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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^{th} edn. *Br J Pharmacol* **164** (Suppl. 1): S1–S324.

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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 α-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 progestin 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 α, β and γ subunits, where the α and βγ subunits are responsible for signalling. The α subunit (tabulated below) allows definition of one series of signalling cascades and permits grouping of GPCRs to suggest common cellular, tissue and behavioural responses. Gβγ subunits (tabulated below) also are able to signal, in a manner independent of the Gα 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 Gα signalling.

Gα_s family: β_1-adrenoceptors (see Page S26) in the heart couple principally through Gα_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$_v$1.2, see Page S142). This, in turn leads to the observed action of noradrenaline (norepinephrine) or adrenaline (epinephrine) in increasing cardiac rate and force of contraction. The identification of other G$_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$-coupled receptors would be predicted to evoke smooth muscle relaxation (e.g. β_2-adrenoceptors in bronchioles, Page S26), enhance secretion (e.g. H$_2$ histamine receptors in gastric parietal cells, Page S70), stimulate lipolysis in adipocytes (e.g. β_3-adrenoceptors, Page S26) and inhibit platelet aggregation (e.g. IP prostanoid receptors, Page S97).

Nomenclature	HGNC nomenclature	Other names	Ensembl ID
α_s	*GNAS*	Stimulatory G protein	ENSG00000087460
α_{olf}	*GNAL*	Olfactory type	ENSG00000141404

Gα_i family: M_2 muscarinic acetylcholine receptors (see Page S20) in the heart couple *via* Gα_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, Gα_i subunits and G$\beta\gamma$ subunits (see below) enhance potassium channel opening (K_{iR}2.x, 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_i-coupled receptors would be predicted to inhibit neurotransmitter release (e.g. μ opioid receptors, Page S88, on parasympathetic nerve terminals in the small intestine), inhibit lipolysis in adipocytes (e.g. A_1 adenosine receptors, Page S22) and enhance platelet aggregation (e.g. $P2Y_{12}$ receptors, Page S91).

In the retina, transducin (α_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
α_{i1}	*GNAI1*	Inhibitory G protein α subunit	ENSG00000127955
α_{i2}	*GNAI2*	Inhibitory G protein α subunit	ENSG00000114353
α_{i3}	*GNAI3*	Inhibitory G protein α subunit	ENSG00000065135
α_{t1}	*GNAT1*	Transducin 1 α subunit	ENSG00000114349
α_{t2}	*GNAT2*	Transducin 2 α subunit	ENSG00000134183
α_{t3}	*GNAT3*	Gustducin α subunit	ENSG00000214415
α_o	*GNAO1*	α other	ENSG00000087258
α_z	*GNAZ*	–	ENSG00000128266

Gα_q family: M_3 muscarinic acetylcholine receptors (see Page S20) in bronchial smooth muscle couple via G$\alpha_{q/11}$ subunits to stimulate phospholipase C-β activity (see Page S302). This leads to an elevation of intracellular calcium ions through inositol 1,4,5-trisphosphate action at IP_3 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_q-coupled receptor activation leads to increased platelet aggregation (e.g. $P2Y_1$ 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 (ENSFM00500000269651), 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
α_q	*GNAQ*	ENSG00000156052
α_{11}	*GNA11*	ENSG00000088256
α_{12}	*GNA12*	ENSG00000146535
α_{13}	*GNA13*	ENSG00000120063
α_{14}	*GNA14*	ENSG00000156049
α_{15}	*GNA15*	ENSG00000060558

GNAQP1 is a pseudogene (ENSG00000214077).

G$\beta\gamma$ subunits: although β and γ 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 β-adrenoceptor kinases (see Page S310). Phosphorylation of particular cytoplasmic serine/threonine residues of GPCR allows binding of β-arrestin (ENSFM00250000000572). 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
β1	*GNB1*	ENSG00000078369
β2	*GNB2*	ENSG00000172354
β3	*GNB3*	ENSG00000111664
β4	*GNB4*	ENSG00000114450
β5	*GNB5*	ENSG00000069966

Nomenclature	HGNC nomenclature	Ensembl ID
γ2	*GNG2*	ENSG00000186469
γ3	*GNG3*	ENSG00000162188
γ4	*GNG4*	ENSG00000168243
γ5	*GNG5*	ENSG00000174021
γ7	*GNG7*	ENSG00000176533
γ8	*GNG8*	ENSG00000167414
γ10	*GNG10*	ENSG00000242616
γ11	*GNG11*	ENSG00000127920
γ12	*GNG12*	ENSG00000172380
γ13	*GNG13*	ENSG00000127588
γt1	*GNGT1*	ENSG00000127928
γt2	*GNGT2*	ENSG00000167083

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

Further Reading

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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, Cmkbr1l2, L-CCR, CRAM	Chemerin (Zabel *et al*., 2008)	–
GPR1	ENSG00000183671	–	Chemerin (Barnea *et al*., 2008)	Reported to act as a co-receptor for HIV (Shimizu *et al*., 1999)
GPR3	ENSG00000181773	ACCA	Fails to respond to a variety of lipid-derived agents (Yin *et al*., 2009)	Reported to activate adenylyl cyclase constitutively through G_s (Eggerickx *et al*., 1995). Gene disruption results in premature ovarian aging (Ledent *et al*., 2005), reduced β-amyloid deposition (Thathiah *et al*., 2009) and heightened pain behaviours (Ruiz-Medina *et al*., 2011) in mice
GPR4	ENSG00000177464	–	Protons (Ludwig *et al*., 2003; Tobo *et al*., 2007; Liu *et al*., 2010a)	An initial report suggesting activation by lysophosphatidylcholine, sphingosylphosphorylcholine (Zhu *et al*., 2001) has been retracted (Zhu *et al*., 2005). Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation (Yang *et al*., 2007)
GPR6	ENSG00000146360	–	Fails to respond to a variety of lipid-derived agents (Yin *et al*., 2009)	Reported to activate adenylyl cyclase constitutively through G_s and to be located intracellularly (Padmanabhan *et al*., 2009)
GPR12	ENSG00000132975	GPCR21, Gpcr01, Gpcr12, Gpcr20	Fails to respond to a variety of lipid-derived agents (Yin *et al*., 2009)	Gene disruption results in dyslipidemia and obesity (Bjursell *et al*., 2006)
GPR15	ENSG00000154165	BOB	–	Reported to act as a co-receptor for HIV (Edinger *et al*., 1997)
GPR17	ENSG00000144230	R12	Dual leukotriene and UDP receptor (Ciana *et al*., 2006)	Reported to antagonize CysLT1 receptor signalling *in vivo* and *in vitro* (Maekawa *et al*., 2009)
GPR20	ENSG00000204882	–	–	Reported to inhibit adenylyl cyclase constitutively through $G_{i/o}$ (Hase *et al*., 2008)
GPR22	ENSG00000172209	–	–	Reported to inhibit adenylyl cyclase constitutively through $G_{i/o}$; gene disruption results in increased severity of functional decompensation following aortic banding (Adams *et al*., 2008). Identified as a susceptibility locus for osteoarthritis (Evangelou *et al*., 2011, Kerkhof *et al*., 2010, Valdes and Spector, 2010)
GPR26	ENSG00000154478	–	–	Reported to activate adenylyl cyclase constitutively through G_s (Jones *et al*., 2007)

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

IUPHAR name	Ensembl ID	Other names	Putative endogenous ligand	Comment
GPR149	ENSG00000174948	PGR10, IEDA		Gene disruption results in enhanced fertility (Edson *et al.*, 2010)
GPR161	ENSG00000143147	RE2	–	Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish (Leung *et al.*, 2008)
GPR183	ENSG00000169508	EBI2, Epstein-Barr virus induced gene 2, lymphocyte-specific G protein-coupled receptor	Oxysterols (Hannedouche *et al.*, 2011; Liu *et al.*, 2011)	–
GPRC$_6$	ENSG00000173612	GPRC6A	Basic amino acids, such as L-arginine, L-lysine and L-ornithine (Wellendorph *et al.*, 2005)	–
LGR4	ENSG00000205213	Leucine-rich repeat-containing G-protein coupled receptor 4, GPR48	R-spondins (Carmon *et al.*, 2011; de Lau *et al.*, 2011)	Gene disruption leads to multiple developmental disorders (Luo *et al.*, 2009; Jin *et al.*, 2008; Song *et al.*, 2008; Weng *et al.*, 2008)
LGR5	ENSG00000139292	Leucine-rich repeat-containing G-protein coupled receptor 5, GPR49, GPR67, FEX, HG38	R-spondins (Carmon *et al.*, 2011; de Lau *et al.*, 2011)	–
LGR6	ENSG00000133067;	FLJ14471, VTS20631	R-spondins (Carmon *et al.*, 2011; de Lau *et al.*, 2011)	–
MAS1	ENSG00000130368	Mas	Angiotensin-(1-7) (Santos *et al.*, 2003)	
MRGPRD	ENSG00000172938	TGR7, Mas-related GPR member D, MrgD	β-Alanine (Shinohara *et al.*, 2004)	Potentially exists as a heteromer with MRGPRE (Milasta *et al.*, 2006)
MRGPRX1	ENSG00000170255	SNSR4, Mas-related GPR member X1, MrgX1	BAM8-22 (Chen and Ikeda, 2004)	Reported to mediate the sensation of itch (Liu *et al.*, 2009; Sikand *et al.*. 2011)
MRGPRX2	ENSG00000183695	Mas-related GPR member X2, MrgX2	PAMP (Kamohara *et al.*, 2005), cortistatin (Robas *et al.*, 2003)	–
P2RY10	ENSG00000078589	Purinergic receptor, P2Y10, P2Y-like	Sphingosine 1-phosphate and lysophosphatidic acid (Murakami *et al.*, 2008)	–
OXGR1	ENSG00000165621	GPR80, GPR99, P2Y15	2-Oxoglutarate (He *et al.*, 2004)	–
SUCNR1	ENSG00000198829	GPR91	Succinate (He *et al.*, 2004; Hogberg *et al.*, 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, D0Kist8
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 *et al.*, 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 *et al.*, 2006) and collagen, which activates the $G_{12/13}$ pathway (Luo *et al.*, 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 *et al.*, 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 α-latrotoxin receptor 1	–
LPHN2	ENSG00000117114	Lectomedin-1, LEC1, latrophilin-2, calcium-independent α-latrotoxin receptor 2, latrophilin homolog 1	–
LPHN3	ENSG00000150471	Lectomedin-3, LEC3, Latrophilin-3, calcium-independent α-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	$RAIG_1$, Retinoic acid-induced protein 3, retinoic acid-induced gene 1 protein, orphan G-protein-coupling receptor PEIG-1
GPRC5B	ENSG00000167191	$RAIG_2$, Retinoic acid-induced gene 2 protein, A-69G12.1
GPRC5C	ENSG00000170412	$RAIG_3$, Retinoic acid-induced gene 3 protein,
GPRC5D	ENSG00000111291	$RAIG_4$, 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 ($G\alpha_{t3}$, see Page S6) and $G\alpha_{14}$-mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involvement of PLCβ2 (Zhang *et al*., 2003), TRPM5 (Zhang *et al*., 2003) and IP_3 (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	*TAS1R1*	ENSG00000173662	GPR70, TR1
T1R2	*TAS1R2*	ENSG00000179002	GPR71, TR2
T1R3	*TAS1R3*	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 (-)-α-thujone and picrotoxinin (Behrens *et al*., 2004).

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

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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$_3$ 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$_{2A}$ (non-functional), 5-HT$_{2C}$ (non-functional), 5-HT$_4$, 5-HT$_6$ (non-functional) and 5-HT$_7$ receptors. Unique amongst the GPCRs, RNA editing produces 5-HT$_{2C}$ receptor isoforms that differ in function, such as efficiency and specificity of coupling to G$_{q/11}$and also pharmacology (reviewed by Bockaert *et al.*, 2006; Werry *et al.*, 2008). Most 5-HT receptors (except 5-ht$_{1e}$ and 5-ht$_{5a/5b}$) play specific roles mediating functional responses in different tissues (reviewed by Villalón and Centurión, 2007; Ramage and Villalón, 2008).

Nomenclature	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-ht$_{1e}$
Other names	–	5-HT$_{1D\beta}$	5-HT$_{1D\alpha}$	–
Ensembl ID	ENSG00000178394	ENSG00000135312	ENSG00000179546	ENSG00000168830
Principal transduction	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Selective agonists (p*K*$_i$)	8-OH-DPAT (8.4–9.4), U92016A (9.7) F15599 (8.6, Newman-Tancredi *et al.*, 2009)	L694247 (9.2), CP94253 (8.7), sumatriptan (6.5–8.1), eliptriptan (8.0)	PNU109291 (9.0 – gorilla, Ennis *et al.*, 1998) sumatriptan (8.0–8.7), eletriptan (8.9), L694247 (9.0, Wurch *et al.*, 1998)	BRL-54443 (8.7, Brown *et al.*, 1998)
Selective antagonists (p*K*$_i$)	($\pm$)WAY100635 (7.9–9.2), (*S*)-UH301 (7.9–8.6), NAD299 (robalzotan, 9.2)	SB236057 (8.2, inverse agonist, Middlemiss *et al.*, 1999), SB224289 (inverse agonist, 8.2–8.6), GR55562 (p*K*$_B$ 7.4, Hoyer *et al.*, 2002)	SB714786 (9.1) BRL15572 (7.9)	–
Probes (*K*$_D$)	[^{3}H]WAY100635 (0.3 nM, Khawaja *et al.*, 1997), [^{3}H]NAD299 (0.16 nM), [^{3}H]8-OH-DPAT (0.4 nM), [^{3}H]F13640 (1.4 nM, Heusler *et al.*, 2010) [^{11}C]WAY100635 (PET ligand), p-[^{18}F]MPPF (PET ligand)	[*N-methyl*-^{3}H$_3$]-AZ10419369 (0.37 nM, Maier *et al.*, 2009) [^{3}H]alniditan (2.0–2.4 nM) [^{3}H]eletriptan (3 nM), [^{3}H]sumatriptan (11 nM) [^{125}I]GTI, [^{3}H]GR125743 (2.6 nM, Xie *et al.*, 1999), [^{11}C]AZ10419369 (PET ligand)	[^{3}H]alniditan (1.2–1.4 nM) [^{3}H]eletriptan (0.9 nM), [^{3}H]sumatriptan (7 nM), [^{125}I]GTI, [^{3}H]GR125743 (2.8 nM, Xie *et al.*, 1999)	[^{3}H]5-HT (6 nM)

Nomenclature	5-HT$_{1F}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$
Other names	5-HT$_{1E\beta}$, 5-HT$_6$	D, 5-HT$_2$	5-HT$_{2F}$	5-HT$_{1C}$
Ensembl ID	ENSG00000179097	ENSG00000102468	ENSG00000135914	ENSG00000147246
Principal transduction	G$_{i/o}$	G$_{q/11}$	G$_{q/11}$	G$_{q/11}$
Selective agonists (p*K*$_i$)	LY344864 (8.2, Phebus *et al.*, 1997) LY334370 (8.7), LY573144 (8.7, Nelson *et al.*, 2010), BRL-54443 (8.9, Brown *et al.*, 1993), elitriptan (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 *et al.*, 2005) Locaserin (7.8, Thomsen *et al.*, 2008)
Selective antagonists (p*K*$_i$)	–	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 *et al.*, 2006)
Probes (*K*$_D$)	[^{3}H]LY334370 (0.5 nM), [^{125}I]LSD	[^{3}H]ketanserin (0.2–1.3 nM), [^{3}H]RP62203 (fananserin, 0.13 nM – rat, Malgouris *et al.*,1993), [^{11}C]M100907 (PET ligand), [^{18}F]altanserin (PET ligand)	[^{3}H]5-HT (8 nM – rat) [^{3}H]mesulergine (5–10 nM), [^{3}H]LSD (5–10 nM), [^{125}I]DOI (20–25 nM)	[^{3}H]mesulergine (0.5–2.2 nM), [^{125}I]DOI (6–25 nM), [^{3}H]LSD

Nomenclature	5-HT$_4$	5-ht$_{5a}$	5-ht$_{5b}$	5-HT$_6$
Other names	–	5-HT$_{5\alpha}$	–	–
Ensembl ID	ENSG00000164270	ENSG00000157219	ENSMUSG00000050534	ENSG00000158748
Principal transduction	G$_s$	G$_i$/G$_o$?	None identified	G$_s$
Selective agonists (pK_i)	BIMU8 (7.3), ML10302 (7.9–9.0), RS67506 (8.8–guinea-pig, Eglen *et al.*, 1995)	–	–	WAY181187 (8.7, Schechter *et al.*, 2008) E6801 (partial agonist, 8.7, Holenz *et al.*, 2005)
Selective antagonists (pK_i)	GR113808 (9.3-10.3), SB204070 (9.8 – 10.4), RS100235 (8.7–12.2)	SB699551 (8.2)	–	SB399886 (9.4, Hirst *et al.*, 2006) SB271046 (8.9), SB357134 (8.5, Bromidge *et al.*, 2001), Ro630563 (7.9–8.4)
Probes (K_D)	[^{3}H]GR113808 (50 – 200 pM), [^{125}I]SB207710 (86 pM – piglet, Brown *et al.*, 1993), [^{3}H]RS57639 (0.25 nM–guinea-pig, Bonhaus *et al.*, 1997) [^{11}C] SB207145 (PET ligand)	[^{3}H]5-CT (2.5 nM), [^{125}I]LSD (0.2 nM)	[^{3}H]5-CT, [^{125}I]LSD	[^{125}I]SB258585 (1.0 nM, Hirst *et al.*, 2000), [^{3}H]Ro630563 (5 nM, Boess *et al.*, 1998), [^{3}H]5-CT, [^{125}I]LSD (2 nM)

Nomenclature	5-HT$_7$
Other names	5-HT$_1$-like, 5-HT$_{1Y}$, orphan
Ensembl ID	ENSG00000148680
Principal transduction	G$_s$
Selective agonists (p*Ki*)	E55888 (8.6, Brenchat *et al.*, 2009)
Selective antagonists (pK_i)	SB656104 (8.7, Forbes *et al.*, 2002), SB269970 (8.6–8.9 Thomas *et al.*, 2000), SB258719 (7.5)
Radioligands (K_D)	[^{3}H]SB269970 (1.2 nM, Thomas *et al.* 2000), [^{3}H]5-CT (0.4 nM, Thomas *et al.*, 2000) [^{3}H]LSD (3 nM), [^{3}H]5-HT (1–8 nM)

Tabulated *pK$_i$* and *K$_D$* 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). The nomenclature of 5-HT$_{1B}$/5-HT$_{1D}$ receptors has been revised (Hartig *et al.*, 1996). Only the non-rodent form of the receptor was previously called 5-HT$_{1D\beta}$. The human 5-HT$_{1B}$ 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$_{1B}$ receptor. Fananserin and ketanserin bind with high affinity to dopamine D4 and histamine H$_1$ receptors respectively, and ketanserin is a potent α1 adrenoceptor antagonist, in addition to blocking 5-HT$_{2A}$ receptors. The human 5-ht$_{5A}$ 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$_{5b}$ receptor is non-functional due to interruption of the gene by stop codons. The 5-ht$_{1e}$ 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$_{1P}$, has been described (Gershon, 1999).

Abbreviations: **5-CT**, 5-carboxamidotryptamine; **8-OH-DPAT**, 8-hydroxy-2-(di-*n*-propylamino)tetralin; **[*N*-methyl-^{3}H$_3$]AZ10419369**, 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylicacid (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-1*H*-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)-1*H*-indole; **BW723C86**, 1-[5(2-thienylmethoxy)-1*H*-3-indolyl]propan-2-amine hydrochloride; **CP94253**: 3- (1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3, 2-b] pyridine; **E6801**, 6-chloro-*N*-(3-(2-dimethylamino)ethyl)-1*H*-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-pyperidin-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-1*H*-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[(methylsuphonyl)amino] ethyl]-4-piperidinyl]methyl-1-methyl-1*H*-indole-3-carboxylate; **GR125743**, *n*-[4-methoxy-3-(4-methyl-1-piperizinyl)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]-1*H*-indol-3yl] ethanamine; **LY334370**, 5-(4-flurobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1*H*-indole fumarate; **LY344864**, *N*-[(6*R*) -6-dimethylamino-6,7,8,9-tetrahydro-5*H*-carbazo-3-yl]-4- fluorobenzamide; **LY573144**, 2,4,6-trifluoro-N-[6-[(1-methylpiperidin-4-yl)carbonyl]pyridin-2yl]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)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulfonate; **p-[^{18}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-1*H*-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-fluroindol-1-yl)-1-methyethylamine; **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-6yl)-propyl]-piperidin-4yl 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-fluoronaphthyl-1-yl)-6-isopropylpyrimidine); **SB204070**, 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1-4-benzoioxan-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]indol3-3,4′-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-methyl-piperazin-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-flurophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB-399885**, *N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide; **SB656104**, 6-((*R*)-2-[2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1*H*-indole hydrochloride; **SB699551**, 3-cyclopentyl-*N*-[2-(dimethylamino)ethyl]-*N*-[(4′-{[(2-phenylethyl)amino]methyl}-4-biphenylyl)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-3*H*-benz[e]indole; **WAY100635**, *N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride, **WAY163909**, (7b*R*, 10a*R*)-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole; **WAY-181187**, 2-[1-(6-chloroimidazo[2,1-b]thiazol-5-ylsulfonyl)-1*H*-indol-3-yl]ethylamine

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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, desmethylclozapine, TBPB and LuAE51090 have been described as functionally selective agonists of the M_1 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_1 receptors, PG135 at M_2 receptors, N-chloromethylbrucine and WIN62,577 at M_3 receptors and thiochrome, LY2033298, VU0152099 and VU0152100 at M_4 receptors, and VU0238429 at M_5 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_4 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_2 receptors can be labelled by [^{3}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_2 muscarinic receptor (Valant *et al*., 2008). THRX-160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M_2 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_1 receptor (Sheffler *et al*., 2009), and LY593093 has recently been described as a selective orthosteric partial agonist of the M_1 receptor (Watt *et al*., 2011).

Nomenclature	M_1	M_2	M_3
Ensembl ID	ENSG00000168539	ENSG00000181072	ENSG00000133019
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{q/11}$
Antagonists (pK_i)	MT7 (10.9-11.0), 4-DAMP (9.2), tripitramine (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)	tripitramine (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), tripitramine (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_D)	[^{3}H]NMS (80-150 pM), [^{3}H]QNB (15-60 pM), [^{3}H]pirenzepine (3-15 nM), (*R,R*)-quinuclidinyl-4-[^{18}F]-fluoromethyl-benzilate (PET ligand), [^{11}C]xanomeline (PET ligand), [^{11}C]butylthio-TZTP (PET ligand)	[^{3}H]NMS (200-400 pM), [^{3}H]QNB (20-50 pM), [^{18}F]FP-TZTP (PET ligand),	[^{3}H]NMS (150-250 pM), [^{3}H]QNB (30-90 pM), [^{3}H]darifenacin (300 pM)

Nomenclature	M_4	M_5
Ensembl ID	ENSG00000180720	ENSG00000184984
Principal transduction	$G_{i/o}$	$G_{q/11}$
Antagonists (pKi)	4-DAMP (8.9), MT3 (8.7), AFDX384 (8.0-8.7), AFDX116 (7-8.7), himbacine (7.9-8.2), tripitramine (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), tripitramine (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_D)	[^{3}H]NMS (50-100 pM), [^{3}H]QNB (20-80 pM)	[^{3}H]NMS (500-700 pM), [^{3}H]QNB (20-60 pM)

Antagonist data tabulated are pK_i 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(1*H*)-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-4*H*-benzo[1,4]oxazin-3-one; **AFDX116** (otenzepad), 1-[2-[2-(diethylaminomethyl)piperidin-1-yl]acetyl]-5*H*-pyrido[2,3-b][1,4]benozodiazepin-6-one; **AFDX384**, (±)-5,11-dihydro-11-([(2-[2-[dipropylamino)methyl]-1-piperidinyl)ethyl)amino)carbonyl)-6*H*-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-diphenylacetoxy-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**, (9*S*,10*S*,12*R*)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3′,2′,1′-*kl*]pyrrolo[3,4-*i*][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-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**, (3a*S*,12*R*,12a*S*,12b*R*)-2-amino-2,3,3a,4,11,12a,12b-octahydro-10-hydroxyisoquino[2,1,8-*lma*]carbazol-5(1*H*)-one hydrochloride; **QNB**, 3-quinuclidinylbenzilate; **TBPB**, 1-(1′-2-methylbenzyl)-1,4′-bipiperidin-4-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one; **THRX160209**, 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-β-hydroxy-17-α-ethynyl-5-α-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole; **WIN62,577**, 17-β-hydroxy-17-α-ethynyl-Δ^4-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole

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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_3 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_{2A} adenosine receptors have been described (Jaakola *et al*., 2008; Xu *et al*., 2011).

Nomenclature	A_1	A_{2A}	A_{2B}	A_3
Ensembl ID	ENSG00000163485	ENSG00000128271	ENSG00000170425	ENSG00000121933
Principal transduction	$G_{i/o}$	G_s	G_s	$G_{i/o}$
Selective agonists	CPA, CCPA, S-ENBA, GR79236	CGS21680, HENECA, ATL-146e (Peirce *et al*., 2001)	Bay60-6583 (Eckle *et al*., 2007)	Cl-IB-MECA, IB-MECA
Selective antagonists	PSB36 (9.8, Abo-Salem *et al*., 2004), DPCPX (8.5), SLV320 (9.0, Kalk *et al*., 2007)	SCH442416 (10.3, Todde *et al*., 2000), ZM241385 (9.0), SCH58261 (7.9–9.5)	PSB603 (9.3, Borrmann *et al*., 2009), MRS1754 (8.7), MRS1706 (8.4), PSB1115 (7.7)	MRS1220 (8.8), VUF5574 (8.4, van Muijlwijk-Koezen *et al*., 2000), MRS1523 (7.7), MRS1191 (7.0)
Probes	$[^3H]$-CCPA, $[^3H]$-DPCPX (0.6–1.2 nM)	$[^3H]$-CGS21680, $[^3H]$-ZM241385 (0.8 nM)	$[^3H]$-MRS1754 (1.1 nM)	$[^{125}I]$-AB-MECA (0.6 nM)

Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (ENSG00000182537) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor. DPCPX also exhibits antagonism at A_{2B} receptors (pK_i ca. 7, Alexander *et al*., 1996; Klotz *et al*., 1998). HENECA also shows activity at A_3 receptors (Varani *et al*., 1998). Antagonists at A_3 receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A_3 receptor. In the absence of other adenosine receptors, $[^3H]$-DPCPX and $[^3H]$-ZM241385 can also be used to label A_{2B} receptors (K_D *ca*. 30 and 60 nM, respectively). $[^{125}I]$-AB-MECA also binds to A_1 receptors (Klotz *et al*., 1998). $[^3H]$-CGS21680 is relatively selective for A_{2A} receptors, but may also bind to other sites in cerebral cortex (Johansson and Fredholm, 1995; Cunha *et al*., 1996). $[^3H]$-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_1 adenosine receptors in living cells, although activity at other adenosine receptors was not examined (Briddon *et al*., 2004).

Abbreviations: **AB-MECA**, N^6-(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^6-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; **Cl-IB-MECA**, 2-chloro-N^6-(3-iodobenzyl)adenosine-5′-*N*-methyluronamide; **CPA**, N^6-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-phenylacetylamino[1,2,4]triazolo[1,5*c*]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-1*H*-purin-8-yl]phenoxy)acetamide; **MRS1754**, 8-(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-1*H*-purin-8-yl)benzenesulphonic acid; **PSB36**, 1-butyl-8-(3-noradamantanyl)-3-(3-hydroxypropyl)xanthine; **PSB603**, 8-[4-[4-(4-chlorophenzyl)piperazide-1-sulfonyl)phenyl]]-1-propylxanthine; **S-ENBA**, (2*S*)-N^6-(2-endonorbanyl)adenosine; **SCH4421416**, 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-phenylethyl-pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5*c*]pyrimidine; **SLV320**, *trans*-4-[(2-phenyl-7*H*-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

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Adrenoceptors, α_1

Overview: α_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 α_1-adrenoceptors relative to α_2-adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are antagonists considered selective for α_1-adrenoceptors relative to α_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 α_1-adrenoceptors exist, some of which may display a different spectrum of signalling properties. One polymorphism of the α_{1A}-adrenoceptor has been described but is not associated with disease.

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

The clone originally called the α_{1C}-adrenoceptor corresponds to the pharmacologically defined α_{1A}-adrenoceptor (see Hieble *et al.*, 1995). Some tissues possess α_{1A}-adrenoceptors that display relatively low affinity in functional and binding assays for prazosin (pKi < 9) that might represent different receptor states (termed α_{1L}-adrenoceptors, Ford *et al.*, 1997; Morishima *et al.*, 2007). α_{1A}-Adrenoceptor C-terminal splice variants form homo and heterodimers, but fail to generate a functional α_{1L}-adrenoceptor (Ramsay *et al.*, 2004). Recent studies suggest that the α_{1L}-adrenoceptor phenotype may result from the interaction of α_{1A}-adrenoceptors with cysteine-rich epidermal growth factor-like domain 1α (CRELD1α) (Nishimune *et al.*, 2010). α_{1D}-Adrenoceptors form heterodimers with α_{1B}- or β_2-adrenoceptors that show increased cell-surface expression (Uberti *et al.*, 2005). Heterodimers formed between α_{1D}- and α_{1B}-adrenoceptors have distinct functional properties (Hague *et al.*, 2004). α_{1D}-Adrenoceptors are mainly located intracellularly. (+)Niguldipine also has high affinity for L-type Ca^{2+} channels.

Signalling is predominantly via $G_{q/11}$ but α_1-adrenoceptors also couple to $G_{i/o}$, G_s, and $G_{12/13}$. Several ligands activating α_{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^{2+} release but does not stimulate cAMP production. Phenylephrine is biased toward ECAR versus Ca^{2+} release or cAMP accumulation but not between Ca^{2+} 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^{2+} 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-1*H*-imidazol-2-y]-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide hydrobromide; **BMY7378**, 8-(2-[4-{2methoxyphenyl}-1-piperazinyl]ethyl)-8-azaspiro[4,5]decane-7,9-dione dihydrochloride; **HEAT**, 2-*β*-4-hydroxy-3-iodophenylethylaminomethyltetralone; **RS17053**, *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-*α*,*α*-dimethyl-1*H*-indole-3-ethanamide; **silodosin**, (-)-(*R*)-1-(3-hydroxypropyl)-5-(2-[2-{2-(2,2,2-trifluoroethoxy)phenoxyl}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

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Adrenoceptors, α_2

Overview: α_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 α_2-adrenoceptors relative to α_1-adrenoceptors. Rauwolscine (9.0) and yohimbine (9.0) are antagonists selective for α_2-adrenoceptors relative to α_1-adrenoceptors. [^{3}H]-rauwolscine (1 nM), [^{3}H]-UK14304 (5 nM) and [^{3}H]-RX821002 (0.5 nM and 0.1 nM at α_{2C}) are relatively selective radioligands. There is species variation in the pharmacology of the α_{2A}-adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine α_{2A}-adrenoceptors compared to the human receptor. These α_{2A} orthologues are sometimes referred to as α_{2D}-adrenoceptors. Multiple mutations of α_2-adrenoceptors have been described, some of which are associated with alterations in function. The effects of classical (not subtype selective) α_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 α_{2A}-adrenoceptors. The roles of α_{2B} and α_{2C}-adrenoceptors are less clear but the α_{2B} subtype appears to be involved in neurotransmission in the spinal cord and α_{2C} in regulating catecholamine release from adrenal chromaffin cells.

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

Oxymetazoline is a reduced efficacy agonist. ARC239 (pK_i 8.0) and prazosin (pK_i 7.5) show selectivity for α_{2B}- and α_{2C}-adrenoceptors over α_{2A}-adrenoceptors. Binding sites for imidazolines, distinct from α_2-adrenoceptors, have been identified and classified as I_1, I_2 and I_3 sites and catecholamines have a low affinity for these sites. I_1-imidazoline receptors are involved in central inhibition of sympathetic tone, I_2-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I_3-imidazoline receptors regulate insulin secretion from pancreatic β-cells.

Abbreviations: ARC239, 2-(2,4-[*O*-methoxyphenyl]-piperazin)-1-yl; **BHT920**, 6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-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**, (2*S*,12*bS*)1′,3′-dimethylspiro(1,3,4,5′,6,6′,7,12*b*-octahydro-2*H*-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

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Adrenoceptors, β

Overview: β-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 β-adrenoceptors relative to α_1- and α_2-adrenoceptors, while propranolol (pK_i 8.2–9.2) and cyanopindolol (pK_i 10.0–11.0) are relatively selective antagonists. β_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 β_1- and β_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 β_1- (Warne *et al*., 2008), agonist-bound (Cherezov *et al*., 2007) and antagonist-bound forms of the β_2-adrenoceptor (Rosenbaum *et al*., 2011; Rasmussen *et al*., 2011a), as well as agonist-bound, G_s protein-coupled β_2-adrenoceptor (Rasmussen *et al*., 2011b).

Nomenclature	β_1	β_2	β_3
Other names	–	–	atypical β
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000188778
Principal transduction	G_s	G_s	G_s
Rank order of potency	Noradenaline>adrenaline	Adrenaline> noradenaline	Noradenaline =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	$[^{125}I]$-ICYP (20–50 pM)+70 nM ICI118551	$[^{125}I]$-ICYP (20–50 pM)+100 nM CGP20712A	$[^{125}I]$-ICYP (0.5 nM)

Noradrenaline, xamoterol and RO363 are agonists that show selectivity for β_1- relative to β_2-adrenoceptors. Pharmacological differences exist between human and mouse β_3-adrenoceptors, and the 'rodent selective' agonists BRL37344 and CL316243 have low efficacy at the human β_3-adrenoceptor whereas CGP12177A and L755507 activate human β_3-adrenoceptors (Sato *et al*., 2008). All β-adrenoceptors couple to G_s (activating adenylyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate other G proteins such as G_i and many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at β_1- and β_2-adrenoceptors are agonists at β_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 β_3-adrenoceptors (Manara *et al*., 1996), but does not discriminate well between the three *β*-adrenoceptor subtypes (Candelore *et al*., 1999) and has been reported to have lower affinity for the β_3-adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

The β_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 *β*-adrenoceptors in turkey (termed the t*β*, t*β*3c and t*β*4c) that have a pharmacology that differs from the human *β*-adrenoceptors (Baker, 2011). The 'putative β_4-adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP12177A and other nonconventional partial agonists at β_1-adrenoceptors, since 'putative β_4-adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking β_1-adrenoceptors (Konkar *et al*., 2000; Kaumann *et al*., 2001).

Radioligand binding with $[^{125}I]$-ICYP can be used to define β_1- or β_2-adrenoceptors when conducted in the presence of a 'saturating' concentration of either a β_1- or β_2-adrenoceptor-selective antagonist. $[^3H]$-CGP12177 or $[^3H]$-dihydroalprenolol can be used in place of $[^{125}I]$-ICYP. Binding of a fluorescent analogue of CGP12177 to β_2-adrenoceptors in living cells has been described (Baker *et al*., 2003b). $[^{125}I]$-ICYP at higher (nM) concentrations can be used to label β_3-adrenoceptors in systems where there are few if any other β-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-[(2*S*)-2-hydroxy-3-[[2-[4-[(phenylsulfonyl)amino]phenyl]ethyl]amino]propoxy]phenyl]methyl]-acetamide; **RO363**, (-)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihdroxyphenoxy)-2-propanol)oxalate; **SB251023**, (4-[1-{2-(*S*)-hydroxy-3-(4-hydroxyphenoxy)-propylamino}cyclopentylmethyl]phenoxymethyl)phenylphosphonic acid lithium salt; **SR59230A**, 3-(2-ethylphenoxy)-1([1s]-1,2,3,4-tetrahydronaphth-1-ylamino)-2*S*-propanol oxalate

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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	$G_{i/o}$, G_z	$G_{i/o}$, G_z, G_{16} (Buhl *et al.*, 1993)
Rank order of potency	C3a>C5a (Ames *et al.*, 1996)	C5a, C5a des Arg>C3a (Ames *et al.*, 1996)
Selective agonists	Trp-Trp-Gly-Lys-Lys-Tyr-Arg-Ala-Ser-Lys-Leu-Gly-Leu-Ala-Arg (Ames *et al.*, 1997)	Phe-Lys-Pro-Cha-Cha-Phe-Lys-D-Cha-Cha-D-Arg (Konteatis *et al.*, 1994), S19 (Yamamoto, 2000)
Selective antagonists	SB290157 (pIC50 7.5, Ames *et al.*, 2001)	NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg (Konteatis *et al.*, 1994), AcPhe-Orn-Pro-D-Cha-Trp-Arg (Wong *et al.*, 1998), W54011 (8.7, Sumichika *et al.*, 2002), CHIPS (Postma *et al.*, 2004)
Probes	$[^{125}I]$-C3a	$[^{125}I]$-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 $[^{125}I]$-C5a, with no clear signalling function, but a putative role opposing inflammatory responses (Cain and Monk, 2002; Gao *et al.*, 2005; Gavrilyuk *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^2-([2,2-diphenylethoxy]acetyl)-L-arg; **W54011**, *N*-([4-dimethylaminophenyl]methyl)-*N*-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-carboxamide hydrochloride

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Angiotensin

Overview: The actions of angiotensin II (Ang II) are mediated by AT$_1$ and AT$_2$ receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; see de Gasparo *et al*., 2000), which have around 30% sequence similarity. AT$_1$ receptors are predominantly coupled to G$_{q/11}$, 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_1 gene, but two related AT_{1A} and AT_{1B} receptor genes are expressed in rodents. The AT$_2$ receptor counteracts several of the growth responses initiated by the AT$_1$ receptors. The AT$_2$ receptor is much less abundant than the AT$_1$ 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$_1$	AT$_2$
Ensembl ID	ENSG00000144891	ENSG00000180772
Principal transduction	G$_{q/11}$	G$_i$ / G$_o$, Tyr & Ser/Thr phosphatases
Selective agonists	L162313	[p-NH$_2$-Phe^6]-Ang II, CGP42112
Selective antagonists	EXP3174, eprosartan, valsartan, irbesartan, losartan, candesartan	PD123319, PD123177
Probes	[^{3}H]-A81988, [^{3}H]-L158809, [^{3}H]-eprosartan, [^{3}H]-losartan, [^{125}I]-EXP985	[^{125}I]-CGP42112

There is also evidence for an AT$_4$ receptor that specifically binds angiotensin IV and is located in the brain and kidney. An additional putative endogenous ligand for the AT$_4$ receptor has been described (LVV-hemorphin, a globin decapeptide) (Moeller *et al*., 1997). The AT$_1$ 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$_1$ receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesized. The best of these compounds bind to AT$_1$ receptors with nanomolar affinity and are slightly more potent than losartan in functional studies (Cappelli *et al*., 2004).

Abbreviations: A81988, 2(*N*-*n*-propyl-*N*-[{2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl}methyl]amino)pyridine-3-carboxylate; **candesartan**, 2-ethoxy-3-[[4-[2-(2H-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-5yl}biphenyl-4-yl]methyl)imidazole-5-carboxylate; **EXP985**, *N*-(2-[4-hydroxy-3-iodophenyl]ethyl)-4-chloro-2-propyl-1-([2′-{1*H*-tetrazol-5yl}biphenyl-4-yl]methyl)imidazole-5-carboxamide; **irbesartan**, 2-butyl-3-[[2′-(1H-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-5yl]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′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine

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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^1)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$_{i/o}$
Rank order of potency	[Pyr^1]apelin-13$\geq$apelin-13>apelin-36 (Tatemoto *et al*., 1998; Fan *et al.,* 2003)
Selective agonists	[Pyr^1]apelin-13, apelin-13, apelin-17, apelin-36
Probes	[^{125}I]-[Pyr^1]Apelin-13 (0.3 nM, Katugampola *et al*., 2001), [^{125}I]-apelin-13 (Fan *et al.,* 2003), [^{3}H]-[Pyr^1][Met(0)^{11}]apelin-13 (Medhurst *et al*., 2003), [^{125}I]-[Nle^{75},Tyr^{77}]apelin-36 (Kawamata *et al*., 2001), [^{125}I]-[Glp^{65}Nle^{75},Tyr^{77}]apelin-13 (Hosoya *et al.,* 2000)

Potency order determined for heterologously expressed human APJ receptor (pD$_2$ 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).

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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_s (Maruyama *et al*., 2002)
Rank order of potency	Lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid (Maruyama *et al*., 2002; Kawamata *et al*., 2003)
Selective agonists	Oleanolic acid (Sato *et al*., 2007), betulinic acid (Genet *et al*., 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).

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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 $G_{q/11}$ family of G proteins (but see also Jian *et al*., 1999). Activation of BB_1 and BB_2 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_3 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_1	BB_2	BB_3
Other names	NMB-R, BB1	GRP-R, BB2	BRS-3, bb3
Ensembl ID	ENSG00000135577	ENSG00000126010	ENSG00000102239
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists	NMB	GRP	[D-Tyr^{6},Apa-4Cl^{11},Phe^{13},Nle^{14}] bombesin$_{6\text{-}14}$,
Selective antagonists	PD165929, dNal-*cyc*(Cys-Tyr-dTrp-Orn-Val)-Nal-NH_2, dNal-Cys-Tyr-dTrp-Lys-Val-Cys-Nal-NH_2, PD168368	[D-Phe^{6},Cpa^{14},ψ13-14]Bn$_{6\text{-}14}$, JMV594, Ac-GRP$_{20\text{-}26}$methylester	–
Probes	[^{125}I]-BH-NMB, [^{125}I]-[Tyr^{4}]bombesin	[^{125}I]-[DTyr^{6}]bombesin-6-13-methylester, [^{125}I]-GRP, [^{125}I]-[Tyr^{4}]bombesin	[^{125}I]-[Tyr^{6},βAla^{11},Phe^{13},Nle^{14}] bombesin-6-14

All three subtypes may be activated by [dPhe^{6},βAla^{11},Phe^{13},Nle^{14}]bombesin-6-14 (Mantey *et al*., 1997). [D-Tyr^{6}, Apa-4Cl, Phe^{13}, Nle^{14}] bombesin-6-14, has more than 200-fold selectivity for BB_3 receptors over BB_1 and BB_2 (Mantey *et al*., 2004).

Abbreviations: PD165929, 2-[3-(2,6-diisopropylphenyl)-ureido]3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-proprionate, **PD168368**, 3-(1*H*-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_2-CH$(CH_3)_2$]-CHOH-$(CH_2)_3$-CH_3.

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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^9]BK, Lys-BK (kallidin), Lys-[des-Arg^9]BK, T-kinin (Ile-Ser-BK), [Hyp^3]BK and Lys-[Hyp^3]BK. The variation in affinity or inactivity of B$_2$ receptor antagonists could reflect the existence of species homologues of B$_2$ receptors.

