

THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: G PROTEIN-COUPLED RECEPTORS

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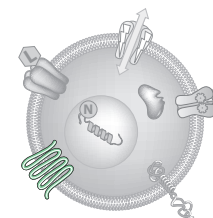
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Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full>.

G protein-coupled receptors are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An introduction to G protein-coupled receptors

G protein-coupled receptors (GPCRs) are the largest class of membrane proteins in the human genome. The term “7TM receptor” is commonly used interchangeably with “GPCR”, although there are some receptors with seven transmembrane domains that do not signal through G proteins. GPCRs share a common architecture, each consisting of a single polypeptide with an extracellular N-terminus, an intracellular C-terminus and seven hydrophobic transmembrane domains (TM1-TM7) linked by three extracellular loops (ECL1-ECL3) and three intracellular loops (ICL1-ICL3). About 800 GPCRs have been identified in man, of which about half have sensory functions, mediating olfaction (~400), taste (33), light perception (10) and pheromone signalling (5) (Mombaerts, 2004). The remaining ~350 non-sensory GPCRs mediate

intercellular signalling by ligands that range in size from small molecules to peptides to large proteins; they are the targets for the majority of drugs in clinical usage (Overington *et al.*, 2006; Rask-Andersen *et al.*, 2011), although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs (Kolakowski, 1994) divided them, on the basis of sequence homology, into six classes. These classes and their prototype members were as follows: **Class A** (rhodopsin-like), **Class B** (secretin receptor family), **Class C** (metabotropic glutamate), **Class D** (fungal mating pheromone receptors), **Class E** (cyclic AMP receptors) and **Class F** (frizzled/smoothened). Of these, classes D and E are not found in vertebrates. An alternative classification scheme “GRAFS” (Schiöth & Fredriksson, 2005)

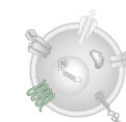
divides vertebrate GPCRs into five classes, overlapping with the A-F nomenclature, *viz*:

Glutamate family (class C), which includes metabotropic glutamate receptors, a calcium-sensing receptor and GABA_B receptors, as well as three taste type 1 receptors (Page 1468) and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man (Mombaerts, 2004).

Rhodopsin family (class A), which includes receptors for a wide variety of small molecules, neurotransmitters, peptides and hormones, together with olfactory receptors, visual pigments, taste type 2 receptors (Page 1469) and five pheromone receptors (V1 receptors).

Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of Concise Guide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full>



Adhesion family GPCRs are phylogenetically related to class B receptors, from which they differ by possessing large extracellular N-termini that are autoproteolytically cleaved from their 7TM domains at a conserved “GPCR proteolysis site” (GPS) which lies within a much larger (~320 residue) “GPCR autoproteolysis-inducing” (GAIN) domain, an evolutionarily ancient motif also found in polycystic kidney disease 1 (PKD1)-like proteins, which has been suggested to be both required and sufficient for autoproteolysis (Promel *et al.*, 2013).

Frizzled family consists of 10 Frizzled proteins (FZD(1-10)) and Smoothened (SMO). The FZDs are activated by secreted lipoglycoproteins of the WNT family, whereas SMO is indirectly activated by the Hedgehog (HH) family of proteins acting on the transmembrane protein Patched (PTCH).

Secretin family, encoded by 15 genes in humans. The ligands for receptors in this family are polypeptide hormones of 27-141 amino-acid residues; nine of the mammalian receptors respond to

ligands that are structurally related to one another (glucagon, glucagon-like peptides (GLP-1, GLP-2), glucose-dependent insulinotropic polypeptide (GIP), secretin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and growth-hormone-releasing hormone (GHRH)) (Harmar, 2001).

GPCR families

Family	Class A (Rhodopsin)	Class B (Secretin)	Class C (Glutamate)	Adhesion	Frizzled
Receptors with known ligands	197 ^a	15	12	0	11
Orphans	87 (54) ^a	–	8 (1) ^a	26 (6) ^a	0
Sensory (olfaction)	390 ^{b,c}	–	–	–	–
Sensory (vision)	10 ^d opsins	–	–	–	–
Sensory (taste)	30 ^c taste 2	–	3 ^c taste 1	–	–
Sensory (pheromone)	5 ^c vomeronasal 1	–	–	–	–
Total	719	15	22	33	11

^aNumbers in brackets refer to orphan receptors for which an endogenous ligand has been proposed in at least one publication, see Davenport *et al.* (2013) ^bOlender *et al.* (2008); ^cMombaerts (2004); ^dTerakita (2005).

Acknowledgements

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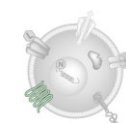
Conflict of interest

The authors state that there is no conflict of interest to disclose.

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacol Rev* 65: 967–986. [PMID:23686350]
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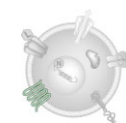


Promel S, Langenhan T, Arac D. (2013) Matching structure with function: the GAIN domain of Adhesion-GPCR and PKD1-like proteins. *Trends Pharmacol Sci* **34**: 470–478. [PMID:23850273]
Rask-Andersen M, Almen MS, Schiöth HB. (2011) Trends in the exploitation of novel drug targets. *Nat Rev Drug Discov* **10**: 579–590. [PMID:21804595]

Schiöth HB, Fredriksson R. (2005) The GRAFS classification system of G-protein coupled receptors in comparative perspective. *Gen Comp Endocrinol* **142**: 94–101. [PMID:15862553]
Terakita A. (2005) The opsins. *Genome Biol* **6**: 213. [PMID:15774036]

List of records presented

- | | |
|--|---|
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Orphan GPCRs

Class A Orphans

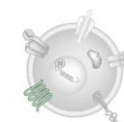
Overview: Table 1 lists a number of putative GPCRs identified by IUPHAR [24], for which preliminary evidence for an endogenous ligand has been published, or for which there exists a potential link to a disease, or disorder. The GPCRs in Table 1 are all Class A, rhodopsin-like GPCRs. Class A orphan GPCRs not listed in Table 1 are putative GPCRs with as-yet unidentified endogenous ligands.

In addition the orphan receptors GPR18, GPR55 and GPR119 which are reported to respond to endogenous agents analogous to the endogenous cannabinoid ligands have been grouped together (see page 1519).

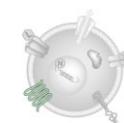
Table 1

Class A orphan GPCRs with putative endogenous ligands

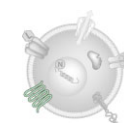
Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Radioligands (K _d)	Selective agonists (pK _i)	Comment
<i>GPR1</i>	<i>GPR1</i> , P46091	–	chemerin (<i>RARRES2</i> , Q99969) (pK _d 8.28) [2]	–	–	Reported to act as a co-receptor for HIV [86].
<i>GPR3</i>	<i>GPR3</i> , P46089	G _s	–	–	–	sphingosine 1-phosphate was reported to be an endogenous agonist [97], but this finding was not replicated in subsequent studies [106]. Reported to activate adenylyl cyclase constitutively through G _s [21]. Gene disruption results in premature ovarian aging [55], reduced β-amyloid deposition [96] and hypersensitivity to thermal pain [81] in mice.
<i>GPR4</i>	<i>GPR4</i> , P46093	G _s	–	–	–	An initial report suggesting activation by lysophosphatidylcholine and sphingosylphosphorylcholine [111] has been retracted [112]. <i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as protein-sensing receptors detecting acidic pH [17,85]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [113].
<i>GPR6</i>	<i>GPR6</i> , P46095	G _s	–	–	–	An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC ₅₀ value of 39nM) [36,97] was not repeated by β-arrestin PathHunter[TM] assays [90,106]. Reported to activate adenylyl cyclase constitutively through G _s and to be located intracellularly [75]. <i>Gpr6</i> -deficient mice showed reduced striatal cyclic AMP production <i>in vitro</i> and selected alterations in instrumental conditioning <i>in vitro</i> . [62].
<i>GPR12</i>	<i>GPR12</i> , P47775	–	–	–	–	Reports that sphingosine 1-phosphate was a ligand of <i>GPR12</i> [35,97] have not been replicated in β-arrestin-based assays [90,106]. Gene disruption results in dyslipidemia and obesity [6].
<i>GPR15</i>	<i>GPR15</i> , P49685	–	–	–	–	Reported to act as a co-receptor for HIV [19]. In an infection-induced colitis model, <i>Gpr15</i> knockout mice were more prone to tissue damage and inflammatory cytokine expression [47].



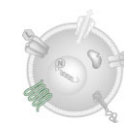
Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Radioligands (K _d)	Selective agonists (pK _i)	Comment
<i>GPR17</i>	<i>GPR17</i> , Q13304	–	LTC ₄ (pEC ₅₀ 7.83 – 9.48) [16], LTD ₄ (pEC ₅₀ 8.14 – 8.36) [16], UDP-glucose (pEC ₅₀ 5.92 – 9.52) [5,16], UDP-galactose (pEC ₅₀ 5.96 – 8.92) [5,16], UDP (pEC ₅₀ 5.97 – 8.8) [5,16]	–	–	Reported to be a dual leukotriene and UDP receptor [16]. Another group instead proposed that GPR17 functions as a negative regulator of the CysLT ₁ receptor response to leukotriene D ₄ (LTD ₄). For further discussion, see [17]. Reported to antagonize CysLT ₁ receptor signalling in vivo and <i>in vitro</i> [65].
<i>GPR20</i>	<i>GPR20</i> , Q99678	–	–	–	–	Reported to inhibit adenylyl cyclase constitutively through G _{i/o} [30]. GPR20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [8].
<i>GPR22</i>	<i>GPR22</i> , Q99680	G _{i/o}	–	–	–	Gene disruption results in increased severity of functional decompensation following aortic banding [1]. Identified as a susceptibility locus for osteoarthritis [23,46,98].
<i>GPR26</i>	<i>GPR26</i> , Q8NDV2	G _s	–	–	–	Has been reported to activate adenylyl cyclase constitutively through G _s [40]. Gpr26 knockout mice show increased levels of anxiety and depression-like behaviours [108].
<i>GPR31</i>	<i>GPR31</i> , O00270	–	12S-HETE (Selective) (pEC ₅₀ 9.55 - Mouse) [27]	–	–	–
<i>GPR32</i>	<i>GPR32</i> , O75388	Not yet established	resolvin D1 (Selective) (pEC ₅₀ 11.06) [51], LXA ₄ (Selective) (pEC ₅₀ 9.7) [51]	[³ H]resolvin D1 (Agonist) (2×10 ⁻¹⁰ M) [51]	–	resolvin D1 (more potently than LxA ₄) has been demonstrated to activate GPR32 in two publications [15,51]. The pairing was not replicated in a recent study based on β-arrestin recruitment [90]. GPR32 is a pseudogene in mice and rats.
<i>GPR34</i>	<i>GPR34</i> , Q9UPC5	G _i /G _o	lysophosphatidylserine (Selective) (pEC ₅₀ 6.57 – 6.89) [48,91]	–	–	Lysophosphatidylserine has been reported to be a ligand of GPR34 in several publications, but the pairing was not replicated in a recent study based on β-arrestin recruitment [90]. Fails to respond to a variety of lipid-derived agents [106]. Gene disruption results in an enhanced immune response [59].
<i>GPR35</i>	<i>GPR35</i> , Q9HC97	–	2-oleoyl-LPA (pEC ₅₀ 7.3 – 7.52) [73], kynurenic acid (pEC ₅₀ 3.9 – 4.41) [90,99]	–	–	Several studies have shown that kynurenic acid is an agonist of GPR35 but it remains controversial whether the proposed endogenous ligand reaches sufficient tissue concentrations to activate the receptor [53]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [73] but these results were not replicated in a recent β-arrestin assay [90]. The phosphodiesterase inhibitor zaprinast [95] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signalling [95]. GPR35 is also activated by the pharmaceutical adjunct pamoic acid [110].
<i>GPR37</i>	<i>GPR37</i> , O15354	G _i /G _o	–	–	neuropeptide head activator (pEC ₅₀ 7.96 – 8.48) [78]	Reported to associate and regulate the dopamine transporter [68] and to be a substrate for parkin [66]. Gene disruption results in altered striatal signalling [67].



Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Radioligands (K _d)	Selective agonists (pK _i)	Comment
<i>GPR39</i>	<i>GPR39</i> , O43194	G _q /G ₁₁	Zn ²⁺ [33]	–	–	Zn ²⁺ has been reported to be a potent and efficacious agonist of human, mouse and rat <i>GPR39</i> [105]. obestatin (<i>GHRL</i> , Q9UBU3), a fragment from the ghrelin precursor, was reported initially as an endogenous ligand, but subsequent studies failed to reproduce these findings. Has been reported to be down-regulated in adipose tissue in obesity-related diabetes [10]. Gene disruption results in obesity and altered adipocyte metabolism [77].
<i>GPR50</i>	<i>GPR50</i> , Q13585	–	–	–	–	<i>GPR50</i> is structurally related to MT ₁ and MT ₂ melatonin receptors, with which it heterodimerises constitutively and specifically [57]. <i>GPR50</i> knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [3].
<i>GPR61</i>	<i>GPR61</i> , Q9BZJ8	G _s	–	–	–	<i>GPR61</i> deficient mice exhibit obesity associated with hyperphagia [70]. Although no endogenous ligands have been identified, 5-(nonyloxy)tryptamine has been reported to be a low affinity inverse agonist [94].
<i>GPR63</i>	<i>GPR63</i> , Q9BZJ6	–	–	–	–	sphingosine 1-phosphate and dioleoylphosphatidic acid have been reported to be low affinity agonists for <i>GPR63</i> [72] but this finding was not replicated in a β -arrestin-based assay [106].
<i>GPR65</i>	<i>GPR65</i> , Q8IYL9	G _s	–	–	–	<i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as proton-sensing receptors detecting acidic pH [17,85]. Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease [50].
<i>GPR68</i>	<i>GPR68</i> , Q15743	–	–	–	–	<i>Gpr68</i> was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [103], but the original publication has been retracted [104]. <i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as protein-sensing receptors detecting acidic pH [17,85]. A family of 3,5-disubstituted isoxazoles were identified as agonists of <i>GPR68</i> [82].
<i>GPR75</i>	<i>GPR75</i> , O95800	G _q /G ₁₁	–	–	–	CCL5 (<i>CCL5</i> , P13501) was reported to be an agonist of <i>GPR75</i> [37], but the pairing could not be repeated in a recent β -arrestin assay [90].
<i>GPR84</i>	<i>GPR84</i> , Q9NQ55	G _i /G _o	–	–	decanoic acid (pEC ₅₀ 5.0 – 5.4) [90,100], undecanoic acid (pEC ₅₀ 5.1) [100], lauric acid (pEC ₅₀ 5.05) [100]	Medium chain free fatty acids with carbon chain lengths of 9–14 activate <i>GPR84</i> [92,100]. A surrogate ligand for <i>GPR84</i> , 6-n-octylaminouracil has also been proposed [92].
<i>GPR87</i>	<i>GPR87</i> , Q9BY21	–	LPA (pEC ₅₀ 7.44) [69,93]	–	–	–
<i>GPR88</i>	<i>GPR88</i> , Q9GZN0	–	–	–	–	Gene disruption results in altered striatal signalling [63].



Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Radioligands (K _d)	Selective agonists (pK _i)	Comment
<i>GPR132</i>	<i>GPR132</i> , Q9UNW8	G _i	–	–	–	<i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as protein-sensing receptors detecting acidic pH [17,85]. Reported to respond to lysophosphatidylcholine [41], but later retracted [102].
<i>GPR149</i>	<i>GPR149</i> , Q86SP6	–	–	–	–	<i>Gpr149</i> knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [20].
<i>GPR183</i>	<i>GPR183</i> , P32249	–	7 α ,25-dihydroxycholesterol (Selective) (pEC ₅₀ 8.1 – 9.85) [28,60], 7 α ,27-dihydroxycholesterol (Selective) (pEC ₅₀ 8.89) [60], 7 β , 25-dihydroxycholesterol (Selective) (pEC ₅₀ 8.68) [60], 7 β , 27-dihydroxycholesterol (Selective) (pEC ₅₀ 7.29) [60]	–	–	Two independent publications have shown that 7 α ,25-dihydroxycholesterol is an agonist of <i>GPR183</i> and have demonstrated by mass spectrometry that this oxysterol is present endogenously in tissues [28,60]. <i>Gpr183</i> -deficient mice show reduction in the early antibody response to a T-dependent antigen. <i>GPR183</i> -deficient B cells fail to migrate to the outer follicle and instead stay in the follicle centre [44,76].
<i>LGR4</i>	<i>LGR4</i> , Q9BXB1	–	R-spondin-2 (<i>RSPO2</i> , Q6UXX9) (Selective) (pEC ₅₀ 12.52) [9], R-spondin-1 (<i>RSPO1</i> , Q2MKA7) (Selective) (pEC ₅₀ 10.7) [9], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) (Selective) (pEC ₅₀ 10.7) [9], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) (Selective) (pEC ₅₀ 10.05) [9]	–	R-spondin-2 (<i>RSPO2</i> , Q6UXX9) (Selective) (pEC ₅₀ 12.52) [9], R-spondin-1 (<i>RSPO1</i> , Q2MKA7) (Selective) (pEC ₅₀ 10.7) [9], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) (Selective) (pEC ₅₀ 10.7) [9], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) (Selective) (pEC ₅₀ 10.05) [9]	<i>LGR4</i> does not couple to heterotrimeric G proteins or to β -arrestin when stimulated by the R-spondins, indicating a unique mechanism of action. R-spondins bind to <i>LGR4</i> , which specifically associates with Frizzled and LRP6—proteins that are activated by the extracellular Wnt molecules and then trigger canonical Wnt signalling to increase gene expression [9,18,80]. Gene disruption leads to multiple developmental disorders [39,64,89,101].
<i>LGR5</i>	<i>LGR5</i> , O75473	–	R-spondin-2 (<i>RSPO2</i> , Q6UXX9) (Selective) (pEC ₅₀ 12.0) [9], R-spondin-1 (<i>RSPO1</i> , Q2MKA7) (Selective) (pEC ₅₀ 11.1) [9], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) (Selective) (pEC ₅₀ 11.0) [9], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) (Selective) (pEC ₅₀ 9.4) [9]	–	R-spondin-2 (<i>RSPO2</i> , Q6UXX9) (Selective) (pEC ₅₀ 12.0) [9], R-spondin-1 (<i>RSPO1</i> , Q2MKA7) (Selective) (pEC ₅₀ 11.1) [9], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) (Selective) (pEC ₅₀ 11.0) [9], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) (Selective) (pEC ₅₀ 9.4) [9]	The four R-spondins can bind to <i>LGR4</i> , <i>LGR5</i> , and <i>LGR6</i> , which specifically associate with Frizzled and LRP6—proteins that are activated by extracellular Wnt molecules- and then trigger canonical Wnt signalling to increase gene expression [9,18].
<i>LGR6</i>	<i>LGR6</i> , Q9HBX8	–	R-spondin-1 (<i>RSPO1</i> , Q2MKA7) (Selective) [9,18], R-spondin-2 (<i>RSPO2</i> , Q6UXX9) (Selective) [9,18], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) (Selective) [9,18], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) (Selective) [9,18]	–	–	–

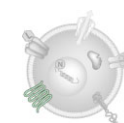


Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Radioligands (K _d)	Selective agonists (pK _i)	Comment
<i>MAS1</i>	<i>MAS1</i> , P04201	G _q /G ₁₁	angiotensin-(1-7) (<i>AGT</i> , P01019) (Selective) [84]	–	–	–
<i>MRGPRD</i>	<i>MRGPRD</i> , Q8TDS7	G _i /G _o	β-alanine (pEC ₅₀ 4.8) [87,90]	–	–	An endogenous peptide with a high degree of sequence similarity to angiotensin-(1-7) (<i>AGT</i> , P01019), alamandine, was shown to promote NO release in MrgD-transfected cells. The binding of alamandine to MRGPRD to was shown to be blocked by D-Pro ⁷ -angiotensin-(1-7), β-alanine and PD123319 [54]. Genetic ablation of MRGPRD ⁺ neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [11].
<i>MRGPRX1</i>	<i>MRGPRX1</i> , Q96LB2	G _q /G ₁₁	BAM8-22 (<i>PENK</i> , P01210) (Selective) (pEC ₅₀ 5.3 – 7.8) [13,56,90]	–	–	Reported to mediate the sensation of itch [61,88]. Reports that BAM8-22 (<i>PENK</i> , P01210) was the most potent of a series of proenkephalin A-derived peptides as an agonist of MRGPRX1 in assays of calcium mobilisation and radioligand binding [56] were replicated in an independent study using a β-arrestin recruitment assay [90].
<i>MRGPRX2</i>	<i>MRGPRX2</i> , Q96LB1	–	PAMP-20 (<i>ADM</i> , P35318) (Selective) [42]	–	PAMP-12 (human) (pEC ₅₀ 7.24 – 7.68) [42], CST-14 {Sp: Mouse, Rat} (pEC ₅₀ 6.9 – 7.6) [42,79,90]	A diverse range of substances has been reported to be agonists of MRGPRX2, with cortistatin 14 the highest potency agonist in assays of calcium mobilisation [79], also confirmed in an independent study using a β-arrestin recruitment assay [90].
<i>P2RY10</i>	<i>P2RY10</i> , O00398	–	sphingosine 1-phosphate (Selective) (pEC ₅₀ 7.3) [69], LPA (Selective) (pEC ₅₀ 6.9) [69]	–	–	–
<i>TAAR2</i>	<i>TAAR2</i> , Q9P1P5	G _s	–	–	–	β-phenylethylamine > tryptamine [7] probable pseudogene in 10–15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [17] see Page 139.

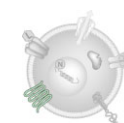
Table 2

Class A Orphan GPCR with limited pharmacological or phenotypic profiles

Nomenclature	HGNC, UniProt	Principal transduction	Comment
<i>GPR19</i>	<i>GPR19</i> , Q15760	–	–
<i>GPR21</i>	<i>GPR21</i> , Q99679	G _q /11	Gpr21 knockout mice were resistant to diet-induced obesity, exhibiting an increase in glucose tolerance and insulin sensitivity and a modest lean phenotype [74].
<i>GPR25</i>	<i>GPR25</i> , O00155	–	–
<i>GPR27</i>	<i>GPR27</i> , Q9NS67	G _q /G ₁₁	Knockdown of Gpr27 reduces endogenous mouse insulin promotor activity and glucose stimulated insulin secretion [52].
<i>GPR33</i>	<i>GPR33</i> , Q49SQ1	G _i /G _o	GPR33 is a pseudogene in most individuals, containing a premature stop codon within the coding sequence of the second intracellular loop [83].
<i>GPR37L1</i>	<i>GPR37L1</i> , O60883	G _i /G _o	–



Nomenclature	HGNC, UniProt	Principal transduction	Comment
<i>GPR45</i>	<i>GPR45</i> , Q9Y5Y3	–	–
<i>GPR52</i>	<i>GPR52</i> , Q9Y2T5	–	–
<i>GPR62</i>	<i>GPR62</i> , Q9BZJ7	–	–
<i>GPR78</i>	<i>GPR78</i> , Q96P69	G _s	GPR78 has been reported to be constitutively active, coupled to elevated cAMP production [40].
<i>GPR82</i>	<i>GPR82</i> , Q96P67	–	Mice with Gpr82 knockout have a lower body weight and body fat content associated with reduced food intake, decreased serum triglyceride levels, higher insulin sensitivity and glucose tolerance [22].
<i>GPR83</i>	<i>GPR83</i> , Q9NYM4	–	One isoform has been implicated in the induction of CD4(+)CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [29].
<i>GPR85</i>	<i>GPR85</i> , P60893	–	Proposed to regulate of hippocampal adult neurogenesis and neurogenesis-dependent learning and memory [14].
<i>GPR135</i>	<i>GPR135</i> , Q8IZ08	–	–
<i>GPR139</i>	<i>GPR139</i> , Q6DWJ6	G _q /G ₁₁	–
<i>GPR141</i>	<i>GPR141</i> , Q7Z602	–	–
<i>GPR142</i>	<i>GPR142</i> , Q7Z601	–	–
<i>GPR146</i>	<i>GPR146</i> , Q96CH1	–	Yosten et al. demonstrated inhibition of proinsulin C-peptide (<i>INS</i> , P01308)-induced stimulation of cFos expression following knockdown of GPR146 in KATOIII cells, suggesting proinsulin C-peptide as an endogenous ligand of the receptor [107].
<i>GPR148</i>	<i>GPR148</i> , Q8TDV2	–	–
<i>GPR150</i>	<i>GPR150</i> , Q8NGU9	–	–
<i>GPR151</i>	<i>GPR151</i> , Q8TDV0	–	GPR151 responded to galanin with an EC ₅₀ value of 2 µM, suggesting that the endogenous ligand shares structural features with galanin (<i>GAL</i> , P22466) [34].
<i>GPR152</i>	<i>GPR152</i> , Q8TDT2	–	–
<i>GPR153</i>	<i>GPR153</i> , Q6NV75	–	–
<i>GPR160</i>	<i>GPR160</i> , Q9UJ42	–	–
<i>GPR162</i>	<i>GPR162</i> , Q16538	–	–
<i>GPR171</i>	<i>GPR171</i> , O14626	–	GPR171 has been shown to be activated by endogenous peptide BigLEN. This receptor-peptide interaction is believed to be involved in regulating feeding and metabolism responses [26].
<i>GPR173</i>	<i>GPR173</i> , Q9NS66	–	–
<i>GPR174</i>	<i>GPR174</i> , Q9BXC1	G _s	Reported to respond to lysophosphatidylserine (pEC ₅₀ 7.1) [38].
<i>GPR176</i>	<i>GPR176</i> , Q14439	–	–
<i>GPR182</i>	<i>GPR182</i> , O15218	–	Rat GPR182 was first proposed as adrenomedullin receptor [43]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [45] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [31].
<i>MAS1L</i>	<i>MAS1L</i> , P35410	–	–
<i>MRGPRX3</i>	<i>MRGPRX3</i> , Q96LB0	G _q /G ₁₁	–
<i>MRGPRX4</i>	<i>MRGPRX4</i> , Q96LA9	G _q /G ₁₁	–
<i>MRGPRE</i>	<i>MRGPRE</i> , Q86SM8	–	–
<i>MRGPRF</i>	<i>MRGPRF</i> , Q96AM1	–	MRGPRF has been reported to respond to stimulation by angiotensin metabolites [25].



Nomenclature	HGNC, UniProt	Principal transduction	Comment
<i>MRGPRG</i>	<i>MRGPRG</i> , Q86SM5	–	–
<i>OPN3</i>	<i>OPN3</i> , Q9H1Y3	–	–
<i>OPN5</i>	<i>OPN5</i> , Q6U736	G _i /G _o	Evidence indicates OPN5 triggers a UV-sensitive G _i -mediated signalling pathway in mammalian tissues [49].
<i>P2RY8</i>	<i>P2RY8</i> , Q86VZ1	–	–

Table 3: Class C Orphans

Nomenclature	HGNC, UniProt
<i>GPR156</i>	<i>GPR156</i> , Q8NFN8
<i>GPR158</i>	<i>GPR158</i> , Q5T848
<i>GPR179</i>	<i>GPR179</i> , Q6PRD1
<i>GPRC5A</i>	<i>GPRC5A</i> , Q8NFJ5
<i>GPRC5B</i>	<i>GPRC5B</i> , Q9NZH0
<i>GPRC5C</i>	<i>GPRC5C</i> , Q9NQ84
<i>GPRC5D</i>	<i>GPRC5D</i> , Q9NZD1

Taste 1 receptors

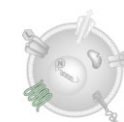
Overview: Whilst the taste of acid and salty foods appear to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin- (*Gαt3*) and *Gα14*-mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involve-

ment of PLCβ2 [109], TRPM5 [109] and IP3 [32] 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, respec-

tively. T1R1/T1R3 heterodimers respond to L-glutamic acid and may be positively allosterically modulated by 5'-nucleoside monophosphates, such as 5'-GMP [58]. T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin [71].

Nomenclature	TAS1R1	TAS1R2	TAS1R3
HGNC, UniProt	<i>TAS1R1</i> , Q7RTX1	<i>TAS1R2</i> , Q8TE23	<i>TAS1R3</i> , Q7RTX0
Principal transduction	–	–	–



Taste 2 receptors

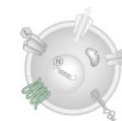
Overview: Whilst the taste of acid and salty foods appear to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin- ($G\alpha t3$) and $G\alpha 14$ -mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involve-

ment of PLC $\beta 2$ [109], TRPM5 [109] and IP3 [32] 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.

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 [12], while T2R14 responded to at least eight different bitter tastants, including (-)- α -thujone and picrotoxinin [4].

Nomenclature	HGNC, UniProt
TAS2R1	TAS2R1, Q9NYW7
TAS2R3	TAS2R3, Q9NYW6
TAS2R4	TAS2R4, Q9NYW5
TAS2R5	TAS2R5, Q9NYW4
TAS2R7	TAS2R7, Q9NYW3
TAS2R8	TAS2R8, Q9NYW2
TAS2R8	TAS2R8, Q9NYW2
TAS2R9	TAS2R9, Q9NYW1
TAS2R10	TAS2R10, Q9NYW0
TAS2R13	TAS2R13, Q9NYV9
TAS2R14	TAS2R14, Q9NYV8
TAS2R16	TAS2R16, Q9NYV7
TAS2R19	TAS2R19, P59542
TAS2R20	TAS2R20, P59543
TAS2R42	TAS2R42, Q7RTR8
TAS2R30	TAS2R30, P59541
TAS2R31	TAS2R31, P59538
TAS2R39	TAS2R39, P59534
TAS2R40	TAS2R40, P59535
TAS2R50	TAS2R50, P59544
TAS2R43	TAS2R43, P59537
TAS2R46	TAS2R46, P59540
TAS2R41	TAS2R41, P59536
TAS2R60	TAS2R60, P59551
TAS2R38	TAS2R38, P59533

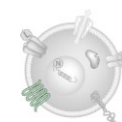


Other 7TM proteins

Nomenclature	HGNC, UniProt	Comment
GPR157	<i>GPR157</i> , Q5UAW9	GPR157 has ambiguous sequence similarities to several different GPCR families (class A, class B and the slime mould cyclic AMP receptor). Because of its distant relationship to other GPCRs, it cannot be readily classified.

Further reading

- Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhanga CP, Bonner TI, Neubig RR *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacol Rev* 65: 967–986. [PMID:23686350]
- Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288. [PMID:15914470]



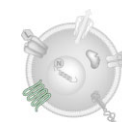
5-Hydroxytryptamine receptors

Overview: 5-HT receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors [158] and subsequently revised [153]] are, with the exception of the ionotropic 5-HT₃ class, GPCR receptors 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-HT₄, 5-HT₆ (non-functional) and 5-HT₇ 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 [124,216]. Most 5-HT receptors (except 5-HT_{1E} and 5-HT_{5a/5b}) play specific roles mediating functional responses in different tissues (reviewed by [197,211]).

