *J Biol Chem* **275**: 1873–1877.
- Xu HE *et al.* (2002). *Nature* **415**: 813–817.
- Xu Y *et al.* (2004). *J Med Chem* **47**: 2422–2425.



# Retinoic acid, retinoid X and retinoic acid-related orphan

**Overview:** Cytoplasmic cellular retinoid binding proteins I (ENSG00000114115), II (ENSG00000114113), III (ENSG00000139194) and IV (ENSG00000162444) are thought to control the levels of intracellular retinoids available for interaction with their receptors (Li, 1999). [<sup>3</sup>H]-ATRA and [<sup>3</sup>H]-9-*cis*-retinoic acid have been used to label RARs and RXRs, respectively.

Retinoic acid receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Germain *et al.*, 2006a) are nuclear hormone receptors of the NR1B family activated by the vitamin A-derived agonists all-*trans* retinoic acid (ATRA) and 9-*cis*-retinoic acid, and the RAR-selective synthetic agonists TTNPB and adapalene.

Nomenclature	RAR $\alpha$	RAR $\beta$	RAR $\gamma$
Systematic nomenclature	NR1B1	NR1B2	NR1B3
Other names	–	HBV-activated protein	–
Ensembl ID	ENSG00000131759	ENSG00000077092	ENSG00000172819
Selective agonists	Ro406055 (Delescluse <i>et al.</i> , 1991)	AC261066 (Lund <i>et al.</i> , 2005), AC55649 (Lund <i>et al.</i> , 2005)	AHPN (Martin <i>et al.</i> , 1992)
Selective antagonists	Ro415253 (Apfel <i>et al.</i> , 1992)	–	MM11253 (Le <i>et al.</i> , 2000)

Ro415253 has been suggested to be a PPAR $\gamma$  agonist (Schupp *et al.*, 2007). LE135 is an antagonist with selectivity for RAR $\alpha$  and RAR $\beta$  compared to RAR $\gamma$  (Li *et al.*, 1999).

Retinoid X receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Germain *et al.*, 2006b) are NR2B family members activated by 9-*cis*-retinoic acid and the RXR-selective agonists LGD1069 and LG100268, sometimes referred to as rexinoids. These receptors form RXR–RAR heterodimers and RXR–RXR homodimers (Mangelsdorf and Evans, 1995; Chambon, 1996).

Nomenclature	RXR $\alpha$	RXR $\beta$	RXR $\gamma$
Systematic nomenclature	NR2B1	NR2B2	NR2B3
Ensembl ID	ENSG00000078380	ENSG00000112472	ENSG00000143171
Selective agonists	CD3254 (Nahoum <i>et al.</i> , 2007)	–	–

UVI3003 has been described as a pan-RXR antagonist (Nahoum *et al.*, 2007).

Retinoic acid-related orphan receptors (ROR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Benoit *et al.*, 2006) have yet to be assigned a definitive endogenous ligand, although ROR $\alpha$  may be synthesised with a ‘captured’ agonist such as cholesterol (Kallen *et al.*, 2002; 2004).

Nomenclature	ROR $\alpha$	ROR $\beta$	ROR $\gamma$
Systematic nomenclature	NR1F1	NR1F2	NR1F3
Other names	RZR $\alpha$	RZR $\beta$	RZR $\gamma$
Ensembl ID	ENSG00000069667	ENSG00000198963	ENSG00000143365
Selective agonists	Cholesterol sulfate, cholesterol, 7-OHC (Bitsch <i>et al.</i> , 2003)	–	–

ATRA shows selectivity for ROR $\beta$  within the ROR family (Stehlin-Gaon *et al.*, 2003). ROR $\alpha$  has been suggested to be a nuclear receptor responding to melatonin (Wiesenberg *et al.*, 1995).

**Abbreviations:** 7-OHC, 7-hydroxycholesterol; AC261066, 4-(4-[2-butoxyethoxy]-5-methyl-2-thiazolyl)-2-fluorobenzoic acid; AC55649, 4'-octyl-[1,1'-biphenyl]-4-carboxylic acid; AHPN, 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid, also known as CD437; ATRA, all-*trans*-retinoic acid; CD1530, 4-(6-hydroxy-7-tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-yl-2-naphthalenyl)benzoic acid; CD3254, (E)-3-[4-hydroxy-3-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)phenyl]prop-2-enoic acid; LE135, 4-(7,8,9,10-tetrahydro-5,7,7,10,10-pentamethyl-5H-benzo[e]naphtho[2,3-*b*][1,4]diazepin-13-yl)benzoic acid; LG100268, 6-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl]cyclopropyl) nicotinic acid; LGD1069, 4-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl]ethenyl) benzoic acid; MM11253, 6-(2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1,3-dithiolan-2-yl)-2-naphthalenecarboxylic acid; Ro406055, 4-([5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]carboxamido)benzoic acid (also known as AM580); Ro415253, 4-[2-(7-heptoxy-4,4-dimethyl-1,1-dioxo-2,3-dihydrothiochromen-6-yl)prop-1-enyl]benzoic acid, also known as LG629; TTNPB, (E)-4-(2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1-propenyl)benzoic acid; UVI3003, 3-(4-hydroxy-3-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(pentyloxy)-2-naphthalenyl]phenyl)-2-propenoic acid

### Further Reading

- Benoit G, Cooney A, Giguere V, Ingraham H, Lazar M, Muscat G *et al.* (2006). International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol Rev* **58**: 798–836.
- Bour G, Lalevee S, Rochette-Egly C (2007). Protein kinases and the proteasome join in the combinatorial control of transcription by nuclear retinoic acid receptors. *Trends Cell Biol* **17**: 302–309.
- Duong V, Rochette-Egly C (2011). The molecular physiology of nuclear retinoic acid receptors. From health to disease. *Biochim Biophys Acta (BBA) Mol Basis Dis* **1812**: 1023–1031.
- Germain P, Chambon P, Eichele G, Evans RM, Lazar MA, Leid M *et al.* (2006a). International Union of Pharmacology. LX. Retinoic acid receptors. *Pharmacol Rev* **58**: 712–725.
- Germain P, Chambon P, Eichele G, Evans RM, Lazar MA, Leid M *et al.* (2006b). International Union of Pharmacology. LXIII. Retinoid X receptors. *Pharmacol Rev* **58**: 760–772.
- Lefebvre P, Benomar Y, Staels B (2010). Retinoid X receptors: common heterodimerization partners with distinct functions. *Trends Endocrinol Metab* **21**: 676–683.
- Maden M (2007). Retinoic acid in the development, regeneration and maintenance of the nervous system. *Nat Rev Neurosci* **8**: 755–765.
- Mark M, Ghyselinck NB, Chambon P (2006). Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signaling pathway during mouse embryogenesis. *Annu Rev Pharmacol Toxicol* **46**: 451–480.
- Perez E, Bourguet W, Gronemeyer H, de Lera AR (2011). Modulation of RXR function through ligand design. *Biochim Biophys Acta* in press.

### References

- Apfel C *et al.* (1992). *Proc Natl Acad Sci U S A* **89**: 7129–7133.
- Bitsch F *et al.* (2003). *Anal Biochem* **323**: 139–149.
- Chambon P (1996). *FASEB J* **10**: 940–954.
- Delescluse C *et al.* (1991). *Mol Pharmacol* **40**: 556–562.
- Kallen J *et al.* (2004). *J Biol Chem* **279**: 14033–14038.
- Kallen JA *et al.* (2002). *Structure* **10**: 1697–1707.
- Le Q *et al.* (2000). *Oncogene* **19**: 1457–1465.
- Li E (1999). *Mol Cell Biochem* **192**: 105–108.
- Li Y *et al.* (1999). *J Biol Chem* **274**: 15360–15366.
- Lund BW *et al.* (2005). *J Med Chem* **48**: 7517–7519.
- Mangelsdorf DJ, Evans RM (1995). *Cell* **83**: 841–850.
- Martin B *et al.* (1992). *Skin Pharmacol* **5**: 57–65.
- Nahoum V *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 17323–17328.
- Schupp M *et al.* (2007). *Mol Pharmacol* **71**: 1251–1257.
- Stehlin-Gaon C *et al.* (2003). *Nat Struct Biol* **10**: 820–825.
- Wiesenberg I *et al.* (1995). *Nucleic Acids Res* **23**: 327–333.

# Steroid hormone

**Overview:** Steroid hormone receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Dahlman-Wright *et al.*, 2006; Lu *et al.*, 2006) are nuclear hormone receptors of the NR3 class, with endogenous agonists that may be divided into 3-hydroxysteroids (oestrone and oestradiol) and 3-ketosteroids (5 $\alpha$ -dihydrotestosterone [DHT], aldosterone, cortisol, corticosterone, progesterone and testosterone). These receptors exist as dimers coupled with chaperone molecules (such as HSP90 [ENSG00000166598] and immunophilin FKBP52 [ENSG0000004478]), which are shed on binding the steroid hormone. Although rapid signalling phenomena are observed (see Levin, 2008; Prossnitz and Maggiolini, 2009), the principal signalling cascade appears to involve binding of the activated receptors to nuclear hormone response elements of the genome, with a 15-nucleotide consensus sequence AGAACAnnnTGTCT (i.e. an inverted palindrome) as homo- or heterodimers. They also affect transcription by protein–protein interactions with other transcription factors, such as activator protein 1 (AP-1) and nuclear factor  $\kappa$ B (NF- $\kappa$ B). Splice variants of each of these receptors can form functional or nonfunctional monomers that can dimerize to form functional or non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce functional AA, AB and BB receptors with distinct characteristics (Vegeto *et al.*, 1993).

A 7TM receptor responsive to estrogen (GPE, also known as GPR30, ENSG00000164850, see Prossnitz *et al.*, 2008) has been described. Human orthologues of 7TM ‘membrane progesterin receptors’ (ENSG00000182749, ENSG00000170915 and ENSG00000137819), initially discovered in fish (Zhu *et al.*, 2003a; 2003b), appear to localize to intracellular membranes and appear to respond to ‘non-genomic’ progesterone analogues independently of G proteins (Smith *et al.*, 2008).

Nomenclature	Glucocorticoid	Mineralocorticoid	Progesterone	Androgen
Preferred abbreviation	GR	MR	PR	AR
Systematic nomenclature	NR3C1	NR3C2	NR3C3	NR3C4
Other names	Type II glucocorticoid receptor	Type I glucocorticoid receptor, aldosterone receptor	–	dihydrotestosterone receptor
Ensembl ID	ENSG00000113580	ENSG00000151623	ENSG00000082175	ENSG00000169083
Rank order of potency	Cortisol, corticosterone >> aldosterone, deoxycortisone (Rupprecht <i>et al.</i> , 1993)	Corticosterone, cortisol, aldosterone, progesterone (Rupprecht <i>et al.</i> , 1993)	Progesterone	DHT > testosterone
Selective agonists	RU28362, RU26988	Aldosterone	ORG2058, progesterone	DHT, mibolerone, R1881
Selective antagonists	Mifepristone, ZK112993, onapristone	RU28318, ZK112993, onapristone	Mifepristone, ZK112993, onapristone	Hydroxyflutamide, nilutamide
Probes	[ <sup>3</sup> H]-Dexamethasone	[ <sup>3</sup> H]-Aldosterone	[ <sup>3</sup> H]-ORG2058	[ <sup>3</sup> H]-DHT, [ <sup>3</sup> H]-mibolerone, [ <sup>3</sup> H]-R1881

[<sup>3</sup>H]-Dexamethasone also binds to MR *in vitro*. PR antagonists have been suggested to subdivide into Type I (e.g. onapristone) and Type II (e.g. ZK112993) groups. These groups appear to promote binding of PR to DNA with different efficacies and evoke distinct conformational changes in the receptor, leading to a transcription-neutral complex (Gass *et al.*, 1998; Leonhardt *et al.*, 1998). Mutations in AR underlie testicular feminization and androgen insensitivity syndromes, spinal and bulbar muscular atrophy (Kennedy’s disease).

Nomenclature	Oestrogen $\alpha$	Oestrogen $\beta$
Preferred abbreviation	ER $\alpha$	ER $\beta$
Systematic nomenclature	NR3A1	NR3A2
Other names	Estradiol	Estradiol
Ensembl ID	ENSG00000091831	ENSG00000140009
Selective agonists	PPT (Kraichely <i>et al.</i> , 2000; Stauffer <i>et al.</i> , 2000)	DPN (Meyers <i>et al.</i> , 2001), WAY200070 (Malamas <i>et al.</i> , 2004)
Selective antagonists	MPP (Sun <i>et al.</i> , 2002)	PHTPP (Compton <i>et al.</i> , 2004), <i>R,R</i> -THC (Meyers <i>et al.</i> , 1999; Sun <i>et al.</i> , 1999)

*R,R*-THC exhibits partial agonist activity at ER $\alpha$  (Meyers *et al.*, 1999; Sun *et al.*, 1999). Estrogen receptors may be blocked non-selectively by tamoxifen and raloxifene, and labelled by [<sup>3</sup>H]-estradiol and [<sup>3</sup>H]-tamoxifen. Many agents thought initially to be antagonists at estrogen receptors appear to have tissue-specific efficacy (e.g. tamoxifen is an antagonist at estrogen receptors in the breast, but is an agonist at estrogen receptors in the uterus), hence the descriptor SERM (selective estrogen receptor modulator) or SnuRM (selective nuclear receptor modulator). Y134 has been suggested to be an ER $\alpha$ -selective estrogen receptor modulator (Ning *et al.*, 2007).

Additional ‘orphan’ estrogen-receptor-related proteins have been described (ERR $\alpha$  ENSG00000173153; ERR $\beta$  ENSG00000119715; ERR $\gamma$  ENSG00000057103); DY131 is an agonist with selectivity for ERR $\beta$  and ERR $\gamma$  compared to ERR $\alpha$ , ER $\alpha$  and ER $\beta$  (Yu and Forman, 2005).

**Abbreviations:** DHT, 5 $\alpha$ -dihydrotestosterone; DPN, 2,3-bis(4-hydroxyphenyl)propionitrile; DY131, *N'*-([1E]-[4-(diethylamino)phenyl]methylene)-4-hydroxybenzohydrazide; MPP, 1,3-bis(4-hydroxyphenyl)-4-methyl-5-(4-[2-piperidinylethoxy]phenol)-1H-pyrazole; ORG2058, 16- $\alpha$ -ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; PPT, 4,4',4''-(4-propyl-[1H]-pyrazole-1,3,5-triyl)trisphenol; PHTPP, 4-(2-phenyl-5,7-bis[trifluoromethyl]pyrazolo[1,5-a]pyrimidin-3-yl)phenol; R1881, 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-estra-4,9,11-triene-3-one, also known as methyl-trienolone; *r,r*-THC, *R,R*-tetrahydrochrysenes; RU26988, 11 $\beta$ ,17 $\beta$ -dihydroxy-21-methyl-17 $\alpha$ -pregna-1,4,6-trien-20-yl-3-on; RU28318, 3-oxo-7-

propyl-17-hydroxy-androstan-4-en-17-yl; RU28362, 11 $\beta$ ,17 $\beta$ -dihydroxy-6-methyl-17-(1-propionyl)androsta-1,4,6-triene-3-one; Y134, (6-hydroxy-2-[4-hydroxyphenyl]-benzo[b]thiophen-3-yl)-(4-[4-isopropylpiperazin-1-yl]-phenyl)methanone; WAY200070, 7-bromo-2-(4-hydroxyphenyl)-1,3-benzoxazol-5-ol; ZK112993, 11 $\beta$ -(4-acetylphenyl)-17 $\beta$ -hydroxyl-17 $\alpha$ -(1-propinyl)-4,8-estradiene-3-one

### Further Reading

- Blaustein JD (2008). Progesterone and progestin receptors in the brain: the neglected ones. *Endocrinology* **149**: 2737–2738.
- Briet M, Schiffrin EL (2010). Aldosterone: effects on the kidney and cardiovascular system. *Nat Rev Nephrol* **6**: 261–273.
- Brinton RD (2009). Estrogen-induced plasticity from cells to circuits: predictions for cognitive function. *Trends Pharmacol Sci* **30**: 212–222.
- Callewaert F, Boonen S, Vanderschueren D (2010). Sex steroids and the male skeleton: a tale of two hormones. *Trends Endocrinol Metab* **21**: 89–95.
- Chen Y, Sawyers CL, Scher HI (2008). Targeting the androgen receptor pathway in prostate cancer. *Curr Opin Pharmacol* **8**: 440–448.
- Dahlman-Wright K, Cavailles V, Fuqua SA, Jordan VC, Katzenellenbogen JA, Korach KS *et al.* (2006). International Union of Pharmacology. LXIV. Estrogen receptors. *Pharmacol Rev* **58**: 773–781.
- Feldman RD, Gros R (2011). Unraveling the mechanisms underlying the rapid vascular effects of steroids: sorting out the receptors and the pathways. *Br J Pharmacol* **163**: 1163–1169.
- Gross KL, Cidlowski JA (2008). Tissue-specific glucocorticoid action: a family affair. *Trends Endocrinol Metab* **19**: 331–339.
- Hadoke PW, Iqbal J, Walker BR (2009). Therapeutic manipulation of glucocorticoid metabolism in cardiovascular disease. *Br J Pharmacol* **156**: 689–712.
- Handelsman DJ (2008). Indirect androgen doping by oestrogen blockade in sports. *Br J Pharmacol* **154**: 598–605.
- Joels M, Karst H, DeRijk R, de Kloet ER (2008). The coming out of the brain mineralocorticoid receptor. *Trends Neurosci* **31**: 1–7.
- Kellner M, Wiedemann K (2008). Mineralocorticoid receptors in brain, in health and disease: possibilities for new pharmacotherapy. *Eur J Pharmacol* **583**: 372–378.
- Kerkhofs S, Denayer S, Haelens A, Claessens F (2009). Androgen receptor knockout and knock-in mouse models. *J Mol Endocrinol* **42**: 11–17.
- Lange CA, Gioeli D, Hammes SR, Marker PC (2007). Integration of rapid signaling events with steroid hormone receptor action in breast and prostate cancer. *Annu Rev Physiol* **69**: 171–199.
- Levin ER (2008). Rapid signaling by steroid receptors. *Am J Physiol Regul Integr Comp Physiol* **295**: R1425–R1430.
- Lu NZ, Wardell SE, Burnstein KL, Defranco D, Fuller PJ, Giguere V *et al.* (2006). International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. *Pharmacol Rev* **58**: 782–797.
- Matsumoto T, Shiina H, Kawano H, Sato T, Kato S (2008). Androgen receptor functions in male and female physiology. *J Steroid Biochem Mol Biol* **109**: 236–241.
- McMaster A, Ray DW (2008). Drug insight: selective agonists and antagonists of the glucocorticoid receptor. *Nat Clin Pract Endocrinol Metab* **4**: 91–101.
- Mohler ML, Bohl CE, Jones A *et al.* (2009). Nonsteroidal selective androgen receptor modulators (SARMs): dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. *J Med Chem* **52**: 3597–3617.
- Pippal JB, Fuller PJ (2008). Structure-function relationships in the mineralocorticoid receptor. *J Mol Endocrinol* **41**: 405–413.
- Prossnitz ER, Maggiolini M (2009). Non-genomic signaling by steroids. *Mol Cell Endocrinol* **308**: 1–2.
- Prossnitz ER, Arterburn JB, Smith HO *et al.* (2008). Estrogen signaling through the transmembrane G protein-coupled receptor GPR30. *Annu Rev Physiol* **70**: 165–190.
- Schumacher M, Sitruk-Ware R, De Nicola AF (2008). Progesterone and progestins: neuroprotection and myelin repair. *Curr Opin Pharmacol* **8**: 740–746.
- Simons SS, Jr. (2010). Glucocorticoid receptor cofactors as therapeutic targets. *Curr Opin Pharmacol* **10**: 613–619.
- Taplin ME (2007). Drug insight: role of the androgen receptor in the development and progression of prostate cancer. *Nat Clin Pract Oncol* **4**: 236–244.
- Weiser MJ, Foradori CD, Handa RJ (2008). Estrogen receptor  $\beta$  in the brain: from form to function. *Brain Res Rev* **57**: 309–320.
- Woolley CS (2007). Acute effects of estrogen on neuronal physiology. *Annu Rev Pharmacol Toxicol* **47**: 657–680.

### References

- Compton DR *et al.* (2004). *J Med Chem* **47**: 5872–5893.
- Gass EK *et al.* (1998). *Endocrinology* **139**: 1905–1919.
- Kraichely DM *et al.* (2000). *Endocrinology* **141**: 3534–3545.
- Leonhardt SA *et al.* (1998). *Mol Endocrinol* **12**: 1914–1930.
- Malamas MS *et al.* (2004). *J Med Chem* **47**: 5021–5040.
- Meyers MJ *et al.* (1999). *J Med Chem* **42**: 2456–2468.
- Meyers MJ *et al.* (2001). *J Med Chem* **44**: 4230–4251.
- Ning M *et al.* (2007). *Br J Pharmacol* **150**: 19–28.
- Rupprecht R *et al.* (1993). *Eur J Pharmacol* **247**: 145–154.
- Smith JL *et al.* (2008). *Steroids* **73**: 1160–1173.
- Stauffer SR *et al.* (2000). *J Med Chem* **43**: 4934–4947.
- Sun J *et al.* (1999). *Endocrinology* **140**: 800–804.
- Sun J *et al.* (2002). *Endocrinology* **143**: 941–947.
- Vegeto E *et al.* (1993). *Mol Endocrinol* **7**: 1244–1255.
- Yu DD, Forman BM (2005). *Bioorg Med Chem Lett* **15**: 1311–1313.
- Zhu Y *et al.* (2003a). *Proc Natl Acad Sci U S A* **100**: 2231–2236.
- Zhu Y *et al.* (2003b). *Proc Natl Acad Sci U S A* **100**: 2237–2242.

# Thyroid hormone

**Overview:** Thyroid hormone receptors (TRs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Flamant *et al.*, 2006) are nuclear hormone receptors of the NR1A family, with diverse roles regulating macronutrient metabolism, cognition and cardiovascular homeostasis. TRs are activated by thyroxine (T4) and thyroid hormone (T3). Once activated by a ligand, the receptor acts as a transcription factor either as a monomer, homodimer or heterodimer with members of the retinoid X receptor family.

Nomenclature	TR $\alpha$	TR $\beta$
Systematic nomenclature	NR1A1	NR1A2
Other names	THRA, erbA $\alpha$ , erbA1, EAR7	THRB, erbA $\beta$ , erbA2
Ensembl ID	ENSG00000126351	ENSG00000151090
Rank order of potency	T3 > T4	T3 > T4
Selective agonists	–	GC1 (Chiellini <i>et al.</i> , 1998)

An interaction with integrin  $\alpha V\beta 3$  has been suggested to underlie plasma membrane localization of thyroid hormone receptors and non-genomic signalling (Bergh *et al.*, 2005). One splice variant, TR $\alpha_2$ , lacks a functional DNA-binding domain and appears to act as a transcription suppressor.

Although radioligand binding assays have been described for these receptors, the radioligands are not commercially available. NH-3 has been described as an antagonist at thyroid hormone receptors with modest selectivity for TR $\beta$  (Nguyen *et al.*, 2002).

**Abbreviations:** GC1, (3,5-dimethyl-4-[4-hydroxy-3-isopropylbenzyl]phenoxy)acetate; NH-3, (4-[4-hydroxy-3-isopropyl-5-[4-nitrophenylethynyl]-benzyl]-3,5-dimethylphenoxy)acetate

## Further Reading

- Baxter JD, Webb P (2009). Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. *Nat Rev Drug Discov* 8: 308–320.
- Bernal J (2007). Thyroid hormone receptors in brain development and function. *Nat Clin Pract Endocrinol Metab* 3: 249–259.
- Cheng SY, Leonard JL, Davis PJ (2010). Molecular aspects of thyroid hormone actions. *Endocr Rev* 31: 139–170.
- Davis PJ, Zhou M, Davis FB, Lansing L, Mousa SA, Lin HY (2010). Mini-review: cell surface receptor for thyroid hormone and nongenomic regulation of ion fluxes in excitable cells. *Physiol Behav* 99: 237–239.
- Davis PJ, Davis FB, Mousa SA, Luidens MK, Lin HY (2011). Membrane receptor for thyroid hormone: physiologic and pharmacologic implications. *Annu Rev Pharmacol Toxicol* 51: 99–115.
- Flamant F, Baxter JD, Forrest D, Refetoff S, Samuels H, Scanlan TS *et al.* (2006). International Union of Pharmacology. LIX. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. *Pharmacol Rev* 58: 705–711.
- Furuya F, Lu C, Guigon CJ, Cheng SY (2009). Nongenomic activation of phosphatidylinositol 3-kinase signaling by thyroid hormone receptors. *Steroids* 74: 628–634.
- Grover GJ, Mellstrom K, Malm J (2007). Therapeutic potential for thyroid hormone receptor- $\beta$  selective agonists for treating obesity, hyperlipidemia and diabetes. *Curr Vasc Pharmacol* 5: 141–154.
- Liu YY, Brent GA (2010). Thyroid hormone crosstalk with nuclear receptor signaling in metabolic regulation. *Trends Endocrinol Metab* 21: 166–173.
- Pramfalk C, Pedrelli M, Parini P (2011). Role of thyroid receptor  $\beta$  in lipid metabolism. *Biochim Biophys Acta (BBA) Mol Basis Dis* 1812: 929–937.
- Visser WE, Friesema EC, Jansen J, Visser TJ (2008). Thyroid hormone transport in and out of cells. *Trends Endocrinol Metab* 19: 50–56.
- Yen PM, Ando S, Feng X, Liu Y, Maruvada P, Xia X (2006). Thyroid hormone action at the cellular, genomic and target gene levels. *Mol Cell Endocrinol* 246: 121–127.

## References

- Bergh JJ *et al.* (2005). *Endocrinology* 146: 2864–2871.
- Chiellini G *et al.* (1998). *Chem Biol* 5: 299–306.
- Nguyen NH *et al.* (2002). *J Med Chem* 45: 3310–3320.

# Vitamin D, Pregnane X and Constitutive Androstane

**Overview:** Vitamin D (VDR), Pregnane X (PXR) and Constitutive Androstane (CAR) receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, Moore *et al.*, 2006) are members of the NR11 family of nuclear receptors, which form heterodimers with members of the retinoid X receptor family. PXR and CAR are activated by a range of exogenous compounds, with no established endogenous physiological agonists, although high concentrations of bile acids and bile pigments activate PXR and CAR (see Moore *et al.*, 2006).

Nomenclature	Vitamin D	Pregnane X	Constitutive Androstane
Systematic nomenclature	NR111	NR112	NR113
Other names	1,25-dihydroxyvitamin D3 receptor	Orphan nuclear receptor PAR1, pregnane-activated receptor, steroid and xenobiotic receptor, SXR	Constitutive activator of retinoid response, constitutive active response, orphan nuclear receptor MB67
Ensembl ID	ENSG00000111424	ENSG00000144852	ENSG00000143257
Selective agonists	1,25-Dihydroxyvitamin D <sub>3</sub> , EB1089 (Colston <i>et al.</i> , 1992)	5 $\beta$ -Pregnane-3,20-dione, estradiol (Jones <i>et al.</i> , 2000), hyperforin (Wentworth <i>et al.</i> , 2000), lovastatin (Lehmann <i>et al.</i> , 1998), rifampicin (Blumberg <i>et al.</i> , 1998; Lehmann <i>et al.</i> , 1998)	TCPOBOP (Tzamei <i>et al.</i> , 2000), CITCO (Maglich <i>et al.</i> , 2003)
Selective antagonists	TEI9647 (Miura <i>et al.</i> , 1999), ZK159222 (Herdick <i>et al.</i> , 2000)	–	–

**Abbreviations:** CITCO, 6-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime; EB1089, (1R,3S,5Z)-5-[(2E)-2-[(1R,3aS,7aR)-1-[(1R,2E,4E)-6-ethyl-6-hydroxy-1-methyl-2,4-octadien-1-yl]-octahydro-7 $\alpha$ -methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-1,3-cyclohexanediol, also known as seocalcitol; TEI9647, (23S)-25-dehydro-1 $\alpha$  hydroxyvitamin D<sub>3</sub>-26,23-lactone; TCPOBOP, 1,4-bis-[2-(3,5-dichloropyridyloxy)]benzene; ZK159222, butyl 1-[(E,1R,4R)-4-[(1R,3aS,4E,7aR)-4-[(2Z)-2-[(3S,5R)-3,5-dihydroxy-2-methylidene-cyclohexylidene]ethylidene]-7 $\alpha$ -methyl-2,3,3a,5,6,7-hexahydro-1H-inden-1-yl]-1-hydroxypent-2-enyl]cyclopropane-1-carboxylate

## Further Reading

- Bikle D (2009). Nonclassic actions of vitamin D. *J Clin Endocrinol Metab* **94**: 26–34.
- Bikle DD (2011). Vitamin D: an ancient hormone. *Exp Dermatol* **20**: 7–13.
- Bouillon R, Carmeliet G, Verlinden L *et al.* (2008). Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* **29**: 726–776.
- Campbell FC, Xu H, El-Tanani M, Crowe P, Bingham V (2010). The yin and yang of vitamin D receptor (VDR) signaling in neoplastic progression: operational networks and tissue-specific growth control. *Biochem Pharmacol* **79**: 1–9.
- Danescu LG, Levy S, Levy J (2009). Vitamin D and diabetes mellitus. *Endocrine* **35**: 11–17.
- Deeb KK, Trump DL, Johnson CS (2007). Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer* **7**: 684–700.
- Haussler MR, Haussler CA, Bartik L *et al.* (2008). Vitamin D receptor: molecular signaling and actions of nutritional ligands in disease prevention. *Nutr Rev* **66**: S98–112.
- Ihannah CA, Jiang M, Xie W (2011). Nuclear receptor PXR, transcriptional circuits and metabolic relevance. *Biochim Biophys Acta (BBA) Mol Basis Dis* **1812**: 956–963.
- Kohle C, Bock KW (2009). Coordinate regulation of human drug-metabolizing enzymes, and conjugate transporters by the Ah receptor, pregnane X receptor and constitutive androstane receptor. *Biochem Pharmacol* **77**: 689–699.
- Krishnan AV, Feldman D (2011). Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. *Annu Rev Pharmacol Toxicol* **51**: 311–336.
- Moore DD, Kato S, Xie W, Mangelsdorf DJ, Schmidt DR, Xiao R *et al.* (2006). International Union of Pharmacology. LXII. The NR1H and NR11 receptors: constitutive androstane receptor, pregnane X receptor, farnesoid X receptor  $\alpha$ , farnesoid X receptor  $\beta$ , liver X receptor  $\alpha$ , liver X receptor  $\beta$ , and vitamin D receptor. *Pharmacol Rev* **58**: 742–759.
- Pittas AG, Dawson-Hughes B (2010). Vitamin D and diabetes. *J Steroid Biochem Mol Biol* **121**: 425–429.
- Plum LA, DeLuca HF (2010). Vitamin D, disease and therapeutic opportunities. *Nat Rev Drug Discov* **9**: 941–955.
- Timsit YE, Negishi M (2007). CAR and PXR: the xenobiotic-sensing receptors. *Steroids* **72**: 231–246.
- Urquhart BL, Tirona RG, Kim RB (2007). Nuclear receptors and the regulation of drug-metabolizing enzymes and drug transporters: implications for interindividual variability in response to drugs. *J Clin Pharmacol* **47**: 566–578.

## References

- Blumberg B *et al.* (1998). *Genes Dev* **12**: 3195–3205.
- Colston KW *et al.* (1992). *Biochem Pharmacol* **44**: 2273–2280.
- Herdick M *et al.* (2000). *Chem Biol* **7**: 885–894.
- Jones SA *et al.* (2000). *Mol Endocrinol* **14**: 27–39.
- Lehmann JM *et al.* (1998). *J Clin Invest* **102**: 1016–1023.
- Maglich JM *et al.* (2003). *J Biol Chem* **278**: 17277–17283.
- Miura D *et al.* (1999). *J Biol Chem* **274**: 16392–16399.
- Tzamei I *et al.* (2000). *Mol Cell Biol* **20**: 2951–2958.
- Wentworth JM *et al.* (2000). *J Endocrinol* **166**: R11–R16.

# CATALYTIC RECEPTORS

Catalytic receptors are cell-surface proteins, usually dimeric in nature, which encompass ligand binding and functional domains typically in one polypeptide chain. The ligand binding domain is placed on the extracellular surface of the plasma membrane and separated from the functional domain by a single transmembrane-spanning domain of 20–25 hydrophobic amino acids. The functional domain on the intracellular face of the plasma membrane has catalytic activity, or interacts with particular enzymes, giving the superfamily of receptors its name. Endogenous agonists of the catalytic receptor superfamily are peptides or proteins, the binding of which may induce dimerization of the receptor, which is the functional version of the receptor.

Amongst the catalytic receptors, particular subfamilies may be readily identified dependent on the function of the enzymatic portion of the receptor. The smallest group is the particulate guanylyl cyclases of the natriuretic peptide receptor family. The most widely recognized group is probably the receptor tyrosine kinase (RTK) family, epitomized by the neurotrophin receptor family, where a crucial initial step is the activation of a signalling cascade by autophosphorylation of the receptor on intracellular tyrosine residue(s) catalyzed by enzyme activity intrinsic to the receptor. A third group is the extrinsic protein tyrosine kinase receptors, where the catalytic activity resides in a separate protein from the binding site. Examples of this group include the GDNF and ErbB receptor families, where one, catalytically silent, member of the heterodimer is activated upon binding the ligand, causing the second member of the heterodimer, lacking ligand binding capacity, to initiate signaling through tyrosine phosphorylation. A fourth group, the receptor threonine/serine kinase (RTSK) family, exemplified by TGF- $\beta$  and BMP receptors, has intrinsic serine/threonine protein kinase activity in the heterodimeric functional unit. The fifth and final group are the receptor tyrosine phosphatases (RTP), which appear to lack cognate ligands, but may be triggered by events such as cell:cell contact and have identified roles in the skeletal, hematopoietic and immune systems.

NC-IUPHAR is currently considering nomenclature of catalytic receptors. It is recommended that nomenclature from the Human Genome Organisation Gene Nomenclature Committee (HGNC) is adopted where the precise complement of receptors is known (e.g. using heterologous expression). The alternative nomenclature recommended in the Guide to Receptors and Channels, Fifth Edition, may be considered as provisional.

# Cytokine receptor family

**Overview:** Cytokines are not a clearly defined group of agents, other than having an impact on immune signalling pathways, although many cytokines have effects on other systems, such as in development. A feature of some cytokines, which allows them to be distinguished from hormones, is that they may be produced by 'non-secretory' cells, for example, endothelial cells. Within the cytokine receptor family, some subfamilies may be identified, which are described elsewhere in the Guide to Receptors and Channels, receptors for the TNF family (see Page S211), the TGF- $\beta$  family (see Page S200) and the chemokines (see Page S39). Within this group of records are described Type I cytokine receptors, typified by interleukin receptors, and Type II cytokine receptors, exemplified by interferon receptors. An unusual feature of this group of agents is the existence of soluble and decoy receptors. These bind cytokines without allowing signalling to occur. A further attribute is the production of endogenous antagonist molecules, which bind to the receptors selectively and prevent signalling.

A commonality of these families of receptors is the ligand-induced homo- or hetero-oligomerization, which results in the recruitment of intracellular protein partners to evoke cellular responses, particularly in inflammatory or haematopoietic signalling. Although not an exclusive signalling pathway, a common feature of the majority of cytokine receptors is activation of the JAK/STAT pathway. This cascade is based around the protein tyrosine kinase activity of the Janus kinases (JAK, ENSFM0025000000777), which phosphorylate the receptor and thereby facilitate the recruitment of signal transducers and activators of transcription (STATs, ENSFM00500000269705, ENSFM00500000269817). The activated homo- or heterodimeric STATs function principally as transcription factors in the nucleus.

## Type I cytokine receptors

The **IL-2 family** of cytokines bind to heterodimeric receptors with ligand-selective  $\alpha$  or  $\beta$  chains, and a common  $\gamma$  chain ( $\gamma_c$ ) (IL2RG, ENSG00000147168, also known as CD132, CIDX, IMD4, severe combined immunodeficiency, SCIDX1).

Nomenclature	Interleukin-2 $\alpha$	Interleukin-2 $\beta$	Interleukin-4	Interleukin-7	Interleukin-9
HGNC nomenclature	IL2RA	IL2RB	IL4R	IL7R	IL9R
Ensembl ID	ENSG00000134460	ENSG00000100385	ENSG00000077238	ENSG00000168685	ENSG00000124334
Other names	CD25, IL2R, TAC antigen	CD122, IL15RB	CD124, P24394	CD127	CD129
Agonist	IL-2	IL-2, IL-15	IL-4, IL-13	IL-7	IL-9

Nomenclature	Interleukin-13 $\alpha$ 1	Interleukin-13 $\alpha$ 2	Interleukin-15 $\alpha$	Interleukin-21	TSLP
HGNC nomenclature	IL13RA1	IL13RA2	IL15RA	IL21R	TSLPR
Ensembl ID	ENSG00000131724	ENSG00000123496	ENSG00000134470	ENSG00000103522	ENSG00000205755
Other names	CD213a1, IL-13Ra, NR4	CD213a2, CT19, IL-13R, IL13BP	–	–	CRLF2
Agonist	IL-13	IL-13	IL-15	IL-21	TSLP

IL13RA2 acts as a substitute for  $\gamma_c$  producing a non-signalling complex; a decoy receptor.

Endogenous agonists include IL-2 (ENSG00000109471, also known as T-cell growth factor, TCGF, aldesleukin), IL-4 (ENSG00000113520, also known as B-cell stimulatory factor 1, lymphocyte stimulatory factor 1, binetrakin, pitrakinra), IL-7 (ENSG00000104432), IL-9 (ENSG00000145839, also known as HP40, P40), IL-13 (ENSG00000169194), IL-15 (ENSG00000164136), IL-21 (ENSG00000138684, also known as ZA11) and thymic stromal lymphopoietin (TSLP, ENSG00000145777).

Ro264550 has been described as a selective IL-2 receptor antagonist, which binds to IL-2 (Tilley *et al.* 1997).

The **IL-3 family** signal through a receptor complex comprising of a ligand-specific  $\alpha$  subunit and a common  $\beta$  chain (CSF2RB, ENSG00000100368, also known as CD131, IL3RB or IL5RB), which is shared between all members of this cytokine family.

Nomenclature	Interleukin-3	Interleukin-5	Granulocyte macrophage colony-stimulating factor
HGNC nomenclature	IL3RA	IL5RA	CSF2RA
Ensembl ID	ENSG00000185291	ENSG00000091181	ENSG00000198223
Other names	CD123, A40266	CD125, CDw125, IL5R	CD116
Agonist	IL-3	IL-5	GM-CSF

Endogenous agonists include IL-3 (ENSG00000164399, also known as multipotential colony-stimulating factor, hematopoietic growth factor, P-cell-stimulating factor, mast cell growth factor), IL-5 (ENSG00000113525, also known as EDF, TRF), GM-CSF (ENSG00000164400), and G-CSF (ENSG00000108342).



YM90709 has been described as a selective IL-5 receptor antagonist (Morokata *et al.*, 2002).

**The IL-6 family** signal through a ternary receptor complex consisting of the cognate receptor and a homodimer of the IL-6 signal transducer gp130 (IL6ST, ENSG00000134352, also known as CD130, oncostatin M receptor), which then activates the JAK/STAT, Ras/Raf/MAPK and PI 3-kinase /PKB signalling modules.

Nomenclature	Interleukin-6	Interleukin-11 $\alpha$	Interleukin-31
HGNC nomenclature	IL6R	IL11RA	IL31RA
Ensembl ID	ENSG00000160712	ENSG00000137070	ENSG00000164509
Other names	CD126	–	CRL, CRL3, gp130-like monocyte, GLM-R
Agonist	IL-6	IL-11	IL-31

Nomenclature	Ciliary neurotrophic factor $\alpha$	Leptin	Leukemia inhibitory factor	Oncostatin-M specific $\beta$
HGNC nomenclature	CNTFR	LEPR	LIFR	OSMR
Ensembl ID	ENSG00000122756	ENSG00000116678	ENSG00000113594	ENSG00000145623
Other names	CNTFR $\alpha$	CD295	CD118	OSMR $\beta$
Agonist	CNTF	Leptin	LIF, CTF1, OSM	OSM

Unusually amongst the cytokine receptors, the CNTF receptor is a glycerophosphatidylinositol-linked protein. CRLF1 (cytokine receptor-like factor 1, ENSG00000006016, also known as CISS, CISS1, CLF, CLF-1, NR6) acts as an endogenous antagonist for the CNTF receptor.

Endogenous agonists include IL-6 (ENSG00000136244, also known as B-cell stimulatory factor 2, interferon  $\beta$ -2, hybridoma growth factor, CTL differentiation factor), IL-11 (ENSG00000095752, also known as adipogenesis inhibitory factor), ciliary neurotrophic factor (CNTF, ENSG00000242689), cardiotrophin-1 (CTF1, ENSG00000150281, also known as B-cell stimulatory factor 3, BSF3), cardiotrophin-like cytokine (CLCF1, ENSG00000175505), leptin (LEP, ENSG00000174697, also known as OB), leukemia inhibitory factor (LIF, ENSG00000128342, also known as cholinergic differentiation factor) and Oncostatin M (OSM, ENSG00000099985).

**The IL-12 receptor family:** IL12RB1 is shared between receptors for IL-12 and IL-23; the functional agonist at IL-12 receptors is a heterodimer of IL-12A/IL-12B or homodimer of IL-12B/IL-2B subunits, while that for IL-23 receptors is a heterodimer of IL-12A/IL-23A.

Nomenclature	Interleukin-12 $\beta$ 1	Interleukin-12 $\beta$ 2	Interleukin 23
HGNC nomenclature	IL12RB1	IL12RB2	IL23R
Ensembl ID	ENSG00000096996	ENSG00000081985	ENSG00000162594
Other names	CD212, IL12RB	–	–
Agonist	IL-12A/IL-12B, IL-12B/IL-12B	IL-12A/IL-12B, IL-12B/IL-12B	IL-12A/IL-23A

Endogenous agonists include IL-12A (ENSG00000168811, also known as CLMF, IL-12A, NFSK, NKSF1, p35), IL-12B (ENSG00000113302, also known as natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40) and IL-23 (ENSG00000110944).

The **prolactin receptor family** is made up of homodimeric receptor tyrosine kinases.

Nomenclature	Erythropoietin	Granulocyte colony-stimulating factor	Growth hormone	Prolactin	Thrombopoietin
HGNC nomenclature	EPOR	CSF3R	GHR	PRLR	TPOR
Ensembl ID	ENSG00000187266	ENSG00000119535	ENSG00000112964	ENSG00000113494	ENSG00000117400
Other names	–	CD114	Somatotropin, GH-binding protein, GHBP, serum-binding protein	–	Myeloproliferative leukemia protein, C-mpl, CD110
Endogenous agonist	Erythropoietin	G-CSF	Growth hormone 1, growth hormone 2, choriomammotropin	Prolactin > growth hormone	Thrombopoietin

Endogenous agonists are large (~200 aa) polypeptides, and include erythropoietin (EPO, ENSG00000130427), granulocyte macrophage colony-stimulating factor (GM-CSF, ENSG00000164400, also known as colony-stimulating factor, CSF, sargramostim, molgramostin), growth hormone 1 (GH1, ENSG00000189162), growth hormone 2 (GH2, ENSG00000136488, also known as placenta-specific growth hormone), choriomam-

motropin (CSH1, ENSG00000136487, also known as lactogen), thrombopoietin (TPO, ENSG00000090534, also known as megakaryocyte colony-stimulating factor, myeloproliferative leukemia virus oncogene ligand, C-mpl ligand, megakaryocyte growth and development factor, MGDF), chorionic somatomotropin hormone 2 (CSH2, ENSG00000213218), chorionic somatomotropin hormone-like 1 (CSHL, ENSG00000204414, also known as lactogen-like) and granulocyte colony stimulating factor (CSF3, ENSG00000108342, also known as G-CSF, pluripoietin, filgrastim, lenograstim).

### Type II cytokine receptors

The **interferon receptor family** includes receptors for type I and type II interferons, that bind to heterodimeric receptors made up of IFNAR1/IFNAR2 or IFNGR1/IFNGR2, respectively.

Nomenclature	Interferon- $\alpha/\beta$ 1	Interferon- $\alpha/\beta$ 2	Interferon- $\gamma$ 1	Interferon- $\gamma$ 2
HGNC nomenclature	IFNAR1	IFNAR2	IFNGR1	IFNGR2
Ensembl ID	ENSG00000142166	ENSG00000159110	ENSG00000027697	ENSG00000159128
Other names	IFNAR, IFRC	IFNABR	CD119, IFNGR	AF-1, IFNGT1
Endogenous agonists	IFN- $\alpha$ , IFN- $\beta$ , IFN- $\omega$ , IFN- $\kappa$	IFN- $\alpha$ , IFN- $\beta$ , IFN- $\omega$ , IFN- $\kappa$	IFN- $\gamma$	IFN- $\gamma$

Endogenous agonists in man include IFN- $\alpha$  (IFNA1, ENSG00000197919), IFN- $\beta$  (IFNB1, ENSG00000171855), IFN- $\gamma$  (IFNG, ENSG00000111537), IFN- $\kappa$  (IFNK, ENSG00000147896) and IFN- $\omega$  (IFNW1, ENSG00000177047).

The **IL-10 family** of receptors are heterodimeric combinations of family members: IL10RA/IL10RB responds to IL-10; IL20RA/IL20RB responds to IL-19, IL-20 and IL-24; IL22RA1/IL20RB responds to IL-20 and IL-24; IL22RA1/IL10RB responds to IL-22; IL28RA/IL10RB responds to IL-28A, IL28B and IL-29.

Nomenclature	Interleukin-10 $\alpha$	Interleukin-10 $\beta$	Interleukin-20 $\alpha$	Interleukin-20 $\beta$
HGNC nomenclature	IL10RA	IL10RB	IL20RA	IL20RB
Ensembl ID	ENSG00000110324	ENSG00000243646	ENSG00000016402	ENSG00000174564
Other names	CDW210A, HIL-10R, IL10R	CDW210B, CRF2-4, CRFB4, D21S58, D21S66, IL-10R2	IL-20R1, ZCYTOR7	DIRS1, FNDC6, IL-20R2, MGC34923

Nomenclature	Interleukin-22 $\alpha$ 1	Interleukin-22 $\alpha$ 2	Interleukin-28 $\alpha$
HGNC nomenclature	IL22RA1	IL22RA2	IL28RA
Ensembl ID	ENSG00000142677	ENSG00000164485	ENSG00000185436
Other names	CRF2-9, IL22R	IL22bP, CRF2-S1	CRF2/12, IFNLR, IL-28R1

Endogenous agonists are IL-10 (ENSG00000136634), IL-19 (ENSG00000142224), IL-20 (ENSG00000162891), IL-22 (ENSG00000127318), IL-24 (ENSG00000162892), IL-28A (IL28A, ENSG00000183709, also known as IFN- $\lambda$ 2), IL-28B (IL28B, ENSG00000197110, also known as IFN- $\lambda$ 3), IL-29 (ENSG00000182393).

**Immunoglobulin-like family of IL-1 receptors** are heterodimeric receptors made up of a cognate receptor subunit and an IL-1 receptor accessory protein (IL1RAP, ENSG00000196083, also known as C3orf13, IL-1RAcP, IL1R3).

Nomenclature	Interleukin-1, type I	Interleukin-1 receptor-like 1	Interleukin-1 receptor-like 2	Interleukin-18 1
HGNC nomenclature	IL1R1	IL1RL1	IL1RL2	IL18R1
Ensembl ID	ENSG00000115594	ENSG00000115602	ENSG00000115598	ENSG00000115604
Other names	CD121A, D2S1473, IL1R, IL1RA	DER4, FIT-1, IL33R, ST2, ST2L, ST2V, T1	IL1R-rp2, IL1RRP2	CD218a, IL-1Rrp, IL1RRP
Endogenous agonists	IL-1 $\alpha$ , IL-1 $\beta$	-	-	IL-18

IL1R2, the type II IL-1 receptor (ENSG00000115590, also known as CD121b, IL1RB), is a decoy receptor, while the IL-1 receptor antagonist (IL1RN, ENSG00000136689, also known as ICIL-1RA, IL1F3, IL1RA, IRAP) prevents IL-1 binding to the receptor. Analogues of IL1RAP have been identified in the human genome: IL-1 receptor accessory protein-like 1 protein (IL1RAPL1, ENSG00000169306, also known as IL1R8, IL1RAPL, MRX10, MRX21, MRX34, OPHN4 or TIGIRR-2), X-linked IL-1 receptor accessory protein-like 2 (IL1RAPL2, ENSG00000189108, also known as IL-1R9, IL1R9, IL1RAPL-2 or TIGIRR-1) and IL-18 receptor accessory protein-like (IL18RAP, ENSG00000115607, also known as AcPL, CD218b).

Endogenous agonists are IL-1 $\alpha$  (IL1A, ENSG00000115008, also known as IL-1 or IL-1F1), IL-1 $\beta$  (ENSG00000125538, also known as IL-1F2) and IL-18 (ENSG00000150782, also known as IFN- $\gamma$ -inducing factor).

AF12198 has been described as a selective Type I IL-1 receptor antagonist (Akeson *et al.*, 1996).

The **IL17 receptor family** appear to represent a distinct class of cytokine receptors with incompletely defined signalling.

Nomenclature	Interleukin 17 $\alpha$	Interleukin 17 $\beta$	Interleukin 17 $\gamma$	Interleukin 17 $\delta$	Interleukin 17 $\epsilon$
HGNC nomenclature	IL17RA	IL17RB	IL17RC	IL17RD	IL17RE
Ensembl ID	ENSG00000177663	ENSG00000056736	ENSG00000163702	ENSG00000144730;	ENSG00000163701
Other names	CD217, CDw217, hIL-17R, IL-17RA, IL17R	CRL4, EVI27, IL17BR, IL17RH1	IL17-RL	SEF	–

Endogenous agonists include IL-17A (ENSG00000112115, also known as cytotoxic T-lymphocyte-associated serine esterase 8; CTLA8).

**Abbreviations:** **AF12198**, AcPheGluTrpThrProGlyTrpTyrGlnAzeTyrAlaLeuProLeu; **CSF**, colony stimulating factor; **EPO**, erythropoietin; **GH**, growth hormone; **G-CSF**, granulocyte colony-stimulating factor; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **IFN**, interferon; **IL**, interleukin; **JAK**, Janus kinase; **LIF**, leukemia inhibitory factor; **OSM**, oncostatin-M; **PRL** prolactin; **Ro264550**, N-[[[(3R)-1-(aminoiminomethyl)-3-piperidinyl]acetyl]-4-(phenylethynyl)-L-phenylalanine methyl ester; **STAT**, signal transducers and activators of transcription; **TPO**, thrombopoietin; **YM90709**, 2,3-dimethoxy-6,6-dimethyl-5,6-dihydrobenzo[7,8]indolizino[2,3-b]quinoxaline

### Further Reading

- Ben-Jonathan N, Hugo ER, Brandebourg TD, LaPensee CR (2006). Focus on prolactin as a metabolic hormone. *Trends Endocrinol Metab* **17**: 110–116.
- Ben-Jonathan N, LaPensee CR, LaPensee EW (2008). What can we learn from rodents about prolactin in humans? *Endocr Rev* **29**: 1–41.
- Constantinescu SN, Girardot M, Pecquet C (2008). Mining for JAK-STAT mutations in cancer. *Trends Biochem Sci* **33**: 122–131.
- Duncan MJ (2007). Circannual prolactin rhythms: calendar-like timer revealed in the pituitary gland. *Trends Endocrinol Metab* **18**: 259–260.
- Giustina A, Mazziotti G, Canalis E (2008). Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev* **29**: 535–559.
- Grattan DR, Kokay IC (2008). Prolactin: a pleiotropic neuroendocrine hormone. *J Neuroendocrinol* **20**: 752–763.
- Holt RI, Sonksen PH (2008). Growth hormone, IGF-I and insulin and their abuse in sport. *Br J Pharmacol* **154**: 542–556.
- van der Lely AJ, Kopchick JJ (2006). Growth hormone receptor antagonists. *Neuroendocrinology* **83**: 264–268.
- Li WX (2008). Canonical and non-canonical JAK-STAT signaling. *Trends Cell Biol* **18**: 545–551.
- Lichanska AM, Waters MJ (2008). How growth hormone controls growth, obesity and sexual dimorphism. *Trends Genet* **24**: 41–47.
- Marcucci R, Romano M (2008). Thrombopoietin and its splicing variants: structure and functions in thrombopoiesis and beyond. *Biochim Biophys Acta* **1782**: 427–432.
- Moller N, Jorgensen JO (2009). Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev* **30**: 152–177.
- Pilecka I, Whatmore A, van Hooft HR, Destenaves B, Clayton P (2007). Growth hormone signalling: sprouting links between pathways, human genetics and therapeutic options. *Trends Endocrinol Metab* **18**: 12–18.
- Schindler C, Levy DE, Decker T (2007). JAK-STAT signaling: from interferons to cytokines. *J Biol Chem* **282**: 20059–20063.
- Soares MJ, Konno T, Alam SM (2007). The prolactin family: effectors of pregnancy-dependent adaptations. *Trends Endocrinol Metab* **18**: 114–121.
- Takano H, Ueda K, Hasegawa H, Komuro I (2007). G-CSF therapy for acute myocardial infarction. *Trends Pharmacol Sci* **28**: 512–517.
- TwoRoger SS, Hankinson SE (2006). Prolactin and breast cancer risk. *Cancer Lett* **243**: 160–169.
- Velloso CP (2008). Regulation of muscle mass by growth hormone and IGF-I. *Br J Pharmacol* **154**: 557–568.
- Ward AC (2007). The role of the granulocyte colony-stimulating factor receptor (G-CSF-R) in disease. *Front Biosci* **12**: 608–618.
- Xu J, Messina JL (2009). Crosstalk between growth hormone and insulin signaling. *Vitam Horm* **80**: 125–153.

### References

- Akeson AL *et al.* (1996). *J Biol Chem* **271**: 30517–30523.
- Morokata T *et al.* (2002). *Int Immunopharmacol* **2**: 1693–1702.
- Tilley JW *et al.* (1997). *J Am Chem Soc* **119**: 7589–7590.

# GDNF family

**Overview:** GDNF family receptors (ENSM00500000269996) are extrinsic tyrosine kinase receptors. Ligand binding to the extracellular domain of the glycosylphosphatidylinositol-linked cell-surface receptors (tabulated below) activates a transmembrane tyrosine kinase enzyme, Ret (Rearranged during transfection, ENSG00000165731). The endogenous ligands are typically dimeric, linked through disulphide bridges: glial cell-derived neurotrophic factor (GDNF, 211 aa, ENSG00000168621); neurturin (NRTN, 197 aa, ENSG00000171119); artemin (ARTN, 237 aa, ENSG00000117407) and persephin (PSPN, 156 aa, ENSG00000125650).

Nomenclature	GDNF family receptor $\alpha 1$	GDNF family receptor $\alpha 2$	GDNF family receptor $\alpha 3$	GDNF family receptor $\alpha 4$
Preferred abbreviation	<b>GFR<math>\alpha 1</math></b>	<b>GFR<math>\alpha 2</math></b>	<b>GFR<math>\alpha 3</math></b>	<b>GFR<math>\alpha 4</math></b>
Other names	GDNF receptor	Neurturin receptor	Artemin receptor	Persephin receptor
Ensembl ID	ENSG00000151892	ENSG00000168546	ENSG00000146013	ENSG00000125861
Potency order	GDNF>NRTN>ARTN	NRTN>GDNF	ARTN	PSPN
Probes	[ <sup>125</sup> I]-GDNF (3-63 pM, Treanor <i>et al.</i> , 1996; Klein <i>et al.</i> , 1997)	–	–	–

Inhibitors of other receptor tyrosine kinases, such as semaxinib, which inhibits VEGF receptor function, may also inhibit Ret function (Mologni *et al.*, 2006). Mutations of Ret and GDNF genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

## Further Reading

- Bespalov MM, Saarma M (2007). GDNF family receptor complexes are emerging drug targets. *Trends Pharmacol Sci* **28**: 68–74.
- Carnicella S, Ron D (2009). GDNF – a potential target to treat addiction. *Pharmacol Ther* **122**: 9–18.
- Ernsberger U (2008). The role of GDNF family ligand signalling in the differentiation of sympathetic and dorsal root ganglion neurons. *Cell Tissue Res* **333**: 353–371.
- Paratcha G, Ledda F (2008). GDNF and GFR $\alpha$ : a versatile molecular complex for developing neurons. *Trends Neurosci* **31**: 384–391.
- Rangasamy SB, Soderstrom K, Bakay RA, Kordower JH (2010). Neurotrophic factor therapy for Parkinson's disease. *Prog Brain Res* **184**: 237–264.
- Schueler-Furman O, Glick E, Segovia J, Linial M (2006). Is GAS1 a co-receptor for the GDNF family of ligands? *Trends Pharmacol Sci* **27**: 72–77.

## References

- Klein RD *et al.* (1997). *Nature* **387**: 717–721.
- Mologni L *et al.* (2006). *J Mol Endocrinol* **37**: 199–212.
- Treanor JJS *et al.* (1996). *Nature* **382**: 80–83.

# Natriuretic peptide

**Overview:** Natriuretic peptide receptors are a family (ENSMF0025000000198) of homodimeric, catalytic receptors with a single TM domain and guanylyl cyclase (EC 4.6.1.2) activity on the intracellular domain of the protein sequence. Isoforms are activated by the peptide hormones atrial natriuretic peptide (ANP, ENSG00000175206), brain natriuretic peptide (BNP, ENSG00000120937) and C-type natriuretic peptide (CNP, ENSG00000163273). Another family member is GC-C, the receptor for guanylin (ENSG00000113389) and uroguanylin (ENSG00000044012). Family members have conserved ligand-binding, catalytic (guanylyl cyclase) and regulatory domains with the exception of NPR-C which has an extracellular binding domain homologous to that of other NPRs, but with a truncated intracellular domain which appears to couple, *via* the G<sub>i/o</sub> family of G proteins to activation of phospholipase C, inwardly-rectifying potassium channels and inhibition of adenylyl cyclase activity (Murthy and Makhlof, 1999).

Nomenclature	NPR-A	NPR-B	NPR-C	GC-C
Other names	NPR1, GC-A, ANP <sub>A</sub> receptor, ANPRA, GUCY2A	NPR2, GC-B, ANP <sub>B</sub> receptor, ANPRB, GUCY2B	NPR3, ANPRC, <i>npr3</i> , clearance receptor	STaR, GUCY2C
Ensembl ID	ENSG00000169418	ENSG00000159899	ENSG00000113389	ENSG00000070019
Potency order	ANP ≥ BNP >> CNP (Suga <i>et al.</i> , 1992)	CNP >> ANP >> BNP (Suga <i>et al.</i> , 1992)	ANP > CNP ≥ BNP (Suga <i>et al.</i> , 1992)	Uroguanylin > guanylin
Selective agonists	ANP, BNP, sANP (Olson <i>et al.</i> , 1996)	CNP (Suga <i>et al.</i> , 1992)	cANF <sup>4-23</sup> (Maack <i>et al.</i> , 1987), osteocrin (Moffatt <i>et al.</i> , 2007).	<i>E. coli</i> heat-stable enterotoxin (ST <sub>a</sub> ), linaclotide (Harris and Crowell, 2007)
Selective antagonists	A71915 (9.2–9.5, Delporte <i>et al.</i> , 1991), [Asu7,23']-β-ANP <sup>7-28</sup> (7.5, Kambayashi <i>et al.</i> , 1989), anantin (Wyss <i>et al.</i> , 1991)	Monoclonal antibody 3G12 (Drewett <i>et al.</i> , 1995), [Ser <sup>11</sup> ](N-CNP,C-ANP)pBNP <sup>2-25</sup> (Deschenes <i>et al.</i> , 2005)	AP811 (9.3, Veale <i>et al.</i> , 2000), M372049 (Hobbs <i>et al.</i> , 2004)	–
Probes	[ <sup>125</sup> I]-ANP	[ <sup>125</sup> I]-CNP	[ <sup>125</sup> I]-ANP	[ <sup>125</sup> I]-ST <sub>a</sub>

The polysaccharide obtained from fermentation of *Aureobasidium* species, HS142-1, acts as an antagonist at both NPR-A and NPR-B receptors (Morishita *et al.*, 1991).

Gucy2D (RetGC1, GC-E, ENSG00000132518) and Gucy2F (RetGC2, GC-F, ENSG00000101890) are predominantly retinal guanylyl cyclase activities, which are inhibited by calcium ions acting through the guanylyl cyclase activating peptides GCAP1 (GUCA1A, ENSG00000048545), GCAP2 (GUCA1B, ENSG00000112599) and GCAP3 (GUCA1C, ENSG00000138472) (see Hunt *et al.*, 2010).

**Abbreviations:** A71915, ([Arg<sup>6</sup>,Cha<sup>8</sup>]ANP<sup>6-15</sup>-d-Tic-Arg-Cys-NH<sub>2</sub>; **anantin**, cyclo(Gly-Phe-Ile-Gly-Trp-Gly-Asn-β-Asp)-Ile-Phe-Gly-His-Tyr-Ser-Gly-Asp-Phe; **AP811**, (s)-N<sup>2</sup>-([4-[(2-naphthalenylcarbonyl)amino]phenyl]acetyl)-l-arginyl-l-isoleucyl-l-α-aspartyl-N-(2-methylbutyl)-l-argininamide; [Asu7,23']-β-ANP(7–28), an antiparallel dimer linked by 7-23' and 7'-23 disulphide bonds (Asu, l-α-aminosuberlic acid); cANF<sup>4-23</sup>, des[Gln<sup>18</sup>,Ser<sup>19</sup>,Gly<sup>20</sup>,Leu<sup>21</sup>,Gly<sup>22</sup>]ANP<sup>4-23</sup>-NH<sub>2</sub>; **HS142-1**, *Aureobasidium*-derived polysaccharide; **M372049**, see Chauhan *et al.* (2003) for structure; sANP, [G9T, R11S, G16R]ANP

## Further Reading

- Hunt DM, Buch P, Michaelides M. (2010) Guanylate cyclases and associated activator proteins in retinal disease. *Mol Cell Biochem* **334**: 157–168.
- van Kimmenade RR, Januzzi JL, Jr. (2009). The evolution of the natriuretic peptides – Current applications in human and animal medicine. *J Vet Cardiol* **11** (Suppl. 1): S9–21.
- Kishimoto I, Tokudome T, Nakao K, Kangawa K (2011). Natriuretic peptide system: an overview of studies using genetically engineered animal models. *FEBS J* **278**: 1830–1841.
- Kuhn M (2009). Function and dysfunction of mammalian membrane guanylyl cyclase receptors: lessons from genetic mouse models and implications for human diseases. *Handb Exp Pharmacol* **191**: 47–69.
- Lanfear DE (2010). Genetic variation in the natriuretic peptide system and heart failure. *Heart Fail Rev* **15**: 219–228.
- Li P, Lin JE, Marszlowicz GP, Valentino MA, Chang C, Schulz S *et al.* (2009). GCC signaling in colorectal cancer: is colorectal cancer a paracrine deficiency syndrome? *Drug News Perspect* **22**: 313–318.
- Misono KS, Philo JS, Arakawa T, Ogata CM, Qiu Y, Ogawa H *et al.* (2011). Structure, signaling mechanism and regulation of the natriuretic peptide receptor guanylate cyclase. *FEBS J* **278**: 1818–1829.
- Pandey KN (2011). The functional genomics of guanylyl cyclase/natriuretic peptide receptor-A: perspectives and paradigms. *FEBS J* **278**: 1792–1807.
- Potter LR (2011). Natriuretic peptide metabolism, clearance and degradation. *FEBS J* **278**: 1808–1817.
- Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM (2009). Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *Handb Exp Pharmacol* **191**: 341–366.
- Rubattu S, Sciarretta S, Morriello A, Calvieri C, Battistoni A, Volpe M (2010). NPR-C: a component of the natriuretic peptide family with implications in human diseases. *J Mol Med* **88**: 889–897.
- Saito Y (2010). Roles of atrial natriuretic peptide and its therapeutic use. *J Cardiol* **56**: 262–270.

## References

- Chauhan S *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 1426–1431.
- Delporte C *et al.* (1991). *Eur J Pharmacol* **207**: 81–88.
- Deschenes J *et al.* (2005). *Peptides* **26**: 517–524.
- Drewett JG *et al.* (1995). *J Biol Chem* **270**: 4668–4674.
- Harris LA, Crowell MD (2007). *Curr Opin Mol Ther* **9**: 403–410.
- Hobbs A *et al.* (2004). *Circulation* **110**: 1231–1235.
- Kambayashi Y *et al.* (1989). *FEBS Lett* **248**: 28–34.
- Maack T *et al.* (1987). *Science* **238**: 675–678.
- Moffatt P *et al.* (2007). *J Biol Chem* **282**: 36454–36262.
- Morishita Y *et al.* (1991). *Biochem Biophys Res Commun* **176**: 949–957.
- Murthy KS, Makhlouf GM (1999). *J Biol Chem* **274**: 17587–17592.
- Olson LJ *et al.* (1996). *Mol Pharmacol* **50**: 430–435.
- Suga S *et al.* (1992). *Endocrinology* **130**: 229–239.
- Veale CA *et al.* (2000). *Bioorg Med Chem Lett* **10**: 1949–1952.
- Wyss DF *et al.* (1991). *J Antibiot (Tokyo)* **44**: 172–180.

# Pattern recognition receptors

**Overview:** pattern recognition receptors (PRR, see Takeuchi and Akira, 2010) participate in the innate immune response to microbial agents, the stimulation of which leads to activation of intracellular enzymes and regulation of gene transcription. PRR include both cell-surface and intracellular proteins, including toll-like receptors (TLR), nucleotide-binding oligomerization domain-like receptors (NLR, also known as NOD-like receptors) and the mannose receptor family (ENSM0025000004089). PRR may be divided into signalling-associated members, identified here, and endocytic members (such as the mannose receptor family), the function of which appears to be to recognise particular microbial motifs for subsequent cell attachment, internalisation and destruction.

PRRs express multiple leucine-rich regions to bind a range of microbially-derived ligands, termed PAMPs or pathogen-associated molecular patterns, which includes peptides, carbohydrates, peptidoglycans, lipoproteins, lipopolysaccharides, and nucleic acids.

## Toll-like receptor family

Members of this family share significant homology with the interleukin-1 receptor family and appear to require dimerization either as homo- or heterodimers for functional activity. Heterodimerization appears to influence the potency of ligand binding substantially (e.g. TLR1/2 and TLR2/6, Takeuchi *et al.*, 2001; 2002). TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11 are cell-surface proteins, while other members are associated with intracellular organelles, signalling through the MyD88-dependent pathways (with the exception of TLR3). As well as responding to exogenous infectious agents, it has been suggested that selected members of the family may be activated by endogenous ligands, such as hsp60 (Ohashi *et al.*, 2000).

Nomenclature	Other names	Ensembl ID	Agonists
TLR1	Toll/interleukin-1 receptor-like protein, CD281, TIL	ENSG00000174125	–
TLR2	CD282, TIL4	ENSG00000137462	Peptidoglycan (Schwandner <i>et al.</i> , 1999; Yoshimura <i>et al.</i> , 1999)
TLR3	CD283	ENSG00000164342	PolyIC (Alexopoulou <i>et al.</i> , 2001)
TLR4	CD284, hToll, ARMD10	ENSG00000136869	LPS (Poltorak <i>et al.</i> , 1998), taxol (Kawasaki <i>et al.</i> , 2000)
TLR5	SLEB1, TIL3	ENSG00000187554	Flagellin (Hayashi <i>et al.</i> , 2001)
TLR6	CD286	ENSG00000174130	–
TLR7	–	ENSG00000196664	R848 (Hemmi <i>et al.</i> , 2002), imiquimod (Hemmi <i>et al.</i> , 2002), loxoribine (Heil <i>et al.</i> , 2003)
TLR8	–	ENSG00000101916	R848 (Hemmi <i>et al.</i> , 2002), imiquimod
TLR9	CD289	ENSG00000173366	CpG (Hemmi <i>et al.</i> , 2000)
TLR10		ENSG00000174123	–
TLR11		ENSMUSG00000051969	–

Eritoran (E5564) is a lipid A analogue, which has been described as a TLR4 antagonist (Ingalls *et al.*, 1998).

## NOD-like receptor family

Structural analysis has identified a common motif of a mid-peptide located nucleotide-binding and oligomerization (NACHT) domain, which allows division of NOD-like receptors into three subfamilies, NLRC (or NODs), NLRP (or NALP) and IPAF (see Schroder and Tschopp, 2010). NLRC members are named on the basis of a sequence motif expressed at their N-termini, the caspase recruitment domain (CARD), while NLRP members have a pyrin domain. NLRs express C-terminal leucine-rich regions which have regulatory function and appear to recognize the microbial products to which the NLRs respond. NLRC family members recruit a serine/threonine kinase RIPK2 (receptor-interacting serine/threonine kinase 2, also known as CARD3, CARDIAK, RICK, RIP2, ENSG00000104312) leading to signalling through NF- $\kappa$ B and MAP kinase. NLRP family members, upon activation, recruit adaptor proteins (e.g. Asc also known as PYCARD, CARD5, TMS-1, ENSG00000103490). Activated NLRs associate in multiprotein complexes, known as inflammasomes (see Schroder and Tschopp, 2010), allowing the recruitment of caspases (see Page S317).

Nomenclature	Other names	Ensembl ID	Agonists
NLRC1	NOD1, CARD4, CLR7.1	ENSG00000106100	meso-DAP
NLRC2	NOD2, BLAU, CARD15, CD, CLR16.3, IBD1, PSORAS1	ENSG00000167207	Muramyl dipeptide
NLRC3	NOD3, CLR16.2s	ENSG00000167984	
NLRC5	NOD4, NOD27, CLR16.1, FLJ21709	ENSG00000140853	
NLRX1	NOD9, CLR11.3	ENSG00000160703	
CIITA	Class II major histocompatibility complex, C2TA, MHC2TA, NLRA	ENSG00000179583	
NLRP1	CARD7, CLR17.1, DEFCAP, DKFZp586O1822, KIAA0926, NAC, NALP1	ENSG00000091592	Muramyl dipeptide

Nomenclature	Other names	Ensembl ID	Agonists
NLRP2	CLR19.9, FLJ20510, NALP2, NBS1, PAN1, PYPAF2	ENSG00000022556	
NLRP3	AGTAVPRL, AII, AVP, C1orf7, CIAS1, CLR1.1, FCAS, FCU, MWS, NALP3, PYPAF1	ENSG00000162711	Multiple virus particles, including Sendai and influenza
NLRP4	CLR19.5, CT58, FLJ32126, NALP4, PAN2, PYPAF4, RNH2	ENSG00000160505	
NLRP5	CLR19.8, MATER, NALP5, PAN11, PYPAF8	ENSG00000171487	
NLRP6	CLR11.4, NALP6, PAN3, PYPAF5	ENSG00000174885	
NLRP7	CLR19.4, NALP7, NOD12, PAN7, PYPAF3	ENSG00000167634	
NLRP8	CLR19.2, NALP8, NOD16, PAN4	ENSG00000179709	
NLRP9	CLR19.1, NALP9, NOD6, PAN12	ENSG00000185792	
NLRP10	CLR11.1, NALP10, NOD8, PAN5, Pynod	ENSG00000182261	
NLRP11	CLR19.6, NALP11, NOD17, PAN10, PYPAF6	ENSG00000179873	
NLRP12	CLR19.3, Monarch1, NALP12, PAN6, PYPAF7, RNO2	ENSG00000142405	
NLRP13	CLR19.7, NALP13, NOD14, PAN13	ENSG00000173572	
NLRP14	CLR11.2, GC-LRR, Nalp-iota, NALP14, NOD5, PAN8	ENSG00000158077	
IPAF	NOD4, NLRC4	ENSG00000091106	
NAIP	BIRC1, NLRB1	ENSG00000249437	

NLRP3 has also been reported to respond to host-derived products, known as danger-associated molecular patterns, or DAMPs, including uric acid (Martinon *et al.*, 2006), ATP, glucose, hyaluronan and amyloid  $\beta$  (see Schroder and Tschopp, 2010).

Loss-of-function mutations of NLRP3 are associated with cold autoinflammatory and Muckle-Wells syndromes.

**Abbreviations:** CpG, DNA enriched in cytosine:guanine pairs; **imiquimod**, 1-(4-amino-imidazo[4,5-c]quinolin-1-yl)-2-methylpropane, also known as R837; **LPS**, lipopolysaccharide derived from Gram-negative bacteria; **meso-DAP**, meso-diaminopimeilic acid; **polyIC**, polyinosine-polycytosine; **R848**, 1-(4-amino-2-ethoxymethyl-imidazo[4,5-c]quinolin-1-yl)-2-methyl-propan-2-ol, also known as resiquimod and S28463

#### Further Reading

- Barton GM, Kagan JC (2009). A cell biological view of Toll-like receptor function: regulation through compartmentalization. *Nat Rev Immunol* **9**: 535–542.
- Buchanan MM, Hutchinson M, Watkins LR, Yin H (2010). Toll-like receptor 4 in CNS pathologies. *J Neurochem* **114**: 13–27.
- Celis E (2007). Toll-like receptor ligands energize peptide vaccines through multiple paths. *Cancer Res* **67**: 7945–7947.
- Chao W (2009). Toll-like receptor signaling: a critical modulator of cell survival and ischemic injury in the heart. *Am J Physiol Heart Circ Physiol* **296**: H1–H12.
- Chiron D, Jegou G, Pellat-Deuceunynck C (2010). Toll-like receptors: expression and involvement in multiple myeloma. *Leuk Res* **34**: 1545–1550.
- Downes CE, Crack PJ (2010). Neural injury following stroke: are Toll-like receptors the link between the immune system and the CNS? *Br J Pharmacol* **160**: 1872–1888.
- Ehlers M, Ravetch JV (2007). Opposing effects of Toll-like receptor stimulation induce autoimmunity or tolerance. *Trends Immunol* **28**: 74–79.
- Garantziotis S, Hollingsworth JW, Zaas AK, Schwartz DA (2008). The effect of toll-like receptors and toll-like receptor genetics in human disease. *Annu Rev Med* **59**: 343–359.
- Hennessy EJ, Parker AE, O'Neill LA (2010). Targeting Toll-like receptors: emerging therapeutics? *Nat Rev Drug Discov* **9**: 293–307.
- Hirsch I, Caux C, Hasan U, Bendriss-Vermare N, Olive D (2010). Impaired Toll-like receptor 7 and 9 signaling: from chronic viral infections to cancer. *Trends Immunol* **31**: 391–397.
- Hori M, Nishida K (2008). Toll-like receptor signaling: defensive or offensive for the heart? *Circ Res* **102**: 137–139.
- Kanzler H, Barrat FJ, Hessel EM, Coffman RL (2007). Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. *Nat Med* **13**: 552–559.
- Konner AC, Bruning JC (2011). Toll-like receptors: linking inflammation to metabolism. *Trends Endocrinol Metab* **22**: 16–23.
- Lecat A, Piette J, Legrand-Poels S (2010). The protein Nod2: an innate receptor more complex than previously assumed. *Biochem Pharmacol* **80**: 2021–2031.
- Li H, Sun B (2007). Toll-like receptor 4 in atherosclerosis. *J Cell Mol Med* **11**: 88–95.
- Marsh BJ, Williams-Karnesky RL, Stenzel-Poore MP (2009). Toll-like receptor signaling in endogenous neuroprotection and stroke. *Neuroscience* **158**: 1007–1020.
- Marshak-Rothstein A, Rifkin IR (2007). Immunologically active autoantigens: the role of toll-like receptors in the development of chronic inflammatory disease. *Annu Rev Immunol* **25**: 419–441.
- Monie TP, Bryant CE, Gay NJ (2009). Activating immunity: lessons from the TLRs and NLRs. *Trends Biochem Sci* **34**: 553–561.
- O'Neill LA, Bowie AG (2007). The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling. *Nat Rev Immunol* **7**: 353–364.
- O'Neill LA, Sheedy FJ, McCoy CE (2011). MicroRNAs: the fine-tuners of Toll-like receptor signalling. *Nat Rev Immunol* **11**: 163–175.
- Sabroe I, Parker LC, Dower SK, Whyte MK (2008). The role of TLR activation in inflammation. *J Pathol* **214**: 126–135.
- Saitoh S, Miyake K (2009). Regulatory molecules required for nucleotide-sensing Toll-like receptors. *Immunol Rev* **227**: 32–43.
- Sanjuan MA, Milasta S, Green DR (2009). Toll-like receptor signaling in the lysosomal pathways. *Immunol Rev* **227**: 203–220.
- Schroder K, Tschopp J (2010). The inflammasomes. *Cell* **140**: 821–832.
- Shaw PJ, Lamkanfi M, Kanneganti TD (2010). NOD-like receptor (NLR) signaling beyond the inflammasome. *Eur J Immunol* **40**: 624–627.
- Takeuchi O, Akira S (2010). Pattern recognition receptors and inflammation. *Cell* **140**: 805–820.



- Trinchieri G, Sher A (2007). Cooperation of Toll-like receptor signals in innate immune defence. *Nat Rev Immunol* 7: 179–190.
- Wenzel J, Tormo D, Tuting T (2008). Toll-like receptor-agonists in the treatment of skin cancer: history, current developments and future prospects. *Handb Exp Pharmacol* 183: 201–220.
- Werling D, Jann OC, Offord V, Glass EJ, Coffey TJ (2009). Variation matters: TLR structure and species-specific pathogen recognition. *Trends Immunol* 30: 124–130.