Nomenclature	B$_1$	B$_2$
Ensembl ID	ENSG00000100739	ENSG00000168398
Principal transduction	G$_{q/11}$	G$_{q/11}$
Rank order of potency	Lys-[des-Arg^9]BK>[des-Arg^9]BK=Lys-BK>BK	Lys-BK≥BK>>[des-Arg^9]BK, Lys-[des-Arg^9]BK
Selective agonists	Lys-[des-Arg^9]BK, Sar[DPhe^8][des-Arg^9]BK	[Phe^8,ψ(CH$_2$-NH)Arg^9]BK, [Hyp^3,Tyr(Me)^8]BK
Selective antagonists	B9958 (9.2, Regoli *et al*., 1998), R914 (8.6, Gobeil *et al*., 1999), R715 (8.5, Gobeil *et al*., 1996a), Lys-[Leu^8][des-Arg^9]BK (8.0)	Icatibant (8.4, Gobeil *et al*., 1996b), FR173657 (8.2, Rizzi *et al*., 1997), LF160687 (Pruneau *et al*., 1999)
Probes	[^{3}H]-Lys-[des-Arg^9]BK (0.4 nM), [^{3}H]-Lys-[Leu^8][des-Arg^9]BK, [^{125}I]-Hpp-desArg^{9}HOE140 (0.1 nM)	[^{3}H]-BK (0.2 nM), [^{3}H]-NPC17731 (50–900 pM), [^{125}I]-[Tyr^8]BK

Abbreviations: **B9958**, Lys-Lys[Hyp^3,Cpg^5,dTic^7,Cpg^8][des-Arg^9]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^3,Thi^5,DTic^7,Oic^8]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^3,DHypE(transpropyl)^7,Oic^8]BK; **R715**, AcLys[D Nal^7,Ile^8][des-Arg^9]BK; **R914**, AcLys-Lys-([αMe]Phe^5δ-βNal^7,Ile^8)desArg^{9}BK

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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, ENSG00000004948). 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, αCGRP (formerly known as CGRP-I), βCGRP (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, *p*Ki ~10.5) and MK0974 (also known as telcagepant, *p*Ki ~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$_1$	AM$_2$
Composition	*CALCRL+RAMP1*	*CALCRL+RAMP2*	*CALCRL+RAMP3*
Principal transduction	G$_s$	G$_s$	G$_s$
Rank order of potency	CGRP > AM ≥ AM2/IMD > AMY ≥ salmon CT	AM > CGRP, AM2/IMD > AMY > salmon CT	AM = AM2/IMD ≥ CGRP > AMY > salmon CT
Selective agonists	αCGRP	AM	AM
Selective antagonists	BIBN4096BS (10.5, Doods *et al*., 2000; Hay *et al*., 2003, 2006); MK0974 (9, Salvatore *et al*., 2008)	AM-(22–52) (7, Hay *et al*., 2003)	–
Probes	[^{125}I]-αCGRP (0.1 nM)	[^{125}I]-AM (rat, 0.1–1.0 nM)	[^{125}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$_{(a)}$) with RAMP1 (i.e. the AMY$_{1(a)}$ receptor) has a high affinity for CGRP, unlike hCT$_{(a)}$–RAMP3 (i.e. AMY$_{3(a)}$ 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$_1$	AMY$_2$	AMY$_3$
Composition	*CALCR*	*CALCR+RAMP1*	*CALCR+RAMP2*	*CALCR+RAMP3*
Principal transduction	G$_s$	G$_s$	G$_s$	G$_s$
Rank order of potency	Salmon CT ≥ human CT ≥ AMY, CGRP > AM, AM2/IMD	AMY$_{1(a)}$: Salmon CT ≥ AMY ≥ CGRP > AM2/IMD > human CT > AM	Poorly defined	AMY$_{3(a)}$: Salmon CT ≥ AMY > CGRP > AM2/IMD > human CT > AM
Selective agonists	Human CT	AMY	AMY	AMY
Probes	[^{125}I]-CT (salmon, 0.1 nM), [^{125}I]-CT (human, 0.1–1.0 nM)	[^{125}I]-BH-AMY (rat, 0.1–1.0 nM)	[^{125}I]-BH-AMY (rat, 0.1–1.0 nM)	[^{125}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$_2$ receptors. AM2/IMD also has high affinity for the AM$_2$ receptor (Hong *et al*., 2011). CGRP-(8-37) acts as an antagonist of CGRP (*p*K$_i$ ~8) and inhibits some AM and AMY responses (pKi ~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 (*p*Ki ~7), limiting its use (Hay *et al*., 2003). AM-(22-52) is slightly more effective at AM$_1$ than AM$_2$ 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$_s$ is a prominent route for effector coupling for CLR and CTR but other pathways (e.g. Ca^{2+}, 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).

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

Some early literature distinguished between *CGRP*$_1$ and *CGRP*$_2$ receptors. It is now clear that *CALCRL/RAMP1* represents the *CGRP*$_1$ subtype and is now known simply as the CGRP receptor (Hay *et al*., 2008). The *CGRP*$_2$ receptor is considered to have arisen from the actions of CGRP at AM$_2$ and AMY receptors. This term should not be used (Hay *et al*., 2008).

Abbreviations: AC187, acetyl-[Asn^{30},Tyr^{32}]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

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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	$G_{q/11}$, $G_{i/o}$, $G_{12/13}$ (Ward, 2004)
Cation rank order of potency	$Gd^{3+} > Ca^{2+} > Mg^{2+}$ (Brown *et al*., 1993)
Polyamine rank order of potency	Spermine>spermidine>putrescine (Quinn *et al*., 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 *et al*., 2000)
Positive allosteric modulators	NPS R568 (Nemeth *et al*., 1998), calindol (Petrel *et al*., 2004), cinacalcet (Nemeth *et al*., 2004), AC265347 (Ma *et al*., 2011)
Negative allosteric modulators	NPS 2143, NPS 89636 (Nemeth *et al*., 2001), Calhex-231 (Petrel *et al*., 2004), 2-benzylpyrrolidine derivatives of NPS 2143 (Yang *et al*., 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^{2+} levels. A gain-of-function mutation in the CaS gene is associated with autosomal dominant hypocalcaemia.

$GPRC_6$ (ENSG00000173612, also known as GPRC6A) is a related G_q-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^1-(4-chlorobenzoyl)-N^2-[1-(1-naphthyl)ethyl]-1,2-diaminocyclohexane; **calindol**, (R)-2-[1-(1-naphthyl) ethylaminomethyl]-1H-indole; **NPS R568**, (*R*)-*N*-(3-methoxy-*α*-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;

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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*-arachidonoylethanolamine (anandamide), *N*-homo-γ-linolenoylethanolamine, *N*-docosatetra-7,10,13,16-enoylethanolamine 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$_1$	CB$_2$
Ensembl ID	ENSG00000118432	ENSG00000188822
Principal transduction	G$_{i/o}$	G$_{i/o}$
Selective agonists	ACEA (Hillard *et al.*, 1999), ACPA (Hillard *et al.*, 1999), methanandamide (Khanolkar *et al.*, 1996), O-1812 (Di Marzo *et al.*, 2001)	HU308 (Hanus *et al.*, 1999), JWH133 (Huffman *et al.*, 1999; Pertwee, 2000), L759633 (Ross *et al.*, 1999), L759656 (Ross *et al.*, 1999), AM1241 (Ibrahim *et al.*, 2003)
Selective antagonists	AM251 (8.1, Lan *et al.*, 1999a), AM281 (7.9, Lan *et al.*, 1999b), rimonabant (7.9, Showalter *et al.*, 1996), LY320135 (6.9, Felder *et al.*, 1998)	SR144528 (9.2, Rinaldi-Carmona *et al.*, 1998), AM630 (7.5, Ross *et al.*, 1999)
Probes	[^{3}H]-rimonabant (0.6 nM, Rinaldi-Carmona *et al.*, 1996)	–

Both CB$_1$ and CB$_2$ receptors may be labelled with [^{3}H]-CP55940 (0.6 nM; Showalter *et al.*, 1996) and [^{3}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$_1$ 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$_1$ and CB$_2$ 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**, (6a*r*,10a*r*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; **L759656**, (6a*r*,10a*r*)-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-tetraenoyl)-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

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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 β-chemokines; $n = 28$), CXC (also known as α-chemokines; $n = 16$) and CX$_3$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$_{50}$ values <50 nM in either Ca^{2+} 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$_{50}$ values from radioligand binding to heterologously expressed receptors.

Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
Other names	CKR1, CC CK$_1$, CC CKR1, MIP-1αR, MIP-1α/RANTES	CKR2, CC CK$_2$, CC CKR2, MCP-1	CKR3, CC CK$_3$, CC CKR3	CKR4, CC CK$_4$, CC CKR4	CKR5, CC CK$_5$, CC CKR$_5$, CHEMR13
Ensembl ID	ENSG00000163823	ENSG00000121807	ENSG00000183625	ENSG00000183813	ENSG00000160791
Principal transduction	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Agonists	CCL3 (MIP-1α), 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-1α), CCL4 (MIP-1β), 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-1β, R5-HIV gp120
Selective antagonists	BX471 (8.3-9), 2b-1 (8.7), UCB35625 (8.0), CP481715 (8.0), CCL4 (MIP-1β)	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	[^{125}I]-MIP-1α,[^{125}I]-RANTES,[^{125}I]-MCP-3	[^{125}I]-MCP-1,[^{125}I]-MCP-3	[^{125}I]-RANTES,[^{125}I]-eotaxin,[^{125}I]-MCP-3	[^{125}I]-TARC,[^{125}I]-CTACK/CCL27	[^{125}I]-RANTES,[^{125}I]-MCP-2,[^{125}I]-MIP-1α,[^{125}I]-MIP-1β

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$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Agonists	CCL20 (LARC), HBD2	CCL19 (ELC, MIP-3β), CCL21 (SLC)	CCL1 (I-309), CCL4 (MIP-1β), 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	[^{125}I]-LARC	[^{125}I]-ELC, [^{125}I]-SLC	[^{125}I]-I309	[^{125}I]-TECK	–

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6
Other names	IL8R$_A$, IL-8 receptor type I, IL-8 receptor *α*	IL8R$_B$, IL-8 receptor type II, IL-8 receptor *β*	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$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Agonists	CXCL6 (GCP-2), CXCL8 (IL-8),	CXCL1 (GRO*α*), CXCL2 (GRO*β*), CXCL3 (GRO*γ*), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2), CXCL8 (IL-8), HCMV UL146 (vCXC-1)	CXCL9 (Mig), CXCL10 (IP10), CXCL11 (I-TAC)	CXCL12*α* (SDF-1*α*),CXCL12*β* (SDF-1*β*)	CXCL13 (BLC, BCA-1)	CXCL16 (SR-PSOX)
Selective agonists	–	GRO*α*, GRO*γ*, GRO*β*, NAP-2, ENA78	IP10, MIG, I-TAC	SDF-1*α*, SDF-1*β*, X4-HIV gp120	BLC	CXCL16
Selective antagonists	–	SB225002 (7.7)	eotaxin, MCP-3	AMD3100, HIV-1 Tat, T134, ALX40-4C	–	–
Probes	[^{125}I]-IL8	[^{125}I]-IL8, [^{125}I]-GRO*α*, [^{125}I]-NAP-2, [^{125}I]-ENA78	[^{125}I]-IP10, [^{125}I]-I-TAC/CXCL11	[^{125}I]-SDF-1	–	[^{125}I]-CXCL16

CXCR1 and CXCR2 also couple to phospholipase C when co-transfected with members of the G$_{q/11}$ 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$_3$CR1	XCR1
Other names	CMKBRL1, V28	GPR5
Ensembl ID	ENSG00000168329	ENSG00000173578
Principal transduction	G$_{i/o}$	G$_{i/o}$
Agonists	CX3CL1 (Fractalkine)	XCL1 α and *β* (Lymphotactin *α* and *β*)
Selective agonists	Fractalkine	Lymphotactin
Probes	[^{125}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*α* (CCL3), MIP-1*β* (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 GROα (CXCL1), GRO*β* (CXCL2), GROγ (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$_3$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 β defensin 2; **HCC**, hemofiltrate CC chemokine; **IL-8**, interleukin 8; **IP-10**, γ-interferon-inducible protein 10; **I-TAC**, interferon-inducible T-cell α chemoattractant; **LARC**, liver and activation-related chemokine (CCL20); **MCP**, monocyte chemoattractant protein; **MDC**, macrophage-derived chemokine; **MEC**, mucosa expressed chemokine; **MIG**, monokine-induced by γ-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

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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_2 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_1	CCK_2
Other names	CCK_A	CCK_B, CCK_B/gastrin
Ensembl ID	ENSG00000163394	ENSG00000110148
Principal transduction	$G_{q/11}/G_s$	G_s
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	[^{3}H]-Devazepide (0.2 nM)	[^{3}H]-Propionyl-BC264 (0.15 nM), [^{3}H]-PD140376 (0.2 nM), [^{3}H]-L365260 (2 nM), [^{3}H]- or [^{125}I]-gastrin (1 nM), [^{125}I]-PD142308 (0.25 nM)

A mitogenic gastrin receptor, which can be radiolabelled with [^{125}I]-gastrin-(1–17) and which appears to couple to the G_s 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-(*N*Me)Phe-NH_2; **BC264**, Tyr(SO_3H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH_2; **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*-(methyoxyphenyl)acetamide; **IQM95333**, (4*αS*,5*R*)-2-benzyl-5[*N*-(*tert*-butoxycarbonyl)-L-Trp]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine; **JMV180**, Boc-Tyr(SO_3H)Ahx-Gly-Trp-Ahx-Asp^{2}phenylethyl ester; **L365260**, 3*R*(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N*apos;-(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-pyrrazolidinecarboxamide(3.3.1.1^{3,7}); **PD140376**, L-3-([4-aminophenyl]methyl)-*N*-(*α*-methyl-*N*-[{tricyclo(3.3.1.1D-Trp)-*β*-Ala; **PD140548**, *N*-(*α*-methyl-*N*-[{tricyclo(3.3.1.1L-Trp)-D-3-(phenylmethyl)-*β*-Ala; **PD142308**, iodinated PD140548; **RB400**, HOOC-CH_2-CO-Trp-NMe(Nle)-Asp-Phe-NH_2; **RP73870**, ({[(*RS*); **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-isoquinolinyl}-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

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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_1 and CRF_2 receptors are activated non-selectively by CRF and urocortin 1. Binding to CRF receptors can be conducted using [^{125}I]-Tyr^0-CRF or [^{125}I]-Tyr^0-sauvagine with K_d values of 0.1–0.4 nM. CRF_1 and CRF_2 receptors are non-selectively antagonized by α-helical CRF-(9-41), D-Phe-CRF-(12-41) and astressin.

Nomenclature	CRF_1	CRF_2
Other names	CRF-RA, PC-CRF	CRF-RB, HM-CRF
Ensembl ID	ENSG00000120088	ENSG00000106113
Principal transduction	G_s	G_s
Selective agonists	–	Urocortin 2 (Reyes *et al*., 2001), urocortin 3 (Lewis *et al*., 2001)
Selective antagonists	CP154526 (8.3–9.0, Lundkvist *et al*., 1996), NBI27914 (8.3–9.0, Chen *et al*., 1996), antalarmin (8.3–9.0, Webster *et al*., 1996), CRA1000 (8.3–9.0, Chaki *et al*., 1999), DMP696 (8.3–9.0, He *et al*., 2000), R121919 (8.3–9.0, Zobel *et al*., 2000), SRA125543A (8.7–9.0, Gully *et al*., 2002) CP376395 (7.8, Chen *et al*., 2008)	K41498 (9.2, Lawrence *et al*., 2002), K31440 (8.7–8.8, Ruhmann *et al*., 2002), antisauvagine-30 (Ruhmann *et al*., 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]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl-amine; **astressin**, *cyc*$^{30-33}$[D-Phe^{12},Nle^{21,38},Glu^{30},Lys^{33}]CRF-(12-41); **CP154526**, butyl-ethyl-(2,5-dimethyl-7-[2,4,6-trimethylphenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amine; **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^{12},Nle^{21,38},αMeLeu^{37}-CRF; **K31440**, Ac-(D-Tyr^{11},His^{12},Nle^{17})sauvagine-(11-40); **K41498**, [D-Phe^{11},His^{12},Nle^{17}]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

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Dopamine

Overview: Dopamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Dopamine Receptors, see Schwartz *et al.*, 1998) are commonly divided into D$_1$-like (D$_1$ and D$_5$) and D$_2$-like (D$_2$, D$_3$ and D$_4$) families, where the endogenous agonist is dopamine. Quinpirole is an agonist with selectivity for D$_2$-like receptors.

Nomenclature	D$_1$	D$_2$	D$_3$	D$_4$	D$_5$
Other names	D$_{1A}$	–	–	–	D$_{1B}$
Ensembl ID	ENSG00000184845	ENSG00000149295	ENSG00000151577	ENSG00000069696	ENSG00000169676
Principal transduction	G$_s$, G$_{olf}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_s$
Selective agonists	*R*(+)SKF81297, *R*(+)SKF38393	Sumanirole (McCall *et al.*, 2005)	PD128907	PD168077, A412997 (Moreland *et al.*, 2005)	–
Selective antagonists	SCH23390, SKF83566, SCH39166	Raclopride, domperidone	S33084 (9.6, Millan *et al.*, 2000), nafadotride (9.5), (+)S14297 (7.9, Millan *et al.*, 1994), SB277011 (8.0, Reavill *et al.*, 2000)	L745870 (9.3), U101958 (8.9, Schlachter *et al.*, 1997), L741742 (8.5)	–
Probes	[^{3}H]-SCH23390 (0.2 nM), [^{125}I]-SCH23982 (0.7 nM)	[^{3}H]-Raclopride, [^{3}H]-spiperone	[^{3}H]-7-OH-DPAT, [^{3}H]-PD128907, [^{3}H]-spiperone	[^{3}H]-NGD941 (5 nM, Primus *et al.*, 1997), [^{125}I]-L750667 (1 nM, Patel *et al.*, 1996), [^{3}H]-spiperone	[^{125}I]-SCH23982 (0.8 nM) [^{3}H]-SCH23390 (0.5 nM)

The selectivity of many of these agents is less than two orders of magnitude. [^{3}H]-Raclopride exhibits similar high affinity for D$_2$ and D$_3$ receptors (low affinity for D$_4$), but has been used to label D$_2$ receptors in the presence of a D$_3$-selective antagonist. [^{3}H]-7-OH-DPAT has similar affinity for D$_2$ and D$_3$ receptors, but labels only D$_3$ receptors in the absence of divalent cations. The pharmacological profile of the D$_5$ receptor is similar to, yet distinct from, that of the D$_1$ receptor. The splice variants of the D$_2$ receptor are commonly termed D$_{2S}$ and D$_{2L}$ (short and long). The *DRD4* gene encoding the D$_4$ 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)-1*H*-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*-3,4,4*a*,10*b*-tetrahydro-4-propyl-2*H*,5*H*-[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*(+)SKF38393**, *R*(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; ***R*(+)SKF81297**, *R*(+)-6-chloro7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-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

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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$_2$ 8.4) and non-peptide (e.g. bosentan, pA$_2$ 6.0–7.2; SB209670, pA$_2$ 9.4) antagonists can block both ET$_A$ and ET$_B$ receptors. Splice variants of the ET$_A$ receptor have been identified in rat pituitary cells; one of these, ET$_A$R-C13, appeared to show loss of function with comparable plasma membrane expression (Hatae *et al*., 2007).

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

Subtypes of the ET$_B$ 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-methoxycarboyl-D-norleucine; **FR139317**, (*R*)2-([*R*-2-{(*S*)-2-([1-{hexahydro-1*H*-azepinyl}carbonyl]amino)methyl}pentanoyl] amino-3-(3-[methyl-1*H*-indodyl])propionylamino-3-(2-pyridyl))propionate; **IRL1620**, Suc[Glu^{9},Ala^{11,15}]ET-1$_{10–21}$; **IRL2500**, *N*-(3,5-dimethylbenzoyl)-*N*-methyl-(D)-(4-phenylphenyl)-Ala-Trp; **LU135252**, (+)-(*S*)-2-(4,6-dimethoxypyrimidin-2-yloxy)-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-hydroxy-phenyl)-ethylcarbamoyl]-propoxy)-4,5-dimethoxy-phenyl-3-(4-methoxy-benzoyl)-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*,*S*-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-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

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Formylpeptide

Overview: The formylpeptide receptors (ENSFM00510000502765, 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 β-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	$G_{i/o}$, G_z	G_i (Maddox *et al.*, 1997)	–
Rank order of potency	fMLP > Cathepsin G > Annexin I (Le *et al.*, 2002; Sun *et al.*, 2004)	LXA$_4$ = ATL = ATLa2 > LTC$_4$ = LTD$_4$ >> 15-deoxy-LXA$_4$ >> fMLP (Clish *et al.*, 1999; Fiore *et al.*, 1994; Fiore and Serhan, 1995; Gronert *et al.*, 2001; Takano *et al.*, 1997)	–
Selective agonists	fMLP (Le *et al.*, 1999)	LXA$_4$, ATL, ATLa2 (Guilford *et al.*, 2004), RvD1 (Krishnamoorthy *et al.*, 2010)	F2L (Migeotte *et al.*, 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 *et al.*, 2001)	–	–
Probes	[^{3}H]-fMLP	[^{3}H]-LXA$_4$ (0.2–1.7 nM; Fiore *et al.*, 1994; Takano *et al.*, 1997)	–

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

Abbreviations: BOC-PLPLP, Boc-Phe-Leu-Phe-Leu-Phe; **ATL**, aspirin-triggered lipoxin A$_4$ [15-*epi*-LXA$_4$, 5S,6R,15R-trihydroxyl-7E,9E,13E,11Z-eicosatetraenoic acid]; **ATLa2**, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA$_4$]; **F2L**, an acetylated 21-aa cleavage protein of haem-binding protein (ENSG00000013583); **LTC$_4$**, leukotriene C$_4$; **LTD$_4$**, leukotriene D$_4$; **LXA$_4$**, lipoxin A$_4$ [5S,6R,15S-trihydroxyl-7E,9E,13E-11Z-eicosatetraenoic acid]; **RvD1**, resolvin D1

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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$_1$ receptors, while short chain fatty acids (C2, C3, C4 and C5) activate FFA$_2$ (Brown *et al.*, 2003; Le Poul *et al.*, 2003; Nilsson *et al.*, 2003) and FFA$_3$ (Brown *et al.*, 2003; Le Poul *et al.*, 2003) receptors. In addition, thiazolidinedione PPARγ agonists such as rosiglitazone activate FFA$_1$ (*p*EC$_{50}$ 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$_2$ (Lee *et al.*, 2008; Smith *et al.*, 2011).

Nomenclature	FFA$_1$	FFA$_2$	FFA$_3$
Other names	GPR40 (Sawzdargo *et al.*, 1997)	GPR43 (Sawzdargo *et al.*, 1997)	GPR41 (Sawzdargo *et al.*, 1997). LSSIG (Senga *et al.*, 2003)
Ensembl ID	ENSG00000126266	ENSG00000126262	ENSG00000185897
Principal transduction	G$_{q/11}$ (Briscoe *et al.*, 2003; Itoh *et al.*, 2003; Stoddart *et al.*, 2007)	G$_{q/11}$, G$_{i/o}$ (Brown *et al.*, 2003; Le Poul *et al.*, 2003; Nilsson *et al.*, 2003)	G$_{i/o}$ (Brown *et al.*, 2003; Le Poul *et al.*, 2003; Stoddart *et al.*, 2007)
Selective agonists	Linoleic acid (Briscoe *et al.*, 2003; Itoh *et al.*, 2003), TUG424 (*p*EC$_{50}$ 7.5, Christiansen *et al.*, 2008), GW9508 (*p*EC$_{50}$ 7.3; Briscoe *et al.*, 2006; Sum *et al.*, 2007), Cpd B (*p*EC$_{50}$ 6.1; Tan *et al.*, 2008)	(*S*)-2-(4-chlorophenyl)-*N*-(5-fluorothiazol-2-yl)-3-methylbutanamide (*p*EC$_{50}$ 6.4 Lee *et al.*, 2008)	–
Selective antagonists	GW1100 (Briscoe *et al.*, 2006; Stoddart *et al.*, 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 (*p*EC$_{50}$ 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**, γ-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-α-(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-fluorophenyl)methyl]thio}-4-oxo-1[4*H*]-pyrimidinyl)benzoate; **GW9508**, 3-(4-[{(3-[phenyloxy] phenyl)methyl}amino]phenyl)propanoic acid; **TUG424**, 4-[2-(2-methylphenyl)ethynyl]-benzenepropanoic acid

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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 *β*-catenin (ENSG00000168036) or being *β*-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 β-catenin. *β*-Catenin, in turn, modifies gene transcription in concert with TCF/LEF transcription factors. *β*-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 β-arrestin scaffolding protein for internalization (Chen *et al.*, 2003), β-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_1	Frizzled-1	ENSG00000157240
FZD_2	Frizzled-2	ENSG00000180340
FZD_3	Frizzled-3	ENSG00000104290
FZD_4	Frizzled-4, CD344	ENSG00000174804
FZD_5	Frizzled-5	ENSG00000163251
FZD_6	Frizzled-6	ENSG00000164930
FZD_7	Frizzled-7	ENSG00000155760
FZD_8	Frizzled-8	ENSG00000177283
FZD_9	Frizzled-9, CD349	ENSG00000188763
FZD_{10}	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 (ENSG00000002745).

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

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GABA$_B$

Overview: Functional GABA$_B$ receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA$_B$ receptors, Bowery *et al.*, 2002; see also Pin *et al.*, 2007) are formed from the heterodimerization of two similar 7TM subunits termed GABA$_{B1}$ and GABA$_{B2}$ (Bowery *et al.*, 2002; Pin *et al.*, 2004; Emson, 2007; Pin *et al.*, 2007; Ulrich and Bettler, 2007). GABA$_B$ receptors are widespread in the CNS and regulate both pre- and post-synaptic activity. The GABA$_{B1}$ 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$_{B1}$ subunit when expressed alone is not transported to the cell membrane and is non-functional. Co-expression of GABA$_{B1}$ and GABA$_{B2}$ subunits allows transport of GABA$_{B1}$ to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca^{2+} channels (Ca$_v$2.1, Ca$_v$2.2), or inwardly rectifying potassium channels (Kir3) (Bowery and Enna, 2000; Bowery *et al.*, 2002; Bettler *et al.*, 2004). The GABA$_{B2}$ subunit also determines the rate of internalisation of the dimeric GABA$_B$ receptor (Hannan *et al.*, 2011). The GABA$_{B1}$ subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA$_{B2}$ 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$_{B2}$ increases the affinity of GABA$_{B1}$ for agonists and reciprocally GABA$_{B1}$ facilitates the coupling of GABA$_{B2}$ to G proteins (Pin *et al.*, 2004; Kubo and Tateyama, 2005). GABA$_{B1}$ and GABA$_{B2}$ subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α-helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the GABA$_{B1}$ 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$_B$ 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$_{B2}$ 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$_{B1}$ subunit have been cloned. The predominant GABA$_{B1(a)}$ and GABA$_{B1(b)}$ 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$_{B1(a)}$-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$_{B1(b)}$-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$_{B1(c)}$ that differs in the ECD, and GABA$_{B1(e)}$, which is a truncated protein that can heterodimerize with the GABA$_{B2}$ 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$_{B1}$ subunit isoforms have been described in rodents and humans (Lee *et al.*, 2010 and reviewed by Bettler *et al.*, 2004).

Nomenclature	GABA$_B$
Ensembl ID	GABA$_{B1}$ ENSG00000237051; GABA$_{B2}$ ENSG00000136928
Principal transduction	G$_{i/o}$
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 μM), 2-hydroxy-s-(-)-saclofen (11 μM), CGP35348 (27 μM)
Probes (K_D)	[^{3}H](*R*)-(-)-baclofen, [^{3}H]CGP54626 (1.5 nM; Bittiger *et al.*, 1992), [^{3}H]CGP62349 (0.9 nM, Keir *et al.*, 1999), [^{125}I]CGP64213 (1 nM, Galvez *et al.*, 2000), [^{125}I]CGP71872 (K_i = 0.5 nM, Belley *et al.*, 1999)

Potencies of agonists and antagonists listed in the table, quantified as IC$_{50}$ values for the inhibition of [^{3}H]CGP27492 binding to rat cerebral cortex membranes, are from Froestl and Mickel (1997), Bowery *et al.* (2002) and Froestl (2011). Radioligand K_D values relate to binding to rat brain membranes. CGP71872 is a photoaffinity ligand for the GABA$_{B1}$ subunit (Belley *et al.*, 1999). CGP27492, CGP35024 and CGP44532 act as antagonists at human GABA$_A$ ρ1 receptors, with potencies in the low micromolar range (Froestl, 2011). In addition to the ligands listed in the table, Ca^{2+} binds to the VTM of the GABA$_{B1}$ subunit to act as a positive allosteric modulator of GABA (Galvez *et al.*, 2000). In cerebellar Purkinje neurones, the interaction of Ca^{2+} with the GABA$_B$ receptor enhances the activity of mGlu$_1$ through functional cross-talk involving G-protein Gβγ subunits (Tabata *et al.*, 2004; Rives *et al.*, 2009). Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF177 and (+)-BHFF (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$_{B2}$ 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$_{B1}$ subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA$_{B1}^{-/-}$ 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$_{B2}^{-/-}$ 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; **(+)-BHFF**, (−)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one; **BHF177**, (1*R*,2*R*,4*S*)-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-dichlorphenyl)-ethyl] amino-2(*S*)-hydroxypropyl-(P-benzyl)-phosphinic acid; **CGP62349**, [3-[1-*R*-[[3-(methoxyphenylmethyl)hydroxyphosphinyl]-2(5)-hydroxypropyl]amino]ethyl]-benzoic acid; **CGP64213**, [3-[-(*R*)-[[3-5*N*-[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**, (+)-(2*S*)-5,5-dimethyl-2-morpholineacetic acid; VTM, Venus flytrap module

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Galanin

Overview: Galanin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous peptides galanin (ENSG00000069482) and galanin-like peptide (GALP, ENSG00000197487). 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_1	GAL_2	GAL_3
Other names	Galanin-1 receptor, GALR1	Galanin-2 receptor, GALR2	Galanin-3 receptor, GALR3
Ensembl ID	ENSG00000166573	ENSG00000182687	ENSG00000128310
Principal transduction	$G_{i/o}$	$G_{i/o}$, $G_{q/11}$	$G_{i/o}$
Rank order of potency	Galanin>GALP (Ohtaki *et al.*, 1999)	GALP≥galanin (Ohtaki *et al.*, 1999)	GALP>galanin (Lang *et al.*, 2005)
Selective agonists	–	Galanin-(2–29) (Fathi *et al.*, 1997; Wang *et al.*, 1997), D-Trp^2-galanin-(1–29) (Smith *et al.*, 1997)	–
Selective antagonists	2,3-Dihydro-dithiin-1,4-dithiin-1,1,4,4-tetroxide (Scott *et al.*, 2000)	M871 (7.9, Sollenberg *et al.*, 2006)	–

Galanin-(1–11) is a high-affinity agonist at GAL_1/GAL_2 (pK_i 9) and galanin-(2–11) is selective for GAL_2 and GAL_3 compared to GAL_1 (Lu *et al.*, 2005). [^{125}I]-[Tyr^{26}]galanin binds to all three subtypes with K_d 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_1, GAL_2 or GAL_3 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_1 receptors expressed endogenously in Bowes human melanoma cells (Ohtaki *et al.*, 1999), and at heterologously expressed recombinant GAL_1, GAL_2 and GAL_3 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)$_3$-(Ala-Leu)$_2$-Ala-amide

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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^{14}-ghrelin with equipotent biological activity (Hosoda *et al*., 2000). A unique post-translational modification (octanoylation of Ser^{3}, 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 release 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	$G_{q/11}$
Rank order of potency	Ghrelin=des-Gln-ghrelin (Matsumoto *et al*., 2001; Bedendi *et al*., 2003)
Selective antagonists	YIL781 (K_B 11 nM) (Esler *et al.,* 2007)
Probes	[^{125}I-His^{9}]-ghrelin (0.4 nM, Katugampola *et al*., 2001), [^{125}I-Tyr^{4}]-ghrelin (0.5 nM, Bedendi *et al*., 2003), [^{125}I]-Tyr^{4}-des-octanoyl (0.7 nM, Bedendi *et al*., 2003)

Des-octanoyl ghrelin has been shown to bind (as [^{125}I]-Tyr^{4}-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 sysytem. A potent inverse agonist has been identified ([D-Arg^{1}, D-Phe^{5}, D-Trp^{7,9},Leu^{11}]-substance P, pD_2 8.3; Holst *et al*., 2003). TZP101, described as a ghrelin receptor agonist (pK_i 7.8 and pD_2 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-([(3*S*)-1-isopropylpiperidin-3-yl]methyl)-2-methylquinazolin-4(3*H*)-one

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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 (ENSG00000070031). 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_s	G_s	G_s
Selective agonists	Glucagon	GLP-1-(7-37) (Dillon *et al*., 1993); GLP-1-(7-36)amide (Thorens *et al*., 1993), exendin-3 (Raufman *et al*., 1991), exendin-4 (Thorens *et al*., 1993)	GLP-2
Selective antagonists	L168049 (Cascieri *et al*., 1999), des-His^{1}-[Glu^{9}]glucagon amide (Post *et al*., 1993), BAY27-9955 (Petersen and Sullivan, 2001), xNNC92-1687 (Madsen *et al*., 1998)	Exendin-(9-39) (Thorens *et al*., 1993); T0632 (Tibaduiza *et al*., 2001)	–
Probes	[^{125}I]-glucagon	[^{125}I]-GLP-1-(7-36) amide, [^{125}I]-exendin, [^{125}I]-exendin-(9-39), [^{125}I]-GLP-1-(7-37)	–

Nomenclature	GIP	GHRH	Secretin
Ensembl ID	ENSG00000010310	ENSG00000106128	ENSG00000080293
Principal transduction	G_s	G_s	G_s
Selective agonists	GIP	BIM28011 (Coy *et al*., 1996)	Secretin
Selective antagonists	[Pro^{3}]GIP	JV-1-36 (Schally and Varga, 1999), JV-1-38 (Schally and Varga, 1999)	[(CH$_2$NH)^{4,5}]secretin (Kim *et al*., 1993)
Probes	[^{125}I]-GIP	[^{125}I]-GHRH	[^{125}I]-(Tyr^{10})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-diiospropyl-2-(1-hydroxyethyl)-6-propyl-4′-fluoro-1,1′-biphenyl; **BIM28011**, [D-Ala^{2},Ala^{8,9,15,27},D-Arg^{29}]hGHRH-(1–29)NH$_2$; **JV-1-36**, [PhAc-Tyr^{1},D-Arg^{2},Phe(4-Cl)^{6},Arg^{9},Abu^{15},Nle^{27},D-Arg^{28},Har^{29}]hGHRH(1–29)NH$_2$; **JV-1-38**, [PhAc-Tyr^{1},D-Arg^{2},Phe(4-Cl)^{6},Har^{9},Tyr(Me)^{10},Abu^{15},Nle^{27},D-Arg^{28},Har^{29}]hGHRH(1–29)NH$_2$; **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-1*H*-indole)propanoate

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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 1*S*,3*R*-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$_2$ and mGlu$_3$ at low nanomolar concentrations, mGlu$_8$ at high nanomolar concentrations, and mGlu$_1$, mGlu$_4$, mGlu$_5$ and mGlu$_7$ 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$_1$ and mGlu$_5$); Group II (mGlu$_2$ and mGlu$_3$) and Group III (mGlu$_4$, mGlu$_6$, mGlu$_7$ and mGlu$_8$) (see Further Reading). Group I mGlu receptors may be activated by DHPG and 3HPG (Brabet *et al.*, 1995), and antagonized by (S)-hexylhomoibotenic 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 2*R*,4*R*-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$_1$	mGlu$_2$	mGlu$_3$	mGlu$_4$
Other names	mGluR$_1$	mGluR$_2$	mGluR$_3$	mGluR$_4$
Ensembl ID	ENSG00000152822	ENSG00000164082	ENSG00000198822	ENSG00000124493
Principal transduction	G$_{q/11}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Selective agonists	–	–	NAAG (Wroblewska *et al.*, 1997)	L-AP4, LSOP (Wu *et al.*, 1998)
Selective positive allosteric modulators	Ro01-6128, Ro67-4853, Ro67-7476 (Knoflach *et al.*, 2001)	LY487379 (Johnson *et al.*, 2003), CBiPES (Johnson *et al.*, 2005), BINA (Bonnefous *et al.*, 2005b)	–	(-)-PHCCC (Maj *et al.*, 2003), SIB1893, MPEP (Mathiesen *et al.*, 2003), VU0155041 (Niswender *et al.*, 2008), VU0361737 (Engers *et al.*, 2009)
Selective competitive antagonists	3-MATIDA (Moroni *et al.*, 2002), AIDA (Moroni *et al.*, 1997), (*S*)-(+)-CBPG (Mannaioni *et al.*, 1999), LY367385 (Clark *et al.*, 1997), (*S*)-TBPG (Costantino *et al.*, 2001)	PCCG-4 (Pellicciari *et al.*, 1996)	–	MAP4
Selective negative allosteric modulators	CPCCOEt (Litschig *et al.*, 1999), BAY36-7620 (Carroll *et al.*, 2001), LY456236 (Li *et al.*, 2002), 3,5-DMPPP (Micheli *et al.*, 2003), EM-TBPC (Malherbe *et al.*, 2003), JNJ16259685 (Lavreysen *et al.*, 2004), A841720 (8.0, Zheng *et al.*, 2005)	Ro64-5229 (Kolczewski *et al.*, 1999)	–	–

The activity of NAAG as an agonist at mGlu$_3$ 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$_5$	mGlu$_6$	mGlu$_7$	mGlu$_8$
Other names	mGluR$_5$	mGluR$_6$	mGluR$_7$	mGluR$_8$
Ensembl ID	ENSG00000168959	ENSG00000113262	ENSG00000196277	ENSG00000179603
Principal transduction	G$_{q/11}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Selective agonists	CHPG (Doherty *et al.*, 1997), (*S*)-(+)-CBPG (Mannaioni *et al.*, 1999)	Homo-AMPA (Bräuner-Osborne *et al.*, 1996), 1-benzyl-APDC (Tuckmantel *et al.*, 1997)	LSOP (Wu *et al.*, 1998), L-AP4	LSOP (Wu *et al.*, 1998), L-AP4, (*S*)-3,4-DCPG (Thomas *et al.*, 2001)

Nomenclature	mGlu$_5$	mGlu$_6$	mGlu$_7$	mGlu$_8$
Selective positive allosteric modulators	DFB (O'Brien *et al.*, 2003), CPPHA (O'Brien *et al.*, 2004), CDPPB (Kinney *et al.*, 2005), VU1545 (de Paulis *et al.*, 2006)	–	AMN082 (Mitsukawa *et al.*, 2005)	–
Selective competitive antagonists	ACDPP (6.5, Bonnefous *et al.*, 2005a)	MAP4, THPG (Thoreson *et al.*, 1997)	–	MPPG (Wu *et al.*, 1998)
Selective negative allosteric modulators	SIB1757 (Varney *et al.*, 1999), SIB1893 (Varney *et al.*, 1999), MPEP (Gasparini *et al.*, 1999b), MTEP (Brodkin *et al.*, 2002), fenobam (Porter *et al.*, 2005), YM298198 (Kohara *et al.*, 2005)	–	MMPIP (Suzuki *et al.*, 2007)	–

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [^{3}H]-R214127 (Lavreysen *et al.*, 2003) and [^{3}H]-YM298198 (Kohara *et al.*, 2005) at mGlu$_1$ receptors and [^{3}H]-methoxyMPEP (Gasparini *et al.*, 2002) and [^{3}H]-methoxymethyl-MTEP (Anderson *et al.*, 2002) at mGlu$_5$ 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$_1$, but is an agonist (albeit of reduced efficacy) at mGlu$_5$ 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-methylhomoibotenic 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]benzothiolo[3,2-d]pyrimidin-4-one; **ACDPP**, 3-amino-6-chloro-5-dimethylamino-*N*-2-pyridinylpyrazinecarboxamide hydrochloride; **1*S*,3*R*-ACPD**, 1-aminocyclopentane-1*S*,3*R*-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; **2*R*,4*R*-APDC**, aminopyrrolidine-2*R*,4*R*-dicarboxylate; also known as LY314593; **BAY 36-7620**, (3a*S*,6a*S*)-6a-naphtalan-2-ylmethyl-5-methyliden-hexahyrol-cyclopenta[c]furan-1-one; **BINA**, 3′-([{2-cyclopentyl-2,3-dihydro-6,7-dimethyl-1-oxo-1H-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*)-(1)-2-(39-carboxybicycle[1.1.1]pentyl)glycine; **L-CCG-I**, (2*S*,3*S*,4*S*)α-(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*)-α-ethylglutamate; **EM-TBPC**, (1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydropyrimidine-5-carbonitrile; **fenobam**, *N*-(3-chlorophenyl)-*N*′-(4,5-dihydrol-1-methyl-4-oxo-1-*H*-imidazole-2-yl)-urea; **3HPG**, 3-hydroxyphenylglycine; **[^{11}C]-JNJ-16567083**, (3-ethyl-2-[^{11}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-dioc acid; **LY341495**, 2*S*-2-amino-2-(1*S*,2*S*-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propanoic acid; **LY354740**, (+)-2-aminobicyclic[3.1.0]hexane-2,6-dicarboxylate; **LY367385**, (+)-2-methyl-4-carboxyphenylglycine; **LY379268**, (-)-2-oxa-4-aminobicylco[3.1.0]hexane-4,6-dicarboxylic acid; **LY389795**, (-)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; **LY393675**, α-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**, α-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*)-α-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)cyclopropa[b]chromen-1a-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]-1H-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-1H-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*-neopentylthiaolo[3,2-a]benzoimidazole-2-carboxamide

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Glycoprotein hormone

Overview: Glycoprotein hormone receptors (provisional nomenclature) are activated by a heterodimeric glycoprotein made up of a common α chain (116 amino-acid ENSG00000135346), with a unique β 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_s	G_s, $G_{q/11}$ and G_i	All four families of G proteins can be activated by this receptor
Selective agonists	FSH	LH, CG	TSH
Probes	$[^{125}I]$-FSH	$[^{125}I]$-LH, $[^{125}I]$-CG	$[^{125}I]$-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).

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Gonadotropin-releasing hormone (GnRH)

Overview: $GnRH_1$ and $GnRH_2$ receptors (provisonal 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_2, 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_2, 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). $GnRH_1$ 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. $GnRH_2$ 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 $GnRH_1$ 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 $GnRH_2$ receptors is unknown.

Nomenclature	$GnRH_1$	$GnRH_2$
Other names	Type I GnRHR, LHRH receptor, GnRH I receptor	Type II GnRHR
Ensembl ID	ENSG00000109163	ENSG00000211451
Principal transduction	$G_{q/11}$	$G_{q/11}$
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 *et al.*, 2003)
Probes	[^{125}I]-GnRH I, [^{125}I]-buserelin	[^{125}I]-GnRH II

$GnRH_1$ and $GnRH_2$ receptors couple primarily to $G_{q/11}$ (Grosse *et al.*, 2000) but coupling to G_s and G_i is evident in some systems (Krsmanovic *et al.*, 2003). $GnRH_2$ 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 $GnRH_2$ receptors (Grundker *et al.*, 2002). However, $GnRH_2$ 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 $GnRH_2$ 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 $GnRH_1$ receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand specificity) than effects on $G_{q/11}$ in pituitary cells (Maudsley *et al.*, 2004). Loss-of-function mutations in the $GnRH_1$ receptor and deficiency of GnRH I are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' $GnRH_1$ 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).

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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_s (Filardo *et al*., 2000), $G_{i/o}$ (Revankar *et al*., 2005)
Selective agonists	G1 (Bologa *et al*., 2006)
Selective antagonists	G15 (Dennis *et al*., 2009)
Probes	[^{3}H]-Oestrogen (Revankar *et al*., 2005; Thomas *et al*., 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-3*H*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*α*-(9-[{4,4,5,5,5,-pentafluoropentyl}sulphinyl]nonyl)estra-1,3,5(10)-triene-3,17*β*-diol

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GPR18, GPR55 and GPR119

Overview: GPR18, GPR55 and GPR119 (provisional nomenclature), although showing little structural similarity to CB_1 and CB_2 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	$G_{i/o}$ (Kohno *et al*., 2006)	$G_{12/13}$ (Ryberg *et al*., 2007)	G_s (Ning *et al*., 2008; Overton *et al*., 2006)
Putative endogenous agonists	*N*-Arachidonoylglycine (Kohno *et al*., 2006)	Lysophosphatidylinositol (Oka *et al*., 2007), 2-arachidonoylglycerolphosphoinositol (Oka *et al*., 2009)	*N*-Oleoylethanolamine > *N*-palmitoylethanolamine > *N*-stearoylethanolamine (anandamide is ineffective, Overton *et al*., 2006)
Synthetic agonists	–	AM251 (Henstridge *et al*., 2009; Kapur *et al*., 2009)	PSN375963, PSN632408 (Overton *et al*., 2006), AS1269574 (Yoshida *et al*., 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^9-tetrahydrocannnabinol (McHugh *et al*., 2011). GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB_1 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

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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_1	H_2	H_3	H_4
Ensembl ID	ENSG00000196639	ENSG00000168546	ENSG00000146013	ENSG00000134489
Principal transduction	$G_{q/11}$	G_s	$G_{i/o}$	$G_{i/o}$
Selective agonists	Histaprodifen, N^{τ}-methylhistaprodifen	Amthamine	Methimepip (Kitbunnadaj *et al.*, 2005), immethridine (Kitbunnadaj *et al.*, 2004)	Clobenpropit, 4-methylhistamine, VUF8430 (Lim *et al.*, 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 *et al.*, 2004), thioperamide (8.4)	JNJ7777120 (8.1)
Probes	[^{3}H]-Mepyramine (1 nM), [^{11}C]-Mepyramine, [^{11}C]-doxepin	[^{3}H]-Tiotidine (15 nM), [^{125}I]-iodoaminopotentidine (0.3 nM)	[^{3}H]-*R*-α-Methylhistamine (0.5 nM), [^{3}H]-N^{α}-methylhistamine (2 nM), [^{125}I]-iodophenpropit (0.6 nM), [^{125}I]-iodoproxyfan (0.06 nM)	[^{3}H]-JNJ7777120 (3.6 nM)

Histaprodifen and N^{τ}-methylhistaprodifen are reduced efficacy agonists. The H_4 receptor appears to exhibit broadly similar pharmacology to the H_3 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_4 receptor (Lim *et al.*, 2005). [^{3}H]-Histamine has been used to label the H_4 receptor in heterologous expression systems.