Nomenclature	5-HT _{1A} receptor	5-HT _{1B} receptor	5-HT _{1D} receptor	5-HT _{1E} receptor	5-HT _{1F} receptor
HGNC, UniProt	<i>HTR1A</i> , P08908	<i>HTR1B</i> , P28222	<i>HTR1D</i> , P28221	<i>HTR1E</i> , P28566	<i>HTR1F</i> , P30939
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists (pK _i)	U92016A (9.7) [178], 8-OH-DPAT (8.4 – 9.4) [140,151,170,183,189,191,191–192], F15599 (8.6) [190]	L-694,247 (9.2) [149], CP94253 (8.7) [167], eletriptan (8.0) [184], sumatriptan (Partial agonist) (6.5 – 8.1) [149,172,183–184,187,194,215]	PNU109291 (9.1 - Gorilla) [143], L-694,247 (9.0) [217], eletriptan (8.9) [184], sumatriptan (8.0 – 8.7) [150,172,183–184,215]	BRL-54443 (8.7) [136]	BRL-54443 (8.9) [136], LY334370 (8.7) [213], LY573144 (8.7) [186], LY344864 (8.2) [195], eletriptan (8.0) [184], sumatriptan (7.2 – 7.9) [114–115,184,213]
Selective antagonists (pK _i)	NAD 299 (9.2) [161], WAY-100635 (7.9 – 9.2) [189,191], (S)-UH 301 (7.9) [189]	GR-55562 (pK _B 7.4) [159], SB 224289 (Inverse agonist) (8.2 – 8.6) [146,187,203], SB236057 (Inverse agonist) (8.2) [182]	SB 714786 (9.1) [214], BRL-15572 (7.9) [196]	–	–
Radioligands (K _d)	p-[¹⁸ F]MPPF, [¹¹ C]WAY100635 (Antagonist), [³ H]NAD 299 (Antagonist) (1.58x10 ⁻¹⁰ M) [160], [³ H]WAY100635 (Antagonist) (3x10 ⁻¹⁰ M) [164], [³ H]F13640 (Agonist, Full agonist) (1.4x10 ⁻⁹ M) [155], [³ H]8-OH-DPAT (Agonist, Full agonist) (3.98x10 ⁻¹⁰ – 1x10 ⁻⁶ M) [122,162,188,191]	[¹¹ C]AZ10419369, [³ H]N-methyl-AZ10419369 (Antagonist) (3.7x10 ⁻¹⁰ M) [175], [¹²⁵ I]GTI (Agonist) (1.3x10 ⁻⁹ M - Rat) [130], [³ H]GR 125,743 (Antagonist) (2.6x10 ⁻⁹ – 7.1x10 ⁻¹⁰ M) [149,218], [³ H]alniditan (Agonist, Full agonist) (1x10 ⁻⁹ – 2.51x10 ⁻⁹ M) [171], [³ H]eletriptan (Agonist, Partial agonist) (3x10 ⁻⁹ M) [184], [³ H]sumatriptan (Agonist, Partial agonist) (1.1x10 ⁻⁸ M) [184]	[³ H]eletriptan (Agonist, Full agonist) (9x10 ⁻¹⁰ M) [184], [¹²⁵ I]GTI (Agonist) (1.3x10 ⁻⁹ M - Rat) [130], [³ H]alniditan (Agonist, Full agonist) (1.2x10 ⁻⁹ – 1.4x10 ⁻⁹ M) [171], [³ H]GR 125,743 (Antagonist) (2.8x10 ⁻⁹ M) [218], [³ H]sumatriptan (Agonist, Full agonist) (7x10 ⁻⁹ M) [184]	[³ H]5-HT (Agonist, Full agonist) (6.31x10 ⁻⁹ – 7.94x10 ⁻⁹ M) [177,194]	[³ H]LY334370 (Agonist, Full agonist) (3.98x10 ⁻¹⁰ M) [213], [¹²⁵ I]LSD (Agonist) (9.8x10 ⁻¹⁰ M - Mouse) [116]



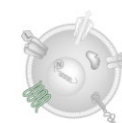
Nomenclature	5-HT _{2A} receptor	5-HT _{2B} receptor	5-HT _{2C} receptor
HGNC, UniProt	<i>HTR2A</i> , P28223	<i>HTR2B</i> , P41595	<i>HTR2C</i> , P28335
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}
Selective agonists (pK _i)	DOI (7.4 – 9.2) [131,185,205]	Ro 60-0175 (8.3) [166], BW723C86 (7.3 – 8.6) [119,166,201], DOI (7.6 – 7.7) [169,185,201],	Ro 60-0175 (7.7 – 8.2) [165–166], DOI (7.2 – 8.6) [142,185,201], lorcaserin (7.8) [209], WAY-163909 (6.7 – 8.0) [141]
Selective antagonists (pK _i)	ketserin (8.1 – 9.7) [137,166,198], MDL-100,907 (pIC ₅₀ 6.5 – 9.3) [166,173,199]	RS-127445 (9.0 – 9.5) [128,166], EGIS-7625 (9.0) [168]	FR260010 (9.0) [152], SB 242084 (8.2 – 9.0) [163,166], RS-102221 (8.3 – 8.4) [129,166]
Radioligands (K _d)	[¹¹ C]MDL100907, [¹⁸ F]altanserin (Antagonist), [³ H]RP62203 (Antagonist) (1.3×10 ⁻¹⁰ M - Rat) [176], [³ H]ketanserin (Antagonist) (2×10 ⁻¹⁰ – 2.9×10 ⁻⁹ M) [166,198]	[³ H]LSD (Agonist, Full agonist) (2.1×10 ⁻⁹ M) [198], [³ H]mesulergine (5×10 ⁻⁹ – 1×10 ⁻⁸ M), [³ H]5-HT (Agonist, Full agonist) (8×10 ⁻⁹ M - Rat) [212], [¹²⁵ I]DOI (2×10 ⁻⁸ – 2.5×10 ⁻⁸ M)	[³ H]LSD (Agonist), [³ H]mesulergine (Antagonist, Inverse agonist) (5×10 ⁻¹⁰ – 2.2×10 ⁻⁹ M) [144,198], [¹²⁵ I]DOI (6×10 ⁻⁹ – 2.5×10 ⁻⁸ M)

Nomenclature	5-HT ₄ receptor	5-HT _{5A} receptor	5-HT _{5B} receptor	5-HT ₆ receptor	5-HT ₇ receptor
HGNC, UniProt	<i>HTR4</i> , Q13639	<i>HTR5A</i> , P47898	<i>HTR5BP</i> , P31387	<i>HTR6</i> , P50406	<i>HTR7</i> , P34969
Principal transduction	G _s	G _i /G _o	None identified	G _s	G _s
Selective agonists (pK _i)	ML 10302 (Partial agonist) (7.9 – 9.0) [121,123,179–181], BIMU 8 (7.3) [138], RS67506 (pEC ₅₀ 8.8 - Rat) [154]	–	–	E-6801 (Partial agonist) (8.7) [157], WAY-181187 (8.7) [202]	E55888 (8.6) [132]
Selective antagonists (pK _i)	RS 100235 (8.7 – 12.2) [138,200], SB 204070 (9.8 – 10.4) [120,179–180,210], GR 113808 (9.3 – 10.3) [117,120,123,138,180,200,210]	SB 699551 (8.2) [139]	–	SB399885 (9.0) [156], SB 271046 (8.9) [133], SB357134 (8.5) [134], Ro 63-0563 (7.9 – 8.4) [126,204]	SB269970 (8.6 – 8.9) [207], SB656104 (8.7) [145], SB 258719 (Inverse agonist) (7.5) [208]
Radioligands (K _d)	[¹²³ I]SB 207710 (8.6×10 ⁻¹¹ M - Pig) [135], [³ H]GR 113808 (Antagonist) (5×10 ⁻¹¹ – 2×10 ⁻¹⁰ M) [117,120,181,210], [³ H]RS 57639 (Agonist) (2×10 ⁻¹⁰ M - Guinea pig) [127], [¹¹ C]SB207145 (Antagonist) (2.8×10 ⁻⁹ M) [174]	[¹²⁵ I]LSD (Agonist, Full agonist) (2×10 ⁻¹⁰ M) [148], [³ H]5-CT (Agonist, Full agonist) (2.5×10 ⁻⁹ M) [148]	[¹²⁵ I]LSD, [³ H]5-CT	[³ H]5-CT (Agonist), [¹²⁵ I]SB258585 (Antagonist) (1×10 ⁻⁹ M) [156], [³ H]LSD (Agonist, Full agonist) (2×10 ⁻⁹ M) [125], [³ H]Ro 63-0563 (Antagonist) (5×10 ⁻⁹ M) [126]	[³ H]5-CT (Agonist) (4×10 ⁻¹⁰ M) [207], [³ H]SB269970 (Antagonist) (1.2×10 ⁻⁹ M) [207], [³ H]5-HT (Agonist, Full agonist) (1×10 ⁻⁹ – 7.94×10 ⁻⁹ M) [118,206], [³ H]LSD (Agonist, Full agonist) (2.51×10 ⁻⁹ – 3.16×10 ⁻⁹ M) [206]

Comments: 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 [153]. Only the non-rodent form of the receptor was previously called 5-HT_{1D}; the human 5-HT_{1B} receptor (tabulated) displays a different pharmacology to the rodent

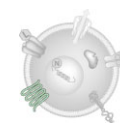
forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS181 is a selective antagonist of the rodent 5-HT_{1B} receptor. fananserine and ketanserin bind with high affinity to dopamine D4 and histamine H₁ receptors respectively, and ketanserin is a potent 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 trans-

duction pathways when stably expressed in C6 glioma cells [193]. 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 [147].



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Acetylcholine receptors (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors, [224]) 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 ana-

logues AC-260584 and 77-LH-28-1, *N*-desmethylozapine, TBPB and LuAE51090 have been described as functionally selective agonists of the M₁ receptor subtype *via* binding in a mode distinct from that utilized by non-selective agonists [220,235,237–238,246,253,256–257,259,259]. There are two

pharmacologically characterised allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine, and the other binds KT 5720, WIN 62,577, WIN 51,708 and staurosporine [240–241].

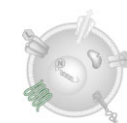
Nomenclature	M ₁ receptor	M ₂ receptor	M ₃ receptor	M ₄ receptor	M ₅ receptor
HGNC, UniProt	<i>CHRM1</i> , P11229	<i>CHRM2</i> , P08172	<i>CHRM3</i> , P20309	<i>CHRM4</i> , P08173	<i>CHRM5</i> , P08912
Principal transduction	G _{q/11}	G _{i/o}	G _{q/11}	G _{i/o}	G _{q/11}
Selective antagonists (pK _i)	MT7 (11.0–11.1) [249], VU0255035 (7.8) [254]	–	–	MT3 (8.7) [234,250]	–
Selective allosteric regulators	BQCA (Positive) [244], brucine (Positive) [221], KT 5720 (Positive) [221], ML169 (Positive) [252], VU0029767 (Positive) [245], VU0090157 (Positive) [245]	–	<i>N</i> -chloromethyl-brucine (Positive) [221], WIN 62,577 (Positive) [221]	LY2033298 (Positive) [226], thiochrome (Positive) [221], VU0152099 (Positive) [222], VU0152100 (Positive) [222]	VU0238429 (Positive) [223]
Radioligands (K _d)	[¹¹ C]butylthio-TZTP, [¹¹ C]xanomeline, [¹⁸ F](R,R)-quinuclidinyl-4-fluoromethylbenzilate, [³ H]QNB (Antagonist) (1.58×10 ^{−11} –2.51×10 ^{−11} M) [229,251], [³ H]N-methyl scopolamine (Antagonist) (5.01×10 ^{−11} –1.58×10 ^{−9} M) [225,228–229,230,232–234,236,239], [³ H]pirenzepine (Antagonist) (1.4×10 ^{−8} M) [263]	[¹⁸ F]FP-TZTP, [³ H]QNB (Antagonist) (2.51×10 ^{−11} –7.94×10 ^{−11} M) [251], [³ H]N-methyl scopolamine (Antagonist) (1.25×10 ^{−10} –5.01×10 ^{−7} M) [225,227,230,232–234,236,239,262]	[³ H]QNB (Antagonist) (3.98×10 ^{−11} M) [251], [³ H]darifenacin (Antagonist) (3.16×10 ^{−10} M) [255], [³ H]N-methyl scopolamine (Antagonist) (3.98×10 ^{−11} –2.51×10 ^{−9} M) [225,227,230–232,234,236,239]	[³ H]QNB (Antagonist) (3.16×10 ^{−11} –2×10 ^{−10} M) [229,251], [³ H]N-methyl scopolamine (Antagonist) (6.3×10 ^{−11} –1.58×10 ^{−8} M) [225,227,229,230,232,234,236,239,250,262]	[³ H]QNB (2×10 ^{−11} –6×10 ^{−11} M), [³ H]N-methyl scopolamine (Antagonist) (2×10 ^{−10} –7.94×10 ^{−9} M) [225,227,230,234,236,262]

Comments: LY2033298 and BQCA have also been shown to directly activate the M₄ and M₁ receptors, respectively, via an allosteric site [242–243,247–248]. The allosteric site for gallamine and strychnine on M₂ receptors can be labelled by [³H]dimethyl-W84 [260]. 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 M₂ muscarinic receptor [261].

THRX-160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M₂ receptors by binding both to the orthosteric and a nearby allosteric site [219,258].

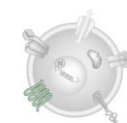
Although numerous ligands for muscarinic acetylcholine receptors have been described, relatively few selective antagonists have been described, so it is common to assess the rank order of

affinity of a number of antagonists of limited selectivity (e.g. 4-DAMP, darifenacin, pirenzepine) in order to identify the involvement of particular subtypes.



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Adenosine receptors

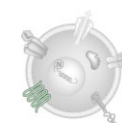
Overview: Adenosine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adenosine Receptors; [280]) are activated by the endogenous ligand adenosine (potentially inosine also at A₃ receptors). Crystal structures for the antagonist-bound and agonist-bound A_{2A} adenosine receptors have been described [287,323].

Nomenclature	A ₁ receptor	A _{2A} receptor	A _{2B} receptor	A ₃ receptor
HGNC, UniProt	<i>ADORA1</i> , P30542	<i>ADORA2A</i> , P29274	<i>ADORA2B</i> , P29275	<i>ADORA3</i> , P33765
Principal transduction	G _{i/o}	G _s	G _s	G _{i/o}
(Sub)family-selective agonists (pK _i)	NECA (5.3 – 8.2) [283,295,311,317,324]	NECA (6.9 – 8.7) [270,276,283,299,303,324]	NECA (5.7 – 6.9) [268,270,292,306,314,319,324]	NECA (7.5 – 8.4) [270,283,289,312,320,324]
Selective agonists (pK _i)	5-Cl-5-deoxy-(±)-ENBA (9.29) [279], GR79236 (8.51 - Rat) [288], cyclopentyladenosine (6.5 – 9.4) [274–275,283,285,288,295,311], CCPA (7.7 – 8.1) [288,308]	apadenoson (9.3) [310], CGS 21680 (6.7 – 8.1) [270,276,283,288,299,302–303,308]	Bay60-6583 (8.0 – 8.52) [277]	IB-MECA (8.7 – 9.2) [278,281,302,320], CI-IB-MECA (8.0 – 8.9) [271,289,298]
(Sub)family-selective antagonists (pK _i)	XAC (pK _i 7.5) [279], CGS 15943 (8.46) [309]	XAC (8.4 – 9.0) [276,302], CGS 15943 (7.7 – 9.4) [276,299,302,309]	XAC (pA ₂ 7.9) [265], CGS 15943 (pA ₂ 7.8) [265], XAC (6.9 – 8.8) [268,292–293,302,306,314], CGS 15943 (6.0 – 8.1) [267,292–293,302,309,314]	CGS 15943 (7.0 – 7.9) [301–302,309,320], XAC (7.0 – 7.4) [302,312,320]
Selective antagonists (pK _i)	PSB36 (9.9 - Rat) [264], SLV320 (9.0) [297], DPCPX (7.4 – 9.2) [275,286,308,311,322]	SCH442416 (8.4 – 10.3) [313,316], ZM-241385 (8.8 – 9.1) [309], SCH 58261 (8.3 – 9.2) [276,303,309]	PSB-0788 (9.4) [269], PSB603 (9.26) [269], MRS1754 (8.8) [292,300], PSB1115 (7.27) [284]	MRS1220 (8.2 – 9.2) [289,301,315,325], VUF5574 (8.39) [318], MRS1523 (7.7) [304], MRS1191 (7.5) [289,294,305]
Radioligands (K _d)	[³ H]CCPA (Agonist, Full agonist) (6.31×10 ⁻¹⁰ M) [302,311], [³ H]DPCPX (Antagonist) (6×10 ⁻¹⁰ – 1.2×10 ⁻⁹ M) [274,278,302,309,311,317]	[³ H]ZM 241385 (Antagonist) (8×10 ⁻¹⁰ – 1.8×10 ⁻⁹ M) [266,282], [³ H]CGS 21680 (Agonist, Full agonist) (1.6×10 ⁻⁸ – 2.2×10 ⁻⁸ M) [291,321]	[³ H]MRS1754 (Antagonist) (1.58×10 ⁻¹⁰ M) [292]	[¹²⁵ I]AB-MECA (Agonist, Full agonist) (6×10 ⁻¹⁰ – 1×10 ⁻⁹ M) [309,320]

Comments: Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (*ADORA2BP1*) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor [290]. DPCPX also exhibits antagonism at A_{2B} receptors (pK_i ca. 7, [265,302]).

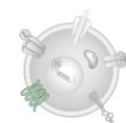
Antagonists at A₃ receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A₃ receptor. In the absence of other adenosine receptors, [³H]DPCPX and [³H]ZM 241385 can also be used to label A_{2B} receptors (K_D ca. 30 and 60 nM respectively). [¹²⁵I]AB-MECA also binds to A₁ receptors [302]. [³H]CGS 21680 is relatively selective for A_{2A} receptors,

but may also bind to other sites in cerebral cortex [273,296]. [³H]NECA binds to other non-receptor elements, which also recognise adenosine [307]. XAC-BY630 has been described as a fluorescent antagonist for labelling A₁ adenosine receptors in living cells, although activity at other adenosine receptors was not examined [272].



Further reading

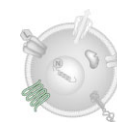
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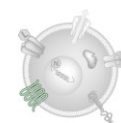
Adhesion Class GPCRs

Overview: 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 [326,331].

Nomenclature	HGNC, UniProt	Comment
<i>BAI1</i>	<i>BAI1</i> , O14514	BAI1 is reported to respond to phosphatidylserine [329].
<i>BAI2</i>	<i>BAI2</i> , O60241	–
<i>BAI3</i>	<i>BAI3</i> , O60242	–
<i>CD97</i>	<i>CD97</i> , P48960	–
<i>CELSR1</i>	<i>CELSR1</i> , Q9NYQ6	–
<i>CELSR2</i>	<i>CELSR2</i> , Q9HCU4	–
<i>CELSR3</i>	<i>CELSR3</i> , Q9NYQ7	–
<i>ELTD1</i>	<i>ELTD1</i> , Q9HBW9	–
<i>EMR1</i>	<i>EMR1</i> , Q14246	–
<i>EMR2</i>	<i>EMR2</i> , Q9UHX3	–
<i>EMR3</i>	<i>EMR3</i> , Q9BY15	–
<i>EMR4P</i>	<i>EMR4P</i> , Q86SQ3	–
<i>GPR56</i>	<i>GPR56</i> , Q9Y653	Reported to bind tissue transglutaminase 2 [330] and collagen, which activates the G _{12/13} pathway [328].
<i>GPR64</i>	<i>GPR64</i> , Q8IZP9	–
<i>GPR97</i>	<i>GPR64</i> , Q8IZP9	–
<i>VLGR1</i>	<i>GPR98</i> , Q8WXG9	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [327].
<i>GPR110</i>	<i>GPR110</i> , Q5T601	–
<i>GPR111</i>	<i>GPR111</i> , Q8IZF7	–
<i>GPR112</i>	<i>GPR112</i> , Q8IZF6	–
<i>GPR113</i>	<i>GPR113</i> , Q8IZF5	–
<i>GPR114</i>	<i>GPR114</i> , Q8IZF4	–
<i>GPR115</i>	<i>GPR115</i> , Q8IZF3	–
<i>GPR116</i>	<i>GPR116</i> , Q8IZF2	–
<i>GPR123</i>	<i>GPR123</i> , Q86SQ6	–
<i>GPR124</i>	<i>GPR124</i> , Q96PE1	–
<i>GPR125</i>	<i>GPR125</i> , Q8IWK6	–
<i>GPR126</i>	<i>GPR126</i> , Q86SQ4	–
<i>GPR128</i>	<i>GPR128</i> , Q96K78	–
<i>GPR133</i>	<i>GPR133</i> , Q6QNK2	–
<i>GPR144</i>	<i>GPR144</i> , Q7Z7M1	–



Nomenclature	HGNC, UniProt	Comment
<i>LPHN1</i>	<i>LPHN1</i> , O94910	–
<i>LPHN2</i>	<i>LPHN2</i> , O95490	–
<i>LPHN3</i>	<i>LPHN3</i> , Q9HAR2	–



Adrenoceptors

Overview: α_1 -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; [340]) are 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. The α_{1A} -adrenoceptor antagonist (+)-niguldipine also has high affinity for L-type Ca^{2+} channels. The conotoxin p-TIA acts as a negative allosteric modulator at the α_{1B} -adrenoceptor [396], while the snake toxin p-Da1a acts as a selective competitive antagonist at the α_{1A} -adrenoceptor [386]. Fluorescent derivatives of prazosin (Bodipy PL-prazosin – QAPB) are increasingly used to examine cellular localisation of α_1 -adrenoceptors. The vasoconstrictor effects of selective α_1 -adrenoceptor agonists have led to their use as nasal decon-

gestants; antagonists are used to treat hypertension (doxazosin, prazosin) and benign prostatic hyperplasia (alfuzosin, tamsulosin). The combined α_1 - and β_2 -adrenoceptor antagonist carvedilol is widely used to treat congestive heart failure, although the contribution of α_1 -adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs possess α_1 -adrenoceptor blocking properties that are believed to contribute to side effects such as orthostatic hypotension and extrapyramidal effects.

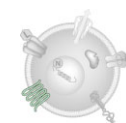
Nomenclature	α_{1A} -adrenoceptor	α_{1B} -adrenoceptor	α_{1D} -adrenoceptor
HGNC, UniProt	ADRA1A, P35348	ADRA1B, P35368	ADRA1D, P25100
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}
Selective agonists (pK _i)	dabuzalgron (7.4) [339], A61603 (pIC ₅₀ 7.8–8.4) [355,369]	–	–
Selective antagonists (pK _i)	silodosin (10.4) [397], tamsulosin (10.0–10.7) [343,346,355,397,410], (+)-niguldipine (9.1–10.0) [355,397], p-Da1a (9.22) [386], SNAP5089 (8.8–9.4) [360,371,409]	–	BMY-7378 (8.7–9.1) [342,413]

Comments: *Adrenoceptors*, α_1 : The clone originally called the α_{1C} -adrenoceptor corresponds to the pharmacologically defined α_{1A} -adrenoceptor [361]. Some tissues possess α_{1A} -adrenoceptors (termed α_{1L} -adrenoceptors [355,381]) that display relatively low affinity in functional and binding assays for prazosin (pK_i < 9) indicative of different receptor states or locations. α_{1A} -adrenoceptor C-terminal splice variants form homo- and heterodimers, but fail to generate a functional α_{1L} -adrenoceptor [387]. A study suggests that the α_{1L} -adrenoceptor phenotype may result from the interaction of α_{1A} -adrenoceptors with cysteine-rich epidermal growth factor-like domain 1 α (CRELD1 α) [382–383,404]. α_{1D} -Adrenoceptors form heterodimers with α_{1B} - or

β_2 -adrenoceptors that show increased cell-surface expression [402]. Heterodimers formed between α_{1D} - and α_{1B} -adrenoceptors have distinct functional properties [359]. Recombinant α_{1D} -adrenoceptors have been shown in some heterologous systems to be mainly located intracellularly but cell-surface localization is attained by truncation of the N-terminus, or by co-expression of α_{1B} - or β_2 -adrenoceptors to form heterodimers [359,402]. In smooth muscle of native blood vessels all three α_1 -adrenoceptor subtypes are located on the surface and intracellularly [377–378].

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 [351]. There are also differences between subtypes in coupling efficiency to different pathways – *e.g.* in some systems coupling efficiency to Ca^{2+} signalling is $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$, but for MAP kinase signalling is $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$. In vascular smooth muscle, potency of agonists is related to the predominant subtype, α_{1D} - conveying greater sensitivity than α_{1A} -adrenoceptors [354].



Adrenoceptors, α_2 : α_2 -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; [340]) are 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. Presynaptic α_2 -adrenoceptors are widespread in the nervous system and regulate many functions, hence the multiplicity of actions. 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. clonidine has been used as an anti-hypertensive and also to counteract opioid withdrawal. Actions

on imidazoline receptors may contribute to the pharmacological effects of clonidine. α_2 -Adrenoceptor agonists such as dexmedetomidine have been widely used as sedatives and analgesics in veterinary medicine (also xylazine) and are now used frequently in humans. α_2 -Adrenoceptor antagonists are relatively little used therapeutically although yohimbine has been used to treat erectile dysfunction and several anti-depressants (cyanopindolol, mirtazepine) that block α_2 -adrenoceptors may work through this mechanism. 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.

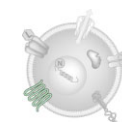
Nomenclature	α_{2A} -adrenoceptor	α_{2B} -adrenoceptor	α_{2C} -adrenoceptor
HGNC, UniProt	ADRA2A, P08913	ADRA2B, P18089	ADRA2C, P18825
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists (pK _i)	oxymetazoline (Partial agonist) (8.0) [365,403], guanfacine (7.1) [374]	–	–
Selective antagonists (pK _i)	BRL 44408 (8.2–8.77) [403,414]	imiloxan (7.3 - Rat) [379]	JP1302 (pK _B 7.8) [392]

Comments: ARC-239 (pK_i 8.0) and prazosin (pK_i 7.5) show selectivity for α_{2B} - and α_{2C} -adrenoceptors over α_{2A} -adrenoceptors. oxymetazoline is a reduced efficacy agonist and is one of many α_2 -adrenoceptor agonists that are imidazolines or closely related compounds. Other binding sites for imidazolines, distinct from α_2 -adrenoceptors, and structurally distinct from the 7TM adrenoceptors, have been identified and classified as I₁, I₂ and I₃ sites; catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands for these sites, evoking hypotensive effects *in vivo*. I₁-imidazoline receptors are involved in central inhibition of sympathetic tone,

I₂-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I₃-imidazoline receptors regulate insulin secretion from pancreatic β -cells. α_{2A} -adrenoceptor stimulation reduces insulin secretion from β -islets [412], with a polymorphism in the 5'-UTR of the ADRA2A gene being associated with increased receptor expression in β -islets and heightened susceptibility to diabetes [391].

α_{2A} - and α_{2C} -adrenoceptors form homodimers [398]. Heterodimers between α_{2A} - and either the α_{2C} -adrenoceptor or μ opioid peptide receptor exhibit altered signalling and trafficking pro-

perties compared to the individual receptors [398,401,405]. Signalling by α_2 -adrenoceptors is primarily via G_{i/o}, however the α_{2A} -adrenoceptor also couples to G_s [350]. Imidazoline compounds display bias at the α_{2A} -adrenoceptor when assayed by [35 S] GTP γ S binding compared to inhibition of cAMP accumulation [384]. The noradrenaline reuptake inhibitor desipramine acts directly on the α_{2A} -adrenoceptor, promoting internalisation via recruitment of β -arrestin without activating G proteins [345].



Adrenoceptors, β : β -Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, [340]) are 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. (-)-noradrenaline, xamoterol and (-)-Ro 363 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 BRL 37344 and CL316243 have low efficacy at the human β_3 -adrenoceptor whereas CGP 12177 and L 755507 activate human β_3 -adrenoceptors [393]. 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,[394]).

SR59230A has reasonably high affinity at β_3 -adrenoceptors [375], but does not discriminate well between the three β -adrenoceptor subtypes [341] and has been reported to have lower affinity for the β_3 -adrenoceptor in some circumstances [368]. [¹²⁵I]-cyanopindolol, [¹²⁵I]-hydroxybenzylpindolol and [³H]-alprenolol are high affinity radioligands widely used to label β_1 - and β_2 -adrenoceptors and β_3 -adrenoceptors can be labelled with higher concentrations (nM) of [¹²⁵I]-cyanopindolol in the presence of appropriate concentrations of β_1 - and β_2 -adrenoceptor antagonists. Fluorescent ligands such as BODIPY-TMR-CGP12177 are also increasingly being used to track β -adrenoceptors at the cellular level [335]. Somewhat selective β_1 -adrenoceptor selective agonists (denopamine, dobutamine) are used short-term to treat cardiogenic shock but, in the longer term, reduce survival. β_1 -Adrenoceptor-preferring antagonists are used to treat hyper-

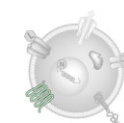
tension (atenolol, betaxolol, bisoprolol, metoprolol and nebivolol), cardiac arrhythmias (atenolol, bisoprolol, esmolol) and cardiac failure (metoprolol, nebivolol). Cardiac failure is also successfully treated with carvedilol which blocks both β_1 - and β_2 -adrenoceptors, as well as α_1 -adrenoceptors. β_2 -Adrenoceptor-selective agonists are powerful bronchodilators widely used to treat respiratory disorders. There are both short (salbutamol, terbutaline) and long acting drugs (formoterol, salmeterol). Although many first generation β -adrenoceptor antagonists (propranolol) block both β_1 - and β_2 -adrenoceptors there are no β_2 -adrenoceptor-selective antagonists used therapeutically. Although potentially useful for the treatment of obesity, there are no β_3 -adrenoceptor-selective agonists used for this purpose currently. Several β_3 -adrenoceptor agonists (mirabegron, amibegron and solabegron) are used to control overactive bladder syndrome.