## References

- Alexopoulou L *et al.* (2001). *Nature* 413: 732–738.
- Hayashi F *et al.* (2001). *Nature* 410: 1099–1103.
- Heil F *et al.* (2003). *Eur J Immunol* 33: 2987–2997.
- Hemmi H *et al.* (2000). *Nature* 408: 740–745.
- Hemmi H *et al.* (2002). *Nat Immunol* 3: 196–200.
- Ingalls RR *et al.* (1998). *J Immunol* 161: 5413–5420.
- Kawasaki K *et al.* (2000). *J Biol Chem* 275: 2251–2254.
- Martinon F *et al.* (2006). *Nature* 440: 237–241.
- Ohashi K *et al.* (2000). *J Immunol* 164: 558–561.
- Poltorak A *et al.* (1998). *Science* 282: 2085–2088.
- Schwandner R *et al.* (1999). *J Biol Chem* 274: 17406–17409.
- Takeuchi O *et al.* (2001). *Int Immunol* 13: 933–940.
- Takeuchi O *et al.* (2002). *J Immunol* 169: 10–14.
- Yoshimura A *et al.* (1999). *J Immunol* 163: 1–5.

# Receptor serine/threonine kinase (RSTK) family (EC 2.7.11.30)

**Overview:** receptor serine/threonine kinases (RSTK) respond to particular cytokines, the transforming growth factor  $\beta$  (TGF $\beta$ ) and bone morphogenetic protein (BMP) families, and may be divided into two subfamilies on the basis of structural similarities. Agonist binding initiates formation of a cell-surface complex of type I and type II RSTK, possibly heterotetrameric, where the type II protein phosphorylates the type I partner's kinase domain, initiating phosphorylation of particular members of the Smad family. These migrate to the nucleus and act as complexes to regulate gene transcription.

**The type I receptor serine/threonine kinases** (ENSM0025000000213) are also known as activin receptors or activin receptor-like kinases, ALKs, for which a systematic nomenclature has been proposed (ALK1-7).

Systematic nomenclature	HGNC nomenclature	Ensembl ID	Other names
ALK1	ACVRL1	ENSG00000139567	Serine/threonine-protein kinase receptor R3, SKR3
ALK2	ACVR1	ENSG00000115170	Activin receptor 1, serine/threonine-protein kinase receptor R1, SKR1
ALK3	BMPR1A	ENSG00000107779	BMP receptor IA, serine/threonine-protein kinase receptor R5, SKR5, CD292
ALK4	ACVR1B	ENSG00000135503	Activin receptor 1B, ACTR-1B, serine/threonine-protein kinase receptor R2, SKR2
ALK5	TGFBRI	ENSG00000106799	TGF $\beta$ receptor I, TGFR-1, serine/threonine-protein kinase receptor R4, SKR4
ALK6	BMPR1B	ENSG00000138696	BMP receptor IB, CDw293
ALK7	ACVR1C	ENSG00000123612	Activin receptor 1C, ACTR-1C

The type II receptor serine/threonine kinases (ENSM00500000269790).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Activin receptor 2A	ACVR2A	ENSG00000121989	ACTR-IIA
Activin receptor 2B	ACVR2B	ENSG00000114739	ACTR-IIB
Anti-Müllerian hormone receptor-II	AMHR2	ENSG00000135409	–
BMP receptor 2	BMPR2	ENSG00000204217	–
TGF $\beta$ receptor II	TGFBRII	ENSG00000163513	TGF $\beta$ R-II
TGF $\beta$ receptor III	TGFBRII	ENSG00000069702	Betaglycan

**Smads** were identified as mammalian orthologues of *Drosophila* genes termed 'mothers against decapentaplegic' and may be divided into Receptor-regulated Smads (R-Smads, including Smad1, Smad2, Smad3, Smad5 and Smad8), Co-mediated Smad (Co-Smad, Smad4) and Inhibitory Smads (I-Smad, Smad6 and Smad7). R-Smads form heteromeric complexes with Co-Smad. I-Smads compete for binding of R-Smad with both receptors and Co-Smad.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Smad1	SMAD1	ENSG00000170365	JV4-1, MADH1, MADR1
Smad2	SMAD2	ENSG00000175387	JV18-1, MADH2, MADR2
Smad3	SMAD3	ENSG00000166949	HsT17436, JV15-2, MADH3
Smad4	SMAD4	ENSG00000141646	DPC4, MADH4
Smad5	SMAD5	ENSG00000113658	Dwfc, JV5-1, MADH5
Smad6	SMAD6	ENSG00000137834	HsT17432, MADH6, MADH7
Smad7	SMAD7	ENSG00000101665	MADH7, MADH8
Smad8	SMAD9	ENSG00000120693	MADH6, MADH9

**Endogenous agonists** are characterized by six conserved cysteine residues and are divided into two subfamilies on the basis of sequence comparison and signalling pathways activated: the TGF $\beta$ /activin/nodal subfamily and the BMP/GDF (growth/differentiation factor)/MIS (Müllerian inhibiting substance) subfamily. Ligands active at RSTKs appear to be generated as large precursors which undergo complex maturation processes (see Li and Flavell, 2008). Some are known to form disulphide-linked homo- and/or heterodimeric complexes. Thus, inhibins are  $\alpha$  subunits linked to a variety of  $\beta$  chains, while activins are combinations of  $\beta$  subunits.

Binding of TGF $\beta$  family members generate complexes of TGF $\beta$  receptor II or activin receptor 2B with ALK4, ALK5 or ALK7 and couple to Smad2 and Smad3 (see Shi and Massague, 2003). Binding of BMP family members generate complexes of BMP receptor 2, activin receptor 2A or activin receptor 2B with ALK1, ALK2, ALK3 or ALK6 and couple to Smad1, Smad5 and Smad8. Activins generate complexes of activin receptor 2A or activin receptor 2B with ALK2 (see Shi and Massague, 2003).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
BMP2	BMP2	ENSG00000125845	BMP2A
BMP3	BMP3	ENSG00000152785	
BMP4	BMP4	ENSG00000125378	BMP2B
BMP5	BMP5	ENSG00000112175	–
BMP6	BMP6	ENSG00000153162	VG1-related sequence, VGR1
BMP7	BMP7	ENSG00000101144	Osteogenic protein 1
BMP8A	BMP8A	ENSG00000183682	–
BMP8B	BMP8B	ENSG00000116985	BMP8, osteogenic protein 2; op2
BMP9	GDF2	ENSG00000128802	Growth/differentiation factor 2
BMP10	BMP10	ENSG00000163217	–
BMP11	GDF11	ENSG00000135414	Growth/differentiation factor 11
BMP12	GDF7	ENSG00000143869	Growth differentiation factor 7
BMP13	GDF6	ENSG00000156466	Growth differentiation factor 6
BMP14	GDF5	ENSG00000125965	Growth differentiation factor 5, CDMP1
BMP15	BMP15	ENSG00000130385	Growth/differentiation factor 9b
GDF1	GDF1	ENSG00000130283	Growth/differentiation factor 1
GDF3	GDF3	ENSG00000184344	Growth/differentiation factor 3
GDF9	GDF9	ENSG00000164404	Growth/differentiation factor
GDF10	GDF10	ENSG00000107623	Growth/differentiation factor 10, BMP3b
GDF11	GDF11	ENSG00000130513	TGF-PL, MIC-1, MIC1, NAG-1, PDF, PLAB, PTGFB
Inhibin $\alpha$	INH A	ENSG00000123999	–
Inhibin $\beta$ A	INH B A	ENSG00000122641	Activin $\beta$ A, follicle-stimulating hormone-releasing protein, erythroid differentiation factor
Inhibin $\beta$ B	INH B B	ENSG00000163083	Activin $\beta$ B
Inhibin $\beta$ C	INH B C	ENSG00000175189	–
Inhibin $\beta$ E	INH B E	ENSG00000139269	Activin, MGC4638
Myostatin	MSTN	ENSG00000138379	Growth/differentiation 8, GDF8
TGF $\beta$ 1	TGFB1	ENSG00000105329	–
TGF $\beta$ 2	TGFB2	ENSG00000092969	Glioblastoma-derived T-cell suppressor factor, G-TSF, BSC-1 cell growth inhibitor, polyergin, cetermin
TGF $\beta$ 3	TGFB3	ENSG00000119699	–

BMP1 is a member of the tolloid-like family (ENSMF00570000851071) of metalloproteinases and does not signal through these receptors.

TGF $\beta$  family ligand signalling may be inhibited by endogenous proteins, such as follistatin (ENSG00000134363), which binds and neutralizes activins to prevent activation of the target receptors.

An appraisal of small molecule inhibitors of TGF $\beta$  and BMP signalling concluded that TGF $\beta$  pathway inhibitors were more selective than BMP signalling inhibitors (Vogt *et al.*, 2011). The authors confirmed the selectivity of SB505124 to inhibit TGF $\beta$  signalling through ALK4, ALK5, ALK7 (Dacosta Byfield *et al.*, 2004). Dorsomorphin inhibits BMP signalling through ALK2 and ALK3; it also inhibits AMP kinase (Zhou *et al.*, 2001).

**Abbreviations:** SB505124, 2-(5-benzo[1,3]dioxol-5-yl-2-tert-butyl-3H-imidazol-4-yl)-6-methylpyridine hydrochloride

#### Further Reading

- Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A (2011). Bone morphogenetic proteins: a critical review. *Cell Signal* **23**: 609–620.
- Clarke DC, Liu X (2008). Decoding the quantitative nature of TGF- $\beta$ /Smad signaling. *Trends Cell Biol* **18**: 430–442.
- Gatza CE, Oh SY, Blobe GC (2010). Roles for the type III TGF- $\beta$  receptor in human cancer. *Cell Signal* **22**: 1163–1174.
- Kang JS, Liu C, Derynck R (2009). New regulatory mechanisms of TGF- $\beta$  receptor function. *Trends Cell Biol* **19**: 385–394.
- Kardassis D, Murphy C, Fotsis T, Moustakas A, Stournaras C (2009). Control of transforming growth factor  $\beta$  signal transduction by small GTPases. *FEBS J* **276**: 2947–2965.
- Li MO, Flavell RA (2008). TGF- $\beta$ : a master of all T cell trades. *Cell* **134**: 392–404.
- Miyazono K, Kamiya Y, Morikawa M (2010). Bone morphogenetic protein receptors and signal transduction. *J Biochem* **147**: 35–51.
- Pardali E, Goumans MJ, Ten DP (2010). Signaling by members of the TGF- $\beta$  family in vascular morphogenesis and disease. *Trends Cell Biol* **20**: 556–567.

- Rider CC, Mulloy B (2010). Bone morphogenetic protein and growth differentiation factor cytokine families and their protein antagonists. *Biochem J* **429**: 1–12.
- Shi Y, Massague J (2003). Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell* **113**: 685–700.
- Sprague AH, Khalil RA (2009). Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochem Pharmacol* **78**: 539–552.
- Xia Y, Schneyer AL (2009). The biology of activin: recent advances in structure, regulation and function. *J Endocrinol* **202**: 1–12.
- Xiao YT, Xiang LX, Shao JZ (2007). Bone morphogenetic protein. *Biochem Biophys Res Commun* **362**: 550–553.
- Yoshimura A, Wakabayashi Y, Mori T (2010). Cellular and molecular basis for the regulation of inflammation by TGF- $\beta$ . *J Biochem* **147**: 781–792.
- Zeng S, Chen J, Shen H (2010). Controlling of bone morphogenetic protein signaling. *Cell Signal* **22**: 888–893.

## References

- Dacosta Byfield S *et al.* (2004). *Mol Pharmacol* **65**: 744–752.
- Vogt J *et al.* (2011). *Cell Signal* **23**: 1831–1842.
- Zhou G *et al.* (2001). *J Clin Invest* **108**: 1167–1174.

# Receptor tyrosine kinases (E.C. 2.7.1.112)

Receptor tyrosine kinases (RTKs) are a family of 58 cell-surface receptors (see Grassot *et al.*, 2003), which transduce signals to polypeptide and protein hormones, cytokines and growth factors. RTKs are of widespread interest not only through physiological functions, but also as drug targets in many types of cancer and other disease states. A high proportion of drugs exploiting these targets are biological, acting to block the receptor or chelate the ligand, thereby preventing the biological activity. RTKs are dimeric proteins and most structurally diverse in the extracellular region, but exhibit marked similarities in the hydrophobic transmembrane region and the intracellular protein tyrosine kinase domain, often split into two regions. Binding of agonist evokes autophosphorylation leading to the stimulation of multiple signal transduction pathways, including phospholipase C- $\gamma$  (see Page S302), mitogen-activated protein kinases (see Page S310) and phosphatidylinositol 3-kinase.

## ErbB (epidermal growth factor) receptor family

**Overview:** ErbB family receptors (ENSM00410000138465) are Class I receptor tyrosine kinases (see Grassot *et al.*, 2003). ErbB2 (also known as HER-2 or NEU, ENSG00000141736) appears to act as an essential partner for the other members of the family without itself being activated by a cognate ligand (Graus-Porta *et al.*, 1997).

Nomenclature	ErbB1	ErbB3	ErbB4
Ensembl ID	ENSG00000146648	ENSG00000065361	ENSG00000178568
Other names	EGF, HER1	HER3	HER4
Endogenous ligands	EGF, amphiregulin, betacellulin, epigen, epiregulin, HB-EGF, TGF $\alpha$	NRG-1, NRG-2	Betacellulin, epiregulin, HB-EGF, NRG-1, NRG-2, NRG-3, NRG-4

[<sup>125</sup>I]-EGF has been used to label the ErbB1 EGF receptor. The extracellular domain of ErbB2 can be targeted by the antibodies trastuzumab and pertuzumab to inhibit ErbB family action. The intracellular ATP-binding site of the tyrosine kinase domain can be inhibited by GW583340 (7.9–8.0, Gaul *et al.*, 2003), gefitinib, erlotinib and tyrphostins AG879 and AG1478.

Ligands of the ErbB family of receptors are peptides including EGF (ENSG00000138798), amphiregulin (also known as colorectal cell-derived growth factor, ENSG00000109321), betacellulin (ENSG00000174808), epigen (ENSG00000182585), epiregulin (ENSG00000124882), heparin-binding EGF-like growth factor (HB-EGF or diphtheria toxin receptor, ENSG00000113070), neuregulins (NRG-1, also known as Neu differentiation factor, acetylcholine receptor-inducing activity, heregulin or glial growth factor, ENSG00000157168; NRG-2, ENSG00000158458; NRG-3, ENSG00000185737 and NRG-4, ENSG00000169752) and transforming growth factor- $\alpha$  (TGF $\alpha$ , ENSG00000163235). These ligands appear to be generated by proteolytic cleavage of cell-surface peptides.

## Insulin receptor family

**Overview:** The circulating peptide hormones insulin and the related insulin-like growth factors (IGF) activate Class II receptor tyrosine kinases (see Grassot *et al.*, 2003), to evoke cellular responses, mediated through multiple intracellular adaptor proteins. Exceptionally amongst the catalytic receptors, the functional receptor in the insulin receptor family is derived from a single gene product, cleaved post-translationally into two peptides, which then cross-link via disulphide bridges to form a heterotetramer. Intriguingly, the endogenous peptide ligands are formed in a parallel fashion with post-translational processing producing a heterodimer linked by disulphide bridges. Signalling through the receptors is mediated through a rapid autophosphorylation event at intracellular tyrosine residues, followed by recruitment of multiple adaptor proteins, notably IRS1 (ENSG00000169047), IRS2 (ENSG00000185950), Shc1 (ENSG00000160691), Grb2 (ENSG00000177885) and Sos1 (ENSG00000115904).

Nomenclature	Insulin	Insulin-like growth factor I	INSRR
Ensembl ID	ENSG00000171105	ENSG00000140443	ENSG00000027644
Other names	CD220 antigen	IGF-I receptor, CD221 antigen	Insulin receptor-related protein, IRR
Endogenous ligands	Insulin (ENSG00000129965)	IGF1 (ENSG00000017427) IGF2 (ENSG000000167244)	–

There is evidence for low potency binding and activation of insulin receptors by IGF1. IGF2 also binds and activates the cation-independent mannose 6-phosphate receptor (CI-MPR, insulin-like growth factor II receptor, 300 kDa mannose 6-phosphate receptor, MPR 300, CD222 antigen ENSG00000197081), which lacks classical signalling capacity and appears to subserve a trafficking role (Macdonald *et al.*, 1988). INSRR, which has a much more discrete localization, being predominant in the kidney (Kurachi *et al.*, 1992), currently lacks a cognate ligand or evidence for functional impact.

PQ401 inhibits the insulin-like growth factor receptor (Gable *et al.*, 2006).

**PDGF (platelet-derived growth factor) receptor family**

**Overview:** PDGF receptors are Class III RTKs, which function as homo- or heterodimers.

Nomenclature	PDGFR $\alpha$	PDGFR $\beta$	KIT	CSF1R	FLT3
Ensembl ID	ENSG00000134853	ENSG00000113721	ENSG00000157404	ENSG00000182578	ENSG00000122025
Other names	Platelet-derived growth factor receptor $\alpha$ , CD140a, PDGFR2	Platelet-derived growth factor receptor $\beta$ , CD140b, PDGFR1, JTK12, PDGFR	CD117, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, C-Kit, PBT, stem cell growth factor receptor, SCFR	Colony stimulating factor 1 receptor, CD115, CSFR, C-FMS, FMS	FMS-related tyrosine kinase 3, CD135, FLK2, STK1
Endogenous ligands	PDGF	PDGF	SCF	CSF1, CSF2, CSF3	FLT3L

Endogenous ligands of PDGF receptors are homo- or heterodimeric: PDGFA (PDGF1, ENSG00000197461), PDGFB (SIS, SSV, ENSG00000100311), PDGFC (fallotin, SCDGF, ENSG00000145431) and PDGFD (IEGF, MSTP036, SCDGF-B, ENSG00000170962) combine as homo- or heterodimers to activate homo- or heterodimeric PDGF receptors. SCF (stem cell factor, KITLG, ENSG00000049130) is a dimeric ligand for KIT. CSF1R may be activated by colony stimulating factor 1 (macrophage-CSE, CSF1, ENSG00000184371), CSF2 (granulocyte-macrophage CSE, GM-CSE, ENSG00000164400) and CSF3 (ENSG00000108342). FLT3L is the cognate ligand of FLT3 (ENSG00000090554).

5'-Fluorouridindirubinoxime has been described as a selective FLT3 inhibitor (Choi *et al.*, 2010).

**FGF (fibroblast growth factor) receptor family**

**Overview:** Fibroblast growth factor (FGF) family receptors are members of the Ret family (ENSM0025000000009), which respond to members of the FGF family. Ret (rearranged during transfection, ENSG00000165731, also known as CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET51) is a signalling partner for the GDNF family of receptors (see Page S194). FGF receptors function as homo- and heterodimers.

Nomenclature	FGFR1	FGFR2	FGFR3	FGFR4
Ensembl ID	ENSG00000077782	ENSG00000066468	ENSG00000068078	ENSG00000160867
Other names	CD331, BFGFR, CEK, FLG, FLT2, H2, H3, H4, H5, KAL2, N-SAM	CD332, BEK, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25	CD333, ACH, CEK2, JTK4	CD334, JTK2
Endogenous ligands	FGF1, FGF2, FGF4 > FGF6 (Ornitz <i>et al.</i> , 1996)	FGF1 > FGF4, FGF7 FGF9 > FGF2, FGF6 (Ornitz <i>et al.</i> , 1996)	FGF1, FGF2, FGF9 > FGF4, FGF8 (Ornitz <i>et al.</i> , 1996)	FGF1, FGF2, FGF4, FGF9 > FGF6, FGF8 (Ornitz <i>et al.</i> , 1996)

Splice variation of the receptors can influence agonist responses.

FGFRL1 (ENSG00000127418) is a truncated kinase-null analogue. Mutations of Ret (and GDNF, see Page S194) genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

At least 22 members of the FGF gene family have been identified in the human genome (see Itoh and Ornitz, 2011). Within this group, subfamilies of FGF may be divided into canonical, intracellular and hormone-like FGFs. FGF1-FGF10 (ENSG00000113578, ENSG00000138685, ENSG00000186895, ENSG00000075388, ENSG00000138675, ENSG00000111241, ENSG00000140285, ENSG00000107831, ENSG00000102678, ENSG00000070193) have been identified to act through FGF receptors, while FGF11-14 appear to signal through intracellular targets. Other family members are less well characterized.

PD173074 has been described to inhibit FGFR1 and FGFR3 (Skaper *et al.*, 2000).

**VEGF (vascular endothelial growth factor) receptor family**

**Overview:** VEGF receptors (ENSM00440000236870) are homo- and heterodimeric proteins, which respond to VEGF proteins, some of which undergo proteolysis prior to receptor binding. Splice variants of VEGFR1 and VEGFR2 generate truncated proteins limited to the extracellular domains, capable of homodimerisation and binding VEGF ligands as a soluble, non-signalling entity.

Nomenclature	VEGFR1	VEGFR2	VEGFR3
Ensembl ID	ENSG00000102755	ENSG00000128052	ENSG00000037280
Other names	FMS-like tyrosine kinase 1, FLT1	KDR, kinase insert domain protein receptor, CD309, FLK1	FMS-like tyrosine kinase 4, FLT4, PCL
Endogenous ligands	VEGFA, VEGFB	VEGFA, VEGFC, VEGFE	VEGFC, VEGFD, VEGFE

Ligands at VEGF receptors are typically homodimeric: VEGFA (ENSG00000112715, also known as vascular permeability factor), VEGFB (ENSG00000173511, also known as VEGF-related factor or VRF), VEGFC (ENSG00000150630), VEGFD (ENSG00000165197, also known as c-fos induced growth factor, FIGF) or placental growth factor (ENSG00000119630, also known as PlGF). VEGFA is able to activate VEGFR1 homodimers, VEGFR1/2 heterodimers and VEGFR2/3 heterodimers. VEGFB and PlGF activate VEGFR1 homodimers, while VEGFC and VEGFD activate VEGFR2/3 heterodimers and VEGFR3 homodimers, and, following proteolysis, VEGFR2 homodimers.

### HGF (hepatocyte growth factor) receptor family

**Overview:** HGF receptors regulate maturation of the liver in the embryo, as well as having roles in the adult, for example, in the innate immune system.

Nomenclature	HGFR	MST1R
Ensembl ID	ENSG00000105976	ENSG00000164078
Other names	MET, RCCP2, hepatocyte growth factor receptor	CD136, CDw136, PTK8, RON, macrophage stimulating 1 receptor , c-met-related tyrosine kinase
Endogenous ligands	HGF	MST1

Ligands at the HGF receptor family include HGF (ENSG0000019991, also known as heparin-binding epidermal growth factor-like factor 1, HEGF), synthesized as a single gene product, which is post-translationally processed to yield a heterodimer linked by a disulphide bridge. The maturation of HGF is enhanced by a serine proteinase, HGF activating complex (HGFAC, ENSG00000109758), and inhibited by HGF-A inhibitor 1, HAI (SPINT1, ENSG00000166145), a serine protease inhibitor. Macrophage stimulating protein 1 (MST1, ENSG00000173531, also known as hepatocyte growth factor-like) is a related gene.

SU11274 is an inhibitor of the HGF receptor (Sattler *et al.*, 2003), with the possibility of further targets (Arena *et al.*, 2007).

### Neurotrophin receptor family

**Overview:** Various isoforms of neurotrophin receptors exist, including truncated forms of trkB and trkC, which lack catalytic domains. p75, which has homologies with tumour necrosis factor receptors (see Page S211), lacks a tyrosine kinase domain, but can signal *via* ceramide release and nuclear factor  $\kappa$ B (NF- $\kappa$ B) activation. Both trkA and trkB contain two leucine-rich regions and can exist in monomeric or dimeric forms.

Nomenclature	trkA	trkB	trkC	p75
Ensembl ID	ENSG00000198400	ENSG00000148053	ENSG00000140538	ENSG00000064300
Other names	gp140 <sup>trk</sup> , high-affinity, slow-dissociating NGF receptor	gp145 <sup>trkB</sup>	gp145 <sup>trkC</sup>	p75 <sup>NTR</sup> , low-affinity neurotrophin receptor, NGFR
Endogenous ligands	NGF>NT3	BDNF, NT4/5>NT3	NT3	NGF, BDNF, NT3, NT4/5

[<sup>125</sup>I]-NGF and [<sup>125</sup>I]-BDNF have been used to label the trkA and trkB receptor, respectively. The selectivity of small molecule peptide mimetics of NGF has not been ascertained (Massa *et al.*, 2003). There are, as yet, no selective antagonists, but activation can be blocked using anti-neurotrophin antisera or selective immunoadhesins that sequester neurotrophins (Shelton *et al.*, 1995). p75 influences the binding of NGF and NT3 to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neurones, it binds NT3 with comparable affinity to trkC (Dechant *et al.*, 1997).

The endogenous ligands of neurotrophin receptors are small proteins (ca. 120 aa) and include nerve growth factor (NGF, ENSG00000134259), neurotrophin (NT) 3 (ENSG00000185652), NT4/5 (ENSG00000167744) and brain-derived neurotrophic factor (BDNF, ENSG00000176697).

The intracellular tyrosine kinase activity of the trkA receptor can be inhibited by GW441756 (8.7, Wood *et al.*, 2004) and tyrphostin AG879 (Ohmichi *et al.*, 1993).

### Ephrin receptor family

Ephrin receptors (ENSM0025000000121) have a role in the regulation of neuronal development. Their ligands are membrane-associated proteins, although the relationship between ligands and receptors has been incompletely defined.

Nomenclature	EPHA1	EPHA2	EPHA3	EPHA4	EPHA5
Ensembl ID	ENSG00000146904	ENSG00000142627	ENSG00000044524	ENSG00000116106	ENSG00000145242
Other names	EPH, EPHT, EPHT1	ECK	ETK, ETK1, HEK, HEK4, TYRO4	Hek8, TYRO1	CEK7, EHK1, Hek7, TYRO4

Nomenclature	EPHA6	EPHA7	EPHA8	EPHA10
Ensembl ID	ENSG00000080224	ENSG00000135333	ENSG00000070886	ENSG00000183317
Other names	EHK2	EHK3, HEK11	EEK, HEK3	–

Nomenclature	EPHB1	EPHB2	EPHB3	EPHB4	EPHB6
Ensembl ID	ENSG00000154928	ENSG00000133216	ENSG00000182580	ENSG00000196411	ENSG00000106123
Other names	EPHT2, Hek6	DRT, EPHT3, ERK, Hek5, Tyro5	ETK2, Hek2, Tyro6	HTK, Tyro11	HEP

Ligands at the ephrin receptors may be divided into two families, ephrin A and ephrin B. Ephrin A are glycosylphosphatidylinositol-linked proteins: EFNA1 (ENSG00000169242, ECKLG, EPLG1, LERK1, TNFAIP4), EFNA2 (ENSG00000099617, ELF-1, EPLG6, LERK6), EFNA3 (ENSG00000143590, EHK1-L, EPLG3, LERK3), EFNA4 (ENSG00000243364, EPLG4, LERK4) and EFNA5 (ENSG00000184349, AF1, EPLG7, LERK7). Ephrin B (ENSM0025000002014) are single TM proteins: EFNB1 (ENSG00000090776), EFNB2 (ENSG00000125266) and EFNB3 (ENSG00000108947).

#### TAM (or AXL) receptor family

Members of this RTK family (ENSM00500000269872) represented a novel structural motif, when sequenced. The ligands for this family are able to bind to negatively-charged surfaces of apoptotic cells.

Nomenclature	AXL	TYRO3	MERTK
Ensembl ID	ENSG00000167601	ENSG00000092445	ENSG00000153208
Other names	JTK11, UFO	Br, Dtk, RSE, Sky, Tif	c-mer proto-oncogene tyrosine kinase, mer, RP38
Endogenous ligands	Gas6 (Nagata <i>et al.</i> , 1996), protein S (Stitt <i>et al.</i> , 1995)	Gas6 (Nagata <i>et al.</i> , 1996), protein S (Stitt <i>et al.</i> , 1995)	Gas6 (Nagata <i>et al.</i> , 1996)

Gas6 (ENSG00000183087, also known as growth arrest specific protein 6, AXLLG, AXSF) and protein S  $\alpha$  (ENSG00000184500) are secreted plasma proteins which undergo vitamin K-dependent post-translational modifications through the generation of carboxyglutamate-rich domains.

#### Leukocyte tyrosine kinase (LTK) receptor family

The LTK family (ENSM00500000270379) appear to lack endogenous ligands.

Nomenclature	LTK	ALK	ROS1
Ensembl ID	ENSG00000062524	ENSG00000171094	ENSG00000047936
Other names	Leukocyte tyrosine kinase, TYK1	Anaplastic lymphoma kinase, CD246	c-ros-1, MCF3

Crizotinib appears to be a selective ALK inhibitor acting on the tyrosine kinase activity (see Gerber and Minna, 2010).

#### TIE family of angiopoietin receptors

The TIE family (ENSM00420000140591) were initially associated with formation of blood vessels and respond to angiopoietins.



Nomenclature	TIE1	TIE2
Ensembl ID	ENSG00000066056	ENSG00000120156
Other names	Tyrosine kinase with immunoglobulin-like and EGF-like domains 1, JTK14	TEK tyrosine kinase, endothelial, CD202b, VMCM, VMCM1
Endogenous ligands	–	Angiopoietin 1, angiopoietin 4

Endogenous ligands (ENSM00500000269808) are angiopoietin 1 (ANGPT1, ENSG00000154188), angiopoietin 2 (Ang2, ENSG00000091879), and angiopoietin 4 (ANGPT4 ENSG00000101280) Related sequences include angiotensin protein-like 1 (ANGPTL1, ENSG00000116194, also known as angiopoietin 3) and ANGPTL7 (ENSG00000171819, AngX, CDT6). Angiopoietin 2 appears to act as an endogenous antagonist of angiopoietin 1 function.

### DDR (collagen receptor) family

**Overview:** Collagen receptors (ENSM00260000050411) are structurally-related membrane protein tyrosine kinases activated by collagen. Collagen is probably the most abundant protein in man, with at least 29 families of genes encoding proteins, which undergo splice variation and post-translational processing, and may exist in monomeric or polymeric forms, producing a triple-stranded, twine-like structure.

Nomenclature	DDR1	DDR2
Ensembl ID	ENSG00000204580	ENSG00000162733
Other names	Epithelial discoidin domain-containing receptor 1, epithelial discoidin domain receptor 1, neuroepithelial tyrosine kinase, cell adhesion kinase, TRK E, protein-tyrosine kinase RTK 6, HGK2, CD167 antigen-like family member A, CD167a antigen	Discoidin domain-containing receptor 2 Precursor (Discoidin domain receptor 2, receptor protein-tyrosine kinase TKT, tyrosine-protein kinase TYRO10, neurotrophic tyrosine kinase, receptor-related 3, CD167 antigen-like family member B, CD167b antigen

In man, principal family members include COL1A1 (ENSG00000108821), COL2A1 (ENSG00000139219), COL3A1 (ENSG00000168542) and COL4A1 (ENSG00000187498).

### ROR family and other RTKs

Members of the ROR family (ENSM00510000502747) appear to be activated by ligands complexing with other cell-surface proteins.

Nomenclature	ROR1	ROR2	MUSK	PTK7	RYK
Ensembl ID	ENSG00000185483	ENSG00000169071	ENSG00000030304	ENSG00000112655	ENSG00000163785
Other names	NTRKR1, receptor tyrosine kinase-like orphan receptor 1	BDB, BDB1, NTRKR2, receptor tyrosine kinase-like orphan receptor 2	Muscle, skeletal, receptor tyrosine kinase	CCK4	JTK5, JTK5A, RYK1

ROR1 and ROR2 appear to be activated by Wnt5a (ENSG00000114251) binding to a Frizzled receptor (see Page S51) and forming a cell-surface multiprotein complex (Grumolato *et al.*, 2010). Agrin (AGRN, ENSG00000188157) forms a complex with LRP4 (ENSG00000134569) to activate MUSK (Kim *et al.*, 2008). PTK7 and RYK also appear to interact with the Wnt signalling system (Fradkin *et al.*, 2010; Puppo *et al.*, 2011).

**Abbreviations:** **BDNF**, brain-derived neurotrophic factor; **erlotinib**, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, also known as OSI774; **gefitinib**, *N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-yl)propanoic acid, also known as ZD1839; **GW441756**, 1,3-dihydro-3-[(1-methyl-1*H*-indol-3-yl)methylene]-2*H*-pyrrolo[3,2-*b*]pyridin-2-one hydrochloride; **GW583340**, *N*-(3-chloro-4-[[3-fluorophenyl]methoxy]phenyl)-6-(2-[[2-[[methylsulfonyl]ethyl]amino]methyl]-4-thiazolyl)-4-quinazolinamine dihydrochloride; **IGF**, insulin-like growth factor; **NGF**, nerve growth factor; **PD173074**, 1-tert-butyl-3-[2-[4-(diethylamino)butylamino]-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl]urea; **PQ401**, 1-(5-chloro-2-methoxyphenyl)-3-(2-methylquinolin-4-yl)urea; **tyrphostin AG1478**, *N*-(3-chlorophenyl)-6,7-dimethoxyquinazolin-4-amine hydrochloride; **tyrphostin AG879**,  $\alpha$ -cyano-(3,5-di-*t*-butyl-4-hydroxy)thiocinnamide

### Further Reading

- Acevedo VD, Ittmann M, Spencer DM (2009). Paths of FGFR-driven tumorigenesis. *Cell Cycle* 8: 580–588.
- Acquaviva J, Wong R, Charest A (2009). The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. *Biochim Biophys Acta* 1795: 37–52.
- Augustin HG, Koh GY, Thurston G, Alitalo K (2009). Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. *Nat Rev Mol Cell Biol* 10: 165–177.

- Avraham R, Yarden Y (2011). Feedback regulation of EGFR signalling: decision making by early and delayed loops. *Nat Rev Mol Cell Biol* **12**: 104–117.
- Banerjee A, Macdonald ML, Borgmann-Winter KE, Hahn CG (2010). Neuregulin 1-erbB4 pathway in schizophrenia: from genes to an interactome. *Brain Res Bull* **83**: 132–139.
- Baselga J, Swain SM (2009). Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer* **9**: 463–475.
- Beekman R, Touw IP (2010). G-CSF and its receptor in myeloid malignancy. *Blood* **115**: 5131–5136.
- Buonanno A (2010). The neuregulin signaling pathway and schizophrenia: from genes to synapses and neural circuits. *Brain Res Bull* **83**: 122–131.
- da Cunha Santos G, Shepherd FA, Tsao MS (2011). EGFR mutations and lung cancer. *Annu Rev Pathol* **6**: 49–69.
- De Palma M, Naldini L (2009). Tie2-expressing monocytes (TEMs): novel targets and vehicles of anticancer therapy? *Biochim Biophys Acta* **1796**: 5–10.
- Eck MJ, Yun CH (2010). Structural and mechanistic underpinnings of the differential drug sensitivity of EGFR mutations in non-small cell lung cancer. *Biochim Biophys Acta* **1804**: 559–566.
- Feigin ME, Muthuswamy SK (2009). ErbB receptors and cell polarity: new pathways and paradigms for understanding cell migration and invasion. *Exp Cell Res* **315**: 707–716.
- Ferguson KM (2008). Structure-based view of epidermal growth factor receptor regulation. *Annu Rev Biophys* **37**: 353–373.
- Fiske WH, Threadgill D, Coffey RJ (2009). ERBBs in the gastrointestinal tract: recent progress and new perspectives. *Exp Cell Res* **315**: 583–601.
- Frank-Raue K, Rondot S, Raue F (2010). Molecular genetics and phenomics of RET mutations: impact on prognosis of MTC. *Mol Cell Endocrinol* **322**: 2–7.
- Fry WH, Kotelawala L, Sweeney C, Carraway KL III (2009). Mechanisms of ErbB receptor negative regulation and relevance in cancer. *Exp Cell Res* **315**: 697–706.
- Garcia-Sainz JA, Romero-Avila MT, Medina LD (2010). Dissecting how receptor tyrosine kinases modulate G protein-coupled receptor function. *Eur J Pharmacol* **648**: 1–5.
- Gerber DE, Minna JD (2010). ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. *Cancer Cell* **18**: 548–551.
- Giustina A, Mazziotti G, Canalis E (2008). Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev* **29**: 535–559.
- Gow DJ, Sester DP, Hume DA (2010). CSF-1, IGF-1, and the control of postnatal growth and development. *J Leukoc Biol* **88**: 475–481.
- Grassot J, Mouchiroud G, Perriere G (2003). RTKdb: database of Receptor Tyrosine Kinase. *Nucleic Acids Res* **31**: 353–358.
- Green JL, Kuntz SG, Sternberg PW (2008). Ror receptor tyrosine kinases: orphans no more. *Trends Cell Biol* **18**: 536–544.
- Harada D, Yamanaka Y, Ueda K, Tanaka H, Seino Y (2009). FGFR3-related dwarfism and cell signaling. *J Bone Miner Metab* **27**: 9–15.
- Hato T, Tabata M, Oike Y (2008). The role of angiopoietin-like proteins in angiogenesis and metabolism. *Trends Cardiovasc Med* **18**: 6–14.
- Holt RI, Sonksen PH (2008). Growth hormone, IGF-I and insulin and their abuse in sport. *Br J Pharmacol* **154**: 542–556.
- Hu Y, Bouloux PM (2010). Novel insights in FGFR1 regulation: lessons from Kallmann syndrome. *Trends Endocrinol Metab* **21**: 385–393.
- Huang H, Bhat A, Woodnutt G, Lappe R (2010). Targeting the ANGPT-TIE2 pathway in malignancy. *Nat Rev Cancer* **10**: 575–585.
- Itoh N, Ornitz DM (2011). Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J Biochem* **149**: 121–130.
- Jaaro-Peled H, Hayashi-Takagi A, Seshadri S, Kamiya A, Brandon NJ, Sawa A (2009). Neurodevelopmental mechanisms of schizophrenia: understanding disturbed postnatal brain maturation through neuregulin-1-ErbB4 and DISC1. *Trends Neurosci* **32**: 485–495.
- Kadomatsu T, Tabata M, Oike Y (2011). Angiopoietin-like proteins: emerging targets for treatment of obesity and related metabolic diseases. *FEBS J* **278**: 559–564.
- Kalkman HO (2009). Altered growth factor signaling pathways as the basis of aberrant stem cell maturation in schizophrenia. *Pharmacol Ther* **121**: 115–122.
- Karam CS, Ballon JS, Bivens NM, Freyberg Z, Girgis RR, Lizardi-Ortiz JE *et al.* (2010). Signaling pathways in schizophrenia: emerging targets and therapeutic strategies. *Trends Pharmacol Sci* **31**: 381–390.
- Klein R (2009). Bidirectional modulation of synaptic functions by Eph/ephrin signaling. *Nat Neurosci* **12**: 15–20.
- Kleinberg DL, Wood TL, Furth PA, Lee AV (2009). Growth hormone and insulin-like growth factor-I in the transition from normal mammary development to preneoplastic mammary lesions. *Endocr Rev* **30**: 51–74.
- Knights V, Cook SJ (2010). De-regulated FGF receptors as therapeutic targets in cancer. *Pharmacol Ther* **125**: 105–117.
- Koch S, Tugues S, Li X, Gualandi L, Claesson-Welsh L (2011). Signal transduction by vascular endothelial growth factor receptors. *Biochem J* **437**: 169–183.
- Kosaka N, Sakamoto H, Terada M, Ochiya T (2009). Pleiotropic function of FGF-4: its role in development and stem cells. *Dev Dyn* **238**: 265–276.
- Laron Z (2008). Insulin – a growth hormone. *Arch Physiol Biochem* **114**: 11–16.
- Lemke G, Rothlin CV (2008). Immunobiology of the TAM receptors. *Nat Rev Immunol* **8**: 327–336.
- Lemmon MA, Schlessinger J (2010). Cell signaling by receptor tyrosine kinases. *Cell* **141**: 1117–1134.
- Lichtenstein L, Kersten S (2010). Modulation of plasma TG lipolysis by Angiopoietin-like proteins and GPIIb/IIIa. *Biochim Biophys Acta* **1801**: 415–420.
- Lin SX, Chen J, Mazumdar M, Poirier D, Wang C, Azzi A *et al.* (2010). Molecular therapy of breast cancer: progress and future directions. *Nat Rev Endocrinol* **6**: 485–493.
- Lu X, Kang Y (2010). Epidermal growth factor signalling and bone metastasis. *Br J Cancer* **102**: 457–461.
- Masson K, Ronnstrand L (2009). Oncogenic signaling from the hematopoietic growth factor receptors c-Kit and Flt3. *Cell Signal* **21**: 1717–1726.
- Minami Y, Oishi I, Endo M, Nishita M (2010). Ror-family receptor tyrosine kinases in noncanonical Wnt signaling: their implications in developmental morphogenesis and human diseases. *Dev Dyn* **239**: 1–15.
- Morandi A, Plaza-Menacho I, Isacke CM (2011). RET in breast cancer: functional and therapeutic implications. *Trends Mol Med* **17**: 149–157.
- Nakamura T, Sakai K, Nakamura T, Matsumoto K (2011). Hepatocyte growth factor twenty years on: much more than a growth factor. *J Gastroenterol Hepatol* **26** (Suppl. 1): 188–202.
- Nishita M, Enomoto M, Yamagata K, Minami Y (2010). Cell/tissue-tropic functions of Wnt5a signaling in normal and cancer cells. *Trends Cell Biol* **20**: 346–354.
- Pasquale EB (2008). Eph-ephrin bidirectional signaling in physiology and disease. *Cell* **133**: 38–52.
- Pines G, Kostler WJ, Yarden Y (2010). Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. *FEBS Lett* **584**: 2699–2706.
- Pitulescu ME, Adams RH (2010). Eph/ephrin molecules—a hub for signaling and endocytosis. *Genes Dev* **24**: 2480–2492.
- Plant AL, Bhadriraju K, Spurlin TA, Elliott JT (2009). Cell response to matrix mechanics: focus on collagen. *Biochim Biophys Acta* **1793**: 893–902.
- Pyne NJ, Pyne S (2011). Receptor tyrosine kinase-G-protein-coupled receptor signalling platforms: out of the shadow? *Trends Pharmacol Sci* **32**: 443–450.
- Ratushny V, Atsaturov I, Burtress BA, Golemis EA, Silverman JS (2009). Targeting EGFR resistance networks in head and neck cancer. *Cell Signal* **21**: 1255–1268.

- Schneider MR, Sibilia M, Erben RG (2009). The EGFR network in bone biology and pathology. *Trends Endocrinol Metab* **20**: 517–524.
- Sharif A, Prevot V (2010). ErbB receptor signaling in astrocytes: a mediator of neuron-glia communication in the mature central nervous system. *Neurochem Int* **57**: 344–358.
- Shoulders MD, Raines RT (2009). Collagen structure and stability. *Annu Rev Biochem* **78**: 929–958.
- Sorkin A, Goh LK (2009). Endocytosis and intracellular trafficking of ErbBs. *Exp Cell Res* **315**: 683–696.
- Takano H, Ueda K, Hasegawa H, Komuro I (2007). G-CSF therapy for acute myocardial infarction. *Trends Pharmacol Sci* **28**: 512–517.
- Underwood CK, Coulson EJ (2008). The p75 neurotrophin receptor. *Int J Biochem Cell Biol* **40**: 1664–1668.
- Vellosio CP (2008). Regulation of muscle mass by growth hormone and IGF-I. *Br J Pharmacol* **154**: 557–568.
- Villegas SN, Canham M, Brickman JM (2010). FGF signalling as a mediator of lineage transitions – evidence from embryonic stem cell differentiation. *J Cell Biochem* **110**: 10–20.
- Wesche J, Haglund K, Haugsten EM (2011). Fibroblast growth factors and their receptors in cancer. *Biochem J* **437**: 199–213.
- Wieduwilt MJ, Moasser MM (2008). The epidermal growth factor receptor family: biology driving targeted therapeutics. *Cell Mol Life Sci* **65**: 1566–1584.
- Wilson KJ, Gilmore JL, Foley J, Lemmon MA, Riese DJ (2009). Functional selectivity of EGF family peptide growth factors: implications for cancer. *Pharmacol Ther* **122**: 1–8.
- Wu X, Liu N (2010). The role of Ang/Tie signaling in lymphangiogenesis. *Lymphology* **43**: 59–72.
- Xu AM, Huang PH (2010). Receptor tyrosine kinase coactivation networks in cancer. *Cancer Res* **70**: 3857–3860.
- Xu J, Messina JL (2009). Crosstalk between growth hormone and insulin signaling. *Vitam Horm* **80**: 125–153.
- Zeng F, Singh AB, Harris RC (2009). The role of the EGF family of ligands and receptors in renal development, physiology and pathophysiology. *Exp Cell Res* **315**: 602–610.

## References

- Arena S *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 11412–11417.
- Choi SJ *et al.* (2010). *Bioorg Med Chem Lett* **20**: 2033–2037.
- Dechant G *et al.* (1997). *J Neurosci* **17**: 5281–5287.
- Fradkin LG *et al.* (2010). *Trends Neurosci* **33**: 84–92.
- Gable KL *et al.* (2006). *Mol Cancer Ther* **5**: 1079–1086.
- Gaul MD *et al.* (2003). *Bioorg Med Chem Lett* **13**: 637–640.
- Graus-Porta D *et al.* (1997). *EMBO J* **16**: 1647–1655.
- Grumolato L *et al.* (2010). *Genes Dev* **24**: 2517–2530.
- Kim N *et al.* (2008). *Cell* **135**: 334–342.
- Kurachi H *et al.* (1992). *Biochem Biophys Res Commun* **187**: 934–939.
- MacDonald RG *et al.* (1988). *Science* **239**: 1134–1137.
- Massa SM *et al.* (2003). *J Mol Neurosci* **20**: 323–326.
- Nagata K *et al.* (1996). *J Biol Chem* **271**: 30022–30027.
- Ohmichi M *et al.* (1993). *Biochemistry* **32**: 4650–4658.
- Ornitz DM *et al.* (1996). *J Biol Chem* **271**: 15292–15297.
- Puppo F *et al.* (2011). *EMBO Rep* **12**: 43–49.
- Sattler M *et al.* (2003). *Cancer Res* **63**: 5462–5469.
- Stitt TN *et al.* (1995). *Cell* **80**: 661–670.
- Shelton DL *et al.* (1995). *J Neurosci* **15**: 477–491.
- Skaper SD *et al.* (2000). *J Neurochem* **75**: 1520–1527.
- Wood ER *et al.* (2004). *Bioorg Med Chem Lett* **14**: 953–957.

# Receptor tyrosine phosphatases (RTP, EC 3.1.3.48)

Overview: receptor tyrosine phosphatases (RTP) are cell-surface proteins with a single TM region and intracellular phosphotyrosine phosphatase activity. Many family members exhibit constitutive activity in heterologous expression, dephosphorylating intracellular targets such as Src tyrosine kinase (ENSG00000197122) to activate signalling cascades. Family members bind components of the extracellular matrix or cell-surface proteins indicating a role in intercellular communication.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Type A	PTPRA	ENSG00000132670	Leukocyte common antigen-related peptide, HLPR, HPTPA, LRP, PTPA, PTPRL2, RPTPA
Type B	PTPRB	ENSG00000127329	R-PTP-beta, vascular endothelial protein tyrosine phosphatase, VEPTP
Type C	PTPRC	ENSG00000081237	CD45, T200 leukocyte common antigen, gp180
Type D	PTPRD	ENSG00000153707	HPTP, R-PTP-delta
Type E	PTPRE	ENSG00000132334	PTPE, R-PTP-epsilon
Type F	PTPRF	ENSG00000142949	Leukocyte antigen-related PTP receptor, LAR
Type G	PTPRG	ENSG00000144724	R-PTP-gamma
Type H	PTPRH	ENSG00000080031	Stomach cancer-associated protein tyrosine phosphatase 1, SAP1
Type J	PTPRJ	ENSG00000149177	R-PTP-eta, CD148, density-enhanced phosphatase 1, DEP1, susceptibility to colon cancer 1 homologue, SCC1
Type K	PTPRK	ENSG00000152894	R-PTP-kappa
Type M	PTPRM	ENSG00000173482	R-PTP-mu, PTPRL1, RPTPM, RPTPU, hR-PTPu
Type N	PTPRN	ENSG00000054356	Islet cell antigen 2, IA-2
Type N2	PTPRN2	ENSG00000155093	Islet cell antigen 2 $\beta$ , IA-2 $\beta$ , phogrin, ICAAR
Type O	PTPRO	ENSG00000151490	PTP-phi, PTPase U2, glomerular epithelial protein 1, GLEPP1, osteoclastic transmembrane protein-tyrosine phosphatase, NPHS6, PTP-OC
Type Q	PTPRQ	ENSG00000139304	PTPGMC1
Type R	PTPRR	ENSG00000153233	Ch-1 PTPase; NC-PTPCOM1; R-PTP-R; ch-1PTPase, EC-PTP, PCPTP1, PTP-SL, PTPBR7, PTPRQ
Type S	PTPRS	ENSG00000105426	R-PTP-sigma
Type T	PTPRT	ENSG00000196090	RPTP-rho
Type U	PTPRU	ENSG00000060656	R-PTP-psi, pancreatic carcinoma phosphatase 2, PCP-2, PTPU2
Type Z1	PTPRZ1	ENSG00000106278	Phosphacan, R-PTP-zeta-2, PTP18, PTPRZ, PTPZ, RPTPB, RPTPZ2

## Further Reading

- Granot-Attas S, Elson A (2008). Protein tyrosine phosphatases in osteoclast differentiation, adhesion, and bone resorption. *Eur J Cell Biol* **87**: 479–490.
- Hendriks WJ, Dilaver G, Noordman YE, Kremer B, Fransen JA (2009). PTPRR protein tyrosine phosphatase isoforms and locomotion of vesicles and mice. *Cerebellum* **8**: 80–88.
- Hermiston ML, Zikherman J, Zhu JW (2009). CD45, CD148, and Lyp/Pep: critical phosphatases regulating Src family kinase signaling networks in immune cells. *Immunol Rev* **228**: 288–311.
- Schmitt I, Bitoun E, Manto M (2009). PTPRR, cerebellum, and motor coordination. *Cerebellum* **8**: 71–73.
- Torii S (2009). Expression and function of IA-2 family proteins, unique neuroendocrine-specific protein-tyrosine phosphatases. *Endocr J* **56**: 639–648.
- Vang T, Miletic AV, Arimura Y, Tautz L, Rickert RC, Mustelin T (2008). Protein tyrosine phosphatases in autoimmunity. *Annu Rev Immunol* **26**: 29–55.

# Tumour necrosis factor (TNF) family

**Overview:** The TNF receptor superfamily (TNFRSF) displays limited homology beyond an extracellular domain rich in cysteine residues and is activated by at least 18 different human homologues of TNF referred to as the TNF superfamily (TNFSF). Some homologues lacking transmembrane and cytoplasmic domains function as decoy receptors binding ligand without inducing cell signalling. Many of these receptors and ligands function as multimeric entities. Signalling through these receptors is complex and involves interaction with cytoplasmic adaptor proteins (such as TRADD and TRAF1). Several of these receptors contain cytoplasmic motifs known as 'death domains', which upon activation serve to recruit death domain- and death effector domain-containing proteins crucial for the initiation of an apoptotic response. Additional signalling pathways include the regulation of the nuclear factor  $\kappa$ B or mitogen-activated protein kinase (see Page S310) pathways. Pharmacological manipulation of these receptors is mainly enacted through chelating the endogenous agonists with humanised monoclonal antibodies (e.g. infliximab or adalimumab) or recombinant fusion proteins of IgG and soluble receptors (e.g. etanercept). Some mutated forms of TNF ligands are capable of selecting for different receptor subtypes.

Nomenclature	Other names	Ensembl ID	Adaptor proteins	Endogenous ligands
TNFRSF1A	TNFR1, CD120a, p55TNFR, TNFAR, TNFR60	ENSG00000067182	TRADD	TNFSF1, TNFSF2
TNFRSF1B	TNFR2, CD120b, p75TNFR, p80, TNFBR	ENSG00000028137	TRAF1, 2, 5	TNFSF1, TNFSF2
TNFRSF3	TNFR III, LTBR, TNFCR, TNFR-RP, TNFR2-RP, CD18	ENSG00000111321	TRAF3, 4, 5	TNFSF3, TNFSF14
TNFRSF4	OX-40, ACT35, TXGP1L, CD134	ENSG00000186827	TRAF1, 2, 3, 5	TNFSF4
TNFRSF5	CD40, Bp50, p50	ENSG00000101017	TRAF1, 2, 3, 5, 6	TNFSF5
TNFRSF6	Fas, CD95, APO-1, APT1, TNFRSF6A	ENSG00000026103	FADD	TNFSF6
TNFRSF7	CD27, S152, Tp55, T14	ENSG00000139193	TRAF2, SIVA	TNFSF7
TNFRSF8	CD30, Ki-1	ENSG00000120949	TRAF1, 2, 3, 5	TNFSF8
TNFRSF9	4-1BB, CDw137, ILA	ENSG00000049249	TRAF1, 2, 3	TNFSF9
TNFRSF10A	DR4, TNF-related apoptosis-inducing ligand receptor 1, TRAIL-R1, APO-2, CD261	ENSG00000104689	FADD	TNFSF10
TNFRSF10B	DR5, TNF-related apoptosis-inducing ligand receptor 2, TRAIL-R2, KILLER, CD262, TRICK2A, TRICKB	ENSG00000120889	FADD	TNFSF10
TNFRSF11A	Receptor activator of NF- $\kappa$ B, RANK, osteoclast differentiation factor receptor, ODFR, TRANCE-R, CD265	ENSG00000141655	TRAF1, 2, 3, 5, 6	TNFSF11
TNFRSF11B	Osteoprotegerin, OPG, osteoclastogenesis inhibitory factor, OCIF, TR1	ENSG00000164761	–	TNFSF11
TNFRSF12	TRS, WSL-1, LARD, WSL-LR, apoptosis-mediating receptor DR3, apoptosis-mediating receptor TRAMP, death domain receptor 3	ENSG00000171680	TRADD	TNFSF15, TNFSF12
TNFRSF12A	TWEAK-R, Fn14, FGF-inducible 14, CD266 antigen	ENSG00000006327	TRAF1, 2, 3, 5	TNFSF12
TNFRSF13B	Transmembrane activator and CAML interactor, TACI, CD267	ENSG00000108516	TRAF2, 5, 6	TNFSF13B
TNFRSF13C	B cell-activating factor receptor, BAFF-R, CD268, BR3	ENSG00000159958	TRAF3	TNFSF13B
TNFRSF14	Herpesvirus entry mediator A, HVEM, tumour necrosis factor receptor-like 2, TR2, LIGHT-R, ATAR, HVEA	ENSG00000157873	TRAF1,2,3,5	TNFSF14, TNFSF1, BTLA
TNFRSF16	Low affinity nerve growth factor receptor, NGF receptor, Gp80-LNGFR, p75, p75 <sup>NTR</sup> , NGF-R, NTR, CD271	ENSG00000064300	TRAF2, 4, 6	NGF, BDNF, NT-3, NT-4
TNFRSF17	BCMA, BCM, TNFRSF13, TNFRSF13a, CD269	ENSG00000048462	TRAF1,2,3,5,6	TNFSF13B, TNFSF13
TNFRSF18	Glucocorticoid-induced TNFR-related protein, GITR, activation-inducible TNFR family receptor, AITR	ENSG00000186891	TRAF1, 2, 3	TNFSF18
TNFRSF19	Toxicity and JNK inducer, TAJ, TROY, TAJ- $\alpha$ , TRADE	ENSG00000127863	TRAF1,2,3,5	
TNFRSF19L	Receptor expressed in lymphoid tissues, RELT	ENSG00000054967	TRAF1	
TNFRSF21	Death receptor 6, DR6	ENSG00000146072	TRADD	
TNFRSF22	SOBa; Tnfrh2, Tnfrsf1a12, mDcTrailr2	ENSMUSG00000010751	–	
TNFRSF23	mSOB, Tnfrh1, mDcTrailr1	ENSMUSG00000037613	–	
TNFRSF27	X-linked ectodysplasin-A2 receptor, EDA-A2 receptor	ENSG00000131080	–	

TNFRSF1A is preferentially activated by the shed form of TNF ligand, whereas the membrane-bound form of TNF serves to activate TNFRSF1A and TNFRSF1B equally.

TNFRSF6B (ENSG00000026036, also known as the decoy receptor for Fas ligand (DcR3), TR6, M68) acts as a non-functional target for TNFSF14, TNFSF15 and TNFSF6. TNFRSF10C (ENSG00000173535, also known as decoy receptor 1, DcR1, decoy TRAIL receptor without death domain, TNF-related apoptosis-inducing ligand receptor 3, TRAIL-R3, LIT, TRID, CD263) and TNFRSF10D (ENSG00000173530, also known as decoy receptor 2, DcR2, TNF-related apoptosis-inducing ligand receptor 4, TRAIL-R4, TRUNDD, CD264) act as non-functional targets for TNFSF10.

The tumour necrosis factor ligand superfamily includes TNFSF1 (ENSG00000204496, TNF $\beta$ , lymphotoxin- $\alpha$ , LT $\alpha$ ), TNFSF2 (ENSG00000204490, TNF, TNF $\alpha$ , cachectin, necrosin, cytotoxin, DIF), TNFSF3 (ENSG00000206327 TNFC, LTB, lymphotoxin- $\beta$ , LT $\beta$ ), TNFSF4 (ENSG00000117586, OX-40 ligand, CD252, glycoprotein Gp34, TAX transcriptionally-activated glycoprotein 1, TXGP-1), TNFSF5 (ENSG00000102245, CD40 ligand, CD154, gp39, TNF-related activation protein, TRAP), TNFSF6 (ENSG00000117560, Fas ligand, CD95L, CD178, ApoL, Apoptosis antigen ligand), TNFSF7 (ENSG00000125726, CD70, CD27 ligand, Ki-24), TNFSF8 (ENSG00000106952, CD30 ligand, CD153), TNFSF9 (ENSG00000125657, 4-1BB ligand, CDw137L), TNFSF10 (ENSG00000121858, TRAIL, Apo-2 ligand (Apo-2L), TL2, CD253), TNFSF11 (ENSG00000120659, Receptor activator of nuclear factor  $\kappa$ B ligand, RANKL, TNF-related activation-induced cytokine, TRANCE, osteoprotegerin ligand, OPGL, osteoclast differentiation factor, ODF, CD254 antigen), TNFSF12 (TNF-related weak inducer of apoptosis, TWEAK, Apo-3 ligand, Apo3L, CD255), TNFSF13 (ENSG00000161955, APRIL, TALL2, TRDL-1, ZTNF2, TNFSF13A, CD256), TNFSF13B (ENSG00000102524, zTNF4, THANK, TNF- and APOL-related leukocyte expressed ligand 1, TALL-1, B lymphocyte stimulator, BlyS, B cell-activating factor, BAFF, dendritic cell-derived TNF-like molecule, DTL, CD257 antigen), TNFSF14 (ENSG00000125735, LIGHT, LTg, TR2, Herpesvirus entry mediator-ligand, CD258), TNFSF15 (ENSG00000181634, TL1, TL1A, VEGI, vascular endothelial cell growth inhibitor, TNF ligand-related molecule 1), and TNFSF18 (ENSG00000120337, TL6, glucocorticoid- induced TNF-related ligand, activation-inducible TNF-related ligand).

**Abbreviations:** BDNF, brain-derived neurotrophic factor (ENSG00000176697); BTLA, B- and T-lymphocyte attenuator (ENSG00000186265); FADD, Fas-associated death domain (ENSG00000168040); NT-3, neurotrophin-3 (ENSG00000185652); NT-4, neurotrophin-4 (ENSG00000167744); SIVA, ENSG00000184990; TRADD, TNF receptor-associated death domain (ENSG00000102871); TRAF, TNF receptor-associated factor (ENSG00000000597)

#### Further Reading

- Cretney E, Takeda K, Smyth MJ (2007). Cancer: novel therapeutic strategies that exploit the TNF-related apoptosis-inducing ligand (TRAIL)/ TRAIL receptor pathway. *Int J Biochem Cell Biol* **39**: 280–286.
- Croft M (2005). The evolving crosstalk between co-stimulatory and co-inhibitory receptors: HVEM-BTLA. *Trends Immunol* **26**: 292–294.
- Elewaut D, Ware CF (2007). The unconventional role of LT  $\alpha\beta$  in T cell differentiation. *Trends Immunol* **28**: 169–175.
- Paul AT, Gohil VM, Bhutani KK (2006). Modulating TNF- $\alpha$  signaling with natural products. *Drug Discov Today* **11**: 725–732.
- Popa C, Netea MG, van Riel PL, van der Meer JW, Stalenhoef AF (2007). The role of TNF- $\alpha$  in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res* **48**: 751–762.
- Scott DL, Kingsley GH (2006). Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med* **355**: 704–712.
- Shen HM, Pervaiz S (2006). TNF receptor superfamily-induced cell death: redox-dependent execution. *FASEB J* **20**: 1589–1598.
- Sriram K, O'Callaghan JP (2007). Divergent roles for tumor necrosis factor- $\alpha$  in the brain. *J Neuroimmune Pharmacol* **2**: 140–153.
- Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP (2008). Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* **117**: 244–279.
- Wullaert A, van Loo G, Heyninck K, Beyaert R (2007). Hepatic tumor necrosis factor signaling and nuclear factor- $\kappa$ B: effects on liver homeostasis and beyond. *Endocr Rev* **28**: 365–386.

# TRANSPORTERS

**Overview:** The majority of biological solutes are charged organic or inorganic molecules. Cellular membranes are hydrophobic and, therefore, effective barriers to separate them allowing the formation of gradients, which can be exploited, for example, in the generation of energy. Membrane transporters carry solutes across cell membranes, which would otherwise be impermeable to them. The energy required for active transport processes is obtained from ATP turnover or by exploiting ion gradients.

ATP-driven transporters can be divided into three major classes: P-type ATPases; F-type and V-type ATPases and ATP-binding cassette transporters. The first of these, P-type ATPases, are multimeric proteins, which transport (primarily) inorganic cations. The second, F-type or V-type ATPases, are proton-coupled motors, which can function either as transporters or as motors. Last, are ATP-binding cassette transporters, heavily involved in drug disposition as well as transporting endogenous solutes.

The second largest family of membrane proteins in the human genome, after the G protein-coupled receptors, are the SLC solute carrier family. Within the solute carrier family, there are not only a great variety of solutes transported, from simple inorganic ions to amino acids and sugars to relatively complex organic molecules like haem. The solute carrier family includes 48 families of almost 400 members, many of whom remain orphan transporters, in as much as a physiological function has yet to be determined. The SLC transporters include members which function as antiports, where solute movement in one direction is balanced by a solute moving in the reverse direction. Symports allow concentration gradients of one solute to allow movement of a second solute across a membrane. A third, relatively small group are equilibrative transporters, which allow solutes to travel across membranes down their concentration gradients. A more complex family of transporters, the SLC27 fatty acid transporters also express enzymatic function. Many of the transporters also express electrogenic properties of ion channels.

# ATP-binding cassette family

**Overview:** ATP-binding cassette transporters are ubiquitous membrane proteins characterized by facilitated movement of a range of substrates, including ions, lipids, peptides, steroids. The functional transporter is probably dimeric, with individual subunits typically made up of two groups of 6TM-spanning domains, with two nucleotide-binding domains (NBD). The majority of eukaryotic ABC transporters are 'full' transporters incorporating both TM and NBD entities. Some ABCs, notably the ABCD and ABCG families, appear relatively truncated and are only functional as homo- or heterodimers. Eukaryotic ABC transporters convey substrates from the cytoplasm, either out of the cell or into intracellular organelles. Their role in the efflux of exogenous compounds, notably chemotherapeutic agents, has led to considerable interest.

## ABCA subfamily

Systematic name	Common abbreviation	Other names	Ensembl ID	Comments
ABCA1	ABC1, CERP	Cholesterol efflux regulatory protein	ENSG00000165029	Loss-of-function mutations are associated with Tangier disease, in which plasma HDL cholesterol levels are greatly reduced
ABCA2	ABC2	–	ENSG00000107331	–
ABCA3	ABC3, ABCC	–	ENSG00000167972	Loss-of-function mutations are associated with pulmonary surfactant deficiency
ABCA4	ABCR	Retinal-specific ATP-binding cassette transporter, RIM ABC transporter, RmP, Stargardt disease protein	ENSG00000198691	Retinal-specific transporter of <i>N</i> -retinylPE; loss-of-function mutations are associated with Stargardt disease, a juvenile onset macular degenerative disease
ABCA5	–	–	ENSG00000154265	–
ABCA6	–	–	ENSG00000154262	–
ABCA7	–	–	ENSG00000064687	Genome wide association studies identify ABCA7 variants as associated with Alzheimer's Disease (Hollingworth <i>et al.</i> , 2011)
ABCA8	–	KIAA0822	ENSG00000141338	–
ABCA9	–	–	ENSG00000154258	–
ABCA10	–	–	ENSG00000154263	–
ABCA12	–	–	ENSG00000144452	Reported to play a role in skin ceramide formation (Zuo <i>et al.</i> , 2008)
ABCA13	–	–	ENSG00000179869	–

A number of structural analogues are not found in man: ABCA14 (ENSMUSG00000062017); ABCA15 (ENSMUSG00000054746); ABCA16 (ENSMUSG00000051900) and ABCA17 (ENSMUSG00000035435).



## ABCB subfamily

Systematic name	Common abbreviation	Other names	Ensembl ID	Comments
ABCB1	MDR1, PGP1	Multi-drug resistance protein 1, P-glycoprotein 1, CD243 antigen	ENSG00000085563	Responsible for the cellular export of many therapeutic drugs
ABCB2	TAP1	Antigen peptide transporter 1, APT1, peptide transporter TAP1, peptide supply factor 1 (PSF-1), peptide transporter involved in antigen processing 1	ENSG00000168394	Endoplasmic reticulum, possibly as heterodimer with TAP2
ABCB3	TAP2	Antigen peptide transporter 2 (APT2), Peptide transporter TAP2, peptide supply factor 2 (PSF-2), peptide transporter involved in antigen processing 2	ENSG00000204267	Endoplasmic reticulum, possibly as heterodimer with TAP1
ABCB4	PGY3	Multi-drug resistance protein 3, P-glycoprotein 3	ENSG00000005471	Transports phosphatidylcholine from intracellular to extracellular face of the hepatocyte canalicular membrane (Oude Elferink and Paulusma, 2007)
ABCB5	–	–	ENSG00000004846	Multidrug resistance protein in, and marker of, melanoma cells (Schatton <i>et al.</i> 2008)
ABCB6	MTABC3	Mitochondrial ABC transporter 3, ubiquitously expressed mammalian ABC half transporter, P-glycoprotein-related protein	ENSG00000115657	Mitochondrial porphyrin transporter (Krishnamurthy <i>et al.</i> , 2006)
ABCB7	ABC7	–	ENSG00000131269	Mitochondrial; reportedly essential for haematopoiesis (Pondarre <i>et al.</i> , 2007)
ABCB8	MABC1	–	ENSG00000197150	Mitochondrial; suggested to play a role in chemoresistance of melanoma (Elliott and Al-Hajj, 2009)
ABCB9	TAPL	TAP-like protein, hABCB9	ENSG00000150967	Reported to be lysosomal (Kamakura <i>et al.</i> , 2008)
ABCB10	MTABC2	Mitochondrial ABC transporter 2	ENSG00000135776	Mitochondrial
ABCB11	ABC16	Bile salt export pump, BSEP, PFIC-2, PFIC2, PGY4, SPGP	ENSG00000073734	Loss-of-function mutations are associated with familial intrahepatic cholestasis (Stieger, 2009)

## ABCC subfamily

Systematic name	Common abbreviation	Other names	Ensembl ID	Comments
ABCC1	MRP1	Multidrug resistance-associated protein 1, leukotriene C <sub>4</sub> transporter	ENSG00000103222	Exhibits a broad substrate specificity (Bakos and Homolya, 2007)
ABCC2	MRP2, cMOAT	Multidrug resistance-associated protein 2, canalicular multispecific organic anion transporter 1, canalicular multidrug resistance protein	ENSG00000023839	Loss-of-function mutations are associated with Dubin-Johnson syndrome, in which plasma levels of conjugated bilirubin are elevated
ABCC3	MRP3	Multidrug resistance-associated protein 3, canalicular multispecific organic anion transporter 2, multi-specific organic anion transporter-D, MOAT-D	ENSG00000108846	Transports conjugates of glutathione, sulfate or glucuronide (see Borst <i>et al.</i> , 2007)
ABCC4	MRP4	Multidrug resistance-associated protein 4, multi-specific organic anion transporter-B, MOAT-B	ENSG00000125257	Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned (see Borst <i>et al.</i> , 2007); reported to export prostaglandins in a manner sensitive to NSAIDs (Reid <i>et al.</i> , 2003)
ABCC5	MRP5	Multidrug resistance-associated protein 5, multi-specific organic anion transporter-C, MOAT-C, pABC11, SMRP	ENSG00000114770	Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned (see Borst <i>et al.</i> , 2007)
ABCC6	MRP6	Multidrug resistance-associated protein 6, anthracycline resistance-associated protein, multi-specific organic anion transporter-E, MOAT-E	ENSG00000091262	–
ABCC7	CFTR	Cystic fibrosis transmembrane conductance regulator, cAMP-dependent chloride channel	ENSG00000001626	See page S214
ABCC10	MRP7	Multidrug resistance-associated protein 7	ENSG00000124574	–
ABCC11	MRP8	Multidrug resistance-associated protein 8	ENSG00000121270	Single nucleotide polymorphisms distinguish wet vs. dry earwax; association between earwax allele and breast cancer risk in Japanese but not European populations
ABCC12	MRP9	Multidrug resistance-associated protein 9	ENSG00000140798	–

ABCC8 (ENSG0000006071, also known as SUR1, sulfonylurea receptor 1) and ABCC9 (ENSG00000069431, also known as SUR2, sulfonylurea receptor 2) are unusual in that they lack transport capacity but regulate the activity of particular K<sup>+</sup> channels (K<sub>ir</sub>6.1-6.2, see Page S158), conferring nucleotide sensitivity to these channels to generate the canonical K<sub>ATP</sub> channels. ABCC13 (ENSG00000155288) is a possible pseudogene.

## ABCD subfamily of peroxisomal ABC transporters

This family of 'half-transporters' act as homo- or heterodimers to accumulate fatty acid-CoA esters into peroxisomes for oxidative metabolism (see Kemp *et al.*, 2011).

Systematic name	Common abbreviation	Other names	Ensembl ID	Substrates
ABCD1	ALDP	Adrenoleukodystrophy protein	ENSG00000101986	Coenzyme A esters of very long chain fatty acids (van Roermund <i>et al.</i> , 2008; 2011)
ABCD2	ALDR	Adrenoleukodystrophy-related protein, adrenoleukodystrophy-like 1	ENSG00000173208	Coenzyme A esters of very long chain unsaturated fatty acids (van Roermund <i>et al.</i> , 2011)
ABCD3	PMP70	70 kDa peroxisomal membrane protein, PXMP1	ENSG00000117528	–

ABCD4 (ENSG00000119688, also known as PMP69, PXMP1-L or P70R) appears to be located on the endoplasmic reticulum (Kashiwayama *et al.*, 2009), with an unclear function. Loss-of-function mutations in the gene encoding ALDP underlie the metabolic storage disorder X-linked adrenoleukodystrophy.

### ABCG subfamily

This family of 'half-transporters' act as homo- or heterodimers; particularly ABCG5 and ABCG8 are thought to be obligate heterodimers. They are associated with cellular export of sterols and phospholipids, as well as exogenous drugs (ABCG2).

Systematic name	Common abbreviation	Other names	Ensembl ID	Comments
ABCG1	ABC8	White protein homolog	ENSG00000160179	Transports sterols and choline phospholipids (see Kerr <i>et al.</i> , 2011)
ABCG2	ABCP	Placenta-specific ATP- binding cassette transporter, breast cancer resistance protein, BCRP, mitoxantrone resistance-associated protein, MXR, CD338 antigen, CDw338	ENSG00000118777	Exhibits a broad substrate specificity, including urate and haem, as well as multiple synthetic compounds (see Kerr <i>et al.</i> , 2011)
ABCG4	–	White2	ENSG00000172350	Putative functional dependence on ABCG1
ABCG5	–	White3, Sterolin-1	ENSG00000138075	Transports phytosterols; forms a heterodimer with ABCG8
ABCG8	–	Sterolin-2	ENSG00000143921	Transports phytosterols; forms a heterodimer with ABCG5

A further group of ABC transporter-like proteins have been identified to lack membrane spanning regions and are not believed to be functional transporters, but appear to have a role in protein translation (Chen *et al.*, 2006; Paytubi *et al.*, 2009): ABCE1 (ENSG00000164163, also known as OABP or 2'-5' oligoadenylate-binding protein); ABCF1 (ENSG00000204574, also known as ABC50 or TNF- $\alpha$ -stimulated ABC protein); ABCF2 (ENSG00000033050, also known as iron-inhibited ABC transporter 2) and ABCF3 (ENSG00000161204).

**Abbreviations:** ABC, ATP-binding cassette; NBD, nucleotide-binding domain; **N-retinylPE**, N-retinylphosphatidylethanolamine; NSAID, non-steroidal anti-inflammatory drugs

### Further Reading

- Aye IL, Singh AT, Keelan JA (2009). Transport of lipids by ABC proteins: interactions and implications for cellular toxicity, viability and function. *Chem Biol Interact* **180**: 327–339.
- Borst P, de Wolf C, van de Wetering K (2007). Multidrug resistance-associated proteins 3, 4, and 5. *Pflugers Arch* **453**: 661–673.
- Bryan J, Munoz A, Zhang X, Dufer M, Drews G, Krippeit-Drews P *et al.* (2007). ABC8 and ABC9: ABC transporters that regulate K<sup>+</sup> channels. *Pflugers Arch* **453**: 703–718.
- Ecker GF, Stockner T, Chiba P (2008). Computational models for prediction of interactions with ABC-transporters. *Drug Discov Today* **13**: 311–317.
- Gutmann DA, Ward A, Urbatsch IL, Chang G, van Veen HW (2010). Understanding polyspecificity of multidrug ABC transporters: closing in on the gaps in ABCB1. *Trends Biochem Sci* **35**: 36–42.
- Kemp S, Theodoulou FL, Wanders RJ (2011). Mammalian peroxisomal ABC transporters: from endogenous substrates to pathology and clinical significance. *Br J Pharmacol* in press.
- Kerr ID, Haider AJ, Gelissen IC (2011). The ABCG family of membrane-associated transporters: you don't have to be big to be mighty. *Br J Pharmacol* in press.
- Linton KJ, Higgins CF (2007). Structure and function of ABC transporters: the ATP switch provides flexible control. *Pflugers Arch* **453**: 555–567.
- Miller DS (2010). Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. *Trends Pharmacol Sci* **31**: 246–254.
- Procko E, O'Mara ML, Bennett WF, Tieleman DP, Gaudet R (2009). The mechanism of ABC transporters: general lessons from structural and functional studies of an antigenic peptide transporter. *FASEB J* **23**: 1287–1302.
- Ravna AW, Sager G (2009). Molecular modeling studies of ABC transporters involved in multidrug resistance. *Mini Rev Med Chem* **9**: 186–193.
- Rees DC, Johnson E, Lewinson O (2009). ABC transporters: the power to change. *Nat Rev Mol Cell Biol* **10**: 218–227.
- Russel FG, Koenderink JB, Masereeuw R (2008). Multidrug resistance protein 4 (MRP4/ABCC4): a versatile efflux transporter for drugs and signalling molecules. *Trends Pharmacol Sci* **29**: 200–207.
- Schrick JA, Fink-Gremmels J (2008). Implications of ABC transporters on the disposition of typical veterinary medicinal products. *Eur J Pharmacol* **585**: 510–519.
- Seeger MA, van Veen HW (2009). Molecular basis of multidrug transport by ABC transporters. *Biochim Biophys Acta* **1794**: 725–737.
- Sharom FJ (2008). ABC multidrug transporters: structure, function and role in chemoresistance. *Pharmacogenomics* **9**: 105–127.
- Szakacs G, Varadi A, Ozvegy-Laczka C, Sarkadi B (2008). The role of ABC transporters in drug absorption, distribution, metabolism, excretion and toxicity (ADME-Tox). *Drug Discov Today* **13**: 379–393.
- Wanders RJ, Visser WF, van Roermund CW, Kemp S, Waterham HR (2007). The peroxisomal ABC transporter family. *Pflugers Arch* **453**: 719–734.

### References

- Bakos E, Homolya L (2007). *Pflugers Arch* **453**: 621–641.
- Chen ZQ *et al.* (2006). *J Biol Chem* **281**: 7452–7457.
- Elliott AM, Al-Hajj MA (2009). *Mol Cancer Res* **7**: 79–87.
- Hollingsworth P *et al.* (2011). *Nat Genet* **43**: 429–435.
- Kamakura A *et al.* (2008). *Biochem Biophys Res Commun* **377**: 847–851.
- Kashiwayama Y *et al.* (2009). *Exp Cell Res* **315**: 190–205.
- Krishnamurthy PC *et al.* (2006). *Nature* **443**: 586–589.
- Oude Elferink RP, Paulusma CC (2007). *Pflugers Arch* **453**: 601–610.
- Paytubi S *et al.* (2009). *J Biol Chem* **284**: 24061–24073.
- Pondarre C *et al.* (2007). *Blood* **109**: 3567–3569.
- Reid G *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 9244–9249.
- Schatton T *et al.* (2008). *Nature* **451**: 345–349.
- Stieger B (2009). *Curr Opin Lipidol* **20**: 176–181.
- van Roermund CW *et al.* (2008). *FASEB J* **22**: 4201–4208.
- van Roermund CW *et al.* (2011). *Biochim Biophys Acta* **1811**: 148–152.
- Zuo Y *et al.* (2008). *J Biol Chem* **283**: 36624–36635.