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Hydroxycarboxylic acid family

Overview: The hydroxycarboxylic acid family of receptors (ENSFM00500000271913, 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_2 receptors only (Tunaru *et al*., 2003; Wise *et al*., 2003).

Nomenclature	HCA_1	HCA_2	HCA_3
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	$G_{i/o}$ (Ge *et al*., 2008)	$G_{i/o}$ (Soga *et al*., 2003; Wise *et al*., 2003; Tunaru *et al*., 2003)	$G_{i/o}$ (Soga *et al*., 2003; Wise *et al*., 2003)
Selective agonists	Lactate (Cai *et al*., 2008; Liu *et al*., 2009)	Nicotinic acid (Soga *et al*., 2003; Wise *et al*., 2003; Tunaru *et al*., 2003), acipimox (Wise *et al*., 2003), 3-hydroxybutyrate (Taggart *et al*., 2005)	3-Hydroxyoctanoic acid (Ahmed *et al*., 2009), IBC293 (Semple *et al*., 2006)
Probes	–	[^{3}H]-Nicotinic acid (Soga *et al*., 2003)	–

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

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

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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_2, neuropeptide FF or F-8-F-amide) and NPSF (SLAAPQRF-NH_2, neuropeptide SF) and the octadecapeptide NPAF (AGEGLSSPFWSLAAPQRF-NH_2, 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 RF amide-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 *et al*., 2001), GPR54, metastin, hypogonadotropin	Neuropeptide FF 1, GPR147 (Bonini *et al*., 2000), OT7T022	Neuropeptide FF 2, GPR74 (Bonini *et al*., 2000), HLWAR77	Prolactin-releasing peptide, GPR10 (Hinuma *et al*., 1998), hGR3, UHR-1	SP9155 (Jiang *et al*., 2003), AQ27 (Fukusumi *et al*., 2003), P518
Ensembl ID	ENSG00000116014	ENSG00000148734	ENSG00000056291	ENSG00000119973	ENSG00000186867
Principal transduction	$G_{q/11}$ (Kotani *et al*., 2001; Muir *et al*., 2001)	$G_{q/11}$	$G_{i/o}$ (Mollereau *et al*., 2005)	$G_{q/11}$ (Langmead *et al*., 2000)	$G_{q/11}$, $G_{i/o}$ (Fukusumi *et al*., 2003)
Potency order	–	FMRF, NPFF > NPAF > NPSF, QRFP, PrP31 (Gouardères *et al*., 2007)	NPAF, NPFF > PrP31 > FMRF, QRFP > NPSF (Gouardères *et al*., 2007)	PrRP20, PrRP31 (Langmead *et al*., 2000)	–
Selective agonists	KP54, KP13, KP10 (Kotani *et al*., 2001; Ohtaki *et al*., 2001), 4-fluorobenzoyl-FGLRW-NH_2 (Tomita *et al*., 2008), $[dY]^1$KP-10 (Curtis *et al*., 2010)	NPFF, NPVF	NPFF, dNPA (Roussin *et al*., 2005), AC263093 (Lameh *et al*., 2010)	PrRP	QRFP
Selective antagonists	Peptide 234 (Roseweir *et al*., 2009)	AC262620, AC262970 (Lameh *et al*., 2010)	–	Neuropeptide Y (Lagerstrom *et al*., 2005)	–
Probes	$[^{125}I]$-KP10 (Kotani *et al*., 2001), $[^{125}I]$KP14 (Mead *et al*., 2007), $[^{125}I\text{-}Tyr^{45}]$-KP15 (Ohtaki *et al*., 2001)	$[^{125}I]$-NPFF, $[^{125}I]$-YVP (Gouardères *et al*., 2002), $[^{3}H]$-NPVF (Talmont *et al*., 2009)	$[^{125}I]$-NPFF, $[^{125}I]$-EYF (Gouardères *et al*., 2002), $[^{3}H]$-EYF (Talmont *et al*., 2009)	$[^{125}I]$-PrRP20 (Langmead *et al*., 2000), $[^{125}I]$-PrRP31 (Ellacott *et al*., 2005)	$[^{125}I]$-QRFP (Takayasu *et al*., 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_2; **NPVF**, Val-Pro-Asn-Leu-Pro-Gln-Arg-Phe-NH_2; **Peptide 234**, ac[(D)-A]NWNGFG[9D)-W]RF; **RF9**, adamantylcarbonyl-arginyl-phenylalaninamide; AC262620, AC262970, AC263093

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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$_4$, LTC$_4$, LTD$_4$, LTE$_4$, 12*R*-HETE and 12*S*-HETE. CysLT$_1$ and CysLT$_2$ are co-expressed by most myeloid cells. However, the function of CysLT$_2$ remains unclear. CysLT$_2$ has been demonstrated to exert a suppressive influence on CysLT$_1$ expression, suggesting an autoregulatory function which is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking CysLT$_2$ receptors (Jiang *et al*., 2007).

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-*S*-transferase/LTC$_4$ synthase, γ-glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator-activated receptor α (PPARα, 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$_4$ is rapidly converted in many systems to LTD$_4$). Metabolic inhibitors (e.g. serine–borate complex) reduce this problem but can also have non-specific effects.

Nomenclature	BLT$_1$	BLT$_2$	CysLT$_1$	CysLT$_2$
Other names	LTB$_4$	–	HG55, HMTMF81, LTD$_4$	HPN321, LTC$_4$
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000173198	ENSG00000152207
Principal transduction	G$_{q/11}$, G$_{i/o}$	G$_{q/11}$, G$_{i/o}$	G$_{q/11}$	G$_{q/11}$
Rank order of potency	LTB$_4$ > 20-hydroxy-LTB$_4$ >> 12*R*-HETE (Yokomizo *et al.*, 2001)	LTB$_4$ > 12*S*-HETE = 12*S*-HPETE > 15*S*-HETE > 12*R*-HETE = 5*S*-HETE > 20-hydroxy-LTB$_4$ (Yokomizo *et al.*, 2001)	LTD$_4$ > LTC$_4$ > LTE$_4$ (Sarau *et al.*, 1999)	LTC$_4$ = LTD$_4$ >> LTE$_4$ (Nothacker *et al.*, 2000)
Selective agonists	–	12*S*-HETE	–	BAYu9773
Selective antagonists	CP105696 (pIC$_{50}$ 7.2), U75302 (pIC$_{50}$ 6.9)	LY255283 (pIC$_{50}$ 6.0)	Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3)	–
Probes	[^{3}H]-LTB$_4$ (0.2–0.7 nM), [^{3}H]-CGS23131 (13 nM)	[^{3}H]-LTB$_4$ (0.2–23 nM)	[^{3}H]-LTD$_4$, [^{3}H]-ICI198615	[^{3}H]-LTD$_4$

BAYu9773 is an antagonist at CysLT$_1$ (6.8–7.7) and a reduced efficacy agonist at CysLT$_2$ receptors. The CysLT$_1$ and CyLT$_2$ 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$_4$ 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$_4$ (LXA$_4$) and 15-epi-LXA$_4$ (aspirin-triggered lipoxin A$_4$, 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-ETE the most potent agonist identified for this receptor.

Nomenclature	FPR2/ALX	OXE
Other names	FPRL1, FPR2, FPRH2, RFP, ALX	TG1019 (Hosoi *et al.*, 2002), R527 (Jones *et al.*, 2003), hGPCR48 (Koike *et al.*, 2006)
Ensembl ID	ENSG00000171049	ENSG00000162881
Principal transduction	G$_i$ (Maddox *et al.*, 1997)	G$_{i/o}$ (O'Flaherty *et al.*, 2000; Hosoi *et al.*, 2002; Jones *et al.*, 2003; Hosoi *et al.*, 2005)
Rank order of potency	LXA$_4$ = ATL = ATLa2 > LTC$_4$ = LTD$_4$ >> 15-deoxy-LXA$_4$ >> fMLP (Clish *et al.*, 1999; Fiore *et al.*, 1994; Fiore and Serhan, 1995; Gronert *et al.*, 2001; Takano *et al.*, 1997)	5-Oxo-ETE, 5-oxo-C20:3 >> 5*S*-HpETE > 5*S*-HETE (Hosoi *et al.*, 2002; Jones *et al.*, 2003, Patel *et al.*, 2008)
Selective agonists	LXA$_4$, ATL, ATLa2 (Guilford *et al.*, 2004), RvD1 (Krishnamoorthy *et al.*, 2010)	5-Oxo-ETE
Probes	[^{3}H]-LXA$_4$ (0.2–1.7 nM; Fiore *et al.*, 1994; Takano *et al.*, 1997)	[^{3}H]-5-oxo-ETE (3.8 nM, O'Flaherty *et al.*, 1998)

Note that the data for FPR2/ALX are also reproduced on the Formylpeptide receptor pages (see Page S48). A receptor selective for LXB$_4$ 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_4 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 > 18*R*-HEPE > EPA (Arita *et al*., 2005a,b)	RvD1 > LXA4
Selective agonists	RvE1	RvD1, LXA_4
Probes	$[^3H]$-RvE1 (11 nM, Arita *et al*., 2005a)	$[^3H]$-RvD1 (0.2 nM, Krishnamoorthy *et al*., 2010)

Abbreviations: **12*R*-HETE**, 12*R*-hydroxyeicosa-5*Z*,8*Z*,10*E*,14*Z*-tetraenoic acid; **18*R*-HEPE**, 18*R*-hydroxyeicosapentaenoic acid; **5*s*-HETE**, 5*s*-hydroxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; **5*s*-HpETE**, 5*s*-hydroperoxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; **5-oxo-C20:3**, 5-oxo-6*E*,8*Z*,11*Z*-eicosatrienoic acid; **5-oxo-ETE**, 5-oxo-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; **ANXA1**, annexin 1; **ATL**, aspirin-triggered lipoxin A_4 [15-*epi*-LXA_4, 5S,6R,15R-trihydroxyl-7*E*,9*E*,13*E*,11*z*-eicosatetraenoic acid]; **ATLa2**, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA_4]; **BAYu9773**, 6(*R*)-(4′-carboxyphenyl-thio)-5(*S*)-hydroxy-7*E*,11*Z*,14*Z*-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**, 4*z*,7*z*,10*z*,13*z*,16*z*,19*z*-docosahexaenoic acid; **EPA**, 5*z*,8*z*,11*z*,14*z*,17*z*-eicosapentaenoic acid; **ICI198615**, (1-[2-methoxy-4-{([phenylsulfonylamino]carbonyl)phenyl}methyl]-1*H*-indazol-6-yl)carbamic acid cyclopentyl ester; **LTC_4**, leukotriene C_4; **LTD_4**, leukotriene D_4; **LXA_4**, lipoxin A_4 [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**, oxoeicosanoid; **RvE1**, resolvin E1 or 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-EPA; **SR2640**, 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid; **U75302**, 6-(6-(3-hydroxy-1*E*,5*Z*-undecadien-1-yl)-2-pyridinyl)-1,5-hexanediol

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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 [^{3}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 PPARγ receptors (McIntyre *et al.*, 2003), although the physiological significance of this observation remains unclear (Simon *et al.*, 2005).

Nomenclature	LPA$_1$	LPA$_2$	LPA$_3$	LPA$_4$	LPA$_5$	LPA$_6$
Other names	VZG-1, Edg2, *lp*$_{A1}$	Edg4, *lp*$_{A2}$	Edg7, *lp*$_{A3}$	p2y9, gpr23	GPR92	P2y5, P2RY5
Ensembl ID	ENSG00000198121	ENSG00000064547	ENSG00000171517	ENSG00000147145	ENSG00000184574	ENSG00000139679
Principal transduction	G$_{i/o}$, G$_{q/11}$, G$_{12/13}$	G$_{i/o}$, G$_{q/11}$, G$_{12/13}$	G$_{i/o}$, G$_{q/11}$, G$_s$	G$_{i/o}$, G$_{q/11}$, G$_s$, G$_{12/13}$ (Lee *et al.*, 2007)	G$_q$, G$_{12/13}$ (Kotarsky *et al.*, 2006; Lee *et al.*, 2006)	G$_{12/13}$ (Yanagida *et al.*, 2009; Kimura *et al.*, 2011)
Selective agonists	–	FAP10, FAP12 (Virag *et al.*, 2003)	OMPT (Hasegawa *et al.*, 2003)	–	–	–
Selective antagonists	Ki16425 (Ohta *et al.*, 2003), AM966 (Swaney *et al.*, 2010)	–	DGPP 8:0 (Ohta *et al.*, 2003)	–	–	–

FAP12, VPC12249 and VPC32179 have antagonist activity at LPA$_1$ and LPA$_3$ 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-y l}-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

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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 (DFDMLRCMLGRVYRPCWQV) generated from a precursor (ENSG00000183395), which also produces neuropeptides EI and GE.

Nomenclature	MCH_1	MCH_2
Other names	SLC-1, GPR24	SLT, GPRv17
Ensembl ID	ENSG00000128285	ENSG00000152034
Principal transduction	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$ (Hill *et al*., 2001; Mori *et al*., 2001; Rodriguez *et al*., 2001)
Rank order of potency	Human MCH > salmon MCH	Human MCH = salmon MCH (Hill *et al*., 2001)
Selective antagonists	SNAP7941 (9.2, Borowsky *et al*., 2002), GW803430 (9, Gehlert *et al*., 2009), ATC0175 (pIC_{50} 7.9-8.2, Chaki *et al*., 2005), T226296 (7.5, Takekawa *et al*., 2002)	–
Probes	[^{3}H]-MCH (Burgaud *et al*., 1997), [Phe^{13},[^{125}I]-Tyr^{19}]MCH (Burgaud *et al*., 1997), [^{125}I]-S36057 (0.04 nM, Audinot *et al*., 2001)	–

The MCH_2 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-dioxyoctanoyl)MCH-(6-17); **SNAP7941**, (+)-methyl(4*S*)-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

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Melanocortin

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

Nomenclature	MC_1	MC_2	MC_3	MC_4	MC_5
Other names	–	ACTH	–	–	–
Ensembl ID	ENSG00000258839	ENSG00000185231	ENSG00000124089	ENSG00000166603	ENSG00000176136
Principal transduction	G_s	G_s	G_s	G_s	G_s
Rank order of potency	α-MSH > β-MSH ≥ ACTH, γ-MSH	ACTH	γ-MSH, β-MSH ≥ ACTH, α-MSH	β-MSH ≥ α-MSH, ACTH > γ-MSH	α-MSH ≥ β-MSH ≥ ACTH > γ-MSH
Selective agonists	–	–	D-Trp^8-γ-MSH (Grieco *et al.*, 2000)	THIQ (Van der Ploeg *et al.*, 2002), MK0493 (Krishna *et al.*, 2009)	–
Selective antagonists	–	–	–	HS014 (8.5, Schiöth *et al.*, 1998), MBP10 (Bednarek *et al.*, 2001)	–
Probes	[^{125}I]-NDP-MSH	[^{125}I]-ACTH-(1–24)	[^{125}I]-NDP-MSH, [^{125}I]-SHU9119	[^{125}I]-NDP-MSH, [^{125}I]-SHU9119	[^{125}I]-NDP-MSH

Polymorphisms of the MC_1 receptor have been linked to variations in skin pigmentation. Defects of the MC_2 receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC_4 receptor have been linked to obesity (Chagnon *et al.*, 1997; Farooqi and O'Rahilly, 2008).

Abbreviations: HS014, *cyc*(*S–S*)-(Ac-Cys^{11},D-Nal^{14},Cys^{18},Asp-NH_2)*β*-MSH-(11-22); **MBP10**, cyclo(6β→10ε)(succinyl(6)-D-(2′)Nal^7-Arg^8-Trp^9-Lys^{10})-NH_2; **MK0493**, *N*-1-(2-[1-{tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl}-5-chlorophenyl]ethyl)acetamide; **NDP-MSH**, [Nle^4,d-Phe^7]α-MSH; **SHU9119**, Ac-Nle-Asp-His-d-Nal^2-Arg-Trp-Lys-NH_2; **THIQ**, *N*-([3R]-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl)-(1R)-1-(4-chlorobenzyl)-2-(4-cyclohexyl-4-[1*H*-1,2,4-triazol-1ylmethyl]piperidin-1-yl)-2-oxoethylamine

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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$_1$	MT$_2$
Other names	MEL$_{1A}$, ML$_{1A}$, Mel$_{1a}$	MEL$_{1B}$, ML$_{1B}$, Mel$_{1b}$
Ensembl ID	ENSG00000168412	ENSG00000134640
Principal transduction	G$_{i/o}$	G$_{i/o}$
Selective agonists	–	IIK7 (Sugden *et al*., 1999), 5-methoxyluzindole (Dubocovich *et al*., 1997)
Selective antagonists	–	K185 (9.3, Sugden *et al*., 1999), 4P-PDOT (8.8, Dubocovich *et al*., 1997), DH97 (8.0, Teh and Sugden, 1998)
Probes	2-Iodo-[^{125}I]-melatonin (Dubocovich *et al*., 1997), [^{3}H]-melatonin (Browning *et al*., 2000)	2-Iodo-[^{125}I]-melatonin (Dubocovich *et al*., 1997), [^{3}H]-melatonin (Browning *et al*., 2000)

Melatonin, 2-iodo-melatonin, S20098, GR196429, LY156735 and TAK375 (Kato *et al*., 2005) are nonselective agonists for MT$_1$ and MT$_2$ receptors. (-)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT$_1$ receptors (Ting *et al*., 1999). Luzindole is an MT$_1$/MT$_2$ melatonin receptor-selective competitive antagonist with some selectivity for the MT$_2$ receptor (Dubocovich *et al*., 1998). MT$_1$/MT$_2$ heterodimers present different pharmacological profiles from MT$_1$ and MT$_2$ receptors (Ayoub *et al*., 2004).

The *MT$_3$* binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML$_2$ receptor, binds selectively 2-iodo-[^{125}I]-5MCA-NAT (Molinari *et al*., 1996). Pharmacological investigations of *MT$_3$* 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$_3$* receptor is in the control of intraocular pressure in rabbits (Pintor *et al*., 2003). The *MT$_3$* 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$_{1C}$) coupled to the G$_{i/o}$ 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; **IIK7**, *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-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

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Motilin

Overview: Motilin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by a 22 amino-acid peptide derived from a precursor (ENSG00000096395), 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 *et al.*, 1999), GPR38 (Mckee *et al.*, 1997)
Ensembl ID	ENSG00000102539
Principal transduction	$G_{q/11}$ (Depoortere and Peeters, 1995; Feighner *et al.*, 1999)
Rank order of potency	Motilin > ABT229, mitemcimal >erythromycin (Clark *et al.*, 1999) = GSK962040 (Sanger *et al.*, 2009)
Selective agonists	ABT229 (Lartey *et al.*, 1995), mitemcinal (Koga *et al.*, 1994; Takanashi *et al.*, 2007), GSK962040 (Sanger *et al.*, 2009)
Selective antagonists	MA2029 (pA_2 9.2, Sudo *et al.*, 2008), GM109 (Takanashi *et al.*, 1995; pA_2 7.2-7.5 Clark *et al.*, 1999)
Probes	$[^{125}I]$-Motilin (0.1 nM, Feighner *et al.*, 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

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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 *et al*., 2000; Hedrick *et al*., 2000; Hosoya *et al*., 2000; Howard *et al*., 2000; Kojima *et al*., 2000; Raddatz *et al*., 2000; Szekeres *et al*., 2000)	FM4, TGR1, SNORF72 (Hosoya *et al*., 2000; Howard *et al*., 2000; Raddatz *et al*., 2000; Shan *et al*., 2000)
Ensembl ID	ENSG00000171596	ENSG00000132911
Principal transduction	$G_{q/11}$ (Hedrick *et al*., 2000; Brighton *et al*., 2004a)	$G_{q/11}$ (Hosoya *et al*., 2000; Brighton *et al*., 2004a)
Antagonists	–	R-PSOP (Liu *et al*., 2009)

NMU1 and NMU2 couple predominantly to $G_{q/11}$ although there is evidence of good coupling to $G_{i/o}$ (see Hosoya *et al*., 2000; Brighton *et al*., 2004a; Hsu and Luo, 2007). NMU1 and NMU2 can be labelled with [^{125}I]-NMU and [^{125}I]-NMS (of various species, e.g. Meng *et al*., 2008); BODIPY® TMR-NMU or Cy3B-NMU-8 (Brighton *et al*., 2004a). A range of radiolabelled (^{125}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]

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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_s, $G_{q/11}$ (Gupte *et al.*, 2004; Vendelin *et al.*, 2005)
Selective agonists	NPS
Probes	[^{125}I-Tyr^{10}]-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).

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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 recepter (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_4 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. [^{125}I]-PYY or [^{125}I]-NPY can be used to label Y_1, Y_2, Y_5 and y_6 subtypes non-selectively, while [^{125}I]-[cPP(1-7),NPY(19-23),Ala^{31},Aib^{32},Gln^{34}]hPP may be used to label Y_5 receptors preferentially.

Nomenclature	Y_1	Y_2	Y_4	Y_5	y_6
Other names	–	–	PP_1	–	Y_5, PP_2, Y_{2B}
Ensembl ID	ENSG00000164128	ENSG00000185149	ENSG00000204174	ENSG00000164129	ENSG00000226306
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Rank order of potency	NPY ≥ PYY >> PP	NPY ≥ PYY >> PP	PP > NPY = PYY	NPY ≥ PYY ≥ PP	NPY = PYY > PP
Selective agonists	[Leu^{31},Pro^{34}]NPY, [Pro^{34}]NPY, [Leu^{31},Pro^{34}]PYY, [Pro^{34}]PYY	NPY-(3-36), PYY-(3-36)	PP	[Ala^{31},Aib^{32}]NPY (Cabrele *et al*., 2000)	–
Selective antagonists	BIBO3304 (9.5, Wieland *et al*., 1998), BIBP3226 (8.2, Gerald *et al*., 1996)	BIIE0246 (8.5, Doods *et al*., 1999), JNJ5207787 (Bonaventure *et al*., 2004)	–	L152804 (7.6, Kanatani *et al*., 2000)	–
Probes	[^{125}I]-[Leu^{31},Pro^{34}] NPY, [^{3}H]-BIBP3226 (2.1 nM)	[^{125}I]-PYY-(3-36)	[^{125}I]-PP	[^{125}I]-[cPP(1-7),NPY(19-23), Ala^{31},Aib^{32},Gln^{34}]hPP (Dumont *et al*., 2004)	–

The Y_1 agonists indicated are selective relative to Y_2 receptors. BIBP3226 is selective relative to Y_2, Y_4 and Y_5 receptors (Gerald *et al*., 1996). NPY-(13-36) is Y_2 selective relative to Y_1 and Y_5 receptors. PYY-(3-36) is Y_2 selective relative to Y_1 receptors.

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

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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	$G_{i/0}$ (Mazzocchi *et al.*, 2005)	$G_{i/0}$ (Mazzocchi *et al.*, 2005)
Rank order of potency	NPB-29 > NPB-23 > NPW-23 > NPW-30 (Brezillon *et al.*, 2003)	NPW-23 > NPW-30 > NPB-29 > NPB-23 (Brezillon *et al.*, 2003)
Selective agonists	Ava-3, Ava-5 (Kanesaka *et al.*, 2007)	–
Probes	[^{125}I]-NPW-23 (0.44 nM, Singh *et al.*, 2004)	[^{125}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_2; **Ava5**, TrpTyrLysAvaAvaAvaAvaAvaAvaGlyArgAlaAlaGlyLeuLeuSerGlyLeu-NH_2

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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_2 receptor. A nonpeptide antagonist, SR142948A, shows high affinity (pK_i~9) at both NTS_1 and NTS_2 receptors (Gully *et al.*, 1997). [^{3}H]-Neurotensin and [^{125}I]-neurotensin may be used to label NTS_1 and NTS_2 receptors at 0.1–0.3 and 3–5 nM concentrations, respectively.

Nomenclature	NTS_1	NTS_2
Other names	High-affinity neurotensin receptor, NTRH, NTR-1, NT_1	Low-affinity neurotensin receptor, NTRL, NTR-1, NT_2
Ensembl ID	ENSG00000101188	ENSG00000169006
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	Neurotensin > neuromedin N (Hermans *et al.*, 1997)	Neurotensin = neuromedin N (Mazella *et al.*, 1996)
Selective agonists	JMV449 (Souaze *et al.*, 1997)	Levocobastine (Mazella *et al.*, 1996)
Selective antagonists	SR48692 (7.5–8.2; Gully *et al.*, 1997)	–
Probes	[^{3}H]-SR48692 (3.4 nM; Labbe-Jullie *et al.*, 1995)	–

Neurotensin appears to be a low-efficacy agonist at the NTS_2 receptor (Vita *et al.*, 1998), while the NTS_1 receptor antagonist SR48692 is an agonist at NTS_2 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_1 receptor (Martin *et al.*, 2002) and has been implicated in hormone trafficking and/or neurotensin uptake.

Abbreviations: JMV449, *H*-Lysψ (CH_2NH)-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-quinolinyl}-5-{2,6-dimethoxyphenyl}pyrazol-3-yl]carboxylamino)tricyclo(3.3.1.1.[3.7])decan-2-carboxylic acid

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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), β-endorphin (β-end), α-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, μ, δ, and κ, 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	δ	κ	μ	NOP
Other names	OP$_1$, DOP, DOR	OP$_2$, KOP, KOR	OP$_3$, MOP, MOR	ORL1, OP$_4$
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Rank order of potency	β-End = leu = met > dynA	Big dyn > dynA >> β-end > leu > met	β-End> met ≥ leu ≥.dynA	N/OFQ >> dynA
Selective agonists	DPDPE (Mosberg *et al.*, 1983), DSBULET (Delay-Goyet *et al.*, 1988), [DAla^2]deltorphin I or II (Erspamer *et al.*, 1989), SNC80 (Bilsky *et al.*, 1995)	U69593 (Lahti *et al.*, 1985), CI977 (Hunter *et al.*, 1990), Salvinorin A (Roth *et al.*, 2002)	Endomorphin-1 and -2 (Zadina *et al.*, 1997), morphine (Goldstein and Naidu, 1989), DAMGO (Handa *et al.*, 1981), sufentanil (Yeadon and Kitchen, 1988), PL017 (Costa *et al.*, 1992)	N/OFQ, N/OFQ-(1-13)-NH$_2$ (Guerrini *et al.*, 1997), Ro646198 (Jenck *et al.*, 2000), UFP-112 (Rizzi *et al.*, 2007)
Selective antagonists	Naltrindole (Portoghese *et al.*, 1988), naltriben (Sofuoglu *et al.*, 1991)	Nor-binaltorphimine (Portoghese *et al.*, 1987), GNTI (Stevens *et al.*, 2000)	CTAP (Pelton *et al.*, 1986)	J113397 (8.3, Kawamoto *et al.*, 1999), SB612111 (9.5, Zaratin *et al.*, 2004), UFP101 (7.2, Calo' *et al.*, 2002)
Probes	[^{3}H]-DPDPE (Goldstein and Naidu, 1989), [^{3}H]-naltrindole (Yamamura *et al.*, 1992), [^{3}H]-deltorphin II (Gomes *et al.*, 2000), [^{3}H]-naltriben (Lever and Scheffel, 1998)	[^{3}H]-U69593 (Lahti *et al.*, 1985), [^{3}H]-CI977 (Simonin *et al.*, 2001)	[^{3}H]-DAMGO (Goldstein and Naidu, 1989), [^{3}H]-PL017 (Hawkins *et al.*, 1987)	[^{3}H]-N/OFQ (Dooley and Houghten, 1996), [^{3}H]-Leu-N/OFQ, [^{125}I]-Tyr^{14}-N/OFQ

Subtypes of μ (μ1, μ2), δ (δ1, δ2) and κ (κ1, κ2, κ3) 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 μ-receptor in particular may be subject to extensive alternative splicing, these putative isforms have not been definitively correlated with any of the proposed subtypes. A distinct met-enkephalin receptor lacking structural resemblence 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 this heterodimerinzation for signalling remains largely unknown. For μ-opioid receptors at least, dimerization does not seem to be required for sigalling (Kuszak *et al.*, 2009).

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human μ-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)-(5α,7α,8β)-(–)-*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$_2$; **DAMGO**, Tyr-DAla-Gly-[*N*MePhe]-NH(CH$_2$)$_2$; **DPDPE**, *cyc*[DPen^2, DPen^5]enkephalin; **DSBULET**, Tyr-DSer(OtBu)-Gly-Phe-Leu-Thr; **GNTI**, 5′-guanidinyl-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-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-2*H*-benzimidazol-2-one; **PL017**, [*N*-MePhe^3,DPro^4]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-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide; **U69593**, 5α,7α,8β-(-)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxasipro(4,5)dec-8-yl)benzene acetamide; **UFP101**, [Nphe^1,Arg^{14},Lys^{15}]nociceptin-NH$_2$; **UFP-112**, [(pF)Phe^{4}Aib^{7}Arg^{14}Lys^{15}]N/OFQ-NH$_2$

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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 [^{125}I]-orexin A (Holmqvist *et al*., 2001).

Nomenclature	OX_1	OX_2
Other names	Hypocretin receptor type 1	Hypocretin receptor type 2
Ensembl ID	ENSG00000121764	ENSG00000137252
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	Orexin-A > orexin-B	Orexin-A = orexin-B
Selective agonists	–	[Ala^{11},D-Leu^{15}]orexin-B (Asahi *et al*., 2003)
Selective antagonists	SB408124 (7.5, Langmead *et al*., 2004), SB334867A (7.2-7.3, Porter *et al*., 2001)	EMPA (8.6–9.0, Malherbe *et al*., 2009), JNJ10397049 (7.9–8.3, McAtee *et al*., 2004), compound 29 (7.4; Hirose *et al*., 2003)

The primary coupling of orexin receptors to $G_{q/11}$ proteins is rather speculative and based on the strong activation of phospholipase C. Coupling of both receptors to $G_{i/o}$ and G_s 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^{11},D-Leu^{15}]orexin-B may show poor OX_2 receptor selectivity (Putula *et al*., 2011).

Loss-of-function mutations in the gene encoding the OX_2 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-methyylbenzoxanzol-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

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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 '$P2Y_1$-like', etc., until further, as yet undefined, corroborative critieria can be applied.

Nomenclature	$P2Y_1$	$P2Y_2$	$P2Y_4$	$P2Y_6$
Ensembl ID	ENSG00000169860	ENSG00000175591	ENSG00000186912	ENSG00000171631
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
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 *et al.*, 2006)	UTPγS (Lazarowski *et al.*, 1996), Ap_4A (Castro *et al.*, 1992), 2-thioUTP (El-Tayeb *et al.*, 2006), MRS2768 (Ko *et al.*, 2008)	UTPγS (Lazarowski *et al.*, 1996), MRS4062 (Maruoka *et al.*, 2011)	UDP, 3-phenacylUDP (PSB0474, El-Tayeb *et al.*, 2006), 5-iodoUDP (Besada *et al.*, 2006)
Selective antagonists	MRS2500 (8.8, Kim *et al.*, 2003), MRS2279 (8.0, Waldo *et al.*, 2002), MRS2179 (7.0, Boyer *et al.*, 1996), PIT (6.8, Gao *et al.*, 2004)	–	ATP (6.2, Kennedy *et al.*, 2000)	MRS2578 (pIC_{50} 7.4, Mamedova *et al.*, 2004)
Probes	$[^3H]$-MRS2279 (8 nM, Waldo *et al.*, 2002), $[^{35}S]$-ADPβS, $[^{35}S]$-ATPαS, $[^{35}S]$-dATPαS	–	–	–

Nomenclature	$P2Y_{11}$	$P2Y_{12}$	$P2Y_{13}$	$P2Y_{14}$
Other names	–	$P2Y_{ADP}$, P_{2T}	GPR86, GPR94, SP174	KIAAA00001, gpr105
Ensembl ID	ENSG00000244165	ENSG00000169313	ENSG00000181631	ENSG00000174944
Principal transduction	G_s, $G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{q/11}$
Rank order of potency	ATP > UTP	ADP >> ATP	ADP >> ATP	UDP-glucose
Selective agonists	ARC67085 (Communi *et al.*, 1999), NAD^+ (Moreschi *et al.*, 2006), $NAADP^+$ (Moreschi *et al.*, 2008), NF546 (Meis *et al.*, 2010)	ADP, 2-MeSADP	–	MRS2690 (Ko *et al.*, 2007)
Selective antagonists	NF157 (Ullmann *et al.*, 2005)	ATP, ARL66096 (Humphries *et al.*, 1995)	MRS2211 (Kim *et al.*, 2005)	–

ARC69931MX shows selectivity for $P2Y_{12}$ and $P2Y_{13}$ receptors compared to other P2Y receptors (Marteau *et al.* 2003; Takasaki *et al.*, 2001). NF157 also has antagonist activity at $P2X_1$ receptors (Ullmann *et al.*, 2005). UDP has been reported to be an antagonist at the $P2Y_{14}$ receptor (Fricks *et al.*, 2008).

An orphan GPCR suggested to be a '$P2Y_{15}$' 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 $p2y_3$ receptor (ENSGALG00000017327), couples to the $G_{q/11}$ 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_4, 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^{2+}-dependent Cl^- 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 $Ap_4A > Ap_5A > Ap_3A$, coupling *via* $G_{q/11}$ (Castro *et al.*, 1992). P2Y-like receptors have recently been described on mitochondria (Belous *et al.*, 2004). $CysLT_1$ and $CysLT_2$ leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes C_4 and D_4 (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-*βγ*-dichloromethylene-ATP; **AR-C69931MX**, *N*^{6}-(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)-*βγ*-dichloromethylene-ATP, also known as cangrelor; **2-MeSADP**, 2-methylthio-adenosine-5′-diphosphate; **2-MeSATP**, 2-methylthio-adenosine-5′-triphosphate; **ARL66096**, 2-propylthio-*βγ*-difluoromethylene ATP (previously FPL66096); **ATPγS**, 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-isothiocynatophenyl)] thiourea; **MRS2690**, 2-thiouridine-5′-diphosphoglucose; **MRS2768**, uridine-5′-tetraphosphate δ-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-xylene-α,α′-diphosphonic acid); **PIT**, 2,2′-pyridylisatogen tosylate

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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). [^{125}I]-PTH may be used to label both PTH_1 and PTH_2 receptors.

Nomenclature	PTH_1	PTH_2
Other names	PTH/PTHrP, PPR	–
Ensembl ID	ENSG00000160801	ENSG00000144407
Principal transduction	G_s, $G_{q/11}$	G_s, $G_{q/11}$
Rank order of potency	PTH = PTHrP	TIP39, PTH >> PTHrP
Selective agonists	–	TIP39 (Hoare *et al*., 2000)
Selective antagonists	–	TIP-9-39 (Jonsson *et al*., 2001)

Although PTH is an agonist at human PTH_2 receptors, it fails to activate the rodent orthologues. TIP39 is a weak antagonist at PTH_1 receptors (Jonsson *et al*., 2001).

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

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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 $G_{q/11}$ and $G_{i/o}$ 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	$G_{q/11}$, G_i, G_o
Selective agonists	mc-PAF
Selective antagonists	CV-6209 (9.5), SR27417 (10.0), WEB2086 (8.0), L659989 (8.1), ginkgolide B (6.4)
Radioligand	[^{3}H]-PAF (1.6 nM, Fukunaga *et al*., 2001)

Note that a previously recommended radioligand ([^{3}H]-WEB2086; K_d 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-methylsulphonyl-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]thoiazol-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

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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 unmasks 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$_1$	PAR$_2$	PAR$_3$	PAR$_4$
Other names	Thrombin receptor, PAR-1, PAR$_1$	PAR-2, PAR$_2$	Thrombin receptor, PAR-3, PAR$_3$	Thrombin receptor, PAR-4, PAR$_4$
Ensembl ID	ENSG00000181104	ENSG00000164251	ENSG00000164220	ENSG00000127533
Principal transduction	$G_{q/11}/G_{i/o}/G_{12/13}$	$G_{q/11}/G_{i/o}/\ G_{12/13}$	$G_{q/11}/G_{i/o}$	$G_{q/11}/G_{i/o}$
Agonist proteases	Thrombin, activated protein C, matrix metalloproteinase 2	Trypsin, tryptase, TF/VIIa, Xa	Thrombin	Thrombin, trypsin, cathepsin G
Selective agonists	TFLLR-NH_2	2-Furoyl-LIGRLO-NH_2 (McGuire *et al.*, 2004), SLIGRL-NH_2, SLIGKV-NH_2	–	AYPGKF-NH_2, GYPGQV-NH_2, GYPGKF-NH_2
Selective antagonists	RWJ56110 (Andrade-Gordon *et al.*, 1999), SCH530348 (Chackalamannil *et al.*, 2008), E5555 (Serebruany *et al.*, 2009)	–	–	–
Probes	[^{3}H]-haTRAP (Ahn *et al.*, 1997)	*Trans*-cinnamoyl-LIGRLO[*N*-[^{3}H]-propionyl]-NH_2 (Al Ani *et al.*, 1999), 2-furoyl-LIGRL[N[^{3}H]propionyl]-O-NH_2 and 2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH_2 (Hollenberg *et al.*, 2008).	–	–

TFLLR-NH_2 is selective relative to the PAR2 receptor (Blackhart *et al.*, 1996; Kawabata *et al.*, 1999). Thrombin is inactive at the PAR$_2$ 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 (α/β1 ENSG00000172236; γ1 ENSG00000116176; δ1 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: **[^{3}H]-haTRAP**, Ala-*p*-fluoroPhe-Ala-Arg-cyclohexylAla-homoArg-[^{3}H]-Tyr-amide; **RWJ56110**, (*αS*)-*N*-([1*S*]-3-amino-1-[{(phenylmethyl)amino}propyl]-*α*-[{(1-[{2,6-dichlorophenyl}methyl]-3-[1-pyrrolidinylmethyl]-1*H*-indol-6-yl)amino}carbonyl]amino)-3,4-difluoro-benzenepropanamide; SCH530348 (chemical name); E5555 (chemical name)

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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_2 (D), PGE_2 (E), $PGF_{2\alpha}$ (F), PGH_2 (H), prostacyclin [PGI_2 (I)] and thromboxane A_2 (T). Measurement of the potency of PGI_2 and TXA_2 is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

Nomenclature	DP_1	DP_2	FP	IP	TP
Other names	–	CRTh2, GPR44	–	–	–
Ensembl ID	ENSG00000168229	ENSG00000183134	ENSG00000122420	ENSG00000160013	ENSG00000006638
Principal transduction	G_s	$G_{i/o}$	$G_{q/11}$	G_s	$G_{q/11}$
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_2, 15*R*-15-methyl PGD_2 (Hata *et al*., 2003; Monneret *et al*., 2003)	Fluprostenol, latanoprost free acid, AL12180 (Sharif *et al*., 2006)	Cicaprost, AFP07, BMY45778 (Seiler *et al*., 1997)	U46619, STA_2, I-BOP, AGN192093
Selective antagonists	BWA868C (9.3, Giles *et al*., 1989), S5751 (8.8, Arimura *et al*., 2001), laropiprant (10.1, Sturino *et al*., 2007)	Ramatroban (Sugimoto *et al*., 2003), CAY10471 (Royer *et al*., 2007)	AS604872 (Cirillo *et al*., 2007)	RO1138452 (8.8), RO3244794 (8.5) (Bley *et al*., 2006)	BMS180291 (9.3–10.0), ONO-3708 (8.9), GR32191 (8.3–9.4, Lumley *et al*., 1989), SQ29548 (8.1–9.1, Swayne *et al*., 1988)
Probes	[^{3}H]-PGD_2 (13–34 nM)	[^{3}H]-PGD_2 (6–11 nM)	[^{3}H]-$PGF_{2\alpha}$ (2–4 nM), [^{3}H]-(+)-fluprostenol (34 nM)	[^{3}H]-Iloprost (1–20 nM)	[^{3}H]-SQ29548 (5–40 nM), [^{125}I]-SAP (0.2–1.0 nM), [^{125}I]-I-BOP (0.3–5.0 nM)

Ramatroban is also a TP receptor antagonist. Cicaprost exhibits moderate EP_4 receptor agonist potency (Abramovitz *et al*., 2000). Iloprost also binds to EP_1 receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail (Raychowdhury *et al*., 1994).

Nomenclature	EP_1	EP_2	EP_3	EP_4
Ensembl ID	ENSG00000160951	ENSG00000125384	ENSG00000050628	ENSG00000171522
Principal transduction	$G_{q/11}$	G_s	$G_{i/o}$	G_s
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_2, ONO-DI-004	Butaprost-free acid, CP533536 (Cameron *et al*., 2009), ONO-AE1–259	Sulprostone, SC46275, ONO-AE-248	ONO-AE1–329, L902688 (Young *et al*., 2004), CP734432 (Prasanna *et al*., 2009)
Selective antagonists	ONO8711 (9.2), GW848687X (9.1, Giblin *et al*., 2007), SC51322 (8.8)	–	L798106 (7.7), ONO-AE3-240 (8.8, Amano *et al*., 2003)	GW627368 (9.2), ONO-AE3–208 (8.5), L161982 (8.5), BGC201531 (7.8, Maubach *et al.* 2009), CJ042794 (8.6, Murase *et al.* 2008), ER819762 (Chen *et al*., 2010), MK2894 (Blouin *et al*., 2010)
Probes	[^{3}H]-PGE_2 (1–25 nM)	[^{3}H]-PGE_2 (5–22 nM)	[^{3}H]-PGE_2 (0.3–7 nM)	[^{3}H]-PGE_2 (0.6–24 nM)

17-Phenyl-PGE_2 also shows agonist activity at EP_3 receptors. Sulprostone also has affinity for EP_1 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_1 and EP_3 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 ($G_{i/o}$, $G_{q/11}$, G_s and $G_{12,13}$) 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 $PGF_{2\alpha}$-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-16*S*,20-dimethyl-18,19-didehydro-PGI$_2$; **AGN192093**, (*Z*)-7-([1α,5α,6α,7β]-7-[{1*E*,3*S*}-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]oct-6-yl)-5-heptenol; **AH23848**, (1α[*z*],2β,5α)-(±)-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)-ω-tetranor-PGF$_{2α}$; **AS604872**, (2*S*)-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)phenoxymethyl]-5-methylfuran-2-carbonyl)-2-methylbenzenesulphonamide; **BMS180291**, (1*s*-(1α,2α,3α,4α)-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-9*H*-carbazole-9-acetic acid; **CJ042794**, 4-{(1*S*)-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-[(2*S*)-2-{(3*R*)-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**, [1*R*-[1(*Z*),2α,3β,5]]-(+)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid; **GW627368**, *N*-(2-[4-{4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-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**, (1*S*-[1α,2β{5*z*},3α[1*e*,3*s*,],4α])-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-[3-hydroxyoctyl]-4-oxo-2-thiazolidinyl}propyl)benzoate racemate; **L798106**, 5-bromo-2-methoxy-*N*-[3-(naphthalen-2-yl-methylphenyl)-acryloyl]-benzenesulphonamide; **L902688**, 8-aza-1-decarboxy-11-deoxy-16,16-difluoro-16-phenyl-ω-tetranor-1-(5-tetrazolo) PGE$_1$; **MK2894**, 4-{1-[({2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl}carbonyl)amino]cyclopropyl}benzoic acid; **ONO3708**, (9,11)-(11,12)-dideoxa-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentanor-15-epi-TXA$_2$; **ONO8711**, 6-[(2*S*,3*S*)-3-(4-chloro-2-methylphenylsulphonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5Z-hexenoic acid; **ONO-DI-004**, 17*S*-17,20-dimethyl-2,5-ethano-6-oxo PGE$_1$; **ONO-AE-248**, 11,15-*O*-dimethyl-PGE$_2$; **ONO-AE1-259**, 16*s*-9-deoxy-9β-chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-PGE$_2$; **ONO-AE1-329**, 16-(3-methoxymethyl)phenyl-ω-tetranor-3,7-dithia-PGE$_1$; **ONO-AE3-208**, 2-(2-(2-methyl-2-naphth-1-ylacetylamino)-phenylmethyl)-benzoic acid; **ONO-AE3-240**, 2-(2-[3-napth-1-yl-3-*sec*-butyl-propionylamino]-4-[pyrazol-1-ylmethyl]phenylmethyl)-benzoic acid; **RO1138452**, 4,5-dihydro-1*H*-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*,1*R*,2*R*,3*S*,6*R*]-2C3′-cyclohexyl-3′-hydroxyprop-1-ynyl)-3-hydroxybicyclo(4.2.0)oct-7-ylidene butyrate; **SAP**, 7-([1*R*,2*S*,3*S*,5*R*]-6,6-dimethyl-3-benzenesulphonamino-bicyclo[3.1.1]hept-2-yl)-5z-heptenoic acid; **SC46275**, methyl-7-(2β-[6-{1-cyclopenten-1-yl}-4*R*-hydroxy-4-methyl-1*e*,5*e*-hexadienyl]-3α-hydroxy-5-oxo-1*R*,1α-cyclopentyl)-4z-heptenoic acid; **SC51322**, 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3-[furanylmethyl)- thio]-1-oxopropyl]hydrazide; **SQ29548**, (1*S*-[1α,2β{5*z*},3β,4β])7-(3-[{2-(phenylamino)carbonyl}hydrazino]methyl)-7-oxabicyclo[2.2.1]hept-2-yl-5-heptenoate; **S5751**, ((*Z*)-7-[1*R*,2*R*,3*S*,5*S*)-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid); **SQ27986**, [1*S*-[1B,2B(5*Z*),3A(1*E*,3*S*)4B]]7-[3-(3-cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-y]5-heptenoic acid; **STA$_2$**, 11α-carba-9α,11β-thia-Txa$_2$; **U46619**, 11α,9α-epoxymethano-PGH$_2$; **ZK 118182**, (5Z,13E)-(9*R*,11*R*,15*S*)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid; **ZK138357**, (5*Z*)-7-([2*RS*,4*S*,5*S*]-2-[2-chlorophenyl]-5-[{1*E*}-{3*R*,*S*}-3-hydroxy-3-cyclohexyl-1-propenyl]-1,3-dioxolan-4-yl)-5-heptanoic acid

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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 polylepis*) 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_1 and PK_2 receptors (Negri *et al*., 2005), and has high potency in macrophage chemotaxis assays, which are lost in PK_1-null mice (Martucci *et al*., 2006).