Nomenclature	β_1 -adrenoceptor	β_2 -adrenoceptor	β_3 -adrenoceptor
HGNC, UniProt	<i>ADRB1</i> , P08588	<i>ADRB2</i> , P07550	<i>ADRB3</i> , P13945
Principal transduction	G _s	G _s	G _s
Rank order of potency	(-)-noradrenaline > (-)-adrenaline	(-)-adrenaline > (-)-noradrenaline	(-)-noradrenaline = (-)-adrenaline
Endogenous agonists (pK _i)	noradrenaline (6.0) [356]	–	–
Selective agonists (pK _i)	(-)-Ro 363 (8.0) [380], xamoterol (Partial agonist) (7.0) [364], denopamine (Partial agonist) (5.8) [364,400]	formoterol (pEC ₅₀ 10.08) [334], salmeterol (pEC ₅₀ 9.9) [334], zinterol (pEC ₅₀ 9.48) [334], procaterol (pEC ₅₀ 8.43) [334]	carazolol (8.7) [376], BRL 37344 (6.4–7.0) [338,348,362,376], CGP 12177 (Partial agonist) (6.1–7.3) [338,373,376,380], CL316243 (5.2) [411], L 755507 (pEC ₅₀ 10.1) [334], L742791 (pEC ₅₀ 8.8) [408], SB251023 (pEC ₅₀ 7.14 - Mouse) [363]
Selective antagonists (pK _i)	CGP 20712A (8.5–9.2) [332,341,373], betaxolol (8.8) [373], atenolol (6.7–7.6) [332,366,373]	ICI 118551 (Inverse agonist) (9.2–9.5) [332,335,373]	L-748337 (8.4) [341], SR59230A (6.9–8.4) [341,347,362]
Radioligands (K _d)	[¹²⁵ I]ICYP (Antagonist, it is necessary to use an excess of a β_2 -AR-selective ligand such as ICI 118551 to allow visualisation of β_1 -AR binding in native tissue) (4.99×10 ⁻¹² –3.28×10 ⁻¹¹ M) [373,395]	[¹²⁵ I]ICYP (Antagonist, it is necessary to use an excess of a β_1 -AR-selective ligand such as CGP20712A to allow visualisation of β_2 -AR binding in native tissues) (7.9×10 ⁻¹² M) [373,395]	[¹²⁵ I]ICYP (Agonist, Partial agonist) (1.58×10 ⁻¹⁰ –6.31×10 ⁻¹⁰ M) [373,380,385,395,399]
Comment	The agonists indicated have less than two orders of magnitude selectivity [334].	–	Agonist SB251023 has a pEC ₅₀ of 6.9 for the splice variant of the mouse β_3 receptor, β_{3b} [363].

Comments: Radioligand binding with [¹²⁵I]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 [¹²⁵I]ICYP. Binding of a fluorescent analogue of CGP 12177 to β_2 -adrenoceptors in living cells has been described [336]. [¹²⁵I]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. Pharmacological differences exist between human and mouse β_3 -adrenoceptors, and the 'rodent selective' agonists BRL 37344 and CL316243 have low efficacy at the human β_3 -adrenoceptor whereas CGP 12177 and L 755507 activate human β_3 -adrenoceptors [394]. The β_3 -adrenoceptor has an intron in the coding region, but splice variants have only been

described for the mouse [352], where the isoforms display different signalling characteristics [363]. 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 [333]. The 'putative β_4 -adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP 12177 and other nonconventional partial agonists at β_1 -adrenoceptors,



since 'putative β_4 -adrenoceptor'-mediated agonist effects of CGP 12177 are absent in mice lacking β_1 -adrenoceptors [367,370]. Numerous polymorphisms have been described for the three β -adrenoceptors; some are associated with alterations in agonist-evoked signalling, trafficking, altered diseases susceptibility and/or altered responses to pharmacotherapy.

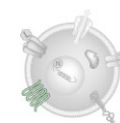
All β -adrenoceptors couple to G_s (activating adenylyl cyclase and elevating cAMP levels), but it is also clear that they activate other G proteins such as G_i and many other G protein-independent signalling pathways, including β -arrestins, which

may in turn lead to activation of mitogen-activated protein kinases. Many antagonists at β_1 - and β_2 -adrenoceptors are agonists at β_3 -adrenoceptors (CL316243, CGP 12177 and carazolol). Many 'antagonists' that block agonist-stimulated cAMP accumulation, for example carvedilol and bucindolol, are able to activate mitogen-activated protein kinase pathways [337,353,357–358,393–394] and thus display 'protean agonism'. bupranolol appears to act as a neutral antagonist in most systems so far examined. Agonists also display biased signalling at the β_2 -adrenoceptor via G_s or β -arrestins [349].

The X-ray crystal structures have been described of the agonist bound [406] and antagonist bound forms of the β_1 - [407], agonist-bound [344] and antagonist-bound forms of the β_2 -adrenoceptor [388,390], as well as a fully active agonist-bound, G_s protein-coupled β_2 -adrenoceptor [389]. carvedilol and bucindolol bind to an extended site of the β_1 -adrenoceptor involving contacts in TM2, 3, and 7 and extracellular loop 2 that may facilitate coupling to β -arrestins [407]. Compounds displaying β -arrestin-biased signalling at the β_2 -adrenoceptor also have a greater effect on the conformation of TM7, whereas full agonists for G_s coupling promote movement of TM5 and TM6 [372].

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Angiotensin receptors

Overview: The actions of angiotensin II (AGT, P01019) (Ang II) are mediated by AT₁ and AT₂ receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; [424]), which have around 30% sequence similarity. Endogenous ligands are angiotensin II (AGT, P01019) and angiotensin III (AGT, P01019) (Ang III), while angiotensin I (AGT, P01019) is weakly active in some systems.

Nomenclature	AT ₁ receptor	AT ₂ receptor
HGNC, UniProt	AGTR1, P30556	AGTR2, P50052
Principal transduction	G _{q/11}	G _i /G _o , Tyr & Ser/Thr phosphatases
Selective agonists (pK _i)	L-162313 (pIC ₅₀ 7.85–7.92) [433]	[p-aminoPhe6]ang II (pK _d 9.1–9.4 - Rat) [426,434], CGP42112 (pIC ₅₀ 9.63) [417]
Selective antagonists (pK _i)	candesartan (pIC ₅₀ 9.5–9.7) [436], irbesartan (pIC ₅₀ 8.7–8.8) [436], valsartan (pIC ₅₀ 8.61) [425], eprosartan (pIC ₅₀ 8.4–8.8) [429], EXP3174 (pIC ₅₀ 7.4–9.5) [435–436], losartan (pIC ₅₀ 7.4–8.7) [426,435]	PD123319 (pK _d 8.7–9.2) [426–427,440], PD123177 (pIC ₅₀ 8.5–9.5 - Rat) [419,422,428]
Radioligands (K _d)	[³ H]eprosartan (Antagonist), [³ H]A81988 (Antagonist) (5.7×10 ⁻¹⁰ M - Rat) [430], [³ H]L158809 (Antagonist) (6.6×10 ⁻¹⁰ M - Rat) [421], [¹²⁵ I]EXP985 (Antagonist) (1.49×10 ⁻⁹ M - Rat) [423], [³ H]losartan (Antagonist) (6.2×10 ⁻⁹ M - Rat) [420], [³ H]valsartan (Antagonist) (IC ₅₀ 1×10 ⁻⁹ – 1.58×10 ⁻⁹ M) [437]	[¹²⁵ I]CGP42112 (Agonist, Full agonist) (2.51×10 ⁻¹¹ M) [426,438–439]

Comments: AT₁ receptors are predominantly coupled to G_{q/11}, however they are also linked to arrestin recruitment and stimulate G protein-independent arrestin signalling [431]. Most species express a single *AGTR1* gene, but two related *agtr1a* and *agtr1b* receptor genes are expressed in rodents. The AT₂ receptor counteracts several of the growth responses initiated by the AT₁ receptors. The AT₂ receptor is much less abundant than the AT₁

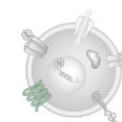
receptor in adult tissues and is upregulated in pathological conditions.

There is also evidence for an AT₄ receptor that specifically binds angiotensin IV (AGT) and is located in the brain and kidney. An additional putative endogenous ligand for the AT₄ receptor has been described (LVV-hemorphin (*HBB*, P68871), a globin deca-

peptide) [432]. The AT₁ and bradykinin B2 receptors have been proposed to form a heterodimeric complex [416]. The antagonist activity of CGP42112 has also been reported [415]. AT₁ receptor antagonists bearing substituted 4-phenylquinoline moieties have been synthesized, which bind to AT₁ receptors with nanomolar affinity and are slightly more potent than losartan in functional studies [418].

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Apelin receptor

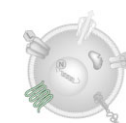
Overview: The apelin receptor (APJ, nomenclature as agreed by NC-IUPHAR on apelin receptors, [449]) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. apelin-36 (*APLN*, Q9ULZ1), apelin-13 (*APLN*, Q9ULZ1) and [Pyr¹]apelin-13 (*APLN*, Q9ULZ1) are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (*APLN*, Q9ULZ1) by a so far unidentified enzymatic pathway [450].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Endogenous agonists (pK _i)	Radioligands (K _d)
apelin receptor	<i>APLNR</i> , P35414	G _{i/o}	[Pyr ¹]apelin-13 ≥ apelin-13 > apelin-36 [443,450]	apelin-13 (Selective) (pIC ₅₀ 8.8 – 9.5) [443–444,448], apelin-17 (Selective) (pIC ₅₀ 7.9 – 9.02) [442,448], apelin-36 (Selective) (pIC ₅₀ 8.2 – 8.6) [443–444,446,448], [Pyr ¹]apelin-13 (Selective) (pIC ₅₀ 7.0 – 8.8) [446,448]	[¹²⁵ I][Nle ⁷⁵ ,Tyr ⁷⁷]apelin-36 (human) (Agonist, Full agonist) (6.3×10 ⁻¹² M) [446], [¹²⁵ I][Glp ⁶⁵ Nle ⁷⁵ ,Tyr ⁷⁷]apelin-13 (Agonist, Full agonist) (2.23×10 ⁻¹¹ M) [444], [¹²⁵ I](Pyr ¹)apelin-13 (Agonist, Full agonist) (3×10 ⁻¹⁰ M) [445], [¹²⁵ I]apelin-13 (Agonist, Full agonist) (7×10 ⁻¹⁰ M) [443], [³ H](Pyr ¹)[Met(0)11]-apelin-13 (Agonist, Full agonist) (2.7×10 ⁻⁹ M) [448]

Comments: Potency order determined for heterologously expressed human APJ receptor (pD₂ 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 [441]. A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* [447], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant APJ receptor [443].

Further reading

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Bile acid receptor

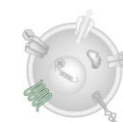
Overview: The bile acid receptor (GPBA) responds to bile acids produced during the liver metabolism of cholesterol. Selective agonists are promising drugs for the treatment of metabolic disorders, such as type II diabetes, obesity and atherosclerosis.

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Selective agonists (pK _i)
GPBA receptor	GPBAR1, Q8TDU6	G _s [454]	lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid [452,454]	betulinic acid (pEC ₅₀ 5.98) [451], oleanolic acid (pEC ₅₀ 5.65) [455]

Comments: The triterpenoid natural product betulinic acid has also been reported to inhibit inflammatory signalling through the NFκB pathway [456]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [457]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [453].

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Bombesin receptors

Overview: Bombesin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, [462]) are activated by the endogenous ligands gastrin-releasing peptide (GRP, P07492) (GRP), NMB (NMB, P08949) (NMB) and GRP-(18–27) (GRP, P07492) (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 [463]). 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 [469]. A physiological role for the BB_3 receptor has yet to be fully defined although receptor knock-out experiments suggest a role in energy balance and the control of body weight [462].

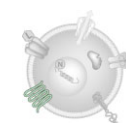
Nomenclature	BB_1 receptor	BB_2 receptor	BB_3 receptor
HGNC, UniProt	<i>NMBR</i> , P28336	<i>GRPR</i> , P30550	<i>BR53</i> , P32247
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Endogenous agonists (pK_i)	NMB (Selective) (8.1 – 10.3) [458,468]	gastrin-releasing peptide (Selective) (6.34 – 8.21) [458,468]	–
Selective antagonists (pK_i)	dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH ₂ , PD 165929 (pK_d 8.2) [460], PD 168368 (pIC_{50} 9.24 – 9.6) [459], D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH ₂ (pIC_{50} 6.22 – 6.56) [459,468]	[D-Phe ⁶ ,Cpa ¹⁴ , ψ 13–14]bombesin-(6–14), JMV594 (pIC_{50} 8.7 - Mouse) [464,470], Ac-GRP-(20–26)-methylester (pIC_{50} 8.4 - Mouse) [461]	–
Selective agonists (pK_i)	–	–	[D-Tyr ⁶ ,Apa-4Cl ¹¹ ,Phe ¹³ ,Nle ¹⁴]bombesin-(6–14) (8.1) [466]
Radioligands (K_d)	[¹²⁵ I]BH-NMB, [¹²⁵ I][Tyr ⁴]bombesin	[¹²⁵ I]GRP (human), [¹²⁵ I][D-Tyr ⁶]bombesin-(6–13)-methyl ester (Antagonist) (5.3×10^{-10} M - Mouse) [465], [¹²⁵ I][Tyr ⁴]bombesin (Agonist, Full agonist) (6.31×10^{-9} M) [458]	[¹²⁵ I][D-Tyr ⁶ , β -Ala ¹¹ ,Phe ¹³ ,Nle ¹⁴]bombesin-(6–14) (Agonist, Full agonist) (1×10^{-8} – 3.98×10^{-9} M) [467]

Comments: All three subtypes may be activated by [D-Phe⁶, β -Ala¹¹,Phe¹³,Nle¹⁴]bombesin-(6–14) [467]. [D-Tyr⁶,Apa-4Cl¹¹,Phe¹³,Nle¹⁴]bombesin-(6–14) has more than 200-fold selectivity for BB_3 receptors over BB_1 and BB_2 [466].

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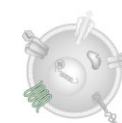
Bradykinin receptors

Overview: Bradykinin (or kinin) receptors (nomenclature recommended by the NC-IUPHAR subcommittee on bradykinin (kinin) receptors, [478]) are activated by the endogenous peptides bradykinin (*KNG1*, P01042) (BK), [des-Arg⁹]bradykinin (*KNG1*, P01042), Lys-BK (kallidin (*KNG1*, P01042)), [des-Arg¹⁰]kallidin (*KNG1*, P01042), T-kinin (*KNG1*, P01042) (Ile-Ser-BK), [Hyp³]-BK (*KNG1*, P01042) and Lys-[Hyp³]-bradykinin (*KNG1*, P01042). The variation in affinity or inactivity of B₂ receptor antagonists could reflect the existence of species homologues of B₂ receptors.

Nomenclature	B ₁ receptor	B ₂ receptor
HGNC, UniProt	<i>BDKRB1</i> , P46663	<i>BDKRB2</i> , P30411
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	[des-Arg ¹⁰]kallidin > [des-Arg ⁹]bradykinin = kallidin > bradykinin	kallidin > bradykinin >> [des-Arg ⁹]bradykinin, [des-Arg ¹⁰]kallidin
Endogenous agonists (pK _i)	[des-Arg ¹⁰]kallidin (<i>KNG1</i> , P01042) (Selective) (9.6 – 10.0) [471–472,477]	–
Selective agonists (pK _i)	[Sar,D-Phe ⁸ ,des-Arg ⁹]bradykinin (5.7) [477]	[Hyp ³ ,Tyr(Me) ⁸]BK, [Phe ⁸ ,ψ(CH ₂ -NH)Arg ⁹]BK
Selective antagonists (pK _i)	R 914 (pA ₂ 8.6) [474], R-715 (pA ₂ 8.5) [475], B-9958 (9.2 – 10.3) [473,480], [Leu ⁹ ,des-Arg ¹⁰]kallidin (9.1 – 9.3) [471–472]	icatibant (pA ₂ 8.4) [476], FR173657 (pA ₂ 8.2) [481], anatibant (8.2) [479]
Radioligands (K _d)	[³ H]Lys-[Leu ⁸][des-Arg ⁹]BK (Antagonist), [¹²⁵ I]Hpp-desArg ¹⁰ HOE140 (1×10 ⁻¹⁰ M), [³ H]Lys-[des-Arg ⁹]BK (Agonist, Full agonist) (4×10 ⁻¹⁰ M)	[¹²⁵ I][Tyr ⁸]bradykinin, [³ H]BK (human, mouse, rat) (Agonist, Full agonist) (3.99×10 ⁻¹⁰ M - Mouse) [482], [³ H]NPC17731 (Antagonist) (3.9×10 ⁻¹⁰ – 7.7×10 ⁻¹⁰ M) [483–484]

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Calcitonin receptors

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, [495,504]) are generated by the genes *CALCR* (which codes for the CT receptor (CTR),) and *CALCL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR,). 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

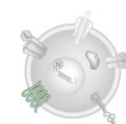
acids, identified as a family of three members; RAMP1, RAMP2 and RAMP3. There are splice variants of CTR; these in turn produce variants of the AMY receptor [504]. The endogenous agonists are the peptides CT (*CALCA*, P01258), α -CGRP (*CALCA*, P06881) (formerly known as CGRP-I), β -CGRP (*CALCB*, P10092) (formerly known as CGRP-II), AMY (*IAPP*, P10997) (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), AM (*ADM*, P35318) and AM2/IMD (*ADM2*, Q7Z4H4) (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 [497]. BIBN4096BS (also known as olcegepant, *pKi*–10.5) and MK-0974 (also known as telcagepant, *pKi*–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 receptor	AM ₁ receptor	AM ₂ receptor
Subunits	RAMP1 (Accessory protein), calcitonin receptor-like receptor	RAMP2 (Accessory protein), calcitonin receptor-like receptor	RAMP3 (Accessory protein), calcitonin receptor-like receptor
Principal transduction	G _s	G _s	G _s
Rank order of potency	α -CGRP > AM $\geq$ AM2/IMD > AMY $\geq$ CT (salmon)	AM > AMY > α -CGRP, AM2/IMD > CT (salmon)	AM $\geq$ AM2/IMD $\geq$ α -CGRP > AMY > CT (salmon)
Endogenous agonists (<i>pK_i</i>)	β -CGRP (9.9 – 11.0) [485,501], α -CGRP (9.7 – 10.0) [485,501]	AM (8.3 – 9.2) [485,501]	AM (8.3 – 9.0) [485,491]
Selective antagonists (<i>pK_i</i>)	BIBN4096BS (10.2 – 10.7) [489,493–494,500], MK-0974 (9.1) [506]	AM-(22-52) (human) (7.0 – 7.8) [485,494,501]	–
Radioligands (<i>K_d</i>)	[¹²⁵ I] α CGRP (mouse, rat) (Agonist, Full agonist), [¹²⁵ I] α CGRP (human) (Agonist, Full agonist) (1×10 ^{–10} M)	[¹²⁵ I]AM (rat) (Agonist, Full agonist) (1×10 ^{–10} – 1×10 ^{–9} M)	[¹²⁵ I]AM (rat) (Agonist, Full agonist) (1×10 ^{–10} – 1×10 ^{–9} M)

Nomenclature	CT receptor	AMY ₁ receptor	AMY ₂ receptor	AMY ₃ receptor
HGNC, UniProt	<i>CALCR</i> , P30988	–	–	–
Subunits	–	RAMP1 (Accessory protein), CT receptor	RAMP2 (Accessory protein), CT receptor	RAMP3 (Accessory protein), CT receptor
Principal transduction	G _s	G _s	G _s	G _s
Rank order of potency	CT (salmon) $\geq$ CT $\geq$ AMY, α -CGRP > AM, AM2/IMD	CT (salmon) $\geq$ AMY $\geq$ α -CGRP > AM2/IMD $\geq$ CT > AM	Poorly defined	CT (salmon) $\geq$ AMY > α -CGRP $\geq$ AM2/IMD $\geq$ CT > AM
Endogenous agonists (<i>pK_i</i>)	CT (Selective) (<i>pEC</i> ₅₀ 9.0 – 11.2) [486–487,492,498–499,503]	AMY	AMY	AMY
Radioligands (<i>K_d</i>)	[¹²⁵ I]CT (salmon) (Agonist, Full agonist) (1×10 ^{–10} M), [¹²⁵ I]CT (human) (Agonist, Full agonist) (1×10 ^{–10} – 1×10 ^{–9} M)	[¹²⁵ I]BH-AMY (rat, mouse) (Agonist, Full agonist) (1×10 ^{–10} – 1×10 ^{–9} M)	[¹²⁵ I]BH-AMY (rat, mouse) (Agonist, Full agonist) (1×10 ^{–10} – 1×10 ^{–9} M)	[¹²⁵ I]BH-AMY (rat, mouse) (Agonist, Full agonist) (1×10 ^{–10} – 1×10 ^{–9} M)



Comments: It is important to note that a complication with the interpretation of pharmacological studies with AMY receptors in transfected cells is that most of this work has likely used a mixed population of receptors, encompassing RAMP-coupled CTR as well as CTR alone. This means that although in binding assays human CT (CALCA, P01258) has low affinity for ^{125}I -AMY binding sites, cells transfected with CTR and RAMPs can display potent CT functional responses. 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 [488,492–493]. 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) [488,492]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [507]. In particular, CGRP is a more potent agonist than AMY (*IAPP*, P10997) at increasing cAMP at the delta 47 hCT(a) receptor, when transfected with RAMP1 (to give the corresponding AMY_{1(a)} receptor) in Cos 7 cells [505].

The ligands described represent the best available but their selectivity is limited, apart from BIBN4096BS and MK-0974. For

example, AM has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM₂ receptors. AM₂/IMD also has high affinity for the AM₂ receptor [496]. CGRP-(8-37) acts as an antagonist of CGRP (pK_i ~8) and inhibits some AM and AMY responses (pK_i ~6–7). It is weak at CT receptors. Salmon CT-(8-32) is an antagonist at both AMY and CT receptors. AC187, a salmon CT analogue, is also an antagonist at AMY and CT receptors. Human AM-(22-52) has some selectivity towards AM receptors, but with modest potency (pK_i ~7), limiting its use [494]. AM-(22-52) is slightly more effective at AM₁ than AM₂ receptors but this difference is not sufficient for this peptide to be a useful discriminator of the AM receptor subtypes.

Ligand responsiveness at CT 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 [502,507].

G_s is a prominent route for effector coupling for CLR and CTR but other pathways (*e.g.* Ca²⁺, ERK, Akt), and G proteins can be activated [508]. There is evidence that CGRP-RCP (a 148

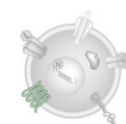
amino-acid hydrophilic protein, ASL (P04424) is important for the coupling of CLR to adenylyl cyclase [490].

[¹²⁵I]-Salmon CT is the most common radioligand for CT receptors but it has high affinity for AMY receptors and is also poorly reversible. [¹²⁵I]-Tyr⁰-CGRP is widely used as a radioligand for CGRP receptors.

Some early literature distinguished between *CGRP₁* and *CGRP₂* receptors. It is now clear that *CLCRL/RAMP1* represents the *CGRP₁* subtype and is now known simply as the CGRP receptor [495]. The *CGRP₂* receptor is now considered to have arisen from the actions of CGRP at AM₂ and AMY receptors. This term should not be used [495].

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Calcium-sensing receptors

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 [509]. The sensitivity of CaS to primary agonists can be increased by aromatic L-amino acids [511] and also by elevated extracellular pH [520] or decreased extracellular ionic strength [521].

This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

Nomenclature	CaS receptor	GPRC ₆ receptor
HGNC, UniProt	CASR, P41180	GPRC6A, Q5T6X5
Principal transduction	G _{q/11} , G _{i/o} , G _{12/13} [523]	–
Amino-acid rank order of potency	L-phenylalanine, L-tryptophan, L-histidine > L-alanine > L-serine, L-proline, L-glutamic acid > L-aspartic acid (not L-lysine, L-arginine, L-leucine and L-isoleucine) [511]	–
Cation rank order of potency	Gd ³⁺ > Ca ²⁺ > Mg ²⁺ [509]	–
Polyamine rank order of potency	spermine > spermidine > putrescine [522]	–
Selective allosteric regulators	NPS 89636 (Negative) [515], NPS R-568 (Positive) (pK _d 6.5) [517], calindol (Positive) (pK _d 6.0 – 6.5) [513], AC265347 (Positive) (pEC ₅₀ 7.6 – 8.1) [514], cinacalcet (Positive) (pEC ₅₀ 7.3) [516], calindol (Positive) (pEC ₅₀ 6.5) [518], NPS 2143 (Negative) (pIC ₅₀ 7.1 – 7.4) [515,525], calhex 231 (Negative) (pIC ₅₀ 6.4) [519]	–
Comment	2-benzylpyrrolidine derivatives of NPS 2143 are also negative allosteric modulators of the calcium sensing receptor [525].	GPRC ₆ is a related G _q -coupled receptor which responds to basic amino acids [524][525].

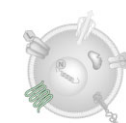
Comments: Positive allosteric modulators of CaS are termed Type II calcimimetics and can suppress parathyroid hormone (PTH (*PTH*, P01270)) secretion [517]. Negative allosteric modulators are called calcilytics and can act to increase PTH (*PTH*, P01270) secretion [515].

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 [510,512], which exhibit similar increases in PTH secretion and blood Ca²⁺ levels. A gain-of-function mutation in the CaS gene is associated with autosomal dominant hypocalcaemia.

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Cannabinoid receptors

Overview: Cannabinoid receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Cannabinoid Receptors; [542]) are activated by endogenous ligands that include N-arachidonylethanolamine (anandamide), N-homo- γ -linolenylethanolamine, N-docosatetra-7,10,13,16-enylethanolamine and 2-arachidonoylglycerol. Potency determinations of endogenous agonists at these receptors are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion [526].

Nomenclature	CB ₁ receptor	CB ₂ receptor
HGNC, UniProt	CNR1, P21554	CNR2, P34972
Principal transduction	G _{i/o}	G _{i/o}
(Sub)family-selective agonists (pK _i)	CP55940 [550], Δ^9 -tetrahydrocannabinol [550], HU-210 [530], WIN55212-2 [550]	CP55940 [550], Δ^9 -tetrahydrocannabinol [550], HU-210 [530], WIN55212-2 [550]
Selective agonists (pK _i)	arachidonyl-2-chloroethylamide (8.9 - Rat) [533], arachidonylcyclopropylamide (8.7 - Rat) [533], O-1812 (8.5 - Rat) [528], R-(+)-methanandamide (7.7 - Rat) [537]	JWH-133 (8.5) [535,541], AM1241 (8.1) [555], L-759,633 (7.7 – 8.2) [531,548], L-759,656 (7.7 – 7.9) [531,548], HU-308 (7.6) [532]
Selective antagonists (pK _i)	rimonabant (7.9 – 8.7) [529–530,545,549,550], AM251 (8.1 - Rat) [539], AM281 (7.9 - Rat) [538], LY320135 (6.9) [529]	SR144528 (8.3 – 9.2) [546,548], AM630 (7.5) [548]
Radioligands (K _d)	[³ H]rimonabant (Antagonist) (1×10 ⁻¹⁰ – 1.2×10 ⁻⁹ M - Rat) [527,534,536,543,547,551,554]	–

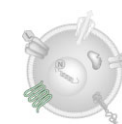
Comments: Both CB₁ and CB₂ receptors may be labelled with [³H]CP55940 (0.5 nM; [550]) and [³H]WIN55212-2 (2–2.4 nM; [552–553]). anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [540,556]. There is evidence for an allosteric

site on the CB₁ receptor [544]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [542]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have

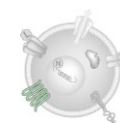
been identified [542]. Moreover, GPR18, GPR55 and GPR119, although showing little structural similarity to CB₁ and CB₂ receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands [542].

Further reading

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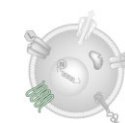
Chemerin receptor

Overview: The chemerin receptor is 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 [557–558]. In addition, 2 GPCRs for resolvin D1 (RvD1) have been identified, FPR2/ALX, the lipoxin A₄ receptor, and GPR32, an orphan receptor [559].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Selective agonists (pK _i)	Radioligands (K _d)	Comment
chemerin receptor	CMKLR1, Q99788	Not yet established	resolvin E1 > chemerin C-terminal peptide > 18R-HEPE > EPA [557]	resolvin E1	[³ H]resolvin E1 (Agonist) (1.1×10 ⁻⁸ M) [557–558]	NC-IUPHAR has issued a recommendation for a formal nomenclature change for this receptor from <i>CMKLR1</i> to 'chemerin receptor' based on new pairings with chemerin [560–562].

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacological reviews* 65: 967–986.



Chemokine receptors

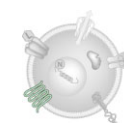
Overview: Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, [600–601]) comprise a large subfamily of 7TM proteins that bind one or more chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes. Chemokine receptors can be divided by function into two main groups: G protein-coupled chemokine receptors, which mediate leukocyte trafficking, and “Atypical chemokine receptors”, which may signal through non-G protein-coupled mechanisms and act as chemokine scavengers to downregulate inflammation or shape chemokine gradients.

Chemokines in turn 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; $n = 17$) and CX3C ($n = 1$) 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. G protein-coupled chemokine receptors are named according to the class of chemokines bound, whereas ACKR is the root acronym for atypical chemokine receptors. Listed are those

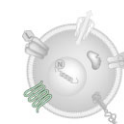
human agonists with EC₅₀ values <50 nM in either Ca²⁺ flux or chemotaxis assays at human recombinant G protein-coupled chemokine receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and microbial non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, but CCR5 is the only one demonstrated to play an essential role in HIV/AIDS pathogenesis. The tables include both standard chemokine receptor names [628] and the most commonly used aliases. Numerical data quoted are typically pK_i or pIC₅₀ values from radioligand binding to heterologously expressed receptors.

Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
HGNC, UniProt	CCR1, P32246	CCR2, P41597	CCR3, P51677	CCR4, P51679	CCR5, P51681
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Endogenous agonists (pK _i)	CCL13, CCL8, CCL3 (7.8 – 10.2) [571,572,588,630], CCL23 (Selective) (8.9) [571], CCL7 (8.1) [571,583], CCL5 (6.8 – 8.2) [572,588], CCL14 (7.4) [571], CCL15 (Selective) (pIC ₅₀ 7.9) [573]	CCL16, CCL2 (pIC ₅₀ 9.3 – 10.2) [573,595,598,605,615], CCL13 (pIC ₅₀ 8.6 – 8.7) [595,615], CCL7 (pIC ₅₀ 8.4 – 8.7) [573,595,615], CCL11 (Partial agonist) (pIC ₅₀ 7.1 – 7.7) [595,605]	CCL28, CCL8, CCL7 (8.6 – 9.2) [575], CCL13 (pIC ₅₀ 8.7 – 10.3) [599,615], CCL11 (Selective) (pIC ₅₀ 8.7 – 9.0) [577,591,599,610,615], CCL24 (Selective) (pIC ₅₀ 8.0 – 9.4) [599,605], CCL15 (pIC ₅₀ 8.6) [573], CCL26 (Selective) (pIC ₅₀ 7.9 – 8.9) [591,599,605]	CCL22 (Selective) (pIC ₅₀ 9.2) [589], CCL17 (Selective) (pIC ₅₀ 8.7) [589]	CCL16, CCL4 (Selective) (9.4 – 9.6) [602,609], CCL5 (9.2 – 9.7) [566,602,609], CCL8 (9.3) [609], CCL3 (8.0 – 8.9) [602,609,630], CCL2 (7.5) [602], CCL14 (7.2) [602], CCL11 (pIC ₅₀ 7.7) [570]
Selective agonists (pK _i)	–	–	CCL11 {Sp: Mouse} (9.5 – 10.0) [575]	–	R5-HIV-1 gp120
Non-selective agonists (pK _i)	–	–	–	vMIP-III	–
Endogenous antagonists (pK _i)	CCL4 (Selective) (7.1 – 7.8) [571,572]	CCL26 (Selective) (pIC ₅₀ 8.5) [605]	CXCL10 (Selective), CXCL11 (CXCL11, O14625) (Selective), CXCL9 (Selective)	–	CCL7 (Selective) (7.5) [602]

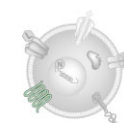


Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
Selective antagonists (pK _i)	CP-481,715 (pK _d 8.0) [579], BX 471 (8.2 – 9.0) [593], 2b-1 (pIC ₅₀ 8.7) [603], UCB35625 (pIC ₅₀ 8.0) [610]	GSK Compound 34 (7.6)	banyu (I) (Inverse agonist) (8.5) [617], SB328437 (8.4), BMS compound 87b (8.1) [616]	–	MRK-1, vicriviroc (9.1) [613], apilavirac (8.5) [596], ancicriviroc (7.8 – 8.7) [596,604,613], TAK-779 (7.5) [596], E913 (pIC ₅₀ 8.7) [597], maraviroc (pIC ₅₀ 8.1) [602]
Radioligands (K _d)	[¹²⁵ I]CCL7 (human) (Agonist, Full agonist) (7×10 ⁻¹⁰ M) [568], [¹²⁵ I]CCL3 (human) (Agonist, Full agonist) (1.58×10 ⁻⁹ – 1×10 ⁻⁸ M) [568,580,611], [¹²⁵ I]CCL5 (human) (Agonist, Full agonist) (7×10 ⁻⁹ M) [611]	[¹²⁵ I]CCL2 (Agonist, Full agonist), [¹²⁵ I]CCL7 (human) (Agonist)	[¹²⁵ I]CCL5 (human) (Agonist), [¹²⁵ I]CCL7 (human) (Agonist), [¹²⁵ I]CCL11 (human) (Antagonist) (5.01×10 ⁻⁹ M) [617]	[¹²⁵ I]CCL17 (Agonist, Full agonist), [¹²⁵ I]CCL27 (Agonist)	[¹²⁵ I]CCL3 (human) (Agonist), [¹²⁵ I]CCL5 (human) (Agonist), [¹²⁵ I]CCL8 (human) (Agonist), [¹²⁵ I]CCL4 (human) (Agonist, Full agonist) (2.51×10 ⁻¹⁰ M) [602]
Comment	–	–	–	Monoclonal antibody mogamulizumab selectively blocks CCR4	–

Nomenclature	CCR6	CCR7	CCR8	CCR9	CCR10
HGNC, UniProt	CCR6, P51684	CCR7, P32248	CCR8, P51685	CCR9, P51686	CCR10, P46092
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Endogenous agonists (pK _i)	beta-defensin 4A (DEFB4A, DEFB4B, O15263) (Selective) [625], CCL20 (pIC ₅₀ 7.9 – 8.5) [564–565,606]	CCL21 (Selective) (pIC ₅₀ 9.3) [627], CCL19 (Selective) (pIC ₅₀ 7.7 – 9.0) [626–627]	CCL8 (Mouse), CCL1 (Selective) (pIC ₅₀ 8.5 – 9.8) [574,585,590]	CCL25 (Selective)	CCL27 (Selective), CCL28 (Selective)
Selective agonists (pK _i)	–	–	vMIP-I (pIC ₅₀ 8.9 – 9.9) [574,590]	–	–
Selective antagonists (pK _i)	–	–	vMCC-I (pIC ₅₀ 9.4) [574]	–	–
Radioligands (K _d)	[¹²⁵ I]CCL20 (Agonist, Full agonist) (~1×10 ⁻¹⁰ M) [582]	[¹²⁵ I]CCL19 (Agonist, Full agonist), [¹²⁵ I]CCL21 (Agonist, Full agonist)	[¹²⁵ I]CCL1 (human) (Agonist, Full agonist) (2.13×10 ⁻¹⁰ – 1.2×10 ⁻⁹ M) [590,608]	[¹²⁵ I]CCL25 (Agonist, Full agonist)	–



Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6
HGNC, UniProt	<i>CXCR1</i> , P25024	<i>CXCR2</i> , P25025	<i>CXCR3</i> , P49682	<i>CXCR4</i> , P61073	<i>CXCR5</i> , P32302	<i>CXCR6</i> , O00574
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Endogenous agonists (pK _i)	CXCL8 (8.8 – 9.5) [569,584,592,622,623], CXCL6 (7.0) [624]	CXCL6 (pK _d 7.0) [624], CXCL8 (8.8 – 9.5) [569,584,592,622,623], CXCL1 (Selective) (8.4 – 9.7) [584,592,623], CXCL3 (Selective) (pIC ₅₀ 7.8 – 9.2) [563], CXCL2 (Selective) (pIC ₅₀ 7.0 – 9.1) [563], CXCL5 (Selective) (pIC ₅₀ 6.9 – 9.0) [563], CXCL7 (Selective) (pIC ₅₀ 6.3 – 9.3) [563]	CXCL11 (Selective) (10.4 – 10.5) [586], CXCL10 (Selective) (7.8 – 9.8) [586,619], CXCL9 (Selective) (7.3 – 8.3) [586,619]	SDF-1α (Selective) (pK _d 7.7 – 8.2) [587,594], SDF-1β (Selective) (pK _d 7.86) [587]	CXCL13 (Selective)	CXCL16 (Selective) (pK _d 9.0) [621]
Endogenous antagonists (pK _i)	–	–	CCL11 (Selective) (7.2) [619], CCL7 (Selective) (6.6) [619]	–	–	–
Selective agonists (pK _i)	–	–	–	X4-HIV-1 gp120, ALX40-4C (Partial agonist) (pIC ₅₀ 6.1) [629]	–	–
Non-selective agonists (pK _i)	–	vCXCL-1	–	–	–	–
Selective antagonists (pK _i)	–	SB 225002 (pIC ₅₀ 7.7) [620]	–	HIV-Tat, plerixafor (7.0) [629], T134 (pIC ₅₀ 8.4) [614]	–	–
Radioligands (K _d)	[¹²⁵ I]CXCL8 (human) (Agonist, Full agonist) (2.51×10 ⁻¹⁰ – 1.2×10 ⁻⁹ M) [584,607]	[¹²⁵ I]CXCL1 (Agonist, Full agonist), [¹²⁵ I]CXCL5 (Agonist, Full agonist), [¹²⁵ I]CXCL7 (Agonist, Full agonist), [¹²⁵ I]CXCL8 (human) (Agonist, Full agonist) (3.98×10 ⁻¹⁰ – 1.02×10 ⁻⁹ M) [584,607]	[¹²⁵ I]CXCL10 (Agonist, Full agonist), [¹²⁵ I]CXCL11 (Agonist, Full agonist)	[¹²⁵ I]SDF-1α (human) (Agonist, Full agonist) (3.98×10 ⁻⁹ – 7.94×10 ⁻⁹ M) [576,587]	–	[¹²⁵ I]CXCL16 (Agonist, Full agonist)



Nomenclature	CX ₃ CR1	XCR1	DARC
HGNC, UniProt	CX3CR1, P49238	XCR1, P46094	DARC, Q16570
Principal transduction	G _{i/o}	G _{i/o}	not defined
Endogenous agonists (pK _i)	CX ₃ CL1 (Selective) (pIC ₅₀ 8.9) [578]	XCL1 (Selective), XCL2 (Selective)	–
Endogenous ligands	–	–	CXCL5, CXCL6, CXCL8, CXCL11, CCL2, CCL5, CCL7, CCL11, CCL14, CCL17
Selective agonists (pK _i)	–	SEAP-XCL1	–
Radioligands (K _d)	[¹²⁵ I]CX ₃ CL1 (human) (Agonist, Full agonist)	–	–
Comment	–	When fused with secreted alkaline phosphatase (SEAP), XCL1 functions as a probe at XCR1	–

Nomenclature	ACKR2	ACKR3	ACKR4	CCRL2
HGNC, UniProt	ACKR2, O00590	ACKR3, P25106	ACKR4, Q9NPB9	CCRL2, O00421
Principal transduction	arrestin	arrestin	not defined	not defined
Endogenous agonists (pK _i)	–	CXCL11, SDF-1 α (pEC ₅₀ 7.52 – 7.9) [581,612]	CCL19 (8.4) [618], CCL25 (7.6) [618], CCL21 (6.9) [618]	–
Endogenous ligands	CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL17, CCL22	–	–	chemerin C-terminal peptide, CCL19 [567]

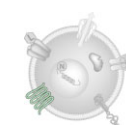
Comments: Mouse Cxcr binds iodinated mouse KC (CXCL1) and mouse MIP-2 (CXCL2) with high affinity (mouse KC and MIP-2 are homologues of human CXCL1 (CXCL1, P09341), CXCL2 (CXCL2, P19875) and CXCL3 (CXCL3, P19876)), but shows low affinity for human IL-8 (CXCL8 (IL8, P10145)).

Specific chemokine receptors facilitate cell entry by microbes, such as ACKR1 for *Plasmodium vivax*, and CCR5 for HIV-1. Virally encoded chemokine receptors are known (*e.g.* US28, a homologue of CCR1 from human cytomegalovirus and ORF74, which encodes a homolog of CXCR2 in *Herpesvirus saimiri* and Herpesvirus-68), 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 (CCL1, P22362)), MCP-1 (CCL2 (CCL2, P13500)), MIP-1 α (CCL3 (CCL3, P10147)), MIP-1 β (CCL4 (CCL4, P13236)), RANTES (CCL5

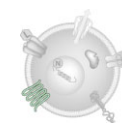
(CCL5, P13501)), MCP-3 (CCL7 (CCL7, P80098)), MCP-2 (CCL8 (CCL8, P80075)), eotaxin (CCL11 (CCL11, P51671)), MCP-4 (CCL13 (CCL13, Q99616)), HCC-1 (CCL14 (CCL14, Q16627)), Lkn-1/HCC-2 (CCL15 (CCL15, Q16663)), TARC (CCL17 (CCL17, Q92583)), ELC (CCL19 (CCL19, Q99731)), LARC (CCL20 (CCL20, P78556)), SLC (CCL21 (CCL21, O00585)), MDC (CCL22 (CCL22, O00626)), MPIF-1 (CCL23 (CCL23, P55773)), eotaxin-2 (CCL24 (CCL24, O00175)), TECK (CCL25 (CCL25, O15444)), eotaxin (CCL26 (CCL26, Q9Y258)), eskine/CTACK (CCL27 (CCL27, Q9Y4X3)) and MEC (CCL28 (CCL28, Q9NRJ3)). The CXC chemokine family (CXCL1–17) includes GRO α (CXCL1 (CXCL1, P09341)), GRO β (CXCL2 (CXCL2, P19875)), GRO γ (CXCL3 (CXCL3, P19876)), platelet factor 4 (CXCL4 (PF4, P02776)), ENA78 (CXCL5 (CXCL5, P42830)), GCP-2 (CXCL6 (CXCL6, P80162)), NAP-2 (CXCL7 (PPBP, P02775)), IL-8 (CXCL8 (IL8, P10145)), MIG (CXCL9 (CXCL9, Q07325)), IP10 (CXCL10 (CXCL10, P02778)), I-TAC (CXCL11 (CXCL11, O14625)), SDF-1 (CXCL12, *i.e.* SDF-1 α (CXCL12, P48061) and SDF-1 β (CXCL12,

P48061)), BLC (CXCL13 (CXCL13, O43927)), BRAK (CXCL14 (CXCL14, O95715)), mouse lungkine (CXCL15) SR-PSOX (CXCL16 (CXCL16, Q9H2A7)) and CXCL17 (CXCL17, Q6UXB2). The CX₃C chemokine (CX₃CL1 (CX3CL1, P78423)) is also known as fractalkine (neurotactin in the mouse). Like CXCL16 (CXCL16, Q9H2A7), and unlike other chemokines, CX₃CL1 (CX3CL1, P78423) 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 (XCL1, P47992)) is also known as lymphotactin. 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 plerixafor (Plerixifor, from Sanofi) for hematopoietic stem cell mobilization with G-CSF (CSF3, P09919) in patients undergoing transplantation in the context of chemotherapy for lymphoma and multiple myeloma.



Further reading

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Cholecystokinin receptors

Overview: Cholecystokinin receptors (nomenclature recommended by the [NC-IUPHAR](#) Subcommittee on CCK receptors, [644]) are activated by the endogenous peptides cholecystokinin-4 (CCK-4 (CCK, P06307)), CCK-8 (CCK, P06307), CCK-33 (CCK, P06307) and gastrin (gastrin-17 (GAST, P01350)).

There are only two distinct subtypes of CCK receptors, CCK₁ and CCK₂ receptors, with some alternatively spliced forms most often identified in neoplastic cells. The CCK receptor subtypes are distinguished by their peptide selectivity, with the CCK₁ receptor requiring the carboxyl-terminal heptapeptide-amide that

includes a sulfated tyrosine for high affinity and potency, while the CCK₂ receptor requires only the carboxyl-terminal tetrapeptide shared by both CCK and gastrin peptides. These receptors have characteristic and distinct distributions, with both present in both the central nervous system and peripheral tissues.

Nomenclature	CCK ₁ receptor	CCK ₂ receptor
HGNC, UniProt	CCKAR, P32238	CCKBR, P32239
Principal transduction	G _{q/11} /G _s	G _s
Rank order of potency	CCK-8 >> gastrin-17, CCK-8 (desulphated) > CCK-4	CCK-8 ≥ gastrin-17, CCK-8 (desulphated), CCK-4
Endogenous agonists (pK _i)	–	CCK-8 (desulphated) (pIC ₅₀ 8.3 – 8.7) [14], CCK-4 (pIC ₅₀ 7.5) [636]
Selective agonists (pK _i)	A-71623 (pIC ₅₀ 8.4 - Rat) [2], JMV180 (pIC ₅₀ 8.3) [639], GW-5823 (pIC ₅₀ 7.6) [633]	RB-400 (9.1 - Rat) [3], PBC-264 (pIC ₅₀ 9.1 – Rat) [638], gastrin-17 (pIC ₅₀ 8.3 - Mouse) [634]
Selective antagonists (pK _i)	devazepide (pIC ₅₀ 9.7 - Rat) [8], T-0632 (pIC ₅₀ 9.6 - Rat) [650], PD-140548 (pIC ₅₀ 8.6 - Rat) [647], lantitript (pIC ₅₀ 8.3) [632], lorglumide (pIC ₅₀ 6.7 – 8.2 - Rat) [634,637]	YF-476 (pIC ₅₀ 9.7) [4,24], GV150013 (pIC ₅₀ 9.4) [651], L-740093 (pIC ₅₀ 9.2) [643], YM-022 (pIC ₅₀ 9.2) [643], JNJ-26070109 (pIC ₅₀ 8.5) [642], L-365260 (pIC ₅₀ 8.4) [640], RP73870 (pIC ₅₀ 8.0 - Rat) [641], LY262691 (pIC ₅₀ 7.5 - Rat) [646]
Radioligands(K _d)	[³ H]devazepide (Antagonist) (2×10 ⁻¹⁰ M) [5]	[³ H]L365260 (Antagonist) (2.9×10 ⁻⁹ – 5.7×10 ⁻⁹ M) [17], [³ H]PD140376 (Antagonist) (K _i 1×10 ⁻¹⁰ – 2×10 ⁻¹⁰ M – Guinea pig) [635], [¹²⁵ I]PD142308 (Antagonist) (K _i 2.5×10 ⁻¹⁰ M), [¹²⁵ I]-BDZ ₂ (Antagonist) (K _i 3.98×10 ⁻⁹ M) [631], [¹²⁵ I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist, Full agonist) (IC ₅₀ 1×10 ⁻⁹ M) [645], [¹²⁵ I]gastrin (Agonist, Full agonist) (IC ₅₀ 1×10 ⁻⁹ M), [³ H]gastrin (Agonist, Full agonist) (IC ₅₀ 1×10 ⁻⁹ M)

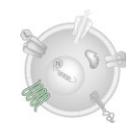
Comments: While a cancer-specific CCK receptor has been postulated to exist, which also might be responsive to incompletely processed forms of CCK (Gly-extended forms), this has never been isolated. An alternatively spliced form of the CCK₂ receptor in which intron 4 is retained, adding 69 amino acids to the

intracellular loop 3 (ICL3) region, has been described to be present particularly in certain neoplasms where mRNA mis-splicing has been commonly observed [648], but it is not clear that this receptor splice form plays a special role in carcinogenesis. Another alternative splicing event for the CCK₂ receptor was

reported [649], with alternative donor sites in exon 4 resulting in long (452 amino acids) and short (447 amino acids) forms of the receptor differing by five residues in ICL3, however, no clear functional differences have been observed.

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Complement peptide receptors

Formerly known as: Anaphylatoxin receptors

Overview: Complement peptide receptors (nomenclature as agreed by the NC-IUPHAR subcommittee on Complement peptide receptors, see [665]) are activated by the endogenous ~75 amino-acid anaphylatoxin polypeptides C3a (C3, P01024). C4a (C4A, P0C0L4) and C5a (C5, P01031), generated upon stimulation of the complement cascade.

Nomenclature	C3a receptor	C5a ₁ receptor	C5a ₂ receptor
HGNC, UniProt	C3AR1, Q16581	C5AR1, P21730	C5AR2, Q9P296
Principal transduction	G _{i/o} , G _z	G _{i/o} , G _z , G ₁₆ (Buhl <i>et al.</i> , 1993)	–
Rank order of potency	C3a > C5a [653]	C5a, C5a des-Arg (C5) > C3a [653]	–
Endogenous agonists (pK _i)	–	RP-S19 (RPS19, P39019) [675]	–
Selective agonists (pK _i)	E7 (pEC ₅₀ 8.7) [654]	N-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO ₂ H (pIC ₅₀ 7.6) [664,666]	–
Selective antagonists (pK _i)	SB290157 (pIC ₅₀ 7.6) [652]	CHIPS (pK _d 9.0) [670], W54011 (8.7) [672], AcPhe-Orn-Pro-D-Cha-Trp-Arg (pIC ₅₀ 7.9) [674], N-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO ₂ H (pIC ₅₀ 7.2) [666]	–
Radioligands (K _d)	[¹²⁵ I]C3a (human) (Agonist, Full agonist) (3.85×10 ^{−9} M) [657]	[¹²⁵ I]C5a (human) (Agonist, Full agonist) (2×10 ^{−9} M) [661]	[¹²⁵ I]C5a (human) (Agonist, Full agonist)
Comment	–	–	Binds C5a complement factor, but appears to lack G protein signalling and has been termed a decoy receptor [671]

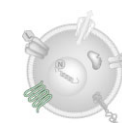
Comments: SB290157 has also been reported to have agonist properties at the C3a receptor [668]. The putative chemoattractant receptor termed C5a₂ (also known as GPR77, C5L2) binds [¹²⁵I]C5a with no clear signalling function, but has a putative role opposing inflammatory responses [656,658–659]. Binding to this

site may be displaced with the rank order C5a des-Arg (C5) > C5a (C5, P01031) [656,669] while there is controversy over the ability of C3a (C3, P01024) and C3a des Arg (C3, P01024) to compete [660,662–663,669]. C5a₂ appears to lack G protein signalling and has been termed a decoy receptor [671]. However, C5a₂ does

recruit β-arrestin after ligand binding, which might provide a signaling pathway for this receptor [655,673]. There are also reports of pro-inflammatory activity of C5a₂, mediated by HMGB1, but the signaling pathway that underlies this is currently unclear (reviewed in [667]).

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Corticotropin-releasing factor receptors

Overview: Corticotropin-releasing factor (CRF, nomenclature as recommended by the [NC-IUPHAR](#) sub-committee on Corticotropin-releasing Factor Receptors, [682]) receptors are activated by the endogenous peptides CRF (*CRH*, P06850), a 41

amino-acid peptide, urocortin 1 (*UCN*, P55089), 40 amino-acids), urocortin 2 (*UCN2*, Q96RP3), 38 amino-acids) and urocortin 3 (*UCN3*, Q969E3), 38 amino-acids). CRF1 and CRF2 receptors are activated non-selectively by CRF (*CRH*, P06850) and urocortin 1

(*UCN*, P55089). Binding to CRF receptors can be conducted using [¹²⁵I]Tyr⁰-CRF or [¹²⁵I]Tyr⁰-sauvagine with *K_d* values of 0.1–0.4 nM. CRF1 and CRF2 receptors are non-selectively antagonized by α -helical CRF, D-Phe-CRF-(12–41) and astressin.

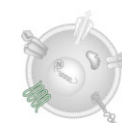
Nomenclature	CRF ₁ receptor	CRF ₂ receptor
HGNC, UniProt	<i>CRHR1</i> , P34998	<i>CRHR2</i> , Q13324
Principal transduction	G _s	G _s
Endogenous agonists	–	urocortin 2 (Selective) (<i>pK_d</i> 8.5 – 8.6) [679], urocortin 3 (Selective) (<i>pK_d</i> 7.9 – 8.0) [679]
Selective antagonists (<i>pK_i</i>)	SSR125543A (8.7) [681], antalarmin (8.3 – 9.0) [688], DMP696 (8.3 – 9.0) [683], NBI27914 (8.3 – 9.0) [677], R121919 (8.3 – 9.0) [689], CP 154,526 (<i>pIC₅₀</i> 9.3 – 10.4 - Rat) [685], CP376395 (<i>pIC₅₀</i> 8.3 - Rat) [678], CRA1000 (<i>pIC₅₀</i> 6.4 – 7.1) [676]	antisauvagine (<i>pK_d</i> 8.8 – 9.6) [680], K41498 (9.2) [684], K31440 (8.7 – 8.8) [687]

Comments: A CRF binding protein has been identified (*CRHBP*, P24387) to which both CRF and urocortin 1 bind with high affinities, which has been suggested to bind and inactivate circulating CRF [686].

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Dopamine receptors

Overview: Dopamine receptors (nomenclature as agreed by [NC-IUPHAR Subcommittee on Dopamine Receptors](#), [723]) are commonly divided into D₁-like (D₁ and D₅) and D₂-like (D₂, D₃ and D₄) families, where the endogenous agonist is dopamine.

Nomenclature	D ₁ receptor	D ₅ receptor	D ₂ receptor	D ₃ receptor	D ₄ receptor
HGNC, UniProt	<i>DRD1</i> , P21728	<i>DRD5</i> , P21918	<i>DRD2</i> , P14416	<i>DRD3</i> , P35462	<i>DRD4</i> , P21917
Principal transduction	G _s , G _{oif}	G _s	G _{i/o}	G _{i/o}	G _{i/o}
(Sub)family-selective agonists (pK _i)	A68930 (pEC ₅₀ 6.82) [712]	A68930 (pEC ₅₀ 6.6) [712]	quinpirole (4.9–7.7) [693,706,713,724–725,729] sumanirole (8.1) [705]	quinpirole (6.4–8.0) [693,706,710,713,724–725,729] PD 128907 (7.6–7.7) [715,720]	quinpirole (7.5) [709,713,729] PD168,077 (Partial agonist) (8.8 - Rat) [700], A412997 (8.1 - Rat) [711]
Selective agonists (pK _i)	SKF-81297 (8.7 - Rat) [691], SKF-38393 (6.2–6.8) [726–727]	–	–	–	–
(Sub)family-selective antagonists (pK _i)	SKF-83556 (9.5) [726], SCH-23390 (7.4–9.5) [726–727], ecopipam (8.3) [728]	SKF-83556 (9.4) [726], SCH-23390 (7.5–9.5) [726], ecopipam (8.3) [726]	haloperidol (7.4–8.8) [695,704,706,724,728]	haloperidol (7.5–8.0) [695,724,728]	haloperidol (8.7) [703,728]
Selective antagonists (pK _i)	–	–	L-741,626 (7.9–8.5) [696,701], domperidone (7.9–8.4) [695,724], raclopride (8.0) [710]	S33084 (9.6) [708], nafadotride (9.52) [721], PG01037 (9.2) [697], NGB 2904 (8.8) [730], SB 277011-A (8.0) [716], (+)-S-14297 (7.9) [707]	L745870 (9.4) [701], sonopiprazole (8.9) [722], L741742 (8.5) [719]
(Sub)family-selective radioligands (K _d)	[³ H]SCH-23390 (Antagonist) (3x10 ⁻¹⁰ M) [732]	[³ H]SCH-23390 (Antagonist) (5.8x10 ⁻¹⁰ M) [717]	[³ H]spiperone (Antagonist) (5.7x10 ⁻¹¹ M - Rat) [692,699,731]	–	[³ H]spiperone (Antagonist) (3x10 ⁻¹⁰ M) [698,729]
Radioligands (K _d)	[¹²⁵ I]SCH23982 (Antagonist) (3.5x10 ⁻¹⁰ M) [694]	[¹²⁵ I]SCH23982 (Antagonist) (8x10 ⁻¹⁰ M)	[³ H]raclopride (Antagonist) (1.2x10 ⁻⁹ M - Rat) [702]	[³ H]spiperone (Antagonist) (1.25x10 ⁻¹⁰ M - Rat) [699,731], [³ H]7-OH-DPAT (Agonist) (2.7x10 ⁻¹⁰ M) [718], [³ H]PD128907 (Agonist) (9.9x10 ⁻¹⁰ M) [690]	[¹²⁵ I]L750667 (Antagonist) (1.6x10 ⁻¹⁰ M) [713], [³ H]NGD941 (Antagonist) (5x10 ⁻⁹ M) [714]
Comment	A68930 is an agonist with selectivity for D ₁ -like receptors [712], SCH-23390 (pK _i 9.5) [726], SKF-83556 (pK _i 9.3) [726] and ecopipam (pK _i 8.3) [728] are antagonists with selectivity for D ₁ -like receptors	A68930 is an agonist with selectivity for D ₁ -like receptors [712], SCH-23390 (pK _i 9.5) [726], SKF-83556 (pK _i 9.3) [726] and ecopipam (pK _i 8.3) [728] are antagonists with selectivity for D ₁ -like receptors	quinpirole is an agonist with selectivity for D ₂ -like receptors [729]	quinpirole is an agonist with selectivity for D ₂ -like receptors [729]	quinpirole is an agonist with selectivity for D ₂ -like receptors [729]

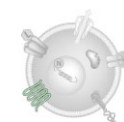
Comments: The selectivity of many of these agents is less than two orders of magnitude. [³H]raclopride exhibits similar high affinity for D₂ and D₃ receptors (low affinity for D₄), but has been used to label D₂ receptors in the presence of a D₃-selective antago-

nist. [³H]7-OH-DPAT has similar affinity for D₂ and D₃ receptors, but labels only D₃ receptors in the absence of divalent cations. The pharmacological profile of the D₅ receptor is similar to, yet distinct from, that of the D₁ receptor. The splice variants of the D₂

receptor are commonly termed D_{2s} and D_{2l} (short and long). The *DRD4* gene encoding the D₄ receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

Searchable database: <http://www.guidetopharmacology.org/index.jsp>

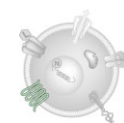
Full Contents of Concise Guide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full>



Dopamine receptors 1503

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Endothelin receptors

Overview: Endothelin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on endothelin receptors, [736]) are activated by the endogenous 21 amino-acid peptides endothelins 1–3 (ET-1 (*EDN1*, P05305), ET-2 (*EDN2*, P20800) and ET-3 (*EDN3*, P14138)).

	ET _A receptor	ET _B receptor
Nomenclature	ET _A receptor	ET _B receptor
HGNC, UniProt	<i>EDNRA</i> , P25101	<i>EDNRB</i> , P24530
Principal transduction	G _{q/11} , G _s	G _{q/11} , G _{i/o}
Family selective agonists	ET-1 = ET-2 > ET-3 [744]	ET-1 = ET-2, ET-3
(Sub)family-selective antagonists (pK _i)	TAK 044 (pA ₂ 8.4 - Rat) [755], bosentan (pA ₂ 7.2 - Rat) [735], SB209670 (pK _i 9.4 - Rat) [739]	–
Selective agonists (pK _i)	–	sarafotoxin S6c (pK _d 8.8–9.8) [743,752], [Ala ^{1,3,11,15}]ET-1 (pK _d 8.7–9.2) [747], BQ 3020 (9.7) [751], IRL 1620 (8.7) [754]
(Sub)family-selective antagonists (pK _i)	–	TAK 044 (pA ₂ 8.4 - Rat) [755], bosentan (pA ₂ 6.0 - Rat) [735], SB209670 (pK _i 9.4 - Rat) [739]
Selective antagonists (pK _i)	A127722 (pA ₂ 9.2–10.5) [749], BQ123 (pA ₂ 6.9–7.4) [744], ambrisentan (pA ₂ 7.1) [733], PD-156707 (pK _d 9.0–9.8) [745], FR139317 (Inverse agonist) (pIC ₅₀ 7.3–7.9) [744]	A192621 (pK _d 8.1) [753], BQ788 (pK _d 7.9–8.0) [752], IRL 2500 (pK _d 7.2) [752], RO4868443 (pIC ₅₀ 7.2) [734]
Radioligands (K _d)	[¹²⁵ I]PD164333 (Antagonist) (1.58×10 ^{–10} –2.5×10 ^{–10} M) [737], [³ H]S0139 (Antagonist) (6×10 ^{–10} M), [¹²⁵ I]PD151242 (Antagonist) (7.9×10 ^{–10} –1×10 ^{–9} M) [738], [³ H]BQ123 (Antagonist) (3.2×10 ^{–9} M) [742]	[¹²⁵ I]IRL1620 (Agonist, Full agonist) (7.9×10 ^{–11} –1.26×10 ^{–10} M) [748], [¹²⁵ I][Ala ^{1,3,11,15}]ET-1 (Agonist, Full agonist) (2×10 ^{–10} M) [747], [¹²⁵ I]BQ3020 (Agonist, Full agonist) (1×10 ^{–10} –5×10 ^{–9} M) [740,747,750]

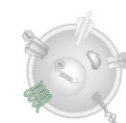
Comments: Splice variants of the ET_A receptor have been identified in rat pituitary cells; one of these, ET_AR-C13, appeared to show loss of function with comparable plasma membrane expression [741]. Subtypes of the ET_B receptor have been proposed, although gene disruption studies in mice suggest that the heterogeneity results from a single gene product [746].

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Endothelin receptors 1505

Estrogen (G protein-coupled) receptor

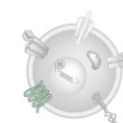
Overview: The G protein-coupled estrogen receptor (GPER, provisional nomenclature) was identified following observations of estrogen-evoked cAMP signalling in breast cancer cells [756], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [758]. There are observations of both cell-surface and intracellular expression of the GPER receptor [763–764].

Nomenclature	HGNC, UniProt	Principal transduction	Selective agonists (pK _i)	Selective antagonists (pK _i)	Radioligands (K _d)
GPER	GPER1, Q99527	G _s [761], G _{i/o} [763]	G-1 (8.0) [757]	G36 (pIC ₅₀ 6.78–6.95) [760], G15 (pIC ₅₀ 6.7) [759]	[³ H]17β-estradiol (Agonist, Full agonist) (2.7×10 ⁻⁹ –3.3×10 ⁻⁹ M) [764]

Comments: Antagonists at the nuclear estrogen receptor, such as fulvestrant and tamoxifen [761], as well as the flavonoid ‘phytoestrogens’ genistein and quercetin [762], are agonists at GPER receptors.