# F-type and V-type ATPases (EC 3.6.3.14)

The F-type (ATP synthase) and the V-type (vacuolar or vesicular proton pump) ATPases, although having distinct subcellular locations and roles, exhibit marked similarities in subunit structure and mechanism. They are both composed of a 'soluble' complex (termed F<sub>1</sub> or V<sub>1</sub>) and a membrane complex (F<sub>0</sub> or V<sub>0</sub>). Within each ATPase complex, the two individual sectors appear to function as connected opposing rotary motors, coupling catalysis of ATP synthesis or hydrolysis to proton transport.

## F-type ATPase

The F-type ATPase, also known as ATP synthase or ATP phosphohydrolase (H<sup>+</sup>-transporting), is a mitochondrial membrane-associated multimeric complex consisting of two domains, an F<sub>0</sub> channel domain in the membrane and an F<sub>1</sub> domain extending into the lumen. Proton transport across the inner mitochondrial membrane is used to drive the synthesis of ATP, although it is also possible for the enzyme to function as an ATPase. The ATP5O subunit (oligomycin sensitivity-conferring protein, OSCP, ENSG00000241837), which acts as a connector between F<sub>1</sub> and F<sub>0</sub> motors,

The F<sub>1</sub> **motor**, responsible for ATP turnover, has the subunit composition  $\alpha 3\beta 3\gamma\delta\epsilon$ .

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
$\alpha$	ATP5A1; ATPAF2	ENSG00000152234; ENSG00000171953	ATP5A, ATP5AL2, ATPM, hATP1, OMR, ORM; ATP synthase mitochondrial F1 complex assembly factor 2, ATP12, Atp12p
$\beta$	ATP5B; ATPAF1	ENSG00000110955; ENSG00000123472	ATP5B; ATP synthase mitochondrial F1 complex assembly factor 1, ATP11, Atp11p, FLJ22351
$\gamma$	ATP5C1	ENSG00000165629	ATP5C, ATP5CL1
$\delta$	ATP5D	ENSG00000099624	–
$\epsilon$	ATP5E	ENSG00000124172	–

The F<sub>0</sub> **motor**, responsible for ion translocation, is complex in mammals, with probably nine subunits centring on A, B, and C subunits in the membrane, together with D, E, F2, F6, G2 and 8 subunits.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
A	MT-ATP6	ENSG00000198899	F-ATPase protein 6
B	ATP5F1	ENSG00000116459	–
C	ATP5G1; ATP5G2; ATP5G3	ENSG00000159199; ENSG00000135390; ENSG00000154518	ATP synthase proteolipid P1, ATPase protein 9
D	ATP5H	ENSG00000167863	ATP5JD, ATPQ
E	ATP5I	ENSG00000169020	ATP5K
F2	ATP5J2	ENSG00000241468	ATP5JL
F6	ATP5J	ENSG00000154723	ATP5, ATP5A, ATPM, CF6, ATP synthase-coupling factor 6
G2	ATP5L2	ENSG00000249222	ATP5K2
8	MT-ATP8	ENSG00000229604	–

Multiple pseudogenes for these proteins have been defined in the human genome.

## V-type ATPase

The V-type ATPase is most prominently associated with lysosomes in mammals, but also appears to be expressed on the plasma membrane and neuronal synaptic vesicles.

The V<sub>1</sub> **motor**, responsible for ATP turnover, has eight subunits with a composition of A-H.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
A	ATP6V1A	ENSG00000114573	ATP6A1, ATP6V1A1, VA68, Vma1, VPP2
B1	ATP6V1B1	ENSG00000116039	ATP6B1, RTA1B, VATB, Vma2, VPP3
B2	ATP6V1B2	ENSG00000147416	ATP6B2, HO57, VATB, Vma2, VPP3
C1	ATP6V1C1	ENSG00000155097	ATP6C, ATP6D, VATC, Vma5
C2	ATP6V1C2	ENSG00000143882	ATP6C2, VMA5
D	ATP6V1D	ENSG00000100554	ATP6M, VATD, VMA8
E1	ATP6V1E1	ENSG00000131100	ATP6E, ATP6E2, ATP6V1E, P31, Vma4
E2	ATP6V1E2	ENSG00000250565	ATP6E1, ATP6EL2, ATP6V1EL2, MGC9341, VMA4
F	ATP6V1F	ENSG00000128524	ATP6S14, VATF, Vma7
G1	ATP6V1G1	ENSG00000136888	ATP6G, ATP6G1, ATP6GL, ATP6J, DKFZp547P234, Vma10
G2	ATP6V1G2	ENSG00000230900; ENSG00000213760; ENSG00000234668; ENSG00000234920; ENSG00000206445; ENSG00000226850	ATP6G, ATP6G2, Em:AC004181.3, NG38, Vma10
G3	ATP6V1G3	ENSG00000151418	ATP6G3, Vma10
H	ATP6V1H	ENSG00000047249	CGI-11, SFD, SFDalpha, SFDbeta, VMA13

The  $V_0$  motor, responsible for ion translocation, has six subunits (a–e).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
a1	ATP6V0A1	ENSG00000033627	ATP6N1, ATP6N1A, Stv1, Vph1, VPP1
a2	ATP6V0A2	ENSG00000185344	ATP6a2, ATP6N1D, J6B7, Stv1, Tj6, Tj6M, Tj6s, Vph1
a3	TCIRG1	ENSG00000110719	T-cell immune regulator 1, Atp6i, ATP6N1C, ATP6V0A3, OC-116, OC116, TIRC7
a4	ATP6V0A4	ENSG00000105929	ATP6N1B, ATP6N2, RDRTA2, RTA1C, RTADR, Stv1, Vph1, VPP2
b	ATP6V0B	ENSG00000117410	ATP6F, HATPL, VMA16
c	ATP6V0C	ENSG00000185883	ATP6C, ATP6L, ATPL, VATL, Vma3
d1	ATP6V0D1	ENSG00000159720	ATP6D, ATP6DV, P39, VATX, Vma6, VPATPD
d2	ATP6V0D2	ENSG00000147614	ATP6D2, FLJ38708, VMA6
e1	ATP6V0E1	ENSG00000113732	ATP6H, ATP6V0E, M9.2
e2	ATP6V0E2	ENSG00000171130	ATP6V0E2L, C7orf32

#### Further Reading

- von Ballmoos C (2007). Alternative proton binding mode in ATP synthases. *J Bioenerg Biomembr* 39: 441–445.
- von Ballmoos C, Cook GM, Dimroth P (2008). Unique rotary ATP synthase and its biological diversity. *Annu Rev Biophys* 37: 43–64.
- von Ballmoos C, Wiedenmann A, Dimroth P (2009). Essentials for ATP synthesis by  $F_1F_0$  ATP synthases. *Annu Rev Biochem* 78: 649–672.
- Junge W, Sialaff H, Engelbrecht S (2009). Torque generation and elastic power transmission in the rotary  $F_0F_1$ -ATPase. *Nature* 459: 364–370.
- Nakamoto RK, Baylis Scanlon JA, Al-Shawi MK (2008). The rotary mechanism of the ATP synthase. *Arch Biochem Biophys* 476: 43–50.
- Nakanishi-Matsui M, Sekiya M, Nakamoto RK, Futai M (2010). The mechanism of rotating proton pumping ATPases. *Biochim Biophys Acta* 1797: 1343–1352.
- Navarro A, Boveris A (2007). The mitochondrial energy transduction system and the aging process. *Am J Physiol Cell Physiol* 292: C670–C686.
- Qi J, Wang Y, Forgac M (2007). The vacuolar ( $H^+$ )-ATPase: subunit arrangement and in vivo regulation. *J Bioenerg Biomembr* 39: 423–426.

# P-type ATPases (EC 3.6.3.-)

Phosphorylation-type ATPases are associated with membranes and the transport of ions or phospholipids. A characteristic is the interconversion between E1 and E2 conformations in the activity cycle of the transporters.

## Na<sup>+</sup>/K<sup>+</sup>-ATPase (EC 3.6.3.9)

The cell-surface Na<sup>+</sup>/K<sup>+</sup>-ATPase is an integral membrane protein which regulates the membrane potential of the cell by maintaining gradients of Na<sup>+</sup> and K<sup>+</sup> ions across the plasma membrane, also making a small, direct contribution to membrane potential, particularly in cardiac cells. The active enzyme is a heteromultimer with incompletely defined stoichiometry, possibly as tetramers of heterodimers, each consisting of one of four large, ten TM domain catalytic  $\alpha$  subunits and one of three smaller single TM domain glycoprotein  $\beta$ -subunits (see table). Additional protein partners known as FXYD proteins (e.g. FXYD2, ENSG00000137731) appear to associate with and regulate the activity of the pump.

Nomenclature	Systematic name	Ensembl ID	Other names
$\alpha$ 1	ATP1A1	ENSG00000163399	Sodium/potassium-transporting ATPase subunit $\alpha$ -1, sodium pump subunit $\alpha$ -1, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -1 subunit
$\alpha$ 2	ATP1A2	ENSG00000018625	Sodium/potassium-transporting ATPase subunit $\alpha$ -1, sodium pump subunit $\alpha$ -1, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -1 subunit
$\alpha$ 3	ATP1A3	ENSG00000105409	Sodium/potassium-transporting ATPase subunit $\alpha$ -3, sodium pump subunit $\alpha$ -3, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -3 subunit
$\alpha$ 4	ATP1A4	ENSG00000132681	Sodium/potassium-transporting ATPase subunit $\alpha$ -4, sodium pump subunit $\alpha$ -4, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -4 subunit
$\beta$ 1	ATP1B1	ENSG00000143153	Sodium/potassium-transporting ATPase subunit $\beta$ -1
$\beta$ 2	ATP1B2	ENSG00000129244	Sodium/potassium-transporting ATPase subunit $\beta$ -2
$\beta$ 3	ATP1B3	ENSG00000069849	Sodium/potassium-transporting ATPase subunit $\beta$ -3, CD298 antigen

Na<sup>+</sup>/K<sup>+</sup>-ATPases are inhibited by ouabain and cardiac glycosides, such as digoxin, as well as potentially endogenous cardiotonic steroids (see Bagrov *et al.*, 2009).

## Ca<sup>2+</sup>-ATPases (EC 3.6.3.8)

The sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) is an intracellular membrane-associated pump for sequestering calcium from the cytosol into intracellular organelles, usually associated with the recovery phase following excitation of muscle and nerves.

Nomenclature	Systematic name	Ensembl ID	Other names
SERCA1	ATP2A1	ENSG00000196296	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1, fast twitch skeletal muscle isoform
SERCA2	ATP2A2	ENSG00000174437	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2, calcium pump 2, slow twitch skeletal muscle isoform
SERCA3	ATP2A3	ENSG00000074370	Sarcoplasmic/endoplasmic reticulum calcium ATPase 3

The fungal toxin ochratoxin A has been described to activate SERCA in kidney microsomes (Chong and Rahimtula, 1992). Cyclopiazonic acid (Seidler *et al.*, 1989), thapsigargin (Lytton *et al.*, 1991) and BHQ are widely employed to block SERCA. Thapsigargin has also been described to block the TRPV1 vanilloid receptor (Toth *et al.*, 2002).

The plasma membrane Ca<sup>2+</sup>-ATPase (PMCA) is a cell-surface pump for extruding calcium from the cytosol, usually associated with the recovery phase following excitation of cells. The active pump is a homodimer, each subunit of which is made up of ten TM segments, with cytosolic C- and N-termini and two large intracellular loops.

Nomenclature	Systematic name	Ensembl ID	Other names
PMCA1	ATP2B1	ENSG00000070961	Plasma membrane calcium ATPase isoform 1
PMCA2	ATP2B2	ENSG00000157087	Plasma membrane calcium ATPase isoform 2
PMCA3	ATP2B3	ENSG00000067842	Plasma membrane calcium ATPase isoform 3
PMCA4	ATP2B4	ENSG00000058668	Plasma membrane calcium ATPase isoform 4, matrix-remodeling-associated protein 1

The stoichiometry of flux through the PMCA differs from SERCA, with the PMCA transporting 1 Ca<sup>2+</sup> while SERCA transports 2 Ca<sup>2+</sup>.

Secretory pathway  $\text{Ca}^{2+}$ -ATPases (SPCA) allow accumulation of calcium and manganese in the Golgi apparatus.

Nomenclature	Systematic name	Ensembl ID	Other names
SPCA1	ATP2C1	ENSG00000017260	ATPase 2C1, ATP-dependent $\text{Ca}^{2+}$ pump PMR1
SPCA2	ATP2C2	ENSG00000064270	ATPase 2C2, secretory pathway $\text{Ca}^{2+}$ -ATPase 2

Loss-of-function mutations in SPCA1 appear to underlie Hailey-Hailey disease (Hu *et al.*, 2000).

#### $\text{H}^+/\text{K}^+$ -ATPase (EC 3.6.3.10)

The  $\text{H}^+/\text{K}^+$  ATPase is a heterodimeric protein, made up of  $\alpha$  and  $\beta$  subunits. The  $\alpha$  subunit has 10 TM domains and exhibits catalytic and pore functions, while the  $\beta$  subunit has a single TM domain, which appears to be required for intracellular trafficking and stabilising the  $\alpha$  subunit. The ATP4A and ATP4B subunits are expressed together, while the ATP12A subunit is suggested to be expressed with the  $\beta$ 1 (ATP1B1) subunit of the  $\text{Na}^+/\text{K}^+$ -ATPase (Pestov *et al.*, 2006).

Nomenclature	Ensembl ID	Other names
ATP4A	ENSG00000105675	Potassium-transporting ATPase $\alpha$ chain 1, gastric $\text{H}^+/\text{K}^+$ -ATPase $\alpha$ subunit, ATP6A
ATP12A	ENSG00000075673	Potassium-transporting ATPase $\alpha$ chain 2, non-gastric $\text{H}^+/\text{K}^+$ -ATPase $\alpha$ subunit, ATP1AL1
ATP4B	ENSG00000186009	Potassium-transporting ATPase $\beta$ chain 1, gastric $\text{H}^+/\text{K}^+$ -ATPase $\beta$ subunit

The gastric  $\text{H}^+/\text{K}^+$ -ATPase is inhibited by (*R*)-lansoprazole and a metabolite of (*S*)-omeprazole.

#### $\text{Cu}^{2+}$ -ATPase (EC 3.6.3.4)

Copper-transporting ATPases convey copper ions across cell-surface and intracellular membranes. They consist of eight TM domains and associate with multiple copper chaperone proteins (e.g. ATOX1, ENSG00000177556).

Nomenclature	Ensembl ID	Other names
ATP7A	ENSG00000165240	Copper-transporting ATPase 1, copper pump 1, Menkes disease-associated protein
ATP7B	ENSG00000123191	Copper-transporting ATPase 2, copper pump 2, Wilson disease-associated protein

#### Phospholipid-transporting ATPase (EC 3.6.3.1)

These transporters are thought to translocate the aminophospholipids phosphatidylserine and phosphatidylethanolamine from one side of the phospholipid bilayer to the other.

Nomenclature	Ensembl ID	Other names
ATP8A1	ENSG00000124406	Probable phospholipid-transporting ATPase IA, chromaffin granule ATPase II
ATP8A2	ENSG00000132932	Probable phospholipid-transporting ATPase IB, ML-1
ATP8B1	ENSG00000081923	Probable phospholipid-transporting ATPase IC, familial intrahepatic cholestasis type 1
ATP8B2	ENSG00000143515	Probable phospholipid-transporting ATPase ID
ATP8B3	ENSG00000130270	Probable phospholipid-transporting ATPase IK
ATP8B4	ENSG00000104043	Probable phospholipid-transporting ATPase IM
ATP9A	ENSG00000054793	Probable phospholipid-transporting ATPase IIA, ATPase IIA
ATP9B	ENSG00000166377	Probable phospholipid-transporting ATPase IIB, ATPase class II type 9B
ATP10A	ENSG00000206190	Probable phospholipid-transporting ATPase VA, ATPase class V type 10A, aminophospholipid translocase VA, ATP10C
ATP10B	ENSG00000118322	Probable phospholipid-transporting ATPase VB, ATPase class V type 10B
ATP10D	ENSG00000145246	Probable phospholipid-transporting ATPase VD, ATPase class V type 10D
ATP11A	ENSG00000068650	Probable phospholipid-transporting ATPase IH, ATPase class VI type 11A, ATPase IS
ATP11B	ENSG00000058063	Probable phospholipid-transporting ATPase IF, ATPase class VI type 11B, ATPase IR
ATP11C	ENSG00000101974	Probable phospholipid-transporting ATPase IG, ATPase class VI type 11C, ATPase IG, ATPase IQ

Loss-of-function mutations in ATP8B1 are associated with type I familial intrahepatic cholestasis.

A further series of structurally-related proteins have been identified in the human genome, with as yet undefined function, including ATP13A1 (ENSG00000105726), ATP13A2 (ENSG00000159363), ATP13A3 (ENSG00000133657), ATP13A4 (ENSG00000127249) and ATP13A5 (ENSG00000187527).

**Abbreviations:** BHQ, 2,5-di-t-butyl-1,4 benzohydroquinone

### Further Reading

- Bagrov AY, Shapiro JI, Fedorova OV (2009). Endogenous cardiotonic steroids: physiology, pharmacology, and novel therapeutic targets. *Pharmacol Rev* **61**: 9–38.
- Benarroch EE (2011). Na<sup>+</sup>, K<sup>+</sup>-ATPase: functions in the nervous system and involvement in neurologic disease. *Neurology* **76**: 287–293.
- Bers DM, Despa S (2009). Na/K-ATPase – an integral player in the adrenergic fight-or-flight response. *Trends Cardiovasc Med* **19**: 111–118.
- Brini M (2009). Plasma membrane Ca<sup>2+</sup>-ATPase: from a housekeeping function to a versatile signaling role. *Pflugers Arch* **457**: 657–664.
- Brini M, Carafoli E (2009). Calcium pumps in health and disease. *Physiol Rev* **89**: 1341–1378.
- Cartwright EJ, Oceandy D, Neyses L (2009). Physiological implications of the interaction between the plasma membrane calcium pump and nNOS. *Pflugers Arch* **457**: 665–671.
- Di Leva F, Domi T, Fedrizzi L, Lim D, Carafoli E (2008). The plasma membrane Ca<sup>2+</sup> ATPase of animal cells: structure, function and regulation. *Arch Biochem Biophys* **476**: 65–74.
- Fedorova OV, Shapiro JI, Bagrov AY (2010). Endogenous cardiotonic steroids and salt-sensitive hypertension. *Biochim Biophys Acta* **1802**: 1230–1236.
- Floyd R, Wray S (2007). Calcium transporters and signalling in smooth muscles. *Cell Calcium* **42**: 467–476.
- Folmer DE, Elferink RP, Paulusma CC (2009). P4 ATPases – lipid flippases and their role in disease. *Biochim Biophys Acta* **1791**: 628–635.
- Inesi G, Prasad AM, Pilankatta R (2008). The Ca<sup>2+</sup> ATPase of cardiac sarcoplasmic reticulum: physiological role and relevance to diseases. *Biochem Biophys Res Commun* **369**: 182–187.
- Jaitovich A, Bertorello AM (2010). Salt, Na<sup>+</sup>, K<sup>+</sup>-ATPase and hypertension. *Life Sci* **86**: 73–78.
- Kaler SG (2011). ATP7A-related copper transport diseases-emerging concepts and future trends. *Nat Rev Neurol* **7**: 15–29.
- Kawase Y, Hajjar RJ (2008). The cardiac sarcoplasmic/endoplasmic reticulum calcium ATPase: a potent target for cardiovascular diseases. *Nat Clin Pract Cardiovasc Med* **5**: 554–565.
- Lingrel JB (2010). The physiological significance of the cardiotonic steroid/ouabain-binding site of the Na,K-ATPase. *Annu Rev Physiol* **72**: 395–412.
- Manunta P, Messaggio E, Casamassima N, Gatti G, Carpini SD, Zagato L *et al.* (2010). Endogenous ouabain in renal Na<sup>+</sup> handling and related diseases. *Biochim Biophys Acta* **1802**: 1214–1218.
- Morth JP, Pedersen BP, Buch-Pedersen MJ, Vilsen B, Palmgren MG *et al.* (2011). A structural overview of the plasma membrane Na<sup>+</sup>,K<sup>+</sup>-ATPase and H<sup>+</sup>-ATPase ion pumps. *Nat Rev Mol Cell Biol* **12**: 60–70.
- Muthusamy BP, Natarajan P, Zhou X, Graham TR (2009). Linking phospholipid flippases to vesicle-mediated protein transport. *Biochim Biophys Acta* **1791**: 612–619.
- Patel S, Docampo R (2010). Acidic calcium stores open for business: expanding the potential for intracellular Ca<sup>2+</sup> signaling. *Trends Cell Biol* **20**: 277–286.
- Poulsen H, Morth P, Egebjerg J, Nissen P (2010). Phosphorylation of the Na<sup>+</sup>,K<sup>+</sup>-ATPase and the H<sup>+</sup>,K<sup>+</sup>-ATPase. *FEBS Lett* **584**: 2589–2595.
- Prassas I, Diamandis EP (2008). Novel therapeutic applications of cardiac glycosides. *Nat Rev Drug Discov* **7**: 926–935.
- Puts CF, Holthuis JC (2009). Mechanism and significance of P4 ATPase-catalyzed lipid transport: lessons from a Na<sup>+</sup>/K<sup>+</sup>-pump. *Biochim Biophys Acta* **1791**: 603–611.
- Rasmussen HH, Hamilton EJ, Liu CC, Figtree GA (2010). Reversible oxidative modification: implications for cardiovascular physiology and pathophysiology. *Trends Cardiovasc Med* **20**: 85–90.
- Rosenberg PB (2009). Calcium entry in skeletal muscle. *J Physiol* **587**: 3149–3151.
- Scarpignato C, Hunt RH (2008). Proton pump inhibitors: the beginning of the end or the end of the beginning? *Curr Opin Pharmacol* **8**: 677–684.
- Tadini-Buoninsegni F, Bartolommei G, Moncelli MR, Fendler K (2008). Charge transfer in P-type ATPases investigated on planar membranes. *Arch Biochem Biophys* **476**: 75–86.
- Taub M, Springate JE, Cutuli F (2010). Targeting of renal proximal tubule Na,K-ATPase by salt-inducible kinase. *Biochem Biophys Res Commun* **393**: 339–344.
- Toyoshima C (2009). How Ca<sup>2+</sup>-ATPase pumps ions across the sarcoplasmic reticulum membrane. *Biochim Biophys Acta* **1793**: 941–946.
- Weidemuller C, Hauser K (2009). Ion transport and energy transduction of P-type ATPases: implications from electrostatic calculations. *Biochim Biophys Acta* **1787**: 721–729.
- Wray S, Burdyga T (2010). Sarcoplasmic reticulum function in smooth muscle. *Physiol Rev* **90**: 113–178.
- Zhang L, Zhang Z, Guo H, Wang Y (2008). Na<sup>+</sup>/K<sup>+</sup>-ATPase-mediated signal transduction and Na<sup>+</sup>/K<sup>+</sup>-ATPase regulation. *Fundam Clin Pharmacol* **22**: 615–621.

### References

- Chong X, Rahimtula AD (1992). *Biochem Pharmacol* **44**: 1401–1409.
- Hu Z *et al.* (2000). *Nat Genet* **24**: 61–65.
- Lytton J *et al.* (1991). *J Biol Chem* **266**: 17067–17071.
- Pestov NB *et al.* (2006). *Am J Physiol -Cell Physiol* **291**: C366–C374.
- Seidler NW *et al.* (1989). *J Biol Chem* **264**: 17816–17823.
- Toth A *et al.* (2002). *Biochem Biophys Res Commun* **293**: 777–782.



# The SLC superfamily of solute carriers

The SLC superfamily of solute carriers is the second largest family of membrane proteins after G protein-coupled receptors, but with a great deal fewer therapeutic drugs that exploit them. As with the ABC transporters, however, they play a major role in drug disposition and so can be hugely influential in determining the clinical efficacy of particular drugs.

48 families are identified on the basis of sequence similarities, but many of them overlap in terms of the solutes that they carry. For example, amino acid accumulation is mediated by members of the SLC1, SLC3/7, SLC6, SLC15, SLC16, SLC17, SLC32, SLC36, SLC38 and SLC43. Further members of the SLC superfamily regulate ion fluxes at the plasma membrane, or solute transport into and out of cellular organelles.

Within the SLC superfamily, there is an abundance in diversity of structure. Two families (SLC3 and SLC7) only generate functional transporters as heteromeric partners, where one partner is a single TM domain protein. Membrane topology predictions for other families suggest 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, or 14 TM domains. Functionally, members may be divided into those dependent on gradients of ions (particularly sodium, chloride or protons), exchange of solutes or simple equilibrative gating. For many members, the stoichiometry of transport is not yet established. Furthermore, one family of transporters also possess enzymatic activity (SLC27), while many members function as ion channels (e.g. SLC1A7/EAAT5), which increases the complexity of function of the SLC superfamily.

## Further Reading

Fredriksson R, Nordstrom KJ, Stephansson O, Hagglund MG, Schioth HB (2008). The solute carrier (SLC) complement of the human genome: phylogenetic classification reveals four major families. *FEBS Lett* 582: 3811–3816.  
Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X *et al.* (2010). Membrane transporters in drug development. *Nat Rev Drug Discovery* 9: 215–236.

## SLC1 family of amino acid transporters

**Overview:** The SLC1 family of sodium dependent transporters includes the plasma membrane located glutamate transporters and the neutral amino acid transporters ASCT1 and ASCT2 (Amara and Arriza, 1993; Palacin *et al.*, 1998; Kanai and Hediger, 2003; 2004; Beart and O'Shea, 2007).

### Glutamate transporter subfamily

Glutamate transporters present the unusual structural motif of 8TM segments and 2 re-entrant loops (Grunwald and Kanner, 2000). The crystal structure of a glutamate transporter homologue (Glt<sub>ph</sub>) from *Pyrococcus horikoshii* supports this topology and indicates that the transporter assembles as a trimer, where each monomer is a functional unit capable of substrate permeation (Yernool *et al.*, 2004; Boudker *et al.*, 2007; Reyes *et al.*, 2009; reviewed by Jiang and Amara, 2011). These structural data are in agreement with the proposed quaternary structure for EAAT2 (Gendreau *et al.*, 2004) and several functional studies that propose the monomer is the functional unit (Ryan *et al.*, 2004; Grewer *et al.*, 2005; Koch *et al.*, 2007; Leary *et al.*, 2007). Recent evidence suggests that EAAT3 and EAAT4 may assemble as heterotrimers (Nothmann *et al.*, 2011). The activity of glutamate transporters located upon both neurones (predominantly EAAT3, 4 and 5) and glia (predominantly EAAT 1 and 2) serves, dependent upon their location, to regulate excitatory neurotransmission, maintain low ambient extracellular concentrations of glutamate (protecting against excitotoxicity) and provide glutamate for metabolism including the glutamate-glutamine cycle. The Na<sup>+</sup>/K<sup>+</sup>-ATPase (see Page S219) that maintains the ion gradients that drive transport has been demonstrated to co-assemble with EAAT1 and EAAT2 (Rose *et al.*, 2009). Recent evidence supports altered glutamate transport and novel roles in brain for splice variants of EAAT1 and EAAT2 (Gebhardt *et al.*, 2010; Lee and Pow, 2010). Three patients with dicarboxylic aminoaciduria (DA) were recently found to have loss-of-function mutations in EAAT3 (Bailey *et al.*, 2011). DA is characterized by excessive excretion of the acidic amino acids glutamate and aspartate and EAAT3 is the predominant glutamate/aspartate transporter in the kidney. Enhanced expression of EAAT2 resulting from administration of β-lactam antibiotics (e.g. ceftriaxone) is neuroprotective and occurs through NF-κB-mediated EAAT2 promoter activation (Rothstein *et al.*, 2005; Ganel *et al.*, 2006; Lee *et al.*, 2008; reviewed by Kim *et al.*, 2010). PPARγ (see Page S181) activation (e.g. by rosiglitazone) also leads to enhanced expression of EAAT through promoter activation (Romera *et al.*, 2007). In addition, several translational activators of EAAT2 have recently been described (Colton *et al.*, 2010) along with treatments that increase the surface expression of EAAT2 (e.g. Lau *et al.*, 2011, Zou *et al.*, 2011), or prevent its down-regulation (e.g. Goursaud *et al.*, 2011). A thermodynamically uncoupled Cl<sup>-</sup> flux, activated by Na<sup>+</sup> and glutamate (Kanai and Hediger, 2003; Grewer and Rauen, 2005; Machtens *et al.*, 2011) (Na<sup>+</sup> and aspartate in the case of Glt<sub>ph</sub>, Ryan and Mindell, 2007), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability (Veruki *et al.*, 2006; Torres-Salazar and Fahlke, 2007). Indeed, it has recently been suggested that the primary function of EAAT5 is as a slow anion channel gated by glutamate, rather than a glutamate transporter (Gameiro *et al.*, 2011).

Common abbreviation	EAAT1	EAAT2	EAAT3
Systematic name	SLC1A3	SLC1A2	SCL1A1
Nomenclature	Excitatory amino acid transporter 1	Excitatory amino acid transporter 2	Excitatory amino acid transporter 3
Other names	GLAST	GLT1	EAAC1
Ensembl ID	ENSG000000079215	ENSG00000110436	ENSG00000106688

Common abbreviation	EAAT1	EAAT2	EAAT3
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate	L-glutamate, L-aspartate, L-cysteine (Zerangue and Kavanaugh, 1996a)
Synthetic substrates	DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate	DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate	DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate
Inhibitors ( $K_B$ or $K_i$ )	UCPH-101 ( $IC_{50}$ = 120 nM – membrane potential assay, Jensen <i>et al.</i> , 2009), DL-TBOA (9 $\mu$ M)	WAY-213613 ( $IC_{50}$ = 130 nM), DL-TBOA (0.12 $\mu$ M), (2 <i>S</i> ,4 <i>R</i> )-4-methylglutamate (3.4 $\mu$ M), dihydrokainate (9 $\mu$ M), <i>Threo</i> -3-methylglutamate (18 $\mu$ M)	NBI-59159 ( $IC_{50}$ = 25 nM), DL-TBOA ( $IC_{50}$ = 8 $\mu$ M), L- $\beta$ -BA ( $IC_{50}$ = 0.8 $\mu$ M – [ $^3$ H]-D-aspartate uptake assay)
Probes	[ $^3$ H]-ETB-TBOA ( $K_D$ = 15.5 nM), [ $^3$ H]-[(2 <i>S</i> ,4 <i>R</i> )-4-methylglutamate, [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate	[ $^3$ H]-ETB-TBOA ( $K_D$ = 16.2 nM), [ $^3$ H]-[(2 <i>S</i> ,4 <i>R</i> )-4-methylglutamate, [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate	[ $^3$ H]-ETB-TBOA ( $K_D$ = 320 nM), [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate
Stoichiometry	Probably 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out)	3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out) (Levy <i>et al.</i> , 1998)	3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out) (Zerangue and Kavanaugh, 1996b)

Common abbreviation	EAAT4	EAAT5
Systematic name	SLC1A6	SLC1A7
Nomenclature	Excitatory amino acid transporter 4	Excitatory amino acid transporter 5
Ensembl ID	ENSG00000105143	ENSG00000162383
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate
Synthetic substrates	DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate	DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate
Inhibitors ( $K_B$ or $K_i$ )	DL-TBOA (4.4 $\mu$ M), <i>Threo</i> -3-methylglutamate (50 $\mu$ M)	DL-TBOA (3.2 $\mu$ M)
Probes	[ $^3$ H]-ETB-TBOA ( $K_D$ = 24.8 nM), [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate	[ $^3$ H]-ETB-TBOA ( $K_D$ = 29.5 nM), [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate
Stoichiometry	Probably 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out)	Probably 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out)

The  $K_B$  (or  $K_i$ ) values reported, unless indicated otherwise, are derived from transporter currents mediated by EAATs expressed in voltage-clamped *Xenopus laevis* oocytes (Vandenberg *et al.*, 1997; Shimamoto *et al.*, 1998; Eliasof *et al.* 2001; Shigeri *et al.* 2001).  $K_B$  (or  $K_i$ ) values derived in uptake assays are generally higher (*e.g.* Shimamoto *et al.*, 1998). In addition to acting as a poorly transportable inhibitor of EAAT2, (2*S*,4*R*)-4-methylglutamate, also known as SYM2081, is a competitive substrate for EAAT1 ( $K_M$  = 54  $\mu$ M; Vandenberg *et al.*, 1997; Huang *et al.*, 2009) and additionally is a potent kainate receptor agonist (Zhou *et al.*, 1997) which renders the compound unsuitable for autoradiographic localisation of EAATs (Apricò *et al.*, 2007). Similarly, at concentrations that inhibit EAAT2, dihydrokainate binds to kainate receptors (Shimamoto *et al.* 1998). WAY-855 and WAY-213613 are both non-substrate inhibitors with a preference for EAAT2 over EAAT3 and EAAT1 (Dunlop *et al.*, 2003; Dunlop *et al.*, 2005). NBI-59159 is a non-substrate inhibitor with modest selectivity for EAAT3 over EAAT1 (>10-fold) and EAAT2 (5-fold) (Coon *et al.*, 2004; Dunlop, 2006). Analogously, L- $\beta$ -*threo*-benzyl-aspartate (L- $\beta$ -BA) is a competitive non-substrate inhibitor that preferentially blocks EAAT3 versus EAAT1, or EAAT2 (Esslinger *et al.*, 2005b). [ $^3$ H]-[(2*S*,4*R*)-4-methylglutamate demonstrates low affinity binding ( $K_D$  = 6.0  $\mu$ M) to EAAT1 and EAAT2 in rat brain homogenates (Apricò *et al.*, 2001) and EAAT1 in murine astrocyte membranes (Apricò *et al.*, 2004), whereas [ $^3$ H]-ETB-TBOA binds with high affinity to all EAATs other than EAAT3 (Shimamoto *et al.*, 2007). The novel isoxazole derivative (-)-HIP-A may interact at the same site as TBOA and preferentially inhibit reverse transport of glutamate (Colleoni *et al.*, 2008). *Threo*-3-methylglutamate induces substrate-like currents at EAAT4, but does not elicit heteroexchange of [ $^3$ H]-aspartate in synaptosome preparations, inconsistent with the behaviour of a substrate inhibitor (Eliasof *et al.*, 2001). Parawixin1, a compound isolated from the venom from the spider *Parawixia bistrata* is a selective enhancer of the glutamate uptake through EAAT2 but not through EAAT1 or EAAT3 (Fontana *et al.*, 2003, 2007). In addition to the agents listed in the table, DL-*threo*- $\beta$ -hydroxyaspartate and L-*trans*-2,4-pyrrolidine dicarboxylate act as non-selective competitive substrate inhibitors of all EAATs. Zn $^{2+}$  and arachidonic acid are putative endogenous modulators of EAATs with actions that differ across transporter subtypes (reviewed by Vandenberg *et al.*, 2004).

#### Alanine/serine/cysteine transporter subfamily

ASC transporters mediate Na $^+$ -dependent exchange of small neutral amino acids such as Ala, Ser, Cys and Thr and their structure is predicted to be similar to that of the glutamate transporters (Arizza *et al.*, 1993; Utsunomiya-Tate *et al.*, 1996). ASCT1 and ASCT2 also exhibit thermodynamically uncoupled chloride channel activity associated with substrate transport (Zerangue and Kavanaugh, 1996c; Bröer *et al.*, 2000). Whereas EAATs counter-transport K $^+$  (see above) ASCTs do not and their function is independent of the intracellular concentration of K $^+$  (Zerangue and Kavanaugh, 1996c).

Common abbreviation	ASCT1	ASCT2
Systematic name	SLC1A4	SLC1A5
Nomenclature	Alanine/serine/cysteine transporter 1	Alanine/serine/cysteine transporter 2

Common abbreviation	ASCT1	ASCT2
Other names	Neutral amino acid transporter A, SATT	Neutral amino acid transporter B(0), hATB <sup>o</sup> , AAAT
Ensembl ID	ENSG00000115902	ENSG00000105281
Endogenous substrates	L-cysteine > L-alanine = L-serine > L-threonine	L-alanine = L-serine = L-cysteine (low $V_{max}$ ) = L-threonine = L-glutamine = L-asparagine >> L-methionine ≡ L-glycine ≡ L-leucine > L-valine > L-glutamate (enhanced at low pH)
Inhibitors	–	<i>p</i> -nitrophenyl glutamyl anilide (Esslinger <i>et al.</i> , 2005a), benzylserine, benzylcysteine (Grewer and Grabsch, 2004)
Predicted stoichiometry	1 Na <sup>+</sup> : 1 amino acid (in): 1 Na <sup>+</sup> : 1 amino acid (out); (homo-, or hetero-exchange; Zerangue and Kavanaugh, 1996b)	1 Na <sup>+</sup> : 1 amino acid (in): 1 Na <sup>+</sup> : 1 amino acid (out); (homo-, or hetero-exchange; Bröer <i>et al.</i> , 1999)

The substrate specificity of ASCT1 may extend to proline and hydroxyproline (Pinilla-Tenas *et al.*, 2003). At low pH (~5.5) both ASCT1 and ASCT2 are able to exchange acidic amino acids such as cysteate and glutamate (Tamarappoo *et al.*, 1996; Utsunomiya-Tate *et al.*, 1996). In addition to the inhibitors tabulated above, HgCl<sub>2</sub>, methylmercury, mersalyl, at low micromolar concentrations, non-competitively inhibit ASCT2 by covalent modification of cysteine residues (Oppedisano *et al.*, 2010).

#### Further Reading

- Beart PM, O'Shea RD (2007). Transporters for L-glutamate: an update on their molecular pharmacology and pathological involvement. *Br J Pharmacol* **150**: 5–17.
- Bridges RJ, Esslinger CS (2005). The excitatory amino acid transporters: pharmacological insights on substrate and inhibitor specificity of the EAAT subtypes. *Pharmacol Ther* **107**: 271–285.
- Bunch L, Erichsen MN, Jensen AA (2009). Excitatory amino acid transporters as potential drug targets. *Expert Opin Ther Targets* **13**: 719–731.
- Chao XD, Fei F, Fei Z (2010). The role of excitatory amino acid transporters in cerebral ischemia. *Neurochem Res* **35**: 1224–1230.
- Danbolt NC (2001). Glutamate uptake. *Prog Neurobiol* **65**: 1–105.
- Dunlop J (2006). Glutamate based therapeutic approaches: targeting the glutamate transport system. *Curr Opin Pharmacol* **6**: 103–107.
- Dunlop J, Butera JA (2006). Ligands targeting the excitatory amino acid transporters (EAATs). *Curr Top Med Chem* **6**: 1897–1906.
- Fuchs BC, Bode BP (2005). Amino acid transporters ASCT2 and LAT1 in cancer: partners in crime? *Semin Cancer Biol* **15**: 254–266.
- Grewer C, Rauen T (2005). Electrogenic glutamate transporters in the CNS: molecular mechanism, pre-steady-state kinetics, and their impact on synaptic signaling. *J Membr Biol* **203**: 1–20.
- Grewer C, Gameiro A, Zhang Z, Tao Z, Braams S, Rauen T (2008). Glutamate forward and reverse transport: from molecular mechanism to transporter-mediated release after ischemia. *IUBMB Life* **60**: 609–619.
- Hinoi E, Takarada T, Tsuchihashi Y, Yoneda Y (2005). Glutamate transporters as drug targets. *Curr Drug Targets CNS Neurol Disord* **4**: 211–220.
- Huang YH, Bergles DE (2004). Glutamate transporters bring competition to the synapse. *Curr Opin Neurobiol* **14**: 346–352.
- Kanai Y, Hediger MA (2003). The glutamate and neutral amino acid transporter family: physiological and pharmacological implications. *Eur J Pharmacol* **479**: 237–247.
- Kanai Y, Hediger MA (2004). The glutamate/neutral amino acid transporter family SLC1: molecular, physiological and pharmacological aspects. *Pflügers Archiv* **447**: 465–468.
- Jiang J, Amara SG (2011). New views of glutamate transporter structure and function: advances and challenges. *Neuropharmacology* **60**: 172–181.
- Kanner BI (2006). Structure and function of sodium-coupled GABA and glutamate transporters. *J Membr Biol* **213**: 89–100.
- Kanner BI, Zomot E (2008). Sodium-coupled neurotransmitter transporters. *Chem Rev* **108**: 1654–1668.
- Kim K, Lee SG, Kegelman TP, Su ZZ, Das SK, Dash R *et al.* (2010). Role of excitatory amino acid transporter-2 (EAAT2) and glutamate in neurodegeneration: opportunities for developing novel therapeutics. *J Cell Physiol* **226**: 2484–2493.
- Lee A, Pow DV (2010). Astrocytes: glutamate transport and alternate splicing of transporters. *Int J Biochem Cell Biol* **42**: 1901–1906.
- McGivan JD, Bungard CI (2007). The transport of glutamine into mammalian cells. *Front Biosci* **12**: 874–882.
- Palacín M, Estévez R, Bertran J, Zorano A (1998). Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol Rev* **78**: 969–1054.
- Ryan RM, Vandenberg RJ (2005). A channel in a transporter. *Clin Exp Pharmacol Physiol* **32**: 1–6.
- Sheldon AL, Robinson MB (2007). The role of glutamate transporters in neurodegenerative diseases and potential opportunities for intervention. *Neurochem Int* **51**: 333–355.
- Shigeri Y, Seal RP, Shimamoto K (2004). Molecular pharmacology of glutamate transporters, EAATs and VGLUTs. *Brain Res Brain Res Rev* **45**: 250–265.
- Shimamoto K (2008). Glutamate transporter blockers for elucidation of the function of excitatory neurotransmission systems. *Chem Rec* **8**: 182–199.
- Sonders MS, Quick M, Javitch JA (2005). How did the neurotransmitter cross the bilayer? A closer look. *Curr Opin Neurobiol* **15**: 296–304.
- Tzingouris AV, Wadiche JI (2007). Glutamate transporters: confining runaway excitation by shaping synaptic transmission. *Nat Rev Neurosci* **8**: 935–947.
- Vandenberg RJ (2006). Mutational analysis of glutamate transporters. *Handb Exp Pharmacol* **175**: 113–135.
- Vandenberg RJ, Ryan RM (2005). How and why are channels in transporters? *Sci STKE* **19**: pe17.
- Vandenberg RJ, Ju P, Aubrey KR, Ryan RM, Mitrovic AD (2004). Allosteric modulation of neurotransmitter transporters at excitatory synapses. *Eur J Pharm Sci* **23**: 1–11.
- Vandenberg RJ, Huang S, Ryan RM (2008). Slips, leaks and channels in glutamate transporters. *Channels (Austin)* **2**: 51–58.

## References

- Amara SG, Arriza JL (1993). *Curr Opin Neurobiol* 3: 337–344.
- Apricò K *et al.* (2001). *J Neurochem* 77: 1218–1225.
- Apricò K *et al.* (2004). *J Neurosci Res* 75: 751–759.
- Apricò K *et al.* (2007). *Neurochem Int* 51: 507–516.
- Arizza J *et al.* (1993). *J Biol Chem* 268: 15329–15332.
- Bailey CG *et al.* (2011). *J Clin Inv* 121: 4464–4453.
- Boudker O *et al.* (2007). *Nature* 445: 387–393.
- Bröer A *et al.* (1999). *J Neurochem* 73: 2184–2194.
- Bröer A *et al.* (2000). *Biochem J* 346: 705–710.
- Colton CK *et al.* (2010). *J Biomol Screen* 15: 653–662.
- Colleoni S *et al.* (2008). *J Pharmacol Exp Ther* 326: 646–656.
- Coon TR *et al.* (2004). *Abstract Viewer/Itinerary Planner*, Program No. 168.10. Society for Neuroscience: Washington, DC.
- Dunlop J *et al.* (2003). *Br J Pharmacol* 140: 839–846.
- Dunlop J *et al.* (2005). *Mol Pharmacol* 68: 974–982.
- Eliasof S *et al.* (2001). *J Neurochem* 77: 550–557.
- Esslinger CS *et al.* (2005a). *Bioorg Med Chem* 13:1111–1118.
- Esslinger CS *et al.* (2005b). *Neuropharmacology* 49: 850–861.
- Fontana AC *et al.* (2003). *Br J Pharmacol* 139: 1297–1309.
- Fontana AC *et al.* (2007). *Mol Pharmacol* 72: 1228–1237.
- Gameiro A *et al.* (2011). *Biophys J* 100: 2623–2632.
- Ganel R *et al.* (2006). *Neurobiol Dis* 21: 556–567.
- Gebhardt FM *et al.* (2010). *J Biol Chem* 285: 31313–31324.
- Gendreau S *et al.* (2004). *J Biol Chem* 279: 39505–39512.
- Goursaud S *et al.* (2011). *FASEB J* doi: 10.1096/Fj.11-182337.
- Greuer C, Grabsch E (2004). *J Physiol* 557:747–759.
- Greuer C *et al.* (2005). *Biochemistry* 44:11913–11923.
- Grunwald M, Kanner BI (2000). *J Biol Chem* 275: 9684–9698.
- Huang S *et al.* (2009). *J Biol Chem* 284: 4510–4515.
- Koch HP *et al.* (2007). *J Neurosci* 27: 2943–2947.
- Jensen AA *et al.* (2009). *J Med Chem* 52: 912–915.
- Lau CL *et al.* (2011). *Br J Pharmacol* 163: 533–545.
- Leary GP *et al.* (2007). *J Neurosci* 27: 2938–2942.
- Lee SG *et al.* (2008). *J Biol Chem* 283:13116–13123.
- Levy L *et al.* (1998). *J Neurosci* 18: 9620–9628.
- Machtens JP *et al.* (2011). *J Biol Chem* 286: 23780–23788.
- Nothmann D *et al.* (2011). *J Biol Chem* 286: 3935–3943.
- Oppedisano F *et al.* (2010). *Biochem Pharmacol* 80: 1266–1273.
- Pinilla-Tenas J *et al.* (2003). *J Membr Biol* 195: 27–32.
- Reyes N *et al.* (2009). *Nature* 462: 880–885.
- Romera C *et al.* (2007). *J Cereb Blood Flow Metab* 27: 1327–1338.
- Rose EM *et al.* (2009). *J Neurosci* 29: 8143–8155.
- Rothstein JD *et al.* (2005). *Nature* 433: 73–77.
- Ryan RM, Mindell JA (2007). *Nat Struct Mol Biol* 14: 365–371.
- Ryan RM *et al.* (2004). *J Biol Chem* 279: 20742–20751.
- Shigeri Y *et al.* (2001). *J Neurochem* 79: 279–302.
- Shimamoto K *et al.* (1998). *Mol Pharmacol* 53: 195–201.
- Shimamoto K *et al.* (2007). *Mol Pharmacol* 71: 294–302.
- Tamarappoo B *et al.* (1996). *Biochim Biophys Acta* 1279: 131–136.
- Torres-Salazar D, Fahlke C (2007). *J Biol Chem* 282: 34719–33426.
- Utsunomiya-Tate N *et al.* (1996). *J Biol Chem* 271:14883–14890.
- Veruki ML *et al.* (2006). *Nat Neurosci* 11: 1388–1396.
- Vandenberg RJ *et al.* (1997). *Mol Pharmacol* 51: 809–815.
- Yernool D *et al.* (2004). *Nature* 431: 811–818.
- Zerangue N, Kavanaugh MP (1996a). *J Physiol* 493: 419–423.
- Zerangue N, Kavanaugh MP (1996b). *Nature* 383: 634–637.
- Zerangue N, Kavanaugh MP (1996c). *J Biol Chem* 271: 27991–27994.
- Zhou LM *et al.* (1997). *J Pharmacol Exp Ther* 280: 422–427.
- Zou S *et al.* (2011). *J Neurochem* 117: 833–840.

## SLC2 family of hexose and sugar alcohol transporters

**Overview:** the SLC2 family transports glucose, fructose, inositol and related hexoses. Three classes of glucose transporter can be identified, separating GLUT1–4 and 14; GLUT6, 8, 10 and 12; and GLUT5, 7, 9 and 11. Modelling suggests a 12 TM membrane topology, with intracellular termini, with functional transporters acting as homodimers or homotetramers.

Class I transporters are able to transport glucose, but not fructose, in the direction of the concentration gradient and may be inhibited non-selectively by phloretin and cytochalasin B. GLUT1 is the major glucose transporter in brain, placenta and erythrocytes, GLUT2 is found in the pancreas, liver and kidneys, GLUT3 is neuronal and placental, while GLUT4 is the insulin-responsive transporter found in skeletal muscle, heart and adipose tissue. GLUT14 appears to result from gene duplication of GLUT3 and is expressed in the testes (Wu and Freeze, 2002).

Systematic name	SLC2A1	SLC2A2	SLC2A3	SLC2A4	SLC2A14
Preferred abbreviation	GLUT1	GLUT2	GLUT3	GLUT4	GLUT14
Nomenclature	Glucose transporter 1	Glucose transporter 2	Glucose transporter 3	Glucose transporter 4	Glucose transporter 14
Other names	HepG2 glucose transporter, erythrocyte/brain glucose transporter	Liver glucose transporter	Fructose transporter, brain glucose transporter	Insulin-responsive glucose transporter	–
Ensembl ID	ENSG00000117394	ENSG00000163581	ENSG00000059804	ENSG00000181856	ENSG00000173262
Substrates	Glucose = glucosamine (Uldry <i>et al.</i> , 2002), dehydroascorbic acid (Bianchi and Rose, 1986)	Glucosamine > glucose (Uldry <i>et al.</i> , 2002)	Glucose	Glucosamine > glucose (Uldry <i>et al.</i> , 2002)	–
Probes	[ <sup>3</sup> H]-2-Deoxyglucose	[ <sup>3</sup> H]-2-Deoxyglucose	[ <sup>3</sup> H]-2-Deoxyglucose	[ <sup>3</sup> H]-2-Deoxyglucose	–

Class II transporters transport fructose and appear to be insensitive to cytochalasin B.

Systematic name	SLC2A5	SLC2A7	SLC2A9	SLC2A11
Preferred abbreviation	GLUT5	GLUT7	GLUT9	GLUT11
Nomenclature	Glucose transporter 5	Glucose transporter 7	Glucose transporter 9	Glucose transporter 11
Other names	Small intestine glucose transporter	–	–	–
Ensembl ID	ENSG00000142583	ENSG00000197241	ENSG00000109667	ENSG00000133460
Substrates	Fructose > glucose (Burant <i>et al.</i> , 1992)	Fructose, glucose (Cheeseman, 2008)	Fructose, uric acid (Caulfield <i>et al.</i> , 2008)	Glucose (Doege <i>et al.</i> , 2001), fructose (Manolescu <i>et al.</i> , 2007)

Class II transporters appear to be predominantly intracellularly located.

Systematic name	SLC2A6	SLC2A8	SLC2A10	SLC2A12
Preferred abbreviation	GLUT6	GLUT8	GLUT10	GLUT12
Nomenclature	Glucose transporter 6	Glucose transporter 8	Glucose transporter 10	Glucose transporter 12
Ensembl ID	ENSG00000160326	ENSG00000136856	ENSG00000197496	ENSG00000146411
Substrates	–	Glucose (Ibberson <i>et al.</i> , 2000)	Glucose, dehydroascorbic acid (Lee <i>et al.</i> , 2010)	Glucose (Rogers <i>et al.</i> , 2003)

Proton-coupled inositol transporters are expressed predominantly in the brain and can be inhibited by phloretin and cytochalasin B (Uldry *et al.*, 2002).

Systematic name	SLC2A13
Preferred abbreviation	HMIT
Nomenclature	Proton <i>myo</i> -inositol cotransporter
Ensembl ID	ENSG00000151229
Other names	H <sup>+</sup> - <i>myo</i> -inositol symporter
Substrates	<i>myo</i> -Inositol, <i>scyllo</i> -inositol, <i>chiro</i> -inositol, <i>muco</i> -inositol (Uldry <i>et al.</i> , 2002)
Stoichiometry	1 H <sup>+</sup> : 1 inositol (in) (Di Daniel <i>et al.</i> , 2009)

### Further Reading

- Augustin R (2010). The protein family of glucose transport facilitators: it's not only about glucose after all. *IUBMB Life* **62**: 315–333.
- Leney SE, Tavare JM (2009). The molecular basis of insulin-stimulated glucose uptake: signalling, trafficking and potential drug targets. *J Endocrinol* **203**: 1–18.
- Uldry M, Thorens B (2004). The SLC2 family of facilitated hexose and polyol transporters. *Pflugers Arch* **447**: 480–489.

### References

- Bianchi J, Rose RC (1986). *Proc Soc Exp Biol Med* **181**: 333–337.
- Burant CF *et al.* (1992). *J Biol Chem* **267**: 14523–14526.
- Caulfield MJ *et al.* (2008). *PLoS Med* **5**: e197.
- Cheeseman C (2008). *Am J Physiol Endocrinol Metab* **295**: E238–E241.
- Di Daniel E *et al.* (2009). *BMC Cell Biol* **10**: 54.
- Doege H *et al.* (2001). *Biochem J* **359**: 443–449.
- Ibberson M *et al.* (2000). *J Biol Chem* **275**: 4607–4612.
- Lee YC *et al.* (2010). *Hum Mol Genet* **19**: 3721–3733.
- Manolescu AR *et al.* (2007). *Mol Membr Biol* **24**: 455–463.
- Rogers S *et al.* (2003). *Biochem Biophys Res Commun* **308**: 422–426.
- Uldry M *et al.* (2002). *FEBS Lett* **524**: 199–203.
- Wu X, Freeze HH (2002). *Genomics* **80**: 553–557.

# SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)

**Overview:** these families combine to generate functional transporters, where the subunit composition is a disulphide-linked combination of a heavy chain (SLC3 family) with a light chain (SLC7 family).

**SLC3 family** members are single TM proteins with extensive glycosylation of the exterior C-terminus, which heterodimerize with SLC7 family members in the endoplasmic reticulum and assist in the plasma membrane localization of the transporter.

Systematic name	SLC3A1	SLC3A2
Common abbreviation	RBAT	4F2hc
Nomenclature	Cystine, dibasic, and neutral amino acid transporter	4F2 cell-surface antigen heavy chain
Ensembl ID	ENSG00000138079	ENSG00000168003
Other names	B <sup>0,+</sup> -type amino acid transport protein; D2H, ATR1	CD98 antigen Lymphocyte activation antigen 4F2 large subunit

**SLC7 family** members may be divided into two major groups: cationic amino acid transporters (CATs) and glycoprotein-associated amino acid transporters (gpaATs).

Cationic amino acid transporters are 14 TM proteins, which mediate pH- and sodium-independent transport of cationic amino acids (system y<sup>+</sup>), apparently as an exchange mechanism. These transporters are sensitive to inhibition by *N*-ethylmaleimide.

Systematic name	SLC7A1	SLC7A2	SLC7A3	SLC7A4	SLC7A14
Preferred abbreviation	CAT1	CAT2	CAT3	CAT4	–
Nomenclature	High affinity cationic amino acid transporter 1	Low affinity cationic amino acid transporter 2	Cationic amino acid transporter 3	Cationic amino acid transporter 4	–
Ensembl ID	ENSG00000139514	ENSG00000003989	ENSG00000165349	ENSG00000099960	ENSG0000013293
Other names	System Y <sup>+</sup> basic amino acid transporter, ecotropic retroviral leukemia receptor homolog, ERR, ATRC1	ATRC2	Cationic amino acid transporter y <sup>+</sup>	–	–
Substrates	L-Arginine, L-lysine, L-ornithine, L-histidine	L-Arginine, L-lysine, L-ornithine, L-histidine	L-Arginine, L-lysine, L-ornithine	–	–

CAT4 appears to be non-functional in heterologous expression (Wolf *et al.*, 2002), while SLC7A14 has yet to be characterized.

Glycoprotein-associated amino acid transporters are 12 TM proteins, which heterodimerize with members of the SLC3 family to act as cell-surface amino acid exchangers.

Heterodimers between 4F2hc and hLAT1 or hLAT2 generate sodium-independent system L transporters. These transport large neutral amino acids (L-leucine, L-isoleucine and L-methionine).

Heterodimers between 4F2hc and y<sup>+</sup>LAT1 or y<sup>+</sup>LAT2 generate sodium-dependent transporters, similar to the system y<sup>+</sup>L transporters. These transporters are *N*-ethylmaleimide-insensitive and transport neutral (L-leucine) as well as cationic (L-arginine, L-lysine and L-ornithine) amino acids. Heterodimers between RBAT and B<sup>0,+</sup>AT appear to mediate sodium-independent system b<sup>0,+</sup> transport of neutral and cationic amino acids (L-leucine, L-arginine, L-lysine and L-ornithine).

Systematic name	SLC7A5	SLC7A8	SLC7A7	SLC7A6	SLC7A9
Preferred abbreviation	hLAT1	hLAT2	y <sup>+</sup> LAT1	y <sup>+</sup> LAT2	B <sup>0,+</sup> AT
Nomenclature	L-type amino acid transporter 1	L-type amino acid transporter 2	y <sup>+</sup> L amino acid transporter 1	y <sup>+</sup> L amino acid transporter 2	B <sup>0,+</sup> -type amino acid transporter 1
Ensembl ID	ENSG00000103257	ENSG00000092068	ENSG00000155465	ENSG00000103064	ENSG00000021488

Systematic name	SLC7A5	SLC7A8	SLC7A7	SLC7A6	SLC7A9
Other names	Large neutral amino acids transporter small subunit 1, $\gamma^+$ system cationic amino acid transporter, 4F2 light chain, 4F2LC, CD98 light chain, integral membrane protein E16	Large neutral amino acids transporter small subunit 2	Monocyte amino acid permease 2, MOP-2	Cationic amino acid transporter, $\gamma^+$ system	Glycoprotein-associated amino acid transporter

Asc-1 appears to heterodimerize with 4F2hc to allow the transport of small neutral amino acids (such as L-alanine, L-serine and glycine), as well as D-serine, in a sodium-independent manner.

xCT generates a heterodimer with 4F2hc for a system  $x^c$  transporter that accumulates cystine in a sodium-independent manner.

AGT has been conjugated with SLC3 members as fusion proteins to generate functional transporters, but the identity of a native heterodimer has yet to be ascertained.

Systematic name	SLC7A10	SLC7A11	SLC7A13
Preferred abbreviation	Asc-1	xCT	XAT2
Nomenclature	Asc-type amino acid transporter 1	–	AGT1
Ensembl ID	ENSG00000130876	ENSG00000151012	ENSG00000164893

**Abbreviations:** CAT, cationic amino acid transporter, **gpaAT**, glycoprotein-associated amino acid transporter

### Further Reading

- Closs EI, Boissel JP, Habermeier A, Rotmann A (2006). Structure and function of cationic amino acid transporters (CATs). *J Membr Biol* **213**: 67–77.
- Palacin M, Kanai Y (2004). The ancillary proteins of HATs: SLC3 family of amino acid transporters. *Pflugers Arch* **447**: 490–494.
- Palacin M, Nunes V, Font-Llitjos M, Jimenez-Vidal M, Fort J, Gasol E *et al.* (2005). The genetics of heteromeric amino acid transporters. *Physiology (Bethesda)* **20**: 112–124.
- Verrey F, Closs EI, Wagner CA, Palacin M, Endou H, Kanai Y (2004). CATs and HATs: the SLC7 family of amino acid transporters. *Pflugers Arch* **447**: 532–542.

### Reference

- Wolf S *et al.* (2002). *Biochem J* **364**: 767–775.

## SLC4 family of bicarbonate transporters

**Overview:** together with the SLC26 family, the SLC4 family of transporters subserve anion exchange, principally of chloride and bicarbonate, but also carbonate and hydrogen sulphate ( $\text{HSO}_4^-$ ). SLC4 family members regulate bicarbonate fluxes as part of carbon dioxide movement, chyme neutralization and reabsorption in the kidney.

Within the family, subgroups of transporters are identifiable: the electroneutral sodium-independent  $\text{Cl}^-/\text{HCO}_3^-$  transporters (AE1, AE2 and AE3), the electrogenic sodium-dependent  $\text{HCO}_3^-$  transporters (NBCe1 and NBCe2) and the electroneutral  $\text{HCO}_3^-$  transporters (NBCn1 and NBCn2). Topographical information derives mainly from study of AE1, abundant in erythrocytes, which suggests a dimeric or tetrameric arrangement, with subunits made up of 13 TM domains and re-entrant loops at TM9/10 and TM11/12. The N terminus exhibits sites for interaction with multiple proteins, including glycolytic enzymes, haemoglobin and cytoskeletal elements.

Anion exchangers

Systematic name	SLC4A1	SLC4A2	SLC4A3	SLC4A9
Common abbreviation	AE1	AE2	AE3	AE4
Nomenclature	Anion exchange protein 1	Anion exchange protein 2	Anion exchange protein 3	Anion exchange protein 4
Ensembl ID	ENSG00000004939	ENSG00000164889	ENSG00000114923	ENSG00000113073
Other names	Band 3, CD233	Non-erythroid band 3-like protein, BND3L	Neuronal band 3-like protein, cardiac/brain band 3-like protein, CAE3/BAE3	Sodium bicarbonate cotransporter 5
Endogenous substrates	Chloride, bicarbonate	Chloride, bicarbonate	Chloride, bicarbonate	–
Stoichiometry	1 Cl <sup>-</sup> (in) : 1 HCO <sub>3</sub> <sup>-</sup> (out)	1 Cl <sup>-</sup> (in) : 1 HCO <sub>3</sub> <sup>-</sup> (out)	1 Cl <sup>-</sup> (in) : 1 HCO <sub>3</sub> <sup>-</sup> (out)	–

Sodium-dependent HCO<sub>3</sub><sup>-</sup> transporters

Systematic name	SLC4A4	SLC4A5	SLC4A7	SLC4A10
Common abbreviation	NBCE1	NBCE2	NBCn1	NBCn2
Nomenclature	Electrogenic sodium bicarbonate cotransporter 1	Electrogenic sodium bicarbonate cotransporter 4	Electroneutral sodium bicarbonate cotransporter 1	Electroneutral sodium bicarbonate cotransporter 2
Ensembl ID	ENSG00000080493	ENSG00000188687	ENSG00000033867	ENSG00000144290
Other names	Sodium bicarbonate cotransporter, kNBC1, NBC2, pNBC	NBC4	Sodium bicarbonate cotransporter 3, NBC3	Sodium-driven chloride bicarbonate exchanger, NCBE
Endogenous substrates	Sodium bicarbonate	Sodium bicarbonate	Sodium bicarbonate	Sodium bicarbonate
Stoichiometry	1 Na <sup>+</sup> : 2/3 HCO <sub>3</sub> <sup>-</sup> (out) or 1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2*</sup> (out) or 1 NaCO <sub>3</sub> <sup>-</sup> (out)	1 Na <sup>+</sup> : 2/3 HCO <sub>3</sub> <sup>-</sup> (out) or 1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2*</sup> (out) or 1 NaCO <sub>3</sub> <sup>-</sup> (out)	1 Na <sup>+</sup> : 1 HCO <sub>3</sub> <sup>-</sup> (out) or 1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2*</sup> (out) or 1 NaCO <sub>3</sub> <sup>-</sup> (out)	1 Na <sup>+</sup> : 1 HCO <sub>3</sub> <sup>-</sup> (out) or 1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2*</sup> (out) or 1 NaCO <sub>3</sub> <sup>-</sup> (out)

Systematic name	SLC4A8	SLC4A11
Common abbreviation	NDCBE	BTR1
Ensembl ID	ENSG00000050438	ENSG00000088836
Other names	Electroneutral Na <sup>+</sup> -driven Cl-HCO <sub>3</sub> exchanger, k-NBC3	NaBC1, bicarbonate transporter-related protein 1
Endogenous substrates	Chloride, sodium bicarbonate	–
Stoichiometry	1 Na <sup>+</sup> : 2HCO <sub>3</sub> <sup>-</sup> (in) : 1 Cl <sup>-</sup> (out)	–

## Further Reading

Alper SL (2009). Molecular physiology and genetics of Na<sup>+</sup>-independent SLC4 anion exchangers. *J Exp Biol* 212: 1672–1683.  
Romero MF, Fulton CM, Boron WF (2004). The SLC4 family of HCO<sub>3</sub><sup>-</sup> transporters. *Pflugers Arch* 447: 495–509.

## SLC5 family of sodium-dependent transporters

**Overview:** The SLC5 family of sodium-dependent transporters includes, in mammals, the Na<sup>+</sup>/substrate co-transporters for choline, glucose, monocarboxylates, *myo*-inositol and iodide (Ferguson and Blakely, 2004; Wright and Turk, 2004; Ganapathy *et al.*, 2008; Wright *et al.*, 2011). Members of the SLC5 and SLC6 families, along with other unrelated Na<sup>+</sup> cotransporters (*i.e.* Mhp1 and BetP), share a common structural core that contains an inverted repeat of 5TM  $\alpha$ -helical domains (Abramson and Wright, 2009).

### Choline transporter

The high affinity, hemicholinium-3-sensitive, choline transporter (CHT) is expressed mainly in cholinergic neurones on nerve cell terminals and synaptic vesicles (keratinocytes being an additional location). In autonomic neurones, expression of CHT requires an activity-dependent retrograde signal from postsynaptic neurones (Krishnaswamy and Cooper 2009). Through recapture of choline generated by the hydrolysis of ACh by acetylcholinesterase, CHT serves to maintain ACh synthesis within the presynaptic terminal (Ferguson and Blakely, 2004). Homozygous mice engineered to lack CHT die within one hour of birth as a result of hypoxia arising from failure of transmission at the neuromuscular junction of the skeletal muscles that support respiration (Ferguson *et al.*, 2004). A low affinity choline uptake mechanism that remains to be identified at the molecular level may involve multiple transporters. In addition, a family of choline transporter-like (CTL) proteins, (which are members of the SLC44 family) with weak Na<sup>+</sup>dependence have been described (Traiffort *et al.*, 2005).



Common abbreviation	CHT
Systematic name	SLC5A7
Other names	CHT1, choline transporter 1
Ensembl ID	ENSG00000115665
Endogenous substrates	Choline
Synthetic substrates	Triethylcholine
Selective inhibitors ( $K_i$ )	HC-3 (1-5 nM)
Probes ( $K_D$ )	[ $^3$ H]-HC-3 (4-6 nM)
Stoichiometry	Na $^+$ : choline (variable stoichiometry); modulated by extracellular Cl $^-$ (Iwamoto <i>et al.</i> , 2006)

$K_i$  and  $K_D$  values for hemicholinium-3 listed in the table are for human CHT expressed in *Xenopus laevis* oocytes (Okuda and Haga, 2000), or COS-7 cells (Apparsundaram *et al.*, 2000). Hemicholinium mustard is a substrate for CHT that causes covalent modification and irreversible inactivation of the transporter. Several exogenous substances (*e.g.* triethylcholine) that are substrates for CHT act as precursors to cholinergic false transmitters.

### Hexose transporter family

Detailed characterisation of members of the hexose transporter family is limited to SGLT1, 2 and 3, which are all inhibited in a competitive manner by phlorizin, a natural dihydrocholine glucoside, that exhibits modest selectivity towards SGLT2 (see Wright *et al.*, 2011 for an extensive review). SGLT1 is predominantly expressed in the small intestine, mediating the absorption of glucose, but also occurs in the brain, heart and in the late proximal straight tubule of the kidney. The expression of SGLT2 is almost exclusively restricted to the early proximal convoluted tubule of the kidney, where it is largely responsible for the renal reabsorption of glucose. SGLT3 is not a transporter but instead acts as a glucosensor generating an inwardly directed flux of Na $^+$  that causes membrane depolarization (Diez-Sampedro *et al.*, 2003).

Common abbreviation	SGLT1	SGLT2	SGLT3	SGLT4	SGLT5
Systematic name	SLC5A1	SLC5A2	SLC5A4	SLC5A9	SLC5A10
Other names	Sodium/glucose cotransporter 1, high affinity sodium-glucose cotransporter	Sodium/glucose cotransporter 2, low affinity sodium-glucose cotransporter	Low affinity sodium-glucose cotransporter, sodium/glucose cotransporter 3 (note, these previous names are a misnomer since SGLT3 is a glucosensor)	Sodium/glucose cotransporter 4	Sodium/glucose cotransporter 5
Ensembl ID	ENSG00000100170	ENSG00000140675	ENSG00000100191	ENSG00000117834	ENSG00000154025
Substrates	D-glucose, D-galactose	D-glucose	Ligands include D-glucose, 1-deoxyojirimycin, miglitol, miglustat, N-ethyl-1-deoxyojirimycin, and 1-deoxyojirimycin-1-sulfonic acid	D-glucose, D-mannose	D-glucose, D-galactose
Synthetic substrates	$\alpha$ MDG	$\alpha$ MDG	–	$\alpha$ MDG	–
Inhibitors (pIC $_{50}$ )	Dapagliflozin (5.9), canagliflozin (6.4), empagliflozin (5.1), remogliflozin (p <i>K<sub>i</sub></i> = 5.4), sergliflozin (p <i>K<sub>i</sub></i> = 5.1)	Dapagliflozin (9.0), canagliflozin (8.7), empagliflozin (8.5), remogliflozin (p <i>K<sub>i</sub></i> = 7.9), sergliflozin (p <i>K<sub>i</sub></i> = 6.8)	–	–	–
Stoichiometry	2 Na $^+$ : 1 glucose (Kanai <i>et al.</i> , 1994)	1 Na $^+$ : 1 glucose (Hummel <i>et al.</i> , 2011)	–	–	–

Recognition and transport of substrate by SGLTs requires that the sugar is a pyranose. De-oxyglucose derivatives have reduced affinity for SGLT1, but the replacement of the sugar equatorial hydroxyl group by fluorine at some positions, excepting C2 and C3, is tolerated (see Wright *et al.*, 2011 for a detailed quantification). Although SGLT1 and SGLT2 have been described as high- and low-affinity sodium glucose co-transporters, respectively, recent work suggests that they have a similar affinity for glucose under physiological conditions (Hummel *et al.*, 2011). Selective blockers of SGLT2, and thus blocking ~50% of renal glucose reabsorption, are in development for the treatment of diabetes (*e.g.* Chao and Henry, 2010).

#### Sodium iodide symporter, sodium-dependent multivitamin transporter and sodium-coupled monocarboxylate transporters

The sodium-iodide symporter (NIS) is an iodide transporter found principally in the thyroid gland where it mediates the accumulation of iodide within thyrocytes. Transport of iodide by NIS from the blood across the basolateral membrane followed by apical efflux into the colloidal lumen, mediated at least in part by pendrin (SLC22A4), and most likely not SMCT1 (SLC5A8) as once thought, provides the iodide required for the synthesis of the thyroid hormones triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) (Bizhanova and Kopp, 2009). NIS is also expressed in the salivary glands, gastric mucosa, intestinal enterocytes and lactating breast. NIS mediates I<sup>-</sup> absorption in the intestine and I<sup>-</sup> secretion into the milk. SMVT is expressed on the apical membrane of intestinal enterocytes and colonocytes and is the main system responsible for biotin (vitamin H) and pantothenic acid (vitamin B<sub>5</sub>) uptake in humans (Said, 2009). SMVT located in kidney proximal tubule epithelial cells mediates the reabsorption of biotin and pantothenic acid. SMCT1 (SLC5A8), which transports a wide range of monocarboxylates, is expressed in the apical membrane of epithelia of the small intestine, colon, kidney, brain neurones and the retinal pigment epithelium (Ganapathy *et al.*, 2008). SMCT2 (SLC5A12) also localises to the apical membrane of kidney, intestine, and colon, but in the brain and retina is restricted to astrocytes and Müller cells, respectively (Ganapathy *et al.*, 2008). SMCT1 is a high-affinity transporter whereas SMCT2 is a low-affinity transporter. The physiological substrates for SMCT1 and SMCT2 are lactate, pyruvate, propionate, and nicotinate in non-colonic tissues such as the kidney. SMCT1 is also likely to be the principal transporter for the absorption of nicotinate (vitamin B<sub>3</sub>) in the intestine and kidney (Gopal *et al.*, 2005). In the small intestine and colon, the physiological substrates for these transporters are nicotinate and the short-chain fatty acids acetate, propionate, and butyrate that are produced by bacterial fermentation of dietary fiber (Miyachi *et al.*, 2004). In the kidney, SMCT2 is responsible for the bulk absorption of lactate because of its low-affinity/high-capacity nature. Absence of both transporters in the kidney leads to massive excretion of lactate in urine and consequently drastic decrease in the circulating levels of lactate in blood (Thangaraju *et al.*, 2006a). SMCT1 also functions as a tumour suppressor in the colon as well as in various other non-colonic tissues (Ganapathy *et al.*, 2009). The tumour-suppressive function of SMCT1 is based on its ability to transport pyruvate, an inhibitor of histone deacetylases, into cells in non-colonic tissues (Thangaraju *et al.*, 2006b); in the colon, the ability of SMCT1 to transport butyrate and propionate, also inhibitors of histone deacetylases, underlies the tumour-suppressive function of this transporter (Gupta *et al.*, 2006; Ganapathy *et al.*, 2008; Ganapathy *et al.*, 2009). The ability of SMCT1 to promote histone acetylase inhibition through accumulation of butyrate and propionate in immune cells is also responsible for suppression of dendritic cell development in the colon (Singh *et al.*, 2010).

Common abbreviation	NIS	SMVT	SMCT1	SMCT2
Systematic name	SLC5A5	SLC5A6	SLC5A8	SLC5A12
Other names	Sodium/iodide cotransporter, sodium-iodide symporter	Sodium-dependent multivitamin transporter	Sodium-coupled monocarboxylate transporter 1, electrogenic sodium monocarboxylate cotransporter, sodium iodide-related cotransporter, apical iodide transporter (AIT)	Sodium-coupled monocarboxylate transporter 2, electroneutral sodium monocarboxylate cotransporter, low-affinity sodium-lactate cotransporter
Ensembl ID	ENSG00000105641	ENSG00000138074	ENSG00000139357	ENSG00000148942
Substrates	I <sup>-</sup> , thiocyanate, nitrate	Pantothenic acid, biotin, lipoic acid, I <sup>-</sup> (de Carvalho and Quick, 2011)	Butyrate, L-lactate, propionate, acetoacetate, α-ketoisocaproate, nicotinate, pyroglutamate, pyruvate, D-lactate, β-D-hydroxybutyrate, γ-hydroxybutyrate, β-L-hydroxybutyrate, acetate	Lactate, pyruvate, nicotinate
Synthetic substrates	Perchlorate, pertectnetate	–	Benzoate, salicylate, 5-aminosalicylate, 2-oxothiazolidine-4-carboxylate, dichloroacetate, 8-bromopyruvate	–
Inhibitors (pIC <sub>50</sub> )	–	–	Ibuprofen (4.2), ketoprofen, fenoprofen	–
Stoichiometry	2 Na <sup>+</sup> : 1 I <sup>-</sup> (Eskandari <i>et al.</i> , 1997); 1 Na <sup>+</sup> : 1 ClO <sub>4</sub> <sup>-</sup> (Dohan <i>et al.</i> , 2007)	2 Na <sup>+</sup> : 1 biotin (or pantothenic acid) (Prasad <i>et al.</i> , 2000)	2 Na <sup>+</sup> : 1 monocarboxylate (Coady <i>et al.</i> , 2007)	–

I-, perchlorate, thiocyanate and nitrate are competitive substrate inhibitors of NIS (Dohan *et al.*, 2007).  $\alpha$ -Lipoic acid appears to act as a competitive substrate inhibitor of SMVT (Wang *et al.*, 1999) and the anticonvulsant drugs primidone and carbamazepine competitively block the transport of biotin by brush border vesicles prepared from human intestine (Said *et al.*, 1998).

### Sodium myo-inositol cotransporter transporters

Three different mammalian myo-inositol cotransporters are currently known; two are the Na<sup>+</sup>-coupled SMIT1 and SMIT2 tabulated below and the third is proton-coupled HMIT (SLC2A13). SMIT1 and SMIT2 have a widespread and overlapping tissue location but in polarized cells, such as the Madin-Darby canine kidney cell line, they segregate to the basolateral and apical membranes, respectively (Bissonnette *et al.*, 2004). In the nephron, SMIT1 mediates myo-inositol uptake as a 'compatible osmolyte' when inner medullary tubules are exposed to increases in extracellular osmolality, whilst SMIT2 mediates the reabsorption of myo-inositol from the filtrate. In some species (*e.g.* rat, but not rabbit) apically located SMIT2 is responsible for the uptake of myo-inositol from the intestinal lumen (Aouameur *et al.*, 2007).