Nomenclature	PK_1	PK_2
Other names	PK-R1, GPR73 (Lin *et al*., 2002; Soga *et al*., 2002), G-protein coupled receptor ZAQ (Masuda *et al*., 2002)	PK-R2, GPR73a (Lin *et al*., 2002), GPRg2 (Soga *et al*., 2002), I5E (Masuda *et al*., 2002)
Ensembl ID	ENSG00000169618	ENSG00000101292
Principal transduction	$G_{q/11}$ (Lin *et al*., 2002; Masuda *et al*., 2002)	$G_{q/11}$ (Lin *et al*., 2002; Masuda *et al*., 2002)
Rank order of potency	PROK2 ≥ PROK1 (Lin *et al*., 2002; Masuda *et al*., 2002; Soga *et al*., 2002)	PROK2 ≥ PROK1 (Lin *et al*., 2002; Masuda *et al*., 2002; Soga *et al*., 2002)

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

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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_s, $G_{\alpha oB}$, $G_{\alpha t3}$ (Halls *et al*., 2006, 2009a; Hsu *et al*., 2002)	G_s, $G_{\alpha oB}$ (Halls *et al*., 2006; Kumagai *et al*., 2002)
Rank order of potency	H2 relaxin > H3 relaxin >> INSL3 (Sudo *et al*., 2003)	INSL3 > H2 relaxin >> H3 relaxin (Kumagai *et al*., 2002; Sudo *et al*., 2003)
Antagonists	LGR7-truncate (Scott *et al*., 2006), B13/17K H2 relaxin (Hossain *et al*., 2010)	INSL3 B-chain analog (Del Borgo *et al*., 2006), (des 1-8) A-chain INSL3 analog (Bullesbach and Schwabe, 2005), INSL3 B chain dimer (Shabanpoor *et al*., 2011).
Probes	[^{33}P]-H2 relaxin (0.2 nM, Sudo *et al*., 2003), Europium-labelled H2 relaxin (1 nM; Hossain *et al*., 2009)	[^{33}P]-H2 relaxin (1.06 nM; Sudo *et al*., 2003), [^{125}I]-INSL3 (0.1 nM; Muda *et al*., 2005), Europium-labelled INSL3 (0.9 nM; Shabanpoor *et al*., 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 $G\alpha_s$, $G\beta\gamma$ 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	$G_{i/o}$ (Matsumoto *et al*., 2000; Van der Westhuizen *et al*., 2007)	$G_{i/o}$ (Liu *et al*., 2003b)
Rank order of potency	H3 relaxin > H3 relaxin B chain (Liu *et al*., 2003a), also H2 relaxin (see below)	INSL5 = H3 relaxin > H3 relaxin B chain (Liu *et al*., 2003b; 2005a)
Antagonists	INSL5 (Liu *et al*., 2005a), R3(BΔ23-27)R/I5 chimeric peptide (Kuei *et al*., 2007), R3 B1-22R (Haugaard-Kedström *et al*., 2011)	R3(BΔ23-27)R/I5 chimeric peptide (Kuei *et al*., 2007)
Probes	[^{125}I]-H3 relaxin (0.3 nM; Liu *et al*., 2003a), [^{125}I]-H3-B/INSL5 A chimera (0.5 nM; Liu *et al*., 2005b), Europium-labelled H3-B/INSL5 A chimera (5 nM; Haugaard-Kedstrom *et al*., 2011)	[^{125}I]-H3 relaxin (0.2 nM; Liu *et al*., 2003b), [^{125}I]-H3-B/INSL5 A chimera (1.2 nM; Liu *et al*., 2005b), Europium-labelled INSL5 (5 nM; Haugaard-Kedstrom *et al*., 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. ^{125}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 ^{125}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

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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$_1$	sst$_2$	sst$_3$	sst$_4$	sst$_5$
Alternative names	SSTR1, SRIF$_2$, SRIF$_{2A}$	SSTR2, SRIF$_1$, SRIF$_{1A}$	SSTR3, SRIF$_1$, SRIF$_{1C}$	SSTR4, SRIF$_2$, SRIF$_{2B}$	SSTR5, SRIF$_1$, SRIF$_{1B}$
Ensembl ID	ENSG00000139874	ENSG00000180616	ENSG00000183473	ENSG00000132671	ENSG00000162009
Principal transduction	G$_i$	G$_i$	G$_i$	G$_i$	G$_i$
Selective agonists	des-Ala^{1,2,5}-[DTrp^8, Iamp^9]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	–	[^{125}I]-[Tyr^3]octreotide (0.13 nM) [^{125}I]-BIM23027	–	–	[^{125}I]-[Tyr^3]octreotide (0.23 nM)

[^{125}I]-[Tyr^{11}]SRIF-14, [^{125}I]-LTT-SRIF-28, [^{125}I]-CGP23996 and [^{125}I]-[Tyr^{10}]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-DTrp-Lys-Thr-Phe-Thr-NH$_2$; **BIM23056**, DPhe-Phe-Tyr-DTrp-Lys-Val-Phe-dNal-NH$_2$; **BIM23268**, *cyc*(Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys)-NH$_2$; **CGP23996**, *cyc*(Asn-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser); **Cyanamid 154806**, Ac-(4-NO$_2$-Phe)-*cyc*(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)-D-Tyr-NH$_2$; **L797591**, (2R)-*N*-(6-amino-2,2,4-trimethylhexyl)-3-(1-naphthyl)-2-({[(2-phenylethyl)2-pyridin-2-ylethyl)amino]carbonyl}amino)propanamide; **L054522**, tert-butyl (b*S*)-b-methyl-*N*{[4-(2-oxo-2,3,-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl}-D-tryptophyl-L-lysinate; **L796778**, methyl (2*S*)-6-amino-2-[((2*R*)-2-{[({(1*S*)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl}amino)carbonyl]amino}hexanoyl)amino]hexanoate; **L803087**, methyl (2*S*)-5-{[amino(imino)methyl]amino}-2-{[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino}pentanoate; **L817818**, (2*R*)-2-aminopropyl N2-{[2-(2-naphthyl)-1H-benzo[g]indo-3-yl]acetyl}-L-lysinat; **LTT-SRIF**-28, [Leu^8,DTrp^{22},DTyr^{25}]SRIF-28; **NNC269100**, 1-[3-[*N*-(5-bromopyridin-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl]-3-[3-(^{1}H-imidazol-1-yl)propyl]thiourea

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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 [^{32}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$_1$	S1P$_2$	S1P$_3$	S1P$_4$	S1P$_5$
Other names	edg1, *lp*$_{B1}$	edg5, *lp*$_{B2}$, AGR16, H218	edg3, *lp*$_{B3}$	*edg6*, *lp*$_{C1}$	*edg8*, *lp*$_{B4}$, NRG-1
Ensembl ID	ENSG00000170989	ENSG00000175898	ENSG00000186354	ENSG00000125910	ENSG00000180739
Principal transduction	G$_{i/o}$	G$_q$, G$_{12/13}$, G$_s$	G$_q$, G$_{i/o}$, G$_s$	G$_{i/o}$, G$_{12/13}$, G$_s$	G$_{i/o}$, G$_{12/13}$
Rank order of potency	S1P > dihydro-S1P > SPC(Okamoto *et al.*, 1998, Ancellin and Hla, 1999)	S1P > dihydro-S1P > SPC (Okamoto *et al.*, 1998, Ancellin and Hla, 1999)	S1P > dihydro-S1P > SPC (Okamoto *et al.*, 1998)	S1P > dihydro-S1P > SPC (Van Brocklyn *et al.*, 2000)	S1P > dihydro-S1P > SPC (Im *et al.*, 2000)
Selective agonists	SEW2871 (Sanna *et al.*, 2004), AUY954 (Pan *et al.*, 2006)	–	–	–	–
Selective antagonists	W146 (Sanna *et al.*, 2006)	JTE013 (Osada *et al.*, 2002)	–	–	–

The immunomodulator fingolimod (FTY720) may be phosphorylated *in vivo* (Albert *et al.*, 2005) to generate a relatively potent agonist with activity at SIP$_1$, SIP$_3$, SIP$_4$ and SIP$_5$ receptors (Brinkmann *et al.*, 2002; Mandala *et al.*, 2002). VPC23019 and VPC44116 have antagonist activity at S1P$_1$ and S1P$_3$ 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

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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 *α*, neuromedin L), neurokinin B (NKB; previously known as neurokinin *β*, neuromedin K), neuropeptide K and neuropeptide *γ* (*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_1	NK_2	NK_3
Other names	Substance P	Substance K	Neurokinin B, neuromedin K
Ensembl ID	ENSG00000115353	ENSG00000075073	ENSG00000169836
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	SP > NKA > NKB	NKA > NKB >> SP	NKB > NKA > SP
Selective agonists	SP methylester, [Sar^9,Met(O_2)^{11}]SP, [Pro^9]SP, septide	[*β*-Ala^8]NKA-(4-10),[Lys^5,Me-Leu^9,Mle^{10}] NKA-(4-10), GR64349	Senktide, [$MePhe^7$]NKB
Selective antagonists	Aprepitant (10.7; Hale *et al*., 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 *et al*., 1998)	SR142802 (9.2), SB223412 (9.0, Sarau *et al*., 1997), PD157672 (7.8)
Probes	[^{3}H]- or [^{125}I]-SP, [^{3}H]- or [^{125}I]-BH-[Sar^9,Met(O_2)^{11}]SP, [^{125}I]-L703606 (0.3 nM), [^{18}F]-SPA-RQ	[^{3}H]-SR48968 (0.5 nM), [^{3}H]-GR100679, [^{125}I]-NKA	[^{3}H]-Senktide, [^{125}I]-[$MePhe^7$]NKB, [^{3}H]-SR142801 (0.13 nM)

The NK_1 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_1 receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK_3 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-[[(2*R*,3*S*]-2-[(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorphenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one (also known as Emend); **CP99994**, (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine; **[^{18}F]-SPA-RQ**, ([[^{18}F]-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine; **GR100679**, cyclohexylcarbonyl-Gly-Ala-DTrp-Phe-NMe_2; **GR159897**, (*R*)-1-(2-[5-fluoro-1*H*-indol-3-yl]ethyl)-4-methoxy-4([phenylsulfinyl]methyl)piperidine; **GR64349**, Lys-Asp-Ser-Phe-Val-Gly-(*R*-*γ*-lactam); **GR94800**, *N*-*α*-benzoyl-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH_2; **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-(1*H*-indol-3yl)-2-(*N*-[2-{4-(piperidin-1-yl)piperidin-1-yl}acetyl]amino)propane; also known as lanepitant; **MEN10627**, *cyc*(2*β*–5*β*)(Met-Asp-Trp-Phe-Dap-Leu); **MEN11420**, *cyc*(2*β*–5*β*)[Asn(2-AcNH-*β*-D-Glc)-Asp-Trp-Phe-Dap-Leu]; also known as nepadutant; **PD157672**, Boc-(*s*)Phe-(*R*)*α*MePheNH$(CH_2)_7$NHCONH_2; **RP67580**, 3*αR*,7*αR*-(1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone; **SB223412**, (*s*)-(-)-*N*-(*α*-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-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide; also known as saredutant

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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_1 is a modulator of monoaminergic activity in the brain (Xie and Miller, 2009) with TA_1 and dopamine D_2 receptors shown to form constitutive heterodimers when co-expressed (Espinoza *et al*., 2011).

Nomenclature	TA_1	TA_2
Other names	TAA1, TaR-1, BO111	TAA2, GPR58
Ensembl ID	ENSG00000146399	ENSG00000146378
Principal transduction	G_s	G_s
Potency order	Tyramine ≥ PEA > octopamine = dopamine (Borowsky *et al*., 2001)	PEA > tryptamine (Borowsky *et al*., 2001)
Probes	$[^3H]$-Tyramine (20 nM, Borowsky *et al*., 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_5 (PNR, Putative Neurotransmitter Receptor, ENSG00000135569), TAA_6 (Trace amine receptor 4, TaR-4, ENSG00000146383), TAA_8 (Trace amine receptor 5, GPR102, ENSG00000146385) and TAA_9 (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_1 (Scanlan *et al*., 2004). An antagonist EPPTB has recently been described that has a pK_i of 9.1 at the mouse TA_1 but less than 5.3 for human TA_1 (Stalder *et al*., 2011).

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

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TRH

Overview: Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) are activated by the endogenous tripeptide TRH (pGlu-His-ProNH_2). TRH and TRH analogues fail to distinguish TRH_1 and TRH_2 receptors (Sun *et al.*, 2003). [^{3}H]-TRH is able to label both TRH_1 and TRH_2 receptors with K_d values of 13 and 9 nM, respectively.

Nomenclature	TRH_1	TRH_2
Other names	TRH receptor, thyroliberin	–
Ensembl ID	ENSG00000174417	ENSMUSG00000039079, ENSRNOG00000012789
Principal transduction	G_q	G_q
Selective antagonists	Midazolam (Drummond *et al.*, 1989), chlordiazepoxide (Straub *et al.*, 1990), diazepam	–

The human orthologue of the rodent TRH_2 receptor has yet to be identified.

Abbreviations: **MeTRH**, pGlu-[N^τ-methyl]His-ProNH_2

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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	$G_{q/11}$
Selective agonists	[Pen^5]U-II-(4–11), U-II-(4–11), U-II (Grieco *et al*., 2002), AC7954 (Lehmann *et al*., 2005), FL104 and analogues (Lehmann *et al*., 2006; 2007)
Selective antagonists	Urantide (8.3, Patacchini *et al*., 2003), SB706375 (7.5-8.0, Douglas *et al*., 2005), palosuran (pIC$_{50}$ 7.1, Clozel *et al*., 2004), SB611812 (6.6, Rakowski *et al*., 2005)
Probes	[^{125}I]-hU-II (0.24 nM, Maguire *et al*., 2000)

In human vasculature, human U-II elicits both vasoconstrictor (pD$_2$ 9.3–10.1, Maguire *et al*., 2000) and vasodilator (pIC$_{50}$ 10.3–10.4, Stirrat *et al*., 2001) responses.

Abbreviations: [Pen^5]U-II-(4-11], [pencillamine, β,β-dimethylcysteine]^{5}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-trifluromethyl-phenyl]-benzenesulphonamide HCl; **urantide**, [Pen^5,DTrp^7,Orn^8]hU-II(4-11)

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Vasopressin & oxytocin

Overview: Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytoxcin 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_{1A}	V_{1B}	V_2	OT
Ensembl ID	ENSG00000166148	ENSG00000198049	ENSG00000126895	ENSG00000180914
Principal transduction	$G_{q/11}$	$G_{q/11}$	G_s	$G_{q/11}$, $G_{i/o}$
Rank order of potency	AVP > OT	AVP > OT	AVP > OT	OT ≥ AVP
Selective agonists	F180, [Phe^2,Orn^8]VT	d[D-3-Pal^2]VP, d(Cha^4]AVP (Derick *et al.*, 2002), d[Leu^4,Lys^8]VP (Pena *et al.*, 2007)	d[Val^4,DArg^8]VP, OPC51803, VNA932	[Thr^4,Gly^7]OT (Elands *et al.*, 1988)
Selective antagonists	d(CH_2)$_5$[Tyr(Me)^2, Arg^8]VP (9.0), SR49059 (8.9), YM087 (8.2)	SSR149415 (8.4; Griebel *et al.*, 2002; Serradeil-Le Gal *et al.*, 2002)	VPA985 (8.9, Albright *et al.*, 1998), d(CH_2)$_5$[D-Ile^2, Ile^4]AVP (8.4), SR121463A (8.4; Serradeil-Le Gal *et al.*, 1996), OPC31260 (7.6; Yamamura *et al.*, 1992), YM087 (8.96)	SSR126768A (9.3; Serradeil-Le Gal *et al.*, 2004) desGlyNH$_2$-d(CH_2)$_5$[Tyr(Me)^2, Thr^4,Orn^8] OT (8.5), L372662 (8.4),
Probes	[^{3}H]-AVP, [^{3}H]-SR49059 (1.5 nM), [^{3}H]-d(CH_2)$_5$[Tyr(Me)^2, Arg^8]AVP (1.1 nM), [^{125}I]-HO-Phaa,D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-NH$_2$ (50 pM)	[^{3}H]-AVP, [^{3}H]-SSR149415 (1 nM; Serradeil-Le Gal *et al.* 2007)	[^{3}H]-AVP, [^{3}H]-desGly-NH$_2$[D-Ile^2,Ile^4]AVP (2.8 nM), [^{3}H]-d[D-Arg^8]AVP (0.8 nM), [^{3}H]-SR121463A (4.1 nM)	[^{3}H]-OT, [^{35}S]-Non Peptide OT Antagonist (42 pM; Lemaire *et al.*, 2002), [^{125}I]-d(CH_2)$_5$[Tyr(Me)^2, Thr^4,Orn^8, Tyr-NH$_2$ ^{9}]OVT (90 pM), [^{111}In]-DOTA-dLVT (4.5 nM; Chini *et al.*, 2003)

The V_2 receptor exhibits marked species differences, such that many ligands (d(CH_2)$_5$[D-Ile^2,Ile^4]VP and [^{3}H]-desGly-NH$_2$[D-Ile^2,Ile^4]VP) exhibit low affinity at human V_2 receptors (Ala *et al.*, 1997). Similarly, [^{3}H]-d[D-Arg^8]VP is V_2 selective in the rat, not in the human (Saito *et al.*, 1997). The gene encoding the V_2 receptor is polymorphic in man, underlying nephrogenic diabetes insipidus (Bichet, 1998). YM087 display high affinity for both human V_{1a} and V_2 receptors (Tahara *et al.*, 1998). d[Cha^4]AVP is selective only for the human and bovine V_{1b} receptors (Derick *et al.*, 2002), while d[Leu^4,Lys^8]VP has high affinity for the rat V_{1b} receptor (Pena *et al.*, 2007).

Abbreviations: F180, Hmp-Phe-Ile-Hgn-Asn-Cys-Pro-Dab(Abu)-Gly-NH$_2$; **[^{111}In]-DOTA-dLVT**, [^{111}In]-DOTA-Lys^8-deamino-vasotocin; **L372662**, 1-(1-{4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxyl]-2-methoxybenzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]]oxazin-2one; **OPC31260**, 5-dimethylamino-1-(4-[2-methylbenzoylamino]benzoyl)-2,3,4,5-tetrahydro-1*H*-benzazepine; **OPC51803**, (5*r*)-2-(1-[2-chloro-4-{1-pyrrolidinyl}benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-*N*-isopropylacetamide; **[^{35}S]-non-peptide OT antagonist**, [^{35}S]-(1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyloxy)phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1*H*)-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-1*H*-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-1*H*-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidine carboxamide; **SSR126768A**, 4-chloro-3-[(3R)-(+)-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-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)

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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$_1$ and VPAC$_2$ 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$_1$ receptor. However, one splice variant of the human PAC$_1$ 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$_2$ receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC$_1$ and PAC$_1$ receptors (Dickson *et al.*, 2006). The selective PAC$_1$ 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$_1$ receptor antagonists, but these peptides have not been extensively characterised.

Nomenclature	VPAC$_1$	VPAC$_2$	PAC$_1$
Other names	VIP$_1$/PACAP, VIP, VIP$_1$, PACAP type II, PVR2	VIP$_2$/PACAP, VIP$_2$, PACAP$_3$, PVR2	PACAP, PACAP type I, PVR1
Ensembl ID	ENSG00000114812	ENSG00000106018	ENSG00000078549
Principal transduction	G$_s$	G$_s$	G$_s$
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^{11,22,28}]VIP, [Lys^{15},Arg^{16},Leu^{27}]VIP(1-7)/ GRF(8-27)-NH$_2$	Ro251553 (Gourlet *et al.*, 1997a, 1997b) Ro251392 (Xia *et al.*, 1997)	Maxadilan (Moro and Lerner, 1997)
Selective antagonists	PG97-269 (Gourlet *et al.*, 1997a)	–	–
Probes	[^{125}I]-VIP, [^{125}I]-PACAP-27	[^{125}I]-VIP, [^{125}I]-PACAP-27	[^{125}I]-PACAP-27

Abbreviations: **PG97-269**, [Ac-His^1,D-Phe^2,Lys^{15},Arg^{16}]VIP(3-7)/GRF(8-27)-NH$_2$; **Ro251392**, Ac-His^1[Glu^8,OCH$_3$-Tyr^{10},Lys^{12},Nle^{17},Ala^{19},Asp^{25},Leu^{26},Lys^{27,28}]VIP (*cyclo* 21–25); **Ro251553**, Ac-His^1[Glu^8,Lys^{12},Nle^{17},Ala^{19},Asp^{25},Leu^{26},Lys^{27,28},Gly^{29,30},Thr^{31}]VIP-NH$_2$ (*cyclo* 21–25)

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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-excitable 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$_3$ (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$_A$ (Olsen and Sieghart, 2008; Belelli *et al.*, 2009) and glycine receptors (Lynch, 2009; Yevenes and Zeilhofer, 2011). The nicotinic acetylcholine, 5-HT$_3$, GABA$_A$ 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 combinational 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.

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5-HT$_3$ (5-Hydroxytryptamine$_3$)

Overview: The 5-HT$_3$ 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$_A$ 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$_3$ receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT3A and hetero-oligomeric assemblies of 5-HT3A and 5-HT3B subunits have been characterised in detail. The 5-HT3C (ENSG00000178084), 5-HT3D (ENSG00000186090) and 5-HT3E (ENSG00000186038) subunits (Karnovsky *et al*., 2003; Niesler *et al*., 2003), like the 5-HT3B subunit, do not form functional homomers, but are reported to assemble with the 5-HT3A subunit to influence its functional expression rather than pharmacological profile (Niesler *et al*., 2007; Holbrook *et al*., 2009; Walstab *et al*., 2010a). 5-HT3A, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT$_3$A receptor (Walstab *et al*., 2010a). The co-expression of 5-HT3A and 5-HT3C-E subunits has been demonstrated in human colon (Kapeller *et al*., 2011). A recombinant hetero-oligomeric 5-HT$_3$AB receptor has been reported to contain two copies of the 5-HT3A subunit and three copies of the 5-HT3B 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-HT3B subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT$_3$AB *versus* homo-oligomeric 5-HT$_3$A 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-HT3A subunits (Lochner and Lummis, 2010; Thompson *et al*., 2011b). However, 5-HT$_3$A and 5-HT$_3$AB receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles (Solt *et al*., 2005; Rüsch *et al*., 2007; Hu and Peoples, 2008). The potential diversity of 5-HT$_3$ 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-HT3 subunits harbouring different N-termini (Tzvetkov *et al*., 2007; Jensen *et al*., 2008; Niesler, 2011). To date, inclusion of the 5-HT3A subunit appears imperative for 5-HT$_3$ receptor function.

Nomenclature	5-HT$_3$
Former names	M
Ensembl ID	5-HT3A ENSG00000166736, 5-HT3B ENSG00000149305
Selective agonists (pEC$_{50}$)	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_i)	(*S*)-Zacopride (9.0), granisetron (8.6–8.8), tropisetron (8.5–8.8), ondansetron (7.8–8.3)
Channel blockers (pIC$_{50}$)	TMB-8 (5.4), diltiazem (4.1–4.8), picrotoxinin (4.9 + 5-HT3B = 4.2), bilobalide (3.3 + 5-HT3B = 2.5); ginkgolide B (3.1 + 5-HT3B > 3.0)
Radioligands (K_D)	[^{3}H]Ramosetron (0.15 nM), [^{3}H]granisetron (1.2 nM), [^{3}H](*S*)-zacopride (2.0 nM), [^{3}H]GR65630 (2.6 nM), [^{3}H]LY278584 (3 nM)
Functional characteristics	γ = 0.4-0.8 pS [+ 5-HT3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT3B, rectification reduced]; n$_H$ 2-3 [+ 5-HT3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit

Quantitative data in the table refer to homo-oligomeric assemblies of the human 5-HT3A subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT3B subunit are indicated in parenthesis. Methadone, although not a selective antagonist, displays multimodal and subunit-dependent antagonism of 5-HT$_3$ receptors (Deeb *et al*., 2009). Similarly, TMB-8, diltiazem, picrotoxin, bilobalide and ginkgolide B are not selective for 5-HT$_3$ receptors (*e.g*. Thompson *et al*., 2011a). The anti-malarial drugs mefloquine and quinine exert a modestly more potent block of 5-HT$_3$A *versus* 5-HT$_3$AB receptor-mediated responses (Thompson and Lummis, 2008). Varenicline, know better as a partial agonist of nicotinic acetylcholine $\alpha4\beta2$ receptors, is also an agonist of the 5-HT$_3$A 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-HT3A 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$_3$ receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT$_3$ 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-1*H*-imidazol-4-yl)-1-(1-methyl-1*H*-indol-3-yl)-1-propanone; **LY278584**, 1-methyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-indazole- 3-carboxamide; **SR57227A**, 4-amino-(6-chloro-2-pyridyl)-1 piperidine hydrochloride, **TMB-8**, 8-(diethylamine)octyl-3,4,5-trimethoxybenzoate

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Acetylcholine (nicotinic)

Overview: Nicotinic acetylcholine receptors are members of the Cys-loop family of transmitter-gated ion channels that includes the $GABA_A$, strychnine-sensitive glycine and $5\text{-}HT_3$ 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 α-helical transmembrane domains. Genes (Ensembl family ID ENSF00000000049) encoding a total of 17 subunits (α1-10, β1-4, γ, δ and ε) have been identified (Kalamida *et al.*, 2007). All subunits with the exception of α8 (present in avian species) have been identified in mammals. All α subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named α lack these residues (Millar and Gotti, 2009). The orthosteric ligand binding site is formed by residues within at least three peptide domains on the α 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 α1 subunit bound to α-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 $(\alpha1)_2\beta1\delta\varepsilon$, whereas an extrajunctional $(\alpha1)_2\beta1\gamma\delta$ receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of α(2-6) and β(2-4) subunits. For α2, α3, α4 and β2 and β4 subunits, pairwise combinations of α and β (*e.g.*, α3β4, α4β2) 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 α and β subunits can occur with variable stoichiometry [*e.g.*, $(\alpha4)_2(\beta2)_2$, or $(\alpha4)_3(\beta2)_2$] which influences the biophysical and pharmacological properties of the receptor (Millar and Gotti, 2009). α5 and β3 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 α and β pair [*e.g.*, α4α5αβ2, α4αβ2β3, α5α6β2, see Millar and Gotti (2009) for further examples]. The α6 subunit can form a functional receptor when co-expressed with β4 *in vitro*, but more efficient expression ensues from incorporation of a third partner, such as β3 (Yang *et al.*, 2009). The α7, α8, and α9 subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (*e.g.*, α7β2 and α9α10). For functional expression of the α10 subunit, co-assembly with α9 is necessary. The latter, along with the α10 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 α subunit contained in that receptor subtype. An asterisk following the indicated α subunit denotes that other subunits are known to, or may, assemble with the indicated α 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	α1*	α2*	α3*
Previous names	Muscle-type, muscle	–	Autonomic, ganglionic
Selective agonists	Succinylcholine (selective for $(\alpha1)_2\beta1\gamma\delta$)	–	–
Positive allosteric modulators	–	LY-2087101 (Broad *et al.*, 2006, also potentiates α4β2 and α4β4)	–
Selective antagonists	Waglerin-1 (selective for $\alpha(1)_2\beta1\delta\varepsilon$), α-bungarotoxin, α-conotoxin GI, α-conotoxin MI, pancuronium	–	α3β2: α-conotoxin MII (also blocks α6-containing), α-conotoxin-GIC, α-conotoxin PnIA, α-conotoxin TxIA α3β4: α-conotoxin AuIB
Commonly used antagonists	$(\alpha1)_2\beta1\gamma\delta$ and $(\alpha1)_2\beta1\delta\varepsilon$: α-bungarotoxin, > pancuronium > vecuronium > rocuronium > (+)-Tc (IC_{50} = 43–82 nM)	α2β2: DHβE (K_B = 0.9 μM), (+)-Tc (K_B = 1.4 μM) α2β4: DHβE (K_B = 3.6 μM), (+)-Tc (K_B = 4.2 μM)	α3β2: DHβE (K_B = 1.6 μM, IC_{50} = 2.0 μM), (+)-Tc (K_B = 2.4 μM) α3β4: DHβE (K_B = 19 μM, IC_{50} = 26 μM), (+)-Tc (K_B = 2.2 μM)
Channel blockers	$\alpha(1)_2\beta1\delta\varepsilon$ and $\alpha(1)_2\beta1y\delta$: gallamine (IC_{50} ~ 1 μM) $\alpha(1)_2\beta1\delta\varepsilon$: mecamylamine ($IC_{50}$ ~ 1.5 μM)	mecamylamine, hexamethonium	α3β2: mecamylamine (IC_{50} = 7.6 μM), hexamethonium α3β4: mecamylamine (IC_{50} = 0.39 μM), hexamethonium
Radioligands (K_d)	$[^3H]/[^{125}I]$-α-bungarotoxin	$[^{3H}]/[^{125I}]$-epibatidine (hα2β4, 42 pM; rα2β2, 10–21 pM; rα2β4, 84–87 pM), $[^3H]$-cytisine	$[^3H]/[^{125}I]$-epibatidine (hα3β2, 7 pM; hα3β4, 230 pM; rα3β2, 14–34 pM, rα3β4, 290–304 pM), $[^3H]$-cytisine
Functional characteristics	$\alpha(1)_2\beta\gamma\delta$: P_{Ca}/P_{Na} = 0.16–0.2, P_f = 2.1–2.9%; $\alpha(1)_2\beta\delta\varepsilon$: P_{Ca}/P_{Na} = 0.65–1.38, P_f = 4.1–7.2%	α2β2: P_{Ca}/P_{Na} ~ 1.5	α3β2: P_{Ca}/P_{Na} = 1.5; α3β4: P_{Ca}/P_{Na} = 0.78–1.1, P_f = 2.7–4.6%

Nomenclature	α4*	α6*	α7*
Previous names	Neuronal, α-bungarotoxin-insensitive	–	Neuronal, α-bungarotoxin-sensitive
Selective agonists	α4β2: TC-2559 (Chen *et al.*, 2003), TC-2403 (RJR-2403, Papke *et al.*, 2000)	–	$(\alpha7)_5$: PNU-282987 (Bodnar *et al.*, 2005), PHA-543613 (Wishka *et al.*, 2006); PHA-709829 (Acker *et al.*, 2008), A-582941 (Bitner *et al.*, 2007, TC-5619 (Hauser *et al.*, 2009)
Allosteric agonists	–	–	4BP-TQS (Gill *et al.*, 2011)
Positive allosteric modulators	α4β2 and α4β4: LY-2087101 (Broad *et al.*, 2006, also potentiates α2*), NS9283 (Lee *et al.*, 2011)	–	$(\alpha7)_5$:Type 1: LY-2087101 (Broad *et al.*, 2006), NS1738 (Timmermann *et al.*, 2007; also blocks α3β4 and α4β2) $(\alpha7)_5$:Type 2: PNU-120596 (Hurst *et al.*, 2005), A-867744 (Malysz *et al.*, 2009; also blocks α3β4 and α4β2) $(\alpha7)_5$:Type 1/2 intermediate: JNJ1930942 (Dinklo *et al.*, 2011)
Selective antagonists	–	α6/α3β2β3 chimera: α-conotoxin PIA α6β2β3: α-conotoxin MII [H9A, L15A] α6β2*: α-conotoxin MII (also blocks α3β2)	$(\alpha7)_5$: α-bungarotoxin, methyllycaconitine, α-conotoxin ImI, α-conotoxin ArIB
Commonly used antagonists	α4β2: DHβE (K_B = 0.1 μM; IC_{50} = 0.08–0.9 μM), (+)-Tc (K_B = 3.2 μM, IC_{50} = 34 μM) α4β4: DHβE (K_B = 0.01 μM, IC_{50} = 0.19–1.2 μM), (+)-Tc (K_B = 0.2 μM, IC_{50} = 50 μM)	α6/α3β2β3 chimera: DHβE (IC_{50} = 1.1 μM)	$(\alpha7)_5$: DHβE (IC_{50} = 8–20 μM) $(\alpha7)_5$: (+)-Tc (IC_{50} = 3.1 μM)
Channel blockers	α4β2: mecamylamine (IC_{50} = 3.6–4.1 μM), hexamethonium (IC_{50} = 6.8–29 μM) α4β4: mecamylamine (IC_{50} = 0.33–4.9 μM), hexamethonium (IC_{50} = 91 μM)	α6/α3β2β3 chimera: mecamylamine (IC_{50} = 11 μM), hexamethonium	$(\alpha7)_5$: mecamylamine (IC_{50} = 15.6 μM)
Radioligands (K_d)	[^{3}H]/[^{125}I]-epibatidine (hα4β2, 10–33 pM; hα4β4, 187 pM; rα4β2, 30–46 pM; rα4β4, 85–94 pM), [^{3}H]-cytisine (hα4β2, 430–630 pM; rα4β2, 100 pM; hα4β4 100 pM), [^{3}H]-nicotine (rα4β2, 400 pM)	[^{3}H]-epibatidine (native cα6β4*, 35 pM), [^{125}I]-α-conotoxin MII	[^{3}H]-epibatidine ($(h\alpha7)_5$, 0.6 pM) [^{3}H]/[^{125}I]-α-bungarotoxin ($(h\alpha7)_5$, 0.7–5 nM), [^{3}H]-methyllycaconitine (native rα7*, 1.9 nM), [^{3}H]-A-585539 (native hα7, 70 pM; Anderson *et al.*, 2008), [^{3}H]AZ11637326 ($h\alpha7)_5$, 230 pM; Gordon *et al.*, 2010)
Functional characteristics	α4β2: P_{Ca}/P_{Na} = 1.65, P_f = 2.6–2.9%; α4β4: P_f = 1.5–3.0 %	–	P_{Ca}/P_{Na} = 6.6-20, P_f = 8.8–11.4%

Nomenclature	α8* (avian)	α9*
Previous names	Neuronal, α-bungarotoxin-sensitive	–
Selective agonists	–	–
Selective antagonists	–	$(\alpha9)_5$: α-bungarotoxin, strychnine, nicotine, muscarine α9α10: α-contoxin RgIA, α-bungarotoxin, strychnine, nicotine, muscarine
Commonly used antagonists	$(\alpha8)_5$: α-bungarotoxin > atropine ≥ (+)-Tc ≥ strychnine	$(\alpha9)_5$: α-bungarotoxin > methyllycaconitine > strychnine ~ tropisetron > (+)-Tc α9α10: α-bungarotoxin > tropisetron = strychnine > (+)-Tc
Channel blockers	–	–
Radioligands (K_d)	[^{3}H]-epibatidine ($(\alpha8)_5$, 0.2 nM) [^{3}H]/[^{125}I]-α-bungarotoxin (native α8*, 5.5 nM)	[^{3}H]-methyllycaconitine (hα9α10, 7.5 nM) [^{3}H]/[^{125}I]-α-bungarotoxin
Functional characteristics	–	$(\alpha9)_5$: P_{Ca}/P_{Na} = 9; α9α10: P_{Ca}/P_{Na} = 9, P_f = 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 α7 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**, (1*S*,4*S*)-2,2-dimethyl-5-(6-phenylpyridazin-3-yl)-5-aza-2-azaniabicyclo[2.2.1] heptane; **A-867744**, 4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl)benzenesulfonamide; **ABT-594**, (*R*)-5-(2-azetidinylmethoxy)-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, **DHβE**, dihydro-β-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)benzonitrile; **PHA-543613**, *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide; **PHA-709829**, *N*-[(3*R*,5*R*)-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*-[(3*R*)-1-azabicyclo[2.2.2] oct-3-yl]-4-chlorobenzamide hydrochloride; **PSAB-OFP**, (*R*)-(-)-5′phenylspiro[1-azabicyclo[2.2.2] octane-3,2′-(3′H)furo[2,3-b]pyridine; **TC-2403** (RJR-2403), (E)-*N*-methyl-4-(3-pyridinyl)-3-butene-1-amine;**TC-2559**, (E)-*N*-methyl-4-[3-(5-ethoxypyridin)yl]-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

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GABA$_A$ (γ-aminobutyric acid)

Overview: The GABA$_A$ receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT$_3$ and strychnine-sensitive glycine receptors. GABA$_A$ receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed 'GABA$_A$, slow' (Campogna and Pearce, 2011). GABA$_A$ 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$_A$ 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$_C$ receptors (Zhang *et al.*, 2001), but they are classified as GABA$_A$ receptors by NC-IUPHAR on the basis of structural and functional criteria (Barnard *et al.*, 1998; Olsen and Sieghart, 2008, 2009).

Many GABA$_A$ 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$_A$ receptors harbour a single type of α- and β-subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of GABA$_A$ 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$_A$ 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 as those incorporating the δ subunit appear to be exclusively extrasynaptic.

NC-IUPHAR (Barnard *et al.* 1998; Olsen and Sieghart, 2008) class GABA$_A$ receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native GABA$_A$ receptors are classed as conclusively identified (*i.e.*, α1β2γ2, α1βγ2, α3βγ2, α4βγ2, α4β2δ, 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$_A$ 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), Krogsgaard-Larsen *et al.* (2002), Johnston (2005), Sieghart (2006), Möhler (2007), Olsen and Sieghart (2008, 2009) and Atack (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$_A$
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), isonipecotic acid (α4 and α6 subunit selective *via* relatively high efficacy, antagonist at ρ subunits), (±)-*cis*-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), *cis*- and *trans*-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 *via* high affinity), ocinaplon (α1 subunit selective as essentially a full agonist *versus* partial agonist at α2, α3 and α5 subunit-containing receptors), L838417 (α2, α3 and α5 subunit selective as a partial agonist *versus* antagonist at α1-subunit-containing receptors), Ro154513 (selective for α4- and α6-subunit-containing receptors as an agonist *versus* inverse agonist at α1-, α2-, α3- and α5-subunit-containing receptors), TP003 (selective for α3-subunit-containing receptors as a high efficacy partial agonist *versus* 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 *versus* 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 *via* antagonist activity *versus* partial agonist at α2-, α3- and α5-subunit subunit containing receptors)
Inverse agonists (negative allosteric modulators) (benzodiazepine site)	DMCM, Ro194603, α3IA (α3 selective *via* higher affinity and greater inverse agonist activity *versus* α1, α2 and α5-subunit containing receptors), L655708, RY024 (α5 selective *via* high affinity), α5IA, MRK016 (α5 selective *versus* α1, α2 and α3-subunit containing receptors *via* greater inverse agonist efficacy), Ro4938581 (α5 selective *versus* α1, α2 and α3-subunit containing receptors *via* higher affinity and greater inverse agonist activity)

Nomenclature	GABA$_A$
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (potentiation), tetrahydrodeoxycorticosterone (potentiation), Zn^{2+} (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 *et al.*, 1998), extracellular protons (subunit dependent activity, Krishek *et al.*, 1996)
Channel blockers	Picrotoxin, TBPS
Probes	
GABA site	[^{3}H]Muscimol, [^{3}H]gabazine (SR95531)
benzodiazepine site	[^{3}H]Flunitrazepam (not α4- or α6-subunit), [^{3}H]zolpidem (α1-subunit selective), [^{3}H]L655708 (α5-subunit selective), [^{3}H]RY80 (α5-subunit selective), [^{3}H]Ro154513 [selectively labels α4- and α6-subunit-containing receptors in the presence of a saturating concentration of a 'classical' benzodiazepine (*e.g.*, diazepam)], [^{3}H]CGS8216, [^{11}C]flumazenil (PET ligand with low affinity for α4- or α6-subunits), [^{18}F]fluoroethylflumazenil (PET ligand)
Anion channel	[^{35}S]TBPS

The potency and efficacy of many GABA agonists varies between receptor GABA$_A$ receptor isoforms (Frolund *et al.*, 2002; Krogsgaard-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$_A$ 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$_A$ 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$_A$ receptor activity (Bonin and Orser, 2008; Olsen and Li, 2011). Specific amino acid residues within GABA$_A$ 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$_A$ receptors by the etomidate derivative, [^{3}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$_A$ receptors (reviewed in detail by Johnston, 2005).