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Formylpeptide receptors

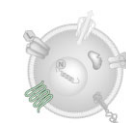
Overview: The formylpeptide receptors, nomenclature agreed by NC-IUPHAR Subcommittee on the formyl peptide receptor family, [787]) respond to exogenous ligands such as the bacterial product fMet-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ANXA1, P04083), cathepsin G (CTSG, P08311), amyloid β 42, serum amyloid A and spinorphin, derived from β -haemoglobin (HBB, P68871).

Nomenclature	FPR1	FPR2/ALX	FPR3
HGNC, UniProt	<i>FPR1</i> , P21462	<i>FPR2</i> , P25090	<i>FPR3</i> , P25089
Principal transduction	G _{i/o} , G _z	G _i [778]	–
Rank order of potency	fMet-Leu-Phe > cathepsin G (CTSG, P08311) > annexin I [776,783]	LXA ₄ =aspirin triggered lipoxin A4=ATLa2>LTC ₄ =LTD ₄ >>15-deoxy-LXA ₄ >>fMet-Leu-Phe [765–766,768,770,784]	–
Selective agonists (pK _i)	fMet-Leu-Phe (pEC ₅₀ 10.1–10.2) [769,782]	–	–
Endogenous antagonists (pK _i)	spinorphin (Selective) (pIC ₅₀ 4.3) [777,780]	aspirin triggered lipoxin A4 (Selective), LXA ₄ (Selective) (pEC ₅₀ ~12.0) [775], resolvin D1 (Selective) (pEC ₅₀ ~11.9) [775]	–
Endogenous agonists(pK _i)	F2L (<i>HEBP1</i> , Q9NRV9) (Selective) (pEC ₅₀ 8.0–8.2) [779]	–	–
Selective antagonists (pK _i)	cyclosporin H (6.1–7.1) [785–786], t-Boc-FLFLF (6.0–6.5) [785]	ATLa2 [771]	–
Radioligands (K _d)	[³ H]fMet-Leu-Phe (Agonist, Full agonist) (5×10 ^{–10} –2.51×10 ^{–8} M) [774]	[³ H]LXA ₄ (Agonist, Full agonist) (5×10 ^{–10} –7×10 ^{–10} M) [766–767]	–
Comment	A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [773]	The agonist activity of the lipid mediators described has been questioned [772,781], which may derive from batch-to-batch differences, partial agonism or biased agonism	–

Comments: Note that the data for FPR2ALX are also reproduced on the leukotriene receptor page.

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Free fatty acid receptors

Overview: Free fatty acid receptors (FFA, nomenclature as agreed by NC-IUPHAR Subcommittee on free fatty acid receptors, [792,814]) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (C14:0 (myristic acid), C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (linoleic acid), C18:3,

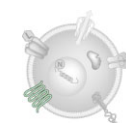
(α -linolenic acid), C20:4 (arachidonic acid), C20:5,n-3 (EPA), C22:6,n-3 (docosahexaenoic acid)) activate FFA₁ [789,797,799] and FFA4 receptors [793,796,807], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA₂ [790,801,806] and FFA₃ [790,801]

receptors. In addition, thiazolidinedione PPAR γ agonists such as rosiglitazone activate FFA₁ (pEC₅₀ 5.2; [800,811,813]) and small molecule allosteric modulators, such as 4-CMTB, have recently been characterised for FFA₂ [795,802,812].

Nomenclature	FFA1 receptor	FFA2 receptor	FFA3 receptor	FFA4 receptor
HGNC, UniProt	<i>FFAR1</i> , O14842	<i>FFAR2</i> , O15552	<i>FFAR3</i> , O14843	<i>FFAR4</i> , Q5NUL3
Principal transduction	G _{q/11} [789,797,809,813]	G _{q/11} , G _{i/o} [790,801,806,808]	G _{i/o} [790,801,808,813]	G _{q/11} [793,807,810,819]
Endogenous agonists (pK _i)	docosahexaenoic acid (pEC ₅₀ 5.4–6.0) [789,797]	–	–	α -linolenic acid (pEC ₅₀ 5.5) [810]
(Sub)family-selective agonists (pK _i)	α -linolenic acid (pEC ₅₀ 4.6–5.7) [789,797,799], myristic acid (pEC ₅₀ 4.5–5.1) [789,797,799], oleic acid (pEC ₅₀ 3.9–5.7) [789,797,799]	propanoic acid (pEC ₅₀ 3.0–4.9) [790,801,806,808], acetic acid (pEC ₅₀ 3.1–4.6) [790,801,806,808], <i>trans</i> -2-methylcrotonic acid (pEC ₅₀ 3.8) [808], butyric acid (pEC ₅₀ 2.9–4.6) [790,801,806,808], 1-methylcyclopropanecarboxylic acid (pEC ₅₀ 2.6) [808]	propanoic acid (pEC ₅₀ 3.9–5.7) [790,801,808,820], butyric acid (pEC ₅₀ 3.8–4.9) [790,801,808,820], 1-methylcyclopropanecarboxylic acid (pEC ₅₀ 3.9) [808], acetic acid (pEC ₅₀ 2.8–3.9) [790,801,808,820]	myristic acid (pEC ₅₀ 5.2) [819], oleic acid (pEC ₅₀ 4.7) [819]
Selective agonists (pK _i)	AMG-837 (pEC ₅₀ 8.5) [804], TUG-770 (pEC ₅₀ 8.2) [791], GW9508 (pEC ₅₀ 7.3) [788], TAK-875 (pEC ₅₀ 7.1) [817], linoleic acid (pEC ₅₀ 4.4–5.7) [789,797,799]	3-benzyl-4-(cyclopropyl-(4-(2,5-dichlorophenyl)thiazol-2-yl)amino)-4-oxobutanoic acid (pEC ₅₀ 7.1 - Rat) [794], (S)-4-CMTB (pEC ₅₀ 6.4) [795,802]	–	TUG-891 (pEC ₅₀ 7.0) [810], NCG21 (pEC ₅₀ 5.92) [816]
Selective antagonists (pK _i)	GW1100 (pIC ₅₀ 6.0) [788]	CATPB (pIC ₅₀ 6.5) [795]	–	–
Comment	Antagonist GW1100 has been shown to reduce [³⁵ S]GTP γ S binding in <i>FFAR1</i> -expressing cells [813]. GW1100 is also an oxytocin receptor antagonist [788]. TUG770 and GW9508 are both approximately 100 fold selective for FFA1 over FFA4 [788,791]. AMG837 and the related analogue AM6331 have been suggested to have an allosteric mechanism of action at FFA1, with respect to the orthosteric fatty acid binding site [804,821]	–	Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [798]. <i>trans</i> -2-methylcrotonic acid is a weak agonist for FFA3, with a pEC of below 1 [808]	TUG891 exhibits 50–1000 fold selectivity for FFA4 over FFA1, dependent on the assay [810]. NCG21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [815]

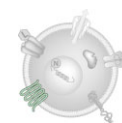
Comments: Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [805], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [819]. The long FFA4 splice variant has not been identified in other primates or rodents to date [793,805].

GPR42 was originally described as a pseudogene within the family (ENSM00250000002583), but the recent discovery of several polymorphisms suggests that some versions of *GPR42* may be functional [803]. *GPR84* is a structurally-unrelated G protein-coupled receptor which has been found to respond to medium chain fatty acids [818].



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Frizzled Class GPCRs

Overview: Receptors of the Class Frizzled (FZD, nomenclature as agreed by the NC-IUPHAR subcommittee [832]), are GPCRs originally identified in *Drosophila* [825], which are highly conserved across species. FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins 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 regulator β -catenin (*CTNNB1*, P35222) or being β -catenin-independent (often referred to as canonical vs non-canonical WNT/FZD signalling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors *LRP5* (O75197) and *LRP6* (O75581),

lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β -catenin and subsequently its translocation to the nucleus. β -Catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors. β -Catenin-independent FZD signalling 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 [830], the elevation of intracellular calcium [833], activation of cGMP-specific PDE6 [822] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [828]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling. As

with other GPCRs, members of the Frizzled family are functionally dependent on the β -arrestin scaffolding protein for internalization [826], β -catenin-dependent [823] and -independent [824,831] signalling. The pattern of cell signalling is complicated by the presence of additional ligands, which can enhance or inhibit FZD signalling (secreted Frizzled-related proteins (sFRP), Wnt-inhibitory factor (*WIF1*, Q9Y5W5) (WIF), Sclerostin (*SOST*, Q9BQB4)) or Dickkopf (*DKK1*), as well as modulatory (co)-receptors with positive Ryk, ROR1, ROR2 and Kremen, which may also function as independent signalling proteins.

Nomenclature	FZD ₁	FZD ₂	FZD ₃	FZD ₄	FZD ₅	FZD ₆	FZD ₇	FZD ₈	FZD ₉	FZD ₁₀	SMO
HGNC,	<i>FZD1</i> ,	<i>FZD2</i> ,	<i>FZD3</i> ,	<i>FZD4</i> ,	<i>FZD5</i> ,	<i>FZD6</i> ,	<i>FZD7</i> ,	<i>FZD8</i> ,	<i>FZD9</i> ,	<i>FZD10</i> ,	<i>SMO</i> ,
UniProt	Q9UP38	Q14332	Q9NPG1	Q9ULV1	Q13467	O60353	O75084	Q9H461	O00144	Q9ULW2	Q99835

Comments: There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. Understanding of the coupling to G proteins is incomplete (see [827]). There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships [829].

Ligands associated with FZD signalling WNTs: Wnt-1 (*WNT1*, P04628), Wnt-2 (*WNT2*, P09544) (also known as Int-1-related protein), Wnt-2b (*WNT2B*, Q93097) (also known as WNT-13), Wnt-3 (*WNT3*, P56703), Wnt-3a (*WNT3A*, P56704), Wnt-4

(*WNT4*, P56705), Wnt-5a (*WNT5A*, P41221), Wnt-5b (*WNT5B*, Q9H1J7), Wnt-6 (*WNT6*, Q9Y6F9), Wnt-7a (*WNT7A*, O00755), Wnt-7b (*WNT7B*, P56706), Wnt-8a (*WNT8A*, Q9H1J5), Wnt-8b (*WNT8B*, Q93098), Wnt-9a (*WNT9A*, O14904) (also known as WNT-14), Wnt-9b (*WNT9B*, O14905) (also known as WNT-15 or WNT-14b), Wnt-10a (*WNT10A*, Q9GZT5), Wnt-10b (*WNT10B*, O00744) (also known as WNT-12), Wnt-11 (*WNT11*, O96014) and Wnt-16 (*WNT16*, Q9UBV4).

Extracellular proteins that interact with FZDs: norrin (*NDP*, Q00604), R-spondin-1 (*RSPO1*, Q2MKA7), R-spondin-2 (*RSPO2*, Q6UXX9), R-spondin-3 (*RSPO3*, Q9BXY4), R-spondin-4 (*RSPO4*,

Q2I0M5), sFRP-1 (*SFRP1*, Q8N474), sFRP-2 (*SFRP2*, Q96HF1), sFRP-3 (*FRZB*, Q92765), sFRP-4 (*SFRP4*, Q6FHJ7), sFRP-5 (*SFRP5*, Q6FHJ7).

Extracellular proteins that interact with WNTs or LRP: Dickkopf 1 (*DKK1*, O94907), *WIF1* (Q9Y5W5), *SOST* (*SOST*, Q9BQB4), kremen 1 (*KREMEN1*, Q96MU8) and kremen 2 (*KREMEN2*, Q8NCW0)

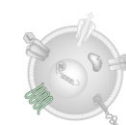
Small exogenous ligands: Foxy-5, Box-5, UM206, and XWnt8 also known as mini-Wnt8.

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GABA_B receptors

Overview: Functional GABA_B receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA_B receptors, [839,860]) are formed from the heterodimerization of two similar 7TM subunits termed GABA_{B1} (*GABBR₁*, Q9UBS5) and GABA_{B2} (*GABBR₂*, O75899) [839,843,859–860,866]. 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 Ca²⁺ channels (Ca_v2.1, Ca_v2.2), or inwardly rectifying potassium channels (Kir3) [837,839–840]. The GABA_{B2} subunit also determines the rate of internalisation of the dimeric GABA_B receptor [850]. 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 [839,849,859]. The two subunits interact by direct allosteric coupling [857], 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 [855,859]. 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 [837,859]. 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 [841,858]. 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 sig-

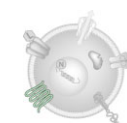
nalling kinetics and agonist potency to the receptor complex [835,864] and reviewed by [861]. Four isoforms of the human GABA_{B1} subunit have been cloned. The predominant GABA_{B1(a)} and GABA_{B1(b)} isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their 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 [862,868]. 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 [839]. Additional GABA_{B1} subunit isoforms have been described in rodents and humans [856] and reviewed by [837].

Nomenclature	Principal transduction	Selective agonists (pK _i)	Selective antagonists (pK _i)	Radioligands (K _d)
GABA _B receptor	G _{i/o}	3-APPA (5.2–7.2) [851], 3-APMPA (5.1) [869], CGP 44532 (pIC ₅₀ 8.6 - Rat) [846], (-)-baclofen (pIC ₅₀ 8.5 - Rat) [846]	CGP 62349 (8.5–8.9) [851,869], CGP 55845 (7.8) [869], SCH 50911 (5.5–6.0) [851,869], CGP 35348 (4.4) [869], 2-hydroxy-saclofen (pIC ₅₀ 4.1 - Rat) [853]	[³ H](R)-(-)-baclofen (Agonist), [³ H]CGP 62349 (Antagonist) (9×10 ⁻¹⁰ M - Rat) [854], [¹²⁵ I]CGP 64213 (Antagonist) (1×10 ⁻⁹ M - Rat) [847], [¹²⁵ I]CGP 71872 (Antagonist) (1×10 ⁻⁹ M - Rat) [853], [³ H]CGP 54626 (Antagonist) (K _d 7.9×10 ⁻¹⁰ M - Rat) [852]

Comments: Potencies of agonists and antagonists listed in the table, quantified as IC₅₀ values for the inhibition of [³H]CGP27492 binding to rat cerebral cortex membranes, are from [839,845–846]. Radioligand K_d values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the GABA_{B1} subunit [836]. CGP27492 (3-APPA), CGP35024 (3-APMPA) and CGP 44532 act as antagonists at human GABA_A ρ 1 receptors, with potencies in the low micromolar range [845]. In addition to the ligands listed in the table, Ca²⁺ binds to the VTM of the GABA_{B1} subunit to act as a positive allosteric

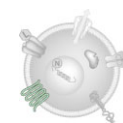
modulator of GABA [847]. In cerebellar Purkinje neurones, the interaction of Ca²⁺ with the GABA_B receptor enhances the activity of mGlu₁, through functional cross-talk involving G-protein G $\beta\gamma$ subunits [863,865]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 and (+)-BHFF [834,837–838,845]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA_{B2} subunit [842,859]. In the presence of CGP7930, or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [845]. 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 [844,867]. A similar phenotype has been found for GABA_{B2}^{-/-} BALB/c mice [848].



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Galanin receptors

Overview: Galanin receptors (provisional nomenclature, [876]) are activated by the endogenous peptides galanin (*GAL*, P22466) and galanin-like peptide (*GALP*, Q9UBC7). Human galanin (*GAL*, P22466) is a 30 amino-acid non-amidated peptide [874]; 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 [872] and porcine galanin-5–29 [885] and N-terminally extended forms (*e.g.* N-terminally seven and nine residue elongated forms of porcine galanin [873,885]) have been reported.

Nomenclature	GAL ₁ receptor	GAL ₂ receptor	GAL ₃ receptor
HGNC, UniProt	<i>GALR1</i> , P47211	<i>GALR2</i> , O43603	<i>GALR3</i> , O60755
Principal transduction	G _{i/o}	G _{i/o} , G _{q/11}	G _{i/o}
Rank order of potency	galanin > galanin-like peptide [881]	galanin-like peptide ≥ galanin [881]	galanin-like peptide > galanin [878]
Selective agonists (pK _i)	–	[D-Trp ²]galanin-(1–29) (8.15 - Rat) [887], galanin(2–29) (rat/mouse) (7.25–8.72 - Rat) [882,891–893]	–
Selective antagonists (pK _i)	2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC ₅₀ 5.57) [884]	M871 (7.88) [889]	–

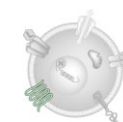
Comments: galanin-(1-11) is a high-affinity agonist at GAL₁/GAL₂ (pK_i 9), and galanin(2–11) is selective for GAL₂ and GAL₃ compared with GAL₁ [880]. [¹²⁵I]-[Tyr²⁶]galanin binds to all three subtypes with K_d values ranging from 0.05 to 1 nM [875,886–888,892]. Porcine galanin-(3–29) does not bind to cloned GAL₁, GAL₂ or GAL₃ receptors, but a receptor that is functionally activated by porcine galanin-(3–29) has been reported in pituitary and gastric smooth muscle cells [877,895]. 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 [890], spinal cord [894], locus coeruleus, hippocampus [870] and hypothalamus [871,879], but exhibit agonist activity at some peripheral sites [871,877]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL₁ receptors expressed endogenously in Bowes human melanoma cells [881], and at heterologously expressed

recombinant GAL₁, GAL₂ and GAL₃ receptors [875,887–888]. Recent studies have described the synthesis of a series of novel, systemically-active, galanin analogues, with modest preferential binding at the GAL₂ receptor. Specific chemical modifications to the galanin backbone increased brain levels of these peptides after *i.v.* injection and several of these peptides exerted a potent antidepressant-like effect in mouse models of depression [883].

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Ghrelin receptor

Overview: Ghrelin receptors (nomenclature approved by NC-IUPHAR, [898]) are activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (*GHRL*, Q9UBU3). 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 [907]. Alternative splicing results in the formation of a second peptide, [des-Gln¹⁴]ghrelin

(*GHRL*, Q9UBU3) with equipotent biological activity [904]. A unique post-translational modification (octanoylation of Ser³, catalysed by ghrelin O-acyltransferase (*MBOAT4*, Q96T53) [913] 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 [906]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [897], and receptor

mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin (*GHRL*, Q9UBU3) function [902]. In cell systems, the ghrelin receptor is constitutively active [903], 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 [910].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Selective antagonists (pK _i)	Radioligands (K _d)
ghrelin receptor	<i>GHSR</i> , Q92847	G _{q/11}	ghrelin = [des-Gln ¹⁴]ghrelin [896,907]	GSK1614343 (pK _B 8.0 - Rat) [911], YIL781 (pK _B 8.0) [899], GSK1614343 (pIC ₅₀ 8.4) [912]	[¹²⁵ I][His ⁹]ghrelin (human) (Agonist, Full agonist) (4×10 ⁻¹⁰ M) [905], [¹²⁵ I][Tyr ⁴]ghrelin (human) (Agonist, Full agonist) (4×10 ⁻¹⁰ M) [909]

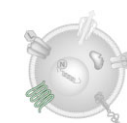
Comments: [des-octanoyl]ghrelin has been shown to bind (as [¹²⁵I]Tyr⁴-des-octanoyl-ghrelin) and have effects in the cardiovascular system [896], which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified ([D-Arg¹,D-Phe⁸,D-Trp^{7,9},Leu¹¹]substance P, pD₂ 8.3; [901]).

TZP101, described as a ghrelin receptor agonist (pK_i 7.8 and pD₂ 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 [900]. A number of selective antagonists have been reported, including peptidomimetic [908] and non-peptide small molecules including GSK1614343 [911–912].

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Glucagon receptor family

Overview: The glucagon family of receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on the Glucagon receptor family, [926]) 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 insulintropic polypeptide, also known as gastric inhibitory polypeptide or GIP (*GIP*, P09681), GHRH (*GHRH*, P01286) and secretin (*SCT*, P09683). One common precursor (*GCG*, P01275) generates glucagon, GLP-1 and GLP-2 peptides [922].

Nomenclature	glucagon receptor	GLP-1 receptor	GLP-2 receptor	GIP receptor	GHRH receptor	secretin receptor
HGNC, UniProt	<i>GCCR</i> , P47871	<i>GLP1R</i> , P43220	<i>GLP2R</i> , O95838	<i>GIPR</i> , P48546	<i>GHRHR</i> , Q02643	<i>SCTR</i> , P47872
Principal transduction	G _s	G _s	G _s	G _s	G _s	G _s
Endogenous agonists (pK _i)	glucagon (Selective) (pEC ₅₀ 9.0) [929]	glucagon-like peptide-1-(7-37) (Selective) [919], glucagon-like peptide 1-(7-36) amide (Selective) (9.2) [923]	GLP-2 (Selective) (pIC ₅₀ 8.5) [932]	GIP (Selective) (pK _d 8.7) [938]	–	secretin (Selective) (pEC ₅₀ 9.7) [916]
Selective agonists (pK _i)	–	exendin-3 (P20394) [930], exendin-4 (8.7 – 9.0) [923]	–	–	BIM28011 [918], JJ-38 (Rat) [924]	–
Selective antagonists (pK _i)	BAY27-9955 [928], des-His ¹ -[Glu ⁹]glucagon-NH ₂ (pA ₂ 7.2 - Rat) [934–935], NNC 92-1687 (5.0) [925], L-168,049 (pIC ₅₀ 8.4) [915]	exendin-(9-39) (8.1) [923], GLP-1-(9-36) (pIC ₅₀ 6.91 - Rat) [927], T-0632 (pIC ₅₀ 4.7) [933]	–	[Pro ³]GIP	JV-1-36 (10.1 – 10.4 - Rat) [931,936–937], JV-1-38 (10.1 - Rat) [931,936–937]	[(CH ₂ NH) ^{4,5}]secretin (5.3) [921]
Radioligands (K _d)	[¹²⁵ I]glucagon (human, mouse, rat) (Agonist, Full agonist)	[¹²⁵ I]exendin, [¹²⁵ I]GLP-1-(7-37) (Agonist, Full agonist), [¹²⁵ I]GLP-1-(7-36)-amide (Agonist, Full agonist) (5x10 ⁻¹⁰ M) [923], [¹²⁵ I]exendin-(9-39) (Antagonist) (5x10 ⁻⁹ M) [923]	–	[¹²⁵ I]GIP (Agonist, Full agonist) (2.51x10 ⁻⁹ M - Rat) [920]	[¹²⁵ I]GHRH (human) (Agonist, Full agonist) (2.8x10 ⁻⁸ M - Rat) [914]	[¹²⁵ I](Tyr ¹⁰)secretin

Comments: The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems [917], although the physiological significance of this has yet to be established.

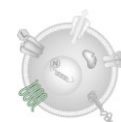
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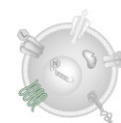
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Glucagon receptor family 1515

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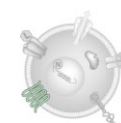
Glycoprotein hormone receptors

Overview: Glycoprotein hormone receptors (provisional nomenclature) are activated by a non-covalent heterodimeric glycoprotein made up of a common α chain (glycoprotein hormone common alpha subunit (CGA, P01215) CGA, P01215), with a unique β chain that confers the biological specificity to FSH (CGA, FSHB, P01215, P01225), LH (LHB, CGA, P01229, P01215), hCG (CGA, CGB, P01233, P01215), CGB2/CGB or TSH (TSHB, CGA, P01222, P01215). 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 [950].

Nomenclature	FSH receptor	LH receptor	TSH receptor
HGNC, UniProt	FSHR, P23945	LHCGR, P22888	TSHR, P16473
Principal transduction	G _s	G _s , G _{q/11} and G _i	All four families of G proteins can be activated by this receptor
Endogenous agonists (pK _i)	FSH (Selective)	hCG (Selective) (pK _d 9.9 – 11.8) [942,946], LH (Selective) (pIC ₅₀ 9.9 – 10.9) [942,946]	TSH (Selective)
Radioligands (K _d)	[¹²⁵ I]FSH (human) (Agonist, Full agonist)	[¹²⁵ I]CG (human) (Agonist, Full agonist), [¹²⁵ I]LH (Agonist, Full agonist)	[¹²⁵ I]TSH (Agonist, Full agonist)
Comment	Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders [939–941,953]. The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein [948].	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 (<i>e.g.</i> [944,951]) and Leydig cell tumours [945].	Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Grave's disease (<i>e.g.</i> [949]). Mutations of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas [947] and congenital hyperthyroidism [943]. TSH receptor loss-of-function mutations are associated with TSH resistance [952].

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Gonadotrophin-releasing hormone receptors

Overview: GnRH₁ and GnRH₂ receptors (provisional nomenclature, also called Type I and Type II, respectively) have been cloned from numerous species (most of which express two or three types of GnRH receptor) and grouped phylogenetically [975]. Designated GnRH I (*GNRH1*, P01148) (to distinguish it from related peptides, such as GnRH II (*GNRH2*, O43555) (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH₂, also known as chicken GnRH-II) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH₂), also known as luteinising

hormone-releasing hormone, gonadoliberein, luliberin, gonadorelin. Receptors for all three ligands exist in amphibians but only GnRH I (*GNRH1*, P01148) and GnRH II (*GNRH2*, O43555) (and their cognate receptors) have been found in mammals [969,974]. GnRH₁ receptors are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I (*GNRH1*, P01148) and all lack the C-terminal tails found in other GPCR. GnRH₂ receptors all possess C-terminal tails and (where tested)

are selective for GnRH II (*GNRH2*, O43555) (over GnRH I (*GNRH1*, P01148)). An alternative phylogenetic classification [970] divided these receptors into three classes and includes both GnRH I-selective mammalian and GnRH II-selective non-mammalian receptors as GnRH₁ receptors. Although thousands of peptide analogues of GnRH I (*GNRH1*, P01148) have been synthesised and several (agonists and antagonists) are used therapeutically [961], the potency of most of these peptides at GnRH₂ receptors is unknown.

Nomenclature	GnRH receptor	GnRH2 receptor
HGNC, UniProt	<i>GNRHR</i> , P30968	<i>GNRHR2</i> , Q96P88
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	GnRH I > GnRH II	GnRH II > GnRH I
Selective agonists (pK _i)	buserelin, goserelin, histrelin, nafarelin, triptorelin (9.3 – 9.5) [954], leuprolide (8.5 – 9.1) [976]	–
Selective antagonists (pK _i)	ganirelix, abarelix (9.1 – 9.5) [976], antide (9.0) [972], cetrorelix (8.8) [972]	trptorelix-1 [967]
Radioligands (K _d)	[¹²⁵ I]GnRH I (human, mouse, rat) (Agonist, Full agonist), [¹²⁵ I]buserelin (Agonist, Full agonist) (4 × 10 ⁻⁸ M - Rat) [964]	[¹²⁵ I]GnRH II (human) (Agonist, Full agonist)

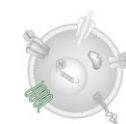
Comments: GnRH₁ and GnRH₂ receptors couple primarily to G_{q/11} [958] but coupling to G_s and G_i is evident in some systems [963]. GnRH₂ receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [955]. There is increasing evidence for expression of GnRH receptors on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues [956,960,966,973]. In some human cancer cell models GnRH II (*GNRH2*, O43555) is more potent than GnRH I (*GNRH1*, P01148), implying mediation

by GnRH₂ receptors [959]. However, GnRH₂ 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 [971]. The possibility remains that this gene generates GnRH₂ receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (*GNRH2*, O43555) (see [972]). Alternatively, there is evidence for multiple active GnRH receptor conformations [955,968,970] raising the possibility that GnRH₁ receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon dif-

ferent conformations (with different ligand specificity) than effects on G_{q/11} in pituitary cells [968]. Loss-of-function mutations in the GnRH₁ receptor and deficiency of GnRH I (*GNRH1*, P01148) are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' GnRH₁ receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists [965]. GnRH receptor signalling may be dependent upon receptor oligomerisation [957,962].

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GPR18, GPR55 and GPR119

Overview: GPR18, GPR55 and GPR119 (provisional nomenclature), although showing little structural similarity to CB₁ and CB₂ cannabinoid receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands [988].

Nomenclature	<i>GPR18</i>	<i>GPR55</i>	<i>GPR119</i>
HGNC, UniProt	<i>GPR18</i> , Q14330	<i>GPR55</i> , Q9Y2T6	<i>GPR119</i> , Q8TDV5
Principal transduction	G _{i/o} [982]	G _{12/13} [989]	G _s [984,987]
Rank order of potency	–	–	N-oleylethanolamide, N-palmitoylethanolamine > SEA (anandamide is ineffective) [987]
Endogenous agonists (pK _i)	N-arachidonoylglycine [982]	2-arachidonoylglycerolphosphoinositol (Selective) [986], lysophosphatidylinositol (pEC ₅₀ 5.5 – 7.3) [978,985,990]	N-palmitoylethanolamine (Selective), SEA (Selective), N-oleylethanolamide (Selective) (pEC ₅₀ 5.4 – 6.3) [977,987,990]
Selective agonists (pK _i)	–	AM251 (pEC ₅₀ 6.2 – 6.3) [978,980]	AS1269574 (pEC ₅₀ 5.6) [993], PSN632408 (pEC ₅₀ 5.3) [987], PSN375963 (pEC ₅₀ 5.1) [987]
Comment	The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on β-arrestin assays [990,992]	–	–

Comments: All listed endogenous agonists are remain currently as putative endogenous agonists.

GPR18 failed to respond to a variety of lipid-derived agents in an in vitro screen [992], but has been reported to be activated by Δ⁹-tetrahydrocannabinol [983]. GPR55 responds to AM251 and

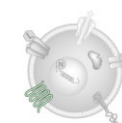
rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB₁ receptor antagonists/inverse agonists [988]. It has been reported lysophosphatidylinositol acts at other sites [991]. CID-16020046 has been described as a selective antagonist at GPR55 [979,981], although it has not yet been fully characterized. It has also been suggested oleoyl-

lysophosphatidylcholine acts, at least in part, through GPR119 [984]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleylethanolamide-mediated responses suggests additional mechanisms of action [984].

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Histamine receptors

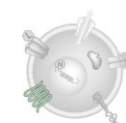
Overview: Histamine receptors (nomenclature as agreed by [NC-IUPHAR Subcommittee on Histamine Receptors](#), [1003]) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues (see [1003]).