Common abbreviation	SMIT1	SMIT2
Systematic name	SLC5A3	SLC5A11
Other names	Sodium/myo-inositol cotransporter (SMIT)	Sodium/myo-inositol cotransporter 2, sodium/glucose cotransporter6, kST1
Ensembl ID	ENSG00000198743	ENSG00000158865
Substrates	Myo-inositol, scyllo-inositol > L-fucose > L-xylose > L-glucose, D-glucose, alpha-methyl-D-glucopyranoside > D-galactose, D-fucose > D-xylose (Hager <i>et al.</i> , 1995)	Myo-inositol = D-chiro-inositol > D-glucose > D-xylose > L-xylose (Coady <i>et al.</i> , 2002)
Inhibitors	Phlorizin	Phlorizin
Stoichiometry	2 Na <sup>+</sup> :1 myo-inositol (Hager <i>et al.</i> , 1995)	2 Na <sup>+</sup> :1 myo-inositol (Bourgeois <i>et al.</i> , 2005)

The data tabulated are those for dog SMIT1 and rabbit SMIT2. SMIT2 transports D-chiro-inositol, but SMIT1 does not. In addition, whereas SMIT1 transports both D- and L-xylose and D- and L-fucose, SMIT2 transports only the D-isomers of these sugars (Hager *et al.*, 1995; Coady *et al.*, 2002). Thus the substrate specificities of SMIT1 (for L-fucose) and SMIT2 (for D-chiro-inositol) allow discrimination between the two SMITs. Human SMIT2 appears not to transport glucose (Lin *et al.*, 2009).

**Abbreviations:** HC-3, hemicholinium-3;  $\alpha$ MDG,  $\alpha$ -methyl-D-glucose pyranoside

### Further Reading

- Abramson J, Wright EM (2009). Structure and function of Na(+)-symporters with inverted repeats. *Curr Opin Struct Biol* 19: 425–432.
- Amenta F, Tayebati SK (2008). Pathways of acetylcholine synthesis, transport and release as targets for treatment of adult-onset cognitive dysfunction. *Curr Med Chem* 15: 488–498.
- Bailey CJ (2011). Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* 32: 63–71.
- Bazalakova MH, Blakely RD (2006). The high-affinity choline transporter: a critical protein for sustaining cholinergic signaling as revealed in studies of genetically altered mice. *Handb Exp Pharmacol* 175: 525–544.
- Bizhanova A, Kopp P (2009). The sodium-iodide symporter NIS and pendrin in iodide homeostasis of the thyroid. *Endocrinology*, 150: 1084–1090.
- Boldys A, Okopien B (2009). Inhibitors of type 2 sodium glucose co-transporters—a new strategy for diabetes treatment. *Pharmacol Rep* 61: 778–784.
- Chao EC, Henry RR (2010). SGLT2 inhibitor – a novel strategy for diabetes treatment. *Nat Rev Drug Dev* 9: 511–559.
- Ferguson SM, Blakely RD (2004). The choline transporter resurfaces: new roles for synaptic vesicles. *Mol Interv* 4: 22–37.
- Ganapathy V, Thangaraju M, Gopal E, Martin PM, Itagaki S, Miyauchi S, Prasad PD (2008). Sodium-coupled monocarboxylate transporters in normal tissues and in cancer. *AAPS J* 10: 193–199.
- Ganapathy V, Thangaraju M, Prasad PD (2009). Nutrient transporters in cancer: relevance to Warburg hypothesis and beyond. *Pharmacol Ther* 121: 29–40.
- Ghosh RK, Ghosh SM, Chawla S, Jasanwala SA (2011). SGLT2 inhibitors: a new emerging therapeutic class in the treatment of type 2 diabetes mellitus. *J Clin Pharmacol* doi: 10-1177/091270011400604.x
- Kinne RK, Castaneda F (2011). SGLT inhibitors as new therapeutic tools in the treatment of diabetes *Handb Exp Pharmacol* 203: 105–126.
- Okuda T, Haga T (2003). High-affinity choline transporter. *Neurochem Res* 28: 483–488.
- Ribeiro FM, Black SA, Prado VF, Rylett RJ, Ferguson SS, Prado MA. (2006). The “ins” and “outs” of the high-affinity choline transporter CHT1. *J Neurochem* 97: 1–12.
- Sabino-Silva R, Mori RC, David-Silva A, Okamoto MM, Freitas HS, Machado UF. (2010). The Na<sup>+</sup>/glucose cotransporters: from genes to therapy. *Braz J Med Biol Res* 43: 1019–1026.
- Said HM (2009). Cell and molecular aspects of human intestinal biotin absorption. *J Nutr* 139: 158–162.
- Sarter M, Parikh V (2005). Choline transporters, cholinergic transmission and cognition. *Nat Rev Neurosci* 6: 48–56.
- Uldry M, Thorens B (2004). The SLC2 family of facilitated hexose and polyol transporters. *Pflügers Arch* 447: 480–489.
- Wright EM, Loo DD, Hirayama BA (2004). Surprising versatility of Na<sup>+</sup>-glucose cotransporters: SLC5. *Physiology* 19: 370–376.
- Wright EM, Loo DD, Hirayama BA (2011). Biology of human sodium glucose transporters. *Physiol Rev* 91: 733–794.
- Wright EM, Turk E (2004). The sodium/glucose cotransport family SLC5. *Pflügers Arch* 447: 510–518.

## References

- Aouameur R *et al.* (2007). *Am J Physiol* **293**: G1300–G1307.
- Apparsundaram S *et al.* (2000). *Biochem Biophys Res Commun* **276**: 862–867.
- Bissonnette P *et al.* (2004). *J Physiol* **558**: 759–768.
- Bourgeois F *et al.* (2005). *J Physiol* **563**: 333–343.
- Coady MJ *et al.* (2002). *J Biol Chem* **277**: 35219–35224.
- Coady MJ *et al.* (2007). *Biophys J* **93**: 2325–2331.
- De Carvalho FD, Quick M (2011). *J Biol Chem* **286**: 131–137.
- Diez-Sampedro A *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 11753–11758.
- Dohan O *et al.* (2007). *Proc Natl Acad Sci U S A* **104**: 20250–20255.
- Eskandari S *et al.* (1997). *J Biol Chem* **272**: 27230–27238.
- Ferguson SM *et al.* (2004). *Proc Natl Acad Sci U S A* **101**: 8762–8767.
- Gopal E *et al.* (2005). *Biochem J* **388**: 309–316.
- Gupta N *et al.* (2006). *Life Sci* **78**: 2419–2425.
- Iwamoto H *et al.* (2006). *J Neurosci* **26**: 9851–9859.
- Hager K *et al.* (1995). *J Membr Biol* **143**: 103–113.
- Hummel CS *et al.* (2011). *Am J Physiol Cell Physiol* **300**: C14–C21.
- Kanai Y *et al.* (1994). *J Clin Invest* **93**: 397–404.
- Krishnaswamy A, Cooper E (2009). *Neuron* **61**: 272–286.
- Lin X *et al.* (2009). *Arch Biochem Biophys* **481**: 197–201.
- Miyauchi S *et al.* (2004). *J Biol Chem* **279**: 13293–13296.
- Okuda T, Haga T (2000). *FEBS Lett* **484**: 92–97.
- Prasad PD *et al.* (2000). *Biochem Biophys Res Commun* **270**: 836–840.
- Said HM *et al.* (1998). *Am J Clin Nutr* **49**: 127–131.
- Singh N *et al.* (2010). *J Biol Chem* **285**: 27601–27608.
- Thangaraju M *et al.* (2006a). *J Biol Chem* **281**: 26769–26773.
- Thangaraju M *et al.* (2006b). *Cancer Res* **66**: 11560–11564.
- Traiffort E *et al.* (2005). *J Neurochem* **92**: 1116–1125.
- Wang H *et al.* (1999). *J Biol Chem* **274**: 14875–14883.

## SLC6 neurotransmitter transporter family

**Overview:** Members of the solute carrier family 6 (SLC6) of sodium- and (sometimes chloride-) dependent neurotransmitter transporters (see Chen *et al.*, 2004; Bröer, 2006; Kristensen *et al.*, 2011) are primarily plasma membrane located and may be divided into four subfamilies that transport monoamines, GABA, glycine and neutral amino acids, plus the related bacterial NSS transporters (see Saier *et al.*, 2009). The members of this superfamily share a structural motif of 10 TM segments that has been observed in crystal structures of the NSS bacterial homolog LeuT<sub>Aa</sub>, a Na<sup>+</sup>-dependent amino acid transporter from *Aquiflex aeolicus* (Yamashita *et al.*, 2005) and in several other transporter families structurally related to LeuT (Forrest and Rudnick, 2009).

### Monoamine transporter subfamily

Monoamine neurotransmission is limited by perisynaptic transporters. Presynaptic monoamine transporters allow recycling of synaptically released noradrenaline, dopamine and 5-hydroxytryptamine.

Common abbreviation	NET	DAT	SERT
Systematic name	SLC6A2	SLC6A3	SLC6A4
Other names	NAT1	DAT1	5-HTT, SERT1
Ensembl ID	ENSG00000103546	ENSG00000142319	ENSG00000108576
Endogenous substrates	Noradrenaline, adrenaline, dopamine	Dopamine, adrenaline, noradrenaline	5-HT
Synthetic substrates	Amphetamine, methamphetamine, MPP <sup>+</sup>	Amphetamine, methamphetamine, MPP <sup>+</sup>	<i>p</i> -Chloroamphetamine, MDMA
Selective inhibitors (pK <sub>i</sub> )	Mazindol (8.9), nisoxetine (8.4), nomifensine (8.1), reboxetine (8.0, Wong <i>et al.</i> , 2000)	Mazindol (8.0), WIN35428 (7.9), GBR12935 (7.6)	Paroxetine (9.6, Tatsumi <i>et al.</i> , 1997), sertraline (9.1), fluoxetine (8.5, Tatsumi <i>et al.</i> , 1997)
Probes	[ <sup>3</sup> H]-Mazindol (0.5 nM), [ <sup>3</sup> H]-nisoxetine (4 nM)	[ <sup>3</sup> H]-GBR12935 (3 nM, Pristupa <i>et al.</i> , 1994), [ <sup>3</sup> H]-WIN35428 (10 nM, Pristupa <i>et al.</i> , 1994)	[ <sup>3</sup> H]-Paroxetine (0.2 nM), [ <sup>3</sup> H]-citalopram (5 nM)
Predicted stoichiometry	1 Noradrenaline: 1 Na <sup>+</sup> :1 Cl <sup>-</sup> (Gu <i>et al.</i> , 1996)	1 Dopamine:1–2 Na <sup>+</sup> :1 Cl <sup>-</sup> (Gu <i>et al.</i> , 1994)	1 5-HT:1 Na <sup>+</sup> :1 Cl <sup>-</sup> (in), + 1 K <sup>+</sup> (out) (Talvenheim <i>et al.</i> , 1983)

[<sup>125</sup>I]-RTI55 labels all three monoamine transporters (NET, DAT and SERT) with affinities between 0.5 and 5 nM. Cocaine is an inhibitor of all three transporters with pK<sub>i</sub> values between 6.5 and 7.2. Potential alternative splicing sites in non-coding regions of SERT and NET have been identified. A bacterial homologue of SERT shows allosteric modulation by selected anti-depressants (Singh *et al.*, 2007).

### GABA transporter subfamily

The activity of GABA-transporters located predominantly upon neurones (GAT1), glia (GAT3) or both (GAT2, BGT1) serves to terminate phasic GABA-ergic transmission, maintain low ambient extracellular concentrations of GABA, and recycle GABA for reuse by neurones. Nonetheless, ambient concentrations of GABA are sufficient to sustain tonic inhibition mediated by high affinity GABA<sub>A</sub> receptors in certain neuronal populations (Semyanov *et al.*, 2004). GAT1 is the predominant GABA transporter in the brain and occurs primarily upon the terminals of presynaptic neurones and to a much lesser extent upon distal astrocytic processes that are in proximity to axons terminals. GAT3 resides predominantly on distal astrocytic terminals that are close to the GABAergic synapse. By contrast, BGT1 occupies an extrasynaptic location possibly along with GAT2 which has limited expression in the brain (Madsen *et al.*, 2010). TauT is a high affinity taurine transporter involved in osmotic balance that occurs in the brain and non-neuronal tissues, such as the kidney, brush border membrane of the intestine and blood

brain barrier (Chen *et al.*, 2004; Han *et al.*, 2006). CT1, which transports creatine, has a ubiquitous expression pattern, often co-localizing with creatine kinase (Chen *et al.*, 2004).

Common abbreviation	GAT1	GAT2	GAT3
Systematic name	SLC6A1	SLC6A13	SLC6A11
Other names	mGAT1, GAT-A	mGAT3	mGAT4, GAT-B
Ensembl ID	ENSG00000157103	ENSG00000010379	ENSG00000132164
Endogenous substrates	GABA	GABA, $\beta$ -alanine	GABA, $\beta$ -alanine
Synthetic substrates	Nipecotic acid, guvacine	Nipecotic acid, guvacine	Nipecotic acid, guvacine
Selective inhibitors (IC <sub>50</sub> )	NNC-711 (0.14–1.4 $\mu$ M), SKF89976A (0.13 $\mu$ M), CI-966 (0.26 $\mu$ M), tiagabine (0.11 – 2.4 $\mu$ M), (R/S) EF-1500 (2 – 13 $\mu$ M) (R)-EF1502 (4 $\mu$ M – 8.9 $\mu$ M), LU32-176B (4 $\mu$ M), (S)-EF-1502 (120 $\mu$ M – > 250 $\mu$ M)	SNAP-5114 (20 $\mu$ M)	SNAP-5114 (6.6 $\mu$ M)
Probes	[ <sup>3</sup> H]Tiagabine	–	–
Predicted stoichiometry	2 Na <sup>+</sup> : 1Cl <sup>-</sup> : 1GABA	2 Na <sup>+</sup> : 1Cl <sup>-</sup> :1GABA	$\geq$ 2 Na <sup>+</sup> : 2 Cl <sup>-</sup> : 1GABA

Common abbreviation	BGT1	TauT	CT1
Systematic name	SLC6A12	SLC6A6	SLC6A8
Other names	mGAT2	Sodium- and chloride-dependent taurine transporter	Sodium- and chloride-dependent creatine transporter 1, CRT, CRTR, SLC6A10
Ensembl ID	ENSG00000111181	ENSG00000131389	ENSG00000130821
Endogenous substrates	GABA, betaine	Taurine, $\beta$ -alanine, GABA (Anderson <i>et al.</i> , 2009)	Creatine
Synthetic substrates	–	–	–
Selective inhibitors (IC <sub>50</sub> )	NNC052090 (1.4 $\mu$ M), (R)-EF-1502 (22 $\mu$ M–180 $\mu$ M), (R/S) EF-1500 (26 $\mu$ M) (S)-EF-1502 (34 $\mu$ M – > 250 $\mu$ M), LU32-176B (>100 $\mu$ M)	–	–
Predicted stoichiometry	3 Na <sup>+</sup> : 1 (or 2) Cl <sup>-</sup> : 1 GABA	2 Na <sup>+</sup> : 1Cl <sup>-</sup> : 1 taurine	Probably 2 Na <sup>+</sup> : 1Cl <sup>-</sup> : 1 creatine

The IC<sub>50</sub> values for GAT1-3 reported in the table reflect the range reported in the literature from studies of both human and mouse transporters. There is a tendency towards lower IC<sub>50</sub> values for the human orthologue (Kvist *et al.* 2009). SNAP-5114 is only weakly selective for GAT2 and GAT3, with IC<sub>50</sub> values in the range 22 to >30  $\mu$ M at GAT1 and BGT1, whereas NNC052090 has at least an order of magnitude selectivity for BGT1 [see Schousboe *et al.* (2004b) and Clausen *et al.* (2006) for reviews]. (R)-(1-[2-[tris(4-methoxyphenyl)methoxy]ethyl]pyrrolidin-2-yl)acetic acid is a compound that displays 20-fold selectivity for GAT3 over GAT1 (Fülep *et al.*, 2006). In addition to the inhibitors listed, EGYT3886 is a moderately potent, though non-selective, inhibitor of all cloned GABA transporters (IC<sub>50</sub> = 26–46  $\mu$ M; Dhar *et al.*, 1994). Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine that potentially inhibit the uptake of [<sup>3</sup>H]GABA into rat synaptosomes have been described (Knutsen *et al.*, 1999). Several derivatives of *exo*-THPO (e.g. *N*-methyl-*exo*-THPO and *N*-acetyloxyethyl-*exo*-THPO) demonstrate selectivity as blockers of astroglial, *versus* neuronal, uptake of GABA [see Schousboe *et al.* (2004a) and Clausen *et al.* (2006) for reviews]. GAT3 is inhibited by physiologically relevant concentrations of Zn<sup>2+</sup> (Cohen-Kfir *et al.*, 2005). TauT transports GABA, but with low affinity, but CT1 does not, although it can be engineered to do so by mutagenesis guided by LeuT as a structural template (Dodds and Christie, 2007). Although inhibitors of creatine transport by CT1 (e.g.  $\beta$ -guanidinopropionic acid, cyclocreatine,  $\gamma$ -guanidino sulphonic acid) are known (e.g. Dai *et al.*, 1999) they are insufficiently characterized to be included in the table.

### Glycine transporter subfamily

Two gene products, GlyT1 and GlyT2, are known that give rise to transporters that are predominantly located on glia and neurones, respectively. Five variants of GlyT1 (a,b,c,d & e) differing in their N- and C-termini are generated by alternative promoter usage and splicing, and three splice variants of GlyT2 (a,b & c) have also been identified (see Supplisson and Roux, 2002; Eulenburg *et al.*, 2005; Betz *et al.*, 2006; Gomeza *et al.*, 2006 for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission (Bergeron *et al.*, 1998; Gabernet *et al.*, 2005), but also are important, in early neonatal life, for regulating glycine concentrations at inhibitory glycinergic synapses (Gomeza *et al.*, 2003a). Homozygous mice engineered to totally lack GlyT1 exhibit severe respiratory and motor deficiencies due to hyperactive glycinergic signalling and die within the first postnatal day (Gomeza *et al.*, 2003a, Tsai *et al.*, 2004). Disruption of GlyT1 restricted to forebrain neurones is associated with enhancement of EPSCs mediated by NMDA receptors and behaviours that are suggestive of a promnesic action (Yee *et al.*, 2006). GlyT2 transporters localised on the axons and boutons of glycinergic neurones appear crucial for efficient transmitter loading of synaptic vesicles but may not be essential for the termination of inhibitory neurotransmission (Gomeza *et al.*, 2003b; Rousseau *et al.*, 2008). Mice in which GlyT2 has been deleted develop a fatal hyperekplexia phenotype during the second postnatal week (Gomeza *et al.*, 2003b) and mutations in the human gene encoding GlyT2 (SLC6A5) have been identified in patients with hyperekplexia (reviewed by Harvey *et al.*, 2008). ATB<sup>Or</sup> (SLC6A14) is a transporter for numerous dipolar and cationic amino acids and thus has a much broader substrate specificity than the glycine transporters alongside which it is grouped on the basis of structural similarity (Chen *et al.*, 2004). ATB<sup>Or</sup> is expressed in various peripheral tissues (Chen *et al.*, 2004). By contrast PROT (SLC6A7), which is expressed only in brain in association with a subset of excitatory nerve terminals, shows specificity for the transport of L-proline.

Common abbreviation	GlyT1	GlyT2	ATB <sup>0+</sup>	PROT
Systematic name	SLC6A9	SLC6A5	SLC6A14	SLC6A7
Other names	Glycine transporter 1	Glycine transporter 2	Sodium- and chloride-dependent neutral and basic amino acid transporter B <sup>0+</sup>	Sodium-dependent proline transporter
Ensembl ID	ENSG00000196517	ENSG00000165970	ENSG00000087916	ENSG00000011083
Endogenous substrates	Glycine, sarcosine	Glycine	Iso > leu, met > phe > trp > val > ser (Sloan and Mager, 1999), $\beta$ -alanine (Anderson <i>et al.</i> , 2008, 2009)	L-Proline
Synthetic substrates	–	–	BCH, 1-methyltryptophan (Karunakaran <i>et al.</i> , 2008), valganciclovir (Umapathy <i>et al.</i> , 2004), zwitterionic or cationic NOS inhibitors (Hatanaka <i>et al.</i> , 2001)	–
Selective inhibitors (IC <sub>50</sub> )	(R)-NFPS (ALX 5407) (0.8 – 3 nM), SSR-103800 (2 nM), N-methyl-SSR-504734 (2.5 nM), NFPS (3 – 100 nM), LY2365109 (16 nM), SSR504734 (18 – 314 nM), GSK931145 (26 nM); RG1678 (30 nM); SB-733993 (31 nM); NPTS (37 nM), Org 24598	ALX 1393, ALX 1405, Org 25543 (20 nM)	$\alpha$ -methyltryptophan (250 $\mu$ M, Karunakaran <i>et al.</i> , 2008)	LP-403812 (0.11 $\mu$ M, Yu <i>et al.</i> , 2009)
Probes (K <sub>d</sub> )	[ <sup>3</sup> H]-(-R)-NPTS (1 nM), [ <sup>3</sup> H]-GSK931145 (1.7 nM), [ <sup>35</sup> S]-ACPPB (2 nM), [ <sup>3</sup> H]-SB-733993 (2.2 nM), [ <sup>3</sup> H]-N-methyl-SSR504734 (3.3 – 8.1 nM), [ <sup>3</sup> H]-NFPS (7–21 nM)	–	–	–
Predicted stoichiometry	2 Na <sup>+</sup> : 1 Cl <sup>-</sup> : 1 glycine	3 Na <sup>+</sup> : 1 Cl <sup>-</sup> : 1 glycine	2–3 Na <sup>+</sup> : 1 Cl <sup>-</sup> : 1 amino acid (Sloan and Mager, 1999)	Probably 2 Na <sup>+</sup> : 1 Cl <sup>-</sup> : 1 L-proline

Sarcosine is a selective transportable inhibitor of GlyT1 and also a weak agonist at the glycine binding site of the NMDA receptor (Zhang *et al.*, 2009), but has no effect on GlyT2. This difference has been attributed to a single glycine residue in TM6 (serine residue in GlyT2) (Vandenberg *et al.*, 2007). Inhibition of GLYT1 by the sarcosine derivatives NFPS, NPTS and Org24598 is non-competitive (Mallorga *et al.*, 2003; Mezler *et al.*, 2008). IC<sub>50</sub> values for Org 24598 reported in the literature vary, most likely due to differences in assay conditions (Brown *et al.*, 2001; Mallorga *et al.*, 2003). The tricyclic antidepressant amoxapine weakly inhibits GlyT2 (IC<sub>50</sub> 92  $\mu$ M) with approximately 10-fold selectivity over GlyT1 (Nunez *et al.*, 2000). The endogenous lipids arachidonic acid and anandamide exert opposing effects upon GlyT1a, inhibiting (IC<sub>50</sub> ~ 2  $\mu$ M) and potentiating (EC<sub>50</sub> ~ 13  $\mu$ M) transport currents, respectively (Pearlman *et al.*, 2003). N-arachidonyl-glycine, N-arachidonyl- $\gamma$ -aminobutyric acid and N-arachidonyl-D-alanine have been described as endogenous non-competitive inhibitors of GlyT2a, but not GlyT1b (Wiles *et al.*, 2006; Edington *et al.*, 2009; Jeong *et al.*, 2010). Protons (Aubrey *et al.*, 2000) and Zn<sup>2+</sup> (Ju *et al.*, 2004) act as non-competitive inhibitors of GlyT1b, with IC<sub>50</sub> values of ~100 nM and ~10  $\mu$ M respectively, but neither ion affects GlyT2 (reviewed by Vandenberg *et al.*, 2004). Glycine transport by GLYT1 is inhibited by lithium, whereas GLYT2 transport is stimulated (both in the presence of Na<sup>+</sup>) (Pérez-Siles *et al.* 2011).

#### Neutral amino acid transporter subfamily

Certain members of neutral amino acid transport family are expressed upon the apical surface of epithelial cells and are important for the absorption of amino acids from the duodenum, jejunum and ileum and their reabsorption within the proximal tubule of the nephron (*i.e.* B<sup>0</sup>AT1 (SLC6A19), SLC6A17, SLC6A18, SLC6A20). Others may function as transporters for neurotransmitters or their precursors (*i.e.* B<sup>0</sup>AT2, SLC6A17) (Bröer, 2008).

Common abbreviation	B <sup>0</sup> AT1	B <sup>0</sup> AT2	B <sup>0</sup> AT3
Systematic name	SLC6A19	SLC6A15	SLC6A18
Other names	B <sup>0</sup> neutral amino acid transporter	NTT73, v7-3, SBAT1	XT2, XTRP2
Ensembl ID	ENSG00000174358	ENSG00000072041	ENSG00000164363
Endogenous substrates	Leu, met, iso, val > asn, phe, ala, ser > thr, gly, pro (Bröer <i>et al.</i> , 2006)	Pro > ala, val, met, leu > iso, thr, asn, ser, phe > gly (Bröer <i>et al.</i> , 2006)	Ala, gly > met, phe, leu, his, gln (Vanslambrouck <i>et al.</i> 2010)
Predicted stoichiometry	1 Na: 1 amino acid (Böhmer <i>et al.</i> , 2005)	1 Na: 1 amino acid (Bröer <i>et al.</i> , 2006)	Na <sup>+</sup> - and Cl <sup>-</sup> -dependent transport (Singer <i>et al.</i> , 2009)

Systematic name	SLC6A16	SLC6A17	SLC6A20
Common abbreviation	–	–	SIT1
Other names	NTT5	NTT4, XT1, XTRP1	XTRP3, rB21A, IMINO, XT3, sodium/imino-acid transporter 1
Ensembl ID	ENSG00000063127	ENSG00000197106	ENSG00000163817
Endogenous substrates	Unknown	Leu, met, pro > cys, ala, gln, ser > his, gly (Zaia and Reimer, 2009)	Proline
Predicted stoichiometry	–	Na <sup>+</sup> -dependent, Cl <sup>-</sup> -independent transport (Zaia and Reimer, 2009)	2 Na <sup>+</sup> : 1 Cl <sup>-</sup> : 1 imino acid (Bröer <i>et al.</i> , 2009)

Mutations in B<sup>0</sup>AT1 are associated with Hartnup disorder.

**Abbreviations:** ACPPB, (S)-2-amino-4-chloro-N-(1-(4-phenyl-1-(propylsulfonyl)piperidin-4-yl)ethyl)benzamide; ALX 1393, O-[2-benzyloxyphenyl-3-fluorophenyl]methyl-L-serine; ALX 1405, structure not available; BCH, 2-aminobicyclo[2.2.1]-heptane-2-carboxylic acid; CI966, [1-[2-[bis(4-(trifluoromethyl)phenyl)methoxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid; EF1500, N-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; EF1502, N-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-(methylamino)4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; EGYT3886, (-)-2-phenyl-2-[(dimethylamino)ethoxy]-(1R)-1,7,7-trimethylbicyclo[2.2.1]heptane; *exo*-THPO, 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-benzisoxazol; GBR12935, 1-(2-[diphenylmethoxy]ethyl)-4-(3-phenylpropyl)piperazine; GSK931145, N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide; LP-403812, see Yu *et al.* (2009) for structure; LU32-176B, N-[4,4-bis(4-fluorophenyl)-butyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; LY2365109, [[2-(4-benzo[1,3]dioxol-5-yl-2-tert-butylphenoxy)ethyl]-methylamino]-acetic acid; MDMA, 3,4-methylenedioxyamphetamine; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; NFPS, N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine; NNC052090, 1-(3-(9H-carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol; NNC711, 1-2-(((diphenylmethylene)amino)oxy)ethyl-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride; NPTS, (N-[3-phenyl-3-(4'-(4-toluoyl) phenoxy)propyl]sarcosine; Org 24598, R-(-)-N-[3-[(4-trifluoromethyl)phenoxy]-3-phenylpropyl]glycine; Org 25543, 4-benzyloxy-3,5-dimethoxy-N-[1-(dimethylaminocyclopentyl) methyl] benzamide; RG1678, [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone; RT155, 2β-carbomethoxy-3β-(4-iodophenyl) tropane (also known as β-CIT); SB-733993, (2R)-3-[(2R,6S)-2,6-dimethylpiperidin-1-yl]-2-hydroxy-S-(naphthalen-1-yl)propane-1-sulfonamide; SKF89976A, 1-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid; SSR103800, structure not available; SSR504734, 2-chloro-N-(S)-phenyl[(2S)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide; WIN35428, 2β-carboxymethyl-3β-(4-fluorophenyl)tropane (also known as β-CFT).

## Further Reading

- Aragón C, Lopez-Córcuera B (2005). Glycine transporters: crucial roles of pharmacological interest revealed by gene deletion. *Trends Pharmacol Sci* 26: 283–286.
- Betz H, Gomez J, Scholze P, Eulenberg V (2006). Glycine transporters: essential regulators of synaptic transmission. *J Neurochem* 97: 1600–1610.
- Bridges TM, Williams R, Lindsley CW (2008). Design of potent GlyT1 inhibitors: *in vitro* and *in vivo* profiles. *Curr Opin Mol Ther* 10: 591–601.
- Bröer S (2006). The SLC6 orphans are forming a family of amino acid transporters. *Neurochem Int* 48: 559–567.
- Bröer S (2008). Apical transporters for neutral amino acids: physiology and pathophysiology. *Physiology* 23: 95–103.
- Chen N-H, Reith MEA, Quick MW (2004). Synaptic uptake and beyond: the sodium and chloride dependent neurotransmitter transporter family SLC6. *Pflügers Archiv* 447: 519–531.
- Christie DL (2007). Functional insights into the creatine transporter. *Subcell Biochem* 46: 99–118.
- Clausen RP, Madsen K, Larsson OM, Frolund B, Krogsgaard-Larsen P, Schousboe A (2006). Structure-activity relationship and pharmacology of gamma-aminobutyric acid (GABA) transport inhibitors. *Adv Pharmacol* 54: 265–284.
- Dai W *et al.* (1999). *Arch Biochem Biophys* 361: 75–84.
- Dalby NO (2003). Inhibition of gamma-aminobutyric acid uptake: anatomy, physiology and effects against epileptic seizures. *Eur J Pharmacol* 479: 127–137.
- Daws LC (2009). Unfaithful neurotransmitter transporters: focus on serotonin uptake and implications for antidepressant efficacy. *Pharmacol Ther* 121: 89–99.
- Dohi T, Morita K, Kitayama T, Motoyama N, Morioka N (2009). Glycine transporter inhibitors as a novel drug discovery strategy for neuropathic pain. *Pharmacol Ther* 123: 54–79.
- Eulenberg V, Armsen W, Betz H, Gomez J (2005). Glycine transporters: essential regulators of neurotransmission. *Trends Biochem Sci* 30: 325–333.
- Foster JD, Cervinski MA, Gorentla BK, Vaughan RA (2006). Regulation of the dopamine transporter by phosphorylation. *Handb Exp Pharmacol* 197–214.

- Gadia A, Lopez-Colome AM (2001). Glial transporters for glutamate, glycine and GABA: II. GABA transporters. *J Neurosci Res* **63**: 461–468.
- Gasnier B (2004). The SLC32 transporter, a key protein for the synaptic release of inhibitory amino acids. *Pflügers Archiv* **447**: 756–759.
- Gether U, Andersen PH, Larsson OM, Schousboe A (2007). Neurotransmitter transporters: molecular function of important drug targets. *Trends Pharmacol Sci* **27**: 375–383.
- Gomez J, Armsen W, Betz H, Eulenburg V (2006). Lessons from the knocked-out glycine transporters. *Handb Exp Pharmacol* **175**: 457–483.
- Gonzalez-Burgos G (2010). GABA transporter GAT1: a crucial determinant of GABA<sub>B</sub> receptor activation in cortical circuits? *Adv Pharmacol* **58**: 175–204.
- Han X, Patters AB, Jones DP, Zelikovic I, Chesney RW (2006). The taurine transporter: mechanisms of regulation. *Acta Physiol (Oxf)* **187**: 61–73.
- Harsing LG Jr, Juranyi Z, Gacsalyi I, Tapolcsanyi P, Czompa A, Matyus P (2006). Glycine transporter type-1 and its inhibitors. *Curr Med Chem* **13**: 1017–1044.
- Harvey RJ, Topf M, Harvey K, Rees MI (2008). The genetics of hyperekplexia: more than startle! *Trends Genet* **24**: 439–447.
- Hashimoto K (2011). Glycine transporter-1: a new potential therapeutic target for schizophrenia. *Curr Pharm Des* **17**: 112–120.
- Hog S, Greenwood JR, Madsen KB, Larsson OM, Frolund B, Schousboe A *et al.* (2006). Structure-activity relationships of selective GABA uptake inhibitors. *Curr Top Med Chem* **6**: 1861–1882.
- Horstmann S, Binder EB (2009). Pharmacogenomics of antidepressant drugs. *Pharmacol Ther* **124**: 57–73.
- Javitt DC (2009). Glycine transport inhibitors for the treatment of schizophrenia: symptom and disease modification. *Curr Opin Drug Discov Devel* **12**: 468–478.
- Kanner BI (2006). Structure and function of sodium-coupled GABA and glutamate transporters. *J Membr Biol* **213**: 89–100.
- Karunakaran S *et al.* (2008). *Biochem J* **414**: 343–355.
- Kristensen AS, Andersen J, Jørgensen TN, Sørensen L, Eriksen J, Claus J, Loland CJ *et al.* (2011). SLC6 Neurotransmitter transporters: structure, function, and regulation. *Pharmacol Rev* **63**: 585–640.
- Kulig K, Szwaczkiewicz M (2008). The role of structure activity relationship studies in the search for new GABA uptake inhibitors. *Mini Rev Med Chem* **8**: 1214–1223.
- Lechner SM (2006). Glutamate-based therapeutic approaches: inhibitors of glycine transport. *Curr Opin Pharmacol* **6**: 75–81.
- Madsen KK, White HS, Schousboe A (2010). Neuronal and non-neuronal GABA transporters as targets for antiepileptic drugs. *Pharmacol Ther* **125**: 394–401.
- Mazei-Robinson MS, Blakely RD (2006). ADHD and the dopamine transporter: are there reasons to pay attention? *Handb Exp Pharmacol* **175**: 373–415.
- Millan MJ (2006). Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther* **110**: 135–370.
- Moltzen EK, Bang-Andersen B (2006). Serotonin reuptake inhibitors: the corner stone in treatment of depression for half a century—a medicinal chemistry survey. *Curr Top Med Chem* **6**: 1801–1823.
- Richerson GB, Wu Y (2004). Role of the GABA transporter in epilepsy. *Adv Exp Med Biol* **548**: 76–91.
- Runyon SP, Carroll FI (2006). Dopamine transporter ligands: recent developments and therapeutic potential. *Curr Top Med Chem* **6**: 1825–1843.
- Sałat K, Kulig K. (2011). GABA transporters as targets for new drugs. *Future Med Chem* **3**: 211–222.
- Saier MH, Yen MR, Noto K, Tamang DG, Elkan C (2009). The Transporter Classification Database: recent advances. *Nucleic Acids Res*, **37**: D274–D278.
- Sarup A, Larsson OM, Schousboe A (2003). GABA Transporters and GABA-Transaminase as Drug Targets. *Curr Drug Target CNS Neurol Disord* **2**: 269–277.
- Schousboe A, Sarup A, Bak LK, Waagepetersen HS, Larsson OM (2004a). Role of astrocytic transport processes in glutamatergic and GABAergic neurotransmission. *Neurochem Int* **45**: 521–527.
- Schousboe A, Sarup A, Larsson OM, White HS (2004b). GABA transporters as drug targets for modulation of GABAergic activity. *Biochem Pharmacol* **68**: 1557–1563.
- Schousboe A, Madsen KK, White HS (2011). GABA transport inhibitors and seizure protection: the past and future. *Future Med Chem* **3**: 183–187.
- Semyanov A, Walker MC, Kullmann DM, Silver RA (2004). Tonically active GABA<sub>A</sub> receptors: modulating gain and maintaining the tone. *Trends Neurosci* **27**: 262–269.
- Soudijn W, van Wijngaarden I (2000). The GABA transporter and its inhibitors. *Curr Med Chem* **7**: 1063–1079.
- Supplisson S, Roux MJ (2002). Why glycine transporters have different stoichiometries. *FEBS Lett* **529**: 93–101.
- Sur C, Kinney GG (2007). Glycine transporter 1 inhibitors and modulation of NMDA receptor-mediated excitatory neurotransmission. *Curr Drug Targets* **8**: 643–649.
- Torres GE, Gainetdinov RR, Caron MG (2003). Plasma membrane monoamine transporters: structure, regulation and function. *Nat Rev Neurosci* **4**: 13–25.
- Vandenberg RJ, Ju P, Aubrey KR, Ryan RM, Mitrovic AD (2004). Allosteric modulation of neurotransmitter transporters at excitatory synapses. *Eur J Pharm Sci* **23**: 1–11.
- Wang CI, Lewis RJ (2010). Emerging structure-function relationships defining monoamine NSS transporter substrate and ligand affinity. *Biochem Pharmacol* **79**: 1083–1091.
- Williams JM, Galli A (2006). The dopamine transporter: a vigilant border control for psychostimulant action. *Handb Exp Pharmacol*: 215–232.
- Wolkenberg SE, Sur C (2010). Recent progress in the discovery of non-sarcosine based GlyT1 inhibitors. *Curr Top Med Chem* **10**: 170–186.
- Zafra F, Giménez C (2008). Glycine transporters and synaptic function. *IUBMB Life* **60**: 810–817.

## References

- Anderson CMH *et al.* (2008). *J Physiol* **586**: 4061–4067.
- Anderson CMH *et al.* (2009). *J Physiol* **587**: 731–744.
- Aubrey KR *et al.* (2000). *Mol Pharmacol* **58**: 129–135.
- Bergeron R *et al.* (1998). *Proc Natl Acad Sci U S A* **95**: 15730–15734.
- Böhmer C *et al.* (2005). *Biochem J* **389**: 745–751.
- Brown A *et al.* (2001). *Bioorg Med Chem Lett* **11**: 2007–2009.
- Bröer A *et al.* (2006). *Biochem J* **393**: 421–430.
- Bröer A *et al.* (2009). *Mol Membr Biol* **26**: 333–346.
- Cohen-Kfir E *et al.* (2005). *Proc Natl Acad Sci U S A* **102**: 6154–6159.
- Dhar TGM *et al.* (1994). *J Med Chem* **37**: 2334–2342.
- Dodd JR, Christie, JL (2007). *J Biol Chem* **282**: 15528–15533.
- Edington AR *et al.* (2009). *J Biol Chem* **284**: 36424–36330.
- Forrest LR, Rudnick G (2009). *Physiology (Bethesda)* **24**: 377–386.
- Fülep GH *et al.* (2006). *Eur J Med Chem* **41**: 809–824.
- Gabernet L *et al.* (2005). *Neurosci Lett* **373**: 79–84.
- Gomez J *et al.* (2003a). *Neuron* **40**: 785–796.
- Gomez J *et al.* (2003b). *Neuron* **40**: 797–806.
- Gu H *et al.* (1994). *J Biol Chem* **269**: 7124–7130.
- Gu HH *et al.* (1996). *J Biol Chem* **271**: 6911–6916.
- Hatanaka T *et al.* (2001). *J Clin Invest* **107**: 1035–1043.
- Jeong HJ *et al.* (2010). *Br J Pharmacol* **161**: 925–935.
- Ju P *et al.* (2004). *J Biol Chem* **279**: 22983–22991.



- Karunakaran S *et al.* (2008). *Biochem J* **414**: 343–355.  
 Knutsen LJS *et al.* (1999). *J Med Chem* **42**: 3447–3462.  
 Kvist T *et al.* (2009). *Comb Chem High Throughput Screen* **12**: 241–249.  
 Mallorga PJ *et al.* (2003). *Neuropharmacology* **45**: 585–593.  
 Mezler M *et al.* (2008). *Mol Pharmacol* **74**: 1705–1715.  
 Nunez E *et al.* (2000). *Br J Pharmacol* **129**: 200–206.  
 Pearlman RJ *et al.* (2003). *J Neurochem* **84**: 592–601.  
 Pérez-Siles G *et al.* (2011). *J Neurochem* **118**: 195–204.  
 Pristupa ZB *et al.* (1994). *Mol Pharmacol* **45**: 125–135.  
 Rousseau F *et al.* (2008). *J Neurosci* **28**: 9755–9768.  
 Singer D *et al.* (2009). *J Biol Chem* **284**: 19953–19960.  
 Singh SK *et al.* (2007). *Nature* **448**: 952–956.  
 Sloan JL, Mager S (1999). *J Biol Chem* **274**: 23740–23745.  
 Talvenheimo J *et al.* (1983). *J Biol Chem* **258**: 6115–6119.  
 Tatsumi M *et al.* (1997). *Eur J Pharmacol* **340**: 249–258.  
 Tsai G *et al.* (2004). *Proc Natl Acad Sci U S A* **101**: 8485–8490.  
 Umopathy NS *et al.* (2004). *Pharm Res* **21**: 1303–1310.  
 Vandenberg RJ *et al.* (2007). *J Biol Chem* **282**: 14447–14453.  
 Vanslambrouck JM *et al.* (2010). *Biochem J* **428**: 397–407.  
 Wong EH *et al.* (2000). *Biol Psychiatry* **47**: 818–829.  
 Wiles AL *et al.* (2006). *J Neurochem* **99**: 781–786.  
 Yamashita A *et al.* (2005). *Nature* **437**: 215–223.  
 Yee BK *et al.* (2006). *J Neurosci* **26**: 3169–3181.  
 Yu X-C *et al.* (2009). *Neurosci Lett* **451**: 212–216.  
 Zaia KA, Reimer RJ (2009). *J Biol Chem* **284**: 8439–8448.  
 Zhang HX *et al.* (2009). *J Physiol* **587**: 3207–3220.

## SLC8 family of sodium/calcium exchangers

**Overview:** the sodium/calcium exchangers (NCX) use the extracellular sodium concentration to facilitate the extrusion of calcium out of the cell. Alongside the plasma membrane Ca<sup>2+</sup>-ATPase (PMCA, see Page S219) and sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA, see Page S219), as well as the sodium/potassium/calcium exchangers (NKCCX, SLC24 family, see Page S255), NCX allow recovery of intracellular calcium back to basal levels after cellular stimulation. When intracellular sodium ion levels rise, for example, following depolarisation, these transporters can operate in the reverse direction to allow calcium influx and sodium efflux, as an electrogenic mechanism. Structural modelling suggests the presence of 9 TM segments, with a large intracellular loop between the fifth and sixth TM segments.

Nomenclature	Sodium/calcium exchanger 1	Sodium/calcium exchanger 2	Sodium/calcium exchanger 3
Systematic name	SLC8A1	SLC8A2	SLC8A3
Preferred abbreviation	NCX1	NCX2	NCX3
Ensembl ID	ENSG00000183023	ENSG00000118160	ENSG00000100678
Stoichiometry	3 Na <sup>+</sup> (in) : 1 Ca <sup>2+</sup> (out) or 4 Na <sup>+</sup> (in) : 1 Ca <sup>2+</sup> (out) (Dong <i>et al.</i> , 2002) Reverse mode 1 Ca <sup>2+</sup> (in): 1 Na <sup>+</sup> (out)	–	–

Although subtype-selective inhibitors of NCX function are not widely available, 3,4-dichlorobenzamil and CBDMB act as non-selective NCX inhibitors, while SEA0400, KB-R7943 and SN6 act to inhibit NCX function selectively in the reverse mode.

**Abbreviations:** CBDMB, 3-amino-6-chloro-5-[(4-chlorophenyl)methylamino]-N-[[2-[(2,4-dimethylphenyl)methyl]hydrazinyl]methylidene]pyrazine-2-carboxamide; KB-R7943, methanesulfonic acid; 2-[4-[(4-nitrophenyl)methoxy]phenyl]ethylcarbamide dithioate; SEA0400, 2-[4-[(2,5-difluorophenyl)methoxy]phenoxy]-5-ethoxyaniline; SN6, N-[4-[(1-methylpyridin-1-ium-4-yl)amino]phenyl]-4-[(1-methylquinolin-1-ium-4-yl)amino]benzamide, also known as SN6999

### Further Reading

- Annunziato L, Pignataro G, Di Renzo GF (2004). Pharmacology of brain Na<sup>+</sup>/Ca<sup>2+</sup> exchanger: from molecular biology to therapeutic perspectives. *Pharmacol Rev* **56**: 633–654.  
 Gabellini N (2004). Transcriptional regulation by cAMP and Ca<sup>2+</sup> links the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger 3 to memory and sensory pathways. *Mol Neurobiol* **30**: 91–116.  
 Lytton J (2007). Na<sup>+</sup>/Ca<sup>2+</sup> exchangers: three mammalian gene families control Ca<sup>2+</sup> transport. *Biochem J* **406**: 365–382.  
 Quednau BD, Nicoll DA, Philipson KD (2004). The sodium/calcium exchanger family-SLC8. *Pflugers Arch* **447**: 543–548.  
 Watanabe Y, Koide Y, Kimura J (2006). Topics on the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger: pharmacological characterization of Na<sup>+</sup>/Ca<sup>2+</sup> exchanger inhibitors. *J Pharmacol Sci* **102**: 7–16.  
 Zhang YH, Hancox JC (2009). Regulation of cardiac Na<sup>+</sup>-Ca<sup>2+</sup> exchanger activity by protein kinase phosphorylation – still a paradox? *Cell Calcium* **45**: 1–10.

### Reference

- Dong H *et al.* (2002). *Biophys J* **82**: 1943–1952.

## SLC9 family of sodium/hydrogen exchangers

**Overview:** sodium/hydrogen exchangers or sodium/proton antiports are a family of transporters that maintain cellular pH by utilising the sodium gradient across the plasma membrane to extrude protons produced by metabolism, in a stoichiometry of 1 Na<sup>+</sup> (in) : 1 H<sup>+</sup> (out). Several isoforms, NHE6, NHE7, NHE8 and NHE9 appear to locate on intracellular membranes (Miyazaki *et al.*, 2001; Numata and Orłowski, 2001;

Nakamura *et al.*, 2005). Li<sup>+</sup> and NH<sub>4</sub><sup>+</sup>, but not K<sup>+</sup>, ions may also be transported by some isoforms. Modelling of the topology of these transporters indicates 12 TM regions with an extended intracellular C-terminus containing multiple regulatory sites.

NHE1 is considered to be a ubiquitously-expressed 'housekeeping' transporter. NHE2 and NHE3 are highly expressed in the intestine and kidneys and regulate sodium movements in those tissues. NHE10 is present in sperm (Wang *et al.*, 2003) and osteoclasts (Lee *et al.*, 2008); gene disruption results in infertile male mice (Wang *et al.*, 2003).

Nomenclature	Systematic name	Common abbreviation	Ensembl ID	Other names
Sodium/hydrogen exchanger 1	SLC9A1	NHE1	ENSG00000090020	Na <sup>+</sup> /H <sup>+</sup> antiporter, amiloride-sensitive, APNH
Sodium/hydrogen exchanger 2	SLC9A2	NHE2	ENSG00000115616	
Sodium/hydrogen exchanger 3	SLC9A3	NHE3	ENSG00000066230	
Sodium/hydrogen exchanger 4	SLC9A4	NHE4	ENSG00000180251	
Sodium/hydrogen exchanger 5	SLC9A5	NHE5	ENSG00000135740	
Sodium/hydrogen exchanger 6	SLC9A6	NHE6	ENSG00000198689	
Sodium/hydrogen exchanger 7	SLC9A7	NHE7	ENSG00000065923	
Sodium/hydrogen exchanger 8	SLC9A8	NHE8	ENSG00000197818	
Sodium/hydrogen exchanger 9	SLC9A9	NHE9	ENSG00000181804	
Sodium/hydrogen exchanger 10	SLC9A10	NHE10	ENSG00000172139	Sperm-specific Na <sup>+</sup> /H <sup>+</sup> exchanger, sNHE
Sodium/hydrogen exchanger 11	SLC9A11	NHE11	ENSG00000162753	

Analogues of the non-selective cation transport inhibitor amiloride appear to inhibit NHE function through competitive inhibition of the extracellular Na<sup>+</sup> binding site. The more selective amiloride analogues MPA and EIPA exhibit a rank order of affinity of inhibition of NHE1 > NHE2 > NHE3 (Counillon *et al.*, 1993; Tse *et al.*, 1993a, 1993b).

**Abbreviations:** EIPA, 3-amino-6-chloro-N-(diaminomethylidene)-5-[ethyl(propan-2-yl)amino]pyrazine-2-carboxamide; MPA, 3-amino-6-chloro-N-(diaminomethylidene)-5-[methyl(propyl)amino]pyrazine-2-carboxamide

### Further Reading

Casey JR, Grinstein S, Orlowski J (2010). Sensors and regulators of intracellular pH. *Nat Rev Mol Cell Biol* **11**: 50–61.  
 Kato A, Romero MF (2011). Regulation of electroneutral NaCl absorption by the small intestine. *Annu Rev Physiol* **73**: 261–281.  
 Kemp G, Young H, Fliegel L (2008). Structure and function of the human Na<sup>+</sup>/H<sup>+</sup> exchanger isoform 1. *Channels (Austin)* **2**: 329–336.  
 Orlowski J, Grinstein S (2004). Diversity of the mammalian sodium/proton exchanger SLC9 gene family. *Pflugers Arch* **447**: 549–565.  
 Slepckov ER, Rainey JK, Sykes BD, Fliegel L (2007). Structural and functional analysis of the Na<sup>+</sup>/H<sup>+</sup> exchanger. *Biochem J* **401**: 623–633.

### References

Counillon L *et al.* (1993). *Mol Pharmacol* **44**: 1041–1045.  
 Lee SH *et al.* (2008). *Biochem Biophys Res Commun* **369**: 320–326.  
 Miyazaki E *et al.* (2001). *J Biol Chem* **276**: 49221–49227.  
 Nakamura N *et al.* (2005). *J Biol Chem* **280**: 1561–1572.  
 Numata M, Orlowski J (2001). *J Biol Chem* **276**: 17387–17394.  
 Tse CM *et al.* (1993a). *Proc Natl Acad Sci U S A* **90**: 9110–9114.  
 Tse CM *et al.* (1993b). *J Biol Chem* **268**: 11917–11924.  
 Wang D *et al.* (2003). *Nat Cell Biol* **5**: 1117–1122.

## SLC10 family of sodium-bile acid co-transporters

**Overview:** the SLC10 family transport bile acids and their derivatives in a sodium-dependent manner. Along with members of the ABC transporter family (MDR1/ABCB1; BSEP/ABCB11; and MRP2/ABCC2) and the organic solute transporter obligate heterodimer OSTα:OSTβ, these transporters allow enterohepatic circulation of bile acids (see Dawson *et al.*, 2009; Klaassen and Aleksunes, 2010).

The SLC10 family appear to be monomeric with external N-termini and cytoplasmic C-termini and seven TM segments (Hallen *et al.*, 1999; Banerjee and Swaan, 2006).

Systematic name	SLC10A1	SLC10A2	SLC10A6
Common abbreviation	NTCP	ASBT	SOAT
Nomenclature	Sodium/bile acid cotransporter 1	Sodium/bile acid cotransporter 2	Sodium/bile acid cotransporter 6
Ensembl ID	ENSG00000100652	ENSG00000125255	ENSG00000145283
Other names	Sodium/bile acid cotransporter, Na <sup>+</sup> /taurocholate transport protein, cell growth-inhibiting gene 29 protein	Apical sodium-dependent bile acid transporter, ileal sodium/bile acid cotransporter, ISBT, IBAT	Sodium-dependent organic anion transporter
Substrates	TUDA, TCA, TCDCA > GCA > CA (Meier <i>et al.</i> , 1997) Thyroid hormone (Friesema <i>et al.</i> , 1999; Visser <i>et al.</i> , 2010)	GDCA > GUDCA, GCDA > TCA > CA (Craddock <i>et al.</i> , 1998)	Estrone-3-sulphate, DHEAS (Geyer <i>et al.</i> , 2004), TLCA, PREGS (Geyer <i>et al.</i> , 2007)
Inhibitors	Cyclosporin, propranolol (Kim <i>et al.</i> , 1999)	–	–
Probes	Chenodeoxychyl-N <sup>5</sup> -nitrobenzoxadiazol-lysine (Weinman <i>et al.</i> , 1998)	[ <sup>3</sup> H]-Taurocholate (Craddock <i>et al.</i> , 1998)	–
Stoichiometry	2 Na <sup>+</sup> : 1 bile acid (Hagenbuch and Meier, 1996; Weinman, 1997)	>1 Na <sup>+</sup> : 1 bile acid (Craddock <i>et al.</i> , 1998)	–

Systematic name	SLC10A3	SLC10A4	SLC10A5	SLC10A7
Common abbreviation	P3	P4	P5	P7
Nomenclature	Sodium/bile acid cotransporter 3	Sodium/bile acid cotransporter 4	Sodium/bile acid cotransporter 5	Sodium/bile acid cotransporter 7
Ensembl ID	ENSG00000126903	ENSG00000145248	ENSG00000205184	ENSG00000120519
Other names	P3 protein	–	–	C4orf13

Heterologously expressed SLC10A4 (Geyer *et al.*, 2008) or SLC10A7 (Godoy *et al.*, 2007) failed to exhibit significant transport of TCA, PREGS, DHEAS or choline. SLC10A4 has recently been suggested to associate with neuronal vesicles (Burger *et al.*, 2011).

**Abbreviations:** CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; DHEAS, dehydroepiandrosterone sulphate; GCA, glychocholic acid; GCDA, glychenodeoxycholic acid; GDCA, glycodeoxycholic acid; GUDCA, glyoursodeoxycholate; PREGS, pregnenolone sulphate; TCA, taurocholic acid; TCDCA, taurochenodeoxycholate; TLCA, tauroolithocholic acid; TUDA, tauroursodeoxycholic acid

### Further Reading

Alrefai WA, Gill RK (2007). Bile acid transporters: structure, function, regulation and pathophysiological implications. *Pharm Res* 24: 1803–1823.  
Dawson PA, Lan T, Rao A (2009). Bile acid transporters. *J Lipid Res* 50: 2340–2357.  
Geyer J, Wilke T, Petzinger E (2006). The solute carrier family SLC10: more than a family of bile acid transporters regarding function and phylogenetic relationships. *Naunyn Schmiedebergs Arch Pharmacol* 372: 413–431.  
Hagenbuch B, Dawson P (2004). The sodium bile salt cotransport family SLC10. *Pflugers Arch* 447: 566–570.  
Klaassen CD, Aleksunes LM (2010). Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol Rev* 62: 1–96.  
Kosters A, Karpen SJ (2008). Bile acid transporters in health and disease. *Xenobiotica* 38: 1043–1071.

### References

- Banerjee A, Swaan PW (2006). *Biochemistry* 45: 943–953.  
Burger S *et al.* (2011). *Neuroscience* 193: 109–21.  
Craddock AL *et al.* (1998). *Am J Physiol Gastrointest Liver Physiol* 274: G157–G169.  
Friesema EC *et al.* (1999). *Biochem Biophys Res Commun* 254: 497–501.  
Geyer J *et al.* (2004). *Biochem Biophys Res Commun* 316: 300–306.  
Geyer J *et al.* (2007). *J Biol Chem* 282: 19728–19741.  
Geyer J *et al.* (2008). *Neuroscience* 152: 990–1005.  
Godoy JR *et al.* (2007). *Eur J Cell Biol* 86: 445–460.  
Hagenbuch B, Meier PJ (1996). *Semin Liver Dis* 16: 129–136.  
Hallen S *et al.* (1999). *Biochemistry* 38: 11379–11388.  
Kim RB *et al.* (1999). *J Pharmacol Exp Ther* 291: 1204–1209.  
Meier PJ *et al.* (1997). *Hepatology* 26: 1667–1677.  
Visser WE *et al.* (2010). *Mol Cell Endocrinol* 315: 138–145.  
Weinman SA (1997). *Yale J Biol Med* 70: 331–340.  
Weinman SA *et al.* (1998). *J Biol Chem* 273: 34691–34695.

# SLC11 family of proton-coupled metal ion transporters

**Overview:** the family of proton-coupled metal ion transporters are responsible for movements of divalent cations, particularly ferrous and manganese ions, across the cell membrane (DMT1) and across endosomal (DMT1) or lysosomal/phagosomal membranes (NRAMP1), dependent on proton transport. Both proteins appear to have 12 TM regions and cytoplasmic N- and C- termini. NRAMP1 is involved in antimicrobial action in macrophages, although its precise mechanism is undefined. Facilitated diffusion of divalent cations into phagosomes may increase intravesicular free radicals to damage the pathogen. Alternatively, export of divalent cations from the phagosome may deprive the pathogen of essential enzyme cofactors. DMT1 is more widely expressed and appears to assist in divalent cation assimilation from the diet, as well as in phagocytotic cells.

Systematic name	SLC11A1	SLC11A2
Preferred abbreviation	NRAMP1	DMT1
Nomenclature		Divalent metal transporter 1
Ensembl ID	ENSG00000018280	ENSG00000110911
Other names	Natural resistance-associated macrophage protein 1	Natural resistance-associated macrophage protein 2, NRAMP2, DCT1
Endogenous substrates	Mn <sup>2+</sup> , Fe <sup>2+</sup>	Fe <sup>2+</sup> , Cd <sup>2+</sup> , Co <sup>2+</sup> , Cu <sup>2+</sup> , Mn <sup>2+</sup>
Stoichiometry	1 H <sup>+</sup> : 1 Fe <sup>2+</sup> (out) or 1 Fe <sup>2+</sup> (in); 1 H <sup>+</sup> (out)	1 H <sup>+</sup> : 1 Fe <sup>2+</sup> (out) (Gunshin <i>et al.</i> , 1997)

Loss-of-function mutations in NRAMP1 are associated with increased susceptibility to microbial infection. Loss-of-function mutations in DMT1 are associated with microcytic anemia.

## Further Reading

Li X, Yang Y, Zhou F, Zhang Y, Lu H, Jin Q *et al.* (2011). SLC11A1 (NRAMP1) polymorphisms and tuberculosis susceptibility: updated systematic review and meta-analysis. *PLoS One* 6: e15831.  
Mackenzie B, Hediger MA (2004). SLC11 family of H<sup>+</sup>-coupled metal-ion transporters NRAMP1 and DMT1. *Pflugers Arch* 447: 571–579.  
Nevo Y, Nelson N (2006). The NRAMP family of metal-ion transporters. *Biochim Biophys Acta* 1763: 609–620.

## Reference

Gunshin H *et al.* (1997). *Nature* 388: 482–488.

# SLC12 family of cation-coupled chloride transporters

**Overview:** the SLC12 family of chloride transporters contribute to ion fluxes across a variety of tissues. Within this family, further subfamilies are identifiable: NKCC1, NKCC2 and NCC constitute a group of therapeutically-relevant transporters, targets for loop and thiazide diuretics. These 12 TM proteins exhibit cytoplasmic termini and an extended extracellular loop at TM7/8 and are kidney-specific (NKCC2 and NCC) or show a more widespread distribution (NKCC1). A second family, the K-Cl co-transporters are also 12 TM domain proteins with cytoplasmic termini, but with an extended extracellular loop at TM 5/6. CCC6 exhibits structural similarities with the K-Cl co-transporters, while CCC9 is divergent, with 11 TM domains and a cytoplasmic N-terminus and extracellular C-terminus.

Systematic name	SLC12A1	SLC12A2	SLC12A3
Preferred abbreviation	NKCC2	NKCC1	NCC
Nomenclature	Kidney-specific Na-K-Cl symporter	Basolateral Na-K-Cl symporter	Na-Cl symporter
Ensembl ID	ENSG00000074803	ENSG00000064651	ENSG00000070915
Other names	Bumetanide-sensitive sodium-(potassium)-chloride cotransporter 2, BSC2	Bumetanide-sensitive sodium-(potassium)-chloride cotransporter 1, BSC1	Thiazide-sensitive sodium-chloride cotransporter, TSC
Inhibitors	Bumetanide, piretanide, frusemide (Hannaert <i>et al.</i> , 2002)	Bumetanide, piretanide, frusemide (Hannaert <i>et al.</i> , 2002)	Hydrochlorothiazide, chlorothiazide, metolazone
Stoichiometry	1 Na <sup>+</sup> : 1 K <sup>+</sup> : 2 Cl <sup>-</sup> (in)	1 Na <sup>+</sup> : 1 K <sup>+</sup> : 2 Cl <sup>-</sup> (in)	1 Na <sup>+</sup> : 1 Cl <sup>-</sup> (in)

Systematic name	SLC12A4	SLC12A5	SLC12A6	SLC12A7
Preferred abbreviation	KCC1	KCC2	KCC3	KCC4
Nomenclature	K-Cl cotransporter 1	K-Cl cotransporter 2	K-Cl cotransporter 3	K-Cl cotransporter 4
Ensembl ID	ENSG00000124067	ENSG00000124140	ENSG00000140199	ENSG00000113504
Other names	Electroneutral potassium-chloride cotransporter 1, erythroid K-Cl cotransporter 1	Electroneutral potassium-chloride cotransporter 2, erythroid K-Cl cotransporter 2	Electroneutral potassium-chloride cotransporter 3	Electroneutral potassium-chloride cotransporter 4
Inhibitors	DIOA	VU0240551 (Delpire <i>et al.</i> , 2009), DIOA	DIOA	DIOA
Stoichiometry	1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)	1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)	1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)	1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)

Systematic name	SLC12A8	SLC12A9
Preferred abbreviation	CCC9	CCC6
Nomenclature	Cation-chloride cotransporter 9	Cation-chloride cotransporter 6
Ensembl ID	ENSG00000221955	ENSG00000146828
Other names	–	Potassium-chloride transporter 9, CCC-interacting protein 1
Substrates	Spermine, spermidine, glutamate, aspartate (Daigle <i>et al.</i> , 2009)	–
Stoichiometry	Unknown	–

CCC6 is regarded as an orphan transporter.

DIOA is able to differentiate KCC isoforms from NKCC and NCC transporters, but also inhibits CFTR (Ito *et al.*, 2001).

**Abbreviations:** DIOA, 2-[(2-butyl-6,7-dichloro-2-cyclopentyl-1-oxo-3H-inden-5-yl)oxy]acetic acid; VU0240551, N-(4-methyl-1,3-thiazol-2-yl)-2-(6-phenylpyridazin-3-yl)sulfanylacetamide

### Further Reading

- Castrop H, Schnermann J (2008). Isoforms of renal Na-K-2Cl cotransporter NKCC2: expression and functional significance. *Am J Physiol Renal Physiol* **295**: F859–F866.
- Gamba G, Friedman PA (2009). Thick ascending limb: the Na<sup>+</sup>:K<sup>+</sup>:2Cl<sup>-</sup> co-transporter, NKCC2, and the calcium-sensing receptor, CaSR. *Pflugers Arch* **458**: 61–76.
- Hebert SC, Mount DB, Gamba G (2004). Molecular physiology of cation-coupled Cl<sup>-</sup> cotransport: the SLC12 family. *Pflugers Arch* **447**: 580–593.
- Kahle KT, Staley KJ, Nahed BV, Gamba G, Hebert SC, Lifton RP *et al.* (2008). Roles of the cation-chloride cotransporters in neurological disease. *Nat Clin Pract Neurol* **4**: 490–503.
- Kahle KT, Rinehart J, Lifton RP (2010). Phosphoregulation of the Na-K-2Cl and K-Cl cotransporters by the WNK kinases. *Biochim Biophys Acta* **1802**: 1150–1158.
- Lang F, Vallon V, Knipper M, Wangemann P (2007). Functional significance of channels and transporters expressed in the inner ear and kidney. *Am J Physiol Cell Physiol* **293**: C1187–C1208.
- Lionetto MG, Schettino T (2006). The Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter and the osmotic stress response in a model salt transport epithelium. *Acta Physiol (Oxf)* **187**: 115–124.
- Wagner CA, Devuyst O, Bourgeois S, Mohebbi N (2009). Regulated acid-base transport in the collecting duct. *Pflugers Arch* **458**: 137–156.

### References

- Daigle ND *et al.* (2009). *J Cell Physiol* **220**: 680–689.
- Delpire E *et al.* (2009). *Proc Natl Acad Sci U S A* **106**: 5383–5388.
- Hannaert P *et al.* (2002). *Naunyn Schmiedebergs Arch Pharmacol* **365**: 193–199.
- Ito Y *et al.* (2001). *Eur J Pharmacol* **426**: 175–178.

## SLC13 family of sodium-dependent sulphate/carboxylate transporters

**Overview:** within the SLC13 family, two groups of transporters may be differentiated on the basis of the substrates transported: NaS1 and NaS2 convey sulphate, while NaC1-3 transport carboxylates. NaS1 and NaS2 transporters are made up of 13 TM domains, with an intracellular N terminus and are electrogenic with physiological roles in the intestine, kidney and placenta. NaC1, NaC2 and NaC3 are made up of 11 TM domains with an intracellular N terminus and are electrogenic, with physiological roles in the kidney and liver.

Systematic name	SLC13A1	SLC13A2	SLC13A3
Preferred abbreviation	NaS1	NaC1	NaC3
Nomenclature	Na <sup>+</sup> /sulfate cotransporter	Na <sup>+</sup> /dicarboxylate cotransporter 1	Na <sup>+</sup> /dicarboxylate cotransporter 3
Other names	Renal sodium/sulfate cotransporter, NaSi-1	Renal sodium/dicarboxylate cotransporter, NaDC1	Sodium-dependent high-affinity dicarboxylate transporter 2, NaDC3
Ensembl ID	ENSG00000081800	ENSG00000007216	ENSG00000158296
Endogenous substrates	Sulphate, thiosulphate, selenate	Succinate, citrate	Succinate, citrate
Stoichiometry	3 Na <sup>+</sup> : 1 SO <sub>4</sub> <sup>2-</sup> (in)	3 Na <sup>+</sup> : 1 dicarboxylate <sup>2-</sup> (in)	Unknown

Systematic name	SLC13A4	SLC13A5
Preferred abbreviation	NaS2	NaC2
Nomenclature	Na <sup>+</sup> /sulfate cotransporter	Na <sup>+</sup> /citrate cotransporter
Other names	SUT1	Sodium-coupled citrate transporter, sodium-dependent citrate transporter, NaCT
Ensembl ID	ENSG00000164707	ENSG00000141485
Endogenous substrates	Sulphate	Citrate, pyruvate
Stoichiometry	3 Na <sup>+</sup> : SO <sub>4</sub> <sup>2-</sup> (in)	Unknown

#### Further Reading

Lee A, Dawson PA, Markovich D (2005). NaSi-1 and Sat-1: structure, function and transcriptional regulation of two genes encoding renal proximal tubular sulfate transporters. *Int J Biochem Cell Biol* **37**: 1350–1356.

Markovich D (2011). Physiological roles of renal anion transporters NaS1 and Sat1. *Am J Physiol Renal Physiol* **300**: F1267–F1270.

Markovich D, Murer H (2004). The SLC13 gene family of sodium sulphate/carboxylate cotransporters. *Pflugers Arch* **447**: 594–602.

Markovich D, Aronson PS (2007). Specificity and regulation of renal sulfate transporters. *Annu Rev Physiol* **69**: 361–375.

## SLC14 family of facilitative urea transporters

**Overview:** as a product of protein catabolism, urea is moved around the body and through the kidneys for excretion. Although there is experimental evidence for concentrative urea transporters, these have not been defined at the molecular level. The SLC14 family are facilitative transporters, allowing urea movement down its concentration gradient. Multiple splice variants of these transporters have been identified; for UT-A transporters, in particular, there is evidence for cell-specific expression of these variants with functional impact (see Stewart, 2011). Topographical modelling suggests that the majority of the variants of SLC14 transporters have 10 TM domains, with a glycosylated extracellular loop at TMS/6, and intracellular C- and N-termini. The UT-A1 splice variant, exceptionally, has 20 TM domains, equivalent to a combination of the UT-A2 and UT-A3 splice variants.

Systematic name	SLC14A1	SLC14A2
Preferred abbreviation	UT-B	UT-A
Nomenclature	Erythrocyte urea transporter	Kidney urea transporter
Ensembl ID	ENSG00000141469	ENSG00000132874
Other names	UTB1	UTA1
Endogenous substrates	Urea, formamide, ammonium carbonate (Zhao <i>et al.</i> , 2007)	Urea (Maciver <i>et al.</i> , 2008)
Synthetic substrates	Acetamide, methylurea, methylformamide, acrylamide (Zhao <i>et al.</i> , 2007)	–
Stoichiometry	Equilibrative	Equilibrative

#### Further Reading

Bagnasco SM (2005). Role and regulation of urea transporters. *Pflugers Arch* **450**: 217–226.

Bagnasco SM (2006). The erythrocyte urea transporter UT-B. *J Membr Biol* **212**: 133–138.

Fenton RA (2009). Essential role of vasopressin-regulated urea transport processes in the mammalian kidney. *Pflugers Arch* **458**: 169–177.

Shayakul C, Hediger MA (2004). The SLC14 gene family of urea transporters. *Pflugers Arch* **447**: 603–609.

Smith CP (2009). Mammalian urea transporters. *Exp Physiol* **94**: 180–185.

Smith CP, Fenton RA (2006). Genomic organization of the mammalian SLC14a2 urea transporter genes. *J Membr Biol* **212**: 109–117.

Stewart G (2011). The emerging physiological roles of the SLC14A family of urea transporters. *Br J Pharmacol* in press.

Yang B, Bankir L (2005). Urea and urine concentrating ability: new insights from studies in mice. *Am J Physiol Renal Physiol* **288**: F881–F896.

## References

- Maciver B *et al.* (2008). *Am J Physiol Renal Physiol* **294**: F956–F964.  
 Zhao D *et al.* (2007). *Biochim Biophys Acta* **1768**: 1815–1821.

## SLC15 family of peptide transporters

**Overview:** the SLC15 family of peptide transporters may be divided on the basis of structural and functional differences into two subfamilies: SLC15A1 (PepT1) and SLC15A2 (PepT2) transport di- and tripeptides, but not amino acids, whereas SLC15A3 (PHT2) and SLC15A4 (PHT1) transport histidine and some di- and tripeptides (see Daniel and Kottra, 2004). The transporters are 12 TM proteins with intracellular termini and an extended extracellular loop at TM 9/10. The crystal structure of PepT<sub>So</sub> (a prokaryote homologue of PepT1 and PepT2 from *Shewanella oneidensis*) confirms many of the predicted structural features of mammalian PepT1 and PepT2 (Newstead *et al.*, 2011).

PHT1 has been suggested to be intracellular (Romano *et al.*, 2010), while PHT2 protein is located on lysosomes in transfected cells (Botka *et al.*, 2000; Sakata *et al.*, 2001; Herrera-Ruiz and Knipp, 2003). PHT1 is hypothesised to mediate efflux of bacterial-derived peptides into the cytosol perhaps in the colon where SLC15A4 mRNA expression is increased in inflammatory bowel disease (Lee *et al.*, 2009). Transport via PHT1 may be important in immune responses as both Toll-like receptor- and NOD1-mediated responses are reduced in PHT1 knockout mice or mouse strains expressing mutations in PHT1 (Blasius *et al.*, 2010; Sasawatari *et al.*, 2011).

Systematic name	SLC15A1	SLC15A2	SLC15A3	SLC15A4
Preferred abbreviation	PepT1	PepT2	PHT2	PHT1
Nomenclature	Peptide transporter 1	Peptide transporter 2	Peptide transporter 3	Peptide transporter 4
Ensembl ID	ENSG000000888386	ENSG00000163406	ENSG00000110446	ENSG00000139370
Other names	Intestinal H <sup>+</sup> /peptide cotransporter, low affinity peptide transporter	Kidney H <sup>+</sup> /peptide cotransporter, high affinity peptide transporter	Peptide/histidine transporter 2, osteoclast transporter, peptide transporter 3, PTR3, cAMP-inducible 1 protein	Peptide/histidine transporter 1, peptide transporter 4, PTR4
Endogenous substrates	Dipeptides, tripeptides, 5-aminolevulinic acid (Doring <i>et al.</i> , 1998)	Dipeptides, tripeptides, 5-aminolevulinic acid	Dipeptides, tripeptides, histidine, carnosine	Dipeptides, tripeptides, histidine, carnosine
Synthetic substrates	Cyclacillin, cefadroxil (Ganapathy <i>et al.</i> , 1995), enalapril, captopril (Temple and Boyd, 1998), muramyl dipeptide (Vavricka <i>et al.</i> , 2004), fMLP (Merlin <i>et al.</i> , 1998)	Cyclacillin, cefadroxil (Ganapathy <i>et al.</i> , 1995)	–	Valacyclovir (Bhardwaj <i>et al.</i> , 2006)
Inhibitors	Lys[Z(NO <sub>2</sub> )]-Pro (Knutter <i>et al.</i> , 2001), 4-AMBA (Darcel <i>et al.</i> , 2005)	Lys[Z(NO <sub>2</sub> )]-Pro, Lys[Z(NO <sub>2</sub> )]-Lys[Z(NO <sub>2</sub> )] (Theis <i>et al.</i> , 2002; Biegel <i>et al.</i> , 2006)		
Probes	[ <sup>3</sup> H]-, [ <sup>14</sup> C]- or [ <sup>14</sup> C]-GlySar	[ <sup>3</sup> H]-, [ <sup>14</sup> C]- or [ <sup>14</sup> C]-GlySar	[ <sup>3</sup> H]-or [ <sup>14</sup> C]-Histidine	[ <sup>3</sup> H]-or [ <sup>14</sup> C]-Histidine
Stoichiometry	2 H <sup>+</sup> : 1 zwitterionic peptide (in)	2 H <sup>+</sup> : 1 zwitterionic peptide (in)	Unknown	Unknown

The PepT1 and PepT2 transporters are particularly promiscuous in the transport of dipeptides and tripeptides of any sequence from the endogenous amino acids, as well as some D-amino acid containing peptides. PepT1 has also been exploited to allow delivery of therapeutic pro-drugs, such as those for zidovudine (Han *et al.*, 1998), sulphiride (Watanabe *et al.*, 2002) and cytarabine (Sun *et al.*, 2009).

D-Ala-Lys-AMCA has been used as a fluorescent probe to identify transport via both PepT1 and PepT2 (Rubio-Aliaga and Daniel, 2008).

**Abbreviations:** d-Ala-Lys-AMCA, d-Ala-Lys-N<sup>6</sup>-7-amino-4-methyl-coumarin-3-acetic acid; 4-AMBA, 4-(aminomethyl)benzoic acid; fMLP, formyl-Met-Leu-Phe

## Further Reading

- Anderson CMH, Thwaites DT (2010). Hijacking solute carriers for proton-coupled drug transport. *Physiology* **25**: 364–377.  
 Biegel A, Knutter I, Hartrodt B, Gebauer S, Theis S, Luckner P *et al.* (2006). The renal type H<sup>+</sup>/peptide symporter PEPT2: structure-affinity relationships. *Amino Acids* **31**: 137–156.  
 Brandsch M (2009). Transport of drugs by proton-coupled peptide transporters: pearls and pitfalls. *Expert Opin Drug Metab Toxicol* **5**: 887–905.  
 Brandsch M, Knutter I, Leibach FH (2004). The intestinal H<sup>+</sup>/peptide symporter PEPT1: structure-affinity relationships. *Eur J Pharm Sci* **21**: 53–60.

Charrier L, Merlin D (2006). The oligopeptide transporter hPepT1: gateway to the innate immune response. *Lab Invest* **86**: 538–546.

Daniel H (2004). Molecular and integrative physiology of intestinal peptide transport. *Annu Rev Physiol* **66**: 361–384.

Daniel H, Kottra G (2004). The proton oligopeptide cotransporter family SLC15 in physiology and pharmacology. *Pflügers Arch* **447**: 610–618.

Kamal MA, Keep RF, Smith DE (2008). Role and relevance of PEPT2 in drug disposition, dynamics, and toxicity. *Drug Metab Pharmacokinet* **23**: 236–242.

Meredith D, Price RA (2006). Molecular modeling of PepT1—towards a structure. *J Membr Biol* **213**: 79–88.

Rubio-Aliaga I, Daniel H (2008). Peptide transporters and their roles in physiological processes and drug disposition. *Xenobiotica* **38**: 1022–1042.

Terada T, Inui K (2007). Gene expression and regulation of drug transporters in the intestine and kidney. *Biochem Pharmacol* **73**: 440–449.

Thwaites DT, Anderson CMH (2007). H<sup>+</sup>-coupled nutrient, micronutrient and drug transporters in the mammalian small intestine. *Exp Physiol* **92**: 603–619.

## References

- Bhardwaj RK *et al.* (2006). *Eur J Pharm Sci* **27**: 533–542.
- Biegel A *et al.* (2006). *Amino Acids* **31**: 137–156.
- Blasius AL *et al.* (2010). *Proc Natl Acad Sci U S A* **107**: 19973–19978.
- Botka CW *et al.* (2000). *AAPS PharmSci* **2**: E16.
- Darcel NP *et al.* (2005). *J Nutr* **135**: 1491–1495.
- Doring F *et al.* (1998). *J Clin Invest* **101**: 2761–2767.
- Ganapathy ME *et al.* (1995). *J Biol Chem* **270**: 25672–25677.
- Han H *et al.* (1998). *Pharm Res* **15**: 1154–1159.
- Herrera-Ruiz D, Knipp GT (2003). *J Pharm Sci* **92**: 691–714.
- Knutter I *et al.* (2001). *Biochemistry* **40**: 4454–4458.
- Lee J *et al.* (2009). *J Biol Chem* **284**: 23818–23829.
- Merlin D *et al.* (1998). *J Clin Invest* **102**: 2011–2018.
- Newstead S *et al.* (2011). *EMBO J* **30**: 417–426.
- Romano A *et al.* (2010). *Mol Cell Endocrinol* **315**: 174–181.
- Sakata K *et al.* (2001). *Biochem J* **356**: 53–60.
- Sasawatari S *et al.* (2011). *Gastroenterology* **140**: 1513–1525.
- Sun Y *et al.* (2009). *Mol Pharm* **6**: 315–325.
- Temple CS, Boyd CA (1998). *Biochim Biophys Acta* **1373**: 277–281.
- Theis S *et al.* (2002). *Mol Pharmacol* **61**: 214–221.
- Vavricka SR *et al.* (2004). *Gastroenterology* **127**: 1401–1409.
- Watanabe K *et al.* (2002). *Biol Pharm Bull* **25**: 885–890.