In addition to the agents listed in the table, modulators of GABA$_A$ 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)]; fragrent 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-assembed 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^{3+} [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-ACPBPA, 3-amino-cyclopentenylbutylphosphonic acid; **5-Me-IAA**, 5-methy-1*H*-imidazole-4-acetic acid; **(±)-*cis*-2-CAMP**, (±)-*cis*-2-aminomethylcyclopropane carboxylic acid; **α3IA**, 6-(4-pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one; **α5IA**, 3-(5-methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyloxy]-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-2*H*-[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-9*H*-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*-butylbicyclophosphorothionate; **TP003**, 4,2′-difluro-5′-[8-fluro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-á]pyridine-3-yl]biphenyl-2-carbonitrile; **TPA023**, 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorphenyl)-1,2,4-triazolo[4,3-*b*]pyridazine; **TPMPA**, (1,2,5,6-tetrahydropyridine-4-yl)methylphosphinic acid; **RY024**, *tert*-butyl-8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazol[1,5-α][1,4]benzodiazepine-3-carboxylate; **RY80**, ethyl-8-acetylene-5, 6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5a][1, 4]benzodiazepine-3-carboxylate; **ZK93423**, 6-benzyloxy-4-methoxymethy-β-carboline-3-carboxylate ethyl ester; **ZK93426**, 5-isopropyl-4-methyl-β-carboline-3-carboxylate ethyl ester

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Glutamate (ionotropic)

Overview: The ionotropic glutamate receptors comprise members of the NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic 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 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^{2+} and is blocked, in a voltage-dependent manner, by Mg^{2+} 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 ≥ GluN2A ≥ 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 *et al.*, 2005), NVP-AAM077 (GluN2A > GluN2B (human), Auberson *et al.* 2002; but weakly selective for rat GluN2A *versus* GluN2B Feng *et al.*, 2004; Frizelle *et al.*, 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-Dichlorokynurenate, L689560, L701324, GV196771A
Channel blockers	Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), (+)-MK801, ketamine, phencyclidine, memantine (GluN2C ≥ GluN2D ≥ GluN2B > GluN2A), amantidine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A), N^1-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D)
Probes	
Glutamate site	[^{3}H]CPP, [^{3}H]CGS19755, [^{3}H]CGP39653
Glycine site	[^{3}H]Glycine, [^{3}H]L689560, [^{3}H]MDL105519, [^{3}H]CGP61594 (photoaffinity ligand)
Cation channel	[^{3}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^{2+}, Zn^{2+}, and protons (see Dingledine *et al.*, 1999; Cull-Candy and Leszkiewicz, 2004; Traynelis *et al.*, 2010). Voltage-independent inhibition by Zn^{2+} binding with high affinity within the ATD is highly subunit selective (GluN2A >> GluN2B > GluN2C ≥ 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^{2+} 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 probablity 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.* γ2, γ3, γ4 and γ8) 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 argiotoxin 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+} permeabilites 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), (2*S*,4*R*)-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 argiotoxin, extracellular Joro toxin, (selective for channels lacking GluA2)	Intracellular polyamines (subtype selective; GluK3 >> GluK2)
Probes (K_d)	$[^3H]$AMPA, $[^3H]$CNQX	$[^3H]$Kainate, $[^3H]$(2*S*,4*R*)-4-methylglutamate, $[^3H]$UBP310 (GluK1, 21 nM, GluK3, 0.56 μM, Atlason *et al.*, 2010)

All AMPA receptors are additionally activated by kainate (and domoate) with relatively low potency, (EC_{50} ~ 100 μM). 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). (2*S*,4*R*)-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 (2*S*,4*R*)-4-methylglutamate and LY339434 have agonist activity at NMDA receptors. (2*S*,4*R*)-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-6*H*-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*)-α-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**, (±)-*cis*-4-phosphonomethylpiperidine-2-carboxylic acid; **CGP 61594**, (±)-trans-4-[2-(4-azidophenyl)-acetylamino]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid; **CNQX**, 6-cyano-7-nitroquinoxaline-2,3-dione; **CP101606**, (1*S*,2*S*)-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-ylidenemethyl)-1*H*-indole-2-carboxylic acid; **GYKI53655**, (±)-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5*H*-2,3-benzodiazepine; also known as LY300168; **GYKI53784**, (-)-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5*H*-2,3-benzodiazepine, also known as LY303070; **HA966**, 3-amino-1-hydroxypyrrolidin-2-one; **IDRA-21**, 7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-*S*,*S*-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**, (±)-*cis*-4-[(2*H*-tetrazol-5-yl)methyl]piperidine-2-carboxylic acid; **LY233536**, (±)-6-(1*H*-tetrazol-5-ylmethyl)decahydraisoquinoline-3-carboxylic acid; **LY293558**, (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*)-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid; **LY339434**, (2*S*,4*R*,6*E*)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid; **LY382884**, (3*S*,4a*R*,6*S*,8a*R*)-6-((4-carboxyphenyl)methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-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**, (3*S*,4*aR*,6*S*,8*aR*)-6-[[(2*S*)-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-carboxyethenyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid; **MSVIII-19**, (2*R*,3a*R*,7a*R*)-2-[(2*S*)-2-amino-2-carboxyethyl]-hexahydro-furo-[3,2-*b*]pyran-2-carboxylic acid; **NBQX**, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*f*)quinoxaline; **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-2*H*-pyridin-1-yl]-2-hydroxypropoxybenzamide; **S18986**, (*S*)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide; **UBP141**, (2*R**,3*S**)-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

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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 $GABA_A$, nicotinic acetylcholine and 5-HT_3 receptors (Lynch 2009b). The receptor is expressed either as a homo-pentamer of α subunits, or a complex now thought to harbour 2α and 3β subunits (Grudzinska *et al*., 2005; Betz and Laube, 2006), that contain an intrinsic anion channel. Four differentially expressed isoforms of the α-subunit (α1-α4) and one variant of the β-subunit (β1, ENSG00000109738) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for α1 ($\alpha1^{INS}$ and $\alpha1^{del}$), α2 (α2A and α2B), α3 (α3S and α3L) and β (βΔ7) subunits and by mRNA editing of the α2 and α3 subunit (Meier *et al*., 2005; Oertel *et al*., 2007; Eichler *et al*., 2008). Both α2 splicing and α3 mRNA editing can produce subunits (*i.e*., α2B and α3P185L) with enhanced agonist sensitivity. Predominantly, the mature form of the receptor contains α1 (or α3) and β subunits while the immature form is mostly composed of only α2 subunits. RNA transcripts encoding the α4-subunit have not been detected in adult humans. The N-terminal domain of the α-subunit contains both the agonist and strychnine binding sites that consist of several discontinuous regions of amino acids. Inclusion of the β-subunit in the pentameric glycine receptor contributes to agonist binding, reduces single channel conductance and alters pharmacology. The β-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 Loebrich, 2007). G-protein βγ subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop (Yevenes *et al*., 2003; 2006). Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors (Pitt *et al*., 2008). Intracellular Ca^{2+} 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	α1	α2	α3
Ensembl ID	ENSG00000145888	ENSG00000101958	ENSG00000145451
Selective agonists (potency order)	Glycine > β-alanine > taurine	Glycine > β-alanine > taurine	Glycine > β-alanine > taurine
Selective antagonists and modulators with subunit selectivity	Strychnine, PMBA, bilobalide (IC_{50} = 20 μM + β = 204 μM), pregnenolone sulphate (K_i = 1.9 μM; + β = 2.7 μM), tropisetron (K_i = 84 μM), colchicine (IC_{50} = 324 μM), nifedepine (IC_{50} = 3.3 μM +β = 1.2 μM), ginkgolide X (IC_{50} = 0.76 μM + β > 300 μM), HU308 (weak inhibition)	Strychnine, PMBA, bilobalide (8 μM + β = 50 μM), pregnenolone sulphate (K_i = 5.5 μM; + β = 10.1 μM), tropisetron (K_i = 13 μM + β = 5.4 μM), colchicine (IC_{50} = 64 μM), DCKA (IC_{50} = 188 μM), ginkgolide X (IC_{50} = 2.8 μM + β > 300 μM), HU210 (90 nM), HU308 (1.1 μM), WIN55,212-2 (220 nM)	Strychnine, nifedepine (IC_{50} = 29.2μM + β = 11.4 μM), HU210 (50 nM), HU 308 (97 nM), WIN55212-2 (97 nM), (12E,20Z,18S)-8-hydroxyvariabilin (IC_{50} = 7.0 μM)
Selective potentiators (EC_{50})	HU210 (270 nM), anandamide (38 nM), Δ^9-tetrahydrocannabinol (~3μM, ~1500% potentiation)	Δ^9-tetrahydrocannabinol (~1μM, ~230% potentiation)	Δ^9-tetrahydrocannabinol (~5μM, ~1500% potentiation)
Endogenous potentiators (EC_{50})	Zn^{2+} (37nM) (not affected by β)	Zn^{2+} (540 nM) (not affected by β)	
Endogenous inhibitors (IC_{50})	Zn^{2+} (15 μM; + β = 13 μM), Cu^{2+} (4-15 μM) (not affected by β), H^+	Zn^{2+} (360 μM; + β = 180 μM), Cu^{2+} (17 μM)	Zn^{2+} (150 μM), Cu^{2+} (9μM)
Channel blockers (IC_{50})	cyanotriphenylborate (1.3 μM + β = 2.8 μM), picrotoxin (6.3 μM + β = 219 μM), picrotoxinin (5.1 μM + β = 27μM), picrotin (5.2 μM + β = 27 μM), ginkgolide B (0.6–8.0 μM + β = 0.18–2.5 μM),	cyanotriphenylborate (>>20 μM; + β = 7.5 μM), picrotoxin (2.3 μM +β = 29.7 μM), picrotoxinin (0.41 μM), picrotin (13.1 μM), ginkgolide B (3.7–11.4 μM + β = 0.14–0.8 μM)	picrotoxin (+β weakens block), picrotoxinin (0.43 μM + β = 8.9 μM), picrotin (6.0 μM + β = 24 μM), ginkgolide B (1.8 μM + β = 0.55 μM)
Probes	$[^3H]$strychnine	$[^3H]$strychnine	$[^3H]$strychnine
Functional characteristics	γ = 86 pS (main state) (+ β = 44 pS)	γ = 111 pS (main state) (+ β = 54 pS)	γ = 105 pS (main state) (+ β = 48)

Data in the table refer to homo-oligomeric assemblies of the α-subunit, significant changes introduced by co-expression of the β1 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. RU5135 demonstrates comparable potency, but additionally blocks $GABA_A$ 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 (α1/α3) in M3 (Xiong *et al*., 2011). Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and $GABA_A$ 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 α1 receptors, their potencies at α2 and α3 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 μM) 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 α1 subunit-containing receptors (Hirzel *et al.*, 2006). Elevation of intracellular Ca^{2+} produces fast potentiation of glycine receptor-mediated responses. Dideoxyforskolin (4 μM) and tamoxifen (0.2–5 μM) both potentiate responses to low glycine concentrations (15 μM), but act as inhibitors at higher glycine concentrations (100 μM). 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 βγ 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 α1 or α2 subunits, or hetero-oligomers of α1/β or α2/β subunits, is differentially affected by the 5-HT$_3$ receptor antagonist tropisetron (ICS 205-930) which may evoke potentiation (which may occur within the femtomolar range at the homomeric glycine α1 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**, 3α-hydroxy-16-imino-5β-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

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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$^+$, K$^+$ and Ca^{2+}, exceptionally Cl$^-$ 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 (*p*IC$_{50}$ 8.9, Virginio *et al*., 1998), Ip$_5$I (*p*IC$_{50}$ 8.5), NF023 (*p*IC$_{50}$ 6.7); NF449 (*p*IC$_{50}$ 6.3, Kassack *et al*., 2004)	–	TNP-ATP (*p*IC$_{50}$ 8.9, Virginio *et al*., 1998), AF353 (*p*IC$_{50}$ 8.0, Gever *et al*., 2010), A317491 (7.5, Jarvis *et al*., 2002), RO3 (*p*IC$_{50}$ 7.5, Ford *et al*., 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$_{2Z}$
Ensembl ID	ENSG00000083454	ENSG00000099957	ENSG00000089041
Potent antagonists	–	–	Brilliant Blue G (*p*IC$_{50}$ 8.0, Jiang *et al*., 2000), A804598 (*p*IC$_{50}$ 8.0), A839977 (*p*IC$_{50}$ 7.7, Donnelly-Roberts and Jarvis, 2007; Donnelly-Roberts *et al*., 2009, Honore *et al*., 2009), decavanadate (*p*A$_2$ 7.4, Michel *et al*., 2006a), KN62 (Gargett and Wiley, 1997), A740003 (*p*IC$_{50}$ 7.4), A438079 (*p*IC$_{50}$ 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$_5$I is inactive at rP2X2, an antagonist at rP2X3 (pIC$_{50}$ 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 [^{35}S]-ATPγS and [^{3}H]-*αβ*-meATP, although the latter can also bind to 5′-nucleotidase (Michel *et al*., 1995). [^{3}H]-A317491 and [^{3}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][(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]amino}carbonyl)-1,2,4-benzenetricarboxylic acid; **A438079**, 3-(5-(2,3-dichlorophenyl)-1*H*-tetrazol-1-yl) methyl pyridine; **A740003**, (*N*-(1-{[(cyanoimino)(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$_5$I**, diinosine-5′,5″-pentaphosphate; **KN62**, 1-(*N,O-bis*[5-isoquinolinesulphonyl]-*N*-methyl-L-tyrosyl)-4-phenylpiperazine; **NF023**, 8,8′-(carbonyl*bis*[imino-3,1-phenylene carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid; **NF449**, 4,4′,4″,4‴-(carbonylbis[imino-5,1,3-benzenetriyl-bis{carbonylimino}])tetrakisbenzene-1,3-disulfonic acid octasodium salt; **PPADS**, pyridoxalphosphate-6-azophenyl-2′,4′-disulphonate; **RO3**, 5-(methyl[2-methylethyl-4,5-dimethoxyphenyl]-2,4pyridinediamine; **SB202190**, 4-[4-(4-fluorophenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]phenol; **TNP-ATP**, 2′,3′-*O*-(2,4,6-trinitrophenyl)-ATP

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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$_3$, GABA$_A$ 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$_{50}$)	Zn^{2+} (3.3)
Selective antagonists (pIC$_{50}$)	(+)-Tubocurarine (5.2)
Functional characteristics	Outwardly rectifying current (both constitutive and evoked by Zn^{2+})

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

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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_3 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.

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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^+ channel superfamily that includes the epithelial Na^+ channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabitis 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^+ permeable, channels (reviewed by Gründer and Chen (2010)). Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASICα, BNaC2α) (Waldmann *et al.* 1997a), ASIC1b (ASICβ, BNaC2β) (Chen *et al.*, 1998) and ASIC1b2 (ASICβ2) (Ugawa *et al.*, 2001); note that ASIC1a is also permeable to Ca^{2+}] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1α, BNC1a) (Price *et al.*, 1996; Waldmann *et al.*, 1996; Garcia-Anoveros *et al.*, 1997) and ASIC2b (MDEG2, BNaC1β); (Lingueglia *et al.*, 1997)] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H^+-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, pH- sensitivity 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^+ (ASIC1a, pEC_{50} ~ 6.2–6.8; ASIC1b, pEC_{50} ~ 5.1–6.2)	Extracellular H^+ (pEC_{50} ~ 4.1–5.0)	Extracellular H^+ (transient component pEC_{50} ~ 6.2–6.7) (sustained component pEC_{50} ~ 3.5–4.3), agmatine (EC_{50} ~ 9.8 mM @ pH 7.4, aracaine (EC_{50} ~ 1.2 mM @ pH 7.4), GMQ (largely non-desensitizing; pEC_{50} ~ 3.0 @ pH 7.4)
Blockers (IC_{50})	ASIC1a: Psalmotoxin 1 (PcTx1) (0.9 nM), Zn^{2+} (~7 nM), A-317567 (~2 μM), Pb^{2+} (~4 μM), Ni^{2+} (~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^{2+} (~1.5 μM), diarylamidines	Amiloride (28 μM), A-317567 (~30 μM), nafamostat (~70 μM), Cd^{2+} (~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^{3+} (40 μM), Zn^{2+} (61 μM), diarylamidines
Functional characteristics	ASIC1a: γ ~14pS; P_{Na}/P_K = 5–13, P_{Na}/P_{Ca} = 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: γ ~ 19 pS; P_{Na}/P_k = 14.0; $P_{Na} >> P_{Ca}$; 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	γ ~10.4–13.4 pS; P_{Na}/P_K = 10, P_{Na}/P_{Ca} = 20; rapid activation rate, moderate inactivation rate (3.3–5.5 s) @ pH 5	γ ~ 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	$[^{125}I]$-PcTx1 (ASIC1a K_D = 213 pM)	–	–

Psalmotoxin 1 (PcTx1) inhibits ASIC1a by modifying activation and desensitization by H^+, 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_{50} 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_{50} values for A-317567 are inferred from blockade of ASIC channels native to dorsal root ganglion neurones (Dube *et al.*, 2005). The pEC_{50} values for proton activation of ASIC channels are influenced by numerous factors including extracellular di- and poly-valent ions, Zn^{2+}, 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$_{50}$ values for H$^+$-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$^+$ (Waldmann *et al.*, 1997b); for hASIC3 the transient component is Na$^+$ selective ($P_{Na}/P_K > 10$) whereas the sustained current appears non-selective ($P_{Na}/P_K = 1.6$) (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^{2+} 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^{2+} by chealation reveals a high affinity block of homomeric ASIC1a and heteromeric ASIC1a+ASIC2 channels by Zn^{2+} indicating complex biphasic actions of the divalent (Chu *et al.*, 2004). Nitric oxide potentiates submaximal currents activated by H$^+$ 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^{2+} (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}-methanediamine, **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

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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^{2+}	Hg^{2+}, TEA, Ag^{+}	Hg^{2+}	Hg^{2+} , 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^{2+}	Hg^{2+}	Hg^{2+}
Permeability	Water (high)	Water (high)	Water (low), anions	Water (high), glycerol

Nomenclature	AQP8	AQP9	AQP10
Ensembl ID	ENSG00000103375	ENSG00000103569	ENSG00000143595
Activators	–	–	–
Inhibitors	Hg^{2+}	Hg^{2+}, phloretin	Hg^{2+}
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).

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Calcium (voltage-gated)

Overview: Calcium (Ca^{2+}) channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for Ca^{2+} channels was proposed by Ertel *et al.* (2000) and approved by the NC-IUPHAR subcommittee on Ca^{2+} channels (Catterall *et al.*, 2005). Ca^{2+} channels form hetero-oligomeric complexes. The α1 subunit is pore-forming and provides the extracellular binding site(s) for practically all agonists and antagonists. The 10 cloned α-subunits can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type, $Ca_V1.x$) channels; (2) the high-voltage activated dihydropyridine-insensitive ($Ca_V2.x$) channels and (3) the low-voltage-activated (T-type, $Ca_V3.x$) channels. Each α1 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 α1-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 α1, β and α2–δ subunits. The γ subunits have not been proven to associate with channels other than α1s. The α2–δ1 and α2–δ2 subunits bind gabapentin and pregabalin.

Nomenclature	$Ca_V1.1$	$Ca_V1.2$	$Ca_V1.3$	$Ca_V1.4$	$Ca_V2.1$
Alternative names	L-type, α_{1S}, skeletal muscle L	L-type, α_{1C}, cardiac or smooth muscle L	L-type, α_{1D}	L-type, α_{1F}	P-type, Q-type, α_{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	ω-Agatoxin IVA (P: IC_{50} ~ 1 nM) (Q: IC_{50} ~ 90 nM) ω-Agatoxin IVB, ω-Conotoxin, MVIIC
Functional characteristics	High voltage-activated, slow inactivation	High voltage-activated, slow inactivation (Ca^{2+} dependent)	Low-moderate voltage-activated, slow inactivation (Ca^{2+} dependent)	Moderate voltage-activated, slow inactivation (Ca^{2+} independent)	Moderate voltage-activated, moderate inactivation

Nomenclature	$Ca_V2.2$	$Ca_V2.3$	$Ca_V3.1$	$Ca_V3.2$	$Ca_V3.3$
Alternative names	N-type, α_{1B}	R-type, α_{1E}	T-type, α_{1G}	T-type, α_{1H}	T-type, α_{1I}
Ensembl ID	ENSG00000148408	ENSG00000198216	ENSG00000006283	ENSG00000196557	ENSG00000100346
Blockers	ω-Conotoxin GVIA, ω-Conotoxin MVIIC	SNX482 (may not be completely specific), high Ni^{2+}	Mibefradil, low sens. to Ni^{2+}, kurtoxin, SB-209712	Mibefradil, high sens. to Ni^{2+}, kurtoxin, SB-209712	Mibefradil, low sens. to Ni^{2+}, 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 ω-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-trifluromethylphenyl)-pyridine-5-carboxylate; **SNX482**, 41 amino acid peptide-(GVDKAGCRYMFGGCSVNDDCCPRLGCHSLFSYCAWDLTFSD); **SZ(+)-(*S*)-202-791**, isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate

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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 α-like subunits and mediate the current $I_{CatSper}$. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_v) (Ren *et al.*, 2001). CatSper1 (Ren *et al.*, 2001), CatSper2 (Quill *et al.*, 2001) and CatSpers 3 and 4 (Lobley *et al.*, 2003; Lin *et al.*, 2005; Qi *et al.*, 2007), in common with a recently identified putative 2TM auxiliary CatSperβ protein (Liu *et al.*, 2007) and two putative 1TM associated CatSperγ and CatSperδ 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_{50} ~ 8 nM) also potentiates the CatSper current ($I_{CatSper}$).	–	–	–
Blockers	Cd^{2+} (200 μM), Ni^{2+} (300 μM), ruthenium red (10 μM), NNC55-0396 (2–10 μM), HC-056456 (20 μM), mibefradil (30 μM)	–	–	–
Functional characteristics	Calcium selective ion channel ($Ba^{2+}>Ca^{2+}>>Mg^{2+}>>Na^+$); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalinization shifts the voltage-dependence of activation towards negative potentials [$V_{½}$ @ pH 6.0 = +87 mV (mouse); $V_{½}$ @ pH 7.5 = +11 mV (mouse) or pH 7.4 = + 85 mV (human)]	Required for $I_{CatSper}$	Required for $I_{CatSper}$	Required for $I_{CatSper}$

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*$^{(-/-)}$ mice (Kirichok *et al.*, 2006) and also mature human sperm (Lishko *et al.*, 2011; Strünker *et al.*, 2011). $I_{CatSper}$ is also undetectable in the spermatozoa of *Catsper2*$^{(-/-)}$,*Catsper3*$^{(-/-)}$, or *Catsper4*$^{(-/-)}$ 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^{2+} 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 CatSpers1-4 (Qi *et al.*, 2007) in association with the auxiliary subunits (β, γ, δ) that are also essential for function (Chung *et al.*, 2011). CatSper channels are required for the increase in intracellular Ca^{2+} concentration in sperm evoked by egg *zona pellucida* glycoproteins (Xia and Ren, 2009). The driving force for Ca^{2+} entry is principally determined by a mildly outwardly rectifying K^+ channel (KSper) that, like CatSpers, 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_v1, a proton channel (Lishko and Kirichok, 2010). Mutations in CatSpers 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.* $PGF_{1\alpha}$, PGE_1) 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**, (1*S*,2*S*)-2-[2-[[3-(1*H*-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl cyclopropanecarboxylate

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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 $GABA_A$ and glycine receptors (see separate tables), well characterised chloride channels can be classified as certain members of the voltage-sensitive ClC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels (Verkman and Galietta, 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).

ClC-family: The mammalian ClC 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; ClC-1, ClC-2, hClC-Ka (rClC-K1) and hClC-Kb (rClC-K2); ClC-3 to ClC-5, and ClC-6 and -7. ClC-1 and ClC-2 are plasma membrane chloride channels. ClC-Ka and ClC-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 ClC 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 ClC-4, ClC-5, ClC-6 and ClC-7 (and by inference ClC-3) function as Cl^-/H^+ antiporters (secondary active transport), rather than classical Cl^- 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 ClC-5 as a Cl^-/H^+ exchanger is important for renal endocytosis. Alternative splicing increases the structural diversity within the ClC family. The crystal structure of two bacterial ClC proteins has been described by Dutzler *et al.* (2002) and a eukaryotic ClC transporter (CmCLC) has recently been described at 3.5 Å resolution (Feng *et al*., 2010). Each ClC subunit, with a complex topology of 18 intramembrane segments, contributes a single pore to a dimeric 'double-barrelled' ClC 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 ClC-4, ClC-5, ClC-6 and ClC-7, the prokaryotic ClC homologue (ClC-ec1) and CmCLC function as H^+/Cl^- antiporters, rather than as ion channels (Accardi and Miller, 2004; Feng *et al*., 2010). The generation of monomers from dimeric ClC-ec1 has firmly established that each ClC subunit is a functional unit for transport and that cross-subunit interaction is not required for Cl^-/H^+ exchange in ClC transporters (Robertson *et al*., 2010).

Nomenclature	ClC-1	ClC-2	ClC-Ka	ClC-Kb
Other names	skeletal muscle Cl^- channel	–	ClC-K1 (rodent)	ClC-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^{2+}, Zn^{2+}, niflumic acid, fenofibric acid	GaTx2 (apparent K_D = 15 pM at -100 mV), NPPB, DPC, Cd^{2+}, Zn^{2+}	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 ClC-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_{Cl} 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 (p*K* = 7.1); potentiated by extracellular Ca^{2+}	Bidirectional rectification; no time dependence; inhibited by extracellular protons; potentiated by extracellular Ca^{2+}

Nomenclature	ClC-3	ClC-4	ClC-5
Ensembl ID	ENSG00000109572	ENSG00000073464	ENSG00000171365
Activators	–	–	–
Blockers	Phloretin (30 μM); insensitive to DIDS and NPPB and tamoxifen (10 μM)	Zn^{2+} (50 μM), Cd^{2+} (68 μM) (IC_{50} 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^-/H^+ antiporter (Matsuda *et al.*, 2008); pronounced outward rectification; slow activation, fast deactivation; activity enhanced by CaM kinase II; inhibited by intracellular Ins(3,4,5,6)P4 and extracellular acidosis	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) Picollo and Pusch, 2005; Scheel *et al.*, 2005; Alekov and Fahlke, 2009); extreme outward rectification; voltage-dependent gating with midpoint of activation at +73 mV (Orhan *et al.*, 2011); rapid activation and deactivation; inhibited by extracellular acidosis; non-hydrolytic nucleotide binding required for full activity	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) (Picollo and Pusch, 2005; Scheel *et al.*, 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 β-synthetase related (CBS) domains activates ClC-5

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

ClC channels display the permeability sequence $Cl^- > Br^- > I^-$ (at physiological pH). ClC-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 ClC-2 by the peptide GaTx2, from *Leiurus quinquestriatus herbareus venom*, is likely to occur through inhibition of channel gating, rather than direct open channel blockade (Thompson *et al.*, 2009). Although ClC-2 can be activated by cell swelling, it does not correspond to the VRAC channel (see below). Alternative potential physiological functions for ClC-2 are reviewed by Planells-Cases and Jentsch (2009). Functional expression of human ClC-Ka and ClC-Kb requires the presence of barttin (Estévez *et al.*, 2001; Scholl *et al.*, 2006; reviewed by Fahlke and Fischer, 2010). The properties of ClC-Ka/barttin and ClC-Kb/barttin tabulated are those observed in mammalian expression systems: in oocytes the channels display time- and voltage-dependent gating. The rodent homologue (ClC-K1) of ClC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin which increases both channel opening probablility in the physiological range of potentials (Estévez *et al.*, 2001; Scholl *et al.*, 2006; Fischer *et al.*, 2010; reviewed by Fahlke and Fischer, 2010). ClC-Ka is approximately 5 to 6-fold more sensitive to block by 3-phenyl-CPP and DIDS than ClC-Kb, while newly synthesized benzofuran derivatives showed the same blocking affinity (<10 μM) on both CLC-K isoforms (Liantonio *et al.* 2008). The biophysical and pharmacological properties of ClC-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 ClC-3 may function as both a Cl^-/H^+ 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 ClC-3, ClC-4 and ClC-5. Activation of heterologously expressed ClC-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^- *versus* Cl^-), 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 ClC-5 (Zdebik *et al.* 2008). ClC-7 associates with a β 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^- channel involved in normal fluid transport across various epithelia. Of the 1700 mutations identified in CFTR, the most common is the deletion mutant ΔF508 (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 ΔF508 mutation that do traffic to the plasma membrane demonstrate gating defects. Thus, pharmacological restoration the function of the ΔF508 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^{2+} 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*H*-indol-3-yl-acetyl)-methylamino]-*N*-(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$_{inh}$-172 (intracellular application prolongs mean closed time), malonic acid hydrazide conjugates (see Verkman and Galietta, 2009), glibenclamide (non-selective)
Functional characteristics	γ = 6-10 pS; permeability sequence = $Br^- \geq Cl^- > I^- > F^-$, ($P_I/P_{Cl}$ = 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 ΔF508CFTR 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 Galietta (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 recapictulate 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 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 Ca^{2+}-activated 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$^{(-/-)}$ mice secretion of Ca^{2+}-dependent Cl^- secretion by several epithelia is reduced (Ousingsawat *et al*., 2009, Rock *et al*., 2009). Alternative splicing regulates the voltage- and 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$^{(-/-)}$ mice Ca-activated Cl- currents in the main olfactory epithelium (MOE) and in the vomeronasal organ are virtually absent (Billig *et al*., 2011).

Nomenclature	CaCC
Other names	Ca^{2+}-activated Cl^- channel
Activators	intracellular Ca^{2+}
Blockers	niflumic acid, flufenamic acid, DCDPC, DIDS, SITS, NPPB, A-9-C, Ins(3,4,5,6)P_4, mibefradil, fluoxetine, tannic acid
Functional characteristics	γ = 0.5–5 pS; permeability sequence, $SCN^- > NO_3^- > I^- > Br^- > Cl^- > F^-$; relative permeability of $SCN^-:Cl^-$ ~8. $I^-:Cl$– ~3, aspartate:Cl^- ~0.15, outward rectification (decreased by increasing $[Ca^{2+}]_i$); sensitivity to activation by $[Ca^{2+}]_i$ decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[Ca^{2+}]_i$); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status

Blockade of $I_{Cl(Ca)}$ 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 $I_{Cl(Ca)}$ in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon $[Ca^{2+}]_i$ (see Leblanc *et al*., 2005 for summary). Considerable crossover in pharmacology with large conductance Ca^{2+}-activated K^+ channels also exists (see Greenwood and Leblanc, 2007 for overview). Two novel compounds, CaCC$_{inh}$-A01 and CaCC$_{inh}$-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 TMEM116A, 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 $I_{Cl(Ca)}$ in T_{84} 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 $I_{Cl(Ca)}$. Intracellular Ins(3,4,5,6)P_4 may act as an endogenous negative regulator of CaCC channels activated by Ca^{2+}, or CaMKII. Smooth muscle CaCC are also regulated positively by Ca^{2+}-dependent phosphatase, calcineurin (see Leblanc *et al*., 2005 for summary).

Maxi chloride channel: Maxi Cl^- 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^- channel is uncertain, but roles in cell volume regulation and apoptosis have been claimed. Evidence suggests a role for maxi Cl^- 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^- channels (TTYH1-3) that resemble Maxi Cl^- channels has been cloned (Suzuki and Mizuno, 2004), but alternatively, Maxi Cl^- 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^-
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, toremifine), extracellular chlorpromazine and triflupromazine, cell swelling
Blockers	SITS, DIDS, NPPB, DPC, intracellular arachidonic acid, extracellular Zn^{2+} and Gd^{3+}
Functional characteristics	γ = 280-430 pS (main state); permeability sequence, I > Br > Cl > F > gluconate ($P_{Cl}P_{Cl}$ = ~1.5); ATP is a voltage dependent permeant blocker of single channel activity (P_{ATP}/P_{Cl} = 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 arachinonic acid (and cis-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down (K_d = 4–5 μM) and a reduction of γ (K_d = 13–14 μM). Blockade of channel activity by SITS, DIDS, Gd^{3+} 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^- 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^- 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 *MDR1* 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, oxalon dye (diBA-(5)-C4), carbenoxolone, IAA-94, extracellular nucleotides, nucleoside analogues, intracellular Mg^{2+}
Functional characteristics	γ = 10–20 pS (negative potentials), 50–90 pS (positive potentials); permeability sequence SCN > I > NO^{3-} >Br^- > Cl^- > F^- > 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^{2+} 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_2O_2 and Src-PLCγ-Ca^{2+} 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^- 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^{2+} 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$_{inh}$-172**, 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-dichlor-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**, nordihydroguiaretic 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-2*H*-benzimidazole-2-one; **NS3728**, *N*-[3,5-bis(trifluromethyl)-phenyl]-*N*′[4-bromo-2-(1*H*-tetrazol-5yl)-phenyl]urea; **NS5818**, *N*-(3,5-dichloro-phenyl)-*N*′-{2-(1*H*-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-1*H*-pyrazol-3-yl)-phenol; **VX-770**, *N*-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

Further Reading

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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_3) 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 α-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 carbenxolone 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.

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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, CNGα1, RCNC1	CNG2, CNGα3, OCNC1	CNG3, CNGα2, CCNC1
Ensembl ID	ENSG00000198515	ENSG00000183862	ENSG00000144191
Activators	Intracellular cyclic nucleotides: cGMP ($EC_{50} \approx 30\ \mu$ M) >> cAMP	Intracellular cyclic nucleotides: cGMP $\approx$ cAMP ($EC_{50} \approx 1\ \mu$ M)	Intracellular cyclic nucleotides: cGMP ($EC_{50} \approx 30\ \mu$ M) >> cAMP
Inhibitors	L-*cis* diltiazem	–	L-*cis* diltiazem
Functional characteristics	γ = 25–30 pS P_{Ca}/P_{Na} = 3.1	γ = 35 pS P_{Ca}/P_{Na} = 6.8	γ = 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: $CNGA1_3$/CNGB1a; Cone: $CNGA3_2$/$CNGB3_2$; Olfactory neurons: $CNGA2_2$/CNGA4/CNGB1b (Weitz *et al*., 2002; Zheng *et al*., 2002; Zhong *et al*., 2002; Peng *et al*., 2004; Zheng and Zagotta, 2004).

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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 α β and γ subunits. The primary structure of αENaC subunit was identified by expression cloning (Canessa *et al*., 1993); β and γ ENaC were identified by functional complementation of the α subunit (Canessa *et al*., 1994). Each ENaC subunit contains 2 TM α 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 1α:1β:1γ subunits (Gonzales *et al*., 2009).

Nomenclature	Epithelial sodium channel (ENaC)
Ensembl ID	Human α subunit, ENSG00000111319; human β subunit, ENSG00000168447; human γ subunit, ENSG00000166828; human δ subunit, ENSG00000162572
Activators (EC_{50})	S3969 (1.2 μM) (Lu *et al*., 2008)
Blockers (IC_{50})	Amiloride (100-200 nM), benzamil (~10 nM), triamterene (~5 μM) (Canessa *et al*., 1994; Kellenberger *et al*., 2003), P552-02 (7.6 nM; Hirsch *et al*., 2008)
Functional characteristics	γ ≈ 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 *et al*., 1990; Sayegh, *et al*., 1999; Richard *et al*., 2004). The density of channels in the apical membrane, and hence G_{Na}, can be controlled *via* both serum and glucocorticoid-regulated kinases (SGK1, 2 and 3) (Debonneville *et al*., 2001; Friedrich *et al*., 2003) and *via* 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 *et al*., 2001, Boarse *et al*. 2011). ENaC is constitutively activated by soluble and membrane-bound serine proteases, such as furin, prostasin (CAP1), plasmin and elastase (Planes and Caughey, 2007; Rotin and Schild, 2008; Kleyman *et al*., 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 *et al*., 2009). Pharmacological inhibitors of proteases (*e.g.* camostat acting upon prostasin) reduce the activity of ENaC (Maekawa *et al*., 2009). Phosphatidylinositides such as PtIns(4,5)P_2 and PtIns(3,4,5)P_3) stabilise channel gating probably by binding to the β and γ ENaC subunits, respectively (Ma *et al*., 2007; Pochynyuk *et al*., 2008), whilst C terminal phosphorylation of β and γ-ENaC by ERK1/2 has been reported to inhibit the withdrawal of the channel complex from the apical membrane (Yang *et al*., 2006). This effect may contribute to the cAMP-mediated increase in sodium conductance.

Data in the table refer to the αβγ 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 β and γ 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^+ 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-1*H*-indol-3-ylthio)pentanamide

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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_f. 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^+, ZD7288, ivabradine	Cs^+, ZD7288, ivabradine	Cs^+, ZD7288, ivabradine	Cs^+, ZD7288, ivabradine

HCN channels are permeable to both Na^+ and K^+ ions, with a Na^+/K^+ 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-{[((7*S*)-3,4-dimethoxybicyclo [4,2,0] octa-1,3,5-trien7-yl) methyl] methylamino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one hydrochloride; **ZD7288**, [4-(*N*-ethyl-*N*-phenyl-amino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride

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IP$_3$ receptor

Overview: The inositol 1,4,5-trisphosphate receptors (IP$_3$R) are ligand-gated Ca^{2+}-release channels on intracellular Ca^{2+} store sites (such as the endoplasmic reticulum). They are responsible for the mobilization of intracellular Ca^{2+} stores and play an important role in intracellular Ca^{2+} 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$_3$Rs are closely associated with certain proteins: calmodulin and FKBP (and calcineurin via FKBP). They are phosphorylated by PKA, PKC, PKG and CaMKII.

Nomenclature	IP$_3$R1	IP$_3$R2	IP$_3$R3
Other names	INSP3R1	INSP3R2	INSP3R3
Ensembl ID	ENSG00000150995	ENSG00000123104	ENSG00000096433
Endogenous activators	Ins(1,4,5)P$_3$ (nM – μM), cytosolic Ca^{2+} (<750 μM), cytosolic ATP (<mM)	Ins(1,4,5)P$_3$ (nM–μM), cytosolic Ca^{2+} (nM)	Ins(1,4,5)P$_3$ (nM–μM), cytosolic Ca^{2+} (nM)
Pharmacological activators	InsP$_3$ analogues including Ins(2,4,5)P$_3$, adenophostin A (nM)	InsP$_3$ analogues including Ins(2,4,5)P$_3$, adenophostin A (nM)	–
Antagonists	Xestospongin C (μM), caffeine (mM), phosphatidylinositol 4,5-bisphosphate (μM), heparin (μg/ml), decavanadate (μM), calmodulin at high cytosolic Ca^{2+}	Heparin (μg/ml), decavanadate (μM)	Heparin (μg/ml), decavanadate (μM)
Functional characteristics	Ca^{2+}: (P_{Ba}/P_K ~6) single-channel conductance ~70 pS (50 mM Ca^{2+})	Ca^{2+}: single-channel conductance ~70 pS (50 mM Ca^{2+}), ~390 pS (220 mM Cs$^+$)	Ca^{2+}: single-channel conductance ~88 pS (55 mM Ba^{2+})

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

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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 α subunit often associated with auxiliary regulatory subunits. Since there are over 70 different genes encoding K channels α 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 ($K_{IR}2.x$), the G-protein-activated inward-rectifier K channels ($K_{IR}3.x$) and the ATP-sensitive K channels ($K_{IR}6.x$, which combine with sulphonylurea receptors (SUR)). The pore-forming α subunits form tetramers, and heteromeric channels may be formed within subfamilies (e.g. $K_{IR}3.2$ with $K_{IR}3.3$).

Subfamily group	$K_{IR}1.x$	$K_{IR}2.x$	$K_{IR}3.x$	$K_{IR}4.x$
Subtypes	$K_{IR}1.1$ (ROMK1)	$K_{IR}2.1$–2.4 (IRK1–4)	$K_{IR}3.1$–3.4 (GIRK1–4)	$K_{IR}4.1$–4.2
Ensembl ID*	ENSG00000151704 ($K_{IR}1.1$)	ENSG00000123700 ($K_{IR}2.1$)	ENSG00000162989 ($K_{IR}3.1$)	ENSG00000177807 ($K_{IR}4.1$)
Activators	–	–	PIP_2, $G\beta\gamma$	–
Inhibitors	–	$[Mg^{2+}]_i$, polyamines (internal)	–	–
Functional characteristic	Inward-rectifier current	IK_1 in heart, 'strong'inward–rectifier current	G-protein-activated inward-rectifier current	Inward-rectifier current

Subfamily Group	$K_{IR}5.x$	$K_{IR}6.x$	$K_{IR}7.x$
Subtypes	$K_{IR}5.1$	$K_{IR}6.1$–6.2 (K_{ATP})	$K_{IR}7.1$
Ensembl ID*	ENSG00000153822 ($K_{IR}5.1$)	ENSG00000121361 ($K_{IR}6.1$)	ENSG00000115474 ($K_{IR}7.1$)
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 αsubunit 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. $K_{2P}3.1$ with $K_{2P}9.1$). 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	$K_{2P}1.1$ (TWIK1) $K_{2P}6.1$ (TWIK2) $K_{2P}7.1$ (KNCK7)	$K_{2P}2.1$ (TREK1) $K_{2P}10.1$ (TREK2) $K_{2P}4.1$ (TRAAK)	$K_{2P}3.1$ (TASK1) $K_{2P}9.1$ (TASK3) $K_{2P}15.1$ (TASK5)	$K_{2P}16.1$ (TALK1) $K_{2P}5.1$ (TASK2) $K_{2P}17.1$ (TASK4)	$K_{2P}13.1$ (THIK1) $K_{2P}12.1$ (THIK2)	$K_{2P}18.1$ (TRESK1)
Ensembl ID*	ENSG00000135750 ($K_{2P}1.1$)	ENSG00000082482 ($K_{2P}2.1$)	ENSG00000171303 ($K_{2P}3.1$)	ENSG00000164626 ($K_{2P}5.1$)	ENSG00000152315 ($K_{2P}13.1$)	ENSG00000186795 ($K_{2P}18.1$)

Subfamily group	'TWIK'	'TREK'	'TASK'	'TALK'	'THIK'	'TRESK'
Activators	–	Halothane (not TRAAK), riluzole, stretch, heat, arachidonic acid, acid pH$_i$	Halothane, alkaline pH$_o$ ($K_{2P}3.1$)	Alkaline pH$_O$	–	–
Inhibitors	Acid pH$_i$	–	Anandamide ($K_{2P}3.1$, $K_{2P}9.1$) ruthenium red ($K_{2P}9.1$) acid pH$_O$	–	Halothane	Arachidonic acid
Functional characteristic	Background current	Background current	Background current	Background current	Background current	Background current

The $K_{2P}7.1$, $K_{2P}15.1$ and $K_{2P}12.1$ 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^{2+} 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_V subfamilies, the KCNQ subfamily the EAG subfamily (which includes herg channels), the Ca^{2+}-activated Slo subfamily (actually with 7TM) and the Ca^{2+}-activated SK subfamily. As for the 2TM family, the pore-forming α subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. $K_V1.1$ with $K_V1.2$; KCNQ2 with KCNQ3).

Subfamily group	$K_V1.x$	$K_V2.x$	$K_V3.x$	$K_V4.x$
Subtypes	$K_V1.1$ – $K_V1.8$ Shaker-related	$K_V2.1$–2.2 Shab-related	$K_V3.1$–3.4 Shal-related	$K_V4.1$–4.3 Shaw-related
Ensembl ID*	ENSG00000111262 ($K_V1.1$)	ENSG00000158445 ($K_V2.1$)	ENSG00000129159 ($K_V3.1$)	ENSG00000102057 ($K_V4.1$)
Inhibitors	TEA potent (1.1), TEA moderate (1.3, 1.6), 4-AP potent (1.4), α-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_V (1.1–1.3, 1.5–1.8), K_A (1.4)	K_V (2.1)	K_V (3.1, 3.2), K_A (3.3, 3.4)	K_A
Associated subunits	K_V β_1, K_V β_2	$K_V5.1$, $K_V6.1$–6.4, $K_V8.1$-8.2,$K_V9.1$–9.3	MiRP2 ($K_V3.4$)	KChIP, KChAP

Subfamily group	$K_V7.x$ ('KCNQ')	$K_V10.x$, $K_V11.x$, $K_V12.x$ ('EAG')	$K_{Ca}1.x$, $K_{Ca}4.x$, $K_{Ca}5.x$ ('Slo')	$K_{Ca}2.x$, $K_{Ca}3.x$ ('SK')
Subtypes	$K_V.7.1$–7.5 (KCNQ1-5)	$K_V10.1$–10.2 (eag1–2) $K_V11.1$–11.3 (erg1-3, herg 1–3) $K_V12.1$–12.3 (elk1-3)	$K_{Ca}1.1$, $K_{Ca}4.1$–4.2, $K_{Ca}5.1$ Slo (BK), Slack, Slick	$K_{Ca}2.1$–2.3 (SK1–SK3) $K_{Ca}3.1$ (SK4, IK)
Ensembl ID*	ENSG00000053918 ($K_V7.1$)	ENSG00000143473 ($K_V10.1$)	ENSG00000156113 ($K_{Ca}1.1$)	ENSG00000105642 ($K_{Ca}2.1$)
Activators	Retigabine ($K_V.7.2$,–5)	–	NS004, NS1619	–
Inhibitors	TEA ($K_V.7.2$, 7.4), XE991 ($K_V.7.1$, 7.2, 7.4, 7.5), linopirdine	E-4031 ($K_V11.1$), astemizole ($K_V11.1$), terfenadine ($K_V11.1$)	TEA, charybdotoxin, iberiotoxin	Charybdotoxin ($K_{Ca}3.1$), apamin ($K_{Ca}2.1$–2.3)
Functional characteristic	$K_V7.1$ – cardiac IK_S $K_V7.2/7.3$–M current	$K_V11.1$ – cardiac IK_R	Maxi K_{Ca} K_{Na} (slack & slick)	SK_{Ca} ($K_{Ca}2.1$–2.3) IK_{Ca} ($K_{Ca}3.1$)
Associated subunits	minK, MiRP2 ($K_V.7.1$)	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-trifluromethyl-2-benzimidazolone; **NS1619**, 1-(2′-hydroxy-5′-trifluromethylphenyl)-5-trifluro-methyl-2(3*H*)benzimidazolone; **PIP$_2$**, phosphatidylinositol 4,5, bisphosphate; **TEA**, tetraethylammonium; **XE991**, 10,10-*bis*(4-pyridinylmethyl)-9(10*H*)-anthracene

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Voltage-gated proton channel

Overview: The voltage-gated proton channel (provisionally denoted H_v1) 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_v1 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_v1 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_v1 expresses largely as a dimer mediated by intracellular C-terminal coiled-coil interactions (Li *et al*., 2010) but individual promoters nonetheless support gated H^+ 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_v1
Other names	Voltage-gated proton channel 1 (HVCN1), Voltage-sensor only protein (VSOP)
Ensembl ID	ENSG00000122986
Activators	–
Blockers (IC_{50})	Zn^{2+} (≈0.5–2.0 μM), Cd^{2+} (≈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 ($\Delta pH = pH_o - pH_i$) across the membrane

The voltage threshold (V_{thr}) for activation of H_v1 is not fixed but is set by the pH gradient across the membrane such that V_{thr} is positive to the Nernst potential for H^+, which ensures that only outwardly directed flux of H^+ occurs under physiological conditions (DeCoursey, 2008a,b; Capasso *et al*., 2011). Phosphorylation of Hv1 within the N-terminal domain by PKC enhances the gating of the channel (Musset *et al*., 2010a). Tabulated IC_{50} values for Zn^{2+} and Cd^{2+} are for heterologously expressed human and mouse Hv1 (Ramsey *et al*., 2006; Sasaki *et al*., 2006). Zn^{2+} is not a conventional pore blocker, but is coordinated by two, or more, external protonation sites involving histamine residues (Ramsey *et al*., 2006). Zn^{2+} 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_v1 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_v1 are reviewed by Capasso *et al*. (2011).