Nomenclature	H ₁ receptor	H ₂ receptor	H ₃ receptor	H ₄ receptor
HGNC, UniProt	<i>HRH1</i> , P35367	<i>HRH2</i> , P25021	<i>HRH3</i> , Q9Y5N1	<i>HRH4</i> , Q9H3N8
Principal transduction	G _{q/11}	G _s	G _{i/o}	G _{i/o}
Selective agonists (pK _i)	methylhistaprodiven (6.4) [1025], histaprodiven (5.7) [1013]	amthamine (pEC ₅₀ 6.4) [1008]	immethridine (9.1) [1007], methimepip (9.0) [1006]	clobenpropit (Partial agonist) (7.4 – 8.3) [1000,1013–1015,1019], 4-methylhistamine (7.3 – 8.2) [1001,1013], VUF 8430 (7.5) [1012]
Selective antagonists (pK _i)	pyrilamine (Inverse agonist) (8.7 – 9.0) [995,1023], triprolidine (8.5 – 9.0) [995,1017]	tiotidine (7.5 - Rat) [994], ranitidine (7.1) [1010]	clobenpropit (8.4 – 9.4) [997,1000,1011,1014,1016,1028–1029], A331440 (8.5) [1002], iodophenpropit (8.2 – 8.7) [1028–1029], thioperamide (7.1 – 7.7) [997,999–1000,1011,1016,1028–1029]	JNJ 7777120 (7.8 – 8.3) [1013,1026–1027]
Radioligands (K _d)	[¹¹ C]pyrilamine, [¹¹ C]doxepin (Antagonist) (1×10 ⁻⁹ M) [1004], [³ H]pyrilamine (Antagonist, Inverse agonist) (7.9×10 ⁻¹⁰ – 4×10 ⁻⁹ M) [998,1017,1024–1025]	[¹²⁵ I]aminopotentialidine (Antagonist) (2×10 ⁻⁹ M - Rat) [1009], [³ H]tiotidine (Antagonist) (2.2×10 ⁻⁹ – 2×10 ⁻⁸ M) [1018]	[¹²³ I]iodoproxyfan (Antagonist) (6.3×10 ⁻¹¹ M) [1011], [¹²⁵ I]iodophenpropit (Antagonist) (6×10 ⁻¹⁰ M - Rat) [1005], [³ H](R)- α -methylhistamine (Agonist, Full agonist) (6×10 ⁻¹⁰ M) [1014], N-[³ H] α -methylhistamine (Agonist, Full agonist) (1×10 ⁻⁹ M - Mouse) [996]	[³ H]JNJ 7777120 (Antagonist) (3.6×10 ⁻⁹ M) [1027]

Comments: histaprodiven and methylhistaprodiven are reduced efficacy agonists. The H₄ receptor appears to exhibit broadly similar pharmacology to the H₃ receptor for imidazole-containing ligands, although (R)- α -methylhistamine and N- α -methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist [1014,1020–1022,1030]. Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H₄ receptor [1013]. [³H]histamine has been used to label the H₄ receptor in heterologous expression systems.

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Hydroxycarboxylic acid receptors

Formerly known as: Nicotinic acid receptor family

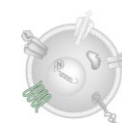
Overview: The hydroxycarboxylic acid family of receptors (ENSFM00500000271913, nomenclature as agreed by [NC-IUPHAR](#) Subcommittee on Hydroxycarboxylic acid receptors, [1037]) respond to organic acids, including the endogenous hydroxy carboxylic acids 3-hydroxy butyric acid and L-lactic acid, as well as the lipid lowering agents nicotinic acid (niacin), acipimox and acifran [1040,1044–1045]. These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA₂ receptors only and is unlikely to be the natural ligand [1044–1045].

Nomenclature	HCA ₁ receptor	HCA ₂ receptor	HCA ₃ receptor
HGNC, UniProt	<i>HCAR1</i> , Q9BXC0	<i>HCAR2</i> , Q8TDS4	<i>HCAR3</i> , P49019
Principal transduction	G _{i/o} [1031,1034,1036].	G _{i/o} [1040,1044–1045]	G _{i/o} [1040,1045]
Endogenous agonists (pK _i)	L-lactic acid (Selective) (pEC ₅₀ 1.3 – 2.89) [1032,1034,1036,1041]	β-D-hydroxybutyric acid (pEC ₅₀ 3.1) [1042]	3-hydroxyoctanoic acid (pEC ₅₀ 5.1) [1031]
Selective agonists (pK _i)	3,5-dihydroxybenzoic acid (pEC ₅₀ 3.72) [1035]	MK 6892 (pEC ₅₀ 7.8) [1039], MK 1903 (pEC ₅₀ 7.56) [1033], nicotinic acid (pEC ₅₀ 6.0 – 7.2) [1040,1044–1045], acipimox (pEC ₅₀ 5.2 – 5.6) [1040,1045], monomethylfumarate (pEC ₅₀ 5.03) [1043]	1-isopropylbenzotriazole-5-carboxylic acid (pEC ₅₀ 6.4) [1038]
Radioligands (K _d)	–	[³ H]nicotinic acid (Agonist, Full agonist) (5.01×10 ⁻⁸ – 1×10 ⁻⁷ M) [1040,1044–1045]	–

Comments: Further closely-related GPCR include the 5-oxoeicosanoid receptor (*OXER1*, Q8TDS5) and *GPR31* (O00270).

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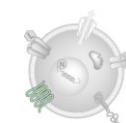
Kisspeptin receptors

Overview: The kisspeptin receptor (nomenclature agreed by NC-IUPHAR committee on kisspeptin receptors, Kirby *et al.*, 2010 [1047]), like neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) responds to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. kisspeptin-54 (*KISS1*, Q15726) (KP54, originally named metastin), kisspeptin-13 (*KISS1*, Q15726) (KP13) and kisspeptin-10 (*KISS1*) (KP10) are biologically-active peptides cleaved from the *KISS1* (Q15726) gene product.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Selective agonists (pK _i)	Selective antagonists (pK _i)	Radioligands (K _d)
kisspeptin receptor	<i>KISS1R</i> , Q969F8	G _{q/11} [1048,1050]	kisspeptin-10 (Selective) (8.6–10.4) [1048,1051], kisspeptin-54 (Selective) (8.8–9.5) [1048,1051], kisspeptin-13 (Selective) (8.4) [1048]	4-fluorobenzoyl-FGLRW-NH2 (pEC ₅₀ 9.2) [1053], [dY] ¹ KP-10 (pIC ₅₀ 8.4 - Mouse) [1046]	peptide 234 [1052]	[¹²⁵ I]kisspeptin-14 (human) [1049], [¹²⁵ I]Tyr ⁴⁵ -kisspeptin-15 (Agonist, Full agonist) (1 × 10 ⁻¹⁰ M) [1051], [¹²⁵ I]kisspeptin-13 (human) (Agonist, Full agonist) (2 × 10 ⁻¹⁰ M) [1049], [¹²⁵ I]kisspeptin-10 (human) (Agonist, Full agonist) (1.9 × 10 ⁻⁹ M) [1048]

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Leukotriene, lipoxin and oxoeicosanoid receptors

Overview: Leukotriene receptors (nomenclature agreed by NC-IUPHAR subcommittee on Leukotriene Receptors, [1057]) are activated by the endogenous ligands leukotriene B₄ (LTB₄), LTC₄, LTD₄, LTE₄, 12R-HETE and 12S-HETE. CysLT₁ and CysLT₂ are co-expressed by most myeloid cells. However, the function of CysLT₂ remains unclear. CysLT₂ has been demonstrated to exert a suppressive influence on CysLT₁ expression, suggesting an

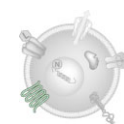
autoregulatory function which is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking CysLT₂ receptors [1073].

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-S-transferase/LTC₄ synthase, γ -glutamyltranspeptidase and several aminopeptidases) and can

also bind to peroxisome proliferator-activated receptor α (PPAR α , [1076]) and the FPR2/ALX lipoxin receptor [1061], complicating the interpretation of radioligand binding and functional studies (e.g. LTC₄ is rapidly converted in many systems to LTD₄). Metabolic inhibitors (e.g. serine–borate complex) reduce this problem but can also have nonspecific effects.

Nomenclature	BLT ₁ receptor	BLT ₂ receptor	CysLT ₁ receptor	CysLT ₂ receptor
HGNC, UniProt	<i>LTB4R</i> , Q15722	<i>LTB4R2</i> , Q9NPC1	<i>CYSLTR1</i> , Q9Y271	<i>CYSLTR2</i> , Q9NS75
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 >> 12R-HETE [1103]	12-HHT > LTB ₄ > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE > 20-hydroxy-LTB ₄ [1085,1103]	LTD ₄ > LTC ₄ > LTE ₄ [1077,1093]	LTC ₄ ≥ LTD ₄ >> LTE ₄ [1068,1082,1099]
Endogenous agonists (pK _i)	–	12S-HETE (Partial agonist) (pEC ₅₀ < 7.52) [1103]	–	–
Selective antagonists (pK _i)	U75302 (6.4) [1055], CP105696 (pIC ₅₀ 8.1) [1095]	LY255283 (pIC ₅₀ 6.0–7.1) [1069,1103]	ICI198615 (8.4–8.6), SR2640 (8.7), sulukast (8.3), zafirlukast (pIC ₅₀ 8.59–8.74) [1077,1093], montelukast (pIC ₅₀ 8.31–8.64) [1077,1093], pobilukast (pIC ₅₀ 7.52) [1093]	BAYu9773 (pA ₂ 6.8–7.7 - Rat) [1100]
Radioligands (K _d)	[³ H]LTB ₄ (Agonist, Full agonist) (1.5×10 ⁻¹⁰ M) [1102], [³ H]CGS23131 (Antagonist) (1.3×10 ⁻⁸ M) [1072]	[³ H]LTB ₄ (2×10 ⁻¹⁰ – 2.3×10 ⁻⁸ M)	[³ H]ICI-198615 (Antagonist, in human lung parenchyma) (2.5×10 ⁻¹¹ M) [1092], [³ H]LTD ₄ (Agonist) (2×10 ⁻¹¹ – 9.3×10 ⁻⁹ M)	[³ H]LTD ₄ (Agonist, Full agonist, K _{d1} and K _{d2} in COS-7 cells) (3.98×10 ⁻¹⁰ – 5.01×10 ⁻⁸ M) [1068]

Nomenclature	FPR2/ALX	OXE receptor
HGNC, UniProt	<i>FPR2</i> , P25090	<i>OXER1</i> , Q8TDS5
Principal transduction	G _i [1078]	G _{i/o} [1070–1071,1074,1083]
Rank order of potency	LXA ₄ =aspirin triggered lipoxin A ₄ =ATLa ₂ >LTC ₄ =LTD ₄ >>15-deoxy-LXA ₄ >>fMet-Leu-Phe [1060–1061,1063,1065,1098]	5-oxo-EETE, 5-oxo-C20:3, 5-oxo-ODE > 5-oxo-15-HETE > 5S-HPETE > 5S-HETE [1070,1074,1086]
Endogenous agonists (pK _i)	aspirin triggered lipoxin A ₄ (Selective), LXA ₄ (Selective) (pEC ₅₀ ~12.0) [1075], resolvin D1 (Selective) (pEC ₅₀ ~11.9) [1075]	5-oxo-EETE (Selective) (pEC ₅₀ 8.3–8.5) [1064,1084,1086,1089,1094]
Selective antagonists (pK _i)	ATLa ₂ [1066]	–
Radioligands (K _d)	[³ H]LXA ₄ (Agonist, Full agonist) (5×10 ⁻¹⁰ – 7×10 ⁻¹⁰ M) [1061–1062]	[³ H]5-oxo-EETE (Agonist) (3.8×10 ⁻⁹ M) [1084]
Comment	The agonist activity of the lipid mediators described has been questioned [1067,1088], which may derive from batch-to-batch differences, partial agonism or biased agonism.	–



Comments: BAYu9773 is an antagonist at CysLT₁ (6.8–7.7) and a reduced efficacy agonist at CysLT₂ receptors. The CysLT₁ and CysLT₂ receptors also respond to uracil nucleotides [1080–1081]. 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 [1059].

Lipoxin A₄ receptors (FPR2/ALX, nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors; [1101]) are activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A₄ (LXA₄) and 15-epi-LXA₄ (aspirin triggered

lipoxin A₄, ATL). The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide [1058] as well as annexin I (ANXA1, P04083) (ANXA1) and its N-terminal peptides [1087]. 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 [1090]. Furthermore, FPR2/ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A [1096–1097].

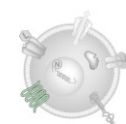
Oxoecosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoecosanoid Receptors; [1056]) are activated

by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-E₂E the most potent agonist identified for this receptor.

Note that the data for FPR2/ALX are also reproduced on the Formylpeptide receptor pages. A receptor selective for LXB₄ has been suggested from functional studies [1054,1079,1091]. Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and EPA, acted as receptor antagonists [1070].

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Lysophospholipid (LPA) receptors

Overview: Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid Receptors; [1104]) 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 recently 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 [³H]LPA (*e.g.* [1107]). 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. Independent validation by multiple groups has been reported in

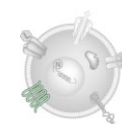
the peer-reviewed literature for all six LPA receptors described in the tables, including further validation using a distinct read-out via a novel TGF α “shedding” assay [1111]. LPA has also been described to be an agonist at other orphan GPCRs (PSP24, GPR87 and GPR35), as well as at the nuclear hormone PPAR γ receptors [1117,1119], although the physiological significance of these observations remain unclear.

Nomenclature	LPA ₁ receptor	LPA ₂ receptor	LPA ₃ receptor	LPA ₄ receptor	LPA ₅ receptor	LPA ₆ receptor
HGNC, UniProt	<i>LPAR1</i> , Q92633	<i>LPAR2</i> , Q9HBW0	<i>LPAR3</i> , Q9UBYS	<i>LPAR4</i> , Q99677	<i>LPAR5</i> , Q9H1C0	<i>LPAR6</i> , P43657
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} [1115]	G _q , G _{12/13} [1114,1116]	G _{12/13} [1112,1122]
Selective agonists (pK _i)	–	dodecylphosphate (pEC ₅₀ 6.2) [1121], decyl dihydrogen phosphate (pEC ₅₀ 5.4) [1121], GRI977143 (pEC ₅₀ 4.48) [1113]	OMPT (pEC ₅₀ 7.17) [1108]	–	–	–
Selective antagonists (pK _i)	AM966 (pIC ₅₀ 7.8) [1120]	H2L5186303 (7.68) [1105]	dioctanoylglycerol pyrophosphate (5.5–7.0) [1106,1118]	–	–	–

Comments: Ki16425 [1118], dodecylphosphate [1121], VPC12249 [1110] and VPC32179 [1109] have antagonist activity at LPA₁ and LPA₃ receptors. The selectivity of these antagonists is less than two orders of magnitude. None of the currently available chemical tools have validated specificity *in vivo*.

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Lysophospholipid (S1P) receptors

Overview: Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by [NC-IUPHAR](#) Subcommittee on Lysophospholipid receptors; [1128]) are activated by the endogenous lipid derivatives sphingosine 1-phosphate (S1P) and with lower apparent affinity, sphingosylphosphorylcholine (SPC). Originally identified as members of the endothelial differentiation gene (*edg*) family along with lysophosphatidic acid receptors, the gene names have been updated to S1PR1, etc. to reflect the receptor

function of these proteins. Most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms; S1P has also been described to act at intracellular sites [1142], still awaiting precise definition. Previously-proposed SPC (or lysophosphophatidylcholine) receptors – G2A, TDAG8, OGR1 and GPR4 – are lacking confirmation of these roles [1130]. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterolo-

gous expression systems using [³²P]S1P (*e.g.* [1137]). 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. A crystal structure of an S1P₁-T4 fusion protein has recently been described [1132].

Nomenclature	S1P ₁ receptor	S1P ₂ receptor	S1P ₃ receptor	S1P ₄ receptor	S1P ₅ receptor
HGNC, UniProt	<i>S1PR1</i> , P21453	<i>S1PR2</i> , O95136	<i>S1PR3</i> , Q99500	<i>S1PR4</i> , O95977	<i>S1PR5</i> , Q9H228
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	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate > sphingosylphosphorylcholine [1124,1137]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate > sphingosylphosphorylcholine [1124,1137]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate > sphingosylphosphorylcholine [1137]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate > sphingosylphosphorylcholine [1143]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate > sphingosylphosphorylcholine [1133]
Selective agonists (pK _i)	SEW2871 (5.5 – 7.7) [1140], AUY954 (pEC ₅₀ 8.92) [1139]	–	–	–	–
Selective antagonists (pK _i)	W146 (7.7) [1141]	JTE-013 (pIC ₅₀ 7.77) [1138]	–	–	–

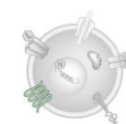
Comments: The immunomodulator fingolimod (FTY720) can be phosphorylated *in vivo* [1123] to generate a relatively potent agonist with activity at S1P₁, S1P₃, S1P₄ and S1P₅ receptors [1125,1134], although its biological activity appears to involve functional antagonism [1127,1129,1136]. This compound has received world-wide approval as the first oral therapy for relapsing forms of Multiple Sclerosis, with a novel mechanism of action involving modulation of S1P receptors in both the immune and nervous systems [1126,1129,1131]. VPC23019 and VPC44116 have antagonist activity at S1P₁ and S1P₃ receptors [1135].

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Full Contents of Concise Guide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full>



Lysophospholipid (S1P) receptors 1526

Melanin-concentrating hormone receptors

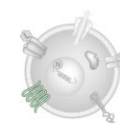
Overview: Melanin-concentrating hormone (MCH) receptors (provisional nomenclature, [1148]) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDML-RCMLGRVYRPCWQV) generated from a precursor (*PMCH*, P20382), which also produces neuropeptide EI and neuropeptide GE.

Nomenclature	MCH ₁ receptor	MCH ₂ receptor
HGNC, UniProt	<i>MCHR1</i> , Q99705	<i>MCHR2</i> , Q969V1
Principal transduction	G _{q/11} , G _{i/o}	G _{q/11} [1150–1152]
Rank order of potency	melanin-concentrating hormone (human) > MCH (salmon)	melanin-concentrating hormone (human) = MCH (salmon) [1150]
Selective antagonists (pK _i)	SNAP-7941 (pA ₂ 9.2) [1145], GW803430 (pIC ₅₀ 9.3) [1149], T-226296 (pIC ₅₀ 8.3) [1153], ATC0175 (pIC ₅₀ 7.9–8.1) [1147]	–
Radioligands (K _d)	[³ H]MCH (human, mouse, rat) (Agonist, Full agonist) [1146], [¹²⁵ I]S36057 (Antagonist) (3.2×10 ^{–10} –6.3×10 ^{–10} M) [1144], [¹²⁵ I][Phe ¹³ ,Tyr ¹⁹]MCH (Agonist, Full agonist) (7×10 ^{–10} M) [1146]	–

Comments: The MCH₂ receptor appears to be a non-functional pseudogene in rodents [1154].

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Melanocortin receptors

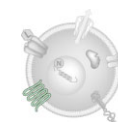
Overview: Melanocortin receptors (provisional nomenclature, [1158]) are activated by members of the melanocortin family (α -MSH, β -MSH and γ -MSH derived from a common precursor, pro-opiomelanocortin (POMC, P01189) forms; – δ form is not found in mammals) and adrenocorticotrophin (ACTH (POMC, P01189)). Endogenous antagonists include agouti (ASIP, P42127) and agouti-related protein (AGRP (AGRP, O00253)).

Nomenclature	MC ₁ receptor	MC ₂ receptor	MC ₃ receptor	MC ₄ receptor	MC ₅ receptor
HGNC, UniProt	MC1R, Q01726	MC2R, Q01718	MC3R, P41968	MC4R, P32245	MC5R, P33032
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 (pK _i)	–	–	[D-Trp ⁸] γ -MSH (pIC ₅₀ 8.2) [1159]	MK-0493 [1162], THIQ (pIC ₅₀ 8.9) [1166]	–
Selective antagonists (pK _i)	–	–	PG-106 (pIC ₅₀ 6.7) [1160]	HS014 (8.5) [1165], MBP10 (pIC ₅₀ 10.0) [1155]	–
Radioligands (K _d)	[¹²⁵ I]NDP-MSH (Agonist, Full agonist) (3.3×10 ^{–10} M) [1161]	[¹²⁵ I]ACTH-(1–24)	[¹²⁵ I]SHU9119 (Antagonist) [1163], [¹²⁵ I]NDP-MSH (Agonist, Full agonist) (2×10 ^{–10} M) [1161]	[¹²⁵ I]SHU9119 (Antagonist) (7×10 ^{–10} M) [1163], [¹²⁵ I]NDP-MSH (Agonist, Full agonist) (1.2×10 ^{–9} –4×10 ^{–9} M) [1161,1164]	[¹²⁵ I]NDP-MSH (Agonist, Full agonist) (2.8×10 ^{–9} M) [1161]

Comments: Polymorphisms of the MC1 receptor have been linked to variations in skin pigmentation. Defects of the MC2 receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC4 receptor have been linked to obesity [1156–1157].

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Melatonin receptors

Overview: Melatonin receptors (nomenclature as agreed by [NC-IUPHAR Subcommittee on melatonin receptors](#), [1170]) are activated by the endogenous ligands melatonin and N-acetylserotonin.

Nomenclature	MT ₁ receptor	MT ₂ receptor
HGNC, UniProt	<i>MTNR1A</i> , P48039	<i>MTNR1B</i> , P49286
Principal transduction	G _{i/o}	G _{i/o}
Selective agonists (pK _i)	–	5-methoxy-luzindole (Partial agonist) (9.6) [1171], lmk7 (pIC ₅₀ 10.3) [1183]
Selective antagonists (pK _i)	–	K185 (9.3) [1175,1183], 4P-PDOT (8.8–9.3) [1167,1171], DH97 (8.0) [1184]
Radioligands (K _d)	2-[¹²⁵ I]MLT (Agonist, Full agonist) (2.13×10 ⁻¹¹ – 1.19×10 ⁻¹⁰ M) [1167,1171], [³ H]melatonin (Agonist, Full agonist) (1.3×10 ⁻¹⁰ – 4×10 ⁻¹⁰ M) [1169]	2-[¹²⁵ I]MLT (Agonist, Full agonist) (1.07×10 ⁻¹⁰ – 1.86×10 ⁻¹⁰ M) [1167,1171], [³ H]melatonin (Agonist, Full agonist) (2.8×10 ⁻¹⁰ – 9.12×10 ⁻¹⁰ M) [1169]

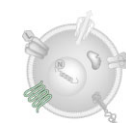
Comments: melatonin, 2-iodo-melatonin, S20098 (agomelatine), GR 196429, LY 156735 and ramelteon [1176] are nonselective agonists for MT₁ and MT₂ receptors. (-)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT₁ receptors (see AMMTC for structure) [1185]. luzindole is an MT₁/MT₂ melatonin receptor-selective competitive antagonist with some selectivity for the MT₂ receptor [1172]. MT₁/MT₂ heterodimers present different pharmacological profiles from MT₁ and MT₂ receptors [1168].

The MT₃ binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML₂ receptor, binds selectively 2-iodo-[¹²⁵I]5MCA-NAT [1178]. Pharmacological investigations of MT₃ binding sites have primarily been conducted in hamster tissues. At this site, N-acetylserotonin [1174,1177–1178,1182] and 5MCA-NAT [1182] appear to function as agonists, while prazosin [1177] functions as an antagonist. A suggested physiological function of the MT₃ receptor is in the control of intraocular pressure in rabbits [1181]. The MT₃ binding

site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (NQO2, P16083 [1179–1180]). *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 [1173] although melatonin does not bind to GPR50 receptors.

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Metabotropic glutamate receptors

Overview: Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by [NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors](#), [1243]) are activated by the endogenous ligands L-glutamic acid, L-serine-O-phosphate (L-SOP), N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are (1S,3R)-ACPD and L-CCG-I, which show limited selectivity for Group II receptors. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu₂ and mGlu₃ at low nanomolar concentrations, mGlu₈ at high nanomolar concentrations, and

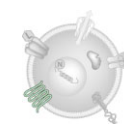
mGlu₃, mGlu₄, mGlu₅ and mGlu₇ in the micromolar range [1210]. Three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G-protein effector coupling: Group I (mGlu₁ and mGlu₅), Group II (mGlu₂ and mGlu₃) and Group III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈) (see Further reading). Group I mGlu receptors may be activated by 3,5-DHPG and (S)-3HPG [1190] and antagonized by (S)-hexylhomobotenic acid [1221]. Group II mGlu receptors may be activated by LY389795 [1229], LY379268 [1229], LY354740 [1244,1254], DCG-IV and (2R,3R)-APDC [1245], and antagonised by eGlu (4.3, [1207] and LY307452

[1200,1253]. Group III mGlu receptors may be activated by (R,S)-4-PPG [1203].

In addition to orthosteric ligands that directly 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 receptor	mGlu ₅ receptor
HGNC, UniProt	GRM1, Q13255	GRM5, P41594
Principal transduction	G _{q/11}	G _{q/11}
Selective agonists (pKi)	–	(S)-(+)-CBPG (Partial agonist) (pEC ₅₀ 4.3 - Rat) [1225], CHPG (pIC ₅₀ 3.4) [1232]
Selective antagonists (pKi)	AIDA (pA ₂ 4.2) [1231], 3-MATIDA (pIC ₅₀ 5.2-Rat) [1230], LY367385 (pIC ₅₀ 5.1) [1196], (S)-(+)-CBPG (pIC ₅₀ 4.2-Rat) [1225], (S)-TBPG (pIC ₅₀ 4.2-Rat) [1197]	ACDPP (pIC ₅₀ 6.9) [1188]
Selective allosteric regulators	PHCCC (Positive), Ro67-7476 (Positive) (pK _i 7.5–7.9 - Rat) [1213], Ro01-6128 (Positive) (pK _i 7.5–7.7 - Rat) [1213], Ro67-4853 (Positive) (pK _i 5.1 - Rat) [1213], JNJ16259685 (Negative) (pIC ₅₀ 8.9) [1217], A-841720 (Negative) (pIC ₅₀ 8.0) [1255], 3,5-dimethyl PPP (Negative) (pIC ₅₀ 7.8-Rat) [1227], YM298198 (Negative) (pIC ₅₀ 7.8-Rat) [1214], BAY 367620 (Negative) (pIC ₅₀ 6.8–8.0-Rat) [1193,1216], EM-TBPC (Negative) (pIC ₅₀ 6.9-Rat) [1223], LY456236 (Negative) (pIC ₅₀ 6.9) [1218], CPCCOEt (Negative) (pIC ₅₀ 5.2–5.8) [1220]	MTEP (Negative) (pK _i 7.8) [1191], VU-1545 (Positive) (pEC ₅₀ 8.0) [1198], CDPPB (Positive) (pEC ₅₀ 7.6–8.0) [1211,1219], MPEP (Negative) (pIC ₅₀ 7.4–7.7) [1202,1204], fenobam (Negative) (pIC ₅₀ 7.2) [1241], DFB (Positive) (pIC ₅₀ 5.6–8.5) [1236–1237], CPPHA (Positive) (pIC ₅₀ 6.3) [1237], SIB-1757 (Negative) (pIC ₅₀ 6.0–6.4) [1202,1252], SIB-1893 (Negative) (pIC ₅₀ 5.9–6.5) [1202,1252]

Nomenclature	mGlu ₂ receptor	mGlu ₃ receptor
HGNC, UniProt	GRM2, Q14416	GRM3, Q14832
Principal transduction	G _{i/o}	G _{i/o}
Selective antagonists (pKi)	PCCG-4 (pIC ₅₀ 5.1 - Rat) [1239]	–
Selective allosteric regulators	biphenylindanone A (Positive) (pEC ₅₀ 7.0) [1189], CBiPES (Positive) (pEC ₅₀ 7.0) [1209], Ro64-5229 (Negative) (pIC ₅₀ 7.0 - Rat) [1215], 4-MPPTS (Positive) (pIC ₅₀ 5.8) [1187,1208–1209,1242]	–
Endogenous agonists (pKi)	–	NAAG (Selective) (4.7) [1246]



Nomenclature	mGlu ₄ receptor	mGlu ₆ receptor	mGlu ₇ receptor	mGlu ₈ receptor
HGNC, UniProt	<i>GRM4</i> , Q14833	<i>GRM6</i> , O15303	<i>GRM7</i> , Q14831	<i>GRM8</i> , O00222
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Endogenous agonists (pKi)	–	–	–	L-SOP (pIC ₅₀ 6.2–7.2) [1224,1254]
Non-selective agonists (pKi)	L-AP4 (pEC ₅₀ 6.5) [1254], L-SOP (pEC ₅₀ 5.9) [1254]	–	L-SOP (pEC ₅₀ 4.5) [1254], L-AP4 (pEC ₅₀ 3.8) [1254]	L-AP4 (pIC ₅₀ 7.0–7.2) [1224]
Selective agonists (pKi)	LSP4-2022 [1205]	1-benzyl-APDC (pEC ₅₀ 4.7 - Rat) [1250], homo-AMPA (pEC ₅₀ 4.1) [1192]	LSP4-2022 (pEC ₅₀ 4.96) [1205]	(S)-3,4-DCPG (pEC ₅₀ 7.5) [1248]
Non-selective antagonists (pKi)	MAP4 (4.6 - Rat) [1206]	MAP4 (pIC ₅₀ 3.5 - Rat) [1240]	–	MPPG (pIC ₅₀ 4.33) [1254]
Selective antagonists (pKi)	–	THPG [1249]	–	–
Non-selective allosteric regulators	SIB-1893 (Positive) (pEC ₅₀ 6.3–6.8) [1226], MPEP (Positive) (pEC ₅₀ 6.3–6.6) [1226], PHCCC (Positive) (pEC ₅₀ 4.5) [1222]	–	AMN082 (Positive) (pEC ₅₀ 6.5–6.8) [1228]	–
Selective allosteric regulators	VU0361737 (Positive) (pEC ₅₀ 6.6) [1199], VU0155041 (Positive) (pEC ₅₀ 6.1) [1235]	–	MMPPI (Negative) (pIC ₅₀ 6.1–7.6 - Rat) [1234,1247]	–
Comment	pEC ₅₀ values for MPEP and SIB-1893 were obtained in the presence of L-AP4 [1226]	–	–	–

Comments: The activity of NAAG as an agonist at mGlu₃ receptors was questioned on the basis of contamination with glutamate [1194,1201], but this has been refuted [1233].

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [³H]R214127 [1216] and [³H]YM298198 [1214] at mGlu₁ receptors and [³H]M-MPEP [1202] and [³H]methoxymethyl-MTEP [1186] at mGlu₅ 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 mGlu₁, but is an agonist (albeit of reduced efficacy) at mGlu₅ receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors [1251], and is an antagonist at all group-III mGluRs with an IC₅₀ of 30 μM. A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomobiotenic acid (ineffective as an

agonist at recombinant Group I metabotropic glutamate receptors), but resistant to LY341495 [1195]. 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 [1212,1238].

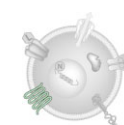
A related class C receptor composed of two distinct subunits, T1R1 +T1R3 is also activated by glutamate and is responsible for umami taste detection.

All selective antagonists at metabotropic glutamate receptors are competitive.