# SLC16 family of monocarboxylate transporters

**Overview:** members of the SLC16 family may be divided into subfamilies on the basis of substrate selectivities, particularly lactate, pyruvate and ketone bodies, as well as aromatic amino acids. Topology modelling suggests 12 TM domains, with intracellular termini and an extended loop at TM 6/7.

The proton-coupled monocarboxylate transporters allow transport of the products of cellular metabolism, principally lactate and pyruvate.

Systematic name	SLC16A1	SLC16A3	SLC16A7	SLC16A8
Preferred abbreviation	MCT1	MCT4	MCT2	MCT3
Nomenclature	Monocarboxylate transporter 1	Monocarboxylate transporter 4	Monocarboxylate transporter 2	Monocarboxylate transporter 3
Ensembl ID	ENSG00000155380	ENSG00000141526	ENSG00000118596	ENSG00000100156
Other names	–	Monocarboxylate transporter 3, MCT 3	–	REMP
Endogenous substrates	Lactate, pyruvate, β-hydroxybutyrate	Lactate, pyruvate	Lactate, pyruvate	Lactate
Synthetic substrates	GHB (Wang <i>et al.</i> , 2006)	–	–	–
Stoichiometry	1 H <sup>+</sup> : 1 monocarboxylate <sup>-</sup> (out)	1 H <sup>+</sup> : 1 monocarboxylate <sup>-</sup> (out)	1 H <sup>+</sup> : 1 monocarboxylate <sup>-</sup> (out)	1 H <sup>+</sup> : 1 monocarboxylate <sup>-</sup> (out)

MCT1 and MCT2, but not MCT3 and MCT4, are inhibited by CHC, which also inhibits members of the mitochondrial transporter family, SLC25 (see Page S256).

Systematic name	SLC16A2	SLC16A10
Preferred abbreviation	MCT8	TAT1
Nomenclature	Monocarboxylate transporter 8	Monocarboxylate transporter 10
Ensembl ID	ENSG00000147100	ENSG00000112394
Other names	Monocarboxylate transporter 7, MCT 7, X-linked PEST-containing transporter	T-type amino acid transporter 1, aromatic amino acid transporter 1, MCT10
Endogenous substrates	T3, T4 (Friesema <i>et al.</i> , 2006)	L-Tryptophan, L-phenylalanine, L-tyrosine, L-DOPA
Stoichiometry	Unknown	Unknown



Systematic name	SLC16A4	SLC16A5	SLC16A6	SLC16A9
Preferred abbreviation	MCT5	MCT6	MCT7	MCT9
Nomenclature	Monocarboxylate transporter 5	Monocarboxylate transporter 6	Monocarboxylate transporter 7	Monocarboxylate transporter 9
Ensembl ID	ENSG00000168679	ENSG00000170190	ENSG00000108932	ENSG00000165449
Other names	Monocarboxylate transporter 4, MCT 4	Monocarboxylate transporter 5, MCT 5	Monocarboxylate transporter 6, MCT 6	–
Stoichiometry	Unknown	Unknown	Unknown	Unknown

MCT6 has been reported to transport bumetamide, but not short chain fatty acids (Murakami *et al.*, 2005).

Systematic name	SLC16A11	SLC16A12	SLC16A13	SLC16A14
Preferred abbreviation	MCT11	MCT12	MCT13	MCT14
Nomenclature	Monocarboxylate transporter 11	Monocarboxylate transporter 12	Monocarboxylate transporter 13	Monocarboxylate transporter 14
Ensembl ID	ENSG00000174326	ENSG00000152779	ENSG00000174327	ENSG00000163053
Stoichiometry	Unknown	Unknown	Unknown	Unknown

MCT5-MCT7, MCT9 and MCT11-14 are regarded as orphan transporters.

**Abbreviations:** **CHC**, (E)-2-cyano-3-(4-hydroxyphenyl)prop-2-enoic acid; **GHB**, gamma-hydroxybutyrate; **T3**, (2S)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propanoic acid, also known as triiodothyronine; **T4**, thyroxine

### Further Reading

- Anderson CM, Thwaites DT (2010). Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* **25**: 364–377.
- Braun D, Wirth EK, Schweizer U (2010). Thyroid hormone transporters in the brain. *Rev Neurosci* **21**: 173–186.
- van der Deure WM, Peeters RP, Visser TJ (2010). Molecular aspects of thyroid hormone transporters, including MCT8, MCT10, and OATPs, and the effects of genetic variation in these transporters. *J Mol Endocrinol* **44**: 1–11.
- Friesema EC, Visser WE, Visser TJ (2010). Genetics and phenomics of thyroid hormone transport by MCT8. *Mol Cell Endocrinol* **322**: 107–113.
- Halestrap AP, Meredith D (2004). The SLC16 gene family—from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. *Pflugers Arch* **447**: 619–628.
- Heuer H, Visser TJ (2009). Pathophysiological importance of thyroid hormone transporters. *Endocrinology* **150**: 1078–1083.
- Jansen J, Friesema EC, Milici C, Visser TJ (2005). Thyroid hormone transporters in health and disease. *Thyroid* **15**: 757–768.
- Meredith D, Christian HC (2008). The SLC16 monocarboxylate transporter family. *Xenobiotica* **38**: 1072–1106.
- Morris ME, Felmler MA (2008). Overview of the proton-coupled MCT (SLC16A) family of transporters: characterization, function and role in the transport of the drug of abuse  $\gamma$ -hydroxybutyric acid. *AAPS J* **10**: 311–321.
- Visser TJ (2007). Thyroid hormone transporters. *Horm Res* **68** (Suppl. 5): 28–30.
- Visser WE, Friesema EC, Jansen J, Visser TJ (2008). Thyroid hormone transport in and out of cells. *Trends Endocrinol Metab* **19**: 50–56.

### References

- Friesema EC *et al.* (2006). *Mol Endocrinol* **20**: 2761–2772.
- Murakami Y *et al.* (2005). *Drug Metab Dispos* **33**: 1845–1851.
- Wang Q *et al.* (2006). *J Pharmacol Exp Ther* **318**: 751–761.

## SLC17 phosphate and organic anion transporter family

**Overview:** The SLC17 family are sometimes referred to as Type I sodium-phosphate co-transporters, alongside Type II (SLC34 family, see Page S265) and Type III (SLC20 family, see Page S251) transporters. Within the SLC17 family, however, further subgroups of organic anion transporters may be defined, allowing the accumulation of sialic acid in the endoplasmic reticulum and glutamate or nucleotides in synaptic and secretory vesicles. Topology modelling suggests 12 TM domains.

**Type I sodium-phosphate co-transporters** are expressed in the kidney and intestine

Systematic name	SLC17A1	SLC17A2	SLC17A3	SLC17A4
Preferred abbreviation	NPT1	NPT3	NPT4	–
Nomenclature	Sodium/phosphate cotransporter 1	Sodium/phosphate cotransporter 3	Sodium/phosphate cotransporter 4	–
Ensembl ID	ENSG00000124568	ENSG00000112337	ENSG00000124564	ENSG00000146039
Other names	NaPi-1, renal sodium-dependent phosphate transport protein 1	–	–	Putative small intestine sodium-dependent phosphate transport protein
Substrates	Phosphate, organic acids, chloride, urate (Iharada <i>et al.</i> , 2010)	–	–	–
Synthetic substrates	Probenecid, penicillin (Busch <i>et al.</i> , 1996)	–	–	–
Stoichiometry	Unknown	Unknown	Unknown	Unknown

The **sialic acid transporter** is expressed on both lysosomes and synaptic vesicles, where it appears to allow export of sialic acid and accumulation of acidic amino acids, respectively (Miyaji *et al.*, 2011), driven by proton gradients. In lysosomes, degradation of glycoproteins generates amino acids and sugar residues, which are metabolized further following export from the lysosome.

Systematic name	SLC17A5
Preferred abbreviation	AST
Nomenclature	Sialin
Ensembl ID	ENSG00000119899
Other names	Sodium/sialic acid cotransporter, membrane glycoprotein HP59
Endogenous substrates	Sialic acid, lactate, glucuronic acid, gluconate (out) Aspartate, glutamate (in) (Miyaji <i>et al.</i> , 2011)
Stoichiometry	1 H <sup>+</sup> : 1 sialic acid (out)

Loss-of-function mutations in sialin are associated with Salla disease, an autosomal recessive neurodegenerative disorder associated with sialic acid storage disease (Verheijen *et al.*, 1999).

**Vesicular glutamate transporters (VGLUTs)** allow accumulation of glutamate into synaptic vesicles, as well as secretory vesicles in endocrine tissues. The roles of VGLUTs in kidney and liver are unclear. These transporters appear to utilize the proton gradient and also express a chloride conductance (Bellocchio *et al.*, 2000).

Systematic name	SLC17A7	SLC17A6	SLC17A8
Preferred abbreviation	VGLUT1	VGLUT2	VGLUT3
Nomenclature	Vesicular glutamate transporter 1	Vesicular glutamate transporter 2	Vesicular glutamate transporter 3
Ensembl ID	ENSG00000104888	ENSG00000091664	ENSG00000179520
Other names	Brain-specific Na <sup>+</sup> -dependent inorganic phosphate cotransporter, BNPI	Differentiation-associated Na <sup>+</sup> -dependent inorganic phosphate cotransporter, differentiation-associated BNPI	–
Endogenous substrates	L-glutamate > D-glutamate	L-glutamate > D-glutamate	L-glutamate > D-glutamate
Stoichiometry	Unknown	Unknown	Unknown

Endogenous ketoacids produced during fasting have been proposed to regulate VGLUT function through blocking chloride ion-mediated allosteric enhancement of transporter function (Juge *et al.*, 2010).

The **vesicular nucleotide transporter** is the most recent member of the SLC17 family to have an assigned function. Uptake of ATP was independent of pH, but dependent on chloride ions and membrane potential (Sawada *et al.*, 2008).

Systematic name	SLC17A9
Preferred abbreviation	VNUT
Nomenclature	Vesicular nucleotide transporter
Ensembl ID	ENSG00000101194
Other names	Uncharacterized MFS-type transporter C20orf59
Endogenous substrates	ATP, GTP, GDP (Sawada <i>et al.</i> , 2008)
Stoichiometry	Unknown

VGLUTs and VNUT can be inhibited by DIDS and Evans blue dye.

**Abbreviations:** DIDS, 5-isothiocyanato-2-[(E)-2-(4-isothiocyanato-2-sulfophenyl)ethenyl]benzenesulfonic acid

### Further Reading

- El Mestikawy S, Wallen-Mackenzie A, Fortin GM, Descarries L, Trudeau LE (2011). From glutamate co-release to vesicular synergy: vesicular glutamate transporters. *Nat Rev Neurosci* **12**: 204–216.
- Erickson JD, De GS, Varoqui H, Schafer MK, Weihe E (2006). Activity-dependent regulation of vesicular glutamate and GABA transporters: a means to scale quantal size. *Neurochem Int* **48**: 643–649.
- Fei H, Grygoruk A, Brooks ES, Chen A, Krantz DE (2008). Trafficking of vesicular neurotransmitter transporters. *Traffic* **9**: 1425–1436.
- Moriyama Y, Omote H (2008). Vesicular glutamate transporter acts as a metabolic regulator. *Biol Pharm Bull* **31**: 1844–1846.
- Omote H, Miyaji T, Juge N, Moriyama Y (2011). Vesicular neurotransmitter transporter: bioenergetics and regulation of glutamate transport. *Biochemistry* **50**: 5558–5565.
- Reimer RJ, Edwards RH (2004). Organic anion transport is the primary function of the SLC17/type I phosphate transporter family. *Pflugers Arch* **447**: 629–635.
- Santos MS, Li H, Voglmaier SM (2009). Synaptic vesicle protein trafficking at the glutamate synapse. *Neuroscience* **158**: 189–203.
- Shigeri Y, Seal RP, Shimamoto K (2004). Molecular pharmacology of glutamate transporters, EAATs and VGLUTs. *Brain Res Brain Res Rev* **45**: 250–265.

### References

- Bellocchio EE *et al.* (2000). *Science* **289**: 957–960.
- Busch AE *et al.* (1996). *Proc Natl Acad Sci U S A* **93**: 5347–5351.
- Iharada M *et al.* (2010). *J Biol Chem* **285**: 26107–26113.
- Juge N *et al.* (2010). *Neuron* **68**: 99–112.
- Miyaji T *et al.* (2011). *J Neurochem* **119**: 1–5.
- Sawada K *et al.* (2008). *Proc Natl Acad Sci U S A* **105**: 5683–5686.
- Verheijen FW *et al.* (1999). *Nat Genet* **23**: 462–465.

## SLC18 family of vesicular amine transporters

**Overview:** The vesicular amine transporters (VATs) are putative 12 TM domain proteins that function to transport singly positively charged amine neurotransmitters and hormones from the cytoplasm and concentrate them within secretory vesicles. They function as amine/proton antiporters driven by secondary active transport utilizing the proton gradient established by a multi-subunit vacuolar ATPase (see Page S218) that acidifies secretory vesicles (reviewed by Eiden *et al.*, 2004). The vesicular acetylcholine transporter (VACHT; Erickson *et al.*, 1994) localizes to cholinergic neurons, but non-neuronal expression has also been claimed (Schirmer *et al.*, 2011). Vesicular monoamine transporter 1 (VMAT1, Erickson and Eiden, 1993) is mainly expressed in peripheral neuroendocrine cells, but most likely not in the CNS, whereas VMAT2 (Erickson *et al.*, 1996) distributes between both central and peripheral sympathetic monoaminergic neurones (Eiden and Weihe, 2011).

Common abbreviation	VMAT1	VMAT2	VACHT
Systematic name	SLC18A1	SLC18A2	SLC18A3
Nomenclature	Vesicular monoamine transporter 1	Vesicular monoamine transporter 2	Vesicular acetylcholine transporter
Other names	Chromaffin granule amine transporter (CGAT), VAT1, MAT	Synaptic vesicular amine transporter (SVAT), SVMAT, VAT2	(VACHT)
Ensembl ID	ENSG00000036565	ENSG00000165646	ENSG00000187714
Endogenous substrates ( $pK_m/pK_i$ )	5-HT (5.8), dopamine (5.4), adrenaline (5.3), noradrenaline (4.9), histamine (2.3) (Erickson <i>et al.</i> , 1996)	5-HT (6.0), dopamine (5.9), adrenaline (5.7), noradrenaline (5.5), histamine (3.8) (Erickson <i>et al.</i> , 1996)	Acetylcholine (3.1), choline (2.3) (Bravo <i>et al.</i> , 2004; Khare <i>et al.</i> , 2010)
Synthetic substrates ( $pK_m/pK_i$ )	Fenfluramine (5.5), MDMA (4.7), D-amphetamine (4.3), MPP <sup>+</sup> (4.2), phenyl-ethylamine (4.5) (Erickson <i>et al.</i> , 1996)	D-amphetamine (5.7), phenylethylamine (5.4), fenfluramine (5.3), MDMA (5.2), MPP <sup>+</sup> (5.1) (Erickson <i>et al.</i> , 1996)	TPP <sup>+</sup> , N-methyl-pyridinium-2-aldoxime, N-(4'-pentanonyl)-4-(4''-dimethylamino-styryl)pyridinium, ethidium (Bravo <i>et al.</i> , 2005)
Inhibitors ( $pK_i$ )	Reserpine (7.45), ketanserin (5.8), TBZ (>4.7) (Erickson <i>et al.</i> , 1996)	Reserpine (7.9), TBZ (7.0), ketanserin (6.3) (Erickson <i>et al.</i> , 1996)	Vesamicol (8.7), aminobenzovesamicol (10.9), (Efang <i>et al.</i> , 1995)
Probes ( $K_d$ )		[ <sup>3</sup> H]-TBZOH (6.6 nM, Varoqui and Erickson, 1996), [ <sup>125</sup> I]-iodovinyl-TBZ (8.2 nM, Kung <i>et al.</i> , 1994); [ <sup>125</sup> I]-8-azido-3-iodoketanserin (photoaffinity ligand), [ <sup>11</sup> C]-DTBZ (PET ligand)	[ <sup>3</sup> H]-vesamicol (4.1 nM, Varoqui and Erickson, 1996), [ <sup>123</sup> I]-iodobenzovesamicol (SPECT ligand)
Stoichiometry	1 amine (in): 2H <sup>+</sup> (out)	1 amine (in): 2H <sup>+</sup> (out)	1 amine (in): 2H <sup>+</sup> (out)

$pK_i$  values for endogenous and synthetic substrate inhibitors of human VMAT1 and VMAT2 are for inhibition of [<sup>3</sup>H]-5-HT uptake in transfected and permeabilised CV-1 cells as detailed by Erickson *et al.* (1996). In addition to the monoamines listed in the table, the trace amines tyramine and phenylethylamine are probable substrates for VMAT2 (Eiden and Weihe, 2011). Probes listed in the table are those currently employed; additional agents have been synthesized (*e.g.* Zhu *et al.*, 2009).

**Abbreviations:** DTBZ, dihydrotetabenazine; MDMA, 3,4-methylenedioxyamphetamine; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; TBZ, tetra-benzazine; TBZOH,  $\alpha$ -[O-methyl-<sup>3</sup>H]dihydrotetabenazine; TPP<sup>+</sup>, tetraphenylphosphonium

### Further Reading

- Chaudhry FA, Edwards RH, Fonnum F (2008). Vesicular neurotransmitter transporters as targets for endogenous and exogenous toxic substances. *Annu Rev Pharmacol Toxicol* **48**: 277–301.
- Eiden LE, Weihe E (2011). VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. *Ann N Y Acad Sci* **1216**: 86–98.
- Eiden LE, Schafer MK, Weihe E, Schutz B (2004). The vesicular amine transporter family (SLC18): amine/proton antiporters required for vesicular accumulation and regulated exocytotic secretion of monoamines and acetylcholine. *Pflugers Arch* **447**: 636–640.
- Fei H, Grygoruk A, Brooks ES, Chen A, Krantz DE (2008). Trafficking of vesicular neurotransmitter transporters. *Traffic* **9**: 1425–1436.
- Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR (2007). New insights into the mechanism of action of amphetamines. *Annu Rev Pharmacol Toxicol* **47**: 681–698.
- Fleckenstein AE, Volz TJ, Hanson GR (2009). Psychostimulant-induced alterations in vesicular monoamine transporter-2 function: neurotoxic and therapeutic implications. *Neuropharmacology* **56** (Suppl. 1): 133–138.
- Giboureau N, Som IM, Boucher-Arnold A, Guilloteau D, Kassiou M (2010). PET Radioligands for the Vesicular Acetylcholine Transporter (VACHT). *Curr Top Med Chem* **10**: 1569–1583.
- Guillot TS, Miller GW (2009). Protective actions of the vesicular monoamine transporter 2 (VMAT2) in monoaminergic neurons. *Mol Neurobiol* **39**: 149–170.
- Khare P, White AR, Mulakaluri A, Parsons SM (2010). Equilibrium binding and transport by vesicular acetylcholine transporter. *Methods Mol Biol* **637**: 181–219.
- Parsons SM (2000). Transport mechanisms in acetylcholine and monoamine storage. *FASEB J* **14**: 2423–2434.
- Schuldiner S, Shirvan A, Linial M (1995). Vesicular neurotransmitter transporters: from bacteria to humans. *Physiol Rev* **75**: 369–392.
- Van der Kloot W (2003). Loading and recycling of synaptic vesicles in the *Torpedo* electric organ and the vertebrate neuromuscular junction. *Prog Neurobiol* **71**: 269–303.
- Zheng G, Dwoskin LP, Crooks PA (2006). Vesicular monoamine transporter 2: role as a novel target for drug development. *AAPS J* **8**: E682–E692.

## References

- Bravo DT *et al.* (2004). *J Neurochem* **91**: 766–768.  
 Bravo DT *et al.* (2005). *Neurochem Int* **47**: 243–247.  
 Efang SMN *et al.* (1995). *Biochem Pharm* **49**: 791–797.  
 Erickson JD, Eiden LE (1993). *J Neurochem* **61**: 2314–2317.  
 Erickson JD *et al.* (1994). *J Biol Chem* **269**: 21929–21932.  
 Erickson JD *et al.* (1996). *Proc Natl Acad Sci U S A* **93**: 5166–5171.  
 Khare P *et al.* (2010). *Biochemistry* **49**: 3049–3059.  
 Kung MP *et al.* (1994). *Synapse* **18**: 225–232.  
 Schirmer S *et al.* (2011). *Reproduction* **142**: 157–166.  
 Varoqui H, Erickson JD. (1996). *J Biol Chem* **271**: 27229–27232.  
 Zhu L *et al.* (2009). *Bioorg Med Chem Lett* **19**: 5026–5028.

## SLC19 family of vitamin transporters

**Overview:** the B vitamins folate and thiamine are transported across the cell membrane, particularly in the intestine, kidneys and placenta, using pH differences as driving forces. Topological modelling suggests the transporters have 12 TM domains.

Systematic name	SLC19A1	SLC19A2	SLC19A3
Nomenclature	Folate transporter 1	Thiamine transporter 1	Thiamine transporter 2
Common abbreviation	FOLT	ThTr1	ThTr2
Ensembl ID	ENSG00000173638	ENSG00000117479	ENSG00000135917
Other names	Reduced folate carrier protein, RFC1, intestinal folate carrier, IFC1, placental folate transporter	Thiamine carrier 1, TC1	
Endogenous substrates	Tetrahydrofolate, N <sup>5</sup> -methylfolate, folate (Prasad <i>et al.</i> , 1995), thiamine monophosphate (Zhao <i>et al.</i> , 2002)	Thiamine	Thiamine
Synthetic substrates	Methotrexate, folinic acid	–	–
Probes	[ <sup>3</sup> H]-Folate, [ <sup>3</sup> H]-methotrexate (Assaraf <i>et al.</i> , 1998)	[ <sup>3</sup> H]-Thiamine (Dutta <i>et al.</i> , 1999)	[ <sup>3</sup> H]-Thiamine (Rajgopal <i>et al.</i> , 2001)
Stoichiometry	1 Folate (in) : 1 OH <sup>-</sup> (out)	1 Thiamine (in) : 1 H <sup>+</sup> (out)	1 Thiamine (in) : 1 H <sup>+</sup> (out)

Loss-of-function mutations in ThTr1 underlie thiamine-responsive megaloblastic anemia syndrome (Diaz *et al.*, 1999).

## Further Reading

- Ganapathy V, Smith SB, Prasad PD (2004). SLC19: the folate/thiamine transporter family. *Pflugers Arch* **447**: 641–646.  
 Yuasa H, Inoue K, Hayashi Y (2009). Molecular and functional characteristics of proton-coupled folate transporter. *J Pharm Sci* **98**: 1608–1616.

## References

- Assaraf YG *et al.* (1998). *J Biol Chem* **273**: 8106–8111.  
 Diaz GA *et al.* (1999). *Nat Genet* **22**: 309–312.  
 Dutta B *et al.* (1999). *J Biol Chem* **274**: 31925–31929.  
 Prasad PD *et al.* (1995). *Biochem Biophys Res Commun* **206**: 681–687.  
 Rajgopal A *et al.* (2001). *Biochim Biophys Acta* **1537**: 175–178.  
 Zhao R *et al.* (2002). *Am J Physiol Cell Physiol* **282**: C1512–C1517.

## SLC20 family of sodium-dependent phosphate transporters

**Overview:** the SLC20 family is looked upon not only as ion transporters, but also as retroviral receptors. As ion transporters, they are sometimes referred to as Type III sodium-phosphate co-transporters, alongside Type I (SLC17 family, see Page S247) and Type II (SLC34 family, see Page S265). PiTs are cell-surface transporters, composed of ten TM domains with cytoplasmic C- and N-termini. PiT1 is a focus for dietary phosphate and vitamin D (see Page S188) regulation of parathyroid hormone secretion from the parathyroid gland. PiT2 appears to be involved in intestinal absorption of dietary phosphate.

Systematic name	SLC20A1	SLC20A2
Preferred abbreviation	PiT1	PiT2
Nomenclature	Sodium-dependent phosphate transporter 1	Sodium-dependent phosphate transporter 2
Ensembl ID	ENSG00000144136	ENSG00000168575
Other names	Gibbon ape leukemia virus receptor 1, GLVR-1	Gibbon ape leukemia virus receptor 2, GLVR-2
Substrates	Phosphate, arsenate (Ravera <i>et al.</i> , 2007)	Phosphate (Ravera <i>et al.</i> , 2007)
Stoichiometry	>1 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in)	>1 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in)

### Further Reading

Collins JF, Bai L, Ghishan FK (2004). The SLC20 family of proteins: dual functions as sodium-phosphate cotransporters and viral receptors. *Pflugers Arch* **447**: 647–652.

Virkki LV, Biber J, Murer H, Forster IC (2007). Phosphate transporters: a tale of two solute carrier families. *Am J Physiol Renal Physiol* **293**: F643–F654.

### Reference

Ravera S *et al.* (2007). *Am J Physiol Cell Physiol* **293**: C606–C620.

## SLC22 family of organic cation and anion transporters

**Overview:** the SLC22 family of transporters is mostly composed of non-selective transporters, which are expressed highly in liver, kidney and intestine, playing a major role in drug disposition. The family may be divided into three subfamilies based on the nature of the substrate transported: organic cations (OCTs), organic anions (OATs) and organic zwitterion/cations (OCTN). Membrane topology is predicted to contain 12 TM domains with intracellular termini, and an extended extracellular loop at TM 1/2.

Organic cation transporters (OCT) are electrogenic, Na<sup>+</sup>-independent and reversible.

Systematic name	SLC22A1	SLC22A2	SLC22A3
Preferred abbreviation	OCT1	OCT2	OCT3
Nomenclature	Organic cation transporter 1	Organic cation transporter 2	Organic cation transporter 3
Ensembl ID	ENSG00000175003	ENSG00000112499	ENSG00000146477
Other names	–	–	Extraneuronal monoamine transporter, EMT
Endogenous substrates	Choline, 5HT, PGE <sub>2</sub> , PGF <sub>2α</sub>	Dopamine, histamine (Grundemann <i>et al.</i> , 1999), PGE <sub>2</sub> (Kimura <i>et al.</i> , 2002)	5HT, noradrenaline, dopamine (Zhu <i>et al.</i> , 2010)
Synthetic substrates	TEA, MPP, desipramine, acyclovir, metformin	MPP, TEA, d-tubocurarine, pancuronium (Gorboulev <i>et al.</i> , 1997)	MPP, TEA, quinidine
Stoichiometry	Unknown	Unknown	Unknown

Corticosterone and quinine are able to inhibit all three organic cation transporters.

Organic zwitterion/cation transporters (OCTN) function as organic cation uniporters, organic cation/proton exchangers or sodium/carnitine co-transporters.

Systematic name	SLC22A4	SLC22A5	SLC22A16
Preferred abbreviation	OCTN1	OCTN2	CT2
Nomenclature	Organic cation/carnitine transporter 1	Organic cation/carnitine transporter 2	Carnitine transporter 2
Ensembl ID	ENSG00000197208	ENSG00000197375	ENSG00000004809
Other names	Ergothioneine transporter, ET	High-affinity sodium-dependent carnitine cotransporter, CT1	Organic cation/carnitine transporter 6, OCT6, organic cation transporter OKB1, Fly-like putative transporter 2, Flipt 2
Endogenous substrates	L-Carnitine	L-Carnitine, acetyl-L-carnitine	L-Carnitine
Synthetic substrates	TEA, MPP, mepyramine, verapamil	TEA, MPP, mepyramine, verapamil	–
Stoichiometry	Unknown	Unknown	Unknown

Organic anion transporters (OATs) are non-selective transporters prominent in the kidney and intestine.

Systematic name	SLC22A6	SLC22A7	SLC22A8	SLC22A9	SLC22A10	SLC22A11
Preferred abbreviation	OAT1	OAT2	OAT3	OAT4	OAT5	
Nomenclature	Organic anion transporter 1	Organic anion transporter 2	Organic anion transporter 3	Organic anion transporter 4	Organic anion transporter 5	Organic anion transporter 4
Ensembl ID	ENSG00000197901	ENSG00000137204	ENSG00000149452	ENSG00000149742	ENSG00000184999	ENSG00000168065
Other names	Renal organic anion transporter 1, hROAT1, PAH transporter, hPAHT	Novel liver transporter	–	UST3	–	OAT4
Synthetic substrates	PAH, non-steroidal anti-inflammatory drugs	PAH, PGE <sub>2</sub> , non-steroidal anti-inflammatory drugs	PAH, ochratoxin A, estrone sulphate, cimetidine (Kusuhara <i>et al.</i> , 1999)	–	Ochratoxin A (Youngblood and Sweet, 2004))	Estrone sulphate, dehydroepiandrosterone sulphate, ochratoxin A (Cha <i>et al.</i> , 2000)
Stoichiometry	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown

Urate transporter.

Systematic name	SLC22A12
Preferred abbreviation	URAT1
Nomenclature	Urate anion exchanger 1
Ensembl ID	ENSG00000197891
Other names	Renal-specific transporter, RST, organic anion transporter 4-like protein
Endogenous substrates	Urate, orotate (Enomoto <i>et al.</i> , 2002)
Stoichiometry	Unknown

Orphan or poorly characterized family members.

Systematic name	Preferred abbreviation	Nomenclature	Ensembl ID	Other names
SLC22A13	ORCTL3	Organic cation transporter-like 3	ENSG00000172940	
SLC22A14	ORCTL4	Organic cation transporter-like 4	ENSG00000144671	
SLC22A15	FLIPT1	Fly-like putative transporter 1	ENSG00000163393	
SLC22A17	BOIT	Brain-type organic cation transporter	ENSG00000092096	BOCT
SLC22A18	ORCTL2	Organic cation transporter-like 2	ENSG00000110628	Imprinted multi-membrane spanning polyspecific transporter-related protein 1, efflux transporter-like protein, tumor-suppressing subchromosomal transferable fragment candidate gene 5 protein, tumor-suppressing STF cDNA 5 protein, Beckwith-Wiedemann syndrome chromosomal region 1 candidate gene A protein
SLC22A20			ENSG00000197847	S22AK_HUMAN Isoform 2 of A6NK97
SLC22A23			ENSG00000137266	
SLC22A24			ENSG00000197658	
SLC22A25			ENSG00000196600	Organic anion transporter UST6

**Abbreviations:** MPP, 1-methyl-4-phenylpyridin-1-ium; PAH, p-aminohippurate; TEA, tetraethylammonium

#### Further Reading

- Anderson CM, Thwaites DT (2010). Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* **25**: 364–377.
- Duan P, You G (2010). Short-term regulation of organic anion transporters. *Pharmacol Ther* **125**: 55–61.
- Koepsell H, Endou H (2004). The SLC22 drug transporter family. *Pflugers Arch* **447**: 666–676.
- Koepsell H, Lips K, Volk C (2007). Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. *Pharm Res* **24**: 1227–1251.
- Miyazaki H, Sekine T, Endou H (2004). The multispecific organic anion transporter family: properties and pharmacological significance. *Trends Pharmacol Sci* **25**: 654–662.
- Nigam SK, Bush KT, Bhatnagar V (2007). Drug and toxicant handling by the OAT organic anion transporters in the kidney and other tissues. *Nat Clin Pract Nephrol* **3**: 443–448.
- Saito H (2010). Pathophysiological regulation of renal SLC22A organic ion transporters in acute kidney injury: pharmacological and toxicological implications. *Pharmacol Ther* **125**: 79–91.
- Sekine T, Miyazaki H, Endou H (2006). Molecular physiology of renal organic anion transporters. *Am J Physiol Renal Physiol* **290**: F251–F261.
- Zhou F, You G (2007). Molecular insights into the structure-function relationship of organic anion transporters OATs. *Pharm Res* **24**: 28–36.

#### References

- Cha SH *et al.* (2000). *J Biol Chem* **275**: 4507–4512.
- Enomoto A *et al.* (2002). *Nature* **417**: 447–452.
- Gorboulev V *et al.* (1997). *DNA Cell Biol* **16**: 871–881.
- Grundemann D *et al.* (1999). *Mol Pharmacol* **56**: 1–10.
- Kimura H *et al.* (2002). *J Pharmacol Exp Ther* **301**: 293–298.
- Kusuhara H *et al.* (1999). *J Biol Chem* **274**: 13675–13680.
- Youngblood GL, Sweet DH (2004). *Am J Physiol Renal Physiol* **287**: F236–F244.
- Zhu HJ *et al.* (2010). *J Neurochem* **114**: 142–149.

## SLC23 family of ascorbic acid transporters

**Overview:** predicted to be 12 TM segment proteins, members of this family transport the reduced form of ascorbic acid (while the oxidized form may be handled by members of the SLC2 family (GLUT1/SLC2A1, GLUT3/SLC2A3 and GLUT4/SLC2A4, see Page S226).



Systematic name	SLC23A1	SLC23A2	SLC23A3	SLC23A4
Preferred abbreviation	SVCT1	SVCT2	SVCT3	SNBT1
Nomenclature	Sodium-dependent vitamin C transporter 1	Sodium-dependent vitamin C transporter 2	Sodium-dependent vitamin C transporter 3	Sodium-dependent nucleobase transporter
Other names	Yolk sac permease-like molecule 3	Na <sup>+</sup> /L-ascorbic acid transporter 2, yolk sac permease-like molecule 2, nucleobase transporter-like 1 protein	Yolk sac permease-like molecule 1	–
Ensembl ID	ENSG00000170482	ENSG00000089057	ENSG00000213901	ENSRNOG00000026919
Substrates	L-Ascorbic acid > D-ascorbic acid > dehydroascorbic acid (Tsukaguchi <i>et al.</i> , 1999)	L-Ascorbic acid > D-ascorbic acid > dehydroascorbic acid (Tsukaguchi <i>et al.</i> , 1999)	–	Uracil > thymine > guanine, hypoxanthine > xanthine, uridine (Yamamoto <i>et al.</i> , 2010)
Synthetic substrates	–	–	–	5-Fluorouracil (Yamamoto <i>et al.</i> , 2010)
Inhibitors	Phloretin (Tsukaguchi <i>et al.</i> , 1999)	–	–	–
Probes	[ <sup>14</sup> C]-Ascorbic acid	[ <sup>14</sup> C]-Ascorbic acid	–	–
Stoichiometry	2 Na <sup>+</sup> : 1 ascorbic acid (in) (Tsukaguchi <i>et al.</i> , 1999)	2 Na <sup>+</sup> : 1 ascorbic acid (in) (Tsukaguchi <i>et al.</i> , 1999)	–	1 Na <sup>+</sup> : 1 uracil (in) (Yamamoto <i>et al.</i> , 2010)

SLC23A3 does not transport ascorbic acid and remains an orphan transporter. SLC23A4/SNBT1 is found in rodents and non-human primates, but the sequence is truncated in the human genome.

#### Further Reading

Rivas CI, Zuniga FA, Salas-Burgos A, Mardones L, Ormazabal V, Vera JC (2008). Vitamin C transporters. *J Physiol Biochem* 64: 357–375.  
 Savini I, Rossi A, Pierro C, Avigliano L, Catani MV (2008). SVCT1 and SVCT2: key proteins for vitamin C uptake. *Amino Acids* 34: 347–355.  
 Takanaga H, Mackenzie B, Hediger MA (2004). Sodium-dependent ascorbic acid transporter family SLC23. *Pflugers Arch* 447: 677–682.

#### References

Tsukaguchi H *et al.* (1999). *Nature* 399: 70–75.  
 Yamamoto S *et al.* (2010). *J Biol Chem* 285: 6522–6531.

## SLC24 family of sodium/potassium/calcium exchangers

**Overview:** The sodium/potassium/calcium exchange family of transporters utilize the extracellular sodium gradient to drive calcium and potassium co-transport out of the cell. As is the case for NCX transporters (SLC8A family, see page S239), NKCX transporters are thought to be bidirectional, with the possibility of calcium influx following depolarization of the plasma membrane. Topological modeling suggests the presence of 10 TM domains, with a large intracellular loop between the fifth and sixth TM regions.

Systematic name	SLC24A1	SLC24A2	SLC24A3
Preferred abbreviation	NKCX1	NKCX2	NKCX3
Nomenclature	Sodium/potassium/calcium exchanger 1	Sodium/potassium/calcium exchanger 2	Sodium/potassium/calcium exchanger 3
Ensembl ID	ENSG00000074621	ENSG00000155886	ENSG00000185052
Other names	Retinal rod Na-Ca+K exchanger	Retinal cone Na-Ca+K exchanger	–
Stoichiometry	4 Na <sup>+</sup> :(1Ca <sup>2+</sup> + 1K <sup>+</sup> )	–	–

Systematic name	SLC24A4	SLC24A5	SLC24A6
Preferred abbreviation	NKCX4	NKCX5	NKCX6
Nomenclature	Sodium/potassium/calcium exchanger 4	Sodium/potassium/calcium exchanger 5	Sodium/potassium/calcium exchanger 6
Ensembl ID	ENSG00000140090	ENSG00000188467	ENSG00000089060

NKCX6 exhibits sufficient structural diversity for it's function as a NKCX to be questioned (see Altimimi and Schnetkamp, 2007).

To date, there are no agents selective for this family of transporters.

### Further Reading

Altimimi HF, Schnetkamp PP (2007). Na<sup>+</sup>/Ca<sup>2+</sup>-K<sup>+</sup> exchangers (NCKX): functional properties and physiological roles. *Channels (Austin)* 1: 62–69.  
Schnetkamp PP (2004). The SLC24 Na<sup>+</sup>/Ca<sup>2+</sup>-K<sup>+</sup> exchanger family: vision and beyond. *Pflugers Arch* 447: 683–688.

## SLC25 family of mitochondrial transporters

**Overview:** mitochondrial transporters are nuclear-encoded proteins, which convey solutes across the inner mitochondrial membrane. Topological modelling suggests homodimeric transporters, each with six TM segments and termini in the cytosol.

**Mitochondrial di- and tri-carboxylic acid transporters** are grouped on the basis of commonality of substrates and include the citrate transporter which facilitates citrate export from the mitochondria to allow the generation of oxaloacetate and acetylCoA through the action of ATP:citrate lyase.

Systematic name	SLC25A1	SLC25A10	SLC25A11
Common abbreviation	CIC	DIC	OGC
Nomenclature	Mitochondrial citrate transporter	Mitochondrial dicarboxylate transporter	Mitochondrial oxoglutarate carrier
Ensembl ID	ENSG00000100075	ENSG00000183048	ENSG00000108528
Other names	Citrate transport protein, CTP, tricarboxylate carrier protein, citrate isocitrate carrier		
Substrates	Citrate, malate, PEP	Malate, phosphate, succinate, sulphate, thiosulphate	Oxoglutarate, malate
Inhibitors	1,2,3-Benzenetricarboxylate		–
Stoichiometry	Malate <sup>2-</sup> (in) : H-citrate <sup>2-</sup> (out)	PO <sub>3</sub> <sup>4-</sup> (in) : malate <sup>2-</sup> (out)	Malate <sup>2-</sup> (in) : oxoglutarate <sup>2-</sup> (out)

Systematic name	SLC25A12	SLC25A13	SLC25A18	SLC25A21	SLC25A22
Common abbreviation	AGC1	AGC2	GC2	OXC	GC1
Nomenclature	Aralar	Citrin	Mitochondrial glutamate carrier 2	Mitochondrial oxodicarboxylate carrier	Mitochondrial glutamate carrier 1
Ensembl ID	ENSG00000115840	ENSG00000004864	ENSG00000182902	ENSG00000183032	ENSG00000177542
Substrates	Aspartate, glutamate, cysteinesulphinat	Aspartate, glutamate, cysteinesulphinat	Glutamate	Oxoadipate, oxoglutarate	Glutamate
Stoichiometry	Aspartate : glutamate H <sup>+</sup> (bidirectional)	Aspartate : glutamate H <sup>+</sup> (bidirectional)	Glutamate : H <sup>+</sup> (bidirectional)	Oxoadipate (in) : oxoglutarate (out)	Glutamate : H <sup>+</sup> (bidirectional)

**Mitochondrial ornithine transporters** play a role in the urea cycle by exchanging cytosolic ornithine for mitochondrial citrulline in equimolar amounts.

Systematic name	SLC25A2	SLC25A15
Common abbreviation	ORC2	ORC1
Nomenclature	Mitochondrial ornithine transporter 2	Mitochondrial ornithine transporter 1
Ensembl ID	ENSG00000120329	ENSG00000102743
Substrates	Ornithine, citrulline, lysine, arginine, histidine (Fiermonte <i>et al.</i> , 2003)	L-Ornithine, L-citrulline, L-lysine, L-arginine (Fiermonte <i>et al.</i> , 2003)
Stoichiometry	1 Ornithine (in) :1 citrulline : 1 H <sup>+</sup> (out)	1 Ornithine (in) :1 citrulline : 1 H <sup>+</sup> (out)

Both transporters are inhibited by the polyamine spermine (Fiermonte *et al.*, 2003). Loss-of-function mutations in these genes are associated with hyperornithinemia-hyperammonemia-homocitrullinuria.

**Mitochondrial phosphate transporters** allow the import of inorganic phosphate for ATP production

Systematic name	SLC25A3
Common abbreviation	PHC
Nomenclature	Mitochondrial phosphate carrier
Ensembl ID	ENSG00000075415
Other names	Phosphate transport protein, PTP, PiC
Stoichiometry	PO <sub>3</sub> <sup>4-</sup> (in) : OH <sup>-</sup> (out) or PO <sub>3</sub> <sup>4-</sup> : H <sup>+</sup> (in)

**Mitochondrial adenine nucleotide translocator family**, under conditions of aerobic metabolism, allow coupling between mitochondrial oxidative phosphorylation and cytosolic energy consumption by exchanging cytosolic ADP for mitochondrial ATP.

Systematic name	SLC25A4	SLC25A5	SLC25A6	SLC25A31
Common abbreviation	ANT1	ANT2	ANT3	ANT4
Nomenclature	Mitochondrial adenine nucleotide translocator 1	Mitochondrial adenine nucleotide translocator 2	Mitochondrial adenine nucleotide translocator 3	Mitochondrial adenine nucleotide translocator 4
Ensembl ID	ENSG00000151729	ENSG00000005022	ENSG00000169100	ENSG00000151475
Other names	Adenine nucleotide translocator 1, ADP,ATP carrier protein 1, ADP,ATP carrier protein, heart/skeletal muscle isoform T1	Adenine nucleotide translocator 2, ADP,ATP carrier protein 2, ADP,ATP carrier protein, fibroblast isoform	Adenine nucleotide translocator 2, ADP,ATP carrier protein 3, ADP,ATP carrier protein, isoform T2	Sperm flagellar energy carrier protein
Inhibitors	CATR, BKA	–	–	–
Stoichiometry	ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)	ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)	ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)	ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)

**Mitochondrial uncoupling proteins** allow dissipation of the mitochondrial proton gradient associated with thermogenesis and regulation of radical formation.

Systematic name	SLC25A7	SLC25A8	SLC25A9	SLC25A27	SLC25A14
Common abbreviation	UCP1	UCP2	UCP3	UCP4	UCP5
Nomenclature	Uncoupling protein 1	Uncoupling protein 2	Uncoupling protein 3		
Ensembl ID	ENSG00000109424	ENSG00000175567	ENSG00000175564	ENSG00000153291	ENSG00000102078
Other names	Thermogenin	–	–	–	Brain mitochondrial carrier
Stoichiometry	H <sup>+</sup> (in)	H <sup>+</sup> (in)	H <sup>+</sup> (in)	H <sup>+</sup> (in)	H <sup>+</sup> (in)

**Mitochondrial nucleotide transporters** convey nucleotides and their derivatives

Systematic name	SLC25A16	SLC25A17	SLC25A19	SLC25A26	SLC25A42
Common abbreviation	GDC	PMP34	DNC1	SAMC	
Nomenclature	Graves disease carrier	Peroxisomal membrane protein	Deoxynucleotide carrier 1	S-Adenosylmethionine carrier	
Ensembl ID	ENSG00000122912	ENSG00000100372	ENSG00000125454	ENSG00000144741	ENSG00000181035
Other names	Graves disease autoantigen	–	Mitochondrial thiamine pyrophosphate carrier	–	–
Substrates	CoA and congeners	ATP, ADP, AMP	dNDPs, dNTPs, NDPs, ddNTPs	S-Adenosylmethionine	ADP, Co A (Fiermonte <i>et al.</i> , 2009)
Stoichiometry	CoA (in)	ATP (in)	dNDP (in) : ATP (out)		

**Miscellaneous:** many of the transporters identified below have yet to be assigned functions and are currently regarded as orphans.

Systematic name	Common abbreviation	Nomenclature	Ensembl ID	Comments
SLC25A20	CAC	Carnitine/acylcarnitine carrier	ENSG00000178537	Exchanges cytosolic acylcarnitine for mitochondrial carnitine
SLC25A24	APC1	Mitochondrial phosphate carrier 1	ENSG00000085491	
SLC25A23	APC2	mitochondrial phosphate carrier 2	ENSG00000125648	
SLC25A25	APC3	mitochondrial phosphate carrier 3	ENSG00000148339	
SLC25A28		Mitoferrin2	ENSG00000155287	
SLC25A29	ORNT3		ENSG00000197119	
SLC25A30			ENSG00000174032	
SLC25A32	MFTC		ENSG00000164933	
SLC25A33			ENSG00000171612	
SLC25A34			ENSG00000162461	
SLC25A35			ENSG00000125434	
SLC25A36			ENSG00000114120	
SLC25A37		Mitoferrin1	ENSG00000147454	
SLC25A38			ENSG00000144659	
SLC25A39			ENSG00000013306	
SLC25A40			ENSG00000181240	
SLC25A41			ENSG00000181240	
SLC25A43			ENSG00000077713	
SLC25A44			ENSG00000160785	
SLC25A45			ENSG00000162241	
SLC25A46			ENSG00000164209	

Further relevant information on tabular data. For example, whether agent selectivity is less than 100-fold, whether evidence exists for further subtypes lacking molecular correlates or overlap with other transporter families; relationship with a common genetic disorder.

**Abbreviations:** BKA, bongkreic acid; CATR, carboxyatractyloside; PEP, phosphoenolpyruvate

#### Further Reading

- Cioffi F, Senese R, de Lange P, Goglia F, Lanni A, Lombardi A (2009). Uncoupling proteins: a complex journey to function discovery. *Biofactors* 35: 417–428.
- Gnoni GV, Priore P, Geelen MJ, Siculella L (2009). The mitochondrial citrate carrier: metabolic role and regulation of its activity and expression. *IUBMB Life* 61: 987–994.
- Halestrap AP (2009). What is the mitochondrial permeability transition pore? *J Mol Cell Cardiol* 46: 821–831.
- Jezeq P, Jaburek M, Garlid KD (2010). Channel character of uncoupling protein-mediated transport. *FEBS Lett* 584: 2135–2141.
- Leung AW, Halestrap AP (2008). Recent progress in elucidating the molecular mechanism of the mitochondrial permeability transition pore. *Biochim Biophys Acta* 1777: 946–952.
- Palmieri F (2004). The mitochondrial transporter family (SLC25): physiological and pathological implications. *Pflugers Arch* 447: 689–709.

## References

- Fiermonte G *et al.* (2003). *J Biol Chem* **278**: 32778–32783.  
 Fiermonte G *et al.* (2009). *J Biol Chem* **284**: 18152–18159.

## SLC26 family of anion exchangers

**Overview:** along with the SLC4 family, the SLC26 family acts to allow movement of monovalent and divalent anions across cell membranes. The predicted topology is of 8–14 TM domains with intracellular C- and N-termini, probably existing as dimers. Within the family, subgroups may be identified on the basis of functional differences.

### Selective sulphate transporters

Systematic name	SLC26A1	SLC26A2
Common nomenclature	Sat-1	DTDST
Ensembl ID	ENSG00000145217	ENSG00000155850
Other names	–	–
Substrates	SO <sub>4</sub> <sup>2-</sup> , oxalate <sup>2-</sup>	SO <sub>4</sub> <sup>2-</sup>
Stoichiometry	SO <sub>4</sub> <sup>2-</sup> (in) : anion (out)	1 SO <sub>4</sub> <sup>2-</sup> (in) : 2 Cl <sup>-</sup> (out)

### Chloride/bicarbonate exchangers

Systematic name	SLC26A3	SLC26A4	SLC26A6
Common nomenclature	DRA	Pendrin	PAT-1
Ensembl ID	ENSG00000091138	ENSG00000091137	ENSG00000225697
Other names	CLD	–	CFEX
Substrates	Cl <sup>-</sup>	Cl <sup>-</sup> , I <sup>-</sup> , OH <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> , HCOO <sup>-</sup>	SO <sub>4</sub> <sup>2-</sup> , oxalate <sup>2-</sup> , Cl <sup>-</sup> , I <sup>-</sup> , OH <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> , HCOO <sup>-</sup>
Stoichiometry	2 Cl <sup>-</sup> (in) : 1 HCO <sub>3</sub> <sup>-</sup> (out) or 2 Cl <sup>-</sup> (in) : 1 OH <sup>-</sup> (out)	Unknown	1 SO <sub>4</sub> <sup>2-</sup> (in) : 2 HCO <sub>3</sub> <sup>-</sup> (out) or 1 Cl <sup>-</sup> (in) : 2 HCO <sub>3</sub> <sup>-</sup> (out)

### Anion channels

Systematic name	SLC26A7	SLC26A9
Ensembl ID	ENSG00000147606	ENSG00000174502
Ion selectivity	NO <sub>3</sub> <sup>-</sup> >> Cl <sup>-</sup> = Br <sup>-</sup> = I <sup>-</sup> > SO <sub>4</sub> <sup>2-</sup> = Glu <sup>-</sup>	I <sup>-</sup> > Br <sup>-</sup> > NO <sub>3</sub> <sup>-</sup> > Cl <sup>-</sup> > Glu <sup>-</sup>
Functional characteristics	Voltage- and time-independent current, linear I-V relationship (Kim <i>et al.</i> , 2005)	Voltage- and time-independent current, linear I-V relationship (Dorwart <i>et al.</i> , 2007)

SLC26A9 has been suggested to operate in two additional modes as a Cl<sup>-</sup>-HCO<sub>3</sub><sup>-</sup> exchanger and as a Na<sup>+</sup>-anion cotransporter (Chang *et al.*, 2009).

### Other

Systematic name	SLC26A5	SLC26A8	SLC26A10	SLC26A11
Common nomenclature	Prestin	Tat1	–	–
Ensembl ID	ENSG00000170615	ENSG00000112053	ENSG00000135502	ENSG00000181045
Substrates	Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	SO <sub>4</sub> <sup>2-</sup> , oxalate <sup>2-</sup> , Cl <sup>-</sup>	–	HSO <sub>4</sub> <sup>-</sup>
Stoichiometry	Unknown	Unknown	Unknown	Unknown

SLC26A5 has been suggested to function as a molecular motor, rather than a transporter, while SLC26A10 is a possible pseudogene.

### Further Reading

- Dorwart MR, Shcheynikov N, Yang D, Muallem S (2008). The solute carrier 26 family of proteins in epithelial ion transport. *Physiology (Bethesda)* **23**: 104–114.

Kato A, Romero MF (2011). Regulation of electroneutral NaCl absorption by the small intestine. *Annu Rev Physiol* 73: 261–281.  
 Mount DB, Romero MF (2004). The SLC26 gene family of multifunctional anion exchangers. *Pflugers Arch* 447: 710–721.  
 Ohana E, Yang D, Shcheynikov N, Muallem S (2009). Diverse transport modes by the solute carrier 26 family of anion transporters. *J Physiol* 587: 2179–2185.

## References

Chang MH *et al.* (2009). *J Membr Biol* 228: 125–140.  
 Dorwart MR *et al.* (2007). *J Physiol* 584: 333–345.  
 Kim KH *et al.* (2005). *J Biol Chem* 280: 6463–6470.

# SLC27 family of fatty acid transporters

**Overview:** Fatty acid transporters are a family of at least one, and possibly six (Schaffer and Lodish, 1994), -TM segment proteins, predicted on the basis of structural similarities to form dimers. These transporters are unusual in that they appear to express intrinsic very long-chain acyl-CoA synthetase (EC 6.2.1.-, EC 6.2.1.7) enzyme activity as well as an intracellular AMP-binding domain. Within the cell, these transporters may associate with plasma and peroxisomal membranes.

Nomenclature	Fatty acid transport protein 1	Fatty acid transport protein 2	Fatty acid transport protein 3
Systematic name	SLC27A1	SLC27A2	SLC27A3
Preferred abbreviation	FATP1	FATP2	FATP3
Ensembl ID	ENSG00000130304	ENSG00000140284	ENSG00000143554
Other names	Long-chain fatty acid transport protein 1	Very-long-chain acyl-CoA synthetase, very-long-chain-fatty-acid-CoA ligase, THCA-CoA ligase, fatty-acid-coenzyme A ligase, very long-chain 1	Long-chain fatty acid transport protein 3, very long-chain acyl-CoA synthetase homolog 3, VLCS-3
Endogenous substrates	C20:4 > C16 > C18:1 > C4 (Schaffer and Lodish, 1994); C16:0 > C18:1 > C18:3 > C8 (Gimeno <i>et al.</i> , 2003)	–	–

Nomenclature	Fatty acid transport protein 4	Fatty acid transport protein 5	Fatty acid transport protein 6
Systematic name	SLC27A4	SLC27A5	SLC27A6
Preferred abbreviation	FATP4	FATP5	FATP6
Ensembl ID	ENSG00000167114	ENSG00000083807	ENSG00000113396
Other names	ACSVL4	Bile acyl-CoA synthetase, BACS, bile acid CoA ligase, BAL, cholate-CoA ligase, very long-chain acyl-CoA synthetase homolog 2, VLCSH2	Long-chain fatty acid transport protein 6, very long-chain acyl-CoA synthetase homolog 1, VLCSH1
Endogenous substrates	C16:0 > C18:1 > C4, C18:3 > C20:4 (Stahl <i>et al.</i> , 1999); C16:0, C18:1 > C18:3 > C8 (Gimeno <i>et al.</i> , 2003)		C16:0 > C18:1 > C18:3 > C8 (Gimeno <i>et al.</i> , 2003)

Although the stoichiometry of fatty acid transport is unclear, it has been proposed to be facilitated by the coupling of fatty acid transport to conjugation with CoA to form fatty acyl CoA esters. Small molecule inhibitors of FATP2 (Sandoval *et al.*, 2010) and FATP4 (Blackburn *et al.*, 2006) have been described; analysis of the mechanism of action of some of these inhibitors suggests that transport may be selectively inhibited without altering enzymatic activity of the FATP.

C1-BODIPY-C12 accumulation has been used as a non-selective index of fatty acid transporter activity.

**Abbreviations:** C12:, C16:0, palmitic acid; C18:0, stearic acid; C18:1, oleic acid; C18:2, linoleic acid; C18:3,n-6,  $\gamma$ -linolenic acid; C2, acetic acid; C20:4, arachidonic acid; C20:5,n-3, 5z,8z,11z,14z,17z-eicosapentaenoic acid, EPA; C22:6,n-3, 4z,7z,10z,13z,16z,19z-docosahexaenoic acid, DHA; C3, propionic acid; C4, butyric acid; C5, valeric acid; C8, octanoic acid

### Further Reading

- Gimeno RE (2007). Fatty acid transport proteins. *Curr Opin Lipidol* **18**: 271–276.  
 Stahl A (2004). A current review of fatty acid transport proteins (SLC27). *Pflugers Arch* **447**: 722–727.  
 Watkins PA (2008). Very-long-chain acyl-CoA synthetases. *J Biol Chem* **283**: 1773–1777.

### References

- Blackburn C *et al.* (2006). *Bioorg Med Chem Lett* **16**: 3504–3509.  
 Gimeno RE *et al.* (2003). *J Biol Chem* **278**: 16039–16044.  
 Sandoval A *et al.* (2010). *Biochem Pharmacol* **79**: 990–999.  
 Schaffer JE, Lodish HF (1994). *Cell* **79**: 427–436.  
 Stahl A *et al.* (1999). *Mol Cell* **4**: 299–308.

## SLC28 and SLC29 families of nucleoside transporters

**Overview:** Nucleoside transporters are divided into two families, the sodium-dependent, solute carrier family 28 (SLC28) and the equilibrative, solute carrier family 29 (SLC29), where the endogenous substrates are nucleosides.

**SLC28 family** members have 13 TM segments with cytoplasmic N-termini and extracellular C-termini.

Systematic name	SLC28A1	SLC28A2	SLC28A3
Common abbreviation	CNT1	CNT2	CNT3
Ensembl ID	ENSG00000156222	ENSG00000137860	ENSG00000099118
Other names	N2/ <i>cit</i> , concentrative nucleoside transporter 1	N1/ <i>cif</i> , SPNT, concentrative nucleoside transporter 2	N3/ <i>cib</i> , concentrative nucleoside transporter 3
Endogenous substrates	Uridine, cytidine, thymidine, adenosine	Adenosine, guanosine, inosine, thymidine	Uridine, cytidine, thymidine, adenosine, guanosine, inosine
Synthetic substrates	AZT, zalcitabine, gemcitabine	Formycin B, cladribine, fludarabine, vidarabine, didanosine	AZT, zalcitabine, didanosine, formycin B, 5-fluorouridine, 5-fluoro-2'-deoxyuridine, zebularine, gemcitabine, cladribine, fludarabine
Predicted stoichiometry	1 Na <sup>+</sup> : 1 nucleoside (in)	1 Na <sup>+</sup> : 1 nucleoside (in)	2 Na <sup>+</sup> : 1 nucleoside (in)

A further two Na<sup>+</sup>-dependent (stoichiometry 1 Na<sup>+</sup> : 1 nucleoside (in)) nucleoside transporters have been defined on the basis of substrate and inhibitor selectivity: CNT4 (N4/*cit*, which transports uridine, thymidine and guanosine) and CNT5 (N5/*csq*, which transports guanosine and adenosine, and may be inhibited by NBTI).

**SLC29 family** members appear to be composed of 11 TM segments with cytoplasmic N-termini and extracellular C-termini. ENT1 and ENT2 are cell-surface transporters, while ENT3 is intracellular, possibly lysosomal (Baldwin *et al.*, 2005). ENT1-3 are described as broad-spectrum nucleoside transporters. Ahas been reported to be intracellular purine nucleoside transporters

Systematic name	SLC29A1	SLC29A2	SLC29A3	SLC29A4
Common abbreviation	ENT1	ENT2	ENT3	PMAT
Nomenclature	Equilibrative nucleoside transporter 1	Equilibrative nucleoside transporter 2	Equilibrative nucleoside transporter 3	Plasma membrane monoamine transporter
Ensembl ID	ENSG00000112759	ENSG00000174669	ENSG00000156604	ENSG00000164638
Other names	<i>es</i> , NBTI-sensitive	<i>ei</i> , NBTI-insensitive	-	Equilibrative nucleoside transporter 4
Endogenous substrates	Adenosine, guanosine, inosine, uridine, thymidine, cytidine, hypoxanthine, adenine, thymine (Yao <i>et al.</i> , 2011)	Adenosine, guanosine, inosine, uridine, thymidine, hypoxanthine	Adenosine, inosine, > guanosine, thymidine, uridine, adenine (Baldwin <i>et al.</i> , 2005)	5HT, dopamine > tyramine, histamine (Engel and Wang, 2005)
Synthetic substrates	2-Chloroadenosine, dideoxyinosine, formycin B, tubercidin, vidarabine, cytarabine, cladribine, pentostatin, zalcitabine, didanosine, floxidine, gemcitabine	2-Chloroadenosine, formycin B, tubercidin, cytarabine, cladribine, vidarabine, AZT, gemcitabine	Tubercidin, cordycepin, cladribine, fludarabine, 5-fluoro-2'-deoxyuridine, zebularine, dideoxyinosine, AZT, dideoxycytidine (Baldwin <i>et al.</i> , 2005)	MPP <sup>+</sup> > TEA (Engel and Wang, 2005)
Selective inhibitors	NBTI (9.7), draflazine (9.5), KF24345 (9.4, Hammond and Archer, 2004), NBTGR (9.3), dilazep (9), dipyridamole (8.5)	-	-	Cimetidine, quinidine, quinine, verapamil, rhodamine123 (Engel and Wang, 2005)
Probes	[ <sup>3</sup> H]-NBTI (0.5 nM), [ <sup>14</sup> C]-adenosine	[ <sup>14</sup> C]-Adenosine	[ <sup>14</sup> C]-Adenosine	-
Predicted stoichiometry	Equilibrative	Equilibrative	Equilibrative	Equilibrative

PMAT also transports adenosine at acidic pH (Barnes *et al.*, 2006; Zhou *et al.*, 2007).

The affinities of draflazine, dilazep, KF24345 and dipyridamole at ENT1 transporters are species dependent, exhibiting lower affinity at rat transporters than at human transporters (Sundaram *et al.*, 1998; Hammond and Archer, 2004).

**Abbreviations:** 5HT, 5-hydroxytryptamine; AZT, 3'-azido-3'-deoxythymidine; MPP<sup>+</sup>, 1-methyl-4-phenylpyridin-1-ium; NBTI, nitrobenzylthioinosine (also known as NBMPR); NBTGR, nitrobenzylthioguanosine; KF24345, 3-(1-[6,7-diethoxy-2-morpholinoquinazolin-4-yl]piperidin-4-yl)-1,6-dimethyl-2,4(1*H*,3*H*)-quinazolinone hydrochloride

### Further Reading

- Baldwin SA, Beal PR, Yao SY, King AE, Cass CE, Young JD (2004). The equilibrative nucleoside transporter family, SLC29. *Pflugers Arch* **447**: 735–743.
- Baldwin SA, McConkey GA, Cass CE, Young JD (2007). Nucleoside transport as a potential target for chemotherapy in malaria. *Curr Pharm Des* **13**: 569–580.
- Daws LC (2009). Unfaithful neurotransmitter transporters: focus on serotonin uptake and implications for antidepressant efficacy. *Pharmacol Ther* **121**: 89–99.
- Errasti-Murugarren E, Pastor-Anglada M (2010). Drug transporter pharmacogenetics in nucleoside-based therapies. *Pharmacogenomics* **11**: 809–841.
- Gray JH, Owen RP, Giacomini KM (2004). The concentrative nucleoside transporter family, SLC28. *Pflugers Arch* **447**: 728–734.
- King AE, Ackley MA, Cass CE, Young JD, Baldwin SA (2006). Nucleoside transporters: from scavengers to novel therapeutic targets. *Trends Pharmacol Sci* **27**: 416–425.
- Pastor-Anglada M, Cano-Soldado P, Errasti-Murugarren E, Casado FJ (2008). SLC28 genes and concentrative nucleoside transporter (CNT) proteins. *Xenobiotica* **38**: 972–994.

### References

- Baldwin SA *et al.* (2005). *J Biol Chem* **280**: 15880–15887.
- Barnes K *et al.* (2006). *Circ Res* **99**: 510–519.
- Engel K, Wang J (2005). *Mol Pharmacol* **68**: 1397–1407.
- Hammond JR, Archer RGE (2004). *J Pharmacol Exp Ther* **308**: 1083–1093.
- Sundaram M *et al.* (1998). *J Biol Chem* **273**: 21519–21525.
- Yao SY *et al.* (2011). *J Biol Chem* **286**: 32552–32562.
- Zhou M *et al.* (2007). *J Biol Chem* **282**: 3188–3195.



# SLC30 zinc transporter family

**Overview:** Along with the SLC39 family (see Page S270), SLC30 transporters regulate the movement of zinc ions around the cell. In particular, these transporters remove zinc ions from the cytosol, allowing accumulation into intracellular compartments or efflux through the plasma membrane. ZNT1 is thought to be placed on the plasma membrane extruding zinc, while ZNT3 is associated with synaptic vesicles and ZNT4 and ZNT5 are linked with secretory granules. Membrane topology predictions suggest a multimeric assembly with subunits having six TM domains, with both termini being cytoplasmic. Dityrosine covalent linking has been suggested as a mechanism for dimerisation, particularly for ZNT3 (Salazar *et al.*, 2009). The mechanism for zinc transport is unknown.

Systematic name	Common abbreviation	Nomenclature	Ensembl ID	Other names
SLC30A1	ZNT1	Zinc transporter 1	ENSG00000170385	
SLC30A2	ZNT2	Zinc transporter 2	ENSG00000158014	
SLC30A3	ZNT3	Zinc transporter 3	ENSG00000115194	
SLC30A4	ZNT4	Zinc transporter 4	ENSG00000104154	
SLC30A5	ZNT5	Zinc transporter 5	ENSG00000145740	
SLC30A6	ZNT6	Zinc transporter 6	ENSG00000152683	
SLC30A7	ZNT7	Zinc transporter 7	ENSG00000162695	
SLC30A8	ZNT8	Zinc transporter 8	ENSG00000164756	
SLC30A9	ZNT9	Zinc transporter 9	ENSG00000014824	Human embryonic lung protein, HUEL
SLC30A10	ZNT10	Zinc transporter 10	ENSG00000196660	

SLC30A8 is described as a type 2 diabetes susceptibility gene.

Zinc fluxes may be monitored through the use of radioisotopic Zn-65 or the fluorescent dye FluoZin 3.

## Further Reading

Palmiter RD, Huang L (2004). Efflux and compartmentalization of zinc by members of the SLC30 family of solute carriers. *Pflügers Arch* **447**: 744–751.

Rungby J (2010). Zinc, zinc transporters and diabetes. *Diabetologia* **53**: 1549–1551.

## Reference

Salazar G *et al.* (2009). *PLoS One* **4**: e5896.

# SLC31 family of copper transporters

**Overview:** SLC31 family members, alongside the Cu-ATPases (see Page S219) are involved in the regulation of cellular copper levels. The CTR1 transporter is a cell-surface transporter to allow monovalent copper accumulation into cells, while CTR2 appears to be a vacuolar/vesicular transporter (Rees *et al.*, 2004). Functional copper transporters appear to be trimeric with each subunit having three TM regions and an extracellular N-terminus. CTR1 is considered to be a higher affinity copper transporter compared to CTR2. The stoichiometry of copper accumulation is unclear, but appears to be energy-independent (Lee *et al.*, 2002).

Systematic name	SLC31A1	SLC31A2
Preferred abbreviation	CTR1	CTR2
Nomenclature	Copper transporter 1	Copper transporter 2
Ensembl ID	ENSG00000136868	ENSG00000136867
Other names	COPT1	COPT2

Copper accumulation through CTR1 is sensitive to silver ions, but not divalent cations (Lee *et al.*, 2002). The CTR1 and CTR2 transporters regulate the cellular levels of the anticancer drug cisplatin (Ishida *et al.*, 2002, Blair *et al.*, 2009).

## Further Reading

De Feo CJ, Aller SG, Unger VM (2007). A structural perspective on copper uptake in eukaryotes. *Biometals* **20**: 705–716.

Howell SB, Safaei R, Larson CA, Sailor MJ (2010). Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. *Mol Pharmacol* **77**: 887–894.

Maryon EB, Molloy SA, Zimnicka AM, Kaplan JH (2007). Copper entry into human cells: progress and unanswered questions. *Biometals* **20**: 355–364.

Nose Y, Rees EM, Thiele DJ (2006). Structure of the Ctr1 copper trans'PORE'ter reveals novel architecture. *Trends Biochem Sci* **31**: 604–607.

Petris MJ (2004). The SLC31 (Ctr) copper transporter family. *Pflugers Arch* **447**: 752–755.

## References

Blair BG *et al.* (2009). *Clin Cancer Res* **15**: 4312–4321.

Ishida S *et al.* (2002). *Proc Natl Acad Sci U S A* **99**: 14298–14302.

Lee J *et al.* (2002). *J Biol Chem* **277**: 4380–4387.

Rees EM *et al.* (2004). *J Biol Chem* **279**: 54221–54229.

# SLC32 vesicular inhibitory amino acid transporter

**Overview:** The vesicular inhibitory amino acid transporter, VIAAT (also termed the vesicular GABA transporter VGAT), which is the sole representative of the SLC32 family, transports GABA, or glycine, into synaptic vesicles (Gasnier, 2000, 2004). VIAAT was originally suggested to be composed of 10 TM segments with cytoplasmic N- and C-termini (McIntire *et al.*, 1997; Sagne *et al.*, 1997). However, an alternative 9TM structure with the N terminus facing the cytoplasm and the C terminus residing in the synaptic vesicle lumen has subsequently been reported (Martens *et al.*, 2008). VIAAT acts as an antiporter for inhibitory amino acids and protons. The accumulation of GABA and glycine within vesicles is driven by both the chemical ( $\Delta\text{pH}$ ) and electrical ( $\Delta\psi$ ) components of the proton electrochemical gradient ( $\Delta\mu_{\text{H}^+}$ ) established by a vacuolar  $\text{H}^+$ -ATPase (McIntire *et al.*, 1997). However, Juge *et al.* (2009) have presented evidence that VIAAT is instead a  $\text{Cl}^-/\text{GABA}$  co-transporter. VIAAT co-exists with VGLUT1 (SLC17A7), or VGLUT2 (SLC17A6), in the synaptic vesicles of selected nerve terminals (Fattorini *et al.*, 2009; Zander *et al.*, 2010). VIAAT knock out mice die between embryonic day 18.5 and birth (Wojcik *et al.*, 2006). In cultures of spinal cord neurones established from earlier embryos, the co-release of GABA and glycine from synaptic vesicles is drastically reduced, providing direct evidence for the role of VIAAT in the sequestration of both transmitters (Wojcik *et al.*, 2006; Saito *et al.*, 2010).

Common abbreviation	VIAAT
Systematic name	SLC32A1
Nomenclature	Vesicular inhibitory amino acid transporter
Other names	VGAT (vesicular GABA transporter)
Ensembl ID	ENSG00000101438
Endogenous substrates ( $K_m$ )	GABA (5 mM; McIntire <i>et al.</i> , 1997), glycine, $\beta$ -alanine, $\gamma$ -hydroxybutyrate
Synthetic substrates	–
Inhibitors ( $\text{IC}_{50}$ )	Vigabatrin (7.5 mM; McIntire <i>et al.</i> , 1997)
Probes	–
Stoichiometry	1 amino acid (in): 1 $\text{H}^+$ (out) (Gasnier, 2004) or 1 amino acid: 2 $\text{Cl}^-$ (in) (Juge <i>et al.</i> , 2009)

## Further Reading

Erickson JD, De Gois S, Varoqui H, Schafer MK, Weihe E (2006). Activity-dependent regulation of vesicular glutamate and GABA transporters: a means to scale quantal size. *Neurochem Int* **48**: 643–649.

Gasnier B (2000). The loading of neurotransmitters into synaptic vesicles. *Biochimie* **82**: 327–337.

Gasnier B (2004). The SLC32 transporter, a key protein for the synaptic release of inhibitory amino acids. *Pflugers Arch* **447**: 756–759.

## References

Fattorini G *et al.* (2009). *J Neurochem* **110**: 1538–1546.

Juge N *et al.* (2009). *J Biol Chem* **284**: 35073–35078.

Martens HJ *et al.* (2008). *J Neurosci* **28**: 13125–13131.

McIntire SL *et al.* (1997). *Nature* **389**: 870–876.

Sagne C *et al.* (1997). *FEBS Lett* **417**: 177–183.

Saito K *et al.* (2010). *Mol Brain* **3**: 40.

Wojcik SM *et al.* (2006). *Neuron* **50**: 575–587.

Zander JF *et al.* (2010). *J Neurosci* **30**: 7634–7645.

# SLC33 acetylCoA transporter

**Overview:** acetylation of proteins is a post-translational modification mediated by specific acetyltransferases, using the donor acetylCoA. SLC33A1/AT1 is a putative 11 TM transporter present on the endoplasmic reticulum, expressed in all tissues, but particularly abundant in the pancreas (Kanamori *et al.*, 1997), which imports cytosolic acetylCoA into these intracellular organelles.

Systematic name	SLC33A1
Preferred abbreviation	AT1
Nomenclature	AcetylCoA transporter
Ensembl ID	ENSG00000169359
Other names	ACATN
Endogenous substrates	AcetylCoA
Probes	[ <sup>14</sup> C]-AcetylCoA
Stoichiometry	Unknown

In heterologous expression studies, acetylCoA transport through AT1 was inhibited by CoA, but not acetate, ATP or UDP-galactose (Jonas *et al.*, 2010). A loss-of-function mutation in SLC33A1 has been associated with spastic paraplegia (SPG42, Lin *et al.*, 2008), although this observation could not be replicated in a subsequent study (Schlipf *et al.*, 2010).

**Abbreviations:** CoA, coenzyme A, [[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydroxy-3-phosphonooxyoxolan-2-yl]methoxyhydroxyphosphoryl] [(3R)-3-hydroxy-2,2-dimethyl-4-oxo-4-[[3-oxo-3-(2-sulfanylethylamino)propyl]amino]butyl]hydrogen phosphate.

### Further Reading

Hirabayashi Y, Kanamori A, Nomura KH, Nomura K (2004). The acetyl-CoA transporter family SLC33. *Pflugers Arch* **447**: 760–762.

### References

- Jonas MC *et al.* (2010). *J Cell Sci* **123**: 3378–3388.  
 Kanamori A *et al.* (1997). *Proc Natl Acad Sci U S A* **94**: 2897–2902.  
 Lin P *et al.* (2008). *Am J Hum Genet* **83**: 752–759.  
 Schlipf NA *et al.* (2010). *Eur J Hum Genet* **18**: 1065–1067.

## SLC34 family of sodium phosphate co-transporters

**Overview:** The SLC34 family are sometimes referred to as Type II sodium-phosphate co-transporters, alongside Type I (SLC17 family, see Page S247) and Type III (SLC20 family, see Page S251) transporters. Topological modelling suggests eight TM domains with C- and N- termini in the cytoplasm, and a re-entrant loop at TM5/6. SLC34 family members are expressed on the apical surfaces of epithelia in the intestine and kidneys to regulate body phosphate levels, principally NaPi-IIa and NaPi-IIb, respectively. NaPi-IIa and NaPi-IIb are electrogenic, while NaPi-IIc is electrogenic (Andrini *et al.*, 2008).

Systematic name	SLC34A1	SLC34A2	SLC34A3
Common abbreviation	NaPi-IIa	NaPi-IIb	NaPi-IIc
Nomenclature	Sodium phosphate 1	Sodium phosphate 2	Sodium phosphate 3
Ensembl ID	ENSG00000131183	ENSG00000157765	ENSG00000198569
Other names	NAPI-3, NPT2, NPTIIa, SLC11, SLC17A2	NAPI-3B	NPTIIc
Stoichiometry	3 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) (Forster <i>et al.</i> , 1999)	3 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) (Andrini <i>et al.</i> , 2008)	2 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) (Andrini <i>et al.</i> , 2008)

These transporters can be inhibited by PFA, in contrast to type III sodium-phosphate cotransporters, the SLC20 family (see Page S251).

**Abbreviations:** PFA, phosphonoformic acid

### Further Reading

Murer H, Forster I, Biber J (2004). The sodium phosphate cotransporter family SLC34. *Pflugers Arch* **447**: 763–767.

### References

- Andrini O *et al.* (2008). *Channels (Austin)* **2**: 346–357.  
 Forster IC *et al.* (1999). *Am J Physiol* **276**: F644–F649.

# SLC35 family of nucleotide sugar transporters

**Overview:** glycoprotein formation in the Golgi and endoplasmic reticulum relies on the accumulation of nucleotide-conjugated sugars via the SLC35 family of transporters. These transporters have a predicted topology of 10 TM domains, with cytoplasmic termini, and function as exchangers, swapping nucleoside monophosphates for the corresponding nucleoside diphosphate conjugated sugar. Five subfamilies of transporters have been identified on the basis of sequence similarity.

Systematic name	SLC35A1	SLC35A2	SLC35A3	SLC35A4	SLC35A5
Nomenclature	CMP-sialic acid transporter	UDP-galactose transporter	UDP-N-acetylglucosamine transporter	–	–
Ensembl ID	ENSG00000164414	ENSG00000102100	ENSG00000117620	ENSG00000176087	ENSG00000138459
Other names	CMPST, hCST	UGALT, UGAT, UGT, UGT1, UGT2, UGTL	–	–	–
Substrates	CMP-sialic acid (Ishida <i>et al.</i> , 1998)	UDP-galactose, UDP-N-acetylglucosamine (Ishida <i>et al.</i> , 1996; Miura <i>et al.</i> , 1996)	UDP-N-acetylglucosamine (Ishida <i>et al.</i> , 1999)	–	–

Systematic name	SLC35B1	SLC35B2	SLC35B3	SLC35B4
Nomenclature	–	PAPS transporter 1	PAPS transporter 2	–
Ensembl ID	ENSG00000121073	ENSG00000157593	ENSG00000124786	ENSG00000205060
Other names	HUT-1	PAPST1, SLL, UGTrel4	PAPST2, C6orf196, CGI-19, dj453H5.1	YEA4
Substrates	–	PAPS (Kamiyama <i>et al.</i> , 2003)	PAPS (Kamiyama <i>et al.</i> , 2006)	UDP-xylose, UDP-N-acetylglucosamine (Ashikov <i>et al.</i> , 2005)

Systematic name	SLC35C1	SLC35C2
Nomenclature	GDP-Fucose transporter	–
Ensembl ID	ENSG00000181830	ENSG00000080189
Other names	FUCT1	–
Substrates	GDP-fucose (Luhn <i>et al.</i> , 2001)	–

Systematic name	SLC35D1	SLC35D2	SLC35D3
Nomenclature	UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter	–	–
Ensembl ID	ENSG00000116704	ENSG00000130958	ENSG00000182747
Other names	UDP-galactose transporter-related 7	SQV7-like protein, UDP-galactose transporter-related 8	FRCL1
Substrates	UDP-glucuronic acid, UDP-N-acetylgalactosamine (Muraoka <i>et al.</i> , 2001)	UDP-N-acetylgalactosamine (Ishida <i>et al.</i> , 2005)	–

## Orphan transporters

Systematic name	SLC35E1	SLC35E2	SLC35E3	SLC35E4
Ensembl ID	ENSG00000127526	ENSG00000175782	ENSG00000215790	ENSG00000100036

Systematic name	SLC35F1	SLC35F2	SLC35F3	SLC35F4	SLC35F5
Ensembl ID	ENSG00000196376	ENSG00000110660	ENSG00000183780	ENSG00000151812	ENSG00000115084

**Abbreviations:** PAPS, [(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydroxy-2-[[oxido(sulfonatooxy)phosphoryl]oxymethyl]oxolan-3-yl] phosphate

### Further Reading

Ishida N, Kawakita M (2004). Molecular physiology and pathology of the nucleotide sugar transporter family (SLC35). *Pflugers Arch* **447**: 768–775.