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Ryanodine receptor

Overview: The ryanodine receptors (RyRs) are found on intracellular Ca^{2+} storage/release organelles. The family of RyR genes encodes three highly related Ca^{2+} 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^{2+} 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 *via* DHP receptor, cytosolic Ca^{2+} (μM), cytosolic ATP (mM), luminal Ca^{2+}, calmodulin at low cytosolic Ca^{2+}, CaM kinase, PKA	Cytosolic Ca^{2+} (μM), cytosolic ATP (mM), luminal Ca^{2+}, CaM kinase, PKA	Cytosolic Ca^{2+} (μM), cytosolic ATP (mM), calmodulin at low cytosolic Ca^{2+}
Pharmacological activators	Ryanodine (nM–μM), caffeine (mM), suramin (μM)	Ryanodine (nM– μM), caffeine (mM), suramin (μM)	Ryanodine (nM–μM), caffeine (mM)
Antagonists	Cytosolic Ca^{2+}(>100 μM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+}, dantrolene	Cytosolic Ca^{2+}(>1 mM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+}	Cytosolic Ca^{2+}(>1 mM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+}, dantrolene
Channel blockers	Ryanodine (>100 μM), ruthenium red, procaine	Ryanodine (>100 μM), ruthenium red, procaine	Ruthenium red
Functional characteristics	Ca^{2+}: ($P_{\mathrm{Ca}}/P_{\mathrm{K}}$~6) single-channel conductance: ~90 pS (50 mM Ca^{2+}), 770 pS (200 mM K^{+})	Ca^{2+}: ($P_{\mathrm{Ca}}/P_{\mathrm{K}}$~6) single-channel conductance: ~90 pS (50 mM Ca^{2+}), 720 pS (210 mM K^{+})	Ca^{2+}: ($P_{\mathrm{Ca}}/P_{\mathrm{K}}$~6) single-channel conductance: ~140 pS (250 mM Ca^{2+}), 777 pS (250 mM K^{+})

The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive Ca^{2+} 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).

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Sodium leak channel, non-selective

Overview: The sodium leak channel, non selective (NC-IUPHAR tentatively recommends the nomenclature Na$_{\mathrm{Vi}}$2.1, W.A. Catterall, personal communication) is structurally a member of the family of voltage-gated sodium channel family (Na$_{\mathrm{v}}$1.1 – Na$_{\mathrm{v}}$1.9) (Lee *et al.*, 1999; Yu and Catterall, 2004). In contrast to the latter, Na$_{\mathrm{Vi}}$2.1, is voltage-insensitive (denoted in the subscript 'vi' in the tentative nomenclature) and possesses distinctive ion selectivity and pharmacological properties. Na$_{\mathrm{Vi}}$2.1, which is insensitive to TTX (10 μM), has been proposed to mediate the TTX-resistant and voltage-insensitive Na$^+$ leak current (I$_{\mathrm{L}}$-Na) observed in many types of neurone (Lu *et al.*, 2007). However, whether Na$_{\mathrm{Vi}}$2.1 is constitutively active has been challenged (Swayne *et al.*, 2009). Na$_{\mathrm{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$_{\mathrm{vi}}$2.1
Other names	NALCN, Nav2.1, Na$_{\mathrm{x}}$, voltage-gated channel like 1 (VGCNL1), Rb21
Ensembl ID	ENSG00000102452
Activators	Constitutively active (Lu *et al.*, 2007), or activated downstream of Src family tyrosine kinases (SFKs) (Lu *et al.*, 2009; Swayne *et al.*, 2009); positively modulated by decreased extracellular Ca^{2+} concentration (Lu *et al.*, 2010)
Blockers (IC$_{50}$)	Gd^{3+} (1.4 μM), Cd^{2+} (0.15 mM), Co^{2+} (0.26 mM), verapamil (0.38 mM)
Functional characteristics	γ = 27 pS (by fluctuation analysis), $P_{\mathrm{Na}}/P_{\mathrm{Cs}}$ = 1.3, $P_{\mathrm{K}}/P_{\mathrm{Cs}}$ = 1.2, $P_{\mathrm{Ca}}/P_{\mathrm{Cs}}$ = 0.5, linear current voltage-relationship, voltage-independent and non-inactivating

In native and recombinant expression systems Na$_{\mathrm{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 β-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 though a pathway that involves the activation of Src family tyrosine kinases. It is suggested that Na$_{\mathrm{Vi}}$2.1 exists as a macromolecular complex with M3 receptors (Swayne *et al.*, 2009) and peptide receptors (Lu *et al.*, 2009), in the latter instance in association with the protein UNC-80, which recruits Src to the channel complex (Lu *et al.*, 2009, Wang and Ren, 2009). By contrast, stimulation of Na$_{\mathrm{vi}}$2.1 by decreased extracellular Ca^{2+} concentration is G-protein dependent and involves a Ca^{2+}-sensing G protein-coupled receptor and UNC80 which links Na$_{\mathrm{vi}}$2.1 to the protein UNC79 in the same complex (Lu *et al.*, 2010). Na$_{\mathrm{Vi}}$2.1 null mutant mice have severe disturbances in respiratory rhythm and die within 24 hours of birth (Lu *et al.*, 2007). Na$_{\mathrm{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).

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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 α subunit, which may be associated with either one or two β subunits (Isom, 2001). α-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 β1, β2, β3 and β4 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	$\mathrm{Na_V}$1.1	$\mathrm{Na_V}$1.2	$\mathrm{Na_V}$1.3	$\mathrm{Na_V}$1.4	$\mathrm{Na_V}$1.5
Alternative names	Brain type I	Brain type II	Brain type III	µ1, 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	µ-Conotoxin GIIIA, tetrodotoxin (5 nM), saxitoxin	Tetrodotoxin (2 µM)
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	$\mathrm{Na_V}$1.6	$\mathrm{Na_V}$1.7	$\mathrm{Na_V}$1.8	$\mathrm{Na_V}$1.9
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 µM)	Tetrodotoxin (40 µM)
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, antiarrythmic drugs and antiepileptic drugs. There are two clear functional fingerprints for distinguishing different subtypes. These are sensitivity to tetrodotoxin ($\mathrm{Na_V}$1.5, $\mathrm{Na_V}$1.8 and $\mathrm{Na_V}$1.9 are much less sensitive to block) and rate of inactivation ($\mathrm{Na_V}$1.8 and particularly $\mathrm{Na_V}$1.9 inactivate more slowly).

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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 phosphoinostides such as PtIns(4,5)P$_2$ and Ins(1,4,5)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 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 compenents of mulimeric complexes that form SOCs), 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 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, La^{3+} (micromolar), potentiated by extracellular protons	NO-mediated cysteine S-nitrosylation (disputed), lysophosphatidylcholine, genesteine (independent of tyrosine kinase inhibition, Wong *et al.*, 2010), diadzein, La^{3+} (micromolar), Gd^{3+} (0.1 mM), Pb^{2+} (5 μM), intracellular Ca^{2+} (EC$_{50}$ = 635 nM at negative potentials), potentiated by extracellular protons
Blockers	GsMTx-4, 2-APB, SKF96365, Gd^{3+}, La^{3+}	ML204 (IC$_{50}$ = 2.9 μM, Miller *et al.*, 2011), 2-APB, SKF96365, niflumic acid, La^{3+} (millimolar)	ML204 (IC$_{50}$ ≈ 10 μM, Miller *et al.*, 2011), GsMTx-4, SKF96365, 2-APB, KB-R7943, BTP2 (Pyr2), flufenamic acid, chlorpromazine, La^{3+} (millimolar)
Functional characteristics	γ = 16 pS (fluctuation analysis), conducts mono- and di-valent cations non-selectively; monovalent cation current suppressed by extracellular Ca^{2+}; non-rectifying, or mildly inwardly rectifying; non-inactivating	γ = 30 –41 pS, conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.1 – 7.7); dual (inward and outward) rectification	γ = 41-63 pS; conducts mono-and di-valent cations non-selectively (P_{Ca}/P_{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 *et al.*, 2007), 2,4 diahexanxoylphloroglucinol (Leuner *et al.*, 2010), diacylglycerols, lysophosphatidylcholine, flufenamate, arachidonic acid, 20-HETE	Diacylglycerols
Blockers	Pyr3 (Kiyonaka *et al.*, 2009), 2-APB, SKF96365, ACA, KB-R7943, BTP2 (Pyr2), Gd^{3+}, La^{3+}, Ni^{2+}	GsMTx-4, SKF96365, 2-APB, amiloride, ACA, KB-R7943, ML-9, La^{3+} (IC$_{50}$ ≅ 6 μM), Gd^{3+}, Cd^{2+}, extracellular protons	SKF96365, 2-APB, amiloride, La^{3+}
Functional characteristics	γ = 66 pS; conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.6); monovalent cation current suppressed by extracellular Ca^{2+}; dual (inward and outward) rectification	γ = 28-37 pS; conducts mono- and divalent cations with a preference for divalents (P_{Ca}/P_{Na} = 4.5–5.0); monovalent cation current suppressed by extracellular Ca^{2+} and Mg^{2+}, dual rectification (inward and outward), or inward rectification	γ = 25–75 pS; conducts mono and divalent cations with a preference for divalents (P_{Ca}/P_{Cs} = 5.9); modest outward rectification (monovalent cation current recorded in the absence of extracellular divalents); monovalent cation current suppressed by extracellular Ca^{2+} and Mg^{2+}

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, hTRPM3a and hTRPM3$_{1325}$) 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$_{10}$ = 7.2 between 15–25°C; Vriens *et al.*, 2011), hypotonic cell swelling
Chemical activators	Pregnenolone sulphate (Lambert *et al.*, 2011)	Pregnenolone sulphate (Wagner *et al.*, 2008), epipregnanolone sulphate (Majeed *et al.*, 2010), nifedipine, D-erythro-sphingosine, dihydrosphingosine
Blockers	Zn^{2+} (IC$_{50}$ = 1 μM)	Rosiglitazone, troglitazone, pioglitazone (independent of PPAR-γ; Majeed *et al.*, 2011), mefenamic acid, Klose *et al.*, 2011), 2-APB, La^{3+}, Gd^{3+}, intracellar Mg^{2+}, extracellular Na^{+} (TRPM3α2 only)
Functional characteristics	Conducts mono- and di-valent cations non-selectively, dual rectification (inward and outward)	TRPM3$_{1235}$: γ = 83 pS (Na^{+} current), 65 pS (Ca^{2+} current); conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.6) TRPM3α1: selective for monovalent cations (P_{Ca}/P_{Cs}~0.1) TRPM3α2: conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Cs} = 1–10) Outwardly rectifying (magnitude varies between spice 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^{2+} *via* calmodulin, intracellular ADP ribose (ADPR) and cyclic ADPR (cADPR); agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (*e.g.* GEA 3162) species;, potentiated by arachidonic acid
Blockers	2-APB, ACA, clotrimazole, miconazole, econazole, flufenamic acid, Zn^{2+}, 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_{Ca}/P_{Na} = 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 APDR formation by glycohydrolase inhibitors

Ca^{2+} 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^{2+} (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^{2+} 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 $[Ca^{2+}]_i$, heat (Q_{10} = 8.5 @ +25 mV between 15–25°C)	Membrane depolarization ($V_{1/2}$ = 0 to +120 mV dependent upon conditions), heat (Q_{10} = 10.3 @ -75 mV between 15 and 25°C)
Chemical activators	Decavanadate, whole cell current transiently activated by intracellular Ca^{2+} (EC_{50} 0.3–20 μM), enhanced by BTP2	Rosiglitazone (Majeed *et al.*, 2011), transiently activated by intracellular Ca^{2+} (EC_{50} 635-840 nM)
Blockers	Clotrimazole, 9-phenanthrol, intracellular nucleotides (ATP^{4-}, ADP, AMP, AMP-PNP – IC_{50} range 1.3–19 μM) and adenosine (IC_{50} 630 μM); intracellular spermine (IC_{50} = 35-61 μM) and flufenamic acid (IC_{50} = 2.8 μM)	Intracellular spermine (IC_{50} = 37 μM) and flufenamic acid (IC_{50} = 24 μM), extracellular protons (IC_{50} = 630 nM), (not inhibited by ATP^{4-})
Functional characteristics	γ = 23 pS (within the range 60 to +60 mV); permeable to monovalent cations; impermeable to Ca^{2+}; strong outward rectification; slow activation at positive potentials, rapid deactivation at negative potentials, deactivation blocked by decavanadate	γ = 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 $[Ca^{2+}]_i$

TRPM4 exists as multiple splice variants: data listed are for TRPM4b. The sensitivity of TRPM4b and TRPM5 to activation by $[Ca^{2+}]_i$ 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^{2+} 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^{2+}, 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^{2+} (IC_{50} = 4.8–5.4 μM) and Mg^{2+} (IC_{50} = 1.1–3.4 μM)	Spermine (permeant blocker), carvacrol, La^{3+}, Mg^{2+}, 2-APB (micromolar)
Functional characteristics	γ = 40–87 pS; permeable to mono- and di-valent cations with a preference for divalents ($Mg^{2+} > Ca^{2+}$; P_{Ca}/P_{Na} = 6.9), conductance sequence $Zn^{2+} > Ba^{2+} > Mg^{2+} = Ca^{2+} = Mn^{2+} > Sr^{2+} > Cd^{2+} > Ni^{2+}$; strong outward rectification abolished by removal of extracellular divalents, inhibited by intracellular Mg^{2+} (IC_{50} = 0.5 mM) and ATP	γ = 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 $Ni^{2+} > Zn^{2+} > Ba^{2+} = Mg^{2+} > Ca^{2+} = Mn^{2+} > Sr^{2+} > Cd^{2+}$; outward rectification, decreased by removal of extracellular divalent cations; inhibited by intracellular Mg^{2+}, Ba^{2+}, Sr^{2+}, Zn^{2+}, Mn^{2+} and Mg.ATP (disputed); activated by and intracellular alkalinization; 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 *et al*., 2008), 5-benzyloxytrytamine, clotrimazole, BCTC, capsazepine, 2-APB, La^{3+}, ACA, anandamide, NADA, linoleic acid, cannabinoids (*e.g*., cannabidiol, THC); insensitive to ruthenium red
Functional characteristics	γ = 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 densensitization 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 $TRPA1^{(-/-)}$ 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	*e.g*. Isothiocyanates, cinnamaldehyde, allicin, acroline, formalin, chlorobenzylidene malononitrile
Non-covalent	*e.g*. URB597 (EC_{50} = 24 μM, Niforatus *et al*., 2007), nicotine ($EC_{50} \approx 20$ μM), icilin (-)-menthol (1–100 μM), thymol (1–100 μM), THC, 1,4-dihydropyridines
Blockers (IC_{50})	AP18 (3.1 μM, Petrus *et al*., 2007), HC030031 (6.2 μM, McNamara *et al*., 2007), ruthenium red (IC_{50} < 1–3 μM)
Functional characteristics	γ = 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 theromosensitive, 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 noxius 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 (Everaerts *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°C), capsaicin, resiniferatoxin, vanillotoxins, phenylaceytlrivanil, olvanil, anandamide, camphor, allicin, some eicosanoids (*e.g.*, 12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene B$_4$), NADA, 2-APB, DPBA, activated by NO-mediated cysteine S-nitrosylation	Probenecid, 2-APB (rodent, not human), DPBA, cannabidiol, THC
Blockers (IC$_{50}$)	Ruthenium red (0.09–0.22 μM), 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 μM), SKF96365, amiloride, TRIM, La^{3+}
Probes (K_D)	[^{3}H]-A778317 (3.4 nM), [^{3}H]-resiniferatoxin, [^{125}I]-resiniferatoxin	–
Functional characteristics	γ = 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^{2+}/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 ($V_{½}$ ~ ≈ +80 mV, reduced to more negative values following heat stimuli), heat (23°–39°C, temperature threshold reduces with repeated heat challenge)	Constitutively active, heat (> 24–32°C), mechanical stimuli
Chemical activators	6-tert-butyl-*m*-cresol, carvacrol, eugenol, thymol, camphor, menthol, incensole acetate, 2-APB, DPBA, NO-mediated cysteine S-nitrosylation	GSK1016790A (EC$_{50}$ = 2.1 nM, Thorneloe *et al.*, 2008), RN1747 (EC$_{50}$ = 0.77 μM, Vincent *et al.*, 2009), bisandrographolide A, 4α-PDH, 4α-PDD, PMA, epoxyeicosatrieonic acids, NO-mediated cysteine S-nitrosylation
Blockers	Ruthenium red (<1 μM), DPTHF (6–10 μM)	HC067047 (IC$_{50}$ = 17 nM, Everaerts *et al*, 2010b), RN1734 (IC$_{50}$ = 2.3 μM, Vincent *et al.*, 2009), ruthenium red (voltage dependent block), La^{3+}, Gd^{3+}
Functional characteristics	γ = 197 pS at = +40 to +80 mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification; potentiated by arachidonic acid	γ = ~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^{2+} *via* Ca^{2+}/calmodulin; inhibited by elevated intracellular Ca^{2+} *via* an unknown mechanism (IC$_{50}$ = 0.4 μM);

Activation of TRPV1 by depolarisation is strongly temperature-dependent *via* a channel opening rate that increases with increasing temperature. The $V_{½}$ 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 4α-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 epoxyeicosatrieonic 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^{2+})	Constitutively active (with strong buffering of intracellular Ca^{2+}), 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 μM), Cd^{2+}, Mg^{2+}, La^{3+}
Functional characteristics	γ = 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	γ = 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 mucolipidosis 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 (V*a*) 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	$TRPML1^{Va}$: Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	$TRPML2^{Va}$: Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	$TRPML3^{va}$: Constitutively active, current inhibited by extracellular acidification (equivalent to intralysosomal acidicification) Wild type TRPML3: Activated by Na^{+}-free extracellular (extracytosolic) solution and membrane depolarization, current inhibited by extracellular acidification (equivalent to intralysosomal acidicification)
Blockers	–	–	Gd^{3+}
Functional characteristics	$TRPML1^{Va}$: γ = 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 (*e.g.* Ca^{2+}, Fe^{2+}); inwardly rectifying	$TRPML1^{Va}$: Conducts Na^{+}; monovalent cation flux suppressed by divalent cations; inwardly rectifying	$TRPML3^{Va}$: γ = 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: γ = 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* $TRPML1^{Va}$, $TRPML2^{Va}$ and $TRPML3^{Va}$) 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 Köttgen, 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_{50})	Amiloride, La^{3+}, Gd^{3+}	Phenamil (0.14 μM), benzamil (1.1 μM), EIPA (10.5 μM), amiloride (143 μM), flufenamate, La^{3+}, Gd^{3+},
Functional characteristics	γ = 123–177 pS (with K^+ as charge carrier); P_{Na}/P_K = 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_{Ca}/P_{Na} = 4.0–4.3); steady state currents rectify outwardly, whereas instantaneous currents show strong inward rectification; activated and subsequently inactivated by intracellular Ca^{2+} (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^{2+}, Ba^{2+} and Sr^{2+} permeate TRPP3, but reduce inward currents carried by Na^+. Mg^{2+} 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-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2*H*)-carbox-amide; **BTP2**, 4-methy-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-((1S)-1-{[4-((2S)-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-7H-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-chloronaphtalene-1-sulphonyl)homopiperazine; **ML204**, structure not available; **NADA**, *N*-arachidonyl dopamine; **PMA**, phorbol 12 myristate 13-acetate; **Pyr3**, ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1H-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-amino-ethoxy)-3-methoxy-benzyl]-3-(4-*tert*-butyl-benzyl)-urea; **SKF96265**, 1-(β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl)-1H-imidazole hydrochloride; **THC**, Δ^9-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

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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.

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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, F, 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-erbα	NR1D1	EAR1, hRev	ENSG00000126368	Haem (Raghuram *et al*., 2007; Yin *et al*., 2007)	A synthetic agonist, GSK4112, has been described (Grant *et al*., 2010)
Rev-erbβ	NR1D2	EAR1β, RVR, BD73	ENSG00000174738	Haem (Raghuram *et al*., 2007; Yin *et al*., 2007)	A synthetic agonist, GSK4112, has been described (Grant *et al*., 2010)
HNF4α	NR2A1	Hepatocyte nuclear factor 4-α, MODY1, TCF14	ENSG00000101076	Linoleic acid (Yuan *et al*., 2009)	–
TR4	NR2C2	Testicular receptor 4, TAK1	ENSG00000177463	Retinol, retinoic acid (Zhou *et al*., 2011)	Forms a heterodimer with TR2 (Young *et al*., 1998)

Orphan nuclear receptors

Common nomenclature	Systematic nomenclature	Other names	Ensembl ID	Comments
HNF4γ	NR2A2	Hepatocyte nuclear factor 4-γ	ENSG00000164749	–
TR2	NR2C1	Testicular receptor 2	ENSG00000120798	Forms a heterodimer with TR4 (Young *et al*., 1998); gene disruption appears without effect on testicular development or function (Shyr *et al*., 2002))
TLX	NR2E1	Tailless homolog, TLL	ENSG00000112333	Gene disruption is associated with abnormal brain development (Monaghan *et al*., 1997; Land and Monaghan, 2003)
PNR	NR2E3	Photoreceptor-specific nuclear receptor, retina-specific nuclear receptor	ENSG00000031544	–
COUP-TFI	NR2F1	COUPα, EAR3, SVP44	ENSG00000175745	Gene disruption is perinatally lethal (Qiu *et al*., 1997)
COUP-TFII	NR2F2	COUPβ, ARP1, SVP40	ENSG00000185551	Gene disruption is embryonically lethal (Pereira *et al*., 1999)
EAR2	NR2F6	V-erb-related gene	ENSG00000160113	Gene disruption impairs CNS development (Warnecke *et al*., 2005)

Common nomenclature	Systematic nomenclature	Other names	Ensembl ID	Comments
ERRα	NR3B1	ESRL1, estrogen-related receptor α, estrogen receptor-like 1	ENSG00000173153	Activated by some dietary flavonoids (Suetsugi *et al.*, 2003); activated by the synthetic agonist GSK4716 (Zuercher *et al.*, 2005) and blocked by XCT790 (Willy *et al.*, 2004)
ERRβ	NR3B2	ESRL2, estrogen-related receptor β, estrogen receptor-like 2	ENSG00000119715	May be activated by DY131 (Yu and Forman, 2005)
ERRγ	NR3B3	ESRL3, estrogen-related receptor γ, estrogen receptor-like 3	ENSG00000196482	May be activated by DY131 (Yu and Forman, 2005)
Nur77	NR4A1	Nerve growth factor IB, NGFI-B, NAK1, ST59, TR3, HMR	ENSG00000123358	An exogenous agonist, cytosporone B, has been described (Zhan *et al.*, 2008), although structural analysis and molecular modelling has not identified a ligand binding site (Baker *et al.*, 2003; Flaig *et al.*, 2005; Wang *et al.*, 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 *et al.*, 2008) and SID7969543 (Madoux *et al.*, 2008)
LRH-1	NR5A2	Liver receptor homolog 1, α1-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-(diethylaminobenzylidenyl)-**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-[(1**E**)-[4-(1-methylethyl)phenyl]methylene]hydrazide; **SID7969543**, ethyl 2-[2-[2-(2,3-dihydro-1,4-benzodioxin-7-ylamino)-2-oxoethyl]-1-oxoisoquinolin-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

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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 (ENSF00000000720), 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	LXRα	LXRβ	FXRα	FXRβ
Systematic nomenclature	NR1H3	NR1H2	NR1H4	NR1H5
Other names	Oxysterols receptor α	Oxysterols receptor β, ubiquitously expressed nuclear receptor	Bile acid receptor	Lanosterol receptor
Ensembl ID	ENSG00000025434	ENSG00000131408	ENSG00000012504	ENSMUSG00000048938 (pseudogene in man)
Potency order	20*S*-OHC, 22*R*-OHC, 24*S*-OHC > 25-OHC, 27-OHC (Lehmann *et al*., 1997)	20*S*-OHC, 22*R*-OHC, 24*S*-OHC > 25-OHC, 27-OHC (Lehmann *et al*., 1997)	Chenodeoxycholate > lithocholate, deoxycholate (Makishima *et al*., 1999; Parks *et al*., 1999)	–
Selective agonists	–	–	ECDCA (Pellicciari *et al*., 2002), fexaramine (Downes *et al*., 2003), GW4064 (Maloney *et al*., 2000)	Lanosterol (Otte *et al*., 2003)
Selective antagonists	–	–	Guggulsterone (Urizar *et al*., 2002)	–

TO901317 (Repa *et al*., 2000) and GW3965 (Collins *et al*., 2002) are synthetic agonists acting at both LXRα and LXRβ with less than 10-fold selectivity.

Abbreviations: ECDCA, 6α-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

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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_2, 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_4. These receptors also bind hypolipidaemic drugs (PPARα) and anti-diabetic thiazolidinediones (PPARγ), 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	PPARα	PPARβ	PPARγ
Systematic nomenclature	NR1C1	NR1C2	NR1C3
Other names	–	PPARδ, 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 *et al*., 2002)	GSK0660 (Shearer *et al*., 2008)	GW9662 (Huang *et al*., 1999), CDDO-Me (Wang *et al*., 2000), diclofenac (6.2, Adamson *et al*., 2002), BADGE (4.0, Wright *et al*., 2000), T0070907 (Lee *et al*., 2002)

As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. Bishop-Bailey, 2000; Rocchi *et al*., 2001; Nakamuta *et al*., 2002). Agonists with mixed activity at PPARα and PPARγ 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-glyceryl-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**, (2*S*)-([2-benzoylphenyl]amino)-3-(4-[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}propoxyl]phenoxy)acetic acid; **Paz-PC**, 1-palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine; **T0070907**, 2-chloro-5-nitro-*N*-(4-pyridyl)benzamide; **WY14643**, *N*-(3-[2-quinolinylmethoxy]phenyl)-trifluoromethanesulphonamide

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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). [^{3}H]-ATRA and [^{3}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	RARα	RARβ	RARγ
Systematic nomenclature	NR1B1	NR1B2	NR1B3
Other names	–	HBV-activated protein	–
Ensembl ID	ENSG00000131759	ENSG00000077092	ENSG00000172819
Selective agonists	Ro406055 (Delescluse *et al*., 1991)	AC261066 (Lund *et al*., 2005), AC55649 (Lund *et al*., 2005)	AHPN (Martin *et al*., 1992)
Selective antagonists	Ro415253 (Apfel *et al*., 1992)	–	MM11253 (Le *et al*., 2000)

Ro415253 has been suggested to be a PPARγ agonist (Schupp *et al*., 2007). LE135 is an antagonist with selectivity for RARα and RARβ compared to RARγ (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	RXRα	RXRβ	RXRγ
Systematic nomenclature	NR2B1	NR2B2	NR2B3
Ensembl ID	ENSG00000078380	ENSG00000112472	ENSG00000143171
Selective agonists	CD3254 (Nahoum *et al*., 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 RORα may be synthesised with a 'captured' agonist such as cholesterol (Kallen *et al*., 2002; 2004).

Nomenclature	RORα	RORβ	RORγ
Systematic nomenclature	NR1F1	NR1F2	NR1F3
Other names	RZRα	RZRβ	RZRγ
Ensembl ID	ENSG00000069667	ENSG00000198963	ENSG00000143365
Selective agonists	Cholesterol sulfate, cholesterol, 7-OHC (Bitsch *et al*., 2003)	–	–

ATRA shows selectivity for RORβ within the ROR family (Stehlin-Gaon *et al*., 2003). RORα 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[3.3.1.13,7]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-5*H*-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

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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 (5α-dihydrotestosterone [DHT], aldosterone, cortisol, corticosterone, progesterone and testosterone). These receptors exist as dimers coupled with chaperone molecules (such as HSP90 [ENSG00000166598] and immunophilin FKBP52 [ENSG00000004478]), 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 AGAACAnnnTGTTCT (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 κB (NF-κB). 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 progestin 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 *et al.*, 1993)	Corticosterone, cortisol, aldosterone, progesterone (Rupprecht *et al.*, 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	[^{3}H]-Dexamethasone	[^{3}H]-Aldosterone	[^{3}H]-ORG2058	[^{3}H]-DHT, [^{3}H]-mibolerone, [^{3}H]-R1881

[^{3}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 insensibility syndromes, spinal and bulbar muscular atrophy (Kennedy's disease).

Nomenclature	Oestrogen α	Oestrogen β
Preferred abbreviation	ERα	ERβ
Systematic nomenclature	NR3A1	NR3A2
Other names	Estradiol	Estradiol
Ensembl ID	ENSG00000091831	ENSG00000140009
Selective agonists	PPT (Kraichely *et al.*, 2000; Stauffer *et al.*, 2000)	DPN (Meyers *et al.*, 2001), WAY200070 (Malamas *et al.*, 2004)
Selective antagonists	MPP (Sun *et al.*, 2002)	PHTPP (Compton *et al.*, 2004), *R,R*-THC (Meyers *et al.*, 1999; Sun *et al.*, 1999)

R,R-THC exhibits partial agonist activity at ERα (Meyers *et al.*, 1999; Sun *et al.*, 1999). Estrogen receptors may be blocked non-selectively by tamoxifen and raloxifene, and labelled by [^{3}H]-estradiol and [^{3}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 ERα-selective estrogen receptor modulator (Ning *et al.*, 2007).

Additional 'orphan' estrogen-receptor-related proteins have been described (ERRα ENSG00000173153; ERRβ ENSG00000119715; ERRγ ENSG00000057103); DY131 is an agonist with selectivity for ERRβ and ERRγ compared to ERRα, ERα and ERβ (Yu and Forman, 2005).

Abbreviations: **DHT**, 5α-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)-1*H*-pyrazole; **ORG2058**, 16-α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; **PPT**, 4,4′,4″-(4-propyl-[1*H*]-pyrazole-1,3,5-triyl)trisphenol; **PHTPP**, 4-(2-phenyl-5,7-bis[trifluoromethyl]pyrazolo[1,5-a]pyrimidin-3-yl)phenol ; **R1881**, 17β-hydroxy-17α-methyl-estra-4,9,11-triene-3-one, also known as methyltrienolone; ***r,r*-THC**, *R,R*-tetrahydrochrysene; **RU26988**, 11β,17β-dihydroxy-21-methyl-17α-pregna-1,4,6-trien-20-yl-3-on; **RU28318**, 3-oxo-7-

propyl-17-hydroxy-androstan-4-en-17-yl; **RU28362**, 11*β*,17*β*-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*β*-(4-acetylphenyl)-17*β*-hydroxyl-17*α*-(1-propinyl)-4,8-estradiene-3-one

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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	TRα	TRβ
Systematic nomenclature	NR1A1	NR1A2
Other names	THRA, erbAα, erbA1, EAR7	THRB, erbAβ, erbA2
Ensembl ID	ENSG00000126351	ENSG00000151090
Rank order of potency	T3 > T4	T3 > T4
Selective agonists	–	GC1 (Chiellini *et al.*, 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, TRα_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 TRβ (Nguyen *et al.*, 2002).

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

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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 NR1I 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	NR1I1	NR1I2	NR1I3
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_3, EB1089 (Colston *et al*., 1992)	5β-Pregnane-3,20-dione, estradiol (Jones *et al*., 2000), hyperforin (Wentworth *et al*., 2000), lovastatin (Lehmann *et al*., 1998), rifampicin (Blumberg *et al*., 1998; Lehmann *et al*., 1998)	TCPOBOP (Tzameli *et al*., 2000), CITCO (Maglich *et al*., 2003)
Selective antagonists	TEI9647 (Miura *et al*., 1999), ZK159222 (Herdick *et al*., 2000)	–	–

Abbreviations: CITCO, 6-(4-chlorophenyl)imidazo[2,1-**b**][1,3]thiazole-5-carbaldehyde-**O**-(3,4-dichlorobenzyl)oxime; **EB1089**, (1**R**,3**S**,5**Z**)-5-[(2**E**)-2-[(1**R**,3a**S**,7a**R**)-1-[(1**R**,2**E**,4**E**)-6-ethyl-6-hydroxy-1-methyl-2,4-octadien-1-yl]-octahydro-7α-methyl-4**H**-inden-4-ylidene]ethylidene]-4-methylene-1,3-cyclohexanediol, also known as seocalcitol; **TEI9647**, (23*s*)-25-dehydro-1α hydroxyvitamin D_3-26,23-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-methylidenecyclohexylidene]ethylidene]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-1-yl]-1-hydroxypent-2-enyl]cyclopropane-1-carboxylate

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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 it's 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-β 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-β 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, ENSFM00250000000777), 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 α or β chains, and a common γ chain (γ_c) (IL2RG, ENSG00000147168, also known as CD132, CIDX, IMD4, severe combined immunodeficiency, SCIDX1).

Nomenclature	Interleukin-2 α	Interleukin-2 β	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 α1	Interleukin-13 α2	Interleukin-15 α	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 γ_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 α subunit and a common β 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 α	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 α	Leptin	Leukemia inhibitory factor	Oncostatin-M specific β
HGNC nomenclature	CNTFR	LEPR	LIFR	OSMR
Ensembl ID	ENSG00000122756	ENSG00000116678	ENSG00000113594	ENSG00000145623
Other names	CNTFRα	CD295	CD118	OSMRβ
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 β-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 β1	Interleukin-12 β2	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	Eythropoietin	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), choriomammotropin (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 somatomammotropin hormone 2 (CSH2, ENSG00000213218), chorionic somatomammotropin 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-α/β 1	Interferon-α/β 2	Interferon-γ 1	Interferon-γ 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-α, IFN-β, IFN-ω, IFN-κ	IFN-α, IFN-β, IFN-ω, IFN-κ	IFN-γ	IFN-γ

Endogenous agonists in man include IFN-α (IFNA1, ENSG00000197919), IFN-β (IFNB1, ENSG00000171855), IFN-γ (IFNG, ENSG00000111537), IFN-κ (IFNK, ENSG00000147896) and IFN-ω (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 α	Interleukin-10 β	Interleukin-20 α	Interleukin-20 β
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 α1	Interleukin-22 α2	Interleukin-28 α
HGNC nomenclature	IL22RA1	IL22RA2	IL28RA
Ensembl ID	ENSG00000142677	ENSG00000164485	ENSG00000185436
Other names	CRF2-9, IL22R	IL22bP, CRF2-S1	CRF2/12, IFNLR, IL-28R1

Endogenous agonsits are IL-10 (ENSG00000136634), IL-19 (ENSG00000142224), IL-20 (ENSG00000162891), IL-22 (ENSG00000127318), IL-24 (ENSG00000162892), IL-28A (IL28A, ENSG00000183709, also known as IFN-λ2), IL-28B (IL28B, ENSG00000197110, also known as IFN-λ3), 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-1α, IL-1β	–	–	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 asAcPL, CD218b).

Endogenous agonists are IL-1α (IL1A, ENSG00000115008, also known as IL-1 or IL-1F1), IL-1β (ENSG00000125538, also known as IL-1F2) and IL-18 (ENSG00000150782, also known as IFN-γ-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 α	Interleukin 17 β	Interleukin 17 γ	Interleukin 17 δ	Interleukin 17 ε
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; **GMCSF**, granulocyte-macrophage colony-stimulating factor; **IFN**, interferon; **IL**, interleukin; **JAK**, Janus kinase; **LIF**, leukemia inhibitory factor; **OSM**, oncostatin-M; **PRL** prolactin; **Ro264550**, *N*-[[(3*R*)-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

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GDNF family

Overview: GDNF family receptors (ENSFM00500000269996) 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	GNDF family receptor α1	GNDF family receptor α2	GNDF family receptor α3	GNDF family receptor α4
Preferred abbreviation	**GFRα1**	**GFRα2**	**GFRα3**	**GFRα4**
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	[^{125}I]-GDNF (3-63 pM, Treanor *et al.*, 1996; Klein *et al.*, 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.

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Natriuretic peptide

Overview: Natriuretic peptide receptors are a family (ENSFM00250000000198) 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 $G_{i/o}$ family of G proteins to activation of phospholipase C, inwardly-rectifying potassium channels and inhibition of adenylyl cyclase activity (Murthy and Makhlouf, 1999).

Nomenclature	NPR-A	NPR-B	NPR-C	GC-C
Other names	NPR1, GC-A, ANP$_A$ receptor, ANPRA, GUCY2A	NPR2, GC-B, ANP$_B$ receptor, ANPRB, GUCY2B	NPR3, ANPRC, *npr3*, clearance receptor	STaR, GUCY2C
Ensembl ID	ENSG00000169418	ENSG00000159899	ENSG00000113389	ENSG00000070019
Potency order	ANP ≥ BNP >> CNP (Suga *et al.*, 1992)	CNP >> ANP >> BNP (Suga *et al.*, 1992)	ANP > CNP ≥ BNP (Suga *et al.*, 1992)	Uroguanylin > guanylin
Selective agonists	ANP, BNP, sANP (Olson *et al.*, 1996)	CNP (Suga *et al.*, 1992)	cANF$^{4–23}$ (Maack *et al.*, 1987), osteocrin (Moffatt *et al.*, 2007).	*E. coli* heat-stable enterotoxin (ST$_a$), linaclotide (Harris and Crowell, 2007)
Selective antagonists	A71915 (9.2–9.5, Delporte *et al.*, 1991), [Asu7,23′]-β-ANP$^{7–28}$ (7.5, Kambayashi *et al.*, 1989), anantin (Wyss *et al.*, 1991)	Monoclonal antibody 3G12 (Drewett *et al.*, 1995), [Ser^{11}](N-CNP,C-ANP)pBNP$^{2-25}$ (Deschenes *et al.*, 2005)	AP811 (9.3, Veale *et al.*, 2000), M372049 (Hobbs *et al.*, 2004)	–
Probes	[^{125}I]-ANP	[^{125}I]-CNP	[^{125}I]-ANP	[^{125}I]-ST$_a$

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^6,Cha^8]ANP$^{6–15}$-d-Tic-Arg-Cys-NH$_2$; **anantin**, cyclo(Gly-Phe-Ile-Gly-Trp-Gly-Asn-*β*-Asp)-Ile-Phe-Gly-His-Tyr-Ser-Gly-Asp-Phe; **AP811**, (s)-N^2-([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*-aminosuberic acid); **cANF$^{4–23}$**, des[Gln^{18},Ser^{19},Gly^{20},Leu^{21},Gly^{22}]ANP$^{4–23}$-NH$_2$; **HS142-1**, *Aureobasidium*-derived polysaccharide; **M372049**, see Chauhan *et al*. (2003) for structure; **sANP**, [G9T, R11S, G16R]ANP

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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 (ENSFM00250000004089). 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 *et al*., 1999; Yoshimura *et al*., 1999)
TLR3	CD283	ENSG00000164342	PolyIC (Alexopoulou *et al*., 2001)
TLR4	CD284, hToll, ARMD10	ENSG00000136869	LPS (Poltorak *et al*., 1998), taxol (Kawasaki *et al*., 2000)
TLR5	SLEB1, TIL3	ENSG00000187554	Flagellin (Hayashi *et al*., 2001)
TLR6	CD286	ENSG00000174130	–
TLR7	–	ENSG00000196664	R848 (Hemmi *et al*., 2002), imiquimod (Hemmi *et al*., 2002), loxoribine (Heil *et al*., 2003)
TLR8	–	ENSG00000101916	R848 (Hemmi *et al*., 2002), imiquimod
TLR9	CD289	ENSG00000173366	CpG (Hemmi *et al*., 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-κB 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 histocompatability 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 β (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:guanosine 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

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Receptor serine/threonine kinase (RSTK) family (EC 2.7.11.30)

Overview: receptor serine/threonine kinases (RTSK) respond to particular cytokines, the transforming growth factor β (TGFβ) 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 (ENSFM00250000000213) 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-IB, serine/threonine-protein kinase receptor R2, SKR2
ALK5	TGFBR1	ENSG00000106799	TGFβ 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-IC

The type II receptor serine/threonine kinases (ENSFM00500000269790).

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
Activin receptor 2A	ACVR2A	ENSG00000121989	ACTR-IIA
Activin receptor 2B	ACVR2B	ENSG00000114739	ACTR-IIB
Anti-Mullerian hormone receptor-II	AMHR2	ENSG00000135409	–
BMP receptor 2	BMPR2	ENSG00000204217	–
TGFβ receptor II	TGFBR2	ENSG00000163513	TGFβR-II
TGFβ receptor III	TGFBR3	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 TGFβ/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 α subunits linked to a variety of β chains, while activins are combinations of β subunits.

Binding of TGFβ family members generate complexes of TGFβ 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 α	INHA	ENSG00000123999	–
Inhibin βA	INHBA	ENSG00000122641	Activin βA, follicle-stimulating hormone-releasing protein, erythroid differentiation factor
Inhibin βB	INHBB	ENSG00000163083	Activin βB
Inhibin βC	INHBC	ENSG00000175189	–
Inhibin βE	INHBE	ENSG00000139269	Activin, MGC4638
Myostatin	MSTN	ENSG00000138379	Growth/differentiation 8, GDF8
TGFβ1	TGFB1	ENSG00000105329	–
TGFβ2	TGFB2	ENSG00000092969	Glioblastoma-derived T-cell suppressor factor, G-TSF, BSC-1 cell growth inhibitor, polyergin, cetermin
TGFβ3	TGFB3	ENSG00000119699	–

BMP1 is a member of the tolloid-like family (ENSFM00570000851071) of metalloproteinases and does not signal through these receptors.

TGFβ 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 TGFβ and BMP signalling concluded that TGFβ pathway inhibitors were more selective than BMP signalling inhibitors (Vogt *et al*., 2011). The authors confirmed the selectivity of SB505124 to inhibit TGFβ 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

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Receptor tyrosine kinases (E.C. 2.7.1.112)

Receptor tyrosine kinases (RTK)s 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-γ (see Page S302), mitogen-activated protein kinases (see Page S310) and phosphatidylinositol 3-kinase.

ErbB (epidermal growth factor) receptor family

Overview: ErbB family receptors (ENSFM00410000138465) 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, TGFα	NRG-1, NRG-2	Betacellulin, epiregulin, HB-EGF, NRG-1, NRG-2, NRG-3, NRG-4

[^{125}I]-EGF has been used to label the ErbB1 EGF receptor. The extracellular domain of ErbB2 can be targetted 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-α (TGFα, 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 (ENSG00000167244)	–

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	PDGFRα	PDGFRβ	KIT	CSF1R	FLT3
Ensembl ID	ENSG00000134853	ENSG00000113721	ENSG00000157404	ENSG00000182578	ENSG00000122025
Other names	Platelet-derived growth factor receptor α, CD140a, PDGFR2	Platelet-derived growth factor receptor β, 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 (fallotein, 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-CSF, CSF1, ENSG00000184371), CSF2 (granulocyte-macrophage CSF, GM-CSF, ENSG00000164400) and CSF3 (ENSG00000108342). FLT3L is the cognate ligand of FLT3 (ENSG00000090554).

5′-Fluoroindirubinoxime 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 (ENSFM0025000000009), 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 > FGF, FGF6 (Ornitz *et al*., 1996)	FGF1 > FGF4, FGF7 FGF9 > FGF2, FGF6 (Ornitz *et al*., 1996)	FGF1, FGF2, FGF9 > FGF4, FGF8 (Ornitz *et al*., 1996)	FGF1, FGF2, FGF4, FGF9 > FGF6, FGF8 (Ornitz *et al*., 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 (ENSFM00440000236870) 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 (ENSG00000019991, also known as hepapoietin A, scatter factor), 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 κB (NF-κB) 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^{trk}, high-affinity, slow-dissociating NGF receptor	gp145^{trkB}	gp145^{trkC}	p75^{NTR}, low-affinity neurotrophin receptor, NGFR
Endogenous ligands	NGF>NT3	BDNF, NT4/5>NT3	NT3	NGF, BDNF, NT3, NT4/5

[^{125}I]-NGF and [^{125}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 (ENSFM00250000000121) 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 (ENSFM00250000002014) are single TM proteins: EFNB1 (ENSG00000090776), EFNB2 (ENSG00000125266) and EFNB3 (ENSG00000108947).