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Motilin receptor

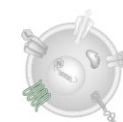
Overview: Motilin receptors (provisional nomenclature, [1261]) are activated by a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a motilin-associated peptide (*MLN*, P12872). These receptors are also suggested to be responsible for the gastrointestinal prokinetic effects of certain macrolide antibiotics (often called motilides; *e.g.* erythromycin), although for many of these molecules the evidence is sparse.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Selective agonists (pK _i)	Selective antagonists (pK _i)	Radioligands (K _d)	Comment
motilin receptor	<i>MLNR</i> , O43193	G _{q/11} [1259–1260]	motilin (8.4 – 8.7) [1258,1265–1267]	GSK962040 (pEC ₅₀ 7.9) [1275], mitemcinal (pEC ₅₀ 7.5 – 7.8 - Rabbit) [1263,1273], azithromycin (pEC ₅₀ 5.5) [1256], mitemcinal (pIC ₅₀ 8.1 – 8.2 - Rabbit) [1257], ABT-229 (pIC ₅₀ 7.2) [1274], erythromycin-A (pIC ₅₀ 5.5 – 6.5) [1260,1274]	MA-2029 (pA ₂ 9.2) [1271], GM-109 (pA ₂ 7.2 – 7.5 - Rabbit) [1257,1272], GM-109 (pIC ₅₀ 8.0 - Pig) [1262]	[¹²⁵ I]motilin (human) (Agonist, Full agonist) (1×10 ⁻¹⁰ M) [1260]	Note that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other actions are possible (<i>e.g.</i> P2X inhibition by erythromycin; [1277]). Small molecule motilin receptor agonists are now described [1264,1270,1276].

Comments: In laboratory rodents, the gene encoding the motilin precursor appears to be absent, while the receptor appears to be a pseudogene. Functions of motilin (*MLN*, P12872) are not usually detected in rodents, although brain and other responses to motilin (*MLN*, P12872) and the macrolide ABT-229 have been reported and the mechanism of these actions are obscure [1268–1269].

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Neuromedin U receptors

Overview: Neuromedin U receptors (provisional nomenclature, [1279]) are activated by the endogenous 25 amino acid peptide neuromedin U (NMU-25 (*NMU*, P48645), NMU), a peptide originally isolated from pig spinal cord [1285]. In humans, NMU-25 appears to be the sole product of a precursor gene (*NMU*, P48645) 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 in 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-33 (*NMS*, Q5H8A3)) has also been identified as an endogenous

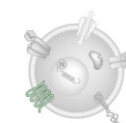
agonist [1286]. NMS-33 is, as its name suggests, a 33 amino-acid product of a precursor protein derived from a single gene and contains an amidated C-terminal heptapeptide identical to NMU. NMS-33 appears to activate NMU receptors with equivalent potency to NMU-25.

Nomenclature	NMU1 receptor	NMU2 receptor
HGNC, UniProt	<i>NMUR1</i> , Q9HB89	<i>NMUR2</i> , Q9GZQ4
Principal transduction	G _{q/11} [1278,1280]	G _{q/11} [1278,1281]
Selective antagonists (pK)	–	R-PSOP (pK _B 7.04) [1283]

Comments: NMU1 and NMU2 couple predominantly to G_{q/11} although there is evidence of good coupling to G_{i/o} [1278,1281,1282]. NMU1 and NMU2 can be labelled with [¹²⁵I]-NMU and [¹²⁵I]-NMS (of various species, *e.g.* [1284]), BODIPY[®] TMR-NMU or Cy3B-NMU-8 [1278]. A range of radiolabelled (¹²⁵I-), fluorescently labelled (*e.g.* Cy3, Cy5, rhodamine and FAM) and biotin labelled versions of NMU-25 (*NMU*, P48645) and NMS-33 (*NMS*, Q5H8A3) are now commercially available.

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Neuropeptide FF/neuropeptide AF receptors

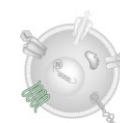
Overview: A single propeptide precursor (*NPFF*, O15130) generates the octapeptides NPFF (FLFQPQRF-NH₂, neuropeptide FF or F-8-F-amide) and NPSF (SLAAPQRF-NH₂, neuropeptide SF) and the octadecapeptide NPAF (AGEGLSSPFWSLAAPQRF-NH₂, neuropeptide AF or A-18-F-amide). NPFF and NPAF were originally isolated from bovine brain [1298].

Nomenclature	NPFF1 receptor	NPFF2 receptor
HGNC, UniProt	<i>NPFFR1</i> , Q9GZQ6	<i>NPFFR2</i> , Q9Y5X5
Principal transduction	G _{q/11}	G _{i/o} [1293]
Rank order of potency	FMRF, NPFF > NPAF > NPSF, QRFP, PrRP-31 (<i>PRLH</i>) [1287]	NPAF, NPFF > PrRP-31 (<i>PRLH</i>) > FMRF, QRFP (<i>QRFP</i> , P83859) > NPSF [1287]
Endogenous agonists (pK _i)	RFRP-3 (<i>NPVF</i> , Q9HCQ7) (Selective) (9.2 – 9.3) [1288–1289,1292], NPFF (<i>NPFF</i> , O15130) (Selective) (8.5 – 9.9) [1287–1288,1292]	NPFF (Selective) (9.7) [1288,1291]
Selective agonists (pK _i)	–	dNPA (10.6) [1294–1295], AC263093 (pEC ₅₀ 5.2 – 5.9) [1290]
Selective antagonists (pK _i)	AC262620 (7.7 – 8.1) [1290], AC262970 (7.4 – 8.1) [1290], RF9 (7.2) [1296]	–
Radioligands (K _d)	[¹²⁵ I]NPFF (Agonist, Full agonist) [1287], [¹²⁵ I]Y-RFRP-3 (Agonist, Full agonist) (8×10 ⁻⁹ M) [1288], [³ H]NPVF (Agonist, Full agonist) (2.65×10 ⁻⁹ M) [1297]	[¹²⁵ I]NPFF (Agonist, Full agonist) [1287], [¹²⁵ I]EYF (Agonist, Full agonist) (6.3×10 ⁻¹¹ M) [1292], [³ H]EYF (Agonist, Full agonist) (5.4×10 ⁻¹⁰ M) [1297]

Comments: An orphan receptor *GPR83* (Q9NYM4) 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, [1296]).

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Neuropeptide S receptor

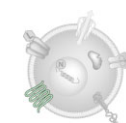
Overview: The neuropeptide S receptor (NPS, provisional nomenclature, [1300]) responds to the 20 amino-acid peptide neuropeptide S derived from the precursor (NPS, POCOP6).

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Radioligands (K _d)
NPS receptor	NPSR1, Q6W5P4	G _s , G _{q/11} [1301–1302]	NPS (pEC ₅₀ 8.0) [1303]	[¹²⁵ I]Tyr ¹⁰ NPS (human) (Agonist, Full agonist) (3.3×10 ^{−10} M) [1303]

Comments: Polymorphisms in the NPS receptor have been suggested to be associated with asthma [1302] and irritable bowel syndrome [1299].

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Neuropeptide W/neuropeptide B receptors

Overview: The neuropeptide BW receptor 1 (NPBW1) is activated by two 23-amino-acid peptides, neuropeptide W (NPW-23 (NPW, Q8N729)) and neuropeptide B (NPB-23 (NPB, Q8NG41)) [1305,1309]. C-terminally extended forms of the peptides (NPW-30 (NPW, Q8N729) and NPB-29 (NPB, Q8NG41)) also activate NPBW1 [1304]. Unique to both forms of NPB is the N-terminal bromination of the first tryptophan residue. des-Br-NPB-23 (NPB, Q8NG41) and des-Br-NPB-29 (NPB, Q8NG41) 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 [1304].

Nomenclature	NPBW1 receptor	NPBW2 receptor
HGNC, UniProt	NPBWR1, P48145	NPBWR2, P48146
Principal transduction	G _{i/o} [1307]	G _{i/o} [1307]
Rank order of potency	NPB-29 > NPB-23 > NPW-23 > NPW-30 [1304]	NPW-23 > NPW-30 > NPB-29 > NPB-23 [1304]
Selective agonists (pK _i)	Ava3 (9.37–9.43) [1306], Ava5 (8.8–9.0) [1306]	–
Radioligands (K _d)	[¹²⁵ I]NPW-23 (human) (Agonist) (4.4x10 ⁻¹⁰ M) [1310]	[¹²⁵ I]NPW-23 (human) (Agonist) (1.99x10 ⁻⁸ M) [1309]

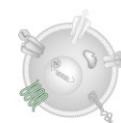
Comments: Potency measurements were conducted with heterologously-expressed receptors with a range of 0.14–0.57 nM (NPBW1) and 0.98–21 nM (NPBW2).

NPBW1^{-/-} mice show changes in social behavior, suggesting that the NPBW1 pathway may have an important role in the emotional responses of social interaction [1308].

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Neuropeptide Y receptors

Overview: Neuropeptide Y (NPY) receptors (nomenclature agreed by NC-IUPHAR on Neuropeptide Y Receptors, [1325]) are activated by the endogenous peptides NPY (NPY, P01303), NPY 3–36 (NPY, P01303), peptide YY (PYY (PYY, P10082)), PYY-(3–36) (PYY, P10082) and pancreatic polypeptide (PP (PPY, P01298)). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine receptor (originally

named LESTR, [1323]). 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 [1321]. Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the relative potency of PP (PPY, P01298) is greater at the rat Y₄ receptor than at the human receptor [1317]. 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. [¹²⁵I]-PYY or [¹²⁵I]-NPY can be used to label Y₁, Y₂, Y₃ and Y₆ subtypes non-selectively, while [¹²⁵I][cPP(1–7), NPY(19–23), Ala³¹, Aib³², Gln³⁴]hPP may be used to label Y₅ receptors preferentially.

Nomenclature	Y ₁ receptor	Y ₂ receptor	Y ₄ receptor	Y ₅ receptor	y ₆ receptor
HGNC, UniProt	NPY1R, P25929	NPY2R, P49146	NPY4R, P50391	NPY5R, Q15761	NPY6R, Q99463
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
Endogenous agonists (pK _i)	–	NPY 3–36 (Selective), PYY-(3–36) (9.2–9.7) [1318,1320]	PP (8.7–10.9) [1311,1324,1327,1329]	–	–
Selective agonists (pK _i)	[Leu ³¹ ,Pro ³⁴]PYY (human), [Pro ³⁴]NPY, [Pro ³⁴]PYY (human), [Leu ³¹ ,Pro ³⁴]NPY (pEC ₅₀ 7.1) [1314]	–	–	[Ala ³¹ ,Aib ³²]NPY (pig) (pIC ₅₀ 8.2) [1313]	–
Selective antagonists (pK _i)	BIBP3226 (8.1–8.2) [1319,1326], BIBO3304 (pIC ₅₀ 9.5) [1328]	BIIE0246 (pIC ₅₀ 8.5) [1315], JNJ-5207787 (pIC ₅₀ 6.9–7.1) [1312]	–	L-152,804 (7.6) [1322]	–
Radioligands (K _d)	[¹²⁵ I][Leu ³¹ ,Pro ³⁴]NPY (Agonist, Full agonist), [³ H]BIBP3226 (Antagonist) (2.1×10 ^{–9} M)	[¹²⁵ I]PYY-(3–36) (human) (Agonist, Full agonist)	[¹²⁵ I]PP (human) (Agonist, Full agonist)	[¹²⁵ I][cPP(1–7), NPY(19–23), Ala ³¹ , Aib ³² , Gln ³⁴]hPP (Agonist) (5×10 ^{–10} –7×10 ^{–10} M – Rat) [1316]	–

Comments: The Y₁ agonists indicated are selective relative to Y₂ receptors. BIBP3226 is selective relative to Y₂, Y₄ and Y₅ receptors [1319]. NPY-(13–36) is Y₂ selective relative to Y₁ and Y₅ receptors. PYY-(3–36) (PYY, P10082) is Y₂ selective relative to Y₁ receptors.

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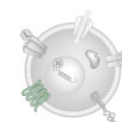
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Neurotensin receptors

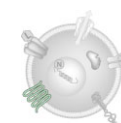
Overview: Neurotensin receptors (provisional nomenclature, [1330]) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (NTS, P30990), which also generates neuromedin N, an agonist at the NTS₂ receptor. A nonpeptide antagonist, SR142948A, shows high affinity (pK_i~9) at both NTS₁ and NTS₂ receptors [1331]. [³H]neurotensin (human, mouse, rat) and [¹²⁵I]neurotensin (human, mouse, rat) may be used to label NTS₁ and NTS₂ receptors at 0.1–0.3 and 3–5 nM concentrations respectively.

Nomenclature	NTS ₁ receptor	NTS ₂ receptor
HGNC, UniProt	NTSR1, P30989	NTSR2, O95665
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	neurotensin > neuromedin N [1332]	neurotensin = neuromedin N [1335]
Selective agonists (pK _i)	JMV449 [1338]	levocabastine (6.8) [1335,1337]
Selective antagonists (pK _i)	SR48692 (pIC ₅₀ 7.5–8.2) [1331]	–
Radioligands (K _d)	[³ H]SR48692 (Antagonist) (3.2x10 ⁻⁹ M – Rat) [1333]	–

Comments: neurotensin (NTS, P30990) appears to be a low-efficacy agonist at the NTS₂ receptor [1339], while the NTS₁ receptor antagonist SR48692 is an agonist at NTS₂ receptors [1339]. 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 [1336]. It has been reported to interact with the NTS₁ receptor [1334] and has been implicated in hormone trafficking and/or neurotensin uptake.

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Opioid receptors

Overview: Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (*PENK*, P01210) (met), [Leu]enkephalin (*PENK*, P01210) (leu), β -endorphin (*POMC*, P01189) (β -end), α -neodynorphin (*PDYN*, P01213), dynorphin A (*PDYN*, P01213) (dynA), dynorphin B

(*PDYN*, P01213) (dynB), big dynorphin (*PDYN*, P01213) (Big dyn), nociceptin/orphanin FQ (N/OFQ (*PNO*C, Q13519)); endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter names for the opioid receptors, μ , δ and κ , are well established, and *IUPHAR* considers these

names most appropriate [1352]. 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 [1368], it displays a distinct pharmacology.

Nomenclature	δ receptor	κ receptor	μ receptor	NOP receptor
HGNC, UniProt	<i>OPRD1</i> , P41143	<i>OPRK1</i> , P41145	<i>OPRM1</i> , P35372	<i>OPRL1</i> , P41146
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Rank order of potency	–	–	–	N/OFQ >> dynorphin A
Principal endogenous agonists	β -endorphin, [Leu]enkephalin, [Met]enkephalin	big dynorphin, dynorphin A	β -endorphin, [Met]enkephalin, [Leu]enkephalin, endomorphin-1, endomorphin-2	–
Endogenous agonists (pK _i)	–	–	endomorphin-2 (Selective) (8.5 – Rat) [1388], endomorphin-1 (8.3) [1353,1388]	N/OFQ (Selective) (9.7–10.4) [1341,1365–1367,1372]
Selective agonists (pK _i)	[D-Ala ²]deltorphin I (pK _a 9.35) [1350,1382], [D-Ala ²]deltorphin II (8.8) [1351], DPDPE (8.8) [1369,1384], SNC80 (7.2) [1345,1376]	enadoline (9.6) [1357,1370], U69593 (9.5) [1363,1384], U50488 (7.8–9.7) [1348,1373,1379,1384,1386,1392–1393], salvinorin A (7.8–8.7) [1343,1377]	sufentanil (9.9) [1385], DAMGO (9.3) [1355,1384], PL017 (8.2) [1347,1384]	N/OFQ-(1–13)-NH ₂ (10.1–10.4) [1341,1354,1365,1372], Ro64-6198 (9.6) [1358]
Selective antagonists (pK _i)	nalttriben (10.0) [1381,1384], naltrindole (9.7) [1375,1384], TIPP ψ (Inverse agonist) (9.0) [1378,1384]	nor-binaltorphimine (8.9–11.0) [1373–1374,1379,1384,1392–1393], GNTI (9.74–9.9) [1359,1373,1383]	CTAP (8.6) [1347,1384]	UFP-101 (10.2) [1346], SB 612111 (9.5) [1391], J-113397 (pIC ₅₀ 8.3) [1361]
Radioligands (K _d)	[³ H]deltorphin II [1344], [³ H]DPDPE [1340], [³ H]nalttriben (Antagonist) [1364], [³ H]naltrindole (Antagonist) [1387]	[³ H]CI977 [1380], [³ H]U69593 (Agonist, Full agonist) (2×10 ^{−9} –1.6×10 ^{−9} M) [1363,1373,1379]	[³ H]DAMGO (Agonist, Full agonist) [1390], [³ H]PL017 (Agonist) [1356]	[³ H]N/OFQ (Agonist, Full agonist) (6.3×10 ^{−11} M) [1349,1367]

Comments: Subtypes of μ (μ 1, μ 2), δ (δ 1, δ 2) and κ (κ 1, κ 2, κ 3) receptor have been proposed based primarily on binding studies with poorly selective ligands or results from *in vivo* studies. Only three naloxone-sensitive opioid receptors have been cloned, and while the μ -receptor in particular may be subject to extensive alternative splicing, these putative isoforms have not been definitively correlated with any of the proposed subtypes. Opioid receptor subtypes may reflect heterodimerization of opioid receptors with each other or with other GPCR [1360], but evidence for heterodimers in native cells is equivocal. A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (*OGFR*, 9NZT2) and termed an opioid growth factor receptor [1389]. Opioid receptor subtypes

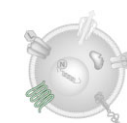
may reflect heterodimerization of opioid receptors with each other or with other GPCR, and while there is increasing evidence for heterodimers in native cells, the consequences this heterodimerization has for signalling remains largely unknown. For μ -opioid receptors at least, dimerization does not seem to be required for signalling [1362].

endomorphin-1 and endomorphin-2 have been identified as highly selective, putative endogenous agonists for the μ -opioid receptor. At present, however, the mechanisms for endomorphin synthesis *in vivo* have not been established, and there is no gene identified that encodes for either. Thus, the status of these peptides as endogenous ligands remains unproven.

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human μ -receptors [1371] and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists [1342]. Pathway bias for agonists makes general rank orders of potency and efficacy somewhat obsolete, and they have, therefore, been removed from the table. As ever, the mechanisms underlying the acute and long term regulation of opioid receptor function are the subject of intense investigation and debate.

Searchable database: <http://www.guidetopharmacology.org/index.jsp>

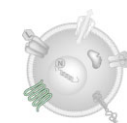
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Opioid receptors 1539

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Orexin receptors

Overview: Orexin receptors (nomenclature as agreed by [NC-IUPHAR](#), see [1395]) are activated by the endogenous polypeptides orexin-A (*HCRT*, O43612) and orexin-B (*HCRT*, O43612) (also known as hypocretin-1 and -2; 33 and 28 aa) derived from a common precursor, preproorexin or orexin precursor, by proteolytic cleavage [1407]. Binding to both receptors may be accomplished with [¹²⁵I]orexin A (human, mouse, rat) [1397].

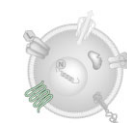
Nomenclature	OX ₁ receptor	OX ₂ receptor
HGNC, UniProt	<i>HCRT1</i> , O43613	<i>HCRT2</i> , O43614
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	orexin-A > orexin-B	orexin-A = orexin-B
Selective agonists (pK _i)	–	[Ala ¹¹ , D-Leu ¹⁵]orexin-B (pEC ₅₀ 9.9) [1394]
Selective antagonists (pK _i)	SB-334867 (7.4 – 7.5) [1402,1404], SB-408124 (7.2 – 7.6) [1399,1402]	N-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulphonyl)-amino]-N-pyridin-3-ylmethyl-acetamide (9.0) [1401], 1-(2,4-dibromo-phenyl)-3-[(4S,5S)-2,2-dimethyl-4-phenyl-[1394,1396]dioxan-5-yl)-urea (7.9 – 8.6) [1403], TCS-OX2-29 (7.4) [1396]

Comments: 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 [1398,1406]; 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 [Ala¹¹, D-Leu¹⁵]orexin-B may show poor OX₂ receptor selectivity [1405].

Loss-of-function mutations in the gene encoding the OX₂ receptor underlie canine hereditary narcolepsy [1400].

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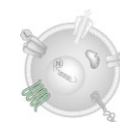
Oxoglutarate receptor

Overview: the oxoglutarate receptor (NC-IUPHAR recommended nomenclature, see Davenport *et al.*, 2004) has been suggested to respond to one of the intermediates of the citric acid cycle [1408].

Nomenclature	HGNC gene symbol	UniProtKB AC	Principal transduction	Endogenous agonists (pK _i)
oxoglutarate receptor	<i>OXGR1</i>	Q96P68	G _q [1408]	α -ketoglutaric acid (pEC ₅₀ 3.3 – 4.49) [1408–1409]

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacological reviews* 65: 967–986.

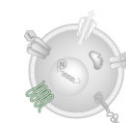


P2Y receptors

Overview: P2Y receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, [1410–1411]) 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 ‘P2Y₁-like’, *etc.*, until further, as yet undefined, corroborative criteria can be applied.

Nomenclature	P2Y ₁ receptor	P2Y ₂ receptor	P2Y ₄ receptor	P2Y ₆ receptor
HGNC, UniProt	<i>P2RY1</i> , P47900	<i>P2RY2</i> , P41231	<i>P2RY4</i> , P51582	<i>P2RY6</i> , Q15077
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
Endogenous agonists (pK _i)	–	–	–	UDP (pEC ₅₀ 6.5) [1423]
Selective agonists (pK _i)	MRS2365 (pEC ₅₀ 9.4) [1421], ADPβS (pEC ₅₀ 7.3) [1459], 2MeSADP (pIC ₅₀ 5.4 – 7.0) [1458,1461]	2-thioUTP (pEC ₅₀ 7.3) [1426], PSB1114 (pEC ₅₀ 6.9) [1427], Ap ₄ A (pEC ₅₀ 6.1) [1419,1457], UTPγS (pEC ₅₀ 5.8) [1443], MRS2768 (pEC ₅₀ 5.7) [1441]	UTPγS [1444], MRS4062 (pEC ₅₀ 7.6) [1448]	MRS2957 (pEC ₅₀ 7.9) [1447], 5-iodoUDP (pEC ₅₀ 7.82) [1416], 3-phenacyl-UDP (pEC ₅₀ 7.2) [1426]
Selective antagonists (pK _i)	MRS2500 (8.8 – 9.1) [1420,1438], MRS2279 (7.9) [1461], MRS2179 (7.0 – 7.1) [1418,1461], 2,2'-pyridylisatogen tosylate (6.8) [1429]	AR-C118925XX (pIC ₅₀ ~6.0) [1436]	ATP (pK _d 6.2) [1437]	MRS2578 (pIC ₅₀ 7.4) [1445]
Radioligands (K _d)	[³⁵ S]ADPβS (Agonist), [³ H]2MeSADP (Agonist), [³ H]MRS2279 (Antagonist) (8×10 ⁻⁹ M) [1461]	–	–	–

Nomenclature	P2Y ₁₁ receptor	P2Y ₁₂ receptor	P2Y ₁₃ receptor	P2Y ₁₄ receptor
HGNC, UniProt	<i>P2RY11</i> , Q96G91	<i>P2RY12</i> , Q9H244	<i>P2RY13</i> , Q9BPV8	<i>P2RY14</i> , Q15391
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
Endogenous agonists (pK _i)	–	ADP (5.9) [1432], ATP (5.2) [1432]	–	–
Selective agonists (pK _i)	NAADP [1452], NAD [1453], AR-C67085 (pEC ₅₀ 8.52) [1413,1424], NF546 (pEC ₅₀ 6.27) [1449]	2MeSADP (9.2) [1432]	–	MRS2690 (pEC ₅₀ 6.64 – 7.31) [1430,1442]
Selective antagonists (pK _i)	NF157 (7.35) [1460], NF340 (pIC ₅₀ 6.4 – 7.1) [1449]	PSB-0739 (7.6) [1414], ARL66096 (pIC ₅₀ 7.95) [1433–1434]	MRS2211 (pIC ₅₀ 5.97) [1439]	–
Radioligands (K _d)	–	[³ H]PSB-0413 (Antagonist) (3.16×10 ⁻⁹ – 4.57×10 ⁻⁹ M) [1425,1455], [³ H]2MeSADP (Agonist, Full agonist) (IC ₅₀ 2.5×10 ⁻¹⁰ – 3.16×10 ⁻⁸ M) [1459]	–	–



Comments: AR-C69931MX (cangrelor) shows selectivity for P2Y₁₂ and P2Y₁₃ receptors compared with other P2Y receptors [1446,1459]. NF157 also has antagonist activity at P2X₁ receptors [1460]. UDP has been reported to be an antagonist at the P2Y₁₄ receptor [1428].

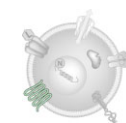
An orphan GPCR suggested to be a 'P2Y₁₅' receptor [1435] appears not to be a genuine nucleotide receptor [1411], but rather responds to dicarboxylic acids [1431]. Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a p2y₃ receptor (ENSGALG00000017327), couples to the G_{q/11} family of G proteins and shows the rank order of potency ADP > UTP > ATP =

UDP [1462]. In addition, human sources have yielded a clone with a preliminary identification of p2y5 (*LPAR6*, P43657) and contradictory evidence of responses to ATP [1440,1463]. This protein is now classified as LPA₄, a receptor for lysophosphatidic acid (LPA) [1456,1464]. The clone termed p2y9 (*LPAR4*, 99677, [1454]). The clone p2y7 (*NOP9*, Q86U38), originally suggested to be a P2Y receptor [1412], has been shown to encode a leukotriene receptor [1465]. 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 Ca²⁺-dependent Cl⁻ current in *Xenopus* oocytes [1417]. The p2y10 clone (*P2RY10*, O00398) lacks functional data. Diadenosine polyphosphates also

have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap₄A > Ap₅A > Ap₃A, coupling via G_{q/11} [1419]. P2Y-like receptors have recently been described on mitochondria [1415]. CysLT1 and CysLT2 leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes LTC₄ and LTD₄ [1450–1451]; Human GPR17 (13304) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes as well as UDP and UDP-glucose [1422]. Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and cangrelor [1422].

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Parathyroid hormone receptors

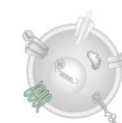
Overview: The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor (PTH₁ receptor) is activated by precursor-derived peptides: PTH (*PTH*, P01270) (84 amino acids), and PTHrP (*PTHrP*, P12272) (141 amino-acids) and related peptides (PTH-(1-34), PTHrP-(1-36)). The parathyroid hormone 2 receptor (PTH₂ receptor) is activated by the precursor-derived peptide TIP39 (39 amino acids, *PTH2*, Q96A98). [¹²⁵I]PTH may be used to label both PTH₁ and PTH₂ receptors.

Nomenclature	PTH ₁ receptor	PTH ₂ receptor
HGNC, UniProt	<i>PTH1R</i> , Q03431	<i>PTH2R</i> , P49190
Principal transduction	G _s , G _{q/11}	G _s , G _{q/11}
Rank order of potency	PTH = PTHrP	TIP39, PTH >> PTHrP
Endogenous agonists (pK _i)	–	TIP39 (pI _{C₅₀ 7.6 – 9.2) [1468–1469]}
Selective agonists (pK _i)	PTHrP-(1-34) (pI _{C₅₀ 7.8 – 8.1 - Rat) [1467], PTH-(1-34) (human) (pI_{C₅₀ 7.4) [1466]}}	–

Comments: Although PTH (*PTH*, P01270) is an agonist at human PTH₂ receptors, it fails to activate the rodent orthologues. TIP39 (*PTH2*, Q96A98) is a weak antagonist at PTH₁ receptors [1470].

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Peptide P518 receptor

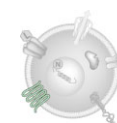
Overview: The peptide P518 receptor is also known as the QRFP receptor and responds to the endogenous peptide agonist QRFP.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (p <i>K</i> _i)	Radioligands (<i>K</i> _d)
QRFP receptor	<i>QRFP</i> , Q96P65	G _{q/11} , G _{i/o} [1471]	QRFP26 (<i>QRFP</i>) (pEC ₅₀ 8.15) [1472], QRFP (<i>QRFP</i> , P83859) (pIC ₅₀ 7.8 – 9.28 – Rat) [1471,1474]	[¹²⁵ I]QRFP (human) (Agonist, Full agonist) (5.01×10 ⁻¹¹ – 1.58×10 ⁻⁸ M) [1471,1473–1474]

Comments: The orphan receptor GPR83 (9NYM4) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors.

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Fukusumi S, Fujii R, Hinuma S. (2006) Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. *Peptides* 27: 1073–1086. [PMID:16500002]



Platelet-activating factor receptor

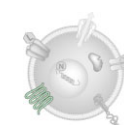
Overview: Platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is an ether phospholipid mediator associated with platelet coagulation, but also subserves inflammatory roles. The PAF receptor (provisional nomenclature, see [1475]) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1479] and lysophosphatidylcholine [1482]. It may also be activated by bacterial lipopolysaccharide [1481].

Nomenclature	HGNC, UniProt	Principal transduction	Selective agonists (pK _i)	Selective antagonists (pK _i)	Radioligands (K _d)
PAF receptor	<i>PTAFR</i> , P25105	G _{q/11} , G _i , G _o	mc-PAF	SR 27417 (10.3) [1478], L659989 (8.1), ginkgolide B (6.4), apafant (5.2 – 7.5) [1483–1484], CV-6209 (pIC ₅₀ 8.1 – 8.3) [1477,1480]	[³ H]PAF (Agonist, Full agonist) (1.6×10 ⁻⁹ – 1.3×10 ⁻⁹ M) [1476,1480]

Comments: Note that a previously recommended radioligand ([³H]apafant; K_d 44.6 nM) is currently unavailable.

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Prokineticin receptors

Overview: Prokineticin receptors (provisional nomenclature, [1486]) respond to the cysteine-rich 81–86 amino-acid peptides prokineticin-1 (*PROK1*, Q9HC23) (also known as endocrine-gland-derived vascular endothelial growth factor, mambakine)

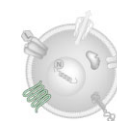
and prokineticin-2 (*PROK2*, Q9HC23) (protein Bv8 homologue). An orthologue of *PROK1* from black mamba (*Dendroaspis polylepis*) venom, mamba intestinal toxin 1 (MIT1, [1491]) is a potent, non-selective agonist at prokineticin receptors [1488],

while Bv8, an orthologue of *PROK2* from amphibians (*Bombina sp.*, [1489]), is equipotent at recombinant PK₁ and PK₂ receptors [1490], and has high potency in macrophage chemotaxis assays, which are lost in PK₁-null mice [1485].

Nomenclature	PKR ₁	PKR ₂
HGNC, UniProt	<i>PROKR1</i> , Q8TCW9	<i>PROKR2</i> , Q8NFJ6
Principal transduction	G _{q/11} [1487–1488]	G _{q/11} [1487–1488]
Rank order of potency	prokineticin-2 > prokineticin-1 [1487–1488,1492]	prokineticin-2 > prokineticin-1 [1487–1488,1492]

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Prolactin-releasing peptide receptor

Overview: The precursor (*PRLH*, P81277) for PrRP generates 31 and 20-amino-acid versions. QRFP (*QRFP*, P83859) (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from QRFP (P83859) and is also known as P518 or 26RFa. RFRP is an RF amide-related peptide [1495] derived from a FMRFamide-related peptide precursor (*NPVF*, Q9HCQ7), which is cleaved to generate neuropeptide NPSF (*NPFF*, O15130), neuropeptide RFRP-1 (*NPVF*, Q9HCQ7), neuropeptide RFRP-2 (*NPVF*, Q9HCQ7) and neuropeptide RFRP-3 (*NPVF*, Q9HCQ7) (neuropeptide NPVF).