### References

- Ashikov A *et al.* (2005). *J Biol Chem* **280**: 27230–27235.  
 Ishida N *et al.* (1996). *J Biochem* **120**: 1074–1078.  
 Ishida N *et al.* (1998). *J Biochem* **124**: 171–178.  
 Ishida N *et al.* (1999). *J Biochem* **126**: 68–77.  
 Ishida N *et al.* (2005). *Genomics* **85**: 106–116.  
 Kamiyama S *et al.* (2003). *J Biol Chem* **278**: 25958–25963.  
 Kamiyama S *et al.* (2006). *J Biol Chem* **281**: 10945–10953.  
 Luhn K *et al.* (2001). *Nat Genet* **28**: 69–72.  
 Miura N *et al.* (1996). *J Biochem* **120**: 236–241.  
 Muraoka M *et al.* (2001). *FEBS Lett* **495**: 87–93.

# SLC36 family of proton-coupled amino acid transporters

**Overview:** the SLC36 family of proton-coupled amino acid transporters (or PAT) is highly expressed in the intestine and kidney, having roles in the disposition of amino acids (see Thwaites and Anderson, 2011). PAT1 is found predominantly in lysosomal membranes where it likely functions as an efflux mechanism for amino acids produced during intralysosomal proteolysis (Sagné *et al.*, 2001; Agulhon *et al.*, 2003). PAT2 is found mainly in the endoplasmic reticulum and, to a lesser extent, in other cellular compartments including the plasma membrane (Rubio-Aliaga *et al.*, 2004). PAT1 and PAT2 are predicted to have 11 TM domains with intracellular termini.

Systematic name	SLC36A1	SLC36A2	SLC36A3	SLC36A4
Preferred abbreviation	PAT1	PAT2	PAT3	PAT4
Nomenclature	Proton-coupled Amino acid Transporter 1	Proton-coupled Amino acid Transporter 2	Proton-coupled Amino acid Transporter 3	Proton-coupled Amino acid Transporter 4
Ensembl ID	ENSG00000123643	ENSG00000186335	ENSG00000186334	ENSG00000180773
Other names	LYAAT-1, LYsosomal Amino Acid Transporter 1, imino acid carrier, Tramdorin-3	Tramdorin-1	Tramdorin-2	LYAAT-2
Substrates	GABA, L- and D-proline, glycine, L- and D-alanine, β-alanine, taurine, D-serine, D-cysteine, sarcosine, <i>trans</i> -4-hydroxy-proline, betaine, 5-aminolevulinic acid, β-guanidinopropionic acid	Glycine, proline, alanine, sarcosine, <i>trans</i> -4-hydroxy-proline	–	Proline, tryptophan (Pillai and Meredith, 2011)
Synthetic substrates	MeAIB (Chen <i>et al.</i> , 2003a), vigabatrin, THPO, gaboxadol (Larsen <i>et al.</i> , 2009)	MeAIB (Chen <i>et al.</i> , 2003b)	–	–
Inhibitors	L-Tryptophan, tryptamine, 5-hydroxy-L-tryptophan, serotonin, indole-3-propionic acid (Metzner <i>et al.</i> , 2005)	5-Hydroxy-L-tryptophan, α-methyl-D,L-tryptophan (Edwards <i>et al.</i> , 2011)	–	–
Probes	[ <sup>3</sup> H] or [ <sup>14</sup> C] substrates as listed above	[ <sup>3</sup> H] or [ <sup>14</sup> C] substrates as listed above	–	–
Stoichiometry	1 H <sup>+</sup> : 1 amino acid (in)	1 H <sup>+</sup> : 1 amino acid (in)	Unknown	Unknown

Both PAT1 and PAT2 can also function as an electroneutral transport system for H<sup>+</sup> and fatty acids including acetate, propionate and butyrate (Foltz *et al.*, 2005).

Loss-of-function mutations in PAT2 lead to iminoglycinuria and hyperglycinuria in man (see Bröer, 2008b).

**Abbreviations:** MeAIB,  $\alpha$ - or 2-(methylamino)isobutyric acid; THPO, 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-ol

### Further Reading

- Anderson CMH, Thwaites DT (2010). Hijacking solute carriers for proton-coupled drug transport. *Physiology* **25**: 364–377.
- Birmingham JR, Pennington J (2004). Organization and expression of the SLC36 cluster of amino acid transporter genes. *Mamm Genome* **14**: 114–125.
- Boll M, Daniel H, Gasnier B (2004). The SLC36 family: proton-coupled transporters for the absorption of selected amino acids from extracellular and intracellular proteolysis. *Pflugers Arch* **447**: 776–779.
- Bröer S (2008a). Amino acid transport across mammalian intestinal and renal epithelia. *Physiol Rev* **88**: 249–286.
- Bröer S (2008b). Apical transporters for neutral amino acids: physiology and pathophysiology. *Physiology* **23**: 95–103.
- Thwaites DT, Anderson CMH (2007). H<sup>+</sup>-coupled nutrient, micronutrient and drug transporters in the mammalian small intestine. *Exp Physiol* **92**: 603–619.
- Thwaites DT, Anderson CMH (2007). Deciphering the mechanisms of intestinal imino (and amino) acid transport: the redemption of SLC36A1. *Biochim Biophys Acta* **1768**: 179–197.
- Thwaites DT, Anderson CMH (2011). The SLC36 family of proton-coupled amino acid transporters and their potential role in drug transport. *Br J Pharmacol* in press.

### References

- Agulhon C *et al.* (2003). *J Comp Neurol* **462**: 71–89.
- Chen Z *et al.* (2003a). *J Physiol* **546**: 349–361.
- Chen Z *et al.* (2003b). *Biochem Biophys Res Commun* **304**: 747–754.
- Edwards N *et al.* (2011). *Biochim Biophys Acta* **1808**: 260–270.
- Foltz M *et al.* (2005). *Biochem J* **386**: 607–616.
- Larsen M *et al.* (2009). *Br J Pharmacol* **157**: 1380–1389.
- Metzner L *et al.* (2005). *FASEB J* **19**: 1468–1473.
- Pillai SM, Meredith D (2011). *J Biol Chem* **286**: 2455–2460.
- Rubio-Aliaga I *et al.* (2004). *J Biol Chem* **279**: 2754–2760.
- Sagné C *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 7206–7211.

## SLC37 family of phosphosugar/phosphate exchangers

**Overview:** the family of sugar-phosphate exchangers pass particular phosphorylated sugars across intracellular membranes, exchanging for inorganic phosphate. Of the family of sugar phosphate transporters, most information is available on SPX4, the glucose-6-phosphate transporter. This is a 10 TM domain protein with cytoplasmic termini and is associated with the endoplasmic reticulum, with tissue-specific splice variation. The SPX1 glycerol 3-phosphate transporter is predicted to be expressed on mitochondria.

Systematic name	SLC37A1	SLC37A2	SLC37A3	SLC37A4
Preferred abbreviation	SPX1	SPX2	SPX3	SPX4
Nomenclature	Glycerol-3-phosphate transporter			Glucose-6-phosphate transporter
Ensembl ID	ENSG00000160190	ENSG00000134955	ENSG00000157800	ENSG00000137700
Other names	G3PP	cAMP-inducible gene 2, cl2	–	G6PT1
Substrates	Glycerol 3-phosphate	–	–	Glucose 6-phosphate
Stoichiometry	Unknown	Unknown	Unknown	Unknown

Multiple polymorphisms have been described for the SLC37A4 gene, some of which associate with a glycogen storage disease (Almqvist *et al.*, 2004).

### Further Reading

- Bartoloni L, Antonarakis SE (2004). The human sugar-phosphate/phosphate exchanger family SLC37. *Pflugers Arch* **447**: 780–783.

### Reference

- Almqvist J *et al.* (2004). *Biochemistry* **43**: 9289–9297.

# SLC38 family of sodium-dependent neutral amino acid transporters

**Overview:** the SLC38 family of transporters appears to be responsible for the functionally-defined system A and system N mechanisms of amino acid transport and are mostly expressed in the CNS. Two distinct subfamilies are identifiable within the SLC38 transporters. SNAT1, SNAT2 and SNAT4 appear to resemble system A transporters in accumulating neutral amino acids under the influence of the sodium gradient. SNAT3 and SNAT5 appear to resemble system N transporters in utilizing proton co-transport to accumulate amino acids. The predicted membrane topology is of 11 TM domains with an extracellular N-terminus and intracellular C-terminus.

## System A-like transporters

Systematic name	SLC38A1	SLC38A2	SLC38A4
Preferred abbreviation	SNAT1	SNAT2	SNAT4
Ensembl ID	ENSG00000111371	ENSG00000134294	ENSG00000139209
Other names	Amino acid transporter system A, member 1, ATA1, N-system amino acid transporter 2, NAT2, glutamine transporter	Amino acid transporter system A, member 2, ATA2, SA1, SAT2	Amino acid transporter A3; ATA3, neutral amino acid transporter 3, NAT3, N-system amino acid transporter 3
Substrates	Ala > Ser, Gln, Asn, His, Cys, Met > Gly, Thr, Pro, Tyr, Val (Albers <i>et al.</i> , 2001)	Ala, Met > Asn, Gln, Ser, Pro, Gly > Thr, Leu, Phe (Hatanaka <i>et al.</i> , 2000)	His > Arg, Ala, Asn, Lys > Gly, Gln, Ser, Pro, Leu, Phe (Hatanaka <i>et al.</i> , 2001)
Synthetic substrates	MeAIB	MeAIB	MeAIB
Probes	[ <sup>3</sup> H] or [ <sup>14</sup> C]-Alanine	[ <sup>3</sup> H] or [ <sup>14</sup> C]-Alanine	[ <sup>3</sup> H] or [ <sup>14</sup> C]-Alanine, [ <sup>3</sup> H] or [ <sup>14</sup> C]-glycine
Stoichiometry	1 Na <sup>+</sup> : 1 amino acid (in) (Albers <i>et al.</i> , 2001)	1 Na <sup>+</sup> : 1 amino acid (in) (Hatanaka <i>et al.</i> , 2000)	1 Na <sup>+</sup> : 1 neutral amino acid (in) (Hatanaka <i>et al.</i> , 2001)

Transport of cationic amino acids by SNAT4 was sodium-independent (Hatanaka *et al.*, 2001).

## System N-like transporters

Systematic name	SLC38A3	SLC38A5
Preferred abbreviation	SNAT3	SNAT5
Ensembl ID	ENSG00000188338	ENSG00000017483
Other names	Transport system N protein 1, SN1, G17, N-system amino acid transporter 1; NAT1	Transport system N protein 2, SN2
Substrates	His, Gln > Asn, Ala > Glu (Fei <i>et al.</i> , 2000)	Asn, Ser, His, Gln > Gly, Ala (Nakanishi <i>et al.</i> , 2001)
Synthetic substrates	MeAIB	–
Probes	[ <sup>3</sup> H] or [ <sup>14</sup> C]-Glutamine	[ <sup>3</sup> H] or [ <sup>14</sup> C]-Histidine
Stoichiometry	1 Na <sup>+</sup> : 1 amino acid (in) : 1 H <sup>+</sup> (out) Broer <i>et al.</i> , 2002)	1 Na <sup>+</sup> : 1 amino acid (in) : 1 H <sup>+</sup> (out) (Nakanishi <i>et al.</i> , 2001)

## Orphan transporters

Systematic name	SLC38A6	SLC38A7	SLC38A8	SLC38A9	SLC38A10	SLC38A11
Preferred abbreviation	SNAT6	SNAT7	–	–	–	–
Ensembl ID	ENSG00000139974	ENSG00000103042	ENSG00000166558	ENSG00000177058	ENSG00000157637	ENSG00000169507

SNAT7/SLC38A7 has recently been described to be a system N-like transporter allowing preferential accumulation of glutamine, histidine and asparagine (Hagglund *et al.*, 2011).

**Abbreviations:** MeAIB, 3-amino-2,2-dimethylpropanoic acid

## Further Reading

- Broer S, Palacin M (2011). The role of amino acid transporters in inherited and acquired diseases. *Biochem J* **436**: 193–211.
- Mackenzie B, Erickson JD (2004). Sodium-coupled neutral amino acid (System N/A) transporters of the SLC38 gene family. *Pflugers Arch* **447**: 784–795.
- Sundberg BE, Waag E, Jacobsson JA, Stephansson O, Rumaks J, Svirskis S *et al.* (2008). The evolutionary history and tissue mapping of amino acid transporters belonging to solute carrier families SLC32, SLC36, and SLC38. *J Mol Neurosci* **35**: 179–193.

## References

- Albers A *et al.* (2001). *Pflugers Arch* **443**: 92–101.
- Broer A *et al.* (2002). *J Physiol* **539**: 3–14.
- Fei YJ *et al.* (2000). *J Biol Chem* **275**: 23707–23717.
- Hagglund MG *et al.* (2011). *J Biol Chem* **286**: 20500–20511.
- Hatanaka T *et al.* (2000). *Biochim Biophys Acta* **1467**: 1–6.
- Hatanaka T *et al.* (2001). *Biochim Biophys Acta* **1510**: 10–17.
- Nakanishi T *et al.* (2001). *Biochem Biophys Res Commun* **281**: 1343–1348.

## SLC39 family of metal ion transporters

**Overview:** along with the SLC30 family (see Page S263), SLC39 family members regulate zinc movement in cells. SLC39 metal ion transporters accumulate zinc into the cytosol. Membrane topology modelling suggests the presence of eight TM regions with both termini extracellular. The mechanism for zinc transport for many members is unknown but appears to involve co-transport of bicarbonate ions (Girijashanker *et al.*, 2008, Liu *et al.*, 2008).

Systematic name	SLC39A1	SLC39A2	SLC39A3	SLC39A4	SLC39A5
Common abbreviation	ZIP1	ZIP2	ZIP3	ZIP4	ZIP5
Nomenclature	Zinc transporter 1	Zinc transporter 2	Zinc transporter 3	Zinc transporter 4	metal ion transporter 5
Ensembl ID	ENSG00000143570	ENSG00000165794	ENSG00000141873	ENSG00000206288	ENSG00000139540
Other names	Zinc/iron-regulated transporter-like; ZIRTL, ZRT- and IRT-like protein 1	ZRT- and IRT-like protein 2	ZRT- and IRT-like protein 3	ZRT- and IRT-like protein 4	Metal ion transporter 5

Systematic name	SLC39A6	SLC39A7	SLC39A8	SLC39A9	SLC39A10
Common abbreviation	ZIP6	ZIP7	ZIP8	ZIP9	ZIP10
Nomenclature	Zinc transporter 6	Zinc transporter 7	Zinc transporter 8	Zinc transporter 9	Zinc transporter 10
Ensembl ID	ENSG00000141424	ENSG00000224399; ENSG00000226614; ENSG00000229802; ENSG00000227402; ENSG00000112473	ENSG00000138821	ENSG0000029364	ENSG00000196950
Other names	LIV1	HKE4	BIGM103	–	KIAA1265
Other substrates	–	–	Cadmium (Dalton <i>et al.</i> , 2005, Liu <i>et al.</i> , 2008)	–	–
Stoichiometry	–	–	1 Zn <sup>2+</sup> (in) : 2 HCO <sub>3</sub> <sup>-</sup> (in) (Liu <i>et al.</i> , 2008)	–	–



Systematic name	SLC39A11	SLC39A12	SLC39A13	SLC39A14
Common abbreviation	ZIP11	ZIP12	ZIP13	ZIP14
Nomenclature	Zinc transporter 11	Zinc transporter 12	Zinc transporter 13	Zinc transporter 14
Ensembl ID	ENSG00000133195	ENSG00000148482	ENSG00000165915	ENSG00000104635
Other names	Metal ion transporter 11	–	–	–
Other substrates	–	–	–	Iron (Liuzzi <i>et al.</i> , 2006), cadmium, manganese (Girijashanker <i>et al.</i> , 2008)

Zinc fluxes may be monitored through the use of radioisotopic Zn-65 or the fluorescent dye FluoZin 3.

The bicarbonate transport inhibitor DIDS has been reported to inhibit cation accumulation through ZIP14 (Girijashanker K *et al.*, 2008).

**Abbreviations:** DIDS, 5-isothiocyanato-2-[(E)-2-(4-isothiocyanato-2-sulfophenyl)ethenyl]benzenesulfonic acid

### Further Reading

- Eide DJ (2004). The SLC39 family of metal ion transporters. *Pflugers Arch* **447**: 796–800.  
 Himeno S, Yanagiya T, Fujishiro H (2009). The role of Zinc transporters in cadmium and manganese transport in mammalian cells. *Biochimie* **91**: 1218–1222.  
 Rungby J (2010). Zinc, Zinc transporters and diabetes. *Diabetologia* **53**: 1549–1551.  
 Thevenod F (2010). Catch me if you can! Novel aspects of cadmium transport in mammalian cells. *Biometals* **23**: 857–875.

### References

- Dalton TP *et al.* (2005). *Proc Natl Acad Sci U S A* **102**: 3401–3406.  
 Girijashanker K *et al.* (2008). *Mol Pharmacol* **73**: 1413–1423.  
 Liu Z *et al.* (2008). *Biochem Biophys Res Commun* **365**: 814–820.  
 Liuzzi JP *et al.* (2006). *Proc Natl Acad Sci U S A* **103**: 13612–13617.

## SLC40 iron transporter

**Overview:** alongside the SLC11 family (see Page S242) of proton-coupled metal transporters, IREG allows the accumulation of iron from the diet on the basolateral side of the enterocyte, as well as regulating macrophage and placental iron levels. The predicted topology is of nine TM domains, with an intracellular N-terminus and extracellular C-terminus, with the functional transporter is suggested to be a dimeric arrangement (Aguirre *et al.*, 2005; De Domenico *et al.*, 2007).

Systematic name	SLC40A1
Preferred abbreviation	IREG1
Nomenclature	Iron-regulated transporter
Ensembl ID	ENSG00000138449
Other names	Ferroportin, metal transporter protein, MTP1, SLC11A3, FPN1, HFE4
Endogenous substrates	Fe <sup>2+</sup>
Stoichiometry	Unknown

Hepcidin (HAMP, ENSG00000105697), a small protein that increases upon inflammation, binds to ferroportin to regulate its cellular distribution and degradation. Gene disruption in mice results in embryonic lethality (Donovan *et al.*, 2005), while loss-of-function mutations in man are associated with haemochromatosis (De Domenico *et al.*, 2005).

### Further Reading

McKie AT, Barlow DJ (2004). The SLC40 basolateral iron transporter family (IREG1/ferroportin/MTP1). *Pflugers Arch* **447**: 801–806.

### References

- Aguirre P *et al.* (2005). *BMC Neurosci* **6**: 3.  
 De Domenico I *et al.* (2005). *Proc Natl Acad Sci U S A* **102**: 8955–8960.  
 De Domenico I *et al.* (2007). *Blood* **109**: 2205–2209.  
 Donovan A *et al.* (2005). *Cell Metab* **1**: 191–200.

# SLC41 family of divalent cation transporters

**Overview:** by analogy with bacterial orthologues, this family is probably magnesium transporters. The prokaryote orthologue, MgtE, is responsible for uptake of divalent cations, while the heterologous expression studies of mammalian proteins suggest Mg<sup>2+</sup> efflux. Topological modelling suggests 10 TM domains with cytoplasmic C- and N- termini.

Systematic name	SLC41A1	SLC41A2	SLC41A3
Ensembl ID	ENSG00000133065	ENSG00000136052	ENSG00000114544
Substrates	Mg <sup>2+</sup> , Sr <sup>2+</sup> , Zn <sup>2+</sup> , Cu <sup>2+</sup> , Fe <sup>2+</sup> , Co <sup>2+</sup> , Ba <sup>2+</sup> , Cd <sup>2+</sup> (Goytain and Quamme, 2005a)	Mg <sup>2+</sup> , Ba <sup>2+</sup> , Ni <sup>2+</sup> , Co <sup>2+</sup> , Fe <sup>2+</sup> , Mn <sup>2+</sup> (Goytain and Quamme, 2005b)	–
Stoichiometry	Unknown	Unknown	Unknown

## Further Reading

Moomaw AS, Maguire ME (2008). The unique nature of Mg<sup>2+</sup> channels. *Physiology (Bethesda)* **23**: 275–285.  
 Quamme GA (2010). Molecular identification of ancient and modern mammalian magnesium transporters. *Am J Physiol -Cell Physiol* **298**: C407–C429.

## References

Goytain A, Quamme GA (2005a). *Physiol Genomics* **21**: 337–342.  
 Goytain A, Quamme GA (2005b). *Biochem Biophys Res Commun* **330**: 701–705.

# SLC42 family of non-erythroid Rhesus glycoprotein ammonium transporters

**Overview:** Rhesus is commonly defined as a ‘factor’ that determines, in part, blood type, and whether neonates suffer from haemolytic disease of the newborn. These glycoprotein antigens derive from two genes, RHCE (ENSG00000188672) and RHD (ENSG00000187010) expressed on the surface of erythrocytes. On erythrocytes, RhAG associates with these antigens and functions as an ammonium transporter. RhBG and RhCG are non-erythroid related sequences associated with epithelia. Topological modelling suggests the presence of 12TM with cytoplasmic N- and C-termini. The majority of information on these transporters derives from orthologues in yeast, plants and bacteria. More recent evidence points to family members being permeable to carbon dioxide, leading to the term gas channels.

Systematic name	SLC42A1	SLC42A2	SLC42A3
Preferred abbreviation	RhAG	RhBG	RhCG
Ensembl ID	ENSG00000112077	ENSG00000132677	ENSG00000140519
Other names	CD241, RH50A	–	C15orf6, PDRC2, RHGK
Substrates	NH <sub>3</sub> (Ripoche <i>et al.</i> , 2004), NH <sub>4</sub> <sup>+</sup> (Westhoff <i>et al.</i> , 2002), CO <sub>2</sub> (Endeward <i>et al.</i> , 2008)	–	NH <sub>3</sub> (Zidi-Yahiaoui <i>et al.</i> , 2009)
Probes	[ <sup>14</sup> C]-Methylamine	–	[ <sup>14</sup> C]-Methylamine
Stoichiometry	Unknown	Unknown	Unknown

RhBG is a possible pseudogene in man.

## Further Reading

Huang CH, Ye M (2010). The Rh protein family: gene evolution, membrane biology, and disease association. *Cell Mol Life Sci* **67**: 1203–1218.  
 Nakhoul NL, Hamm LL (2004). Non-erythroid Rh glycoproteins: a putative new family of mammalian ammonium transporters. *Pflugers Arch* **447**: 807–812.  
 Weiner ID, Verlander JW (2011). Role of NH<sub>3</sub> and NH<sub>4</sub><sup>+</sup> transporters in renal acid-base transport. *Am J Physiol -Renal Physiol* **300**: F11–F23.

## References

Endeward V *et al.* (2008). *FASEB J* **22**: 64–73.  
 Ripoche P *et al.* (2004). *Proc Natl Acad Sci U S A* **101**: 17222–17227.  
 Westhoff CM *et al.* (2002). *J Biol Chem* **277**: 12499–12502.  
 Zidi-Yahiaoui N *et al.* (2009). *Am J Physiol Cell Physiol* **297**: C537–C547.

# SLC43 family of large neutral amino acid transporters

**Overview:** LAT3 (SLC43A1) and LAT4 (SLC43A2) are transporters with system L amino acid transporter activity, along with the structurally and functionally distinct transporters LAT1 and LAT2 that are members of the SLC7 family (see Page S227). LAT3 and LAT4 contain 12 putative TM domains with both N and C termini located intracellularly. They transport neutral amino acids in a manner independent of Na<sup>+</sup> and Cl<sup>-</sup> and with two kinetic components (Babu *et al.*, 2003; Bodoy *et al.*, 2005). LAT3/SLC43A1 is expressed in human tissues at high levels in the pancreas, liver, skeletal muscle and fetal liver (Babu *et al.*, 2003) whereas LAT4/SLC43A2 is primarily expressed in the placenta, kidney and peripheral blood leukocytes (Bodoy *et al.*, 2005). SLC43A3 is expressed in vascular endothelial cells (Wallgard *et al.*, 2008) but remains to be characterised.

Systematic name	SLC43A1	SLC43A2	SLC43A3
Preferred abbreviation	LAT3	LAT4	–
Nomenclature	L-type amino acid transporter 3	L-type amino acid transporter 4	–
Other names	Large neutral amino acids transporter 1, prostate cancer overexpressed gene 1, POV1	–	–
Ensembl ID	ENSG00000149150	ENSG00000167703	ENSG00000134802
Substrates	L-leucine, L-isoleucine, L-valine, L-phenylalanine, L-methionine	L-leucine, L-isoleucine, L-valine, L-phenylalanine, L-methionine	–
Synthetic substrates	L-leucinol, L-valinol, L-phenylalaninol	L-leucinol, L-valinol	–
Stoichiometry	Operates by facilitative diffusion	Operates by facilitative diffusion	–

Covalent modification of LAT3 by *N*-ethylmaleimide inhibits its function (Babu *et al.*, 2003) and at LAT4 inhibits the low-, but not high-affinity component of transport (Bodoy *et al.*, 2005).

## References

- Babu E *et al.* (2003). *J Biol Chem* **278**: 43838–43845.  
 Bodoy S *et al.* (2005). *J Biol Chem* **280**: 12002.  
 Wallgard E *et al.* (2008). *Arterioscler Thromb Vasc Biol* **28**: 1469–1476.

# SLC44 family of choline transporters

**Overview:** Members of the choline transporter-like family are encoded by five genes (CTL1-CTL5) with further diversity occurring through alternative splicing of CTL1, 4 and 5 (Traiffort *et al.*, 2005). CTL family members are putative 10TM domain proteins that mediate Na<sup>+</sup>-independent transport of choline with an affinity that is intermediate to that of the high affinity choline transporter CHT1 (SLC5A7) and the low affinity organic-cation transporters [OCT1 (SLC22A1) and OCT2 (SLC22A2)] (Michel *et al.*, 2006). CLT1 is expressed almost ubiquitously in human tissues (Wille *et al.*, 2001) and mediates choline transport across the plasma and mitochondrial membranes (Michel and Bakovic, 2009). Transport of choline by CTL2, which in rodents is expressed as two isoforms (CTL2P1 and CLTP2; Kommareddi *et al.*, 2010) in lung, colon, inner ear and spleen and to a lesser extent in brain, tongue, liver, and kidney, has only recently been demonstrated (Kommareddi *et al.*, 2010; Nakamura *et al.*, 2010). CTL3-5 remain to be characterized functionally.

Common name	CTL1	CTL2	CTL3	CTL4	CTL5
Systematic name	SLC44A1	SLC44A2	SLC44A3	SLC44A4	SLC44A5
Nomenclature	Choline transporter-like 1	Choline transporter-like 2	Choline transporter-like 3	Choline transporter-like 4	Choline transporter-like 5
Other names	CHTL1, CDW92	–	–	–	–
Ensembl ID	ENSG00000070214	ENSG00000129353	ENSG00000143036	ENSG00000204385	ENSG00000137968
Substrates	Choline	Choline	–	–	–
Synthetic substrates	–	–	–	–	–
Inhibitors (pK)	HC-3 (4.5–5.3)	–	–	–	–
Stoichiometry	Unknown: uptake enhanced in the absence of extracellular Na <sup>+</sup> , reduced by membrane depolarization, extracellular acidification and collapse of plasma membrane H <sup>+</sup> electrochemical gradient	–	–	–	–

Data tabulated are features observed for CLT1 endogenous to: rat astrocytes (Inazu *et al.*, 2005); rat renal tubule epithelial cells (Yabuki *et al.*, 2009); human colon carcinoma cells (Kouji *et al.*, 2009); human keratinocytes (Uchida *et al.*, 2009) and human neuroblastoma cells (Yamada *et al.*, 2011). Choline uptake by CLT1 is inhibited by numerous organic cations (*e.g.* Inazu *et al.*, 2005; Yabuki *et al.*, 2009; Yamada *et al.*, 2011). In the guinea-pig, CTL2 is a target for antibody-induced hearing loss (Nair *et al.*, 2004) and in man a polymorphism in CTL2 constitutes the human neutrophil alloantigen-3a (HNA-3a; Greinacher *et al.*, 2010).

**Abbreviations:** HC-3, hemicholinium 3

#### Further Reading

Lockman PR, Allen DD (2002). The transport of choline. *Drug Dev Ind Pharm* **28**: 749–771.  
Michel V, Yuan Z, Ramsuiri S, Bakovic M (2006). Choline transport for phospholipid synthesis. *Exp Biol Med (Maywood)* **231**: 490–504.

#### References

- Greinacher A *et al.* (2010). *Nat Med* **16**: 45–48.  
Inazu M *et al.* (2005). *J Neurochem* **94**: 1427–1437.  
Kommareddi PK *et al.* (2010). *Protein J* **29**: 417–426.  
Kouji H *et al.* (2009). *Arch Biochem Biophys* **483**: 90–98.  
Nair TS *et al.* (2004). *J Neurosci* **24**: 1772–1779.  
Nakamura T *et al.* (2010). *Biol Pharm Bull* **33**: 691–696.  
Michel V, Bakovic M (2009). *FASEB J* **23**: 2749–2758.  
Traiffort E *et al.* (2005). *J Neurochem* **92**: 1116–1125.  
Uchida Y *et al.* (2009). *J Pharmacol Sci* **109**: 102–109.  
Wille S *et al.* (2001). *J Immunol* **167**: 5795–5804.  
Yabuki M *et al.* (2009). *Arch Biochem Biophys* **485**: 88–96.  
Yamada T *et al.* (2011). *Neurochem Int* **58**: 354–365.

## SLC45 orphans

**Overview:** Members of the SLC45 family remain to be functionally characterised. However, the *SLC45A2* gene is thought to encode a transporter protein that mediates melanin synthesis. Mutations in *SLC45A2* are a cause of oculocutaneous albinism type 4 (*e.g.* Newton *et al.*, 2001), and polymorphisms in this gene are associated with variations in skin and hair color (*e.g.* Graf *et al.*, 2005).

Systematic name	SLC45A1	SLC45A2	SLC45A3	SLC45A4
Other names	DNB5	Melanin associated transporter protein (MATP), AIM1	Prostate cancer associated protein 6 (PCANAP6), prostein (PRST)	–
Ensembl ID	ENSG00000162426	ENSG00000164175	ENSG00000158715	ENSG00000022567

#### References

- Graf J *et al.* (2005). *Hum Mutat* **25**: 278–284.  
Newton JM *et al.* (2001). *Am J Hum Genet* **69**: 981–988.

## SLC46 family of folate transporters

**Overview:** Based on the prototypical member of this family, PCFT, this family are proton-driven transporters with 11 TM segments. SLC46A1 has been described to act as an intestinal proton-coupled high-affinity folate transporter (Qiu *et al.*, 2006), with lower affinity for haem. Folate accumulation is independent of Na<sup>+</sup> or K<sup>+</sup> ion concentrations, but driven by extracellular protons with an as-yet undefined stoichiometry.

Systematic name	SLC46A1	SLC46A2	SLC46A3
Preferred abbreviation	PCFT	TSCOT	–
Nomenclature	Proton-coupled folate transporter	Thymic stromal co-transporter	–
Ensembl ID	ENSG00000076351	ENSG00000119457	ENSG00000139508
Other names	Heme carrier protein-1, HCP-1	–	–
Substrates	Folate (1.3 μM) > haem (>100 μM, Nakai <i>et al.</i> , 2007)	–	–
Synthetic substrates	Methotrexate (Qiu <i>et al.</i> , 2006), folinic acid (Nakai <i>et al.</i> , 2007)	–	–
Inhibitors	Sulfasalazine (60 μM, Qiu <i>et al.</i> , 2006), indomethacin (~200 μM, Qiu <i>et al.</i> , 2006)	–	–
Probes	[ <sup>3</sup> H]-folate, [ <sup>3</sup> H]-methotrexate	–	–

Loss-of-function mutations in PCFT (SLC46A1) are associated with hereditary folate malabsorption.

### Further Reading

Anderson CM, Thwaites DT (2010). Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* 25: 364–377.  
 Krishnamurthy P, Xie T, Schuetz JD (2007). The role of transporters in cellular heme and porphyrin homeostasis. *Pharmacol Ther* 114: 345–358.  
 Latunde-Dada GO, Simpson RJ, McKie AT (2006). Recent advances in mammalian haem transport. *Trends Biochem Sci* 31: 182–188.  
 Thwaites DT, Anderson CM (2007). H<sup>+</sup>-coupled nutrient, micronutrient and drug transporters in the mammalian small intestine. *Exp Physiol* 92: 603–619.  
 Wolf G (2007). Identification of proton-coupled high-affinity human intestinal folate transporter mutated in human hereditary familial folate malabsorption. *Nutr Rev* 65: 554–557.  
 Yuasa H, Inoue K, Hayashi Y (2009). Molecular and functional characteristics of proton-coupled folate transporter. *J Pharm Sci* 98: 1608–1616.

### References

Nakai Y *et al.* (2007). *J Pharmacol Exp Ther* 322: 469–476.  
 Qiu A *et al.* (2006). *Cell* 127: 917–928.

## SLC47 family of multidrug and toxin extrusion transporters

**Overview:** these proton:organic cation exchangers are predicted to have 13 TM segments (Zhang and Wright, 2009) and are suggested to be responsible for excretion of many drugs in the liver and kidneys.

Systematic name	SLC47A1	SLC47A2
Preferred abbreviation	MATE1	MATE2-K
Nomenclature	Multi antimicrobial extrusion protein	
Other names	Multidrug and toxin extrusion protein 1	
Ensembl ID	ENSG00000142494	ENSG00000180638
Synthetic substrates	Cimetidine (Ohta <i>et al.</i> , 2006), cephalixin, cephadrine, quinidine (Tanihara <i>et al.</i> , 2007), paraquat (Chen <i>et al.</i> , 2007)	Cimetidine, 1-methyl-4-phenylpyridinium, procainamide, metformin, N <sup>1</sup> -methylnicotinamide (Masuda <i>et al.</i> , 2006), guanidine, acyclovir (Tanihara <i>et al.</i> , 2007)
Inhibitors	Pyrimethamine (0.15 μM, Ito <i>et al.</i> , 2010)	
Probes	[ <sup>14</sup> C]-TEA (Otsuka <i>et al.</i> , 2005), [ <sup>14</sup> C]-metformin (Tanihara <i>et al.</i> , 2007)	[ <sup>14</sup> C]-TEA (Tanihara <i>et al.</i> , 2007)

DAPI has been used to allow quantification of MATE1 and MATE2-mediated transport activity (Yasujima *et al.*, 2010).

**Abbreviations:** DAPI, 4',6-diamidino-2-phenylindole; MPP, 1-methyl-4-phenylpyridinium

### Further Reading

- Terada T, Inui K (2008). Physiological and pharmacokinetic roles of H<sup>+</sup>/organic cation antiporters (MATE/SLC47A). *Biochem Pharmacol* 75: 1689–1696.
- Yonezawa A, Inui KI (2011). Importance of the Multidrug and Toxin Extrusion MATE/SLC47A Family to Pharmacokinetics, Pharmacodynamics/ Toxicodynamics and Pharmacogenomics. *Br J Pharmacol* in press.

### References

- Chen Y *et al.* (2007). *J Pharmacol Exp Ther* 322: 695–700.
- Ito S *et al.* (2010). *J Pharmacol Exp Ther* 333: 341–350.
- Masuda S *et al.* (2006). *J Am Soc Nephrol* 17: 2127–2135.
- Ohta KY *et al.* (2006). *Drug Metab Dispos* 34: 1868–1874.
- Otsuka M *et al.* (2005). *Proc Natl Acad Sci U S A* 102: 17923–17928.
- Tanihara Y *et al.* (2007). *Biochem Pharmacol* 74: 359–371.
- Yasujima T *et al.* (2010). *Drug Metab Dispos* 38: 715–721.
- Zhang X, Wright SH (2009). *Am J Physiol -Renal Physiol* 297: F263–F271.

## SLC48 haem transporter

**Overview:** although identified as a heme transporter (Rajagopal *et al.*, 2008), subsequent evidence suggests this 4TM-containing protein associates with the V-type ATPase (see Page S218) in lysosomes for haem degradation (O'Callaghan *et al.*, 2010). As yet, this transporter awaits characterization.

Systematic name	SLC48A1
Preferred abbreviation	HRG1
Nomenclature	Heme transporter
Ensembl ID	ENSG00000211584
Other names	Heme-responsive gene 1, hHRG-1

### References

- O'Callaghan KM *et al.* (2010). *J Biol Chem* 285: 381–391.
- Rajagopal A *et al.* (2008). *Nature* 453: 1127–1131.

## SLCO family of organic anion transporting polypeptides

**Overview:** The SLCO superfamily is comprised of the organic anion transporting polypeptides (OATPs). The 11 human OATPs are divided into 6 families and ten subfamilies based on amino acid identity. These proteins are located on the plasma membrane of cells throughout the body. They have 12 TM domains and intracellular termini, with multiple putative glycosylation sites. OATPs mediate the sodium-independent uptake of a wide range of amphiphilic substrates, including many drugs and toxins. Due to the multispecificity of these proteins, this guide lists classes of substrates and inhibitors for each family member. More comprehensive lists of substrates, inhibitors, and their relative affinities may be found in the review articles listed below.

Nomenclature	OATP1A2	OATP1B1	OATP1B3	OATP1C1
HGNC nomenclature	SLCO1A2	SLCO1B1	SLCO1B3	SLCO1C1
Ensembl ID	ENSG00000084453	ENSG00000134538	ENSG00000111700	ENSG00000139155
Other names	OATP, OATP-A, SLC21A3	OATP-C, OATP2, LST-1, SLC21A6	OATP8, LST-2, SLC21A8	OATP-F, OATP1, SLC21A14, OATP14
Endogenous substrates	Bile acids, bilirubin, BSP, steroid conjugates, thyroid hormones	Bile acids, bilirubin, BSP, leukotrienes, steroid conjugates, thyroid hormones	Bile acids, bilirubin, BSP, CCK-8, leukotriene C4, steroid conjugates, thyroid hormones	Thyroid hormones, steroid conjugates, BSP
Exogenous substrates	Antibiotics, anticancer drugs, beta blockers, deltorphin II, fexofenadine, fluoroquinolones, HIV protease inhibitors, microcystin, ouabain, rosuvastatin, talinolol	ACE inhibitors, anticancer drugs, antifungals, $\beta$ -lactam antibiotics, bile acid derivatives and conjugates, endothelin receptor antagonists, fexofenadine, HIV protease inhibitors, opioids, rifampicin, sartans, statins	Amanitin, anticancer drugs, $\beta$ -lactam antibiotics, bile acid derivatives and conjugates, digoxin, erythromycin, fexofenadine, opioids, ouabain, phalloidin, rifampicin, saquinavir, sartans, statins	Statins
Inhibitors	Naringin, rifampicin, rifamycin SV	Cyclosporine A, fibrates, flavonoids, gemfibrozil, glitazones, glycyrrhizin, indocyanine green, macrolide antibiotics, rifampicin, rifamycin SV, sildenafil	Cyclosporine A, gemfibrozil, glitazones, glycyrrhizin, HIV protease inhibitors, macrolide antibiotics, rifampicin, rifamycin SV, sildenafil	Probenicid, taurocholate, DPDPE
Common probes	[ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-DPDPE, [ <sup>3</sup> H]-estrone-3-sulfate	[ <sup>3</sup> H]-estradiol-17 $\beta$ -glucuronide, [ <sup>3</sup> H]-estrone-3-sulfate, pravastatin	[ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-CCK-8, [ <sup>3</sup> H]-estradiol-17 $\beta$ -glucuronide	[ <sup>125</sup> I]-thyroxine, [ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-estrone-3-sulfate

Nomenclature	OATP2A1	OATP2B1	OATP3A1
HGNC nomenclature	SLCO2A1	SLCO2B1	SLCO3A1
Ensembl ID	ENSG000000174640	ENSG000000137491	ENSG000000176463
Other names	PGT, SLC21A2	OATP-B, SLC21A9	OATP-D, SLC21A11
Endogenous substrates	Prostaglandins, eicosanoids	BSP, DHEAS, estrone-3-sulfate, thyroxine	Prostaglandins, thyroid hormones, BQ123, vasopressin
Exogenous substrates	Synthetic prostaglandin derivatives	Aliskiren, amiodarone, bosentan, fexofenadine, glibenclamide, statins, talinolol, telmisartan	–
Inhibitors	Bromocresol green, BSP, NSAIDs	Citrus juices, gemfibrozil, glitazones, glyburide, rifamycin SV, rifampicin	–
Common probes	[ <sup>3</sup> H]-prostaglandin E <sub>2</sub>	[ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-estrone-3-sulfate	[ <sup>3</sup> H]-estrone-3-sulfate, [ <sup>3</sup> H]-prostaglandin E <sub>2</sub>

Nomenclature	OATP4A1	OATP4C1	OATP5A1	OATP6A1
HGNC nomenclature	SLCO4A1	SLCO4C1	SLCO5A1	SLCO6A1
Ensembl ID	ENSG000000101187	ENSG000000173930	ENSG000000137571	ENSG000000205359
Other names	OATP-E, SLC21A12	SLC21A20, OATPX, OATP-H, OATP-M1	OATPRP4, OATP-J	OATPY, MGC26949, OATP-I, gonad specific transporter
Endogenous substrates	Steroid conjugates, thyroid hormones, prostaglandins, bile acids	Thyroid hormones, steroid conjugates, cAMP	–	–
Exogenous substrates	Benzylpenicillin	Cardiac glycosides, anticancer drugs, dipeptidyl peptidase-4 inhibitors	–	–
Common probes	[ <sup>3</sup> H]-estrone-3-sulfate	[ <sup>3</sup> H]-digoxin	–	–

**Abbreviations:** BSP, bromosulphothalein; CCK-8, Cholecystokinin octapeptide; DHEAS, dehydroepiandrosterone-3-sulfate; DPDPE, [d-Pen<sup>2</sup>,d-Pen<sup>5</sup>]-Enkephalin; PGT, prostaglandin transporter

#### Further Reading

- Hagenbuch B (2010). Drug uptake systems in liver and kidney: a historic perspective. *Clin Pharmacol Ther* **87**: 39–47.
- Hagenbuch B, Meier PJ (2004). Organic anion transporting polypeptides of the OATP/ SLC21 family: phylogenetic classification as OATP/ SLCO superfamily, new nomenclature and molecular/functional properties. *Pflugers Arch* **447**: 653–665.
- Konig J (2011). Uptake transporters of the human OATP family: molecular characteristics, substrates, their role in drug-drug interactions, and functional consequences of polymorphisms. *Handb Exp Pharmacol* 1–28.
- Niemi M, Pasanen MK, Neuvonen PJ (2011). Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev* **63**: 157–181.



# ENZYMES

Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four number code, on the basis of the reactions they catalyse. There are six main families: EC 1.-.-.- Oxidoreductases; EC 2.-.-.- Transferases; EC 3.-.-.- Hydrolases; EC 4.-.-.- Lyases; EC 5.-.-.- Isomerases; EC 6.-.-.- Ligases.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2).

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme.

Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small (Overington *et al.*, 2006), which is not to say that they are of modest importance.

## Further Reading

Overington JP, Al-Lazikani B, Hopkins AL (2006). How many drug targets are there? *Nat Rev Drug Discovery* 5: 993–996.  
<http://www.chem.qmul.ac.uk/iubmb/>

# Adenosine turnover

**Overview:** Adenosine is a multifunctional, ubiquitous molecule that acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5'-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing ammonia) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5'-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing homocysteine).

Nomenclature	Adenosine deaminase	Adenosine kinase	Ecto-5'-Nucleotidase	S-Adenosylhomocysteine hydrolase
E.C.	3.5.4.4	2.7.1.20	3.1.3.5	3.3.1.1
Preferred abbreviation	ADA	ADK	NT5E	SAHH
Ensembl ID	ENSG00000196839	ENSG00000156110	ENSG00000135318	ENSG00000101444
Other names	Adenosine aminohydrolase, ADA1	–	CD73, 5'-NT	Adenosylhomocysteinase
Rank order of affinity	2'-Deoxyadenosine ≥ adenosine	Adenosine	5'-AMP, 5'-GMP, 5'-IMP, 5'-UMP > 5'-dAMP, 5'-dGMP	S-Adenosylhomocysteine
Nucleoside products	2'-Deoxyinosine, inosine	5'-AMP	Adenosine, guanine, inosine, uridine	Adenosine
Selective inhibitors (pIC <sub>50</sub> )	EHNA, 2'-deoxycoformycin	A134974 (10.2, McGaraughty <i>et al.</i> , 2001), ABT702 (8.8, Jarvis <i>et al.</i> , 2000)	αβ-methyleneADP	3-Deazaadenosine (8.5, Guranowski <i>et al.</i> , 1981)

An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, CECR1, ENSG00000093072) has been identified (see Maier *et al.*, 2005), which is insensitive to EHNA (Zavialov *et al.*, 2010). Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: ADAT1 (ENSG00000065457) deaminates transfer RNA; ADAR (EC 3.5.4.-, ENSG00000160710, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); ADARB1 (EC 3.5.-., ENSG00000197381, also known as dsRNA adenosine deaminase) and ADARB2 (EC 3.5.-., ENSG00000185736, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, ENSG00000197635, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity (Kameoka *et al.*, 1993).

## Other 5'-nucleotidases

Nomenclature	HGNC nomenclature	Ensembl ID
IA	NT5C1A	ENSG00000116981
IB	NT5C1B	ENSG00000185013
II	NT5C2	ENSG00000076685
III	NT5C3	ENSG00000122643
5'(3')-nucleotidases	NT5C	ENSG00000125458
Mitochondrial	NT5M	ENSG00000205309

**Abbreviations:** 5'-AMP, adenosine 5'-monophosphate; 5'NT, 5'-nucleotidase; A134974, N<sup>7</sup>-[(1'R,2'S,3' R,4'S)-2',3'-dihydroxy-4'-aminocyclopentyl]-4-amino-5-iodopyrrolopyrimidine; ABT702, 4-amino-5-(3-bromophenyl)-7-(6-morpholinopyridin-3-yl)pyrido[2,3-d]pyrimidine; ADA, adenosine deaminase; ADK, adenosine kinase, EHNA, *erythro*-9-(2-hydroxy-3-nonyl)adenine hydrochloride;

## Further Reading

- Aiuti A, Cattaneo F, Galimberti S *et al.* (2009). Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N Engl J Med* **360**: 447–458.
- Blackburn MR, Kellems RE (2005). Adenosine deaminase deficiency: metabolic basis of immune deficiency and pulmonary inflammation. *Adv Immunol* **86**: 1–41.
- Boison D (2006). Adenosine kinase, epilepsy and stroke: mechanisms and therapies. *Trends Pharmacol Sci* **27**: 652–658.

- Cristalli G, Costanzi S, Lambertucci C, Lupidi G, Vittori S, Volpini R *et al.* (2001). Adenosine deaminase: functional implications and different classes of inhibitors. *Med Res Rev* **21**: 105–128.
- Hershfield MS (2005). New insights into adenosine-receptor-mediated immunosuppression and the role of adenosine in causing the immunodeficiency associated with adenosine deaminase deficiency. *Eur J Immunol* **35**: 25–30.
- Hunsucker SA, Mitchell BS, Spychala J (2005). The 5'-nucleotidases as regulators of nucleotide and drug metabolism. *Pharmacol Ther* **107**: 1–30.
- Kloor D, Osswald H (2004). S-Adenosylhomocysteine hydrolase as a target for intracellular adenosine action. *Trends Pharmacol Sci* **25**: 294–297.
- Maier SA, Galellis JR, McDermid HE (2005). Phylogenetic analysis reveals a novel protein family closely related to adenosine deaminase. *J Mol Evol* **61**: 776–794.

## References

- Guranowski A *et al.* (1981). *Biochemistry* **20**: 110–115.
- Jarvis MF *et al.* (2000). *J Pharmacol Exp Ther* **295**: 1156–1164.
- Kameoka J *et al.* (1993). *Science* **261**: 466–469.
- McGarraughty S *et al.* (2001). *J Pharmacol Exp Ther* **296**: 501–509.
- Zavialov AV *et al.* (2010). *J Biol Chem* **285**: 12367–12377.

# Amino acid hydroxylases (E.C.1.14.16.-)

**Overview:** The amino acid hydroxylases (monooxygenases) are iron-containing enzymes which utilise molecular oxygen and tetrahydrobiopterin as co-substrate and co-factor, respectively.

Nomenclature	L-Phenylalanine hydroxylase	L-Tryptophan hydroxylase	L-Tyrosine hydroxylase
E.C.	1.14.16.1	1.14.16.4	1.14.16.2
Preferred abbreviation	PH	TPH	TH
Ensembl ID	ENSG00000171759	TPH1 ENSG00000129167; TPH2 ENSG00000139287	ENSG00000180176
Other names	Phenylalanine 4-monooxygenase	Tryptophan 5-monooxygenase	Tyrosine 3-monooxygenase
Product	Tyrosine	5-Hydroxytryptophan	DOPA
Selective inhibitors	$\alpha$ -Methylphenylalanine (Greengard <i>et al.</i> , 1976), PCPA	Fenfluramine, PCPA, $\alpha$ -propylidopacetamide, 6-fluorotryptophan (Nicholson and Wright, 1981)	3-Chlorotyrosine, 3-iodotyrosine, $\alpha$ -methyltyrosine, $\alpha$ -propylidopacetamide

**Abbreviations:** DOPA, 3,4-dihydroxyphenylalanine; PCPA, 4-chlorophenylalanine

## Further Reading

- Daubner SC, Le T, Wang S (2011). Tyrosine hydroxylase and regulation of dopamine synthesis. *Arch Biochem Biophys* **508**: 1–12.
- Lehmann IT, Bobrovskaya L, Gordon SL, Dunkley PR, Dickson PW (2006). Differential regulation of the human tyrosine hydroxylase isoforms via hierarchical phosphorylation. *J Biol Chem* **281**: 17644–17651.
- Matthes S, Mosienko V, Bashammakh S, Alenina N, Bader M (2010). Tryptophan hydroxylase as novel target for the treatment of depressive disorders. *Pharmacology* **85**: 95–109.
- Waider J, Araragi N, Gutknecht L, Lesch KP (2011). Tryptophan hydroxylase-2 (TPH2) in disorders of cognitive control and emotion regulation: a perspective. *Psychoneuroendocrinology* **36**: 393–405.
- Zhang X, Beaulieu JM, Gainetdinov RR, Caron MG (2006). Functional polymorphisms of the brain serotonin synthesizing enzyme tryptophan hydroxylase-2. *Cell Mol Life Sci* **63**: 6–11.

## References

- Greengard O *et al.* (1976). *Science* **192**: 1007–1008.
- Nicholson AN, Wright CM (1981). *Neuropharmacology* **20**: 335–339.

# L-Arginine turnover

**Overview:** L-arginine is a basic amino acid with a guanidino sidechain. As an amino acid, metabolism of L-arginine to form L-ornithine, catalysed by arginase, forms the last step of the urea production cycle. L-Ornithine may be utilised as a precursor of polyamines (see Carboxylases and Decarboxylases, Page S286) or recycled via L-arginosuccinate to L-arginine. L-Arginine may itself be decarboxylated (see Page S286) to form agmatine, although the prominence of this pathway in human tissues is uncertain. L-Arginine may be used as a precursor for guanidinoacetate formation in the creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate nitric oxide, with L-citrulline also as a byproduct.

L-Arginine in proteins may be subject to post-translational modification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric  $N^G,N^G$ -dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

**Arginase** (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.

Nomenclature	Arginase I	Arginase II
Preferred abbreviation	ARG1	ARG2
Ensembl ID	ENSG00000118520	ENSG00000081181
Other names	Liver arginase, cytosolic arginase	Mitochondrial arginase

$N^{\omega}$ -Hydroxyarginine, an intermediate in NOS metabolism of L-arginine acts as a weak inhibitor and may function as a physiological regulator of arginase activity. Although isoform-selective inhibitors of arginase are not available, examples of inhibitors selective for arginase compared to NOS are  $N^{\omega}$ -hydroxy-nor-L-arginine (Tenu *et al.*, 1999), S-(2-boronoethyl)-L-cysteine (Colleluori and Ash, 2001; Kim *et al.*, 2001) and 2(S)-amino-6-borono-hexanoic acid (Baggio *et al.*, 1999; Colleluori and Ash, 2001).

**Arginine:glycine amidinotransferase** (AGAT, E.C. 2.1.4.1)

Nomenclature	Arginine:glycine amidinotransferase
Preferred abbreviation	AGAT
Ensembl ID	ENSG00000171766
Other names	GATM, glycine amidinotransferase

**Dimethylarginine dimethylaminohydrolases** (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse  $N^G,N^G$ -dimethyl-L-arginine to form dimethylamine and L-citrulline.

Nomenclature	$N^G,N^G$ -Dimethylarginine dimethylaminohydrolase 1	$N^G,N^G$ -Dimethylarginine dimethylaminohydrolase 2
Preferred abbreviation	DDAH1	DDAH2
Ensembl ID	ENSG00000153904	ENSG00000213722
Other names	Dimethylarginine dimethylaminohydrolase 1, DDAH1, dimethylargininase-1	Dimethylarginine dimethylaminohydrolase 2, DDAHII, dimethylargininase-2, S-phase protein, protein G6a
Cofactor	Zn <sup>2+</sup>	–

**Nitric oxide synthases** (NOS, E.C. 1.14.13.39) utilise L-arginine (not D-arginine) and molecular oxygen to generate nitric oxide and L-citrulline. The nomenclature suggested by NC-IUPHAR of NOS I, II and III (see Moncada *et al.*, 1997) has not gained wide acceptance. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca<sup>2+</sup>/calmodulin and thus appears to be constitutively active. All the three isoforms are homodimers and require tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all three isoforms, with an IC<sub>50</sub> value in the micromolar range.

Nomenclature	Endothelial NOS	Inducible NOS	Neuronal NOS
Preferred abbreviation	eNOS	iNOS	nNOS
Ensembl ID	ENSG00000164867	ENSG00000007171	ENSG000000089250
Other names	NOS III, NOS-3, ecNOS	NOS II, NOS-2	NOS I, NOS-1, brain NOS
Selective inhibitors	–	1400W (8.2, Garvey <i>et al.</i> , 1997), 2-amino-4-methylpyridine (7.4, Faraci <i>et al.</i> , 1996), PIBTU (7.3, Garvey <i>et al.</i> , 1994), NIL (5.5, Moore <i>et al.</i> , 1994), aminoguanidine (Corbett and McDaniel, 1992)	3-Bromo-7NI (6.1–6.5, Bland-Ward and Moore, 1995), 7NI (5.3, Babbedge <i>et al.</i> , 1993)

The reductase domain of NOS catalyses the reduction of cytochrome *c* and other redox-active dyes (Mayer and Hemmens, 1997). NADPH:O<sub>2</sub> oxidoreductase catalyses the formation of superoxide anion/H<sub>2</sub>O<sub>2</sub> in the absence of arginine and tetrahydrobiopterin.

**Protein arginine N-methyltransferases** (PRMT, EC 2.1.1.-) encompass histone arginine N-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein N-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl-L-methionine as a methyl donor, generating S-adenosyl-L-homocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (ADMA) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Nomenclature	Ensembl ID	Other names
PRMT1	ENSG00000126457	Interferon receptor 1-bound protein 4, ANM1, HCP1, HRMT1L2
PRMT2	ENSG00000160310	–
PRMT3	ENSG00000185238	Heterogeneous nuclear ribonucleoprotein methyltransferase-like protein 3
PRMT4	ENSG00000142453	Histone-arginine methyltransferase CARM1, coactivator-associated arginine methyltransferase 1
PRMT5	ENSG00000100462	Histone-arginine N-methyltransferase, Shk1 kinase-binding protein 1 homolog, SKB1Hs, Jak-binding protein 1, 72 kDa ICLN-binding protein
PRMT6	ENSG00000198890	Heterogeneous nuclear ribonucleoprotein methyltransferase-like protein 6
PRMT7	ENSG00000132600	Histone-arginine N-methyltransferase, myelin basic protein-arginine N-methyltransferase
PRMT8	ENSG00000111218	Heterogeneous nuclear ribonucleoprotein methyltransferase-like protein 4
PRMT9	ENSG00000138081	FBXO11, F-box only protein 11, vitiligo-associated protein 1, VIT-1
PRMT10	ENSG00000164169	TPR repeat-containing protein LOC90826

A related gene has been described, CARM1L (Coactivator associated arginine methyltransferase 1-like fragment, ENSG00000227835).

**Abbreviations:** 1400W, N-(3-(aminomethyl) benzyl)acetamidine; ADMA, asymmetric dimethylarginine; DDAH, dimethylarginine dimethylaminohydrolase; NADPH, reduced nicotinamide adenosine dinucleotide phosphate; 7NI, 7-nitroindazole; NIL, L-N<sup>6</sup>-(1-iminoethyl)lysine; NOS, nitric oxide synthase; PIBTU, 13-phenylen-bis(1,2-ethanediy)bis-thiourea; PRMT, protein arginine methyltransferase; SDMA, symmetric dimethylarginine

### Further Reading

- Bedford MT, Clarke SG (2009). Protein arginine methylation in mammals: who, what, and why. *Mol Cell* **33**: 1–13.
- Heemskerk S, Masereeuw R, Russel FG, Pickkers P (2009). Selective iNOS inhibition for the treatment of sepsis-induced acute kidney injury. *Nat Rev Nephrol* **5**: 629–640.
- Huang PL (2009). eNOS, metabolic syndrome and cardiovascular disease. *Trends Endocrinol Metab* **20**: 295–302.
- Krause CD, Yang ZH, Kim YS, Lee JH, Cook JR, Pestka S (2007). Protein arginine methyltransferases: evolution and assessment of their pharmacological and therapeutic potential. *Pharmacol Ther* **113**: 50–87.
- Kukreja RC, Xi L (2007). eNOS phosphorylation: a pivotal molecular switch in vasodilation and cardioprotection? *J Mol Cell Cardiol* **42**: 280–282.
- Leiper J, Nandi M (2011). The therapeutic potential of targeting endogenous inhibitors of nitric oxide synthesis. *Nat Rev Drug Discov* **10**: 277–291.
- Lundberg JO, Weitzberg E (2010). NO-synthase independent NO generation in mammals. *Biochem Biophys Res Commun* **396**: 39–45.
- Maarsingh H, Pera T, Meurs H (2008). Arginase and pulmonary diseases. *Naunyn Schmiedeberg's Arch Pharmacol* **378**: 171–184.
- Maarsingh H, Zaagsma J, Meurs H (2009). Arginase: a key enzyme in the pathophysiology of allergic asthma opening novel therapeutic perspectives. *Br J Pharmacol* **158**: 652–664.
- Melikian N, Seddon MD, Casadei B, Chowienczyk PJ, Shah AM (2009). Neuronal nitric oxide synthase and human vascular regulation. *Trends Cardiovasc Med* **19**: 256–262.
- Moncada S, Higgs A, Furchgott R (1997). International Union of Pharmacology Nomenclature in Nitric Oxide Research. *Pharmacol Rev* **49**: 137–142.
- Morris SM Jr. (2009). Recent advances in arginine metabolism: roles and regulation of the arginases. *Br J Pharmacol* **157**: 922–930.
- Mount PF, Kemp BE, Power DA (2007). Regulation of endothelial and myocardial NO synthesis by multi-site eNOS phosphorylation. *J Mol Cell Cardiol* **42**: 271–279.
- Munder M (2009). Arginase: an emerging key player in the mammalian immune system. *Br J Pharmacol* **158**: 638–651.
- Palm F, Onozato ML, Luo Z, Wilcox CS (2007). Dimethylarginine dimethylaminohydrolase (DDAH): expression, regulation, and function in the cardiovascular and renal systems. *Am J Physiol Heart Circ Physiol* **293**: H3227–H3245.

- Teyssier C, Le Romancer M, Sentis S, Jalaguier S, Corbo L, Cavailles V (2010). Protein arginine methylation in estrogen signaling and estrogen-related cancers. *Trends Endocrinol Metab* **21**: 181–189.
- Toda N, Ayajiki K, Okamura T (2009). Cerebral blood flow regulation by nitric oxide: recent advances. *Pharmacol Rev* **61**: 62–97.
- Tousoulis D, Boger RH, Antoniadis C, Siasos G, Stefanadi E, Stefanadis C (2007). Mechanisms of disease: L-arginine in coronary atherosclerosis—a clinical perspective. *Nat Clin Pract Cardiovasc Med* **4**: 274–283.
- Tsutsui M, Shimokawa H, Otsuji Y, Yanagihara N (2010). Pathophysiological relevance of NO signaling in the cardiovascular system: novel insight from mice lacking all NO synthases. *Pharmacol Ther* **128**: 499–508.

## References

- Babbedge RC *et al.* (1993). *Br J Pharmacol* **110**: 225–228.
- Baggio R *et al.* (1999). *J Pharmacol Exp Ther* **290**: 1409–1416.
- Bland-Ward PA, Moore PK (1995). *Life Sci* **57**: PL131–PL135.
- Colleluori DM, Ash DE (2001). *Biochemistry* **40**: 9356–9362.
- Corbett JA, McDaniel ML (1992). *Diabetes* **41**: 897–903.
- Faraci WS *et al.* (1996). *Br J Pharmacol* **119**: 1101–1108.
- Garvey EP *et al.* (1994). *J Biol Chem* **269**: 26669–26676.
- Garvey EP *et al.* (1997). *J Biol Chem* **272**: 4959–4963.
- Kim NN *et al.* (2001). *Biochemistry* **40**: 2678–2688.
- Mayer B, Hemmens B (1997). *Trends Biochem Sci* **22**: 477–481.
- Moore WM *et al.* (1994). *J Med Chem* **37**: 3886–3888.
- Tenu JP *et al.* (1999). *Nitric Oxide* **3**: 427–438.

# Carboxylases and decarboxylases

**Carboxylases:** The carboxylases allow the production of new carbon-carbon bonds by introducing  $\text{HCO}_3^-$  or  $\text{CO}_2$  into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K (EC 4.1.1.-).

Nomenclature	Pyruvate carboxylase	Acetyl-CoA carboxylase	Propionyl-CoA carboxylase	$\gamma$ -Glutamyl carboxylase
E.C.	6.4.1.1	6.4.1.2	6.4.1.3	4.1.1.90
Preferred abbreviation	PC	ACC1, ACC2	PCCA, PCCB	GGCX
Ensembl ID	ENSG0000017359	ENSG00000132142, ENSG00000076555	ENSG00000175198 ENSG00000114054	ENSG00000115486
Other names	PCB	ACACA, ACC $\alpha$ ; ACACB, ACC $\beta$	PCC $\alpha$ , PCC $\beta$	–
Cofactors	Biotin	Biotin	Biotin	Vitamin K, NADPH
Substrate(s)	Pyruvate, ATP	Acetyl-CoA, ATP	Propionyl-CoA, ATP	Glutamyl peptides
Product(s)	Oxaloacetate, ADP, P <sub>i</sub>	Malonyl-CoA, ADP, P <sub>i</sub>	Methylmalonyl-CoA, ADP, P <sub>i</sub>	Carboxyglutamyl (Gla) peptides
Selective inhibitors	–	TOFA (Loftus <i>et al.</i> , 2000)	–	–

Citrate and other dicarboxylic acids are able to activate ACC1/ACC2 activity allosterically. PCC is able to function in forward and reverse modes as a ligase (carboxylase) or lyase (decarboxylase) activity, respectively. Loss-of-function mutations in GGXX are associated with clotting disorders.

**Decarboxylases:** The decarboxylases generate  $\text{CO}_2$  and the indicated products from acidic substrates, requiring pyridoxal phosphate (ADC, AADC, GAD, HDC, ODC and PSDC) or pyruvate (SAMDC and PSDC) as a co-factor.

Nomenclature	S-Adenosylmethionine decarboxylase	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Glutamic acid decarboxylase
E.C.	4.1.1.50	4.1.1.19	4.1.1.28	4.1.1.15
Preferred abbreviation	SAMDC	ADC	AADC	GAD
Ensembl ID	ENSG00000123505	ENSG00000142920	ENSG00000132437	ENSG00000128683, ENSG00000136750
Other names	–	Ornithine decarboxylase-like protein (Zhu <i>et al.</i> , 2004)	DOPA decarboxylase (DDC), 5-hydroxytryptophan decarboxylase	GAD1 (GAD65), GAD2 (GAD67)
Substrate(s)	S-Adenosylmethionine	L-Arginine	DOPA, L-tryptophan, 5-hydroxy-L-tryptophan	L-Glutamate, L-aspartate
Product(s)	5'-Deoxyadenosyl-(3-aminopropyl) methylsulfonium	Agmatine	5-Hydroxytryptophan, dopamine	GABA

The presence of a functional ADC activity in human tissues has been questioned (Coleman *et al.*, 2004). *s*-Allylglycine is also an inhibitor of SAMDC (Pajunen *et al.*, 1979).

Nomenclature	Histidine decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase
E.C.	4.1.1.22	4.1.1.9	4.1.1.17	4.1.1.65
Preferred abbreviation	HDC	MLYCD	ODC	PSDC
Ensembl ID	ENSG00000140287	ENSG00000103150	ENSG00000115758	ENSG00000100141
Substrate(s)	L-Histidine	Malonyl-CoA	L-Ornithine	Phosphatidylserine
Product	Histamine	Acetyl-CoA	Putrescine	Phosphatidylethanolamine
Selective inhibitors	FMH (Garbarg <i>et al.</i> , 1980)	AMP-activated protein kinase-evoked phosphorylation (Saha <i>et al.</i> , 2000)	DFMO, APA	–
Selective inhibitors	SAM486A (8.0; Stanek <i>et al.</i> , 1993), AMA	–	Benserazide, carbidopa, 3-hydroxybenzylhydrazine, L- $\alpha$ -methyl-dopa	<i>s</i> -Allylglycine



The activity of ODC is regulated by the presence of an antizyme (ENSF0000002504) and an ODC antizyme inhibitor (ENSF0000002504).

**Abbreviations:** **AMA**, S-(5'-deoxy-5'-adenosyl)-methylthioethyl-hydroxylamine; **APA**, 1-aminooxy-3-aminopropane; **DFMO**,  $\alpha$ -difluoromethyl-L-ornithine, also known as eflornithine; **FMH**,  $\alpha$ -fluoromethylhistidine; **SAM**, S-adenosylmethionine; **SAM486A**, 1-guanidinoimino-2,3-dihydroindene-4-carboximidamide, also known as CGP48664; **TOFA**, 5-(tetradecyloxy)-2-furancarboxylic acid

### Further Reading

- Akbarian S, Huang HS (2006). Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. *Brain Res Rev* **52**: 293–304.
- Bale S, Ealick SE (2010). Structural biology of S-adenosylmethionine decarboxylase. *Amino Acids* **38**: 451–460.
- Brownsey RW, Boone AN, Elliott JE, Kulpa JE, Lee WM (2006). Regulation of acetyl-CoA carboxylase. *Biochem Soc Trans* **34**: 223–227.
- Elmets CA, Athar M (2010). Targeting ornithine decarboxylase for the prevention of nonmelanoma skin cancer in humans. *Cancer Prev Res (Phila)* **3**: 8–11.
- Jitrapakdee S, St MM, Rayment I, Cleland WW, Wallace JC, Attwood PV (2008). Structure, mechanism and regulation of pyruvate carboxylase. *Biochem J* **413**: 369–387.
- Jitrapakdee S, Vidal-Puig A, Wallace JC (2006). Anaplerotic roles of pyruvate carboxylase in mammalian tissues. *Cell Mol Life Sci* **63**: 843–854.
- Marin-Valencia I, Roe CR, Pascual JM (2010). Pyruvate carboxylase deficiency: mechanisms, mimics and anaplerosis. *Mol Genet Metab* **101**: 9–17.
- Moya-Garcia AA, Pino-Angeles A, Gil-Redondo R, Morreale A, Sanchez-Jimenez F (2009). Structural features of mammalian histidine decarboxylase reveal the basis for specific inhibition. *Br J Pharmacol* **157**: 4–13.
- Pegg AE (2006). Regulation of ornithine decarboxylase. *J Biol Chem* **281**: 14529–14532.
- Pegg AE (2009). S-Adenosylmethionine decarboxylase. *Essays Biochem* **46**: 25–45.
- Saggerson D (2008). Malonyl-CoA, a key signaling molecule in mammalian cells. *Annu Rev Nutr* **28**: 253–272.
- Smith KJ, Skelton H (2006).  $\alpha$ -Difluoromethylornithine, a polyamine inhibitor: its potential role in controlling hair growth and in cancer treatment and chemo-prevention. *Int J Dermatol* **45**: 337–344.
- Tong L, Harwood HJ Jr. (2006). Acetyl-coenzyme A carboxylases: versatile targets for drug discovery. *J Cell Biochem* **99**: 1476–1488.
- Wolfgang MJ, Lane MD (2006). The role of hypothalamic malonyl-CoA in energy homeostasis. *J Biol Chem* **281**: 37265–37269.

### References

- Coleman CS *et al.* (2004). *Biochem J* **379**: 849–855.
- Garbarg M *et al.* (1980). *J Neurochem* **35**: 1045–1052.
- Loftus TM *et al.* (2000). *Science* **288**: 2379–2381.
- Pajunen AE *et al.* (1979). *J Neurochem* **32**: 1401–1408.
- Saha AK *et al.* (2000). *J Biol Chem* **275**: 24279–24283.
- Stanek J *et al.* (1993). *J Med Chem* **36**: 2168–2171.
- Zhu MY *et al.* (2004). *Biochim Biophys Acta* **1670**: 156–164.

# Cyclic nucleotide turnover

**Overview:** cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases, see page S310), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN, see Pages S153 & S156) and guanine nucleotide exchange factors (GEFs, Epac).

## Adenylyl cyclases (E.C. 4.6.1.1)

**Overview:** Adenylyl cyclase (ENSG00000000188) converts 5'-ATP to 3',5'-adenosine monophosphate and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, Premont *et al.*, 1996) and  $G\alpha_s$  (the stimulatory G protein  $\alpha$  subunit, see Page S5). Adenosine and its derivatives (e.g. 2',5'-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity (Tesmer *et al.*, 2000). Three families of adenylyl cyclase are distinguishable:  $Ca^{2+}$ /CaM-stimulated (AC1, AC3 and AC8),  $Ca^{2+}$ -inhibitable (AC5 and AC6) and  $Ca^{2+}$ -insensitive (AC2, AC4 and AC7) forms.

Nomenclature	AC1	AC2	AC3	AC4	AC5
Ensembl ID	ENSG00000164742	ENSG00000078295	ENSG00000138031	ENSG00000129467	ENSG00000173175
Other names	AC I	AC II, HBCA2	AC III, olfactory type	AC IV	AC V
Endogenous activators	$Ca^{2+}$ /CaM (Tang <i>et al.</i> , 1991), PKC-evoked phosphorylation (Jacobowitz <i>et al.</i> , 1993)	$G\beta\gamma$ (Taussig <i>et al.</i> , 1993), PKC-evoked phosphorylation (Chen and Iyengar, 1993; Lustig <i>et al.</i> , 1993)	$Ca^{2+}$ /CaM (Choi <i>et al.</i> , 1992), PKC-evoked phosphorylation (Jacobowitz <i>et al.</i> , 1993)	$G\beta\gamma$ (Gao and Gilman, 1991)	PKC-evoked phosphorylation (Kawabe <i>et al.</i> , 1994)
Endogenous inhibitors	$G\alpha_i$ (Taussig <i>et al.</i> , 1994), $G\alpha_o$ (Taussig <i>et al.</i> , 1994), $G\beta\gamma$ (Taussig <i>et al.</i> , 1993)	–	$G\alpha_i$ (Taussig <i>et al.</i> , 1994), RGS2 (Sinnarajah <i>et al.</i> , 2001), CaM kinase II-evoked phosphorylation (Wayman <i>et al.</i> , 1995)	PKC-evoked phosphorylation (Zimmermann and Taussig, 1996)	$G\alpha_i$ (Taussig <i>et al.</i> , 1994), $Ca^{2+}$ (Ishikawa <i>et al.</i> , 1992), PKA-evoked phosphorylation (Iwami <i>et al.</i> , 1995)
Selective inhibitors	–	–	–	–	NKY80 (Onda <i>et al.</i> , 2001)

Nomenclature	AC6	AC7	AC8	AC9
Ensembl ID	ENSG00000174233	ENSG00000121281	ENSG00000155897	ENSG00000162104
Other names	AC VI, $Ca^{2+}$ -inhibitable cyclase	AC VII	AC VIII	AC IX
Endogenous activators	–	PKC-evoked phosphorylation (Watson <i>et al.</i> , 1994)	$Ca^{2+}$ (Cali <i>et al.</i> , 1994)	–
Endogenous inhibitors	$G\alpha_i$ (Taussig <i>et al.</i> , 1994), $Ca^{2+}$ (Yoshimura and Cooper, 1992), PKA-evoked phosphorylation (Chen <i>et al.</i> , 1997), PKC-evoked phosphorylation (Lai <i>et al.</i> , 1999)	–	–	$Ca^{2+}$ /calcineurin (Paterson <i>et al.</i> , 2000)

Nitric oxide has been proposed to inhibit AC5 and AC6 selectively (Hill *et al.*, 2000), although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (ENSG00000143199, Buck *et al.*, 1999), unaffected by either  $G\alpha$  or  $G\beta\gamma$  subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor (Chen *et al.*, 2000).

## Soluble guanylyl cyclase (E.C. 4.6.1.2)

**Overview:** Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)) is a heterodimer comprising  $\alpha$  and  $\beta$  chains, both of which have two subtypes in man (predominantly  $\alpha 1\beta 1$ ; see Zabel *et al.*, 1998). A haem group is associated with the  $\beta$  chain and is the target for the endogenous ligand nitric oxide (NO $\bullet$ ), and, potentially, carbon monoxide (Friebe *et al.*, 1996). The enzyme converts guanosine-5'-triphosphate (GTP) to the intracellular second messenger 3',5'-guanosine monophosphate (cGMP).

Nomenclature	Soluble guanylyl cyclase
Preferred abbreviation	sGC
Ensembl ID	$\alpha 1$ ENSG00000164116; $\alpha 2$ ENSG00000152402; $\beta 1$ ENSG00000061918; $\beta 2$ ENSG00000123201
Selective activators	NO•, YC1 (Friebe <i>et al.</i> , 1996), BAY412272 (Stasch <i>et al.</i> , 2001), cinaciguat (Stasch <i>et al.</i> , 2002), riociguat (Stasch <i>et al.</i> , 2002), ataciguat (Schindler <i>et al.</i> , 2006)
Selective inhibitors	ODQ (7.5; Garthwaite <i>et al.</i> , 1995)

ODQ also shows activity at other haem-containing proteins (Feelisch *et al.*, 1999), while YC1 may also inhibit cGMP-hydrolysing phosphodiesterases (Friebe *et al.* 1998; Galle *et al.*, 1999).

### Exchange protein activated by cyclic AMP (Epac)

**Overview:** Epacs are members of a family of guanine nucleotide exchange factors (ENSM0025000000899), which also includes RapGEF5 (GFR, KIAA0277, MR-GEF, ENSG00000136237) and RapGEFL1 (Link-GEFII, ENSG00000108352). They are activated endogenously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2'-O-Me-cAMP (Enserink *et al.*, 2002). Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of GTP in place of GDP, leading to activation of phospholipase C (Schmidt *et al.*, 2001) (see Page S302).