TAM (or AXL) receptor family

Members of this RTK family (ENSFM00500000269872) 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	Brt, Dtk, RSE, Sky, Tif	c-mer proto-oncogene tyrosine kinase, mer, RP38
Endogenous ligands	Gas6 (Nagata *et al.*, 1996), protein S (Stitt *et al.*, 1995)	Gas6 (Nagata *et al.*, 1996), protein S (Stitt *et al.*, 1995)	Gas6 (Nagata *et al.*, 1996)

Gas6 (ENSG00000183087, also known as growth arrest specific protein 6, AXLLG, AXSF) and protein S α (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 (ENSFM00500000270379) 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 (ENSFM00420000140591) 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 (ENSFM00500000269808) 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 (ENSFM00260000050411) 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 (ENSFM00510000502747) 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-ylpropoxy)quinazolin-4-amine, 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**, α-cyano-(3,5-di-t-butyl-4-hydroxy)thiocinnamide

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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 2β, IA-2β, 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

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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 κB 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-κB, 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, $p75^{NTR}$, 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-α, 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, Tnfrsf1al2, 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*β*, lymphotoxin-*α*, LT*α*), TNFSF2 (ENSG00000204490, TNF, TNF*α*, cachectin, necrosin, cytotoxin, DIF), TNFSF3 (ENSG00000206327 TNFC, LTB, lymphotoxin-*β*, LT*β*), 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, ApoI L, 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 κB 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 (ENSF00000000597)

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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 *N*-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 *et al.*, 2011)
ABCA8	–	KIAA0822	ENSG00000141338	–
ABCA9	–	–	ENSG00000154258	–
ABCA10	–	–	ENSG00000154263	–
ABCA12	–	–	ENSG00000144452	Reported to play a role in skin ceramide formation (Zuo *et al.*, 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 *et al.* 2008)
ABCB6	MTABC3	Mitochondrial ABC transporter 3, ubiquitously expressed mammalian ABC half transporter, P-glycoprotein-related protein	ENSG00000115657	Mitochondrial porphyrin transporter (Krishnamurthy *et al.*, 2006)
ABCB7	ABC7	–	ENSG00000131269	Mitochondrial; reportedly essential for haematopoiesis (Pondarre *et al.*, 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 *et al.*, 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_4 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 *et al.*, 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 *et al.*, 2007); reported to export prostaglandins in a manner sensitive to NSAIDS (Reid *et al.*, 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 *et al.*, 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 (ENSG00000006071, 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^+ channels (K_{ir}6.1-6.2, see Page S158), conferring nucleotide sensitivity to these channels to generate the canonical K_{ATP} 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 *et al.*, 2008; 2011)
ABCD2	ALDR	Adrenoleukodystrophy- related protein, adrenoleukodystrophy-like 1	ENSG00000173208	Coenzyme A esters of very long chain unsaturated fatty acids (van Roermund *et al.*, 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 *et al.*, 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 *et al.*, 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-α-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

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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_1 or V_1) and a membrane complex (F_o or V_o). 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^+-transporting), is a mitochondrial membrane-associated multimeric complex consisting of two domains, an F_O channel domain in the membrane and an F_1 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_1 and F_0 motors,

The **F_1 motor**, responsible for ATP turnover, has the subunit composition α3β3γδε.

Nomenclature	HGNC nomenclature	Ensembl ID	Other names
α	ATP5A1; ATPAF2	ENSG00000152234; ENSG00000171953	ATP5A, ATP5AL2, ATPM, hATP1, OMR, ORM; ATP synthase mitochondrial F1 complex assembly factor 2, ATP12, Atp12p
β	ATP5B; ATPAF1	ENSG00000110955; ENSG00000123472	ATPSB; ATP synthase mitochondrial F1 complex assembly factor 1, ATP11, Atp11p, FLJ22351
γ	ATP5C1	ENSG00000165629	ATP5C, ATP5CL1
δ	ATP5D	ENSG00000099624	–
ε	ATP5E	ENSG00000124172	–

The **F_0 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_1 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	ATP61VE1	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_o 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

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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$^+$/K$^+$-ATPase (EC 3.6.3.9)

The cell-surface Na$^+$/K$^+$-ATPase is an integral membrane protein which regulates the membrane potential of the cell by maintaining gradients of Na$^+$ and K$^+$ 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 α subunits and one of three smaller single TM domain glycoprotein β-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
α1	ATP1A1	ENSG00000163399	Sodium/potassium-transporting ATPase subunit α-1, sodium pump subunit α-1, Na$^+$/K$^+$ ATPase α-1 subunit
α2	ATP1A2	ENSG00000018625	Sodium/potassium-transporting ATPase subunit α-1, sodium pump subunit α-1, Na$^+$/K$^+$ ATPase α-1 subunit
α3	ATP1A3	ENSG00000105409	Sodium/potassium-transporting ATPase subunit α-3, sodium pump subunit α-3, Na$^+$/K$^+$ ATPase α-3 subunit
α4	ATP1A4	ENSG00000132681	Sodium/potassium-transporting ATPase subunit α-4, sodium pump subunit α-4, Na$^+$/K$^+$ ATPase α-4 subunit
β1	ATP1B1	ENSG00000143153	Sodium/potassium-transporting ATPase subunit β-1
β2	ATP1B2	ENSG00000129244	Sodium/potassium-transporting ATPase subunit β-2
β3	ATP1B3	ENSG00000069849	Sodium/potassium-transporting ATPase subunit β-3, CD298 antigen

Na$^+$/K$^+$-ATPases are inhibited by ouabain and cardiac glycosides, such as digoxin, as well as potentially endogenous cardiotonic steroids (see Bagrov *et al*., 2009).

Ca^{2+}-ATPases (EC 3.6.3.8)

The sarcoplasmic/endoplasmic reticulum Ca^{2+}-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^{2+}-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^{2+} while SERCA transports 2 Ca^{2+}.

Secretory pathway 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 Ca^{2+} pump PMR1
SPCA2	ATP2C2	ENSG00000064270	ATPase 2C2, secretory pathway Ca^{2+}-ATPase 2

Loss-of-function mutations in SPCA1 appear to underlie Hailey-Hailey disease (Hu *et al*., 2000).

H^+/K^+-ATPase (EC 3.6.3.10)

The H^+/K^+ ATPase is a heterodimeric protein, made up of α and β subunits. The α subunit has 10 TM domains and exhibits catalytic and pore functions, while the β subunit has a single TM domain, which appears to be required for intracellular trafficking and stabilising the α subunit. The ATP4A and ATP4B subunits are expressed together, while the ATP12A subunit is suggested to be expressed with the β1 (ATP1B1) subunit of the Na^+/K^+-ATPase (Pestov *et al*., 2006).

Nomenclature	Ensembl ID	Other names
ATP4A	ENSG00000105675	Potassium-transporting ATPase α chain 1, gastric H^+/K^+-ATPase α subunit, ATP6A
ATP12A	ENSG00000075673	Potassium-transporting ATPase α chain 2, non-gastric H^+/K^+-ATPase α subunit, ATP1AL1
ATP4B	ENSG00000186009	Potassium-transporting ATPase β chain 1, gastric H^+/K^+-ATPase β subunit

The gastric H^+/K^+-ATPase is inhibited by (*R*)-lansoprazole and a metabolite of (*S*)-omeprazole.

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

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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.

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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; Palacín *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_{Ph}) 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^+/K^+-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 ß-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 though 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^- flux, activated by Na^+ and glutamate (Kanai and Hediger, 2003; Grewer and Rauen, 2005; Machtens *et al*., 2011) (Na^+ and aspartate in the case of Glt_{Ph}, 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-*threo*-β-hydroxyaspartate, L-*trans*-2,4-pyrolidine dicarboxylate	DL-*threo*-β-hydroxyaspartate, L-*trans*-2,4-pyrolidine dicarboxylate	DL-*threo*-β-hydroxyaspartate, L-*trans*-2,4-pyrolidine dicarboxylate
Inhibitors (K_B or K_i)	UCPH-101 (IC_{50} = 120 nM – membrane potential assay, Jensen *et al.*, 2009), DL-TBOA (9 μM)	WAY-213613 (IC_{50} = 130 nM), DL-TBOA (0.12 μM), (2*S*,4*R*)-4-methylglutamate (3.4 μM), dihydrokainate (9 μM), *Threo*-3-methylglutamate (18 μM)	NBI-59159 (IC_{50} = 25 nM), DL-TBOA (IC_{50} =8 μM), L-β-BA (IC_{50} =0.8 μM – [^{3}H]-D-aspartate uptake assay)
Probes	[^{3}H]-ETB-TBOA (K_D = 15.5 nM), [^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 16.2 nM), [^{3}H]-[(2*S*,4*R*)-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 *et al.*, 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-*threo*-β-hydroxyaspartate, L-*trans*-2,4-pyrolidine dicarboxylate	DL-*threo*-β-hydroxyaspartate, L-*trans*-2,4-pyrolidine dicarboxylate
Inhibitors (K_B or K_i)	DL-TBOA (4.4 μM), *Threo*-3-methylglutamate (50 μM)	DL-TBOA (3.2 μM)
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 μM; 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-β-*threo*-benzyl-aspartate (L-β-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 ($K_D \cong 6.0$ μM) 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 bistriata* 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*-β-hydroxyaspartate and L-*trans*-2,4-pyrolidine 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^0, 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-asparaginine >> L-methionine ≅ L-glycine ≅ L-leucine > L-valine > L-glutamate (enhanced at low pH)
Inhibitors	–	*p*-nitrophenyl glutamyl anilide (Esslinger *et al.*, 2005a), benzylserine, benzylcysteine (Grewer and Grabsch, 2004)
Predicted stoichiometry	1 Na$^+$: 1 amino acid (in): 1 Na$^+$: 1 amino acid (out); (homo-, or hetero-exchange; Zerangue and Kavanaugh, 1996b)	1 Na$^+$: 1 amino acid (in): 1 Na$^+$: 1 amino acid (out); (homo-, or hetero-exchange; Bröer *et al.*, 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, $HgCl_2$, methymercury, mersalyl, at low micromolar concentrations, non-competitively inhibit ASCT2 by covalent modification of cysteine residues (Oppedisano *et al.*, 2010).

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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 GLUTS5, 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 *et al.*, 2002), dehydroascorbic acid (Bianchi and Rose, 1986)	Glucosamine > glucose (Uldry *et al.*, 2002)	Glucose	Glucosamine ≥ glucose (Uldry *et al.*, 2002)	–
Probes	[^{3}H]-2-Deoxyglucose	[^{3}H]-2-Deoxyglucose	[^{3}H]-2-Deoxyglucose	[^{3}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 *et al.*, 1992)	Fructose, glucose (Cheeseman, 2008)	Fructose, uric acid (Caulfield *et al.*, 2008)	Glucose (Doege *et al.*, 2001), fructose (Manolescu *et al.*, 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 *et al.*, 2000)	Glucose, dehydroascorbic acid (Lee *et al.*, 2010)	Glucose (Rogers *et al.*, 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 *myo*-inositol cotransporter
Ensembl ID	ENSG00000151229
Other names	H^+-*myo*-inositol symporter
Substrates	*myo*-Inositol, *scyllo*-inositol, *chiro*-inositol, *muco*-inositol (Uldry *et al.*, 2002)
Stoichiometry	1 H^+: 1 inositol (in) (Di Daniel *et al.*, 2009)

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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	$B^{0,+}$-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^+), 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	ENSG00000013293
Other names	System Y^+ basic amino acid transporter, ecotropic retroviral leukemia receptor homolog, ERR, ATRC1	ATRC2	Cationic amino acid transporter y+	–	–
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+LAT1 or y+LAT2 generate sodium-dependent transporters, similar to the system y^+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 $B^{0,+}AT$ appear to mediate sodium-independent system $b^{0,+}$ 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+LAT1	y+LAT2	$B^{0,+}AT$
Nomenclature	L-type amino acid transporter 1	L-type amino acid transporter 2	y+L amino acid transporter 1	y+L amino acid transporter 2	$B^{0,+}$-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, y+ 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, y+ 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

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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 (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 Cl^-/HCO_3^- transporters (AE1, AE2 and AE3), the electrogenic sodium-dependent HCO_3^- transporters (NBCe1 and NBCe2) and the electroneutral 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^- (in) : 1 HCO_3^- (out)	1 Cl^- (in) : 1 HCO_3^- (out)	1 Cl^- (in) : 1 HCO_3^- (out)	–

Sodium-dependent HCO_3^- 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^+: 2/3 HCO_3^- (out) or 1 Na^+: CO_3^{2*} (out) or 1 $NaCO_3^-$ (out)	1 Na^+: 2/3 HCO_3^- (out) or 1 Na^+: CO_3^{2*} (out) or 1 $NaCO_3^-$ (out)	1 Na^+: 1 HCO_3^- (out) or 1 Na^+: CO_3^{2*} (out) or 1 $NaCO_3^-$ (out)	1 Na^+: 1 HCO_3^- (out) or 1 Na^+: CO_3^{2*} (out) or 1 $NaCO_3^-$ (out)

Systematic name	SLC4A8	SLC4A11
Common abbreviation	NDCBE	BTR1
Ensembl ID	ENSG00000050438	ENSG00000088836
Other names	Electroneutral Na^+-driven Cl-HCO_3 exchanger, k-NBC3	NaBC1, bicarbonate transporter-related protein 1
Endogenous substrates	Chloride, sodium bicarbonate	–
Stoichiometry	1 Na^+: 2HCO_3^- (in) : 1 Cl^- (out)	–

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SLC5 family of sodium-dependent transporters

Overview: The SLC5 family of sodium-dependent transporters includes, in mammals, the Na^+/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^+ cotransporters (*i.e.* Mhp1 and BetP), share a common structural core that contains an inverted repeat of 5TM α-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^+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 stoichimetry); modulated by extracellular Cl$^-$ (Iwamoto *et al.*, 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-deoxynojirimycin, miglitol, miglustat, N-ethyl-1-deoxynojirimycin, and 1-deoxynojirimycin-1-sulfonic acid	D-glucose, D-mannose	D-glucose, D-galactose
Synthetic substrates	αMDG	αMDG	–	αMDG	–
Inhibitors (pIC_{50})	Dapaglifozin (5.9), canaglifozin (6.4), empaglifozin (5.1), remogliflozin (pK_i = 5.4), sergliflozin (pK_i = 5.1)	Dapagliflozin (9.0), canaglifozin (8.7), empaglifozin (8.5) remogliflozin (pK_i = 7.9), sergliflozin (pK_i = 6.8)	–	–	–
Stoichiometry	2 Na$^+$: 1 glucose (Kanai *et al.*, 1994)	1 Na$^+$: 1 glucose (Hummel *et al.*, 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_3) and thyroxine (T_4) (Bizhanova and Kopp, 2009). NIS is also expressed in the salivary glands, gastric mucosa, intestinal enterocytes and lactating breast. NIS mediates I^- absorption in the intestine and I^- 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_5) 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 B3) 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 (Miyauchi *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^-, thiocyanate, nitrate	Pantothenic acid, biotin, lipoic acid, I^- (de Carvalho and Quick, 2011)	Butyrate, L-lactate, propionate, acetoacetate, α-ketoisocaproate, nicotinate, pyroglutamate, pyruvate, D-lactate, β-D-hydroxybutyrate, γ-hydroxybutyrate, β-L-hydroxybutryrate, acetate	Lactate, pyruvate, nicotinate
Synthetic substrates	Perchlorate, pertectnetate	–	Benzoate, salicylate, 5-aminosalicylate, 2-oxothiazolidine-4-carboxylate, dichloroacetate, 8-bromopyruvate	–
Inhibitors (pIC_{50})	–	–	Ibuprofen (4.2) , ketoprofen, fenoprofen	–
Stoichiometry	2 Na^+: 1 I^- (Eskandari *et al.*, 1997); 1 Na^+: 1 ClO_4^- (Dohan *et al.*, 2007)	2 Na^+: 1biotin (or pantothenic acid) (Prasad *et al.*, 2000)	2 Na^+: 1 monocarboxylate (Coady *et al.*, 2007)	–

I-, perchlorate, thiocyanate and nitrate are competitive substrate inhibitors of NIS (Dohan *et al*., 2007). α-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$^+$-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 *et al.*, 1995)	*Myo*-inositol = D-*chiro*-inositol> D-glucose > D-xylose > L-xylose (Coady *et al.*, 2002)
Inhibitors	Phlorizin	Phlorizin
Stoichiometry	2 Na$^+$:1 *myo*-inositol (Hager *et al.*, 1995)	2 Na$^+$:1 *myo*-inositol (Bourgeois *et al.*, 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; **αMDG**, α-methyl-D-glucose pyranoside

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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$_{Aa}$, a Na$^+$-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$^+$	Amphetamine, methamphetamine, MPP$^+$	*p*-Chloroamphetamine, MDMA
Selective inhibitors (pK_i)	Mazindol (8.9), nisoxetine (8.4), nomifensine (8.1), reboxetine (8.0, Wong *et al*., 2000)	Mazindol (8.0), WIN35428 (7.9), GBR12935 (7.6)	Paroxetine (9.6, Tatsumi *et al*., 1997), sertraline (9.1), fluoxetine (8.5, Tatsumi *et al*., 1997)
Probes	[^{3}H]-Mazindol (0.5 nM), [^{3}H]-nisoxetine (4 nM)	[^{3}H]-GBR12935 (3 nM, Pristupa *et al*., 1994), [^{3}H]-WIN35428 (10 nM, Pristupa *et al*., 1994)	[^{3}H]-Paroxetine (0.2 nM), [^{3}H]-citalopram (5 nM)
Predicted stoichiometry	1 Noradrenaline: 1 Na$^+$:1 Cl$^-$ (Gu *et al*., 1996)	1 Dopamine:1–2 Na$^+$:1 Cl$^-$ (Gu *et al*., 1994)	1 5-HT:1 Na$^+$:1 Cl$^-$ (in), + 1 K$^+$ (out) (Talvenheimo *et al*., 1983)

[^{125}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_i 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$_A$ 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 astocytic 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, β-alanine	GABA, β-alanine
Synthetic substrates	Nipecotic acid, guvacine	Nipecotic acid, guvacine	Nipecotic acid, guvacine
Selective inhibitors (IC$_{50}$)	NNC-711 (0.14–1.4 μM), SKF89976A (0.13 μM), CI-966 (0.26 μM), tiagabine (0.11 – 2.4 μM), (*R*/*S*) EF-1500 (2 – 13 μM) (*R*)-EF1502 (4 μM – 8.9 μM), LU32-176B (4 μM), (*S*)-EF-1502 (120 μM – > 250 μM)	SNAP-5114 (20 μM)	SNAP-5114 (6.6 μM)
Probes	[^{3}H]Tiagabine	–	–
Predicted stoichiometry	2 Na$^+$: 1Cl$^-$: 1GABA	2 Na$^+$: 1Cl$^-$:1GABA	≥2 Na$^+$: 2 Cl$^-$: 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, β-alanine, GABA (Anderson *et al*., 2009)	Creatine
Synthetic substrates	–	–	–
Selective inhibitors (IC$_{50}$)	NNC052090 (1.4 μM), (*R*)-EF-1502 (22 μM–180 μM), (*R*/*S*) EF-1500 (26 μM) (*S*)-EF-1502 (34 μM – > 250 μM), LU32-176B (>100 μM)		–
Predicted stoichiometry	3 Na$^+$: 1 (or 2) Cl$^-$: 1 GABA	2 Na$^+$: 1Cl$^-$: 1 taurine	Probably 2 Na$^+$: 1Cl$^-$: 1 creatine

The IC$_{50}$ 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$_{50}$ values for the human orthologue (Kvist *et al.* 2009). SNAP-5114 is only weakly selective for GAT2 and GAT3, with IC$_{50}$ values in the range 22 to >30 μM 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$_{50}$ = 26–46 μM; Dhar *et al*., 1994). Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine that potently inhibit the uptake of [^{3}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^{2+} (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 (Dodd and Christie, 2007). Although inhibitors of creatine transport by CT1 (*e.g.* β-guanidinopropionic acid, cyclocreatine, γ-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^{0+} (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^{0+} 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$^{0,+}$	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$^{0,+}$	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), β-alanine (Anderson *et al.*, 2008, 2009)	L-Proline
Synthetic substrates	–	–	BCH , 1-methytryptophan (Karunakaran *et al.*, 2008), valganciclovir (Umapathy *et al.*, 2004), zwitterionic or cationic NOS inhibitors (Hatanaka *et al.*, 2001)	–
Selective inhibitors (IC$_{50}$)	(*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)	α-methyltryptophan (250 μM, Karunakaran *et al.*, 2008)	LP-403812 (0.11 μM, Yu *et al.*, 2009)
Probes (K_d)	$[^3H]$-(*R*)-NPTS (1 nM), $[^3H]$-GSK931145 (1.7 nM), $[^{35}S]$-ACPPB (2 nM), $[^3H]$-SB-733993 (2.2 nM), $[^3H]$-*N*-methyl-SSR504734 (3.3 -8.1 nM), $[^3H]$-NFPS (7-21 nM)	–	–	–
Predicted stoichiometry	2 Na$^+$: 1 Cl$^-$: 1 glycine	3 Na$^+$: 1 Cl$^-$: 1 glycine	2-3 Na$^+$: 1 Cl$^-$: 1 amino acid (Sloan and Mager, 1999)	Probably 2 Na$^+$: 1 Cl$^-$: 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$_{50}$ 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$_{50}$ 92 μM) 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$_{50}$ ~ 2 μM) and potentiating (EC$_{50}$ ~ 13 μM) transport currents, respectively (Pearlman *et al.*, 2003). *N*-arachidonyl-glycine, *N*-arachidonyl-γ-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^{2+} (Ju *et al.*, 2004) act as non-competitive inhibitors of GlyT1b, with IC$_{50}$ values of ~100 nM and ~10 μM 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$^+$) (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^{0}AT1 (SLC6A19), SLC6A17, SLC6A18, SLC6A20). Others may function as transporters for neurotransmitters or their precursors (*i.e.* B^{0}AT2, SLC6A17) (Bröer, 2008).

Common abbreviation	B^{0}AT1	B^{o}AT2	B^{0}AT3
Systematic name	SLC6A19	SLC6A15	SLC6A18
Other names	B^0 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 *et al.*, 2006)	Pro > ala, val, met, leu > iso, thr, asn, ser, phe > gly (Bröer *et al.*, 2006)	Ala, gly > met, phe, leu, his, gln (Vanslambrouck *et al.* 2010)
Predicted stoichiometry	1 Na: 1 amino acid (Böhmer *et al.*, 2005)	1 Na: 1 amino acid (Bröer *et al.*, 2006)	Na$^+$- and Cl$^-$ -dependent transport (Singer *et al.*, 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$^+$-dependent, Cl$^-$-indpendent transport (Zaia and Reimer, 2009)	2 Na$^+$: 1 Cl$^-$: 1 imino acid (Bröer *et al.*, 2009)

Mutations in B^{0}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-flurophenyl]methyl-L-serine; **ALX 1405**, structure not available; **BCH**, 2-aminobicyclo-[2.2.1]-heptane-2-carboxylic acid; **CI966**, [1-[2-[bis-4(trifluromethyl)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,tetrabenzo[*d*]isoxazol-3-ol; **EGYT3886**, (-)-2-phenyl-2-[(dimethylamino)ethoxy]-(1*R*)-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-methylenedioxymethamphetamine; **MPP$^+$**, 1-methyl-4-phenylpyridinium; **NFPS**, N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine; **NNC052090**, 1-(3-(9*H*-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-triflouromethyl)phenoxy]-3-phenylpropylglycine; **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; **RTI55**, 2*β*-carbomethoxy-3*β*-(4-iodophenyl) tropane (also known as *β*-CIT); **SB-733993**, (2*R*)-3-[(2*R*,6*S*)-2,6-dimethylpiperidin-1-yl]-2-hydroxy-S-(naphthalen-1-yl)propane-1-sulfonamido; **SKF89976A**, 1-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid; **SSR103800**, structure not available; **SSR504734**, 2-chloro-[*N*-(*S*)-phenyl[(2*S*)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide; **WIN35428**, 2*β*-carboxymethy-3*β*-(4-fluorophenyl)tropane (also known as *β*-CFT).

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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^{2+}-ATPase (PMCA, see Page S219) and sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA, see Page S219), as well as the sodium/potassium/calcium exchangers (NKCX, 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^+ (in) : 1 Ca^{2+} (out) or 4 Na^+ (in) : 1 Ca^{2+} (out) (Dong *et al*., 2002) Reverse mode 1 Ca^{2+} (in): 1 Na^+ (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]ethylcarbamimidothioate; **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

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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^+ (in) : 1 H^+ (out). Several isoforms, NHE6, NHE7, NHE8 and NHE9 appear to locate on intracellular membranes (Miyazaki *et al*., 2001; Numata and Orlowski, 2001;

Nakamura *et al.*, 2005). Li^+ and NH_4^+, but not K^+, 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^+/H^+ 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^+/H^+ 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^+ 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

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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$^+$/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 *et al*., 1997) Thyroid hormone (Friesema *et al*., 1999; Visser *et al*., 2010)	GDCA > GUDCA, GCDA > TCA > CA (Craddock *et al*., 1998)	Estrone-3-sulphate, DHEAS (Geyer *et al*., 2004), TLCA, PREGS (Geyer *et al*., 2007)
Inhibitors	Cyclosporin, propranolol (Kim *et al*., 1999)	–	–
Probes	Chenodeoxycholyl-N^{ε}-nitrobenzoxadiazol-lysine (Weinman *et al*., 1998)	[^{3}H]-Taurocholate (Craddock *et al*., 1998)	–
Stoichiometry	2 Na$^+$: 1 bile acid (Hagenbuch and Meier, 1996; Weinman, 1997)	>1 Na$^+$: 1 bile acid (Craddock *et al*., 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**, glycochenodeoxycholic acid; **GDCA**, glycodeoxycholic acid; **GUDCA**, glycoursodeoxycholate; **PREGS**, pregnenolone sulphate; **TCA**, taurocholic acid; **TCDCA**, taurochenodeoxycholate; **TLCA**, taurolithocholic acid; **TUDA**, tauroursodeoxycholic acid

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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 it's 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^{2+}, Fe^{2+}	Fe^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Mn^{2+}
Stoichiometry	1 H^+ : 1 Fe^{2+} (out) or 1 Fe^{2+} (in); 1 H^+ (out)	1 H^+ : 1 Fe^{2+} (out) (Gunshin *et al.*, 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.

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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 *et al.*, 2002)	Bumetanide, piretanide, frusemide (Hannaert *et al.*, 2002)	Hydrochlorothiazide, chlorothiazide, metolazone
Stoichiometry	1 Na^+ : 1 K^+ : 2 Cl^- (in)	1 Na^+ : 1 K^+ : 2 Cl^- (in)	1 Na^+ : 1 Cl^- (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 *et al.*, 2009), DIOA	DIOA	DIOA
Stoichiometry	1 K^+ : 1 Cl^- (out)	1 K^+ : 1 Cl^- (out)	1 K^+ : 1 Cl^- (out)	1 K^+ : 1 Cl^- (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 *et al.*, 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

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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^+/sulfate cotransporter	Na^+/dicarboxylate cotransporter 1	Na^+/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^+ : 1 SO_4^{2-} (in)	3 Na^+ : 1 dicarboxylate^{2-} (in)	Unknown

Systematic name	SLC13A4	SLC13A5
Preferred abbreviation	NaS2	NaC2
Nomenclature	Na^+/sulfate cotransporter	Na^+/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^+ : SO_4^{2-} (in)	Unknown

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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 it's 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 TM5/6, 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 *et al*., 2007)	Urea (Maciver *et al*., 2008)
Synthetic substrates	Acetamide, methylurea, methylformamide, acrylamide (Zhao *et al*., 2007)	–
Stoichiometry	Equilibrative	Equilibrative

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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$_{So}$ (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	ENSG00000088386	ENSG00000163406	ENSG00000110446	ENSG00000139370
Other names	Intestinal H$^+$/peptide cotransporter, low affinity peptide transporter	Kidney H$^+$/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 *et al*., 1998)	Dipeptides, tripeptides, 5-aminolevulinic acid	Dipeptides, tripeptides, histidine, carnosine	Dipeptides, tripeptides, histidine, carnosine
Synthetic substrates	Cyclacillin, cefadroxil (Ganapathy *et al*., 1995), enalapril, captopril (Temple and Boyd, 1998), muramyl dipeptide (Vavricka *et al*., 2004), fMLP (Merlin *et al*., 1998)	Cyclacillin, cefadroxil (Ganapathy *et al*., 1995)	–	Valacyclovir (Bhardwaj *et al*., 2006)
Inhibitors	Lys[Z(NO$_2$)]-Pro (Knutter *et al*., 2001), 4-AMBA (Darcel *et al*., 2005)	Lys[Z(NO$_2$)]-Pro, Lys[Z(NO$_2$)]-Lys[Z(NO$_2$)] (Theis *et al*., 2002; Biegel *et al*., 2006)		
Probes	[^{3}H]-, [^{11}C]- or [^{14}C]-GlySar	[^{3}H]-, [^{11}C]- or [^{14}C]-GlySar	[^{3}H]-or [^{14}C]-Histidine	[^{3}H]-or [^{14}C]-Histidine
Stoichiometry	2 H$^+$: 1 zwitterionic peptide (in)	2 H$^+$: 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), sulpiride (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$^{\varepsilon}$-7-amino-4-methyl-coumarin-3-acetic acid; **4-AMBA**, 4-(aminomethyl)benzoic acid; fMLP, formyl-Met-Leu-Phe

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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 *et al.*, 2006)	–	–	–
Stoichiometry	1 H^+ : 1 monocarboxylate$^-$ (out)	1 H^+ : 1 monocarboxylate$^-$ (out)	1 H^+ : 1 monocarboxylate$^-$ (out)	1 H^+ : 1 monocarboxylate$^-$ (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 *et al.*, 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

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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 *et al.*, 2010)	–	–	–
Synthetic substrates	Probenecid, penicillin (Busch *et al.*, 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 *et al.*, 2011)
Stoichiometry	1 H^+ : 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^+-dependent inorganic phosphate cotransporter, BNPI	Differentiation-associated Na^+-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 *et al.*, 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

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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), SVMT, VAT2	(VAChT)
Ensembl ID	ENSG00000036565	ENSG00000165646	ENSG00000187714
Endogenous substrates (pK_M/p*Ki*)	5-HT (5.8) , dopamine (5.4), adrenaline (5.3), noradrenaline (4.9), histamine (2.3) (Erickson *et al.*, 1996)	5-HT (6.0), dopamine (5.9), adrenaline (5.7), noradrenaline (5.5), histamine (3.8) (Erickson *et al.*, 1996)	Acetylcholine (3.1), choline (2.3) (Bravo *et al.*, 2004; Khare *et al.*, 2010)
Synthetic substrates (pK_M/p*Ki*)	Fenfluramine (5.5), MDMA (4.7), D-am-phetamine (4.3), MPP$^+$ (4.2), phenyl-ethylamine (4.5) (Erickson *et al.*, 1996)	D-amphetamine (5.7), phenyethylamine (5.4), fenfluramine (5.3), MDMA (5.2), MPP$^+$ (5.1) (Erickson *et al.*, 1996)	TPP$^+$, N-methyl-pyridinium-2-aldoxime, N-(4′-pentanonyl)-4-(4″-dimethylamino-styryl)pyridinium, ethididium (Bravo *et al.*, 2005)
Inhibitors (pK_i)	Reserpine (7.45), ketanserin (5.8), TBZ (>4.7) (Erickson *et al.*, 1996)	Reserpine (7.9), TBZ (7.0), ketanserin (6.3) (Erickson *et al.*, 1996)	Vesamicol (8.7), aminobenzovesamicol (10.9), (Efange *et al.*, 1995)
Probes (K_d)		[^{3}H]-TBZOH (6.6 nM, Varoqui and Erickson, 1996), [^{125}I]-iodovinyl-TBZ (8.2 nM, Kung *et al.*, 1994); [^{125}I]-8-azido-3-iodoketanserine (photoaffinity ligand), [^{11}C]-DTBZ (PET ligand)	[^{3}H]-vesamicol (4.1 nM, Varoqui and Erickson, 1996), [^{123}I]-iodobenzovesamicol (SPECT ligand)
Stoichiometry	1 amine (in): 2H$^+$ (out)	1 amine (in): 2H$^+$ (out)	1 amine (in): 2H$^+$ (out)

p*Ki* values for endogenous and synthetic substrate inhibitors of human VMAT1 and VMAT2 are for inhibition of [^{3}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, dihydrotetrabenazine; **MDMA**, 3,4-methylenedioxymethamphetamine; **MPP$^+$**, 1-methyl-4-phenylpyridinium; **TBZ**, tetrabenazine; **TBZOH**, α-[O-methyl-^{3}H]dihydrotetrabenazine; **TPP$^+$**, tetraphenylphosphonium

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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^5-methylfolate, folate (Prasad *et al*., 1995), thiamine monophosphate (Zhao *et al*., 2002)	Thiamine	Thiamine
Synthetic substrates	Methotrexate, folinic acid	–	–
Probes	$[^3H]$-Folate, $[^3H]$-methotrexate (Assaraf *et al*., 1998)	$[^3H]$-Thiamine (Dutta *et al*., 1999)	$[^3H]$-Thiamine (Rajgopal *et al*., 2001)
Stoichiometry	1 Folate (in) : 1 OH^- (out)	1 Thiamine (in) : 1 H^+ (out)	1 Thiamine (in) : 1 H^+ (out)

Loss-of-function mutations in ThTr1 underlie thiamine-responsive megaloblastic anemia syndrome (Diaz *et al*., 1999).

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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 *et al.*, 2007)	Phosphate (Ravera *et al.*, 2007)
Stoichiometry	>1 Na^+ : 1 HPO_4^{2-} (in)	>1 Na^+ : 1 HPO_4^{2-} (in)

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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 zwiterrion/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^+-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_2, $PGF_{2\alpha}$	Dopamine, histamine (Grundemann *et al.*, 1999), PGE_2 (Kimura *et al.*, 2002)	5HT, noradrenaline, dopamine (Zhu *et al.*, 2010)
Synthetic substrates	TEA, MPP, desipramine, acyclovir, metformin	MPP, TEA, d-tubocurarine, pancuronium (Gorboulev *et al.*, 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_2, non-steroidal anti-inflammatory drugs	PAH, ochratoxin A, estrone sulphate, cimetidine (Kusuhara *et al.*, 1999)	–	Ochratoxin A (Youngblood and Sweet, 2004))	Estrone sulphate, dehydroepiandrosterone sulphate, ochratoxin A (Cha *et al.*, 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 *et al.*, 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

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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^+/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 *et al.*, 1999)	L-Ascorbic acid > D-ascorbic acid > dehydroascorbic acid (Tsukaguchi *et al.*, 1999)	–	Uracil > thymine > guanine, hypoxanthine > xanthine, uridine (Yamamoto *et al.*, 2010)
Synthetic substrates	–	–	–	5-Fluorouracil (Yamamoto *et al.*, 2010)
Inhibitors	Phloretin (Tsukaguchi *et al.*, 1999)	–	–	
Probes	[^{14}C]-Ascorbic acid	[^{14}C]-Ascorbic acid	–	
Stoichiometry	2 Na^+: 1 ascorbic acid (in) (Tsukaguchi *et al.*, 1999)	2 Na^+: 1 ascorbic acid (in) (Tsukaguchi *et al.*, 1999)	–	1 Na^+ : 1 uracil (in) (Yamamoto *et al.*, 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.

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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^+:(1Ca^{2+} + 1K^+)	–	–

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.

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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 facititates 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^{2-} (in) : H-citrate^{2-} (out)	PO_3^{4-} (in) : malate^{2-} (out)	Malate^{2-} (in) : oxoglutarate^{2-} (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, cysteinesulphinate	Aspartate, glutamate, cysteinesulphinate	Glutamate	Oxoadipate, oxoglutarate	Glutamate
Stoichiometry	Aspartate : glutamate H^+ (bidirectional)	Aspartate : glutamate H^+ (bidirectional)	Glutamate : H^+ (bidirectional)	Oxoadipate (in) : oxoglutarate (out)	Glutamate : H^+ (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 *et al.*, 2003)	L-Ornithine, L-citrulline, L-lysine, L-arginine (Fiermonte *et al.*, 2003)
Stoichiometry	1 Ornithine (in) :1 citrulline : 1 H$^+$ (out)	1 Ornithine (in) :1 citrulline : 1 H$^+$ (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$_3^{4-}$ (in) : OH$^-$ (out) or PO$_3^{4-}$: H$^+$ (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^{3-} (in) : ATP^{4-} (out)	ADP^{3-} (in) : ATP^{4-} (out)	ADP^{3-} (in) : ATP^{4-} (out)	ADP^{3-} (in) : ATP^{4-} (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$^+$ (in)	H$^+$ (in)	H$^+$ (in)	H$^+$ (in)	H$^+$ (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 *et al.*, 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, bongkrekic acid; **CATR**, carboxyatractyloside; **PEP**, phosphonenolpyruvate

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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_4^{2-}, oxalate^{2-}	SO_4^{2-}
Stoichiometry	SO_4^{2-} (in) : anion (out)	1 SO_4^{2-} (in) : 2 Cl^- (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^-	Cl^-, I^-, OH^-, HCO_3^-, $HCOO^-$	SO_4^{2-}, oxalate^{2-}, Cl^-, I^-, OH^-, HCO_3^-, $HCOO^-$
Stoichiometry	2 Cl^- (in) : 1 HCO_3^- (out) or 2 Cl^- (in) : 1 OH^- (out)	Unknown	1 SO_4^{2-} (in) : 2 HCO_3^- (out) or 1 Cl^- (in) : 2 HCO_3^- (out)

Anion channels

Systematic name	SLC26A7	SLC26A9
Ensembl ID	ENSG00000147606	ENSG00000174502
Ion selectivity	$NO_3^- >> Cl^- = Br^- = I^- > SO_4^{2-} = Glu^-$	$I^- > Br^- > NO_3^- > Cl^- > Glu^-$
Functional characteristics	Voltage- and time-independent current, linear I-V relationship (Kim *et al.*, 2005)	Voltage- and time-independent current, linear I-V relationship (Dorwart *et al.*, 2007)

SLC26A9 has been suggested to operate in two additional modes as a Cl^--HCO_3^- exchanger and as a Na^+-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^-, HCO_3^-	SO_4^{2-}, oxalate^{2-}, Cl^-		HSO_4^-
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.

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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 *et al*., 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 *et al*., 1999); C16:0, C18:1 > C18:3 > C8 (Gimeno *et al*., 2003)		C16:0 > C18:1 > C18:3 > C8 (Gimeno *et al*., 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**, γ-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

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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/*cit*, concentrative nucleoside transporter 1	N1/*cif*, SPNT, concentrative nucleoside transporter 2	N3/*cib*, 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^+ : 1 nucleoside (in)	1 Na^+ : 1 nucleoside (in)	2 Na^+ : 1 nucleoside (in)

A further two Na^+-dependent (stoichiometry 1 Na^+ : 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/*csg*, 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	*es*, NBTI-sensitive	*ei*, NBTI-insensitive	-	Equilibrative nucleoside transporter 4
Endogenous substrates	Adenosine, guanosine, inosine, uridine, thymidine, cytidine, hypoxanthine, adenine, thymine (Yao *et al.*, 2011)	Adenosine, guanosine, inosine, uridine, thymidine, hypoxanthine	Adenosine, inosine, > guanosine, thymidine, uridine, adenine (Baldwin *et al.*, 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 *et al.*, 2005)	MPP$^+$ > 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	$[^{3}H]$-NBTI (0.5 nM), $[^{14}C]$-adenosine	$[^{14}C]$-Adenosine	$[^{14}C]$-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$^+$**, 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*)-quinazolinedione hydrochloride

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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.

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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).

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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 (ΔpH) and electrical (Δψ) components of the proton electrochemical gradient ($\Delta\mu_{\text{H}}+$) established by a vacuolar H^+-ATPase (McIntire *et al*., 1997). However, Juge *et al*. (2009) have presented evidence that VIAAT is instead a Cl^-/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 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 *et al*., 1997), glycine, β-alanine, γ-hydroxybutyrate
Synthetic substrates	–
Inhibitors (IC_{50})	Vigabatrin (7.5 mM; McIntire *et al*., 1997)
Probes	–
Stoichiometry	1 amino acid (in): 1 H^+ (out) (Gasnier, 2004) or 1 amino acid: 2Cl^- (in) (Juge *et al*., 2009)

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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	[^{14}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]methoxy-hydroxyphosphoryl][(3R)-3-hydroxy-2,2-dimethyl-4-oxo-4-[[3-oxo-3-(2-sulfanylethylamino)propyl]amino]butyl]hydrogen phosphate.

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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 NaPiIIc 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^+ : 1 HPO_4^{2-} (in) (Forster *et al.*, 1999)	3 Na^+ : 1 HPO_4^{2-} (in) (Andrini *et al.*, 2008)	2 Na^+ : 1 HPO_4^{2-} (in) (Andrini *et al.*, 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

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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, swopping 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 *et al.*, 1998)	UDP-galactose, UDP-N-acetylglucosamine (Ishida *et al.*, 1996; Miura *et al.*, 1996)	UDP-N-acetylglucosamine (Ishida *et al.*, 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 *et al.*, 2003)	PAPS (Kamiyama *et al.*, 2006)	UDP-xylose, UDP-N-acetylglucosamine (Ashikov *et al.*, 2005)

Systematic name	SLC35C1	SLC35C2
Nomenclature	GDP-Fucose transporter	–
Ensembl ID	ENSG00000181830	ENSG00000080189
Other names	FUCT1	–
Substrates	GDP-fucose (Luhn *et al.*, 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 *et al.*, 2001)	UDP-N-acetylgalactosamine (Ishida *et al.*, 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

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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, *trans*-4-hydroxy-proline, betaine, 5-aminolevulinic acid, β-guanidinopropionic acid	Glycine, proline, alanine, sarcosine, *trans*-4-hydroxy-proline	–	Proline, tryptophan (Pillai and Meredith, 2011)
Synthetic substrates	MeAIB (Chen *et al*., 2003a), vigabatrin, THPO, gaboxadol (Larsen *et al*., 2009)	MeAIB (Chen *et al*., 2003b)	–	–
Inhibitors	L-Tryptophan, tryptamine, 5-hydroxy-L-tryptophan, serotonin, indole-3-propionic acid (Metzner *et al*., 2005)	5-Hydroxy-L-tryptophan, α-methyl-D,L-tryptophan (Edwards *et al*., 2011)	–	–
Probes	[^{3}H] or [^{14}C] substrates as listed above	[^{3}H] or [^{14}C] substrates as listed above	–	–
Stoichiometry	1 H^{+} : 1 amino acid (in)	1 H^{+} : 1 amino acid (in)	Unknown	Unknown

Both PAT1 and PAT2 can also function as an electroneutral transport system for H^+ 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, α- or 2-(methylamino)isobutyric acid; **THPO**, 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol

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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, cI2	–	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).

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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 *et al.*, 2001)	Ala, Met > Asn, Gln, Ser, Pro, Gly > Thr, Leu, Phe (Hatanaka *et al.*, 2000)	His > Arg, Ala, Asn, Lys > Gly, Gln, Ser, Pro, Leu, Phe (Hatanaka *et al.*, 2001)
Synthetic substrates	MeAIB	MeAIB	MeAIB
Probes	[^{3}H] or [^{14}C]-Alanine	[^{3}H] or [^{14}C]-Alanine	[^{3}H] or [^{14}C]-Alanine, [^{3}H] or [^{14}C]-glycine
Stoichiometry	1 Na$^+$: 1 amino acid (in) (Albers *et al.*, 2001)	1 Na$^+$: 1 amino acid (in) (Hatanaka *et al.*, 2000)	1 Na$^+$: 1 neutral amino acid (in) (Hatanaka *et al.*, 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 *et al.*, 2000)	Asn, Ser, His, Gln > Gly, Ala (Nakanishi *et al.*, 2001)
Synthetic substrates	MeAIB	–
Probes	[^{3}H] or [^{14}C]-Glutamine	[^{3}H] or [^{14}C]-Histidine
Stoichiometry	1 Na$^+$: 1 amino acid (in) : 1 H$^+$ (out) Broer *et al.*, 2002)	1 Na$^+$: 1 amino acid (in) : 1 H$^+$ (out) (Nakanishi *et al.*, 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

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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	ENSG00000029364	ENSG00000196950
Other names	LIV1	HKE4	BIGM103	–	KIAA1265
Other substrates	–	–	Cadmium (Dalton *et al*., 2005, Liu *et al*., 2008)	–	–
Stoichiometry	–	–	1 Zn^{2+} (in) : 2 HCO_3^- (in) (Liu *et al*., 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 *et al.*, 2006), cadmium, manganese (Girijashanker *et al.*, 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

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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^{2+}
Stoichiometry	Unknown

Hepcidin (HAMP, ENSG00000105697), a small protein that increases upon inflammation, binds to ferroportin to regulate it's 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).

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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^{2+} 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^{2+}, Sr^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+}, Ba^{2+}, Cd^{2+} (Goytain and Quamme, 2005a)	Mg^{2+}, Ba^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+} (Goytain and Quamme, 2005b)	–
Stoichiometry	Unknown	Unknown	Unknown

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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 RhBG 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_3 (Ripoche *et al.*, 2004), NH_4^+ (Westhoff *et al.*, 2002), CO_2 (Endeward *et al.*, 2008)		NH_3 (Zidi-Yahiaoui *et al.*, 2009)
Probes	[^{14}C]-Methylamine	–	[^{14}C]-Methylamine
Stoichiometry	Unknown	Unknown	Unknown

RhBG is a possible pseudogene in man.

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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^+ and Cl^- 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).