Nomenclature	Ensembl ID	Other names
Epac1	ENSG00000079337	RapGEF3, bcm910, cAMP-GEFI
Epac2	ENSG00000091428	RapGEF4, cAMP-GEFII, CGEF2

### Phosphodiesterases, 3',5'-cyclic nucleotide (E.C.3.1.4.17)

**Overview:** 3',5'-Cyclic nucleotide phosphodiesterases (PDEs, 3',5'-cyclic-nucleotide 5'-nucleotidohydrolase) catalyse the hydrolysis of a 3',5'-cyclic nucleotide (usually cyclic AMP or cyclic GMP). IBMX is a nonselective inhibitor with an IC<sub>50</sub> value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2',3'-cyclic nucleotide 3'-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

Nomenclature	PDE1A	PDE1B	PDE1C	PDE2A
Ensembl ID	ENSG00000115252	ENSG00000123360	ENSG00000154678	SwissProt O00408
Other names	PDE I	PDE I	PDE I	PDE II, cGMP-stimulated cAMP-PDE, CGS-PDE
Rank order of affinity	cGMP > cAMP	cGMP > cAMP	cGMP = cAMP	cAMP >> cGMP
Activators	Ca <sup>2+</sup> /CaM	Ca <sup>2+</sup> /CaM	Ca <sup>2+</sup> /CaM	cGMP
Selective inhibitors	SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), vinpocetine (5.1, Loughney <i>et al.</i> , 1996)	SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996)	SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), vinpocetine (4.3, Loughney <i>et al.</i> , 1996)	BAY607550 (8.3–8.8, Boess <i>et al.</i> , 2004), EHNA (5.3, Michie <i>et al.</i> , 1996)

PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4) (see Page S280).

Nomenclature	PDE3A	PDE3B
Ensembl ID	ENSG00000172572	ENSG00000152270
Other names	PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE A	PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE B
Selective inhibitors	Cilostamide (7.5, Sudo <i>et al.</i> , 2000), milrinone (6.3, Sudo <i>et al.</i> , 2000), cGMP	Cilostamide (7.3, Sudo <i>et al.</i> , 2000), milrinone (6.0, Sudo <i>et al.</i> , 2000), cGMP

PDE3A and PDE3B are membrane-bound.

Nomenclature	PDE4A	PDE4B	PDE4C	PDE4D
Ensembl ID	ENSG00000065989	ENSG00000184588	ENSG00000105650	ENSG00000113448
Other names	PDE IV	PDE IV	PDE IV	PDE IV
Rank order of affinity	cAMP >> cGMP	cAMP >> cGMP	cAMP >> cGMP	cAMP >> cGMP
Activators	–	–	–	PKA-mediated phosphorylation (Houslay and Adams, 2003)
Selective inhibitors	Rolipram (9.0, Wang <i>et al.</i> , 1997), YM976 (8.3, Aoki <i>et al.</i> , 2000), Ro201724 (6.5, Wang <i>et al.</i> , 1997)	Rolipram (9.0, Wang <i>et al.</i> , 1997), Ro201724 (6.4, Wang <i>et al.</i> , 1997)	Rolipram (6.5, Wang <i>et al.</i> , 1997), Ro201724 (5.4, Wang <i>et al.</i> , 1997)	Rolipram (7.2, Wang <i>et al.</i> , 1997), Ro201724 (6.2, Wang <i>et al.</i> , 1997)

PDE4 isoforms are essentially cAMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation (Hoffmann *et al.*, 1998; Hoffmann *et al.*, 1999). PDE4A–D splice variants can be membrane-bound or cytosolic (Houslay and Adams, 2003). PDE4 isoforms may be labelled with [<sup>3</sup>H]-rolipram.

Nomenclature	PDE5A	PDE7A	PDE7B	PDE8A	PDE8B
Ensembl ID	ENSG00000138735	ENSG00000104732	ENSG00000171408	ENSG00000073417	ENSG00000113231
Other names	PDE V, cGMP-specific PDE	HCP1	–	High-affinity cAMP-specific and IBMX-insensitive PDE	–
Rank order of affinity	cGMP > cAMP	cAMP >> cGMP (Michaeli <i>et al.</i> , 1993)	cAMP >> cGMP (Gardner <i>et al.</i> , 2000)	cAMP >> cGMP (Fisher <i>et al.</i> , 1998a)	cAMP >> cGMP (Hayashi <i>et al.</i> , 1998)
Activators	PKA (Corbin <i>et al.</i> , 2000), PKG (Corbin <i>et al.</i> , 2000)	–	–	–	–
Selective inhibitors	T0156 (9.5, Mochida <i>et al.</i> , 2002), sildenafil (9.0, Turko <i>et al.</i> , 1999), SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), zaprinast (6.8, Turko <i>et al.</i> , 1999)	BRL50481 (6.7, Smith <i>et al.</i> , 2004)	Dipyridamole (5.7–6.0, Gardner <i>et al.</i> , 2000; Sasaki <i>et al.</i> , 2000), SCH51866 (5.8, Sasaki <i>et al.</i> , 2000)	Dipyridamole (5.1, Fisher <i>et al.</i> , 1998a)	Dipyridamole (4.3, Hayashi <i>et al.</i> , 1998)

PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively. BRL50481 appears not to have been examined as an inhibitor of PDE7B.

Nomenclature	PDE9A	PDE10A	PDE11A
Ensembl ID	ENSG00000160191	ENSG00000112541	ENSG00000128655
Substrate specificity	cGMP >> cAMP (Fisher <i>et al.</i> , 1998b)	cAMP, cGMP (Fujishige <i>et al.</i> , 1999)	cAMP, cGMP (Fawcett <i>et al.</i> , 2000)
Selective inhibitors	SCH51866 (5.8, Fisher <i>et al.</i> , 1998b), zaprinast (4.5, Fisher <i>et al.</i> , 1998b)	–	–

Nomenclature	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
Ensembl ID	ENSG00000132915	ENSG00000133256	ENSG00000095464	ENSG00000156973	ENSG00000185527	ENSG00000139053
Other names	cGMP-PDE $\alpha$ , PDE V-b1	cGMP-PDE $\beta$	cGMP-PDE $\alpha$ , PDEA2	cGMP-PDE $\delta$	cGMP-PDE $\gamma$	cGMP-PDE $\gamma$

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cGMP specific and is activated by the  $\alpha$ -subunit of transducin ( $G\alpha_t$ , see Page 55) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

**Abbreviations:** BAY412272, 5-cyclopropyl-2-[1-(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-pyrimidin-4-ylamine); BAY607550, 2-(3,4-dimethoxybenzyl)-7-[(1R)-1-[(1R)-1-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one; BRL50481, 5-nitro-2,N,N-trimethylbenzenesulfonamide; CaM, calmodulin; EHNA, *erythro*-9-(2-hydroxy-3-nonyl)adenine; NKH477, 6-(3-dimethylaminopropionyl) forskolin hydrochloride; NKY80, 2-amino-7-(2-furanyl)-7,8-dihydro-5(6H)-quinazolinone; ODO, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one;

PKA, protein kinase A or cyclic AMP-dependent protein kinase; PKC, protein kinase C; PKG, protein kinase G or cyclic GMP-dependent protein kinase; RGS2, Regulator of G-protein signalling 2 (ENSG00000116741); Ro201724, 4-(3-butoxy-4-methoxyphenyl)methyl-2-imidazolidone; SCH51866, *cis*-5,6a,7,8,9,9a-hexahydro-2-(4-[trifluoromethyl]phenylmethyl)-5-methyl-cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one; YC1, 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole; YM976, (4-[3-chlorophenyl]-1,7-diethylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one);

### Further Reading

- Borland G, Smith BO, Yarwood SJ (2009). EPAC proteins transduce diverse cellular actions of cAMP. *Br J Pharmacol* **158**: 70–86.
- Cerra MC, Pellegrino D (2007). Cardiovascular cGMP-generating systems in physiological and pathological conditions. *Curr Med Chem* **14**: 585–599.
- Cheng X, Ji Z, Tsalkova T, Mei F (2008). Epac and PKA: a tale of two intracellular cAMP receptors. *Acta Biochim Biophys Sin (Shanghai)* **40**: 651–662.
- Feldman RD, Gros R (2007). New insights into the regulation of cAMP synthesis beyond GPCR/G protein activation: implications in cardiovascular regulation. *Life Sci* **81**: 267–271.
- Gloerich M, Bos JL (2010). Epac: defining a new mechanism for cAMP action. *Annu Rev Pharmacol Toxicol* **50**: 355–375.
- Grandoch M, Roscioni SS, Schmidt M (2007). The role of Epac proteins, novel cAMP mediators, in the regulation of immune, lung and neuronal function. *Br J Pharmacol* **159**: 265–284.
- Holz GG, Chepurny OG, Schwede F (2008). Epac-selective cAMP analogs: new tools with which to evaluate the signal transduction properties of cAMP-regulated guanine nucleotide exchange factors. *Cell Signal* **20**: 10–20.
- Jackson EB, Mukhopadhyay S, Tulis DA (2007). Pharmacologic modulators of soluble guanylate cyclase/cyclic guanosine monophosphate in the vascular system – from bench top to bedside. *Curr Vasc Pharmacol* **5**: 1–14.
- Metrich M, Berthouze M, Morel E, Crozatier B, Gomez AM, Lezoualc'h F (2010). Role of the cAMP-binding protein Epac in cardiovascular physiology and pathophysiology. *Pflugers Arch* **459**: 535–546.
- Roscioni SS, Elzinga CRS, Schmidt M (2008). Epac: effects and biological functions. *Naunyn-Schmiedeberg's Arch Pharmacol* **377**: 345–357.
- Schmidt M, Sand C, Jakobs KH, Michel MC, Oude Weernink PA (2007). Epac and the cardiovascular system. *Curr Opin Pharmacol* **7**: 193–200.
- Willoughby D, Cooper DMF (2007). Organization and Ca<sup>2+</sup> regulation of adenylyl cyclases in cAMP microdomains. *Physiol Rev* **87**: 965–1010.

### References

- Aoki M *et al.* (2000). *J Pharmacol Exp Ther* **295**: 255–260.
- Boess FG *et al.* (2004). *Neuropharmacology* **47**: 1081–1092.
- Buck J *et al.* (1999). *Proc Natl Acad Sci U S A* **96**: 79–84.
- Cali JJ *et al.* (1994). *J Biol Chem* **269**: 12190–12195.
- Chen JQ, Iyengar R (1993). *J Biol Chem* **268**: 12253–12256.
- Chen Y *et al.* (1997). *Proc Natl Acad Sci U S A* **94**: 14100–14104.
- Chen Y *et al.* (2000). *Science* **289**: 625–628.
- Choi EJ *et al.* (1992). *Biochemistry* **31**: 6492–6498.
- Corbin JD *et al.* (2000). *Eur J Biochem* **267**: 2760–2767.
- Enserink JM *et al.* (2002). *Nat Cell Biol* **4**: 901–906.
- Fawcett L *et al.* (2000). *Proc Natl Acad Sci U S A* **97**: 3702–3707.
- Feelisch M *et al.* (1999). *Mol Pharmacol* **56**: 243–253.
- Fisher DA *et al.* (1998a). *Biochem Biophys Res Commun* **246**: 570–577.
- Fisher DA *et al.* (1998b). *J Biol Chem* **273**: 15559–15564.
- Friebe A *et al.* (1996). *EMBO J* **15**: 6863–6868.
- Friebe A *et al.* (1998). *Mol Pharmacol* **54**: 962–967.
- Fujishige K *et al.* (1999). *J Biol Chem* **274**: 18438–18445.
- Galle J *et al.* (1999). *Br J Pharmacol* **127**: 195–203.
- Gao BN, Gilman AG (1991). *Proc Natl Acad Sci U S A* **88**: 10178–10182.
- Gardner C *et al.* (2000). *Biochem Biophys Res Commun* **272**: 186–192.
- Garthwaite J *et al.* (1995). *Mol Pharmacol* **48**: 184–188.
- Hayashi M *et al.* (1998). *Biochem Biophys Res Commun* **250**: 751–756.
- Hill J *et al.* (2000). *Cell Signal* **12**: 233–237.
- Hoffmann R *et al.* (1998). *Biochem J* **333**: 139–149.
- Hoffmann R *et al.* (1999). *EMBO J* **18**: 893–903.
- Houslay MD, Adams DR (2003). *Biochem J* **370**: 1–18.
- Ishikawa Y *et al.* (1992). *J Biol Chem* **267**: 13553–13557.
- Iwami G *et al.* (1995). *J Biol Chem* **270**: 12481–12484.
- Jacobowitz O *et al.* (1993). *J Biol Chem* **268**: 3829–3832.
- Kawabe J-I *et al.* (1994). *J Biol Chem* **269**: 16554–16558.
- Lai H-L *et al.* (1999). *Mol Pharmacol* **56**: 644–650.
- Loughney K *et al.* (1996). *J Biol Chem* **271**: 796–806.
- Lustig KD *et al.* (1993). *J Biol Chem* **268**: 13900–13905.
- Michaeli T *et al.* (1993). *J Biol Chem* **268**: 12925–12932.
- Michie AM *et al.* (1996). *Cell Signal* **8**: 97–110.
- Mochida H *et al.* (2002). *Eur J Pharmacol* **456**: 91–98.
- Onda T *et al.* (2001). *J Biol Chem* **276**: 47785–47793.
- Paterson JM *et al.* (2000). *J Neurochem* **75**: 1358–1367.
- Premont RT *et al.* (1996). *J Biol Chem* **271**: 13900–13907.
- Sasaki T *et al.* (2000). *Biochem Biophys Res Commun* **271**: 575–583.
- Schindler U *et al.* (2006). *Mol Pharmacol* **69**: 1260–1268.
- Schmidt M *et al.* (2001). *Nat Cell Biol* **3**: 1020–1024.
- Sinnarajah S *et al.* (2001). *Nature* **409**: 1051–1055.
- Smith SJ *et al.* (2004). *Mol Pharmacol* **66**: 1679–1689.
- Stasch JP *et al.* (2001). *Nature* **410**: 212–215.
- Stasch JP *et al.* (2002). *Br J Pharmacol* **136**: 773–783.
- Sudo T *et al.* (2000). *Biochem Pharmacol* **59**: 347–356.
- Tang WJ *et al.* (1991). *J Biol Chem* **266**: 8595–8603.
- Taussig R *et al.* (1993). *J Biol Chem* **268**: 9–12.
- Taussig R *et al.* (1994). *J Biol Chem* **269**: 6093–6100.
- Tesmer JJ *et al.* (2000). *Biochemistry* **39**: 14464–14471.
- Turko IV *et al.* (1999). *Mol Pharmacol* **56**: 124–130.
- Vemulapalli S *et al.* (1996). *J Cardiovasc Pharmacol* **28**: 862–869.
- Wang P *et al.* (1997). *Biochem Biophys Res Commun* **234**: 320–324.
- Watson PA *et al.* (1994). *J Biol Chem* **269**: 28893–28898.
- Wayman GA *et al.* (1995). *J Biol Chem* **270**: 21480–21486.
- Yoshimura M, Cooper DM (1992). *Proc Natl Acad Sci U S A* **89**: 6716–6720.
- Zabel U (1998). *Biochem J* **335**: 51–57.
- Zimmermann G, Taussig R (1996). *J Biol Chem* **271**: 27161–27166.

# Cytochrome P450 (E.C. 1.14.-.-)

**Overview:** the cytochrome P450 enzyme family (CYP450) were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not mediate metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extrahepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration.

## CYP1 family (ENSMF0025000000349) (E.C. 1.14.1.1)

Nomenclature	Ensembl ID	Other names	Comments
CYP1A1	ENSG00000140465	Aryl hydrocarbon hydroxylase, CP11, CYP1, P1-450, P450-C, P450DX	-
CYP1A2	ENSG00000140505	Phenacetin O-deethylase, CP12, P3-450	-
CYP1B1	ENSG00000138061	CP1B, GLC3A	Mutations have been associated with primary congenital glaucoma (Stoilov <i>et al.</i> , 1997)

## CYP2 family (ENSMF00400000131704, ENSMF00400000131705, ENSMF00550000747662)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP2A6/2A7	1.14.14.1	ENSG00000198077	Coumarin 7-hydroxylase, CPA6, CYP2A, CYP2A3, CYP2A, CYPIIA7, P450-IIA4	Metabolises nicotine
CYP2A13	1.14.14.1	ENSG00000197838	CYPIIA13	-
CYP2B6	1.14.14.1	ENSG00000197408	CYPIIB6, P450 IIB1	-
CYP2C8	1.14.14.1	ENSG00000138115	CYPIIC8, P450 form 1, P450 MP-12/MP-20, P450 IIC2, S-mephenytoin 4-hydroxylase	-
CYP2C9	1.14.13.80, 1.14.13.48, 1.14.13.49	ENSG00000138109	(R)-Limonene 6-monooxygenase, (S)-limonene 6-monooxygenase, (S)-limonene 7-monooxygenase, CYPIIC9, P450 PB-1, P450 MP-4/MP-8, S-mephenytoin 4-hydroxylase, P-450MP	-
CYP2C18	1.14.14.1	ENSG00000108242	CYPIIC18, P450-6B/29C	-
CYP2C19	1.14.13.80, 1.14.13.48, 1.14.13.49	ENSG00000165841	(R)-limonene 6-monooxygenase, (S)-limonene 6-monooxygenase, (S)-limonene 7-monooxygenase, CYPIIC19, P450-11A, mephenytoin 4-hydroxylase, CYPIIC17, P450-254C	-
CYP2D6	1.14.14.1	ENSG00000100197	Debrisoquine 4-hydroxylase, CYPIID6, P450-DB1	-
CYP2E1	1.14.14.1	ENSG00000130649	CYPIIE1, P450-J	-
CYP2F1	1.14.14.1	ENSG00000197446	CYPIIF1	-
CYP2J2	1.14.14.1	ENSG00000134716	Arachidonic acid epoxygenase, CYPIIJ2	-
CYP2R1	1.14.13.15	ENSG00000186104	Vitamin D 25-hydroxylase	-
CYP2S1	1.14.14.1	ENSG00000167600	CYPIIS1	-
CYP2U1	1.14.14.1	ENSG00000155016		-
CYP2W1	1.14.14.-	ENSG00000073067	CYPIIW1	-

CYP2A7P1 (ENSG00000213908), CYP2D7P1 (ENSG00000205702), CYP2G1P (ENSG00000130612) and AC008537.5-2 (ENSG00000198251, fragment) are uncharacterized potential pseudogenes from the same families.

## CYP3 family (ENSMF00310000088994)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP3A4	1.14.13.67, 1.14.13.97, 1.14.13.32	ENSG00000160868	Quinine 3-monooxygenase, CYP3A4, Nifedipine oxidase, CYP4503A3, CYP3A3, HLP, taurochenodeoxycholate 6- $\alpha$ -hydroxylase, NF-25, P450-PCN1, albendazole monooxygenase, albendazole sulfoxidase	Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents
CYP3A5	1.14.14.1	ENSG00000106258	CYP3A5, P450-PCN3, HLP2	–
CYP3A7	1.14.14.1	ENSG00000160870	CYP3A7, P450-HFLA	–
CYP3A43	1.14.14.1	ENSG00000021461	Cytochrome P450 3A43	–

## CYP4 family (ENSMF00400000131716, ENSMF00400000131707)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP4A11	1.14.15.3	ENSG00000187048	CYP4A11, lauric acid $\omega$ -hydroxylase, fatty acid $\omega$ -hydroxylase, P-450 HK $\omega$ , CYP4A11, P450-HL- $\omega$ , 20-hydroxyeicosatetraenoic acid synthase, 20-HETE synthase	–
CYP4A22	1.14.15.3	ENSG00000162365	CYP4A22, lauric acid $\omega$ -hydroxylase, fatty acid $\omega$ -hydroxylase	–
CYP4B1	1.14.14.1	ENSG00000142973	CYP4B1, P450-HP	–
CYP4F2	1.14.13.30	ENSG00000186115	Leukotriene B <sub>4</sub> 20-monooxygenase 1, leukotriene B <sub>4</sub> $\omega$ -hydroxylase 1, CYP4F2, cytochrome P450-LTB- $\omega$	Responsible for $\omega$ -hydroxylation of leukotriene B <sub>4</sub> , lipoxin B <sub>4</sub> (Mizukami <i>et al.</i> , 1993) and tocopherols, including vitamin E (Sontag and Parker, 2002)
CYP4F3	1.14.13.30	ENSG00000186529	Leukotriene B <sub>4</sub> 20-monooxygenase 2, leukotriene B <sub>4</sub> $\omega$ -hydroxylase 2, CYP4F3, cytochrome P450-LTB- $\omega$	Responsible for $\omega$ -hydroxylation of leukotriene B <sub>4</sub> , lipoxin B <sub>4</sub> (Mizukami <i>et al.</i> , 1993) and polyunsaturated fatty acids (Harmon <i>et al.</i> , 2006; Fer <i>et al.</i> , 2008)
CYP4F8	1.14.14.1	ENSG00000186526	CYP4F8	–
CYP4F11	1.14.14.1	ENSG00000171903	CYP4F11	–
CYP4F12	1.14.14.1	ENSG00000186204	CYP4F12	–
CYP4F22	1.14.14.-	ENSG00000171954		–
CYP4V2	1.14.-.-	ENSG00000145476		–
CYP4X1	1.14.14.1	ENSG00000186377	CYP4X1	–
CYP4Z1	1.14.14.1	ENSG00000186160	CYP4Z1	–

AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12.

## CYP5, CYP7 and CYP8 families (ENSMF0025000001362)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP5A1	5.3.99.5	ENSG00000059377	Thromboxane synthase, TXA synthase, TBXA1, CYP5, THAS, TS, TXAS, TXS, TXS	Converts prostaglandin H <sub>2</sub> to thromboxane A <sub>2</sub> . Inhibited by dazoxiben (Randall <i>et al.</i> , 1981) and camonagrel (Gryglewski <i>et al.</i> , 1995)
CYP7A1	1.14.13.17	ENSG00000167910	Cholesterol 7- $\alpha$ -monooxygenase, cholesterol 7- $\alpha$ -hydroxylase, CYP7A1	–
CYP7B1	1.14.13.100	ENSG00000172817	Oxysterol 7- $\alpha$ -hydroxylase, 25-hydroxycholesterol 7- $\alpha$ -hydroxylase	–

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP8A1	5.3.99.4	ENSG00000124212	Prostaglandin I <sub>2</sub> synthase, PTGIS	Inhibited by tranlylcypromine (Gryglewski <i>et al.</i> , 1976)
CYP8B1	1.14.13.95	ENSG00000180432	7- $\alpha$ -Hydroxycholest-4-en-3-one 12- $\alpha$ -hydroxylase, CYPVIII B1, 7- $\alpha$ -hydroxy-4-cholesten-3-one 12- $\alpha$ -hydroxylase, sterol 12- $\alpha$ -hydroxylase	-

## CYP11 (ENSM00500000269868), CYP17, CYP19, CYP20 and CYP21 families

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP11A1	1.14.15.6	ENSG00000140459	Cholesterol side-chain cleavage enzyme, cholesterol desmolase, CYPXIA1, P450 <sub>sc</sub>	Converts cholesterol to pregnenolone
CYP11B1	1.14.15.4	ENSG00000160882	Steroid 11 $\beta$ -hydroxylase, CYPXIB1, P450C11, P-450c11	Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone (Watanuki <i>et al.</i> , 1978)
CYP11B2	1.14.15.4, 1.14.15.5	ENSG00000179142	Aldosterone synthase, ALDOS, CYPXIB2, P-450Aldo, aldosterone-synthesizing enzyme, steroid 18-hydroxylase, P-450C18	Converts corticosterone to aldosterone
CYP17A1	1.14.99.9	ENSG00000148795	Steroid 17- $\alpha$ -hydroxylase/17,20 lyase, CYPXVII, P450-C17, P450c17, steroid 17- $\alpha$ -monooxygenase	Converts pregnenolone and progesterone to 17 $\alpha$ -hydroxypregnenolone and 17 $\alpha$ -hydroxyprogesterone, respectively. Converts 17 $\alpha$ -hydroxypregnenolone and 17 $\alpha$ -hydroxyprogesterone to dehydroepiandrostandione and androstenedione, respectively. Converts corticosterone to cortisol
CYP19A1	1.14.14.1	ENSG00000137869	Aromatase, estrogen synthetase, P-450AROM, CYPXIX	Converts androstenedione and testosterone to estrone and estradiol, respectively. Inhibited by anastrozole (Plourde <i>et al.</i> , 1994) and letrozole (Bhatnagar <i>et al.</i> , 1990)
CYP20A1	1.14.-.-	ENSG00000119004	CYP-M	-
CYP21A2	1.14.99.10	ENSG00000198457	Steroid 21-hydroxylase, cytochrome P450 XXI, 21-OHase, P450-C21, P-450c21, P450-C21B	Converts progesterone and 17 $\alpha$ -hydroxyprogesterone to deoxycortisone and 11-deoxycortisone, respectively

## CYP24, CYP26 and CYP27 families (ENSM00500000269772, ENSFM00250000002048)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP24A1	1.14.13.n4	ENSG00000019186	1,25-Dihydroxyvitamin D <sub>3</sub> 24-hydroxylase, vitamin D <sub>3</sub> 24-hydroxylase, 24-OHase, P450-CC24	-
CYP26A1	1.14.-.-	ENSG00000095596	Retinoic acid-metabolizing cytochrome, P450 retinoic acid-inactivating 1, P450RAI, retinoic acid 4-hydroxylase	Inhibited by liarozole
CYP26B1	1.14.-.-	ENSG00000003137	Retinoic acid-metabolizing cytochrome, P450 retinoic acid-inactivating 2, P450RAI-2, P450 26A2	-
CYP26C1	1.14.-.-	ENSG00000187553	-	-
CYP27A1	1.14.13.15	ENSG00000135929	Sterol 26-hydroxylase, cytochrome P-450C27/25, sterol 27-hydroxylase, vitamin D <sub>3</sub> 25-hydroxylase, 5- $\beta$ -cholestane-3- $\alpha$ ,7- $\alpha$ ,12- $\alpha$ -triol 27-hydroxylase	-



Nomenclature	EC	Ensembl ID	Other names	Comments
CYP27B1	1.14.13.13	ENSG00000111012	25-hydroxyvitamin D-1 $\alpha$ hydroxylase, cytochrome P450 subfamily XXVIIIB polypeptide 1, calcidiol 1-monoxygenase, 25-OHD-1 $\alpha$ -hydroxylase, 25-hydroxyvitamin D <sub>3</sub> 1- $\alpha$ -hydroxylase, VD3 1A hydroxylase, P450C1 $\alpha$ , P450VD1- $\alpha$	–
CYP27C1	1.14.-.-	ENSG00000186684	–	–

### CYP39, CYP46 and CYP51 families

Nomenclature	EC	Ensembl ID	Other names
CYP39A1	1.14.13.99	ENSG00000146233	Oxysterol 7- $\alpha$ -hydroxylase, 24-hydroxycholesterol 7- $\alpha$ -hydroxylase
CYP46A1	1.14.13.98	ENSG00000036530	Cholesterol 24-hydroxylase, CH24H
CYP51A1		ENSG00000001630	Lanosterol 14- $\alpha$ -demethylase, leucine-rich repeat and death domain-containing protein LOC401387, CP51, CYP51, CYPL1, LDM, P450-14 DM, P450L1

### Further Reading

- Cipollone F, Cicolini G, Bucci M (2008). Cyclooxygenase and prostaglandin synthases in atherosclerosis: recent insights and future perspectives. *Pharmacol Ther* **118**: 161–180.
- Fleming I (2008). Vascular cytochrome P450 enzymes: physiology and pathophysiology. *Trends Cardiovasc Med* **18**: 20–25.
- Haining RL, Nichols-Haining M (2007). Cytochrome P450-catalyzed pathways in human brain: metabolism meets pharmacology or old drugs with new mechanism of action? *Pharmacol Ther* **113**: 537–545.
- Hisaka A, Ohno Y, Yamamoto T, Suzuki H (2010). Prediction of pharmacokinetic drug-drug interaction caused by changes in cytochrome P450 activity using in vivo information. *Pharmacol Ther* **125**: 230–248.
- Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C (2007). Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoeigenetic and clinical aspects. *Pharmacol Ther* **116**: 496–526.
- Johnson WW (2008). Cytochrome P450 inactivation by pharmaceuticals and phytochemicals: therapeutic relevance. *Drug Metab Rev* **40**: 101–147.
- Johnston JB, Ouellet H, Podust LM, Ortiz de Montellano PR (2011). Structural control of cytochrome P450-catalyzed  $\omega$ -hydroxylation. *Arch Biochem Biophys* **507**: 86–94.
- Kirchheiner J, Seeringer A (2007). Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. *Biochim Biophys Acta* **1770**: 489–494.
- Laursen T, Jensen K, Moller BL (2011). Conformational changes of the NADPH-dependent cytochrome P450 reductase in the course of electron transfer to cytochromes P450. *Biochim Biophys Acta* **1814**: 132–138.
- Omura T (2010). Structural diversity of cytochrome P450 enzyme system. *J Biochem* **147**: 297–306.
- Ortiz de Montellano PR (2010). Hydrocarbon hydroxylation by cytochrome P450 enzymes. *Chem Rev* **110**: 932–948.
- Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J, Raunio H (2008). Inhibition and induction of human cytochrome P450 enzymes: current status. *Arch Toxicol* **82**: 667–715.
- Rezen T, Contreras JA, Rozman D (2007). Functional genomics approaches to studies of the cytochrome P450 superfamily. *Drug Metab Rev* **39**: 389–399.
- Schuster I (2011). Cytochromes P450 are essential players in the vitamin D signaling system. *Biochim Biophys Acta* **1814**: 186–199.
- Shaik S, Cohen S, Wang Y, Chen H, Kumar D, Thiel W (2010). P450 enzymes: their structure, reactivity, and selectivity-modeled by QM/MM calculations. *Chem Rev* **110**: 949–1017.
- Wijnen PA, Op den Buijsch RA, Drent M, Kuijpers PM, Neef C, Bast A, Bekers O, Koek GH (2007). The prevalence and clinical relevance of cytochrome P450 polymorphisms. *Aliment Pharmacol Ther* **26** (Suppl. 2): 211–219.
- Zanger UM, Turpeinen M, Klein K, Schwab M (2008). Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem* **392**: 1093–1108.

### References

- Bhatnagar AS *et al.* (1990). *J Steroid Biochem Mol Biol* **37**: 1021–1027.
- Fer M *et al.* (2008). *J Lipid Res* **49**: 2379–2389.
- Gryglewski RJ *et al.* (1976). *Prostaglandins* **12**: 685–713.
- Gryglewski RJ *et al.* (1995). *Wien Klin Wochenschr* **107**: 283–289.
- Harmon SD *et al.* (2006). *Prostaglandins Leukot Essent Fatty Acids* **75**: 169–177.
- Mizukami Y *et al.* (1993). *Biochim Biophys Acta* **1168**: 87–93.
- Plourde PV *et al.* (1994). *Breast Cancer Res Treat* **30**: 103–111.
- Randall MJ *et al.* (1981). *Thromb Res* **23**: 145–162.
- Sontag TJ, Parker RS (2002). *J Biol Chem* **277**: 25290–25296.
- Stoilov I *et al.* (1997). *Hum Mol Genet* **6**: 641–647.
- Watanuki M *et al.* (1978). *Biochemistry* **17**: 127–130.

# Eicosanoid turnover

Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and its metabolites. Arachidonic acid is thought primarily to derive from phospholipase A<sub>2</sub> action on membrane phosphatidylcholine (see Page S302), and may be re-cycled to form phospholipid through conjugation with coenzyme A and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly CYP2J2 (see Page S293). Isoprostanes are structural analogues of the prostanoids (hence the nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

## Cyclooxygenase (E.C. 1.14.99.1)

**Overview:** Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PG G<sub>2</sub> from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH<sub>2</sub> from PGG<sub>2</sub>. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indometacin and paracetamol (acetaminophen). PGH<sub>2</sub> may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Nomenclature	COX-1	COX-2
Ensembl ID	ENSG00000095303	ENSG00000073756
Other names	Prostaglandin G <sub>2</sub> /H <sub>2</sub> synthase-1	Prostaglandin G <sub>2</sub> /H <sub>2</sub> synthase-2
Substrates	Arachidonic acid	Arachidonic acid, docosahexaenoic acid (see Smith, 2008)
Selective inhibitors	FR122047 (7.5, Ochi <i>et al.</i> , 2000), valeroylsalicylate (Bhattacharyya <i>et al.</i> , 1995)	Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib

## Prostaglandin synthases

Subsequent to the formation of PGH<sub>2</sub>, the cytochrome P450 activities (see Page S293) thromboxane synthase (CYP5A1, EC 5.3.99.5, ENSG00000059377) and prostacyclin synthase (CYP8A1, EC 5.3.99.4, ENSG00000124212) generate thromboxane A<sub>2</sub> and prostacyclin (PGI<sub>2</sub>), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E<sub>2</sub>, prostaglandin D<sub>2</sub> and prostaglandin F<sub>2α</sub> (see tables).

Nomenclature	EC	Ensembl ID	Other names
mPGES1	5.3.99.3	ENSG00000148344	Prostaglandin E synthase, microsomal glutathione S-transferase 1-like 1, MGST1-L1, p53-induced gene 12 protein, p53-induced gene 12; PIG12
mPGES2	5.3.99.3	ENSG00000148334	Prostaglandin E synthase 2, microsomal prostaglandin E synthase 2, mPGES-2
cPGES	5.3.99.3	ENSG00000110958	Cytosolic prostaglandin E <sub>2</sub> synthase, prostaglandin E synthase 3, telomerase-binding protein p23, hsp90 co-chaperone, progesterone receptor complex p23
L-PGDS	5.3.99.2	ENSG00000107317	Lipocalin-type prostaglandin-D synthase, prostaglandin D <sub>2</sub> synthase, prostaglandin H <sub>2</sub> D-isomerase, glutathione-independent PGD synthetase, β-trace protein, cerebrin-28
H-PGDS	5.3.99.2	ENSG00000163106	Hematopoietic prostaglandin D synthase, glutathione-requiring prostaglandin D synthase, glutathione-dependent PGD synthetase, prostaglandin-H <sub>2</sub> D-isomerase

YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC<sub>50</sub> value of 5.5 (Koeberle *et al.*, 2008).

Prostaglandin D<sub>2</sub> can be metabolised to 9α,11β-prostaglandin F<sub>2α</sub> through the multifunctional enzyme activity AKR1C3. Prostaglandin E<sub>2</sub> can be metabolised to 9α,11α-prostaglandin F<sub>2α</sub> through the 9-ketoreductase activity of CBR1. Conversion of the 15-hydroxyeicosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

Nomenclature	AKR1C3	CBR1	HPGD
EC	1.1.1.188, 1.3.1.20, 1.1.1.213, 1.1.1.63, 1.1.1.64	1.1.1.197, 1.1.1.184, 1.1.1.189	1.1.1.141
Ensembl ID	ENSG00000196139	ENSG00000159228	ENSG00000164120

Nomenclature	AKR1C3	CBR1	HPGD
Other names	Aldo-keto reductase family 1 member C3, prostaglandin F synthase, PGFS, <i>trans</i> -1,2-dihydrobenzene-1,2-diol dehydrogenase, 3 $\alpha$ -hydroxysteroid dehydrogenase type 2, 3 $\alpha$ -HSD type 2, testosterone 17 $\beta$ -dehydrogenase 5, 17 $\beta$ -hydroxysteroid dehydrogenase type 5, 17 $\beta$ -HSD 5, dihydrodiol dehydrogenase type I, dihydrodiol dehydrogenase 3, chlordecone reductase homolog HAKRb, HA1753	Carbonyl reductase [NADPH] 1, prostaglandin E <sub>2</sub> 9-reductase, prostaglandin 9-ketoreductase, NADPH-dependent carbonyl reductase 1, 15-hydroxyprostaglandin dehydrogenase [NADP+]	15-hydroxyprostaglandin dehydrogenase (NAD)
Inhibitors	Flufenamic acid, indometacin (Matsuura <i>et al.</i> , 1998), flavonoids (Skarydova <i>et al.</i> , 2009)	–	–

### Lipoxygenases (E.C. 1.13.11.-)

**Overview:** The lipoxygenases (LOXs) are a structurally related family of non-haem iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. For arachidonic acid as substrate, these products are hydroperoxyeicosatetraenoic acids (HPETEs). In humans there are five lipoxygenases, the 5S-(arachidonate : oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, 12R-, or 15S-hydroperoxides, respectively. The sixth lipoxygenase member, epidermal lipoxygenase 3 (E-LOX), metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound (Yu *et al.*, 2003).

Nomenclature	5-LOX	12R-LOX	12S-LOX
E.C.	1.13.11.34	1.13.11.-	1.13.11.31
Ensembl ID	ENSG00000012779	ENSG00000179477	ENSG00000108839
Other names	ALOX5	ALOX12B	ALOX12, platelet-type 12-lipoxygenase
Substrates	Arachidonic acid	Methyl arachidonate	Arachidonic acid
Activators	FLAP	–	–
Selective inhibitors	Zileuton, CJ13610 (Fischer <i>et al.</i> , 2004)	–	–

FLAP activity can be inhibited by MK886 (Dixon *et al.*, 1990) and BAY-X1005 (Hatzelmann *et al.*, 1993) leading to a selective inhibition of 5-LOX activity.

Nomenclature	15-LOX-1	15-LOX-2	E-LOX
E.C.	1.13.11.33	1.13.11.33	1.13.11.-
Ensembl ID	ENSG00000161905	ENSG00000179593	ENSG00000179148
Other names	ALOX15, arachidonate $\omega$ -6 lipoxygenase	ALOX15B	Epidermis type LOX 3
Substrates	Linoleic acid, arachidonic acid	Arachidonic acid	12R-HPETE

An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 (Furstenberger *et al.*, 2002). Some general LOX inhibitors are NDGA and esculetin. Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baicalein and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 (Sadik *et al.*, 2003).

### Leukotriene and lipoxin metabolism

Leukotriene A<sub>4</sub>, produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism;  $\omega$ -hydroxylation is mediated by CYP4F2 and CYP4F3 (see Page S293), while  $\beta$ -oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA<sub>4</sub> at the 6 position with reduced glutathione to generate LTC<sub>4</sub> occurs under the influence of leukotriene C<sub>4</sub> synthase, with the subsequent formation of LTD<sub>4</sub> and LTE<sub>4</sub>, all three of which are agonists at CysLT receptors (see Page S74). LTD<sub>4</sub> formation is

catalysed by  $\gamma$ -glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD<sub>4</sub> to generate LTE<sub>4</sub>. Leukotriene A<sub>4</sub> hydrolase converts the 5,6-epoxide LTA<sub>4</sub> to the 5-hydroxylated LTB<sub>4</sub>, an agonist for BLT receptors (see Page S74). LTA<sub>4</sub> is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA<sub>4</sub> and LXB<sub>4</sub>. Treatment with an LTA<sub>4</sub> hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA<sub>4</sub> levels, in addition to reducing LTB<sub>4</sub>, in lung lavage fluid (Rao *et al.*, 2010)

LTA<sub>4</sub> hydrolase is also involved in biosynthesis of resolvin Es (see Page S74). Aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant 5-LOX; recombinant LTA<sub>4</sub> hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 (Oh *et al.*, 2011).

Nomenclature	Leukotriene C <sub>4</sub> synthase	$\gamma$ -Glutamyltransferase	Dipeptidase 1	Dipeptidase 2	Leukotriene A <sub>4</sub> hydrolase
E.C.	4.4.1.20	2.3.2.2	2.3.2._	2.3.2._	3.3.2.6
Ensembl ID	ENSG00000213316	ENSG00000006625	ENSG00000015413	ENSG00000167261	ENSG00000111144
Other names	LTC4S	GGT	DPEP1	DPEP2	LTA4H
Inhibitors	–	–	Cilastatin (Koller <i>et al.</i> , 1985)	–	Bestatin (Orning <i>et al.</i> , 1991)

LTA4H is a member of a family of arginyl aminopeptidases (ENSMF0025000001675), which also includes aminopeptidase B (RNPEP, ENSG00000176393) and aminopeptidase B-like 1 (RNPEPL1, ENSG00000142327). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases (ENSMF00250000001170), which also includes DPEP3 (ENSG00000141096) for which LTD<sub>4</sub> appears not to be a substrate.

**Abbreviations:** CDC, cinnamyl-3,4-dihydroxy- $\alpha$ -cyanocinnamate; **CJ13610**, 1-carboxamido-1-(3-*S*-[4-[2-methylimidazole]-thiophenyl]-4-cyclopentylether; **esculetin**, 6,7-dihydroxycoumarin; **FR122047**, 1-([4,5-bis(methoxyphenyl)-2-thiazoyl]carbonyl)-4-methylpiperazine hydrochloride; **12R-HPETE**, 12R-hydroperoxyeicosatetraenoic acid; **FLAP**, 5-lipoxygenase-activating protein, also known as MK-886-binding protein (ENSG00000132965); **NDGA**, nordihydroguaiaretic acid

#### Further Reading

- Austen KF (2007). Additional functions for the cysteinyl leukotrienes recognized through studies of inflammatory processes in null strains. *Prostaglandins Other Lipid Mediat* **83**: 182–187.
- Blobaum AL, Marnett LJ (2007). Structural and functional basis of cyclooxygenase inhibition. *J Med Chem* **50**: 1425–1441.
- Cha YI, DuBois RN (2007). NSAIDs and cancer prevention: targets downstream of COX-2. *Annu Rev Med* **58**: 239–252.
- Choi SH, Aid S, Bosetti F (2009). The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research. *Trends Pharmacol Sci* **30**: 174–181.
- Clarke DL, Dakshinamurti S, Larsson AK, Ward JE, Yamasaki A (2009). Lipid metabolites as regulators of airway smooth muscle function. *Pulm Pharmacol Ther* **22**: 426–435.
- Durand T, Bultel-Ponce V, Guy A, El FS, Rossi JC, Galano JM (2011). Isoprostanes and phytoprostanes: bioactive lipids. *Biochimie* **93**: 52–60.
- Eisinger AL, Prescott SM, Jones DA, Stafforini DM (2007). The role of cyclooxygenase-2 and prostaglandins in colon cancer. *Prostaglandins Other Lipid Mediat* **82**: 147–154.
- Fornai M, Antonioli L, Colucci R, Bernardini N, Ghisu N, Tuccori M *et al.* (2010). Emerging role of cyclooxygenase isoforms in the control of gastrointestinal neuromuscular functions. *Pharmacol Ther* **125**: 62–78.
- Furstenberger G, Epp N, Eckl KM, Hennies HC, Jorgensen C, Hallenborg P *et al.* (2007). Role of epidermis-type lipoxygenases for skin barrier function and adipocyte differentiation. *Prostaglandins Other Lipid Mediat* **82**: 128–134.
- Kang YJ, Mbonye UR, DeLong CJ, Wada M, Smith WL (2007). Regulation of intracellular cyclooxygenase levels by gene transcription and protein degradation. *Prog Lipid Res* **46**: 108–125.
- Murphy RC, Gijón MA (2007). Biosynthesis and metabolism of leukotrienes. *Biochem J* **405**: 379–395.
- Nikolaidis MG, Kyparos A, Vrabas IS (2011). F-isoprostane formation, measurement and interpretation: the role of exercise. *Prog Lipid Res* **50**: 89–103.
- O'Banion MK (2010). Prostaglandin E<sub>2</sub> synthases in neurologic homeostasis and disease. *Prostaglandins Other Lipid Mediat* **91**: 113–117.
- Osher E, Weisinger G, Limor R, Tordjman K, Stern N (2006). The 5 lipoxygenase system in the vasculature: emerging role in health and disease. *Mol Cell Endocrinol* **252**: 201–206.
- Poedel D, Funk CD (2010). The 5-lipoxygenase/leukotriene pathway in preclinical models of cardiovascular disease. *Cardiovasc Res* **86**: 243–253.
- Radmark O, Samuelsson B (2007). 5-lipoxygenase: regulation and possible involvement in atherosclerosis. *Prostaglandins Other Lipid Mediat* **83**: 162–174.
- Radmark O, Samuelsson B (2010). Regulation of the activity of 5-lipoxygenase, a key enzyme in leukotriene biosynthesis. *Biochem Biophys Res Commun* **396**: 105–110.
- Rinaldo-Matthis A, Haeggstrom JZ (2010). Structures and mechanisms of enzymes in the leukotriene cascade. *Biochimie* **92**: 676–681.
- Rubin P, Mollison KW (2007). Pharmacotherapy of diseases mediated by 5-lipoxygenase pathway eicosanoids. *Prostaglandins Other Lipid Mediat* **83**: 188–197.
- Samuelsson B, Morgenstern R, Jakobsson PJ (2007). Membrane prostaglandin E synthase-1: a novel therapeutic target. *Pharmacol Rev* **59**: 207–224.
- Sarkar FH, Adsule S, Li Y, Padhye S (2007). Back to the future: COX-2 inhibitors for chemoprevention and cancer therapy. *Mini Rev Med Chem* **7**: 599–608.
- Smith WL (2008). Nutritionally essential fatty acids and biologically indispensable cyclooxygenases. *Trends Biochem Sci* **33**: 27–37.
- Smyth EM, Grosser T, Wang M, Yu Y, FitzGerald GA (2009). Prostanoids in health and disease. *J Lipid Res* **50** (Suppl.), S423–S428.
- Tai HH, Tong M, Ding Y (2007). 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and lung cancer. *Prostaglandins Other Lipid Mediat* **83**: 203–208.

**References**

- Bhattacharyya DK *et al.* (1995). *Arch Biochem Biophys* **317**: 19–24.  
Dixon RA *et al.* (1990). *Nature* **343**: 282–284.  
Fischer L *et al.* (2004). *Br J Pharmacol* **142**: 861–868.  
Furstenberger G *et al.* (2002). *Prostaglandins Other Lipid Mediat* **68–69**: 235–243.  
Hatzelmann A *et al.* (1993). *Biochem Pharmacol* **45**: 101–111.  
Koeberle A *et al.* (2008). *J Med Chem* **51**: 8068–8076.  
Koller M *et al.* (1985). *Biochem Biophys Res Commun* **131**: 974–979.  
Matsuura K *et al.* (1998). *J Biochem* **124**: 940–946.  
Ochi T *et al.* (2000). *Eur J Pharmacol* **391**: 49–54.  
Oh SF *et al.* (2011). *J Clin Invest* **121**: 569–581.  
Orning L *et al.* (1991). *J Biol Chem* **266**: 1375–1378.  
Rao NL *et al.* (2010). *Am J Respir Crit Care Med* **181**: 899–907.  
Sadik CD *et al.* (2003). *Biochem Pharmacol* **65**: 773–781.  
Skarydova L *et al.* (2009). *Chem Biol Interact* **178**: 138–144.  
Yu Z *et al.* (2003). *Proc Natl Acad Sci U S A* **100**: 9162–9167.

# Endocannabinoid turnover

**Overview:** the principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (*N*-arachidonylethanolamine, AEA), thought to be generated on demand rather than stored. For 2AG, the key enzyme involved is diacylglycerol lipase (DGL), whilst several routes for AEA synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, see Simon and Cravatt, 2010). Inactivation of these endocannabinoids appears to occur predominantly through monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH) for 2AG and AEA, respectively. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism via cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities (see Alexander and Kendall, 2007; Fowler, 2007, Snider *et al.*, 2010).

Nomenclature	Diacylglycerol lipase $\alpha$	Diacylglycerol lipase $\beta$	<i>N</i> -Acylphosphatidylethanolamine-phospholipase D
Preferred abbreviation	DGL $\alpha$	DGL $\beta$	NAPE-PLD
E.C.	3.1.1.-	3.1.1.-	–
Ensembl ID	ENSG00000134780	ENSG00000164535	ENSG00000161048
Other names	Neural stem cell-derived dendrite regulator	KCCR13L	–
Selective inhibitors ( $pIC_{50}$ )	Tetrahydrolipstatin (7.2, Bisogno <i>et al.</i> , 2003), RHC80267	Tetrahydrolipstatin (7.0, Bisogno <i>et al.</i> , 2003), RHC80267	–

NAPE-PLD activity appears to be enhanced by polyamines in the physiological range (Liu *et al.*, 2002), but fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999) unlike phosphatidylcholine-specific phospholipase D.

Nomenclature	Monoacylglycerol lipase	Fatty acid amide hydrolase-1	Fatty acid amide hydrolase-2	<i>N</i> -Acylethanolamine acid amidase
Preferred abbreviation	MGL	FAAH	FAAH2	NAAA
E.C.	3.1.1.23	3.5.1._	3.5.1._	3.5.1._
Ensembl ID	ENSG00000074416	ENSG00000117480	ENSG00000165591	ENSG00000138744
Other names	HU-K5, lysophospholipase homolog	Oleamide hydrolase, anandamide hydrolase, FAAH1	–	Acid ceramidase-like protein, <i>N</i> -acylsphingosine amidohydrolase-like, <i>N</i> -palmitoylethanolamine acid amidase
Substrate potency order	2OG = 2AG >> AEA (Ghafouri <i>et al.</i> , 2004)	AEA > ODA > OEA > PEA (Wei <i>et al.</i> , 2006)	ODA > OEA > AEA > PEA (Wei <i>et al.</i> , 2006)	PEA > MEA > SEA > OEA > AEA (Ueda <i>et al.</i> , 2001)
Selective inhibitors ( $pIC_{50}$ )	JZL184 (8.1, Long <i>et al.</i> , 2009)	PF3845 (6.6, Ahn <i>et al.</i> , 2009), PF750 (6.3-7.8, Ahn <i>et al.</i> , 2007), JNJ1661010 (7.8, Keith <i>et al.</i> , 2008), URB597 (6.3-7.0, Wei <i>et al.</i> , 2006), OL135 (7.4, Wei <i>et al.</i> , 2006)	URB597 (7.5-8.3, Wei <i>et al.</i> , 2006), OL135 (7.9, Wei <i>et al.</i> , 2006)	CCP (5.3, Tsuboi <i>et al.</i> , 2004)

Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents (Wei *et al.*, 2006). 2AG has been reported to be hydrolysed by multiple enzyme activities from neural preparations, including ABHD6 (ENSG00000163686, Blankman *et al.*, 2007), ABHD12 (ENSG00000100997, Blankman *et al.*, 2007), neuropathy target esterase (PNPLA6, ENSG00000032444, Marrs *et al.*, 2010) and carboxylesterase 1 (CES1, ENSG00000198848, Xie *et al.*, 2010). Although these have been incompletely defined, WWL70 has been described to inhibit ABHD6 selectively with a  $pIC_{50}$  value of 7.2 (Li *et al.*, 2007).

**Abbreviations:** 2AG, 2-arachidonoylglycerol; 2OG, 2-oleoylglycerol; AEA, anandamide; CCP, *N*-cyclohexylcarbonylpentadecylamine; DGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; JNJ1661010, 4-(3-phenyl-[1,2,4] thiadiazol-5-yl)-piperazine-1-carboxylic acid phenylamide; JZL184, 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxymethyl)piperidine-1-carboxylate); MGL, monoacylglycerol lipase; MEA, *N*-myristoylethanolamine; NAAA, *N*-acylethanolamine acid amidase; NAPE-PLD, *N*-acylphosphatidylethanolamine-phospholipase D; ODA, octadec(9,10z)enamide; OEA, *N*-oleoylethanolamine OL135, 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-phenylheptane; PEA, *N*-palmitoylethanolamine; PF3845, 4-(3-[5-(trifluoromethyl)pyridin-2-yloxy]benzyl)-*N*-(pyridin-3-yl)piperidine-1-carboxamide; PF750, *N*-phenyl-4-(quinolin-3-ylmethyl)piperidine-1-carboxamide; RHC80267, 1,6-bis(cyclohexyloximinocarbonylamino)hexane; SEA, *N*-stearoylethanolamine; URB597, cyclohexyl carbamic acid 3'-carbamoyl-biphenyl-3-yl ester; WWL70, 4'-carbamoylbiphenyl-4-yl methyl(3-pyridin-4-yl)benzyl)carbamate

## Further Reading

Alexander SPH, Kendall DA (2007). The complications of promiscuity: endocannabinoid action and metabolism. *Br J Pharmacol* 152: 602–623.  
Bisogno T (2008). Endogenous cannabinoids: structure and metabolism. *J Neuroendocrinol* 20: 1–9.

- Di Marzo V, Bisogno T, De Petrocellis L (2007). Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. *Chem Biol* **14**: 741–756.
- Di Marzo V, Petrosino S (2007). Endocannabinoids and the regulation of their levels in health and disease. *Curr Opin Lipidol* **18**: 129–140.
- Farrell EK, Merkler DJ (2008). Biosynthesis, degradation and pharmacological importance of the fatty acid amides. *Drug Discov Today* **13**: 558–568.
- Fowler CJ (2007). The contribution of cyclooxygenase-2 to endocannabinoid metabolism and action. *Br J Pharmacol* **152**: 594–601.
- Fowler CJ, Naidu PS, Lichtman A, Onnis V (2009). The case for the development of novel analgesic agents targeting both fatty acid amide hydrolase and either cyclooxygenase or TRPV1. *Br J Pharmacol* **156**: 412–419.
- Hwang J, Adamson C, Butler D, Janero DR, Makriyannis A, Bahr BA (2010). Enhancement of endocannabinoid signaling by fatty acid amide hydrolase inhibition: a neuroprotective therapeutic modality. *Life Sci* **86**: 615–623.
- Savinainen JR, Saario SM, Laitinen JT (2011). The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. *Acta Physiol (Oxf)* in press.
- Simon GM, Cravatt BF (2010). Characterization of mice lacking candidate *N*-acyl ethanolamine biosynthetic enzymes provides evidence for multiple pathways that contribute to endocannabinoid production *in vivo*. *Mol Biosyst* **6**: 1411–1418.
- Snider NT, Walker VJ, Hollenberg PF (2010). Oxidation of the endogenous cannabinoid arachidonoyl ethanolamide by the cytochrome P450 monooxygenases: physiological and pharmacological implications. *Pharmacol Rev* **62**: 136–154.
- Wang J, Ueda N (2009). Biology of endocannabinoid synthesis system. *Prostaglandins Other Lipid Mediat* **89**: 112–119.
- Yates ML, Barker EL (2009). Inactivation and biotransformation of the endogenous cannabinoids anandamide and 2-arachidonoylglycerol. *Mol Pharmacol* **76**: 11–17.

## References

- Ahn K *et al.* (2007). *Biochemistry* **46**: 13019–13030.
- Ahn K *et al.* (2009). *Chem Biol* **16**: 411–420.
- Bisogno T *et al.* (2003). *J Cell Biol* **163**: 463–468.
- Blankman JL *et al.* (2007). *Chem Biol* **14**: 1347–1356.
- Ghafouri N *et al.* (2004). *Br J Pharmacol* **143**: 774–784.
- Keith JM *et al.* (2008). *Bioorg Med Chem Lett* **18**: 4838–4843.
- Li W *et al.* (2007). *J Am Chem Soc* **129**: 9594–9595.
- Liu Q *et al.* (2002). *Chem Phys Lipids* **115**: 77–84.
- Long JZ *et al.* (2009). *Nat Chem Biol* **5**: 37–44.
- Marrs WR *et al.* (2010). *Nat Neurosci* **13**: 951–957.
- Petersen G, Hansen HS (1999). *FEBS Lett* **455**: 41–44.
- Tsuboi K *et al.* (2004). *Biochem J* **379**: 99–106.
- Ueda N *et al.* (2001). *J Biol Chem* **276**: 35552–35557.
- Wei BQ *et al.* (2006). *J Biol Chem* **281**: 36569–36578.
- Xie SQ *et al.* (2010). *Chem Res Toxicol* **23**: 1890–1904.

# Glycerophospholipid turnover

**Overview:** phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and its phosphorylated derivatives) and sphingolipids (ceramide phosphorylcholine and ceramide phosphorylethanolamine).

## Phosphoinositide-specific phospholipase C (E.C. 3.1.4.11)

**Overview:** Phosphoinositide-specific phospholipase C (PLC) catalyses the hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC- $\beta$  (ENSF00000000466) are activated primarily by G protein-coupled receptors through members of the G<sub>q/11</sub> family of G proteins. The receptor-mediated activation of PLC- $\gamma$  involves their phosphorylation by receptor tyrosine kinases (RTK, see Page S203) in response to activation of a variety of growth factor receptors and immune system receptors. PLC- $\epsilon$ 1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca<sup>2+</sup> ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC- $\delta$  activity. PLC has been suggested to be activated non-selectively by the small molecule *m*-3M3FBS (Bae *et al.*, 2003), although this mechanism of action has been questioned (Krkjova *et al.*, 2004). The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC (Smith *et al.*, 1990), although its selectivity among the isoforms is untested and it has been reported to occupy the H<sub>1</sub> histamine receptor (Hughes *et al.*, 2000).

Nomenclature	PLC $\beta$ 1	PLC $\beta$ 2	PLC $\beta$ 3	PLC $\beta$ 4
Ensembl ID	ENSG00000182621	ENSG00000137841	ENSG00000149782	ENSG00000101333
Other names	PLC-I, PLC-154, KIAA0581	–	–	–
Endogenous activators	G $\alpha$ q (Smrcka <i>et al.</i> , 1991; Hepler <i>et al.</i> , 1993), G $\alpha$ 11 (Hepler <i>et al.</i> , 1993), G $\beta$ $\gamma$ (Park <i>et al.</i> , 1993)	G $\alpha$ 16 (Lee <i>et al.</i> , 1992), G $\beta$ $\gamma$ (Camps <i>et al.</i> , 1992; Park <i>et al.</i> , 1993), rac2 (Illenberger <i>et al.</i> , 2003a,b)	G $\alpha$ q (Lee <i>et al.</i> , 1992), G $\beta$ $\gamma$ (Carozzi <i>et al.</i> , 1993; Park <i>et al.</i> , 1993)	G $\alpha$ q (Jhon <i>et al.</i> , 1993)

Nomenclature	PLC $\gamma$ 1	PLC $\gamma$ 2	PLC $\delta$ 1	PLC $\delta$ 3	PLC $\delta$ 4
Ensembl ID	ENSG00000124181	ENSG00000197943	ENSG00000187091	ENSG00000161714	ENSG00000115556
Other names	PLC-II, PLC-148	PLC-IV	PLC-III	–	–
Endogenous activators	PIP <sub>3</sub> (Bae <i>et al.</i> , 1998)	PIP <sub>3</sub> (Bae <i>et al.</i> , 1998)	Transglutaminase II (Murthy <i>et al.</i> , 1999), p122-RhoGAP (Homma and Emori, 1995), spermine (Haber <i>et al.</i> , 1991), G $\beta$ $\gamma$ (Park <i>et al.</i> , 1993)	–	–
Inhibitors	–	Rac1, rac2, rac3 (Piechulek <i>et al.</i> , 2005; Walliser <i>et al.</i> , 2008)	Sphingomyelin (Pawelczyk and Lowenstein, 1992)	–	–

PLC- $\delta$ 2 has been cloned from bovine sources (Meldrum *et al.*, 1991).

Nomenclature	PLC $\epsilon$ 1	PLC $\zeta$ 1	PLC $\eta$ 1	PLC $\eta$ 2
Ensembl ID	ENSG00000138193	ENSG00000139151	ENSG00000114805	ENSG00000149527
Other names	Pancreas-enriched PLC	Testis-development protein NYD-SP27	–	–
Endogenous activators	Ras (Song <i>et al.</i> , 2001), Rho (Wing <i>et al.</i> , 2003)	–	–	G $\beta$ $\gamma$ (Zhou <i>et al.</i> , 2005)

A series of PLC-like proteins (PLCL1 ENSG00000115896; PLCL2 ENSG00000154822 and PLCL3 ENSG00000114805) form a family (ENSF00000000386) with PLC $\delta$  and PLC $\zeta$ 1 isoforms, but appear to lack catalytic activity.



**Phospholipase A<sub>2</sub> (E.C. 3.1.1.4)**

**Overview:** Phospholipase A<sub>2</sub> (PLA<sub>2</sub>) cleaves the *sn*-2 fatty acid of glycerophospholipids, primarily phosphatidylcholine, to generate lysophosphatidylcholine and arachidonic acid. Most commonly-used inhibitors (e.g. BEL, ATFMK or MAFP) are either non-selective within the family of phospholipase A<sub>2</sub> enzymes or have activity against other eicosanoid-metabolising enzymes.

**Secreted or extracellular forms**

Nomenclature	Ensembl ID	Other names
sPLA <sub>2</sub> -1B	ENSG00000170890	GIB, pancreatic PLA <sub>2</sub>
sPLA <sub>2</sub> -2A	ENSG00000188257	GIIA, GIIC sPLA <sub>2</sub> , non-pancreatic secretory phospholipase A <sub>2</sub> , NPS-PLA <sub>2</sub> , synovial PLA <sub>2</sub>
sPLA <sub>2</sub> -2D	ENSG00000117215	GIID, GIID sPLA <sub>2</sub> , secretory-type PLA <sub>2</sub> , stroma-associated homolog
sPLA <sub>2</sub> -2E	ENSG00000188784	GIIE, GIIE sPLA <sub>2</sub>
sPLA <sub>2</sub> -2F	ENSG00000158786	GIIF, GIIF sPLA <sub>2</sub>
sPLA <sub>2</sub> -3	ENSG00000100078	GIII, GIII sPLA <sub>2</sub>
sPLA <sub>2</sub> -10	ENSG00000069764	GX, GX sPLA <sub>2</sub>
sPLA <sub>2</sub> -12A	ENSG00000123739	GXIIA, GXII sPLA <sub>2</sub>

PLA<sub>2</sub>-2C (ENSG00000187980) may be a pseudogene, while PLA<sub>2</sub>-12B (GXII B, GXIII sPLA<sub>2</sub>-like, ENSG00000138308) appears to be catalytically inactive (Rouault *et al.*, 2003). A further fragment has been identified with sequence similarities to Group II PLA<sub>2</sub> members (ENSG00000187980).

A binding protein for secretory phospholipase A<sub>2</sub> has been identified (ENSG00000153246) which shows modest selectivity for sPLA<sub>2</sub>-1B over sPLA<sub>2</sub>-2A, and also binds snake toxin phospholipase A<sub>2</sub> (Ancian *et al.*, 1995). The binding protein appears to have clearance function for circulating secretory phospholipase A<sub>2</sub>, as well as signalling functions, and is a candidate antigen for idiopathic membranous nephropathy (Beck *et al.*, 2009).

**Cytosolic, calcium-dependent forms**

Nomenclature	Ensembl ID	Other names
cPLA <sub>2</sub> -4A	ENSG00000116711	GIVA, Calcium-dependent PLA <sub>2</sub> , cytosolic phospholipase A <sub>2</sub> α
cPLA <sub>2</sub> -4B	ENSG00000168970	GIVB, cytosolic phospholipase A <sub>2</sub> β
cPLA <sub>2</sub> -4C	ENSG00000105499	GIVC, cytosolic phospholipase A <sub>2</sub> γ
cPLA <sub>2</sub> -4D	ENSG00000159337	GIVD, cytosolic phospholipase A <sub>2</sub> δ
cPLA <sub>2</sub> -4E	ENSG00000188089	GIVE, cytosolic phospholipase A <sub>2</sub> ε
cPLA <sub>2</sub> -4F	ENSG00000168907	GIVF, cytosolic phospholipase A <sub>2</sub> ζ

cPLA<sub>2</sub>-4A also expresses lysophospholipase (EC 3.1.1.5) activity (Sharp *et al.*, 1994).

**Other forms**

Nomenclature	Ensembl ID	Other names
PLA <sub>2</sub> -G5	ENSG00000127472	GV, PLA <sub>2</sub> -10
iPLA <sub>2</sub> -G6	ENSG00000184381	GVI, 85 kDa Ca <sup>2+</sup> -independent, iPLA <sub>2</sub> , PNPLA9
PLA <sub>2</sub> -G7	ENSG00000146070	GVII, LDL-associated phospholipase A <sub>2</sub>

PLA<sub>2</sub>-G7 and a close homologue (HSD-PLA<sub>2</sub>, also known as serine-dependent phospholipase A<sub>2</sub>, PAFAH2, ENSG00000158006) also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47). Otoconin 90 (OC90, ENSG00000132297) shows sequence homology to PLA<sub>2</sub>-G10.

**Phosphatidylcholine-specific phospholipase D (E.C. 3.1.4.4)**

**Overview:** Phosphatidylcholine-specific phospholipase D (PLD, ENSF0000001451) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction (Randall *et al.*, 1990).

Nomenclature	PLD1	PLD2
Ensembl ID	ENSG00000075651	ENSG00000129219
Other names	Choline phosphatase 1	Choline phosphatase 2
Endogenous activators	ARF, PIP <sub>2</sub> , RhoA, PKC-evoked phosphorylation (Hammond <i>et al.</i> , 1997), RalA (Luo <i>et al.</i> , 1997)	ARF, PIP <sub>2</sub> (Lopez <i>et al.</i> , 1998), oleic acid (Sarri <i>et al.</i> , 2003)
Endogenous inhibitors	Gβγ (Preininger <i>et al.</i> , 2006)	Gβγ (Preininger <i>et al.</i> , 2006)
Selective inhibitors	–	VU0364739 (pIC <sub>50</sub> 7.7, Lavieri <i>et al.</i> , 2010)

A lysophospholipase D activity (ENPP2, ENSG00000136960, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003). Additionally, an *N*-acylethanolamine-specific phospholipase D (NAPE-PLD, ENSG00000161048) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids (see Page S300), including anandamide (Okamoto *et al.*, 2004). This enzyme activity appears to be enhanced by polyamines in the physiological range (Liu *et al.*, 2002) and fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999).

**Lipid phosphate phosphatases (E.C. 3.1.3.4)**

**Overview:** Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases (ENSM00260000050433) or lipins (ENSM00250000001227), catalyse the dephosphorylation of phosphatidic acid to generate inorganic phosphate and diacylglycerol.

Nomenclature	Ensembl ID	Other names
Lipin1	ENSG00000134324	–
Lipin2	ENSG00000101577	–
Lipin3	ENSG00000132793	SMP2
PPA2A	ENSG00000067113	LPP1
PPA2B	ENSG00000162407	LPP3
PPA3A	ENSG00000141934	LPP2

**Abbreviations:** *m*-3M3FBS, 2,4,6-trimethyl-*N*-(*meta*-3-trifluoromethylphenyl)-benzenesulphonamide; ARF, ADP-ribosylation factor; ATFMK, arachidonoyltrifluoromethylketone; BEL, bromoenolactone; MAFP, methylarachidonoylfluorophosphonate; NAPE-PLD, *N*-acylethanolamine-specific phospholipase D; PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate; PIP<sub>3</sub>, phosphatidylinositol 3,4,5-trisphosphate; PKC, protein kinase C; U73122, 1-(6-[[[(17β)-3-methoxyestra-1,3,5[10]-trien-17-yl]amino]hexyl]-1*H*-pyrrole-2,5-dione); VU0364739, *N*-[2-[4-(3-fluorophenyl)-1-oxo-2,4,8-triazaspiro[4.5]decan-8-yl]ethyl]naphthalene-2-carboxamide;

**Further Reading**

- Bader MF, Vitale N (2009). Phospholipase D in calcium-regulated exocytosis: lessons from chromaffin cells. *Biochim Biophys Acta* 1791: 936–941.
- Balla T (2009). Regulation of Ca<sup>2+</sup> entry by inositol lipids in mammalian cells by multiple mechanisms. *Cell Calcium* 45: 527–534.
- Berridge MJ (2009). Inositol trisphosphate and calcium signalling mechanisms. *Biochim Biophys Acta* 1793: 933–940.
- Birts CN, Barton CH, Wilton DC (2010). Catalytic and non-catalytic functions of human IIA phospholipase A<sub>2</sub>. *Trends Biochem Sci* 35: 28–35.
- van den Bout I, Divecha N (2009). PIP5K-driven PtdIns(4,5)P<sub>2</sub> synthesis: regulation and cellular functions. *J Cell Sci* 122: 3837–3850.
- Brindley DN, Pilquill C (2009). Lipid phosphate phosphatases and signaling. *J Lipid Res* 50: S225–S230.
- Brindley DN, Pilquill C, Sariahmetoglu M, Reue K (2009). Phosphatidate degradation: phosphatidate phosphatases (lipins) and lipid phosphate phosphatases. *Biochim Biophys Acta* 1791: 956–961.
- Bunney TD, Baxendale RW, Katan M (2009). Regulatory links between PLC enzymes and Ras superfamily GTPases: signalling via PLCε. *Adv Enzyme Regul* 49: 54–58.
- Bunney TD, Katan M (2010). Phosphoinositide signalling in cancer: beyond PI3K and PTEN. *Nat Rev Cancer* 10: 342–352.
- Burke JE, Dennis EA (2009). Phospholipase A<sub>2</sub> structure/function, mechanism, and signaling. *J Lipid Res* 50 (Suppl.): S237–S242.
- Cocco L, Faenza I, Follo MY, Billi AM, Ramazzotti G, Papa V *et al.* (2009). Nuclear inositides: PI-PLC signaling in cell growth, differentiation and pathology. *Adv Enzyme Regul* 49: 2–10.
- Donaldson JG (2009). Phospholipase D in endocytosis and endosomal recycling pathways. *Biochim Biophys Acta* 1791: 845–849.
- Drin G, Scarlata S (2007). Stimulation of phospholipase Cβ by membrane interactions, interdomain movement, and G protein binding. How many ways can you activate an enzyme? *Cell Signal* 19: 1383–1392.
- Falkenburger BH, Jensen JB, Dickson EJ, Suh BC, Hille B (2010). Phosphoinositides: lipid regulators of membrane proteins. *J Physiol* 588: 3179–3185.
- Fukami K, Inanobe S, Kanemaru K, Nakamura Y (2010). Phospholipase C is a key enzyme regulating intracellular calcium and modulating the phosphoinositide balance. *Prog Lipid Res* 49: 429–437.

- Harden TK, Hicks SN, Sondek J (2009). Phospholipase C isozymes as effectors of Ras superfamily GTPases. *J Lipid Res* **50**: S243–S248.
- Hooks SB, Cummings BS (2008). Role of Ca<sup>2+</sup>-independent phospholipase A<sub>2</sub> in cell growth and signaling. *Biochem Pharmacol* **76**: 1059–1067.
- Khalil MB, Blais A, Figeys D, Yao Z (2010). Lipin – The bridge between hepatic glycerolipid biosynthesis and lipoprotein metabolism. *Biochim Biophys Acta* **1801**: 1249–1259.
- Lambeau G, Gelb MH (2008). Biochemistry and physiology of mammalian secreted phospholipases A<sub>2</sub>. *Annu Rev Biochem* **77**: 495–520.
- Lee JC, Simonyi A, Sun AY, Sun GY (2011). Phospholipases A<sub>2</sub> and neural membrane dynamics: implications for Alzheimer's disease. *J Neurochem* **116**: 813–819.
- Mallat Z, Lambeau G, Tedgui A (2010). Lipoprotein-associated and secreted phospholipases A<sub>2</sub> in cardiovascular disease: roles as biological effectors and biomarkers. *Circulation* **122**: 2183–2200.
- Mansfeld J, Ulbrich-Hofmann R (2009). Modulation of phospholipase D activity in vitro. *Biochim Biophys Acta* **1791**: 913–926.
- Nevalainen TJ, Graham GG, Scott KF (2008). Antibacterial actions of secreted phospholipases A<sub>2</sub>. *Biochim Biophys Acta* **1781**: 1–9.
- Oude Weernink PA, Han L, Jakobs KH, Schmidt M (2007). Dynamic phospholipid signaling by G protein-coupled receptors. *Biochim Biophys Acta* **1768**: 888–900.
- Oude Weernink PA, de Lopez JM, Schmidt M (2007). Phospholipase D signaling: orchestration by PIP<sub>2</sub> and small GTPases. *Naunyn Schmiedeberg's Arch Pharmacol* **374**: 399–411.
- Pyne S, Lee SC, Long J, Pyne NJ (2009). Role of sphingosine kinases and lipid phosphate phosphatases in regulating spatial sphingosine 1-phosphate signalling in health and disease. *Cell Signal* **21**: 14–21.
- Qin H, Zheng X, Zhong X, Shetty AK, Elias PM, Bollag WB (2011). Aquaporin-3 in keratinocytes and skin: its role and interaction with phospholipase D2. *Arch Biochem Biophys* **508**: 138–143.
- Rosa AO, Rapoport SI (2009). Intracellular- and extracellular-derived Ca<sup>2+</sup> influence phospholipase A<sub>2</sub>-mediated fatty acid release from brain phospholipids. *Biochim Biophys Acta* **1791**: 697–705.
- Samadi N, Bekele R, Capatos D, Venkatraman G, Sariahmetoglu M, Brindley DN (2011). Regulation of lysophosphatidate signaling by autotaxin and lipid phosphate phosphatases with respect to tumor progression, angiogenesis, metastasis and chemo-resistance. *Biochimie* **93**: 61–70.
- Scott SA, Selvy PE, Buck JR et al (2009). Design of isoform-selective phospholipase D inhibitors that modulate cancer cell invasiveness. *Nat Chem Biol* **5**: 108–117.
- Shayman JA, Kelly R, Kollmeyer J, He Y, Abe A (2011). Group XV phospholipase A<sub>2</sub>, a lysosomal phospholipase A. *Prog Lipid Res* **50**: 1–13.
- Su W, Yeku O, Olepu S et al (2009). 5-Fluoro-2-indolyl des-chlorohalopemide (FIFI), a phospholipase D pharmacological inhibitor that alters cell spreading and inhibits chemotaxis. *Mol Pharmacol* **75**: 437–446.
- Suh PG, Park JI, Manzoli L et al (2008). Multiple roles of phosphoinositide-specific phospholipase C isozymes. *BMB Rep* **41**: 415–434.
- Tsui MM, York JD (2010). Roles of inositol phosphates and inositol pyrophosphates in development, cell signaling and nuclear processes. *Adv Enzyme Regul* **50**: 324–337.
- Zhang Y, Du G (2009). Phosphatidic acid signaling regulation of Ras superfamily of small guanosine triphosphatases. *Biochim Biophys Acta* **1791**: 850–855.
- Zhao Y, Natarajan V (2009). Lysophosphatidic acid signaling in airway epithelium: role in airway inflammation and remodeling. *Cell Signal* **21**: 367–377.

## References

- Ancian P et al. (1995). *Biochemistry* **34**: 13146–13151.
- Bae YS et al. (1998). *J Biol Chem* **273**: 4465–4469.
- Bae YS et al. (2003). *Mol Pharmacol* **63**: 1043.
- Beck LH et al. (2009). *N Engl J Med* **361**: 11–21.
- Camps M et al. (1992). *Nature* **360**: 684–686.
- Carozzi A et al. (1993). *FEBS Lett* **315**: 340–342.
- Goding JW et al. (2003). *Biochim Biophys Acta* **1638**: 1–19.
- Haber MT et al. (1991). *Arch Biochem Biophys* **288**: 243–249.
- Hammond SM et al. (1997). *J Biol Chem* **272**: 3860–3868.
- Hepler JR et al. (1993). *J Biol Chem* **268**: 14367–14375.
- Homma Y, Emori Y (1995). *EMBO J* **14**: 286–291.
- Hughes SA et al. (2000). *Naunyn-Schmiedeberg's Arch Pharmacol* **362**: 555–558.
- Illenberger D et al. (2003a). *J Biol Chem* **278**: 3006–3014.
- Illenberger D et al. (2003b). *J Biol Chem* **278**: 8645–8652.
- Jhon D-Y et al. (1993). *J Biol Chem* **268**: 6654–6661.
- Krjukova J et al. (2004). *Br J Pharmacol* **143**: 3–7.
- Lavieri RR et al. (2010). *J Med Chem* **53**: 6706–6719.
- Lee CH et al. (1992). *J Biol Chem* **267**: 16044–16047.
- Liu Q et al. (2002). *Chem Phys Lipids* **115**: 77–84.
- Lopez I et al. (1998). *J Biol Chem* **273**: 12846–12852.
- Luo JQ et al. (1997). *Biochem Biophys Res Commun* **235**: 854–859.
- Meldrum E et al. (1991). *Eur J Biochem* **196**: 159–165.
- Murthy SNP et al. (1999). *Proc Natl Acad Sci U S A* **96**: 11815–11819.
- Okamoto Y et al. (2004). *J Biol Chem* **279**: 5298–5305.
- Park D et al. (1993). *J Biol Chem* **268**: 4573–4576.
- Pawelczyk T, Lowenstein JM (1992). *Arch Biochem Biophys* **297**: 328–333.
- Petersen G, Hansen HS (1999). *FEBS Lett* **455**: 41–44.
- Piechulek T et al. (2005). *J Biol Chem* **280**: 38923–38931.
- Preininger AM et al. (2006). *Mol Pharmacol* **70**: 311–318.
- Randall RW et al. (1990). *FEBS Lett* **264**: 87–90.
- Rouault M et al. (2003). *Biochemistry* **42**: 11494–11503.
- Sarri E et al. (2003). *Biochem J* **369**: 319–329.
- Sharp JD et al. (1994). *J Biol Chem* **269**: 23250–23254.
- Smith RJ et al. (1990). *J Pharmacol Exp Ther* **253**: 688–697.
- Smrcka AV et al. (1991). *Science* **251**: 804–807.
- Song C et al. (2001). *J Biol Chem* **276**: 2752–2757.
- Walliser C et al. (2008). *J Biol Chem* **283**: 30351–30362.
- Wing MR et al. (2003). *Mol Interv* **3**: 273–280.
- Zhou Y et al. (2005). *Biochem J* **391**: 667–676.

# Haem oxygenase (EC 1.14.99.3)

**Overview:** Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase ( $\alpha$ -methene-oxidizing, hydroxylating)) converts haem into biliverdin and carbon monoxide, utilizing NADPH as cofactor.

Nomenclature	Haem oxygenase 1	Haem oxygenase 2
Preferred abbreviation	HO1	HO2
Ensembl ID	ENSG00000100292	ENSG00000103415
Other names	Inducible form, HMOX1, hsp32	Constitutive form, HMOX2

The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene (Hayashi *et al.*, 2004).

Tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an  $IC_{50}$  value of 11 nM (Drummond and Kappas, 1981).

## Further Reading

- Abraham NG, Kappas A (2008). Pharmacological and clinical aspects of heme oxygenase. *Pharmacol Rev* **60**: 79–127.
- Bilban M, Haschemi A, Wegiel B *et al* (2008). Heme oxygenase and carbon monoxide initiate homeostatic signaling. *J Mol Med* **86**: 267–279.
- Chan KH, Ng MK, Stocker R (2011). Haem oxygenase-1 and cardiovascular disease: mechanisms and therapeutic potential. *Clin Sci (Lond)* **120**: 493–504.
- Dulak J, Deshane J, Jozkowicz A, Agarwal A (2008). Heme oxygenase-1 and carbon monoxide in vascular pathobiology: focus on angiogenesis. *Circulation* **117**: 231–241.
- Gozzelino R, Jeney V, Soares MP (2010). Mechanisms of cell protection by heme oxygenase-1. *Annu Rev Pharmacol Toxicol* **50**: 323–354.
- Kim HP, Pae HO, Back SH, Chung SW, Woo JM, Son Y *et al.* (2011). Heme oxygenase-1 comes back to endoplasmic reticulum. *Biochem Biophys Res Commun* **404**: 1–5.
- Larsen K, Cheng C, Duckers HJ (2010). Regulation of vulnerable plaque development by the heme oxygenase/carbon monoxide system. *Trends Cardiovasc Med* **20**: 58–65.
- Paine A, Eiz-Vesper B, Blasczyk R, Immenschuh S (2010). Signaling to heme oxygenase-1 and its anti-inflammatory therapeutic potential. *Biochem Pharmacol* **80**: 1895–1903.
- Soares MP, Marguti I, Cunha A, Larsen R (2009). Immunoregulatory effects of HO-1: how does it work? *Curr Opin Pharmacol* **9**: 482–489.
- Syapin PJ (2008). Regulation of haeme oxygenase-1 for treatment of neuroinflammation and brain disorders. *Br J Pharmacol* **155**: 623–640.
- Zhu Y, Silverman RB (2008). Revisiting heme mechanisms. A perspective on the mechanisms of nitric oxide synthase (NOS), Heme oxygenase (HO), and cytochrome P450s (CYP450s). *Biochemistry* **47**: 2231–2243.

## References

- Drummond GS, Kappas A (1981). *Proc Natl Acad Sci U S A* **78**: 6466–6470.
- Hayashi S *et al* (2004). *Gene* **336**: 241–250.

# Hydrogen sulphide synthesis

**Overview:** Hydrogen sulfide is a putative gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated have multiple enzymatic activities, the focus of this table is the generation of hydrogen sulfide and the enzymatic characteristics are described accordingly.

Nomenclature	Cystathionine $\beta$ -synthase	Cystathionine $\gamma$ -lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Preferred abbreviation	CBS	CSE	CAT	MPST
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Ensembl ID	ENSG00000160200	ENSG00000116761	ENSG00000171097	ENSG00000128309
Other names	Serine sulfhydrase, $\beta$ -thionase	CGL, $\gamma$ -cystathioninase, CTH	Kynurenine:2-oxoglutarate transaminase (EC 2.6.1.7), glutamine-phnylpyruvate transaminase (EC 2.6.1.64), cysteine transaminase, cysteine aminotransferase	–
Cofactor/s	Pyridoxal phosphate	Pyridoxal phosphate	Pyridoxal phosphate	Zinc
Substrates ( $K_m$ )	Cysteine (6 mM, Chen <i>et al.</i> , 2004), homocysteine	Cysteine	Cysteine	3-Mercaptopyruvate (1.2 mM, Nagahara <i>et al.</i> , 1995)
Products	Cystathionine	Pyruvate, ammonia	Pyruvate, ammonia	Pyruvate
Inhibitors	Aminoxyacetic acid	Propargylglycine		

## Further Reading

- d'Emmanuele di Villa Bianca R, Sorrentino R, Mirone V, Cirino G (2011). Hydrogen sulfide and erectile function: a novel therapeutic target. *Nat Rev Urol* 8: 286–289.
- Kimura H (2011). Hydrogen sulfide: its production, release and functions. *Amino Acids* 41: 113–121.
- Li L, Moore PK (2008). Putative biological roles of hydrogen sulfide in health and disease: a breath of not so fresh air? *Trends Pharmacol Sci* 29: 84–90.
- Li L, Hsu A, Moore PK (2009). Actions and interactions of nitric oxide, carbon monoxide and hydrogen sulphide in the cardiovascular system and in inflammation – a tale of three gases! *Pharmacol Ther* 123: 386–400.
- Li L, Rose P, Moore PK (2011). Hydrogen sulfide and cell signaling. *Annu Rev Pharmacol Toxicol* 51: 169–187.
- Mancardi D, Penna C, Merlino A, del Soldato P, Wink DA, Pagliaro P (2009). Physiological and pharmacological features of the novel gasotransmitter: hydrogen sulfide. *Biochim Biophys Acta* 1787: 864–872.
- Martelli A, Testai L, Breschi MC, Blandizzi C, Viridis A, Taddei S *et al.* (2010). Hydrogen sulphide: novel opportunity for drug discovery. *Med Res Rev* in press.
- Mustafa AK, Gadalla MM, Snyder SH (2009). Signaling by gasotransmitters. *Sci Signal* 2: re2.
- Olson KR (2009). Is hydrogen sulfide a circulating 'gasotransmitter' in vertebrate blood? *Biochim Biophys Acta* 1787: 856–863.
- Olson KR (2011). The therapeutic potential of hydrogen sulfide: separating hype from hope. *Am J Physiol Regul Integr Comp Physiol* 301: R297–R312.

## References

- Chen X *et al.* (2004). *J Biol Chem* 279: 52082–52086.
- Nagahara N *et al.* (1995). *J Biol Chem* 270: 16230–16235.

# Inositol phosphate turnover

**Overview:** the sugar alcohol *D*-myo-inositol is a component of the phosphatidylinositol signalling cycle (see Page S302), where the principal second messenger is inositol 1,4,5-trisphosphate, IP<sub>3</sub>, which acts at intracellular ligand-gated ion channels, IP<sub>3</sub> receptors (see Page S157) to elevate intracellular calcium. IP<sub>3</sub> is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP<sub>3</sub> is recycled into membrane phospholipid under the influence of phosphatidylinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [EC 2.7.8.11]).

**Inositol 1,4,5-trisphosphate 3-kinases** (E.C. 2.7.1.127, ENSFM0025000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP<sub>4</sub>) from IP<sub>3</sub>. IP<sub>3</sub> kinase activity is enhanced in the presence of calcium/calmodulin (Conigrave and Roufogalis, 1989).

Nomenclature	IP <sub>3</sub> kinase A	IP <sub>3</sub> kinase B	IP <sub>3</sub> kinase C
HGNC nomenclature	ITPKA	ITPKB	ITPKC
Ensembl ID	ENSG00000137825	ENSG00000143772	ENSG00000086544
Other names	IP3-3KC, IP3KA	IP3-3KB, IP3KB	IP3-3KC, IP3KC

**Inositol polyphosphate phosphatases:** members of this family exhibit phosphatase activity towards IP<sub>3</sub>, as well as towards other inositol derivatives, including the phospholipids PIP<sub>2</sub> and PIP<sub>3</sub>. With 1,4,5-IP<sub>3</sub> as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5-IP<sub>2</sub>, 4-phosphatases (EC 3.1.3.66, ENSFM0025000001432) generate 1,5-IP<sub>2</sub> and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4-IP<sub>2</sub>.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Inositol polyphosphate 1-phosphatase	INPP1	ENSG00000151689	–
Inositol polyphosphate 4-phosphatases	INPP4A; INPP4B	ENSG00000040933; ENSG00000109452	Type I, 107 kDa INPP4; Type II, 105 kDa INPP4
Inositol polyphosphate 5-phosphatases	INPP5A; INPP5B; INPP5D; INPP5E; INPP5J; INPP5K; INPPL1 OCRL; SYNJ1; SYNJ2	ENSG00000068383; ENSG00000204084; ENSG00000168918; ENSG00000148384; ENSG00000185133; ENSG00000132376; ENSG00000165458 ENSG00000122126; ENSG00000159082; ENSG00000078269	SPTASE; 75 kDa inositol polyphosphate-5-phosphatase; hp51CN, SHIP; COR1, JBTS1, PPI5PIV; – SKIP; SHIP2, SH2-containing inositol phosphatase 2; Oculocerebrorenal syndrome of Lowe, OCSL; Synaptojanin 1; Synaptojanin 2

*In vitro* analysis suggested IP<sub>3</sub> and IP<sub>4</sub> were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP<sub>2</sub> and PIP<sub>3</sub> were more efficiently hydrolysed (Schmid *et al.*, 2004).

**Inositol monophosphatase** (E.C.3.1.3.25, IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. Lithium is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK<sub>i</sub> ca. 3.5, McAllister *et al.*, 1992; pI<sub>C50</sub> 3.2, Ohnishi *et al.*, 2007) than IMPase 2 (pI<sub>C50</sub> 1.8-2.1, Ohnishi *et al.*, 2007). IMPase activity may be inhibited competitively by L690330 (pK<sub>i</sub> 5.5, McAllister *et al.*, 1992), although the enzyme selectivity is not yet established.

Nomenclature	Ensembl ID	Other names	Substrate rank order
IMPase 1	ENSG00000133731	IMPA1	Inositol 4-phosphate>inositol 3-phosphate>inositol 1-phosphate (McAllister <i>et al.</i> , 1992)
IMPase 2	ENSG00000141401	IMPA2	–

Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder (Sjoholt *et al.*, 1997; 2000; Yoshikawa *et al.*, 1997). Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of lithium in mice (Cryns *et al.*, 2007; 2008).

**Abbreviations:** IP<sub>3</sub>, inositol 1,4,5-trisphosphate; L690330, 1-(4-hydroxyphenoxy)ethane-1,1-bisphosphonate; PIP<sub>2</sub>, phosphatidylinositol-4,5,-bisphosphate; PIP<sub>3</sub>, phosphatidylinositol-3,4,5,-trisphosphate

## Further Reading

- Leung WH, Tarasenko T, Bolland S (2009). Differential roles for the inositol phosphatase SHIP in the regulation of macrophages and lymphocytes. *Immunol Res* 43: 243–251.
- Liu Y, Bankaitis VA (2010). Phosphoinositide phosphatases in cell biology and disease. *Prog Lipid Res* 49: 201–217.
- Miller DJ, Allemann RK (2007). *myo*-Inositol monophosphatase: a challenging target for mood stabilising drugs. *Mini Rev Med Chem* 7: 107–113.

- Ooms LM, Horan KA, Rahman P, Seaton G, Gurung R, Kethesparan DS et al. (2009). The role of the inositol polyphosphate 5-phosphatases in cellular function and human disease. *Biochem J* **419**: 29–49.
- Parry RV, Harris SJ, Ward SG (2010). Fine tuning T lymphocytes: a role for the lipid phosphatase SHIP-1. *Biochim Biophys Acta* **1804**: 592–597.
- Pasquali L, Busceti CL, Fulceri F, Paparelli A, Fornai F (2010). Intracellular pathways underlying the effects of lithium. *Behav Pharmacol* **21**: 473–492.
- Schell MJ (2010). Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. *Cell Mol Life Sci* **67**: 1755–1778.

## References

- Conigrave AD, Roufogalis BD (1989). *Cell Calcium* **10**: 543–550.
- Cryns K et al (2007). *Neuropsychopharmacology* **32**: 881–891.
- Cryns K et al (2008). *Neuropsychopharmacology* **33**: 674–684.
- McAllister G et al. (1992). *Biochem J* **284**: 749–754.
- Ohnishi T et al (2007). *J Biol Chem* **282**: 637–646.
- Schmid AC et al. (2004). *FEBS Lett* **576**: 9–13.
- Sjoholt G et al. (1997). *Genomics* **45**: 113–122.
- Sjoholt G et al. (2000). *Mol Psychiatry* **5**: 172–180.
- Yoshikawa T et al. (1997). *Mol Psychiatry* **2**: 393–397.

# Protein serine/threonine kinases (E.C. 2.7.1.-)

**Overview:** Protein serine/threonine kinases use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man, with over 100 protein kinase-like pseudogenes (see Manning *et al.*, 2002). It is beyond the scope of the Guide to list all these protein kinase activities; this summary focusses on AGC protein kinases associated with GPCR signalling, which may be divided into 15 subfamilies in man.

Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site (Davies *et al.*, 2000).

## G protein coupled receptor kinases

G protein-coupled receptor kinases, epitomized by  $\beta$ ARK, are involved in the rapid phosphorylation and desensitization of GPCR. Classically, high concentrations of  $\beta_2$ -adrenoceptor agonists (see Page S26) binding to the receptor lead to the consequent activation and dissociation of the heterotrimeric G protein  $G_s$ .  $G_\alpha$ , activates adenylyl cyclase activity (see Page S288), while  $G\beta\gamma$  subunits perform other functions, one of which is to recruit  $\beta$ ARK to phosphorylate serine/threonine residues in the cytoplasmic tail of the  $\beta_2$ -adrenoceptor. The phosphorylated receptor binds, with high affinity, a member of the arrestin family (ENSM0025000000572), which prevents further signalling through the G protein (uncoupling) and may allow interaction with scaffolding proteins, such as clathrin, with the possible consequence of internalization and/or degradation.

Systematic nomenclature	Preferred abbreviation	Ensembl ID	Other names	Comment
GRK1	RHOK	ENSG00000185974	Rhodopsin kinase, G protein-coupled receptor kinase 1, GPRK1, RK	–
GRK2	$\beta$ ARK	ENSG00000173020	$\beta$ -Adrenergic receptor kinase, ADRBK1	Protein kinase C-mediated phosphorylation increases membrane association (Chuang <i>et al.</i> , 1995; Winstel <i>et al.</i> , 1996)
GRK3	$\beta$ ARK2	ENSG00000100077	$\beta$ -Adrenergic receptor kinase 2, ADRBK2	–
GRK4	–	ENSG00000125388	G protein-coupled receptor kinase 4, GPRK2L	Inhibited by $Ca^{2+}$ /calmodulin (Sallese <i>et al.</i> , 1997)
GRK5	–	ENSG00000198873	G protein-coupled receptor kinase 5	Phosphorylated and inhibited by protein kinase C (Pronin and Benovic, 1997)
GRK6	–	ENSG00000198055	G protein-coupled receptor kinase 6	–
GRK7	–	ENSG00000114124	G protein-coupled receptor kinase 7	–

Loss-of-function mutations in RHOK or retinal and pineal gland arrestin (ENSG00000130561) are associated with Oguchi disease, a form of congenital stationary night blindness.

## Protein kinase A (PKA)

Cyclic AMP-mediated signalling involves regulation of ion channels (see Page S153 and S156), members of the Rap guanine nucleotide exchange family (Epac, ENSFM00250000000899, see Page S288) and activation of protein kinase A (PKA, also known as cyclic AMP-dependent protein kinase). PKA is a heterotetrameric enzyme composed of two regulatory and two catalytic subunits, which can be distinguished from Epac (exchange protein directly activated by cAMP, de Rooij *et al.*, 1998) by differential activation by  $N^6$ -benzyl-cAMP (see Table) and CPT-2'OMe-cAMP, respectively (Kang *et al.*, 2005).

Nomenclature	Regulatory subunits	Catalytic subunits:
Ensembl ID	PRKAR1A (ENSG00000108946); PRKAR1B (ENSG00000188191); PRKAR2A (ENSG00000114302); PRKAR2B (ENSG00000005249);	PRKACA (ENSG00000072062); PRKACB (ENSG00000142875); PRKACG (ENSG00000165059)
Selective activator	$N^6$ -Benzyl-cAMP (Christensen <i>et al.</i> , 2003)	–
Selective inhibitor	Rp-cAMPS	–
Probe	[ $^3H$ ]-cAMP	–

Other members of the PKA family are PRKX (X-linked protein kinase, PKX1, ENSG00000183943) and PRKY (Y-linked protein kinase, ENSG00000099725). PRKX and PRKY are expressed on X and Y chromosomes, respectively, and appear to interchange in some XX males and XY females (Schiebel *et al.*, 1997).



**Protein kinase B (PKB)**

The action of phosphatidylinositol 3-kinase (PI3K), a downstream kinase activated by receptor tyrosine kinases (see Page S203), produces a series of phosphorylated phosphoinositides, which recruit 3-phosphoinositide-dependent kinase (PDK1, see below) activity to the plasma membrane, leading to activation of PKB (also known as Akt, Rac serine/threonine protein kinase, v-akt murine thymoma viral oncogene). PKB may be activated by PIP<sub>3</sub>, PDK1-mediated phosphorylation (Alessi *et al.*, 1997) and mTORC2-mediated phosphorylation (Hresko and Mueckler, 2005, Sarbassov *et al.*, 2005).

Nomenclature	PKB1	PKB2	PKB2
HGNC nomenclature	AKT1	AKT2	AKT3
Ensembl ID	ENSG00000142208	ENSG00000105221	ENSG00000117020
Other names	PKB $\alpha$	PKB $\beta$	PKB $\gamma$
Selective inhibitor	GSK690693 (Heering <i>et al.</i> , 2008)		

**Protein kinase C**

Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl- $\beta$ -phorbol acetate (TPA, also known as PMA).

*Classical protein kinase C isoforms:* Members of the classical protein kinase C family are activated by Ca<sup>2+</sup> and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö6983, chelerythrine and Ro318220.

Nomenclature	PKC $\alpha$	PKC $\beta$	PKC $\gamma$
HGNC nomenclature	PRKCA	PRKCB	PRKCG
Ensembl ID	ENSG00000154229	ENSG00000166501	ENSG00000126583
Selective inhibitors	–	Ruboxistaurin (8.3, Jirousek <i>et al.</i> , 1996), CGP53353 (6.4, Chalfant <i>et al.</i> , 1996)	

*Novel protein kinase C isoforms:* Members of the classical protein kinase C family are activated by diacylglycerol and may be inhibited by calphostin C, Gö6983 and chelerythrine.

Nomenclature	PKC $\delta$	PKC $\epsilon$	PKC $\eta$	PKC $\theta$	PKC $\mu$
HGNC nomenclature	PRKCD	PRKCE	PRKCH	PRKCQ	PRKD1
Ensembl ID	ENSG00000163932	ENSG00000171132	ENSG00000027075	ENSG00000065675	ENSG00000184304
Other names	–	–	–	–	PKCM, PRKCM, protein kinase D, PKD

**Atypical protein kinase C isoforms**

Nomenclature	PKC $\iota$	PKC $\zeta$
HGNC nomenclature	PRKCI	PRKCZ
Ensembl ID	ENSG00000163558	ENSG00000067606
Other names	PKC $\lambda$ in rodents	–
Endogenous activators	–	Arachidonic acid

**Protein kinase G (PKG)**

Cyclic GMP-dependent protein kinase is a dimeric enzyme activated by cGMP generated by particulate guanylyl cyclases (see Page S195) or soluble guanylyl cyclases (see Page S288).

Preferred abbreviation	PKG1	PKG2
HGNC nomenclature	PRKG1	PRKG2
Ensembl ID	ENSG00000185532	ENSG00000138669
Selective inhibitors	Rp-8-CPT-cGMPS (Butt <i>et al.</i> , 1994)	

**Mitogen-activated protein kinases (MAP kinases)**

MAP kinases (CMGC kinases, ENSF00000000137) may be divided into three major families: ERK, JNK and p38 MAP kinases.

**ERK** may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, MAP2K1 (also known as MEK1, ENSG00000169032) and MAP2K2 (also known as MEK2, ENSG00000126934). The inhibitors PD98059 (Alessi *et al.*, 1995; Dudley *et al.*, 1995) and U0126 (Duncia *et al.*, 1998; Favata *et al.*, 1998) act to inhibit these enzymes (Davies *et al.*, 2000), and are used to inhibit ERK1 and ERK2.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
ERK1	MAPK3	ENSG00000102882	Insulin-stimulated MAP2 kinase, ERT2, p44-MAPK, microtubule-associated protein-2 kinase
ERK2	MAPK1	ENSG00000100030	Mitogen-activated protein kinase 2, p42-MAPK, ERT1

**JNK** may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, MAP2K4 (also known as JNKK1, ENSG00000065559) and MAP2K7 (also known as JNKK2, ENSG00000076984).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
JNK1	MAPK8	ENSG00000107643	SAPK1, c-Jun N-terminal kinase 1, JNK-46
JNK2	MAPK9	ENSG00000050748	c-Jun N-terminal kinase 2, JNK-55
JNK3	MAPK10	ENSG00000109339	c-Jun N-terminal kinase 3, MAP kinase p49 3F12

SP600125 is able to inhibit all three isoforms of JNK with  $pIC_{50}$  values of 6.7 (Bennett *et al.*, 2001).

**p38** may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, MAP2K3 (also known as MEK3, ENSG00000034152) and MAP2K6 (also known as SAPKK3, ENSG00000108984).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
p38 $\alpha$	MAPK14	ENSG00000112062	Cytokine suppressive anti-inflammatory drug binding protein, MAX-interacting protein 2
p38 $\beta$	MAPK11	ENSG00000185386	p38-2, SAPK2
p38 $\gamma$	MAPK12	ENSG00000188130	ERK-6, ERK5, SAPK3
p38 $\delta$	MAPK13	ENSG00000156711	SAPK4

SB203580 has been reported to inhibit p38 $\alpha$  and p38 $\beta$  with  $pIC_{50}$  values of 8.0 and 7.0, respectively (Eyers *et al.*, 1998). SB202190 inhibits p38 $\beta$  (Lee *et al.*, 1994).

**Rho kinase**

Rho kinase (also known as P160ROCK, Rho-activated kinase) is activated by members of the Rho small G protein family (ENSMF00500000269651), which are activated by GTP exchange factors, such as ARHGEF1 (p115-RhoGEF, ENSG00000076928), which in turn may be activated by  $G\alpha_{12/13}$  subunits (Kozasa *et al.*, 1998).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Rho kinase 1	ROCK1	ENSG00000067900	p160ROCK
Rho kinase 2	ROCK2	ENSG00000134318	–

Rho kinase may be inhibited selectively by Y27362 (Uehata *et al.*, 1997) or fasudil (Asano *et al.*, 1989).

**Other AGC kinases**

For many of these remaining protein kinases, there is less information about the regulation and substrate specificity, as well as a paucity of pharmacological data.

Subfamily	Nomenclature	HGNC nomenclature	Ensembl ID	Other names	Comment
DMPK	DMPK	DMPK	ENSG00000104936	Dystrophia myotonica-protein kinase, myotonin-protein kinase	Reduced expression of DMPK is associated with myotonic dystrophy 1 (see Kaliman and Lagostera 2008)
	DMPK2	CDC42BPG	ENSG00000171219	Myotonic dystrophy kinase-related CDC42 binding protein kinase $\gamma$ , HSMDPKIN, kappa-200, MRCK $\gamma$	
	MRCK $\alpha$	CDC42BPA	ENSG00000143776	MRCKA, myotonic dystrophy kinase-related CDC42-binding protein kinase $\alpha$	Reported to have a role in cellular iron regulation (Cmejla <i>et al.</i> , 2010)
	MRCK $\beta$	CDC42BPB	ENSG00000198752	MRCKB, myotonic dystrophy kinase-related CDC42-binding protein kinase $\beta$	Reported to be involved in cell migration (Huo <i>et al.</i> , 2011)
	CRICK	CIT	ENSG00000122966	Citron Rho-interacting kinase, serine/threonine-protein kinase 21	Shares structural homology with the Rho kinases
MAST	MAST1	MAST1	ENSG00000105613	Syntrophin-associated protein kinase	Members of the microtubule-associated serine/threonine kinase family appear to have a role in platelet production (Johnson <i>et al.</i> , 2009) and inflammatory bowel disease (Labbe <i>et al.</i> , 2008).
	MAST2	MAST2	ENSG00000086015	–	
	MAST3	MAST3	ENSG00000099308	–	
	MAST4	MAST4	ENSG00000069020	–	
	MASTL	MASTL	ENSG00000120539	Microtubule associated serine/threonine kinase-like, greatwall, GWL	
NDR	LATS1	LATS1	ENSG00000131023	Large tumor suppressor homologue 1, WARTS	The large tumour suppressor protein kinases are phosphorylated and activated by MST2 kinase (serine/threonine kinase 3, ENSG00000104375, Chan <i>et al.</i> , 2005)
	LATS2	LATS2	ENSG00000150457	Large tumor suppressor homologue 2, KPM	
	NDR1	STK38	ENSG00000112079	Serine/threonine kinase 38, nuclear Dbf2-related kinase 1	
	NDR2	STK38L	ENSG00000211455	Serine/threonine kinase 38 like, nuclear Dbf2-related kinase 2	
PKB	PDK1	PDPK1	ENSG00000140992	3-Phosphoinositide-dependent protein kinase 1	

Subfamily	Nomenclature	HGNC nomenclature	Ensembl ID	Other names	Comment
PKN	PKN1	PKN1	ENSG00000123143	Protein kinase N1, protein kinase C-related kinase 1, PAK1, PKN, PRK1, PRKCL1	PKN family members are activated by Rho, PIP <sub>3</sub> and PDK1 (Dong <i>et al.</i> , 2000)
	PKN2	PKN2	ENSG00000065243	Protein kinase N2, pak-2, PRK2, PRKCL2	
	PKN3	PKN3	ENSG00000160447	Protein kinase N3, PKNβ	
RSK	MSK1	RPS6KA5	ENSG00000100784	Ribosomal protein S6 kinase α5, nuclear mitogen- and stress-activated protein kinase 1, RSK-like protein kinase	The mitogen- and stress-acted protein kinases are activated by phosphorylation evoked by MAP kinases and appear to be central to that pathway of cAMP response element-binding protein phosphorylation (Wiggin <i>et al.</i> , 2002)
	MSK2	RPS6KA4	ENSG00000162302	Ribosomal protein S6 kinase α4, nuclear mitogen- and stress-activated protein kinase 2, ribosomal protein kinase B	
	S6K1	RPS6KB1	ENSG00000108443	S6Kβ1	
	S6K2	RPS6KB2	ENSG00000175634	S6Kβ, S6Kβ2	
	RSK1	RPS6KA1	ENSG00000117676	MAPKAPK1A, RSKα1	
	RSK2	RPS6KA3	ENSG00000177189	MAPKAPK1B, RSKα3, ISPK1	
	RSK3	RPS6KA2	ENSG00000071242	MAPKAPK1C, RSKα2	
	RSK4	RPS6KA6	ENSG00000072133	RSKα6	
	SGK494	–	ENSG00000167524	AC005726.6	
	RSKL		RPS6KC1	ENSG00000136643	
		RPS6KL1	ENSG00000198208	ribosomal protein S6 kinase-like 1	
SGK	SGK1	SGK1	ENSG00000118515	SGK	Serum- and glucocorticoid-inducible kinases are regulated at the transcriptional level by serum and glucocorticoids. SGK1 has been reported to be phosphorylated and activated by mTORC2 (Garcia-Martinez and Alessi, 2008)
	SGK2	SGK2	ENSG00000101049	–	
	SGK3	SGK3	ENSG00000104205	SGK2, SGKL	
YANK	YANK1	STK32A	ENSG00000169302		
	YANK2	STK32B	ENSG00000152953	STK32, STKG6	
	YANK3	STK32C	ENSG00000165752	PKE	

## Selected non-AGC protein kinase activities

Nomenclature	AMP kinase	Casein kinase 2	Myosin light chain kinase	Calmodulin-dependent kinase II
Preferred abbreviation	AMPK	CK2	MLCK1 (smooth muscle and non-muscle isoform), MLCK2 (skeletal muscle isoform)	CaMKII
Ensembl ID	$\alpha$ 1 (ENSG00000132356); $\alpha$ 2 (ENSG00000162409); $\beta$ 1 (ENSG00000111725); $\beta$ 2 (ENSG00000131791); $\gamma$ 1 (ENSG00000181929); $\gamma$ 2 (ENSG00000106617); $\gamma$ 3 (ENSG00000115592)	$\alpha$ ENSG00000101266; $\alpha'$ ENSG00000070770; $\beta$ ENSG00000204435	MLCK1 ENSG00000065534; MLCK2 ENSG00000101306	$\alpha$ (ENSG00000070808); $\beta$ (ENSG00000058404); $\gamma$ (ENSG00000148660); $\delta$ (ENSG00000145349)
Other names	–	–	MYLK	–
Endogenous activator	AMP	–	Ca <sup>2+</sup> -calmodulin	Ca <sup>2+</sup> -calmodulin
Selective activators	AICA-riboside (Corton <i>et al.</i> , 1995)	–	–	–
Selective inhibitors	Dorsomorphin (Zhou <i>et al.</i> , 2001)	DRB (Zandomeni <i>et al.</i> , 1986)	–	K252a (Hashimoto <i>et al.</i> , 1991)

AMP-activated protein kinase is a heterotrimeric protein kinase, made up of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, while casein kinase 2 is a heterotetrameric protein kinase, made up of 2  $\beta$  subunits with two other subunits of  $\alpha$  and/or  $\alpha'$  composition. STO609 is an inhibitor of calmodulin kinase kinase (ENSM0025000001201, Tokumitsu *et al.*, 2002), an upstream activator of calmodulin-dependent kinase.

**Abbreviations:** AICA-riboside, 5-aminoimidazole-4-carboxamide-1- $\beta$ -ribose, also known as acadesine; API2, 1,5-dihydro-5-methyl-1- $\beta$ -D-ribofuranosyl-1,4,5,6,8-pentaazaacennaphthylen-3-amine, also known as triciribine; CGP53353, 5,6-bis([4-fluorophenyl]amino)-2H-isoindole-1,3-dione; CPT-2'-Ome-cAMP, 8-(4-chlorophenylthio)-2'-O-methyladenosine 3',5'-cyclic monophosphate monosodium hydrate; DRB, 5,6-dichloro-1- $\beta$ -D-ribofuranosylbenzimidazole; fasudil, 1-(5-isoquinolylsulfonyl)homopiperazine dihydrochloride, also known as HA1077; GSK690693, 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[[3(S)-piperidin-3-yl]methoxy]imidazo[4,5-c]pyridin-4-yl]-2-methylbut-3-yn-2-ol; PD98059, 2-(2-amino-3-methoxy-phenyl)chromen-4-one; PDK1, phosphoinositide-dependent protein kinase 1 (ENSG00000140992); Rp-8-CPT-cGMPs, Rp-8-[(4-chlorophenyl)thio]-guanosine-cyclic 3',5'-hydrogen phosphorothioate; ruboxistaurin, (S)-13-[(dimethylamino)methyl]-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1H,13H-dibenzo[*e,k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-1,3(2H)-dione, also known as LY333531; SB203580, 4-(5-[4-fluorophenyl]-2-[4-methylsulfinylphenyl]-3H-imidazol-4-yl)pyridine; SP600125, anthra[1,9-*cd*]pyrazol-6(2H)-one; STO609, trans-4-[(1R)-1-aminoethyl]-N-4-pyridinyl-cyclohexane carboxamide (Y-27632), and 7-oxo-7H-benzimidazo(2,1a) benz (de) isoquinoline-3-carboxy acid acetate

## Further Reading

- Akritopoulou-Zanze I, Hajduk PJ (2009). Kinase-targeted libraries: the design and synthesis of novel, potent, and selective kinase inhibitors. *Drug Discov Today* **14**: 291–297.
- Bayasas JR (2008). Dissecting the role of the 3-phosphoinositide-dependent protein kinase-1 (PDK1) signalling pathways. *Cell Cycle* **7**: 2978–2982.
- Borders AS, de AL, Van Eldik LJ, Watterson DM (2008). The p38alpha mitogen-activated protein kinase as a central nervous system drug discovery target. *BMC Neurosci* **9**: S12.
- Boutros T, Chevet E, Metrakos P (2008). Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: roles in cell growth, death, and cancer. *Pharmacol Rev* **60**: 261–310.
- Brown MD, Sacks DB (2009). Protein scaffolds in MAP kinase signalling. *Cell Signal* **21**: 462–469.
- Chene P (2008). Challenges in design of biochemical assays for the identification of small molecules to target multiple conformations of protein kinases. *Drug Discov Today* **13**: S22–S29.
- Duronio V (2008). The life of a cell: apoptosis regulation by the PI3K/PKB pathway. *Biochem J* **415**: 333–344.
- Goldstein DM, Gray NS, Zarrinkar PP (2008). High-throughput kinase profiling as a platform for drug discovery. *Nat Rev Drug Discov* **7**: 391–397.
- Hofmann F, Bernhard D, Lukowski R, Weinmeister P (2009). cGMP regulated protein kinases (cGK). *Handb Exp Pharmacol* **137**: 162.
- Johnson L (2007). Protein kinases and their therapeutic exploitation. *Biochem Soc Trans* **35**: 7–11.
- Kaliman P, Llagostera E (2008). Myotonic dystrophy protein kinase (DMPK) and its role in the pathogenesis of myotonic dystrophy 1. *Cell Signal* **20**: 1935–1941.
- Kelly E, Bailey CP, Henderson G (2007). Agonist-selective mechanisms of GPCR desensitization. *Br J Pharmacol* **153**: S379–S388.
- Kondoh K, Nishida E (2007). Regulation of MAP kinases by MAP kinase phosphatases. *Biochim Biophys Acta* **1773**: 1227–1237.
- Krishna M, Narang H (2008). The complexity of mitogen-activated protein kinases (MAPKs) made simple. *Cell Mol Life Sci* **65**: 3525–3544.
- Lang F, Strutz-Seeböhm N, Seeböhm G, Lang UE (2010). Significance of SGK1 in the regulation of neuronal function. *J Physiol* **588**: 3349–3354.
- Lawrence MC, Jivan A, Shao C, Duan L, Goad D, Zaganjor E *et al.* (2008). The roles of MAPKs in disease. *Cell Res* **18**: 436–442.
- Liao JJ (2007). Molecular recognition of protein kinase binding pockets for design of potent and selective kinase inhibitors. *J Med Chem* **50**: 409–424.
- Malemud CJ (2007). Inhibitors of stress-activated protein/mitogen-activated protein kinase pathways. *Curr Opin Pharmacol* **7**: 339–343.
- Manning BD, Cantley LC (2007). AKT/PKB signaling: navigating downstream. *Cell* **129**: 1261–1274.
- Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S (2002). The protein kinase complement of the human genome. *Science* **298**: 1912–1934.

- May LT, Hill SJ (2008). ERK phosphorylation: spatial and temporal regulation by G protein-coupled receptors. *Int J Biochem Cell Biol* **40**: 2013–2017.
- Meloche S, Pouyssegur J (2007). The ERK1/2 mitogen-activated protein kinase pathway as a master regulator of the G1- to S-phase transition. *Oncogene* **26**: 3227–3239.
- Pearce LR, Komander D, Alessi DR (2010). The nuts and bolts of AGC protein kinases. *Nat Rev Mol Cell Biol* **11**: 9–22.
- Premont RT, Gainetdinov RR (2007). Physiological roles of G protein-coupled receptor kinases and arrestins. *Annu Rev Physiol* **69**: 511–534.
- Prudent R, Cochet C (2009). New protein kinase CK2 inhibitors: jumping out of the catalytic box. *Chem Biol* **16**: 112–120.
- Roberts PJ, Der CJ (2007). Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene* **26**: 3291–3310.
- Rozenfurt E (2007). Mitogenic signaling pathways induced by G protein-coupled receptors. *J Cell Physiol* **213**: 589–602.
- Sale EM, Sale GJ (2008). Protein kinase B: signalling roles and therapeutic targeting. *Cell Mol Life Sci* **65**: 113–127.
- Sharma V, Wang Q, Lawrence DS (2008). Peptide-based fluorescent sensors of protein kinase activity: design and applications. *Biochim Biophys Acta* **1784**: 94–99.
- Shaul YD, Seger R (2007). The MEK/ERK cascade: from signaling specificity to diverse functions. *Biochim Biophys Acta* **1773**: 1213–1226.
- Steinberg GR, Jorgensen SB (2007). The AMP-activated protein kinase: role in regulation of skeletal muscle metabolism and insulin sensitivity. *Mini Rev Med Chem* **7**: 519–526.
- Tarrant MK, Cole PA (2009). The chemical biology of protein phosphorylation. *Annu Rev Biochem* **78**: 797–825.
- Towler MC, Hardie DG (2007). AMP-activated protein kinase in metabolic control and insulin signaling. *Circ Res* **100**: 328–341.
- Turk BE (2008). Understanding and exploiting substrate recognition by protein kinases. *Curr Opin Chem Biol* **12**: 4–10.
- Ubersax JA, Ferrell JE (2007). Mechanisms of specificity in protein phosphorylation. *Nat Rev Mol Cell Biol* **8**: 530–541.
- Wagner EF, Nebreda AR (2009). Signal integration by JNK and p38 MAPK pathways in cancer development. *Nat Rev Cancer* **9**: 537–549.
- Witczak CA, Sharoff CG, Goodyear LJ (2008). AMP-activated protein kinase in skeletal muscle: from structure and localization to its role as a master regulator of cellular metabolism. *Cell Mol Life Sci* **65**: 3737–3755.
- Zhang J, Yang PL, Gray NS (2009). Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* **9**: 28–39.
- Zhang Y, Dong C (2007). Regulatory mechanisms of mitogen-activated kinase signaling. *Cell Mol Life Sci* **64**: 2771–2789.
- <http://www.kinase.com/human/kinome/>

## References

- Alessi DR *et al.* (1995). *J Biol Chem* **270**: 27489–27494.
- Alessi DR *et al.* (1997). *Curr Biol* **7**: 261–269.
- Asano T *et al.* (1989). *Br J Pharmacol* **98**: 1091–1100.
- Bennett BL *et al.* (2001). *Proc Natl Acad Sci U S A* **98**: 13681–13686.
- Butt E *et al.* (1994). *Eur J Pharmacol* **269**: 265–268.
- Chalfant CE *et al.* (1996). *Mol Endocrinol* **10**: 1273–1281.
- Chan EH *et al.* (2005). *Oncogene* **24**: 2076–2086.
- Christensen AE *et al.* (2003). *J Biol Chem* **278**: 35394–35402.
- Chuang TT *et al.* (1995). *J Biol Chem* **270**: 18660–18665.
- Cmejla R *et al.* (2010). *Biochem Biophys Res Commun* **395**: 163–167.
- Corton JM *et al.* (1995). *Eur J Biochem* **229**: 558–565.
- Davies SP *et al.* (2000). *Biochem J* **351**: 95–105.
- Dong LQ *et al.* (2000). *Proc Natl Acad Sci U S A* **97**: 5089–5094.
- Dudley DT *et al.* (1995). *Proc Natl Acad Sci U S A* **92**: 7686–7689.
- Duncia JV *et al.* (1998). *Bioorg Med Chem Lett* **8**: 2839–2844.
- Eyers PA *et al.* (1998). *Chem Biol* **5**: 321–328.
- Favata MF *et al.* (1998). *J Biol Chem* **273**: 18623–18632.
- Garcia-Martinez JM, Alessi DR (2008). *Biochem J* **416**: 375–385.
- Hara K *et al.* (2002). *Cell* **110**: 177–189.
- Hashimoto Y *et al.* (1991). *Biochem Biophys Res Commun* **181**: 423–429.
- Heerding DA *et al.* (2008). *J Med Chem* **51**: 5663–5679.
- Hresko RC, Mueckler M (2005). *J Biol Chem* **280**: 40406–40416.
- Huo L *et al.* (2011). *EMBO J* **30**: 665–678.
- Jensen CJ *et al.* (1999). *J Biol Chem* **274**: 27168–27176.
- Jirousek MR *et al.* (1996). *J Med Chem* **39**: 2664–2671.
- Johnson HJ *et al.* (2009). *Exp Hematol* **37**: 901–908.
- Kang G *et al.* (2005). *J Physiol* **566**: 173–188.
- Kim DH *et al.* (2002). *Cell* **110**: 163–175.
- Kozasa T *et al.* (1998). *Science* **280**: 2109–2111.
- Labbe C *et al.* (2008). *Genes Immun* **9**: 602–612.
- Lee JC *et al.* (1994). *Nature* **372**: 739–746.
- Pronin AN, Benovic JL (1997). *J Biol Chem* **272**: 3806–3812.
- de Rooij J *et al.* (1998). *Nature* **396**: 474–477.
- Saltese M *et al.* (1997). *J Biol Chem* **272**: 10188–10195.
- Sarbassov DD *et al.* (2005). *Science* **307**: 1098–1101.
- Schiebel K *et al.* (1997). *Hum Mol Genet* **6**: 1985–1989.
- Strachan RT *et al.* (2009). *J Biol Chem* **284**: 5557–5573.
- Sutherland C *et al.* (1993). *Biochem J* **296**: 15–19.
- Tokumitsu H *et al.* (2002). *J Biol Chem* **277**: 15813–15818.
- Uehata M *et al.* (1997). *Nature* **389**: 990–994.
- Wiggin GR *et al.* (2002). *Mol Cell Biol* **22**: 2871–2881.
- Winstel R *et al.* (1996). *Proc Natl Acad Sci U S A* **93**: 2105–2109.
- Zandomeni R *et al.* (1986). *J Biol Chem* **261**: 3414–3419.
- Zhou G *et al.* (2001). *J Clin Invest* **108**: 1167–1174.

# Protein turnover

**Overview:** peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases (EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-).

It is beyond the scope of the Guide to list all peptidase and proteinase activities; this summary focusses on selected enzymes of significant pharmacological interest.

## Aminopeptidases (E.C. 3.4.11.-)

Nomenclature	HGNC nomenclature	Ensembl ID	Other names	Comments
Aminopeptidase A	DNPEP	ENSG00000123992	Aspartyl aminopeptidase, ASPEP, DAP	Hydrolyses CCK-8 (Migaud <i>et al.</i> , 1996); angiotensin-II (Zini <i>et al.</i> , 1996), neurokinin B, chromogranin A, kallidin (Goto <i>et al.</i> , 2006)
Aminopeptidase N	ANPEP	ENSG00000166825	Alanyl aminopeptidase, microsomal aminopeptidase, gp150, myeloid plasma membrane glycoprotein CD13	–
Aminopeptidase O	C9orf3	ENSG00000148120	AOPEP	–
Aminopeptidase Q	–	ENSG00000172901	Laeverin, AC010282.1	–
Aminopeptidase-like 1	NPEPL1	ENSG00000215440	–	–
Arginyl aminopeptidase	RNPEP	ENSG00000176393	Aminopeptidase B	–
Arginyl aminopeptidase-like 1	RNPEPL1	ENSG00000142327	Aminopeptidase B-like	–
Endoplasmic reticulum aminopeptidase 1	ERAP1	ENSG00000164307	Adipocyte-derived leucine aminopeptidase, puromycin-insensitive leucyl-specific aminopeptidase, type 1 tumor necrosis factor receptor shedding aminopeptidase regulator	–
Endoplasmic reticulum aminopeptidase 2	ERAP2	ENSG00000164308	Leukocyte-derived arginine aminopeptidase	–
Glutamyl aminopeptidase	ENPEP	ENSG00000138792	EAP, aminopeptidase A, differentiation antigen gp160, CD249 antigen	–
Leucine aminopeptidase 3	LAP3	ENSG00000002549	LAP, LAPEP	–
Leucyl-cysteinyl aminopeptidase	LNPEP	ENSG00000113441	Oxytocinase, OTase, insulin-regulated membrane aminopeptidase, insulin-responsive aminopeptidase, IRAP, placental leucine aminopeptidase, P-LAP	Hydrolyses vasopressin, oxytocin, kallidin, met-enkephalin, dynorphin A
Leukotriene A <sub>4</sub> hydrolase	LTA4H	ENSG00000111144	–	Hydrolyses leukotriene A <sub>4</sub> (see Page S296)
Methionyl aminopeptidase 1	METAP1	ENSG00000164024	MAP1A	–
Methionyl aminopeptidase 2	METAP2	ENSG00000111142	–	–
Methionyl aminopeptidase type 1D (mitochondrial)	METAP1D	ENSG00000172878	MAP1D	–
Puromycin-sensitive aminopeptidase	NPEPPS	ENSG00000141279	Aminopeptidase puromycin sensitive	–

Nomenclature	HGNC nomenclature	Ensembl ID	Other names	Comments
Puromycin-sensitive aminopeptidase-like protein	–	ENSG00000174093	RP11-1407O15.2	–
TRH-specific aminopeptidase	TRHDE	ENSG00000072657	Thyrotropin-releasing hormone-degrading ectoenzyme, thyroliberinase, pyroglutamyl-peptidase II, PAP-II	–
X-prolyl aminopeptidase 1	XPNPEP1	ENSG00000108039	Aminopeptidase P 1, soluble X-prolyl aminopeptidase	–
X-prolyl aminopeptidase 2	XPNPEP2	ENSG00000122121	Aminopeptidase P 2, membrane-bound X-prolyl aminopeptidase	–
X-prolyl aminopeptidase 3	XPNPEP3	ENSG00000196236	Aminopeptidase P 3, APP3, NPHPL1	–

### Serine-type carboxypeptidases (3.4.16.-)

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Cathepsin A	CTSA	ENSG00000064601	GSL, PPGB, carboxypeptidase C
Carboxypeptidase D	CPD	ENSG00000108582	–
Vitellogenin carboxypeptidase-like protein	CPVL	ENSG00000106066	–
Prolylcarboxypeptidase	PRCP	ENSG00000137509	Angiotensinase C, HUMPCP, PCP, lysosomal Pro-X carboxypeptidase
Serine carboxypeptidase 1	SCPEP1	ENSG00000121064	RISC

### Metallo-carboxypeptidases (3.4.17.-)

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
AE binding protein 1	AEBP1	ENSG00000106624	Aortic carboxypeptidase-like protein ACLP
Carboxypeptidase A1 (pancreatic)	CPA1	ENSG00000091704	–
Carboxypeptidase A2 (pancreatic)	CPA2	ENSG00000158516	–
Carboxypeptidase A3 (mast cell)	CPA3	ENSG00000163751	–
Carboxypeptidase A4	CPA4	ENSG00000128510	–
Carboxypeptidase A5	CPA5	ENSG00000158525	–
Carboxypeptidase A6	CPA6	ENSG00000165078	CPAH
Carboxypeptidase B1 (tissue)	CPB1	ENSG00000153002	–
Carboxypeptidase B2 (plasma)	CPB2	ENSG00000080618	CPU, PCPB, TAFI
Carboxypeptidase E	CPE	ENSG00000109472	
Carboxypeptidase M	CPM	ENSG00000135678	
Carboxypeptidase N, polypeptide 1	CPN1	ENSG00000120054	Carboxypeptidase N, polypeptide 1
Carboxypeptidase N, polypeptide 2	CPN2	ENSG00000178772	ACBP
Carboxypeptidase O	CPO	ENSG00000144410	
Carboxypeptidase X (M14 family), member 1	CPXM1	ENSG00000088882	CPX-1, CPX1, CPXM
Carboxypeptidase X (M14 family), member 2	CPXM2	ENSG00000121898	
Carboxypeptidase Z	CPZ	ENSG00000109625	
Carnosine dipeptidase 1 (metallopeptidase M20 family)	CNDP1	ENSG00000150656	Glutamate carboxypeptidase-like protein 2
Carnosine dipeptidase 2	CNDP2	ENSG00000133313	HsT2298, PEPA
Dipeptidyl-peptidase 7	DPP7	ENSG00000176978	DPPII



Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Folate hydrolase (prostate-specific membrane antigen) 1	FOLH1	ENSG00000086205	GCP2, GCPII, NAALAD1, NAALADase, PSM, PSMA
Folate hydrolase 1B	FOLH1B	ENSG00000134612	FOLH2, FOLHP, GCPIII, PSMAL
N-Acetylated $\alpha$ -linked acidic dipeptidase-like 1	NAALADL1	ENSG00000168060	–
N-Acetylated $\alpha$ -linked acidic dipeptidase 2	NAALAD2	ENSG00000077616	–
Plasma glutamate carboxypeptidase	–	ENSG00000104324	AC010859.1

### Endopeptidases

Nomenclature	Neutral endopeptidase	Dipeptidyl peptidase IV
E.C.	3.4.24.11	3.4.14.5
HGNC nomenclature	MME	DPP4
Ensembl ID	ENSG00000196549	ENSG00000197635
Other names	Enkephalinase, neprilysin, NEP	CD26, adenosine deaminase complexing protein-2
Endogenous substrates	Enkephalins	GLP1
Selective inhibitors	Thiorphan	–

Nomenclature	Angiotensin-converting enzyme 1	Angiotensin-converting enzyme 2	Endothelin-converting enzyme 1	Endothelin-converting enzyme 2
E.C.	3.4.15.1	3.4.15.1	3.4.24.71	3.4.24.71
HGNC nomenclature	ACE	ACE2	ECE1	ECE2
Ensembl ID	ENSG00000159640	ENSG00000130234	ENSG00000117298	ENSG00000145194
Other names	Dipeptidyl carboxypeptidase I, Kininase II, CD143	–	–	–
Endogenous substrates	Angiotensin I > angiotensin II	Angiotensin I > angiotensin I-9 (Donoghue <i>et al.</i> , 2000)	Endothelin-1, -2, -3	Endothelin-1, -2, -3
Selective inhibitors	Captopril	Captopril	SM19712 (Umekawa <i>et al.</i> , 2000)	–
Probes	Hip-His Leu	Abz-Ser-Pro-Tyr(NO <sub>2</sub> )-OH	–	–

ACE1 appears to express a distinct GPI hydrolase activity (Kondoh *et al.* 2005).

### Caspases (E.C. 3.4.22.-)

**Overview:** Caspases, which derive their name from Cysteine ASpartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (caspases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

Nomenclature	Caspase 1	Caspase 2	Caspase 3	Caspase 4
EC	3.4.22.36	3.4.22.55	3.4.22.56	3.4.22.57
Ensembl ID	ENSG00000137752	ENSG00000106144	ENSG00000164305	ENSG00000196954
Other names	CASP1, interleukin-1 $\beta$ convertase, IL-1BC, interleukin-1 $\beta$ -converting enzyme, IL-1 $\beta$ -converting enzyme, ICE, p45	CASP2, ICH-1 protease, neural precursor cell expressed developmentally down-regulated protein 2, NEDD-2	CASP3, apopain, cysteine protease CPP32, Yama protein, SREBP cleavage activity 1, SCA-1	CASP4, ICH-2 protease, TX protease, ICE(rel)-II,
Subunits	Caspase-1 subunit p20; caspase-1 subunit p10	Caspase-2 subunit p18; caspase-2 subunit p13; caspase-2 subunit p12	Caspase-3 subunit p17; caspase-3 subunit p12	Caspase-4 subunit 1; caspase-4 subunit 2

Nomenclature	Caspase 1	Caspase 2	Caspase 3	Caspase 4
Substrates	Pro-caspase 4, pro-interleukin-1 $\beta$ , D4-GD1, parkin		Pro-caspase 7, caspase 3, PARP, ICAD, Rb, PKC $\delta$ , Huntingtin	Pro-caspase 1
Endogenous activators	–	–	Caspase 8, caspase 9, caspase 10, GrB	–
Activators	–	–	PAC1 (Putt <i>et al.</i> , 2006), PETCM (Jiang <i>et al.</i> , 2003)	–
Selective inhibitors	Z-YVAD-FMK (Avivi-Green <i>et al.</i> , 2002)	Z-VDVAD-FMK (Gamen <i>et al.</i> , 2000)	AZ10417808 (Scott <i>et al.</i> , 2003), Z-DEVD-FMK (Brockstedt <i>et al.</i> , 1998), Z-DQMD-FMK (Izban <i>et al.</i> , 2001)	–

CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1 $\beta$  converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.

Nomenclature	Caspase 5	Caspase 6	Caspase 7	Caspase 8
EC	3.4.22.58	3.4.22.59	3.4.22.60	3.4.22.61
Ensembl ID	ENSG00000137757	ENSG00000138794	ENSG00000165806	ENSG00000064012
Other names	CASP5, ICH-3 protease, TY protease, ICE(rel)-III	CASP6, apoptotic protease Mch-2	CASP7, ICE-like apoptotic protease 3, ICE-LAP3, apoptotic protease Mch-3, CMH-1	CASP8, CE-like apoptotic protease 5, MORT1-associated CED-3 homolog, MACH, FADD-homologous ICE/ CED-3-like protease, FADD-like ICE, FLICE, apoptotic cysteine protease, apoptotic protease Mch-5, CAP4
Subunits	Caspase-5 subunit p20; caspase-5 subunit p10	Caspase-6 subunit p18; caspase-6 subunit p11	Caspase-7 subunit p20; caspase-7 subunit p11	Caspase-8 subunit p18; caspase-8 subunit p10
Substrates	–	–	Pro-caspase 7, caspase 3, PARP, ICAD, Rb, PKC $\delta$ , Huntingtin	Pro-caspase 3, pro-caspase 7, caspase 8, Bid, FLIP, pro-caspase 6
Endogenous activators		–Caspase 8, caspase 9, caspase 10, GrB	Caspase 8, caspase 9, caspase 10, GrB	DISC
Selective inhibitors	Z-WEHD-FMK (Naito <i>et al.</i> , 2002)	Z-VEID-FMK (Ruchaud <i>et al.</i> , 2002)	–	Z-IETD-FMK (Gregoli and Bondurant, 1999)

Nomenclature	Caspase 9	Caspase 10	Caspase 14
EC	3.4.22.62	3.4.22.63	3.4.22.-
Ensembl ID	ENSG00000132906	ENSG00000003400	ENSG00000105141
Other names	CASP, ICE-like apoptotic protease 6, ICE-LAP6, apoptotic protease Mch-6, apoptotic protease-activating factor 3, APAF-3	CASP10, ICE-like apoptotic protease 4, apoptotic protease Mch-4, FAS-associated death domain protein interleukin-1 $\beta$ -converting enzyme 2, FLICE2	CASP14
Subunits	Caspase-9 subunit p35; caspase-9 subunit p10	Caspase-10 subunit p23/17; caspase-10 subunit p12	Caspase-14 subunit p19; caspase-14 subunit p10
Substrates	Pro-caspase 3, pro-caspase 7, caspase 9, pro-caspase 6, PARP	Pro-caspase 3, pro-caspase 7, caspase 10, pro-caspase 6	–
Endogenous activators	–	DISC	–
Selective inhibitors	Z-LEHD-FMK (Mocanu <i>et al.</i> , 2000)	–	–

**Cell-surface protein and extracellular matrix metalloproteinases (E.C. 3.4.24.-)**

**Matrix metalloproteinases (MMP)** are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (e.g. Verma and Hansch, 2007) on functional and structural bases into gelatinases, collagenases, stromelysins and matrilysins, as well as membrane type-MMP (MT-MMP).

Nomenclature	Ensembl ID	Other names	Selective inhibitors
MMP1	ENSG00000196611	Collagenase-1, interstitial collagenase, fibroblast collagenase	
MMP2	ENSG00000087245	Gelatinase-A, 72 kDa type IV collagenase precursor, TBE- 1	ARP100 (Tuccinardi <i>et al.</i> , 2006)
MMP3	ENSG00000149968	Stromelysin-1, transin-1	
MMP7	ENSG00000137673	Matrilysin, PUMP-1 protease, uterine metalloproteinase, matrin	
MMP8	ENSG00000118113	Neutrophil collagenase, PMNL collagenase	
MMP9	ENSG00000100985	Gelatinases-B, 92 kDa type IV collagenase, GELB	
MMP10	ENSG00000166670	Stromelysin-2, transin-2	
MMP11	ENSG00000099953	Stromelysin-3	
MMP12	ENSG00000110347	Macrophage metalloelastase, macrophage elastase, HME	
MMP13	ENSG00000137745	Collagenase-3	CL82198, WAY170523 (Chen <i>et al.</i> , 2000)
MMP14	ENSG00000157227	MT1-MMP, MMP- X1	
MMP15	ENSG00000102996	MT2-MMP, SMCP- 2	
MMP16	ENSG00000156103	MT3-MMP, MMP- X2	
MMP17	ENSG00000198598	MT4-MMP	
MMP19	ENSG00000123342	Matrix metalloproteinase RASI, MMP18	
MMP20	ENSG00000137674	Enamelysin, enamel metalloproteinase	
MMP21	ENSG00000154485	–	
MMP23	ENSG00000189409	Matrix metalloproteinase 21, MMP-21, matrix metalloproteinase 22, MMP-22, Femalysin, MIFR-1	
MMP24	ENSG00000125966	MT5-MMP	
MMP25	ENSG00000008516	MT6-MMP, leukolysin	
MMP26	ENSG00000167346	Matrilysin-2, endometase	
MMP27	ENSG00000137675	–	
MMP28	ENSG00000129270	Epilysin	

A number of small molecule ‘broad spectrum’ inhibitors of MMP have been described, including marimastat and batimastat.

**Tissue inhibitors of metalloproteinase (TIMP)** proteins are endogenous inhibitors acting to chelate MMP proteins.

Nomenclature	Ensembl ID	Other names
TIMP1	ENSG00000102265	Tissue inhibitor of metalloproteinases 1, metalloproteinase inhibitor 1, erythroid-potentiating activity, EPA, fibroblast collagenase inhibitor, collagenase inhibitor
TIMP2	ENSG00000035862	CSC-21K
TIMP3	ENSG00000100234	Tissue inhibitor of metalloproteinases 3, metalloproteinase inhibitor 3 Precursor , MIG-5
TIMP4	ENSG00000157150	Tissue inhibitor of metalloproteinases 4, metalloproteinase inhibitor 4

**ADAM** (A Disintegrin And Metalloproteinase domain containing proteins) and **ADAMTS** (with thrombospondin motifs) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

Nomenclature	Ensembl ID	Other names
ADAM2	ENSG00000104755	Fertilin subunit $\beta$ , PH30 $\beta$ , cancer/testis antigen 15, CT15
ADAM3	ENSG00000197475	ADAM3A, cyritestin 1, CYRN1, tMDCI
ADAM5	ENSG00000196115	Transmembrane metalloproteinase-like, disintegrin-like, and cysteine-rich protein II, tMDC II
ADAM6	ENSG00000233988	C14orf96, tMDCIV

Nomenclature	Ensembl ID	Other names
ADAM7	ENSG00000069206	Sperm maturation-related glycoprotein GP-83
ADAM8	ENSG00000151651	Cell surface antigen MS2, CD156a antigen
ADAM9	ENSG00000168615	Metalloprotease/disintegrin/cysteine-rich protein 9, myeloma cell metalloproteinase, meltrin $\gamma$ , cellular disintegrin-related protein
ADAM10	ENSG00000137845	Mammalian disintegrin-metalloprotease, Kuzbanian protein homolog, CDw156, CD156c antigen
ADAM11	ENSG00000073670	Metalloproteinase-like, disintegrin-like, and cysteine-rich protein, MDC
ADAM12	ENSG00000148848	Meltrin $\alpha$
ADAM15	ENSG00000143537	Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 15, MDC-15, Metalloprotease RGD disintegrin protein, metargidin
ADAM17	ENSG00000151694	TNF $\alpha$ -converting enzyme, TNF $\alpha$ convertase, snake venom-like protease, CD156b antigen
ADAM18	ENSG00000168619	Transmembrane metalloproteinase-like, disintegrin-like, and cysteine-rich protein III, tMDC III, ADAM27
ADAM19	ENSG00000135074	Meltrin $\beta$ , metalloprotease and disintegrin dendritic antigen marker, MADDAM
ADAM20	ENSG00000134007	–
ADAM21	ENSG00000139985	ADAM21P, ADAM31
ADAM22	ENSG00000008277	Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 2, metalloproteinase-disintegrin ADAM22-3
ADAM23	ENSG00000114948	Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 3, MDC-3
ADAM28	ENSG00000042980	Metalloproteinase-like, disintegrin-like, and cysteine-rich protein L, MDC-L, epididymial metalloproteinase-like, disintegrin-like, and cysteine-rich protein II, eMDC II
ADAM29	ENSG00000168594	Cancer/testis antigen 73, CT73
ADAM30	ENSG00000134249	–
ADAM32	ENSG00000197140	–
ADAM33	ENSG00000149451	–

Additional family members include AC123767.2 (cDNA FLJ58962, moderately similar to mouse ADAM3, ENSG00000231168), AL160191.3 (ADAM21-like protein, ENSG00000235812), AC136428.3-2 (ENSG00000185520) and ADAMDEC1 (decysin 1, ENSG00000134028).

#### ADAMTS family

Nomenclature	EC	Ensembl ID	Other names	Comment
ADAMTS1		ENSG00000154734	METH-1	
ADAMTS2	3.4.24.14	ENSG00000087116	Procollagen I/II amino propeptide-processing enzyme, procollagen I N-proteinase, PC I-NP, procollagen N-endopeptidase, pNPI	
ADAMTS3		ENSG00000156140	Procollagen II amino propeptide-processing enzyme, procollagen II N-proteinase, PC II-NP	
ADAMTS4	3.4.24.82	ENSG00000158859	Aggrecanase-1, ADMP-1	
ADAMTS5		ENSG00000154736	Aggrecanase-2, ADMP-2, ADAMTS11	
ADAMTS6		ENSG00000049192	–	
ADAMTS7		ENSG00000136378	COMPase	
ADAMTS8		ENSG00000134917	METH-2, METH-8	
ADAMTS9		ENSG00000163638	–	
ADAMTS10		ENSG00000142303	–	
ADAMTS12		ENSG00000151388	–	
ADAMTS13		ENSG00000160323	von Willebrand factor-cleaving protease, vWF-CP	Loss-of-function mutations of autoimmune antibodies are associated with thrombotic thrombocytopenic purpura
ADAMTS14		ENSG00000138316	–	
ADAMTS15		ENSG00000166106	–	
ADAMTS16		ENSG00000145536	–	
ADAMTS17		ENSG00000140470	–	

Nomenclature	EC	Ensembl ID	Other names	Comment
ADAMTS18		ENSG00000140873	ADAMTS21	
ADAMTS19		ENSG00000145808	–	
ADAMTS20		ENSG00000173157	–	
PAPLN		ENSG00000100767	Papilin	

Other family members include AC104758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

**Abbreviations:** **ARP100**, 2-([(1,1'-biphenyl)-4-ylsulfanyl]-[1-methylethoxy]amino)-N-hydroxyacetamide, **AZ10417808**, 2-([(3,4-dichlorophenyl)amino]-1,4-dihydro-6-nitro-4-oxo-N-2-propenyl-8-quinazolinocarboxamide; **CL82189**, N-(4-[4-morpholinyl]butyl)-2-benzofurancarboxamide hydrochloride; **PAC1**, 4-(phenylmethyl)-1-piperazineacetic acid ([2-hydroxy-3-(2-propenyl)phenyl]methylene)hydrazide; **PETCM**, 1-(trichloromethyl)-2-(4-pyridine)ethanol; **WAY170523**, N-(2-[4-([(2-(hydroxyamino)carbonyl]-4,6-dimethylphenyl) (phenylmethyl) amino]sulfonyl) phenoxy]ethyl)-2-benzofurancarboxamide; **Z-DEVD-FMK**, benzyloxycarbonyl-Asp(OMe)-Glu(OMe)-Val-Asp(OMe)-fluoromethylketone; **Z-DQMD-FMK**, benzyloxycarbonyl-Asp(OMe)-Gln-Met-Asp(OMe)-fluoromethylketone; **Z-LEHD-FMK**, benzyloxycarbonyl-Leu-Glu(OMe)-His-Asp(OMe)-fluoromethylketone; **Z-VDVAD-FMK**, benzyloxycarbonyl-Val-Asp(OMe)-Val-Ala-Asp(OMe)-fluoromethylketone; **Z-VEID-FMK**, benzyloxycarbonyl-Val-Glu(OMe)-Ile-Asp(OMe)-fluoromethylketone; **Z-VYAD-FMK**, benzyloxycarbonyl-Tyr-Val-Ala-Asp(OMe)-fluoromethylketone; **Z-WEHD-FMK**, benzyloxycarbonyl-Trp-Glu(OMe)-His-Asp(OMe)-fluoromethylketone

### Further Reading

- Aiken A, Khokha R (2010). Unraveling metalloproteinase function in skeletal biology and disease using genetically altered mice. *Biochim Biophys Acta* **1803**: 121–132.
- Bindom SM, Lazartigues E (2009). The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol* **302**: 193–202.
- Catania JM, Chen G, Parrish AR (2007). Role of matrix metalloproteinases in renal pathophysiology. *Am J Physiol -Renal Physiol* **292**: F905–F911.
- Charrier-Hismuddin L, Laboisse CL, Merlin D (2008). ADAM-15: a metalloprotease that mediates inflammation. *FASEB J* **22**: 641–653.
- Clark IM, Swingler TE, Sampieri CL, Edwards DR (2008). The regulation of matrix metalloproteinases and their inhibitors. *Int J Biochem Cell Biol* **40**: 1362–1378.
- Danser AH, Batenburg WW, van den Meiracker AH, Danilov SM (2007). ACE phenotyping as a first step toward personalized medicine for ACE inhibitors. Why does ACE genotyping not predict the therapeutic efficacy of ACE inhibition? *Pharmacol Ther* **113**: 607–618.
- DasGupta S, Murumkar PR, Giridhar R, Yadav MR (2009). Current perspective of TACE inhibitors: a review. *Bioorg Med Chem* **17**: 444–459.
- Datta B (2009). Roles of P67/MetAP2 as a tumor suppressor. *Biochim Biophys Acta* **1796**: 281–292.
- Deitersen K, Hendriks D, Scharpe S, Lambeir AM (2009). Carboxypeptidase M: multiple alliances and unknown partners. *Clin Chim Acta* **399**: 24–39.
- Demon D, Van DP, Vanden Berghe T, Vandekerckhove J, Declercq W, Gevaert K *et al.* (2009). Caspase substrates: easily caught in deep waters? *Trends Biotechnol* **27**: 680–688.
- Devel L, Czarny B, Beau F, Georgiadis D, Stura E, Dive V (2010). Third generation of matrix metalloprotease inhibitors: gain in selectivity by targeting the depth of the S1' cavity. *Biochimie* **92**: 1501–1508.
- Drucker DJ (2007). The role of gut hormones in glucose homeostasis. *J Clin Invest* **117**: 24–32.
- van Enderd P (2011). Post-proteasomal and proteasome-independent generation of MHC class I ligands. *Cell Mol Life Sci* **68**: 1553–1567.
- Ferrario CM, Varagic J (2010). The ANG-(1-7)/ACE2/mas axis in the regulation of nephron function. *Am J Physiol Renal Physiol* **298**: F1297–F1305.
- Ferrario CM (2011). ACE2: more of Ang-(1-7) or less Ang II? *Curr Opin Nephrol Hypertens* **20**: 1–6.
- Franchi L, Eigenbrod T, Munoz-Planillo R, Nunez G (2009). The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. *Nat Immunol* **10**: 241–247.
- Gingras D, Beliveau R (2010). Emerging concepts in the regulation of membrane-type 1 matrix metalloproteinase activity. *Biochim Biophys Acta* **1803**: 142–150.
- Greenlee KJ, Werb Z, Kheradmand F (2007). Matrix metalloproteinases in lung: multiple, multifarious, and multifaceted. *Physiol Rev* **87**: 69–98.
- Gupta SP (2007). Quantitative structure-activity relationship studies on zinc-containing metalloproteinase inhibitors. *Chem Rev* **107**: 3042–3087.
- Gyrd-Hansen M, Meier P (2010). IAPs: from caspase inhibitors to modulators of NF-kappaB, inflammation and cancer. *Nat Rev Cancer* **10**: 561–574.
- Hadler-Olsen E, Fadnes B, Sylte I, Uhlin-Hansen L, Winberg JO (2011). Regulation of matrix metalloproteinase activity in health and disease. *FEBS J* **278**: 28–45.
- Haroon N, Inman RD (2010). Endoplasmic reticulum aminopeptidases: biology and pathogenic potential. *Nat Rev Rheumatol* **6**: 461–467.
- Hu J, Van den Steen PE, Sang QX, Opdenakker G (2007). Matrix metalloproteinase inhibitors as therapy for inflammatory and vascular diseases. *Nat Rev Drug Discovery* **6**: 480–498.
- Hui KS (2007). Brain-specific aminopeptidase: from enkephalinase to protector against neurodegeneration. *Neurochem Res* **32**: 2062–2071.
- Imai Y, Kuba K, Penninger JM (2007). Angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Cell Mol Life Sci* **64**: 2006–2012.
- Janecka A, Staniszewska R, Gach K, Fichna J (2008). Enzymatic degradation of endomorphins. *Peptides* **29**: 2066–2073.
- Kantari C, Walczak H (2011). Caspase-8 and bid: caught in the act between death receptors and mitochondria. *Biochim Biophys Acta* **1813**: 558–563.
- Kawanabe Y, Nauli SM (2011). Endothelin. *Cell Mol Life Sci* **68**: 195–203.
- Kirby M, Yu DM, O'Connor S, Gorrell MD (2010). Inhibitor selectivity in the clinical application of dipeptidyl peptidase-4 inhibition. *Clin Sci (Lond)* **118**: 31–41.
- Kirkby NS, Hadoke PW, Bagnall AJ, Webb DJ (2008). The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? *Br J Pharmacol* **153**: 1105–1119.
- Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM (2010). Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther* **128**: 119–128.
- Lambert DW, Hooper NM, Turner AJ (2008). Angiotensin-converting enzyme 2 and new insights into the renin-angiotensin system. *Biochem Pharmacol* **75**: 781–786.
- Lambert DW, Clarke NE, Turner AJ (2010). Not just angiotensinases: new roles for the angiotensin-converting enzymes. *Cell Mol Life Sci* **67**: 89–98.
- Lopez-Otin C, Matrisian LM (2007). Emerging roles of proteases in tumour suppression. *Nat Rev Cancer* **7**: 800–808.

- MacFadyen RJ (2007). Can matrix metalloproteinase inhibitors provide a realistic therapy in cardiovascular medicine? *Curr Opin Pharmacol* **7**: 171–178.
- Mastroianni CM, Liuzzi GM (2007). Matrix metalloproteinase dysregulation in HIV infection: implications for therapeutic strategies. *Trends Mol Med* **13**: 449–459.
- Mogk A, Schmidt R, Bukau B (2007). The N-end rule pathway for regulated proteolysis: prokaryotic and eukaryotic strategies. *Trends Cell Biol* **17**: 165–172.
- Mucha A, Drag M, Dalton JP, Kafarski P (2010). Metallo-aminopeptidase inhibitors. *Biochimie* **92**: 1509–1529.
- Murphy G (2008). The ADAMs: signalling scissors in the tumour microenvironment. *Nat Rev Cancer* **8**: 929–941.
- Murphy G, Nagase H (2011). Localizing matrix metalloproteinase activities in the pericellular environment. *FEBS J* **278**: 2–15.
- Norton GR, Brooksbank R, Woodiwiss AJ (2010). Gene variants of the renin-angiotensin system and hypertension: from a trough of disillusionment to a welcome phase of enlightenment? *Clin Sci (Lond)* **118**: 487–506.
- O'Brien P, O'Connor BF (2008). Seprase: an overview of an important matrix serine protease. *Biochim Biophys Acta* **1784**: 1130–1145.
- Ohnuma K, Dang NH, Morimoto C (2008). Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. *Trends Immunol* **29**: 295–301.
- Okun I, Balakin KV, Tkachenko SE, Ivachtchenko AV (2008). Caspase activity modulators as anticancer agents. *Anticancer Agents Med Chem* **8**: 322–341.
- Page-McCaw A, Ewald AJ, Werb Z (2007). Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol* **8**: 221–233.
- Pejler G, Knight SD, Henningsson F, Wernersson S (2009). Novel insights into the biological function of mast cell carboxypeptidase A. *Trends Immunol* **30**: 401–408.
- Pirard B (2007). Insight into the structural determinants for selective inhibition of matrix metalloproteinases. *Drug Discov Today* **12**: 640–646.
- Pradelli LA, Beneteau M, Ricci JE (2010). Mitochondrial control of caspase-dependent and -independent cell death. *Cell Mol Life Sci* **67**: 1589–1597.
- Raizada MK, Ferreira AJ (2007). ACE2: a new target for cardiovascular disease therapeutics. *J Cardiovasc Pharmacol* **50**: 112–119.
- Ramos-Fernandez M, Bellolio MF, Stead LG (2011). Matrix metalloproteinase-9 as a marker for acute ischemic stroke: a systematic review. *J Stroke Cerebrovasc Dis* **20**: 47–54.
- Rengel Y, Ospelt C, Gay S (2007). Proteinases in the joint: clinical relevance of proteinases in joint destruction. *Arthritis Res Ther* **9**: 221.
- Rocks N, Paulissen G, El Hour M *et al* (2008). Emerging roles of ADAM and ADAMTS metalloproteinases in cancer. *Biochimie* **90**: 369–379.
- Rosell A, Lo EH (2008). Multiphasic roles for matrix metalloproteinases after stroke. *Curr Opin Pharmacol* **8**: 82–89.
- Rosenberg GA (2009). Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. *Lancet Neurol* **8**: 205–216.
- Rudnicki M, Mayer G (2009). Significance of genetic polymorphisms of the renin-angiotensin-aldosterone system in cardiovascular and renal disease. *Pharmacogenomics* **10**: 463–476.
- Schrader K, Huai J, Jockel L, Oberle C, Borner C (2010). Non-caspase proteases: triggers or amplifiers of apoptosis? *Cell Mol Life Sci* **67**: 1607–1618.
- Schulz R (2007). Intracellular targets of matrix metalloproteinase-2 in cardiac disease: rationale and therapeutic approaches. *Annu Rev Pharmacol Toxicol* **47**: 211–242.
- Shi L, Mao C, Xu Z, Zhang L (2010). Angiotensin-converting enzymes and drug discovery in cardiovascular diseases. *Drug Discov Today* **15**: 332–341.
- Shi YB, Fu L, Hasebe T, Ishizuya-Oka A (2007). Regulation of extracellular matrix remodeling and cell fate determination by matrix metalloproteinase stromelysin-3 during thyroid hormone-dependent post-embryonic development. *Pharmacol Ther* **116**: 391–400.
- Taylor RC, Cullen SP, Martin SJ (2008). Apoptosis: controlled demolition at the cellular level. *Nat Rev Mol Cell Biol* **9**: 231–241.
- Tsakamoto T, Wozniak KM, Slusher BS (2007). Progress in the discovery and development of glutamate carboxypeptidase II inhibitors. *Drug Discov Today* **12**: 767–776.
- Tveita A, Rekvig OP, Zykova SN (2008). Glomerular matrix metalloproteinases and their regulators in the pathogenesis of lupus nephritis. *Arthritis Res Ther* **10**: 229.
- Vakifahmetoglu-Norberg H, Zhivotovsky B (2010). The unpredictable caspase-2: what can it do? *Trends Cell Biol* **20**: 150–159.
- Verma RP, Hansch C (2007). Matrix metalloproteinases (MMPs): chemical-biological functions and (Q)SARs. *Bioorg Med Chem* **15**: 2223–2268.
- Vincenti MP, Brinckerhoff CE (2007). Signal transduction and cell-type specific regulation of matrix metalloproteinase gene expression: can MMPs be good for you? *J Cell Physiol* **213**: 355–364.
- Wilson TJ, Singh RK (2008). Proteases as modulators of tumor-stromal interaction: primary tumors to bone metastases. *Biochim Biophys Acta* **1785**: 85–95.
- Wolfe MS (2009). Intramembrane proteolysis. *Chem Rev* **109**: 1599–1612.
- Xu P, Sriramula S, Lazzarini E (2011). ACE2/ANG-(1-7)/Mas pathway in the brain: the axis of good. *Am J Physiol Regul Integr Comp Physiol* **300**: R804–R817.
- Yan C, Boyd DD (2007). Regulation of matrix metalloproteinase gene expression. *J Cell Physiol* **211**: 19–26.
- Yazbeck R, Howarth GS, Abbott CA (2009). Dipeptidyl peptidase inhibitors, an emerging drug class for inflammatory disease? *Trends Pharmacol Sci* **30**: 600–607.
- Zolkiewska A (2008). ADAM proteases: ligand processing and modulation of the Notch pathway. *Cell Mol Life Sci* **65**: 2056–2068.

## References

- Avivi-Green C *et al.* (2002). *J Nutr* **132**: 1812–1818.
- Brockstedt E *et al.* (1998). *J Biol Chem* **273**: 28057–28064.
- Chen JM *et al.* (2000). *J Am Chem Soc* **122**: 9648–9654.
- Donoghue M *et al.* (2000). *Circ Res* **87**: E1–E9.
- Gamen S *et al.* (2000). *Exp Cell Res* **258**: 223–235.
- Goto Y *et al.* (2006). *J Biol Chem* **281**: 23503–23513.
- Gregoli PA, Bondurant MC (1999). *J Cell Physiol* **178**: 133–143.
- Izban KF *et al.* (2001). *Mod Pathol* **14**: 297–310.
- Jiang X *et al.* (2003). *Science* **299**: 223–226.
- Kondoh G *et al.* (2005). *Nat Med* **11**: 160–166.
- Migaud M *et al.* (1996). *Peptides* **17**: 601–607.
- Mocanu MM *et al.* (2000). *Br J Pharmacol* **130**: 197–200.
- Naito T *et al.* (2002). *Nucleic Acids Res Suppl* **2**: 241–242.
- Putt KS *et al.* (2006). *Nat Chem Biol* **2**: 543–550.
- Ruchaud S *et al.* (2002). *EMBO J* **21**: 1967–1977.
- Scott CW *et al.* (2003). *J Pharmacol Exp Ther* **304**: 433–440.
- Tuccinardi T *et al.* (2006). *Bioorg Med Chem* **14**: 4260–4276.
- Umekawa K *et al.* (2000). *Jpn J Pharmacol* **84**: 7–15.
- Zini S *et al.* (1996). *Proc Natl Acad Sci U S A* **93**: 11968–11973.