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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^+-independent transport of choline with an affinity that is intermediate to that of the high affinity choline tranporter 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_i)	HC-3 (4.5–5.3)	–	–	–	–
Stoichiometry	Unknown: uptake enhanced in the absence of extracellular Na^+, reduced by membrane depolarization, extracellular acidification and collapse of plasma membrane H^+ 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

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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

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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^+ or K^+ 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 *et al.*, 2007)	–	–
Synthetic substrates	Methotrexate (Qiu *et al.*, 2006), folinic acid (Nakai *et al.*, 2007)	–	–
Inhibitors	Sulfasalazine (60 μM, Qiu *et al.*, 2006), indomethacin (~200 μM, Qiu *et al.*, 2006)	–	–
Probes	[^{3}H]-folate, [^{3}H]-methotrexate	–	–

Loss-of-function mutations in PCFT (SLC46A1) are associated with hereditary folate maladsorption.

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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 *et al.*, 2006), cephalexin, cephadrine, quinidine (Tanihara *et al.*, 2007), paraquat (Chen *et al.*, 2007)	Cimetidine, 1-methyl-4-phenylpyridinium, procainamide, metformin, N^1-methylnicotinamide (Masuda *et al.*, 2006), guanidine, acyclovir (Tanihara *et al.*, 2007)
Inhibitors	Pyrimethamine (0.15 μM, Ito *et al.*, 2010)	
Probes	[^{14}C]-TEA (Otsuka *et al.*, 2005), [^{14}C]-metformin (Tanihara *et al.*, 2007)	[^{14}C]-TEA (Tanihara *et al.*, 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

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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

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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, β-lactam antibiotics, bile acid derivatives and conjugates, endothelin receptor antagonists, fexofenadine, HIV protease inhibitors, opioids, rifampicin, sartans, statins	Amanitin, anticancer drugs, β-lactam antibiotics, bile acid derivatives and conjugates, digoxin, erythromycin, fexofenadine, opiods, 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	[^{3}H]-BSP, [^{3}H]-DPDPE, [^{3}H]-estrone-3-sulfate	[^{3}H]-estradiol-17β-glucuronide, [^{3}H]-estrone-3-sulfate, pravastatin	[^{3}H]-BSP, [^{3}H]-CCK-8, [^{3}H]-estradiol-17β-glucuronide	[^{125}I]-thyroxine, [^{3}H]-BSP, [^{3}H]-estrone-3-sulfate

Nomenclature	OATP2A1	OATP2B1	OATP3A1
HGNC nomenclature	SLCO2A1	SLCO2B1	SLCO3A1
Ensembl ID	ENSG00000174640	ENSG00000137491	ENSG00000176463
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	[^{3}H]-prostaglandin E_2	[^{3}H]-BSP, [^{3}H]-estrone-3-sulfate	[^{3}H]-estrone-3-sulfate, [^{3}H]-prostaglandin E_2

Nomenclature	OATP4A1	OATP4C1	OATP5A1	OATP6A1
HGNC nomenclature	SLCO4A1	SLCO4C1	SLCO5A1	SLCO6A1
Ensembl ID	ENSG00000101187	ENSG00000173930	ENSG00000137571	ENSG00000205359
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	[^{3}H]-estrone-3-sulfate	[^{3}H]-digoxin	–	–

Abbreviations: **BSP**, bromosulfophthalein; **CCK-8**, Cholecystokinin octapeptide; **DHEAS**, dehydroepiandrosterone-3-sulfate; **DPDPE**, [d-Pen2,d-Pen5]-Enkephalin; **PGT**, prostaglandin transporter

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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-enymes 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-competititve 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

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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 (*p*IC$_{50}$)	EHNA, 2′-deoxycoformycin	A134974 (10.2, McGaraughty *et al.*, 2001), ABT702 (8.8, Jarvis *et al.*, 2000)	$\alpha\beta$-methyleneADP	3-Deazaadenosine (8.5, Guranowski *et al.*, 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^7-[(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;

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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	α-Methylphenylalanine (Greengard *et al.*, 1976), PCPA	Fenfluramine, PCPA, α-propyldopacetamide, 6-fluorotryptophan (Nicholson and Wright, 1981)	3-Chlorotyrosine, 3-iodotyrosine, α-methyltyrosine, α-propyldopacetamide

Abbreviations: **DOPA**, 3,4-dihydroxyphenylalanine; **PCPA**, 4-chlorophenylalanine

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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^ω-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^ω-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-boronohexanoic 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, DDAHI, dimethylargininase-1	Dimethylarginine dimethylaminohydrolase 2, DDAHII, dimethylargininase-2, S-phase protein, protein G6a
Cofactor	Zn^{2+}	–

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^{2+}/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_{50} value in the micromolar range.

Nomenclature	Endothelial NOS	Inducible NOS	Neuronal NOS
Preferred abbreviation	eNOS	iNOS	nNOS
Ensembl ID	ENSG00000164867	ENSG00000007171	ENSG00000089250
Other names	NOS III, NOS-3, ecNOS	NOS II, NOS-2	NOS I, NOS-1, brain NOS
Selective inhibitors	–	1400W (8.2, Garvey *et al.*, 1997), 2-amino-4-methylpyridine (7.4, Faraci *et al.*, 1996), PIBTU (7.3, Garvey *et al.*, 1994), NIL (5.5, Moore *et al.*, 1994), aminoguanidine (Corbett and McDaniel, 1992)	3-Bromo-7NI (6.1-6.5, Bland-Ward and Moore, 1995), 7NI (5.3, Babbedge *et al.*, 1993)

The reductase domain of NOS catalyses the reduction of cytochrome *c* and other redox-active dyes (Mayer and Hemmens, 1997). NADPH:O_2 oxidoreductase catalyses the formation of superoxide anion/H_2O_2 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^6-(1-iminoethyl)lysine; **NOS**, nitric oxide synthase; **PIBTU**, 13-phenylen-bis(1,2-ethanediyl)bis-thiourea; **PRMT**, protein arginine methyltransferase; **SDMA**, symmetric dimethylarginine

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Carboxylases and decarboxylases

Carboxylases: The carboxylases allow the production of new carbon-carbon bonds by introducing HCO_3^- or 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	γ-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, ACCα; ACACB, ACCβ	PCCα, PCCβ	–
Cofactors	Biotin	Biotin	Biotin	Vitamin K, NADPH
Substrate(s)	Pyruvate, ATP	Acetyl-CoA, ATP	Propionyl-CoA, ATP	Glutamyl peptides
Product(s)	Oxaloacetate, ADP, P_i	Malonyl-CoA, ADP, P_i	Methylmalonyl-CoA, ADP, P_i	Carboxyglutamyl (Gla) peptides
Selective inhibitors	–	TOFA (Loftus *et al.*, 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 GGCX are associated with clotting disorders.

Decarboxylases: The decarboxylases generate 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 *et al.*, 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 *et al.*, 1980)	AMP-activated protein kinase-evoked phosphorylation (Saha *et al.*, 2000)	DFMO, APA	–
Selective inhibitors	SAM486A (8.0; Stanek *et al.*, 1993), AMA	–	Benserazide, carbidopa, 3-hydroxybenzylhydrazine, L-α-methyldopa	S-Allylglycine

The activity of ODC is regulated by the presence of an antizyme (ENSF00000002504) and an ODC antizyme inhibitor (ENSF00000002504).

Abbreviations: **AMA**, S-(5′-deoxy-5′-adenosyl)-methylthioethyl-hydroxylamine; **APA**, 1-aminooxy-3-aminopropane; **DFMO**, α-difluoromethyl-**L**-ornithine, also known as eflornithine; **FMH**, α-fluoromethylhistidine; **SAM**, S-adenosylmethionine; **SAM486A**, 1-guanidinoimino-2,3-dihydroindene-4-carboximidamide, also known as CGP48664; **TOFA**, 5-(tetradecyloxy)-2-furancarboxylic acid

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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 (ENSF00000000188) 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 Gα_s (the stimulatory G protein α 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 *et al.*, 1991), PKC-evoked phosphorylation (Jacobowitz *et al.*, 1993)	G$\beta\gamma$ (Taussig *et al.*, 1993), PKC-evoked phosphorylation (Chen and Iyengar, 1993; Lustig *et al.*, 1993)	Ca^{2+}/CaM (Choi *et al.*, 1992), PKC-evoked phosphorylation (Jacobowitz *et al.*, 1993)	G$\beta\gamma$ (Gao and Gilman, 1991)	PKC-evoked phosphorylation (Kawabe *et al.*, 1994)
Endogenous inhibitors	Gα_i (Taussig *et al.*, 1994), Gα_o (Taussig *et al.*, 1994), G$\beta\gamma$ (Taussig *et al.*, 1993)	–	Gα_i (Taussig *et al.*, 1994), RGS2 (Sinnarajah *et al.*, 2001), CaM kinase II-evoked phosphorylation (Wayman *et al.*, 1995)	PKC-evoked phosphorylation (Zimmermann and Taussig, 1996)	Gα_i (Taussig *et al.*, 1994), Ca^{2+} (Ishikawa *et al.*, 1992), PKA-evoked phosphorylation (Iwami *et al.*, 1995)
Selective inhibitors	–	–	–	–	NKY80 (Onda *et al.*, 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 *et al.*, 1994)	Ca^{2+} (Cali *et al.*, 1994)	–
Endogenous inhibitors	Gα_i (Taussig *et al.*, 1994), Ca^{2+} (Yoshimura and Cooper, 1992), PKA-evoked phosphorylation (Chen *et al.*, 1997), PKC-evoked phosphorylation (Lai *et al.*, 1999)	–	–	Ca^{2+}/calcineurin (Paterson *et al.*, 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 Gα 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 α and β 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 β chain and is the target for the endogenous ligand nitric oxide (NO•), 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	α1 ENSG00000164116; α2 ENSG00000152402; β1 ENSG00000061918; β2 ENSG00000123201
Selective activators	NO•, YC1 (Friebe *et al.*, 1996), BAY412272 (Stasch *et al.*, 2001), cinaciguat (Stasch *et al.*, 2002), riociguat (Stasch *et al.*, 2002), ataciguat (Schindler *et al.*, 2006)
Selective inhibitors	ODQ (7.5; Garthwaite *et al.*, 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 (ENSFM00250000000899), 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_{50} 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^{2+}/CaM	Ca^{2+}/CaM	Ca^{2+}/CaM	cGMP
Selective inhibitors	SCH51866 (7.2, Vemulapalli *et al.*, 1996), vinpocetine (5.1, Loughney *et al.*, 1996)	SCH51866 (7.2, Vemulapalli *et al.*, 1996)	SCH51866 (7.2, Vemulapalli *et al.*, 1996), vinpocetine (4.3, Loughney *et al.*, 1996)	BAY607550 (8.3–8.8, Boess *et al.*, 2004), EHNA (5.3, Michie *et al.*, 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 *et al.*, 2000), milrinone (6.3, Sudo *et al.*, 2000), cGMP	Cilostamide (7.3, Sudo *et al.*, 2000), milrinone (6.0, Sudo *et al.*, 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 *et al.*, 1997), YM976 (8.3, Aoki *et al.*, 2000), Ro201724 (6.5, Wang *et al.*, 1997)	Rolipram (9.0, Wang *et al.*, 1997), Ro201724 (6.4, Wang *et al.*, 1997)	Rolipram (6.5, Wang *et al.*, 1997), Ro201724 (5.4, Wang *et al.*, 1997)	Rolipram (7.2, Wang *et al.*, 1997), Ro201724 (6.2, Wang *et al.*, 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 [^{3}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 *et al.*, 1993)	cAMP >> cGMP (Gardner *et al.*, 2000)	cAMP >> cGMP (Fisher *et al.*, 1998a)	cAMP >> cGMP (Hayashi *et al.*, 1998)
Activators	PKA (Corbin *et al.*, 2000), PKG (Corbin *et al.*, 2000)	–	–	–	–
Selective inhibitors	T0156 (9.5, Mochida *et al.*, 2002), sildenafil (9.0, Turko *et al.*, 1999), SCH51866 (7.2, Vemulapalli *et al.*, 1996), zaprinast (6.8, Turko *et al.*, 1999)	BRL50481 (6.7, Smith *et al.*, 2004)	Dipyridamole (5.7–6.0, Gardner *et al.*, 2000; Sasaki *et al.*, 2000), SCH51866 (5.8, Sasaki *et al.*, 2000)	Dipyridamole (5.1, Fisher *et al.*, 1998a)	Dipyridamole (4.3, Hayashi *et al.*, 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 *et al.*, 1998b)	cAMP, cGMP (Fujishige *et al.*, 1999)	cAMP, cGMP (Fawcett *et al.*, 2000)
Selective inhibitors	SCH51866 (5.8, Fisher *et al.*, 1998b), zaprinast (4.5, Fisher *et al.*, 1998b)	–	–

Nomenclature	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
Ensembl ID	ENSG00000132915	ENSG00000133256	ENSG00000095464	ENSG00000156973	ENSG00000185527	ENSG00000139053
Other names	cGMP-PDE α, PDE V-b1	cGMP-PDE β	cGMP-PDE α, PDEA2	cGMP-PDE δ	cGMP-PDE γ	cGMP-PDE γ

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 α-subunit of transducin (Gα_t, see Page S5) 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)-1*H*-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(3*H*)-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(6*H*)-quinazolinone; **ODQ**, 1*H*-[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*-5,6*a*,7,8,9,9*a*-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);

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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 (ENSFM00250000000349) (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 *et al.*, 1997)

CYP2 family (ENSFM00400000131704, ENSFM00400000131705, ENSFM00550000747662)

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 (ENSFM00310000088994)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP3A4	1.14.13.67, 1.14.13.97, 1.14.13.32	ENSG00000160868	Quinine 3-monooxygenase, CYPIIIA4, Nifedipine oxidase, CYP4503A3, CYPIIIA3, HLp, taurochenodeoxycholate 6-α-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	CYPIIIA5, P450-PCN3, HLp2	–
CYP3A7	1.14.14.1	ENSG00000160870	CYPIIIA7, P450-HFLA	–
CYP3A43	1.14.14.1	ENSG00000021461	Cytochrome P450 3A43	–

CYP4 family (ENSFM00400000131716, ENSFM00400000131707)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP4A11	1.14.15.3	ENSG00000187048	CYPIVA11, lauric acid ω-hydroxylase, fatty acid ω-hydroxylase, P-450 HK ω, CYP4AII, P450-HL-ω, 20-hydroxyeicosatetraenoic acid synthase, 20-HETE synthase	–
CYP4A22	1.14.15.3	ENSG00000162365	CYPIVA22, lauric acid ω-hydroxylase, fatty acid ω-hydroxylase	–
CYP4B1	1.14.14.1	ENSG00000142973	CYPIVB1, P450-HP	–
CYP4F2	1.14.13.30	ENSG00000186115	Leukotriene B_4 20-monooxygenase 1, leukotriene B_4 ω-hydroxylase 1, CYPIVF2, cytochrome P450-LTB-ω	Responsible for ω-hydroxylation of leukotriene B_4, lipoxin B_4 (Mizukami *et al.*, 1993) and tocopherols, including vitamin E (Sontag and Parker, 2002)
CYP4F3	1.14.13.30	ENSG00000186529	Leukotriene B_4 20-monooxygenase 2, leukotriene B_4 ω-hydroxylase 2, CYPIVF3, cytochrome P450-LTB-ω	Responsible for ω-hydroxylation of leukotriene B_4, lipoxin B_4 (Mizukami *et al.*, 1993) and polyunsaturated fatty acids (Harmon *et al.*, 2006; Fer *et al.*, 2008)
CYP4F8	1.14.14.1	ENSG00000186526	CYPIVF8	–
CYP4F11	1.14.14.1	ENSG00000171903	CYPIVF11	–
CYP4F12	1.14.14.1	ENSG00000186204	CYPIVF12	–
CYP4F22	1.14.14.-	ENSG00000171954		–
CYP4V2	1.14.-.-	ENSG00000145476		–
CYP4X1	1.14.14.1	ENSG00000186377	CYPIVX1	–
CYP4Z1	1.14.14.1	ENSG00000186160	CYPIVZ1	–

AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12.

CYP5, CYP7 and CYP8 families (ENSFM00250000001362)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP5A1	5.3.99.5	ENSG00000059377	Thromboxane synthase, TXA synthase, TBXAS1, CYP5, THAS, TS, TXAS, TXS, TXS	Converts prostaglandin H_2 to thromboxane A_2. Inhibited by dazoxiben (Randall *et al.*, 1981) and camonagrel (Gryglewski *et al.*, 1995)
CYP7A1	1.14.13.17	ENSG00000167910	Cholesterol 7-α-monooxygenase, cholesterol 7-α-hydroxylase, CYPVII	–
CYP7B1	1.14.13.100	ENSG00000172817	Oxysterol 7-α-hydroxylase, 25-hydroxycholesterol 7-α-hydroxylase	–

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP8A1	5.3.99.4	ENSG00000124212	Prostaglandin I_2 synthase, PTGIS	Inhibited by tranylcypromine (Gryglewski *et al.*, 1976)
CYP8B1	1.14.13.95	ENSG00000180432	7-α-Hydroxycholest-4-en-3-one 12-α-hydroxylase, CYPVIIIB1, 7-α-hydroxy-4-cholesten-3-one 12-α-hydroxylase, sterol 12-α-hydroxylase	–

CYP11 (ENSFM00500000269868), 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, $P450_{scc}$	Converts cholesterol to pregnenolone
CYP11B1	1.14.15.4	ENSG00000160882	Steroid 11β-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 *et al.*, 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-α-hydroxylase/17,20 lyase, CYPXVII, P450-C17, P450c17, steroid 17-α-monooxygenase	Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxypregnenolone and 17α-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 anastrazole (Plourde *et al.*, 1994) and letrozole (Bhatnagar *et al.*, 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 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisone, respectively

CYP24, CYP26 and CYP27 families (ENSFM00500000269772, ENSFM00250000002048)

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP24A1	1.14.13.n4	ENSG00000019186	1,25-Dihydroxyvitamin D_3 24-hydroxylase, vitamin D_3 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_3 25-hydroxylase, 5-β-cholestane-3-α,7-α,12-α-triol 27-hydroxylase	–

Nomenclature	EC	Ensembl ID	Other names	Comments
CYP27B1	1.14.13.13	ENSG00000111012	25-hydroxyvitamin D-1 α hydroxylase, cytochrome P450 subfamily XXVIIB polypeptide 1, calcidiol 1-monooxygenase, 25-OHD-1 α-hydroxylase, 25-hydroxyvitamin D_3 1-α-hydroxylase, VD3 1A hydroxylase, P450C1 α, P450VD1-α	–
CYP27C1	1.14.-.-	ENSG00000186684	–	–

CYP39, CYP46 and CYP51 families

Nomenclature	EC	Ensembl ID	Other names
CYP39A1	1.14.13.99	ENSG00000146233	Oxysterol 7-α-hydroxylase, 24-hydroxycholesterol 7-α-hydroxylase
CYP46A1	1.14.13.98	ENSG00000036530	Cholesterol 24-hydroxylase, CH24H
CYP51A1		ENSG00000001630	Lanosterol 14-α-demethylase, leucine-rich repeat and death domain-containing protein LOC401387, CP51, CYP51, CYPL1, LDM, P450-14 DM, P450L1

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Eicosanoid turnover

Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and it's metabolites. Arachidonic acid is thought primarily to derive from phospholipase A_2 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_2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH_2 from PGG_2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indometacin and paracetamol (acetaminophen). PGH_2 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_2/H_2 synthase-1	Prostaglandin G_2/H_2 synthase-2
Substrates	Arachidonic acid	Arachidonic acid, docosahexaenoic acid (see Smith, 2008)
Selective inhibitors	FR122047 (7.5, Ochi *et al.*, 2000), valeroylsalicylate (Bhattacharyya *et al.*, 1995)	Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib

Prostaglandin synthases

Subsequent to the formation of PGH_2, 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_2 and prostacyclin (PGI_2), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E_2, prostaglandin D_2 and prostaglandin $F_{2\alpha}$ (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_2 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_2 synthase, prostaglandin H_2 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_2 D-isomerase

YS121 has been reported to inhibit mPGES1 and 5-LOX with a $p\text{IC}_{50}$ value of 5.5 (Koeberle *et al.*, 2008).

Prostaglandin D_2 can be metabolised to 9α,11β-prostaglandin $F_{2\alpha}$ through the multifunctional enzyme activity AKR1C3. Prostaglandin E_2 can be metabolised to 9α,11α-prostaglandin $F_{2\alpha}$ 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, *trans*-1,2-dihydrobenzene-1,2-diol dehydrogenase, 3α-hydroxysteroid dehydrogenase type 2, 3α-HSD type 2, testosterone 17β-dehydrogenase 5, 17β-hydroxysteroid dehydrogenase type 5, 17β-HSD 5, dihydrodiol dehydrogenase type I, dihydrodiol dehydrogenase 3, chlordecone reductase homolog HAKRb, HA1753	Carbonyl reductase [NADPH] 1, prostaglandin E_2 9-reductase, prostaglandin 9-ketoreductase, NADPH-dependent carbonyl reductase 1, 15-hydroxyprostaglandin dehydrogenase [NADP+]	15-hydroxyprostaglandin dehydrogenase (NAD)
Inhibitors	Flufenamic acid, indometacin (Matsuura *et al.*, 1998), flavonoids (Skarydova *et al.*, 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 5*S*-(arachidonate : oxygen 5-oxidoreductase), 12*R*-(arachidonate 12-lipoxygenase, 12*R*-type), 12*S*-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15*s*-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5*S*-, 12*S*-, 12*R*-, or 15*S*-hydroperoxides, respectively. The sixth lipoxygenase member, epidermal lipoxygenase 3 (E-LOX), metabolises the product from the 12*R*-lipoxygenase (12*R*-HPETE) to a specific epoxyalcohol compound (Yu *et al.*, 2003).

Nomenclature	5-LOX	12*R*-LOX	12*S*-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 *et al.*, 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 ω-6 lipoxygenase	ALOX15B	Epidermis type LOX 3
Substrates	Linoleic acid, arachidonic acid	Arachidonic acid	12*R*-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_4, produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; ω-hydroxylation is mediated by CYP4F2 and CYP4F3 (see Page S293), while β-oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA_4 at the 6 position with reduced glutathione to generate LTC_4 occurs under the influence of leukotriene C_4 synthase, with the subsequent formation of LTD_4 and LTE_4, all three of which are agonists at CysLT receptors (see Page S74). LTD_4 formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD_4 to generate LTE_4. Leukotriene A_4 hydrolase converts the 5,6-epoxide LTA_4 to the 5-hydroxylated LTB_4, an agonist for BLT receptors (see Page S74). LTA_4 is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA_4 and LXB_4. Treatment with an LTA_4 hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA_4 levels, in addition to reducing LTB_4, in lung lavage fluid (Rao *et al*., 2010)

LTA_4 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_4 hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 (Oh *et al*., 2011).

Nomenclature	Leukotriene C_4 synthase	γ-Glutamyltransferase	Dipeptidase 1	Dipeptidase 2	Leukotriene A_4 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 *et al*., 1985)	–	Bestatin (Orning *et al*., 1991)

LTA4H is a member of a family of arginyl aminopeptidases (ENSFM00250000001675), 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 (ENSFM00250000001170), which also includes DPEP3 (ENSG00000141096) for which LTD_4 appears not to be a substrate.

Abbreviations: **CDC**, cinnamyl-3,4-dihydroxy-α-cyanocinnamate; **CJ13610**, 1-carboxamido-1-(3-*S*-[4-{2-methylimididazole}-thiophenyl])-4-cyclopentylether; **esculetin**, 6,7-dihydroxycoumarin; **FR122047**, 1-([4,5-bis{methoxyphenyl}-2-thazoyl]carbonyl)-4-methyl)piperazine hydrochloride; **12*R*-HPETE**, 12*R*-hydroperoxyeicosatetraenoic acid; **FLAP**, 5-lipoxygenase-activating protein, also known as MK-886-binding protein (ENSG00000132965); **NDGA**, nordihydroguaiaretic acid

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Endocannabinoid turnover

Overview: the principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (*N*-arachidonoylethanolamine, 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 α	Diacylglycerol lipase β	*N*-Acylphosphatidylethanolamine-phospholipase D
Preferred abbreviation	DGLα	DGLβ	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 *et al*., 2003), RHC80267	Tetrahydrolipstatin (7.0, Bisogno *et al*., 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	*N*-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, *N*-acylsphingosine amidohydrolase-like, N-palmitoylethanolamine acid amidase
Substrate potency order	2OG = 2AG >> AEA (Ghafouri *et al*., 2004)	AEA > ODA > OEA > PEA (Wei *et al*., 2006)	ODA > OEA > AEA > PEA (Wei *et al*., 2006)	PEA > MEA > SEA ≥ OEA > AEA (Ueda *et al*., 2001)
Selective inhibitors (pIC$_{50}$)	JZL184 (8.1, Long *et al*., 2009)	PF3845 (6.6, Ahn *et al*., 2009), PF750 (6.3-7.8, Ahn *et al*., 2007), JNJ1661010 (7.8, Keith *et al*., 2008), URB597 (6.3-7.0, Wei *et al*., 2006), OL135 (7.4, Wei *et al*., 2006)	URB597 (7.5-8.3, Wei *et al*., 2006), OL135 (7.9, Wei *et al*., 2006)	CCP (5.3, Tsuboi *et al*., 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(hydroxy)methyl)piperidine-1-carboxylate; **MGL**, monoacylglycerol lipase; **MEA**, *N*-myristoylethanolamine; **NAAA**, *N*-acylethanolamine acid amidase; **NAPE-PLD**, *N*-acylphosphatidylethanolamine-phospholipase D; **ODA**, octadec(9,10*z*)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

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Glycerophospholipid turnover

Overview: phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and it's 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-β (ENSF00000000466) are activated primarily by G protein-coupled receptors through members of the $G_{q/11}$ family of G proteins. The receptor-mediated activation of PLC-γ 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-ε1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca^{2+} ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ 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 (Krjukova *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_1 histamine receptor (Hughes *et al*., 2000).

Nomenclature	PLCβ1	PLCβ2	PLCβ3	PLCβ4
Ensembl ID	ENSG00000182621	ENSG00000137841	ENSG00000149782	ENSG00000101333
Other names	PLC-I, PLC-154, KIAA0581	–	–	–
Endogenous activators	Gαq (Smrcka *et al*., 1991; Hepler *et al*., 1993), Gα11 (Hepler *et al*., 1993), G$\beta\gamma$ (Park *et al*., 1993)	Gα16 (Lee *et al*., 1992), G$\beta\gamma$ (Camps *et al*., 1992; Park *et al*., 1993), rac2 (Illenberger *et al*., 2003a,b)	Gαq (Lee *et al*., 1992), G$\beta\gamma$ (Carozzi *et al*., 1993; Park *et al*., 1993)	Gαq (Jhon *et al*., 1993)

Nomenclature	PLCγ1	PLCγ2	PLCδ1	PLCδ3	PLCδ4
Ensembl ID	ENSG00000124181	ENSG00000197943	ENSG00000187091	ENSG00000161714	ENSG00000115556
Other names	PLC-II, PLC-148	PLC-IV	PLC-III	–	–
Endogenous activators	PIP_3 (Bae *et al*., 1998)	PIP_3 (Bae *et al*., 1998)	Transglutaminase II (Murthy *et al*., 1999), p122-RhoGAP (Homma and Emori, 1995), spermine (Haber *et al*., 1991), G$\beta\gamma$ (Park *et al*., 1993)	–	–
Inhibitors	–	Rac1, rac2, rac3 (Piechulek *et al*., 2005; Walliser *et al*., 2008)	Sphingomyelin (Pawelczyk and Lowenstein, 1992)	–	–

PLC-δ2 has been cloned from bovine sources (Meldrum *et al*., 1991).

Nomenclature	PLCε1	PLCζ1	PLCη1	PLCη2
Ensembl ID	ENSG00000138193	ENSG00000139151	ENSG00000114805	ENSG00000149527
Other names	Pancreas-enriched PLC	Testis-development protein NYD-SP27	–	–
Endogenous activators	Ras (Song *et al*., 2001), Rho (Wing *et al*., 2003)	–	–	G$\beta\gamma$ (Zhou *et al*., 2005)

A series of PLC-like proteins (PLCL1 ENSG00000115896; PLCL2 ENSG00000154822 and PLCL3 ENSG00000114805) form a family (ENSF00000000386) with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity.

Phospholipase A_2 (E.C. 3.1.1.4)

Overview: Phospholipase A_2 (PLA_2) cleaves the *sn*-2 fatty acid of glycero phospholipids, 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_2 enzymes or have activity against other eicosanoid-metabolising enzymes.

Secreted or extracellular forms

Nomenclature	Ensembl ID	Other names
$sPLA_2$-1B	ENSG00000170890	GIB, pancreatic PLA_2
$sPLA_2$-2A	ENSG00000188257	GIIA, GIIC sPLA2, non-pancreatic secretory phospholipase A_2, NPS-PLA_2, synovial PLA_2
$sPLA_2$-2D	ENSG00000117215	GIID, GIID $sPLA_2$, secretory-type PLA_2, stroma-associated homolog
$sPLA_2$-2E	ENSG00000188784	GIIE, GIIE $sPLA_2$
$sPLA_2$-2F	ENSG00000158786	GIIF, GIIF $sPLA_2$
$sPLA_2$-3	ENSG00000100078	GIII, GIII $sPLA_2$
$sPLA_2$-10	ENSG00000069764	GX, GX sPLA2
$sPLA_2$-12A	ENSG00000123739	GXIIA, GXII sPLA2

PLA_2-2C (ENSG00000187980) may be a pseudogene, while PLA_2-12B (GXIIB, GXIII $sPLA_2$-like, ENSG00000138308) appears to be catalytically inactive (Rouault *et al*., 2003). A further fragment has been identified with sequence similarities to Group II PLA_2 members (ENSG00000187980).

A binding protein for secretory phospholipase A_2 has been identified (ENSG00000153246) which shows modest selectivity for $sPLA_2$-1B over $sPLA_2$-2A, and also binds snake toxin phospholipase A_2 (Ancian *et al*., 1995). The binding protein appears to have clearance function for circulating secretory phospholipase A_2, as well as signalling functions, and is a candidate antigen for idiopathic membraneous nephropathy (Beck *et al*., 2009).

Cytosolic, calcium-dependent forms

Nomenclature	Ensembl ID	Other names
$cPLA_2$-4A	ENSG00000116711	GIVA, Calcium-dependent PLA_2, cytosolic phospholipase A_2 α
$cPLA_2$-4B	ENSG00000168970	GIVB, cytosolic phospholipase A_2 β
$cPLA_2$-4C	ENSG00000105499	GIVC, cytosolic phospholipase A_2 γ
$cPLA_2$-4D	ENSG00000159337	GIVD, cytosolic phospholipase A_2 δ
$cPLA_2$-4E	ENSG00000188089	GIVE, cytosolic phospholipase A_2 ε
$cPLA_2$-4F	ENSG00000168907	GIVF, cytosolic phospholipase A_2 ζ

$cPLA_2$-4A also expresses lysophospholipase (EC 3.1.1.5) activity (Sharp *et al*., 1994).

Other forms

Nomenclature	Ensembl ID	Other names
PLA_2-G5	ENSG00000127472	GV, PLA_2-10
$iPLA_2$-G6	ENSG00000184381	GVI, 85 kDa Ca^{2+}-independent, $iPLA_2$, PNPLA9
PLA_2-G7	ENSG00000146070	GVII, LDL-associated phospholipase A_2

PLA_2-G7 and a close homologue (HSD-PLA_2, also known as serine-dependent phospholipase A_2, PAFAH2, ENSG00000158006) also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47). Otoconin 90 (OC90, ENSG00000132297) shows sequence homology to PLA_2-G10.

Phosphatidylcholine-specific phospholipase D (E.C. 3.1.4.4)

Overview: Phosphatidylcholine-specific phospholipase D (PLD, ENSF00000001451) 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_2, RhoA, PKC-evoked phosphorylation (Hammond *et al*., 1997), RalA (Luo *et al*., 1997)	ARF, PIP_2 (Lopez *et al*., 1998), oleic acid (Sarri *et al*., 2003)
Endogenous inhibitors	Gβγ (Preininger *et al*., 2006)	Gβγ (Preininger *et al*., 2006)
Selective inhibitors	–	VU0364739 (pIC_{50} 7.7, Lavieri *et al*., 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 (ENSFM00260000050433) or lipins (ENSFM00250000001227), 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**, methylarachidonoylflurophosphonate; **NAPE-PLD**, *N*-acylethanolamine-specific phospholipase D; **PIP_2**, phosphatidylinositol 4,5-bisphosphate; **PIP_3**, phosphatidylinositol 3,4,5-trisphosphate; **PKC**, protein kinase C; **U73122**, 1-(6-[{(17*β*)-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;

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Haem oxygenase (EC 1.14.99.3)

Overview: Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase (α-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).

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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 β-synthase	Cystathionine γ-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, β-thionase	CGL, γ-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 *et al.*, 2004), homocysteine	Cysteine	Cysteine	3-Mercaptopyruvate (1.2 mM,Nagahara *et al.*, 1995)
Products	Cystathionine	Pyruvate, ammonia	Pyruvate, ammonia	Pyruvate
Inhibitors	Aminooxyacetic acid	Propargylglycine		

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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_3, which acts at intracellular ligand-gated ion channels, IP_3 receptors (see Page S157) to elevate intracellular calcium. IP_3 is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP_3 is recycled into membrane phospholipid under the influence of phosphatidyinositol 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, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP_4) from IP_3. IP_3 kinase activity is enhanced in the presence of calcium/calmodulin (Conigrave and Roufogalis, 1989).

Nomenclature	IP_3 kinase A	IP_3 kinase B	IP_3 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_3, as well as towards other inositol derivatives, including the phospholipids PIP_2 and PIP_3. With 1,4,5-IP_3 as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5-IP_2, 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5-IP_2 and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4-IP_2.

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	5PTASE; 75 kDa inositol polyphosphate-5-phosphatase; hp51CN, SHIP; CORS1, JBTS1, PPI5PIV; – SKIP; SHIP2, SH2-containing inositol phosphatase 2; Oculocerebrorenal syndrome of Lowe, OCSL; Synaptojanin 1; Synaptojanin 2

In vitro analysis suggested IP_3 and IP_4 were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP_2 and PIP_3 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_i *ca*. 3.5, McAllister *et al*., 1992; pIC_{50} 3.2, Ohnishi *et al*., 2007) than IMPase 2 (pIC_{50} 1.8-2.1, Ohnishi *et al*., 2007). IMPase activity may be inhibited competitively by L690330 (pK_i 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 *et al*., 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_3, inositol 1,4,5-trisphosphate; **L690330**, 1-(4-hydroxyphenoxy)ethane-1,1-bisphosphonate; **PIP_2**, phosphatidylinositol-4,5,-bisphosphate; **PIP_3**, phosphatidylinositol-3,4,5,-trisphosphate

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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 βARK, are involved in the rapid phosphorylation and desensitization of GPCR. Classically, high concentrations of β_2-adrenoceptor agonists (see Page S26) binding to the receptor lead to the consequent activation and dissociation of the heterotrimeric G protein G_s. $G\alpha_s$ activates adenylyl cyclase activity (see Page S288), while $G\beta\gamma$ subunits perform other functions, one of which is to recruit βARK to phosphorylate serine/threonine residues in the cytoplasmic tail of the β_2-adrenoceptor. The phosphorylated receptor binds, with high affinity, a member of the arrestin family (ENSFM00250000000572), 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	βARK	ENSG00000173020	β-Adrenergic receptor kinase, ADRBK1	Protein kinase C-mediated phosphorylation increases membrane association (Chuang *et al.*, 1995; Winstel *et al.*, 1996)
GRK3	βARK2	ENSG00000100077	β-Adrenergic receptor kinase 2, ADRBK2	–
GRK4	–	ENSG00000125388	G protein-coupled receptor kinase 4, GPRK2L	Inhibited by Ca^{2+}/calmodulin (Sallese *et al.*, 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′*O*Me-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 *et al.*, 2003)	–
Selective inhibitor	Rp-cAMPS	–
Probe	[^{3}H]-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_3, 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	PKBα	PKBβ	PKBγ
Selective inhibitor	GSK690693 (Heerding *et al*., 2008)		

Protein kinase C

Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA, also known as PMA).

Classical protein kinase C isoforms: Members of the classical protein kinase C family are activated by Ca^{2+} and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö6983, chelerythrine and Ro318220.

Nomenclature	PKCα	PKCβ	PKCγ
HGNC nomenclature	PRKCA	PRKCB	PRKCG
Ensembl ID	ENSG00000154229	ENSG00000166501	ENSG00000126583
Selective inhibitors	–	Ruboxistaurin (8.3, Jirousek *et al*., 1996), CGP53353 (6.4, Chalfant *et al*., 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	PKCδ	PKCε	PKCη	PKCθ	PKCμ
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	PKCι	PKCζ
HGNC nomenclature	PRKCI	PRKCZ
Ensembl ID	ENSG00000163558	ENSG00000067606
Other names	PKCλ 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 *et al.*, 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 $p\mathrm{IC}_{50}$ 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
p38α	MAPK14	ENSG00000112062	Cytokine suppressive anti-inflammatory drug binding protein, MAX-interacting protein 2
p38β	MAPK11	ENSG00000185386	p38-2, SAPK2
p38γ	MAPK12	ENSG00000188130	ERK-6, ERK5, SAPK3
p38δ	MAPK13	ENSG00000156711	SAPK4

SB203580 has been reported to inhibit p38α and p38β with $p\mathrm{IC}_{50}$ values of 8.0 and 7.0, respectively (Eyers *et al.*, 1998). SB202190 inhibits p38β (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 (ENSFM00500000269651), 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 Llagostera 2008)
	DMPK2	CDC42BPG	ENSG00000171219	Myotonic dystrophy kinase-related CDC42 binding protein kinase γ, HSMDPKIN, kappa-200, MRCKγ	
	MRCKα	CDC42BPA	ENSG00000143776	MRCKA, myotonic dystrophy kinase-related CDC42-binding protein kinase α	Reported to have a role in cellular iron regulation (Cmejla *et al*., 2010)
	MRCKβ	CDC42BPB	ENSG00000198752	MRCKB, myotonic dystrophy kinase-related CDC42-binding protein kinase β	Reported to be involved in cell migration (Huo *et al*., 2011)
	CRIK	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 *et al*., 2009) and inflammatory bowel disease (Labbe *et al*., 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 *et al*., 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$_3$ and PDK1 (Dong *et al.*, 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 *et al.*, 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	Ribosomal S6 kinases 70 kDa, also known as p70^{rsk}, are activated by MAP kinase-mediated phosphorylation
	S6K2	RPS6KB2	ENSG00000175634	S6Kβ, S6Kβ2	
	RSK1	RPS6KA1	ENSG00000117676	MAPKAPK1A, RSKα1	Ribosomal S6 kinase 90 kDa serine/threonine kinases, also known as p90^{rsk} or MAPK-activated protein kinase-1 (MAPKAP-K1), are activated by MAP kinase -mediated phosphorylation. RSK protein kinases are also activated by phosphorylation by TORC1 (Hara *et al.*, 2002; Kim *et al.*, 2002) and PDK1 (Jensen *et al.*, 1999). Substrates include ribosomal S6 protein (ENSG00000137154), GSK3β (ENSG00000082701, Sutherland *et al.*, 1993) and the 5HT$_{2A}$ receptor (Strachan *et al.*, 2009).
	RSK2	RPS6KA3	ENSG00000177189	MAPKAPK1B, RSKα3, ISPK1	
	RSK3	RPS6KA2	ENSG00000071242	MAPKAPK1C, RSKα2	
	RSK4	RPS6KA6	ENSG00000072133	RSKα6	
	SGK494	–	ENSG00000167524	AC005726.6	
RSKL		RPS6KC1	ENSG00000136643	52 kDa ribosomal protein S6 kinase, RPK118, humS6PKh1	
		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	α1 (ENSG00000132356); α2 (ENSG00000162409); β1 (ENSG00000111725); β2 (ENSG00000131791); γ1 (ENSG00000181929), γ2 (ENSG00000106617); γ3 (ENSG00000115592)	α ENSG00000101266; α′ ENSG00000070770; β ENSG00000204435	MLCK1 ENSG00000065534; MLCK2 ENSG00000101306	α (ENSG00000070808); β (ENSG00000058404); γ (ENSG00000148660); δ (ENSG00000145349)
Other names	–	–	MYLK	–
Endogenous activator	AMP	–	Ca^{2+}-calmodulin	Ca^{2+}-calmodulin
Selective activators	AICA-riboside (Corton *et al.*, 1995)	–	–	–
Selective inhibitors	Dorsomorphin (Zhou *et al.*, 2001)	DRB (Zandomeni *et al.*, 1986)	–	K252a (Hashimoto *et al.*, 1991)

AMP-activated protein kinase is a heterotrimeric protein kinase, made up of *α*, *β* and *γ* subunits, while casein kinase 2 is a heterotetrameric protein kinase, made up of 2 β subunits with two other subunits of α and/or α′ composition. STO609 is an inhibitor of calmodulin kinase kinase (ENSFM00250000001201, Tokumitsu *et al.*, 2002), an upstream activator of calmodulin-dependent kinase.

Abbreviations: **AICA-riboside**, 5-aminoimidazole-4-carboxamide-1-*β*-riboside, also known as acadesine; **API2**, 1,5-dihydro-5-methyl-1-β-D-ribofuranosyl-1,4,5,6,8-pentaazaacennaphthylen-3-amine, also known as triciribine; **CGP53353**, 5,6-bis([4-fluorophenyl]amino)-2*H*-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-β-D-ribofuranosylbenzimidazole; **fasudil**, 1-(5-isoquinolinylsulfonyl)homopiperazine dihydrochloride, also known as HA1077; **GSK690693**, 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[[(3S)-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-1*H*,13*H*-dibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-1,3(2*H*)-dione, also known as LY333531; **SB203580**, 4-(5-[4-fluorophenyl]-2-[4-methylsulfinylphenyl]-3*H*-imidazol-4-yl)pyridine; **SP600125**, anthra[1,9-*cd*]pyrazol-6(2*H*)-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

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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 *et al.*, 1996); angiotensin-II (Zini *et al.*, 1996), neurokinin B, chromogranin A, kallidin (Goto *et al.*, 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_4 hydrolase	LTA4H	ENSG00000111144	–	Hydrolyses leukotriene A_4 (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	–
Vitellogenic carboxypeptidase-like protein	CPVL	ENSG00000106066	–
Prolylcarboxypeptidase	PRCP	ENSG00000137509	Angiotensinase C, HUMPCP, PCP, lysosomal Pro-X carboxypeptidase
Serine carboxypeptidase 1	SCPEP1	ENSG00000121064	RISC

Metallocarboxypeptidases (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 α-linked acidic dipeptidase-like 1	NAALADL1	ENSG00000168060	–
N-Acetylated α-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 *et al.*, 2000)	Endothelin-1, -2, -3	Endothelin-1, -2, -3
Selective inhibitors	Captopril	Captopril	SM19712 (Umekawa *et al.*, 2000)	
Probes	Hip-His Leu	Abz-Ser-Pro-Tyr(NO_2)-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-1β convertase, IL-1BC, interleukin-1 β-converting enzyme, IL-1 β-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-1β, D4-GD1, parkin		Pro-caspase 7, caspase 3, PARP, ICAD, Rb, PKCδ, Huntingtin	Pro-caspase 1
Endogenous activators	–	–	Caspase 8, caspase 9, caspase 10, GrB	–
Activators	–	–	PAC1 (Putt *et al.*, 2006), PETCM (Jiang *et al.*, 2003)	–
Selective inhibitors	Z-YVAD-FMK (Avivi-Green *et al.*, 2002)	Z-VDVAD-FMK (Gamen *et al.*, 2000)	AZ10417808 (Scott *et al.*, 2003), Z-DEVD-FMK (Brockstedt *et al.*, 1998), Z-DQMD-FMK (Izban *et al.*, 2001)	–

CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1β 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, PKCδ, 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 *et al.*, 2002)	Z-VEID-FMK (Ruchaud *et al.*, 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-1B-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 *et al.*, 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, stromyelinases 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 *et al.*, 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 *et al.*, 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 metallopeptidase 21, MMP-21, matrix metalloprotease 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 β, PH30β, 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 γ, 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 α
ADAM15	ENSG00000143537	Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 15, MDC-15, Metalloprotease RGD disintegrin protein, metargidin
ADAM17	ENSG00000151694	TNF α-converting enzyme, TNF α 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 β, 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-ylsulfonyl]-[1-methylethoxy]amino)-*N*-hydroxyacetamide, **AZ10417808**, 2-([3,4-dichlorophenyl]amino)-1,4-dihydro-6-nitro-4-oxo-*N*-2-propenyl-8-quinazolinecarboxamide; **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

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