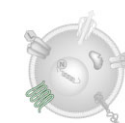
Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Endogenous agonists (pK _i)	Endogenous antagonists (pK _i)	Radioligands (K _d)
PRRP receptor	<i>PRLHR</i> , P49683	G _{q/11} [1497]	PrRP-20, PrRP-31 [1497]	PrRP-20 (Selective) (9.0–9.6) [1494,1497], PrRP-31 (Selective) (9.0–9.2) [1494,1497]	NPY (<i>NPY</i> , P01303) (Selective) (5.4) [1496]	[¹²⁵ I]PrRP31 [1493], [¹²⁵ I]PrRP-20 (human) (Agonist, Full agonist) (2.6×10 ⁻¹¹ –5.7×10 ⁻¹⁰ M) [1497]

Comments: The orphan receptor *GPR83* (Q9NYM4) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors.

Further reading

Samson WK, Taylor MM. (2006) Prolactin releasing peptide (PrRP): an endogenous regulator of cell growth. *Peptides* 27: 1099–1103. [PMID:16500730]

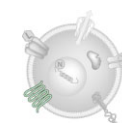
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Prostanoid receptors

Overview: Prostanoid receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors, [1512]) are activated by the endogenous ligands prostaglandins PGD₂, PGE₂, PGF_{2α}, PGH₂, prostacyclin [PGI₂] and thromboxane A₂. Measurement of the potency of PGI₂ and thromboxane A₂ 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 receptor	DP ₂ receptor	FP receptor	IP ₁ receptor	TP receptor
HGNC, UniProt	<i>PTGDR</i> , Q13258	<i>PTGDR2</i> , Q9Y5Y4	<i>PTGFR</i> , P43088	<i>PTGIR</i> , P43119	<i>TBXA2R</i> , P21731
Principal transduction	G _s	G _{i/o}	G _{q/11}	–	G _{q/11}
Rank order of potency	PGD ₂ >> PGE ₂ > PGF _{2α} > PGI ₂ , thromboxane A ₂	PGD ₂ >> PGF _{2α} , PGE ₂ > PGI ₂ , thromboxane A ₂	PGF _{2α} > PGD ₂ > PGE ₂ > PGI ₂ , thromboxane A ₂	PGI ₂ >> PGD ₂ , PGE ₂ , PGF _{2α} > thromboxane A ₂	thromboxane A ₂ = PGH ₂ >> PGD ₂ , PGE ₂ , PGF _{2α} , PGI ₂
Selective agonists (pK _i)	L-644,698 (9.0–9.3) [1563–1564], BW 245C (8.4–9.4) [1506,1563–1564], SQ-27986 (8.0) [1545], RS 93520 (Partial agonist) (7.5) [1545], ZK118182 (7.3) [1545]	15(R)-15-methyl-PGD ₂ (8.9) [1518,1533,1552], 13,14-dihydro-15-keto-PGD ₂ (7.4–8.5) [1518,1544,1552]	fluprostenol (8.6) [1498], latanoprost (free acid form) (8.6) [1498], AL12180 (pEC ₅₀ 7.7–7.9) [1547]	cicaprost (7.8) [1498], AFP-07 (pIC ₅₀ 8.5) [1508], BMY 45778 (pIC ₅₀ 8.0) [1520]	I-BOP (pK _d 8.94–9.32) [1532], U46619 (7.5) [1498], STA ₂ (pIC ₅₀ 6.38–7.06) [1502]
Selective antagonists (pK _i)	laropiprant (10.1) [1550], BWA868C (8.6–9.3) [1506,1517,1563], S-5751 (8.8) [1501]	ramatroban (7.4) [1552], CAY 10471 (pIC ₅₀ 8.92) [1543,1556]	AS604872 (7.5) [1510]	RO3244794 (pA ₂ 8.5) [1503], RO1138452 (8.7) [1503]	ifetroban (8.4–10.0) [1538], GR 32191 (8.3–9.4) [1502,1528], SQ-29548 (8.1–9.1) [1498,1554,1559], ONO 3708 (7.4–8.9) [1522]
Radioligands (K _d)	[³ H]PGD ₂ (Agonist, Full agonist) (1.3×10 ⁻⁸ – 3×10 ⁻¹⁰ M) [1559,1563]	[³ H]PGD ₂ (Agonist, Full agonist) (1.6×10 ⁻⁸ – 6×10 ⁻⁹ M) [1530,1548]	[³ H]PGF _{2α} (Agonist, Full agonist) (7.9×10 ⁻⁹ – 1×10 ⁻⁹ M) [1498–1499,1559], [³ H](+)-fluprostenol (Agonist) (3.4×10 ⁻⁸ M)	[³ H]iloprost (Agonist, Full agonist) (2×10 ⁻⁸ – 1×10 ⁻⁹ M) [1498,1505,1559]	[¹²⁵ I]BOP (Agonist, Full agonist) (2×10 ⁻⁹ M) [1534], [¹²⁵ I]SAP (Antagonist) (2×10 ⁻⁸ – 5×10 ⁻¹⁰ M) [1536], [³ H]SQ-29548 (Antagonist) (4×10 ⁻⁸ – 6.3×10 ⁻⁹ M) [1498,1559]



Nomenclature	EP ₁ receptor	EP ₂ receptor	EP ₃ receptor	EP ₄ receptor
HGNC, UniProt	<i>PTGER1</i> , P34995	<i>PTGER2</i> , P43116	<i>PTGER3</i> , P43115	<i>PTGER4</i> , P35408
Principal transduction	G _{q/11}	G _s	G _{i/o}	G _s
Rank order of potency	PGE ₂ > PGF _{2α} , PGI ₂ > PGD ₂ , thromboxane A ₂	PGE ₂ > PGF _{2α} , PGI ₂ > PGD ₂ , thromboxane A ₂	PGE ₂ > PGF _{2α} , PGI ₂ > PGD ₂ , thromboxane A ₂	PGE ₂ > PGF _{2α} , PGI ₂ > PGD ₂ , thromboxane A ₂
Selective agonists (pK _i)	17-phenyl-ω-trinor-PGE ₂ (8.1) [1546], ONO-DI-004 (6.8 - Mouse) [1553]	ONO-AE1-259 (8.5 - Mouse) [1553], butaprost (free acid form) (5.9–7.0) [1498,1549], CP-533536 (pIC ₅₀ 7.3 - Rat) [1507]	SC46275 (pEC ₅₀ 8.74 - Rat) [1519], ONO-AE-248 (pEC ₅₀ 5.64–6.7) [1514,1527]	L902688 (pEC ₅₀ 8.05–10.3) [1515,1525], ONO-AE1-329 (pEC ₅₀ 7.66–7.8) [1514–1515], CP734432 (pIC ₅₀ 8.7) [1540]
Selective antagonists (pK _i)	ONO-8711 (9.2) [1557], SC-51322 (7.9) [1498], GW848687X (pIC ₅₀ 8.6) [1516]	–	L-798,106 (9.52–9.62) [1521,1551], ONO-AE3-240 (pIC ₅₀ 8.8 - Mouse) [1500]	MK-2894 (9.25) [1498,1504,1511], CP-533536 (8.6) [1535], ONO-AE3-208 (8.5), EP ₄ A (7.6–8.5) [1529,1565], BGC201531 (7.9) [1531], GW 627368 (7.0–7.1) [1559–1560], ER819762 (pIC ₅₀ 7.15) [1509]
Radioligands (K _d)	[³ H]PGE ₂ (Agonist, Full agonist) (1×10 ⁻⁹ – 2.5×10 ⁻⁸ M) [1498,1546,1559]	[³ H]PGE ₂ (Agonist, Full agonist) (1.25×10 ⁻⁸ – 1.99×10 ⁻⁸ M) [1498,1559]	[³ H]PGE ₂ (Agonist, Full agonist) (3×10 ⁻¹⁰ – 7×10 ⁻⁹ M) [1498,1559]	[³ H]PGE ₂ (Agonist, Full agonist) (2.4×10 ⁻⁸ – 3×10 ⁻¹⁰ M) [1498,1513,1558–1559]

Comments: ramatroban is also a TP receptor antagonist. cicaprost exhibits moderate EP₄ receptor agonist potency [1498]. iloprost also binds to EP₁ receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail [1542].

17-phenyl-ω-trinor-PGE₂ also shows agonist activity at EP₃ receptors. sulprostone also has affinity for EP₁ receptors. butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1526], IP

[1555,1561] and TP [1524] receptors. mRNA for the EP₁ and EP₃ receptors undergo alternative splicing to produce two [1539] and at least six variants, respectively, which can interfere with signalling [1539] or generate complex patterns of G-protein (G_{i/o}, G_{q/11}, G_s and G_{12,13}) coupling (*e.g.* [1523,1537]). The possibility of additional receptors for the isoprostanes has been suggested [1541]. Receptors (prostanoid F, which as yet lack a molecular correlate) that preferentially recognize PGF₂-1-ethanolamide and its analogues (*e.g.* bimatoprost) have been identified, together with moderate-potency antagonists (*e.g.* AGN 211334) [1562].

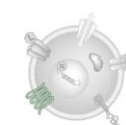
The free acid form of AL-12182, AL-12180, used in *in vitro* studies, has a EC₅₀ value of 15nM which is the concentration of the compound giving half-maximal stimulation of IP turnover in HEK-293 cells expressing the human FP receptor [1547].

References given alongside the TP receptor agonists I-BOP [1532] and STA₂ [1502] use human platelets as the source of TP receptors for competition radio-ligand binding assays to determine the indicated activity values.

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Proteinase-activated receptors

Overview: Proteinase-activated receptors (PARs, nomenclature as agreed by [NC-IUPHAR](#) Subcommittee on Protease-activated Receptors, [1574]) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmask a tethered ligand (TL) at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the

receptor to effect transmembrane signalling. TL sequences at human PAR1–4 are SLLRN-NH₂, SLIGKV-NH₂, TFRGAP-NH₂ and GYPGQV-NH₂, 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 PAR1 and PAR2 such

that they cleave the exodomain of the receptor without inducing activation of G_{αq}-coupled calcium signaling, thereby preventing activation by activating proteinases but not by agonist peptides. Neutrophil elastase cleavage of PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [1581]. The role of such an action *in vivo* is unclear.

Nomenclature	PAR1	PAR2	PAR3	PAR4
HGNC, UniProt	<i>F2R</i> , P25116	<i>F2RL1</i> , P55085	<i>F2RL2</i> , O00254	<i>F2RL3</i> , Q96RI0
Principal transduction	G _{q/11} /G _{i/o} /G _{12/13}	G _{q/11} /G _{i/o}	Not known	G _{q/11} /G _{i/o}
Agonist proteases	thrombin (<i>F2</i> , P00734), activated protein C (<i>PROC</i> , P04070), matrix metalloproteinase 1 (<i>MMP1</i> , P45452), matrix metalloproteinase 13 (<i>MMP13</i> , P45452) [1569]	Trypsin, tryptase, TF/VIIa, Xa	thrombin (<i>F2</i> , P00734)	thrombin (<i>F2</i> , P00734), trypsin, cathepsin G (<i>CTSG</i> , P08311)
Selective agonists (pK _i)	TFLLR-NH ₂ (pEC ₅₀ 5.41) [1573]	SLIGKV-NH ₂ [1579], SLIGRL-NH ₂ [1579], 2-furoyl-LIGRLO-amide (5.4) [1580], GB 110 (pEC ₅₀ 6.55) [1570], P2pal18s [1582], GB88 (pIC ₅₀ 5.7) [1583]	–	AYPGKF-NH ₂ , GYPGKF-NH ₂ , GYPGQV-NH ₂
Selective antagonists (pK _i)	SCH530348 (8.09) [1572], atopaxar (pIC ₅₀ 7.72) [1578], RWJ-56110 (pIC ₅₀ 6.36) [1568]	–	–	–
Radioligands (K _d)	[³ H]haTRAP (Agonist) (1.5×10 ⁸ M) [1566]	2-furoyl-LIGRL[N ³ H]propionyl]-O-NH ₂ [1575], [³ H]2-furoyl-LIGRL-NH ₂ (Agonist) [1576], trans-cinnamoyl-LIGRLO [N-[³ H]propionyl]-NH ₂ [1567]	–	–

Comments: TFLLR-NH₂ is selective relative to the PAR₂ receptor [1571,1577]. thrombin (*F2*, P00734) is inactive at the PAR₂ receptor.

Endogenous serine proteases (EC 3.4.21.) active at the proteinase-activated receptors include: thrombin (*F2*, P00734), generated by

the action of Factor X (*F10*, P00742) on liver-derived prothrombin (*F2*, P00734); trypsin, generated by the action of enterokinase (*TMPS15*, P98073) on pancreatic-derived trypsinogen (*PRSS1*, P07477); tryptase, a family of enzymes (α/β 1 *TPSAB1*, Q15661; γ 1 *TPSG1*, Q9NRR2; δ 1 *TPSD1*, Q9BZJ3) secreted from mast cells; cathepsin G (*CTSG*, P08311) generated from leukocytes; liver-

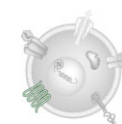
derived protein C (*PROC*, P04070) generated in plasma by thrombin (*F2*, P00734) and matrix metalloproteinase 1 (*MMP1*, P45452).

2-Furoyl-LIGRLO-NH₂ activity was measured via calcium mobilisation in HEK 293 cells which constitutively coexpress human PAR₁ and PAR₂.

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Relaxin family peptide receptors

Overview: Relaxin family peptide receptors (RXFP, nomenclature as recommended by the [NC-IUPHAR](#) committee on relaxin family peptide receptors, [1584]) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: H1 relaxin (*RLN1*, P04808), H2 relaxin (*RLN2*, P04090), H3 relaxin (*RLN3*, Q8WXF3) (also known as INSL7), insulin-like peptide 3 (*INSL3* (*INSL3*, P51460)) and INSL5 (*INSL5*, Q9Y5Q6).

Species homologues of relaxin have distinct pharmacology – H2 relaxin (*RLN2*, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [1611] and porcine relaxin may have a higher efficacy than H2 relaxin (*RLN2*, P04090) [1591]. H3 relaxin (*RLN3*, Q8WXF3) has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (*RLN3*, Q8WXF3) [1610]. At least two binding sites

have been identified on the 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 domain [1591,1618]. The unique N-terminal LDLa module of RXFP1 and RXFP2 is essential for receptor signalling [1612].

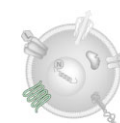
Nomenclature	RXFP1 receptor	RXFP2 receptor	RXFP3 receptor	RXFP4 receptor
HGNC, UniProt	<i>RXFP1</i> , Q9HBX9	<i>RXFP2</i> , Q8WXD0	<i>RXFP3</i> , Q9NSD7	<i>RXFP4</i> , Q8TDU9
Principal transduction	G _s , G _{α0B} , G _{α3} [1590,1595,1599]	G _s , G _{α0B} [1590,1601]	G _{i/o} [1606,1620]	G _{i/o} [1604]
Rank order of potency	H2 relaxin > H3 relaxin >> INSL3 [1618]	INSL3 > H2 relaxin >> H3 relaxin [1601,1618]	H3 relaxin > H3 relaxin (B chain) [1604]	INSL5 = H3 relaxin > H3 relaxin (B chain) [1602–1603]
Endogenous antagonists (pK)	–	–	INSL5 (pIC ₅₀ 6.3) [1605]	–
Selective antagonists (pK)	LGR7-truncate [1612], B-R13/17K H2 relaxin (pEC ₅₀ 6.7) [1597],	(des 1-8) A-chain INSL3 analogue [1586], INSL3 B-chain analogue [1587], INSL3 B chain dimer [1616],	H3 relaxin analogue 3 [1613], R3(BΔ23-27)R/I5 chimeric peptide (pIC ₅₀ 9.2) [1600], R3-B1-22R (pIC ₅₀ 7.4) [1596]	R3(BΔ23-27)R/I5 chimeric peptide (pIC ₅₀ 8.64) [1600]
Radioligands (K _d)	[¹²⁵ I]H2 relaxin (Agonist, Full agonist), [³³ P]H2 relaxin (Agonist, Full agonist) (5x10 ⁻¹⁰ –2x10 ⁻¹⁰ M) [1591,1618],	[¹²⁵ I]INSL3 (human) (Agonist, Full agonist) (1x10 ⁻¹⁰ M) [1608], [³³ P]H2 relaxin (Agonist, Full agonist) (1.06x10 ⁻⁹ –6.3x10 ⁻¹⁰ M) [1591,1618],	[¹²⁵ I]H3 relaxin (Agonist, Full agonist) (3x10 ⁻¹⁰ M) [1604], [¹²⁵ I]H3-B/INSL5 A chimera (Agonist) (5x10 ⁻¹⁰ M) [1602],	[¹²⁵ I]H3 relaxin (Agonist, Full agonist) (2x10 ⁻⁹ –2x10 ⁻¹⁰ M) [1603], [¹²⁵ I]H3-B/INSL5 A chimera (Agonist) (1.2x10 ⁻⁹ M) [1602],
Comment	europium-labelled H2 relaxin is a fluorescent ligand for this receptor (K _d =0.5 nM) [1614].	europium-labelled INSL3 is a fluorescent ligand for this receptor (K _d =1 nM) [1615].	europium-labelled H3-B/INSL5 A chimera is a fluorescent ligand for this receptor (K _d =5 nM) [1596].	europium-labelled H3-B/INSL5 A chimera is a fluorescent probe at this receptor (K _d =5 nM) [1596], europium-labelled mouse INSL5 is a fluorescent ligand at this receptor (K _d =5 nM) [1585].

Comments: H2 relaxin has recently successfully completed a Phase III clinical trial for the treatment of acute heart failure. 48 hr infusion of H2 relaxin reduced dyspnoea and 180 day mortality [1607]. Small molecule agonists active at RXFP1 receptors have been developed [1617,1622]. Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism [1588]. Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, most of which do not bind relaxin family peptides [1608]. Splice variants of RXFP1 encoding the N-terminal LDLa module act as

antagonists of RXFP1 signalling [1610,1612]. cAMP elevation appears to be a major signalling pathway for RXFP1 and RXFP2 [1598–1599], but RXFP1 also activates MAP kinases, nitric oxide signalling and interacts with tyrosine kinases and glucocorticoid receptors [1594]. RXFP1 signalling involves lipid rafts, residues in the C-terminus of the receptor and activation of phosphatidylinositol-3-kinase [1595]. More recent studies provide evidence that RXFP1 is pre-assembled in signalosomes with other signalling proteins including G_{αs}, G_{βγ} and adenylyl cyclase 2 that display constitutive activity and are exquisitely

sensitive to sub-picomolar concentrations of relaxin [1592]. The cAMP signalling pattern is highly dependent on the cell type in which RXFP1 is expressed [1593].

The receptor expression profiles suggest that RXFP3 is a neuro-peptide receptor and RXFP4 a gut hormone receptor. The relaxin 3 RXFP3 system has roles in feeding and anxiety [1589,1609]. H3 relaxin (*RLN3*, Q8WXF3) acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 (*INSL5*, Q9Y5Q6) is an agonist at RXFP4 and a weak antagonist at RXFP3. Unlike RXFP1 and RXFP2 both



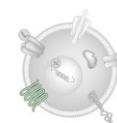
RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino-acids at the N-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes [1621]. RXFP3 couples to $G_{i/o}$ and inhibits adenylyl cyclase [1604,1619], and also causes Erk1/2 phosphorylation [1619]. Relatively little is known about RXFP4 signalling but like RXFP3 it couples to inhibitory G-proteins [1605]. Recent studies suggest that H2 relaxin (*RLN2*, P04090)

also interacts with RXFP3 to cause a pattern of activation of signalling pathways that are a subset of those activated by H3 relaxin (*RLN3*, Q8WXF3). 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 NF κ -B reporter gene activation with H3 relaxin (*RLN3*, Q8WXF3), and weaker activity with H2 relaxin (*RLN2*, P04090), porcine relaxin, or insulin-like peptide 3 (INSL3 (*INSL3*, P51460)) and a strong stimulation of activator protein (AP)-1 reporter genes with H2 relaxin (*RLN2*, P04090), and weaker acti-

vation with H3 relaxin (*RLN3*, Q8WXF3) or porcine relaxin [1619]. Two pharmacologically distinct ligand binding sites were also identified on RXFP3-expressing cells using [125 I]H3-B/INSL5 A chimera which binds with high affinity with competition by H3 relaxin (*RLN3*, Q8WXF3) or a H3 relaxin (B chain) (*RLN3*, Q8WXF3) peptide, and [125 I]H2 relaxin which displays competition by H2 relaxin (*RLN2*, P04090), H3 relaxin (*RLN3*, Q8WXF3), or INSL3 (*INSL3*, P51460) and weakly by porcine relaxin. Thus at RXFP3, H2 relaxin (*RLN2*, P04090) is a biased ligand compared to the cognate ligand H3 relaxin (*RLN3*, Q8WXF3).

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Somatostatin receptors

Overview: Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (ssr_1 – ssr_5 ; **nomenclature approved by the NC-IUPHAR Subcommittee on Somatostatin Receptors**, [1628]). 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 (SST, P61278)) and somatostatin-28

(SRIF-28 (SST, P61278)). Cortistatin (CST-14) has also been suggested to be an endogenous ligand for somatostatin receptors [1625].

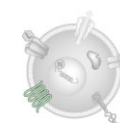
Nomenclature	ssr_1 receptor	ssr_2 receptor	ssr_3 receptor	ssr_4 receptor	ssr_5 receptor
HGNC, UniProt	<i>SSTR1</i> , P30872	<i>SSTR2</i> , P30874	<i>SSTR3</i> , P32745	<i>SSTR4</i> , P31391	<i>SSTR5</i> , P35346
Principal transduction	G_i	G_i	G_i	G_i	G_i
Selective agonists (pK _i)	L-797,591 (8.8) [1635], Des-Ala ^{1,2,5} -[D-Trp ⁸ ,Ile ⁹]SRIF (pIC ₅₀ 7.5) [1626]	L-054,522 (11.0) [1640], MK-678 (8.8 – 10.3) [1623,1634,1636–1638,1640], octreotide (8.7 – 9.9) [1623,1634,1636–1638,1640], BIM 23027 (pIC ₅₀ 10.85) [1624]	L-796,778 (7.6) [1635]	L-803,087 (9.2) [1635], NNC269100 (8.2) [1631]	L-817,818 (9.4) [1635], BIM 23268 (8.7) [1632], BIM 23052 (7.4 – 9.6) [1632,1636–1638]
Selective antagonists (pK _i)	SRA880 (pK _d 8.0 – 8.1) [1629]	[D-Tyr ⁸]CYN 154806 (pK _d 8.1 – 8.9) [1633]	NVP ACQ090 (7.9) [1630]	–	BIM 23627 (pIC ₅₀ 7.1) [1639]
Radioligands (K _d)	–	[¹²⁵ I]Tyr ³ SMS 201-995 (Agonist, Full agonist) (1.3×10 ^{−10} M) [1637–1638], [¹²⁵ I]BIM23027 (Agonist, Full agonist) (IC ₅₀ 2.2×10 ^{−10} M - Rat) [1627]	–	–	[¹²⁵ I]Tyr ³ SMS 201-995 (Agonist, Full agonist) (2.3×10 ^{−10} M) [1637–1638]

Comments: [¹²⁵I]Tyr¹¹-SRIF-14, [¹²⁵I]LTT-SRIF-28, [¹²⁵I]CGP 23996 and [¹²⁵I]Tyr¹⁰-CST14 may be used to label somatostatin receptors nonselectively; BIM 23052 is said to be selective in rat but not human receptor [1634]. A number of nonpeptide subtype-selective agonists have been synthesised [1635].

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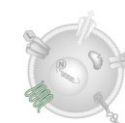
Succinate receptor

Overview: the succinate receptor (NC-IUPHAR recommended nomenclature, see Davenport *et al.*, 2004) has been reported to respond to an intermediate of the citric acid cycle [1641].

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)
succinate receptor	<i>SUCNR1</i> , Q9BXA5	–	succinic acid (pEC ₅₀ 3.1–4.7) [1641–1642]

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacological reviews* 65: 967–986.



Tachykinin receptors

Overview: Tachykinin receptors (provisional nomenclature, [1658]) are activated by the endogenous peptides substance P (*TAC1*, P20366) (SP), neurokinin A (*TAC1*, P20366) (NKA; previously known as substance K, neurokinin α , neuromedin L), neurokinin B (*TAC3*, Q9UHF0) (NKB; previously known as

neurokinin β , neuromedin K), neuropeptide K (*TAC1*, P20366) and neuropeptide γ (*TAC1*, P20366) (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 *in vitro* pharmacology exist for all three receptors, in the context of nonpeptide ligands.

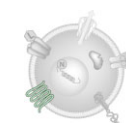
Nomenclature	NK ₁ receptor	NK ₂ receptor	NK ₃ receptor
HGNC, UniProt	<i>TACR1</i> , P25103	<i>TACR2</i> , P21452	<i>TACR3</i> , P29371
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}
Rank order of potency	substance P > neurokinin A > neurokinin B	neurokinin A > neurokinin B >> substance P	neurokinin B > neurokinin A > substance P
Selective agonists (pK _i)	[Pro ⁹]SP, septide (7.0–9.3) [1645,1663], [Sar ⁹ ,Met(O ₂) ¹¹]SP (pIC ₅₀ 9.7–9.9) [1673], substance P-OMe (pIC ₅₀ 7.4–7.5) [1673]	[βAla ⁸]neurokinin A-(4–10) (pK _d 6.0) [1656], GR64349 (pEC ₅₀ 8.4 – Rat) [1653], [Lys ⁵ ,Me-Leu ⁹ ,Nle ¹⁰]NKA-(4–10) (pIC ₅₀ 8.8–9.4 – Rat) [1667]	[Phe(Me) ⁷]neurokinin B (8.7–9.6) [1670–1671], senktide (7.1–8.6) [1670–1671,1673]
Selective antagonists (pK _i)	aprepitant (10.7) [1662], LY303870 (9.8–10.0) [1660], CP 99994 (9.3–9.7) [1643,1671], LY303870 (pIC ₅₀ 9.82) [1664], SR 140,333 (pIC ₅₀ 8.9–9.0) [1673], RP67580 (pIC ₅₀ 7.7) [1657]	GR159897 (pK _d 7.8–9.5) [1647,1656,1672], GR94800 (9.8) [1649], saredutant (9.4–9.7) [1643,1656,1671], MEN10627 (9.2), nepadutant (8.5–8.7) [1650,1652]	osanetant (8.4–9.7) [1643–1644,1651,1655,1665,1668,1670–1671,1673], SB 223412 (7.4–9.0) [1646,1659,1670–1671], PD157672 (pIC ₅₀ 7.8) [1648]
Radioligands (K _d)	[¹²⁵ I]SP (human, mouse, rat) (Agonist, Full agonist), [¹⁸ F]SPA-RQ (Antagonist), [³ H]BH-[Sar ⁹ ,Met(O ₂) ¹¹]SP, [³ H]SP (human, mouse, rat) (Agonist, Full agonist), [¹²⁵ I]L703,606 (Antagonist) (3×10 ⁻¹⁰ M), [¹²⁵ I]BH-[Sar ⁹ ,Met(O ₂) ¹¹]SP (Agonist, Full agonist) (1×10 ⁻⁹ M – Rat) [1674]	[¹²⁵ I]NKA (human, mouse, rat), [³ H]GR100679, [³ H]SR48,968 (Antagonist) (2×10 ⁻¹⁰ M – Rat) [1661]	[¹²⁵ I][MePhe ⁷]NKB, [³ H]senktide, [³ H]SR142,801 (Antagonist) (1.3×10 ⁻¹⁰ M)

Comments: The NK₁ receptor has also been described to couple to other G proteins [1669]. The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to substance P (*TAC1*, P20366) on the NK₁ receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK₃ receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells [1654,1666].

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Thyrotropin-releasing hormone receptors

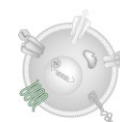
Overview: Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) are activated by the endogenous tripeptide TRH (*TRH*, P20396) (pGlu-His-ProNH₂). TRH (*TRH*, P20396) and TRH analogues fail to distinguish TRH₁ and TRH₂ receptors [1677]. [³H]TRH (human, mouse, rat) is able to label both TRH₁ and TRH₂ receptors with K_d values of 13 and 9 nM respectively.

Nomenclature	TRH ₁ receptor	TRH ₂ receptor
HGNC, UniProt	<i>TRHR</i> , P34981	<i>Trhr2</i> , Q9ERT2
Principal transduction	G _q	G _q
Selective antagonists (pK _i)	midazolam (5.49 - Rat) [1675], diazepam (5.15 - Rat) [1675], chlordiazepoxide (4.82 - Rat) [1675], chlordiazepoxide (4.7 - Mouse) [1676]	–
Comment	–	A class A G protein-coupled receptor: not present in man

Comments: The human orthologue of the rodent TRH₂ receptor has yet to be identified.

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Trace amine receptor

Overview: Trace amine-associated receptors (nomenclature as agreed by NC-IUPHAR for trace amine receptors, [1680]) were initially discovered as a result of a search for novel 5-HT receptors [1678], where 15 mammalian orthologues were identified and divided into two families. The TA₁ receptor has been shown to have affinity for the endogenous trace amines tyramine, β-phenylethylamine and octopamine in addition to the classical amine dopamine [1678]. Emerging evidence suggests that TA₁ is a modulator of monoaminergic activity in the brain [1683] with TA₁ and dopamine D₂ receptors shown to form constitutive heterodimers when co-expressed [1679].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Radioligands (K _d)
TA ₁ receptor	TAAR1 (Hs), Taar1 (Mm), Taar1 (Rn), Q96RJ0	G _s	tyramine > β-phenylethylamine > octopamine = dopamine [1678]	[³ H]tyramine (Agonist, Full agonist) (2×10 ⁻⁸ M) [1678]

Comments: The product of the gene *TAAR2* (also known as GPR58) appears to respond to β-phenylethylamine > tyramine and to couple through G_s [1678] See Orphan GPCR (Page 1462).

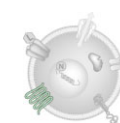
TAAR3, in some individuals, and TAAR4 are pseudogenes in man, although functional in rodents. The signalling characteristics

and pharmacology of TAA₅ (PNR, Putative Neurotransmitter Receptor: TAAR5, O14804), TAA₆ (Trace amine receptor 4, TaR-4: TAAR6, 96RI8), TAA₈ (Trace amine receptor 5, GPR102: TAAR8, Q969N4) and TAA₉ (trace amine associated receptor 9: TAAR9, 96RI9) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have been shown to have affinity for rodent

cloned trace amine receptors, including TA₁ [1681]. An antagonist EPPTB has recently been described that has a pK_i of 9.1 at the mouse TA₁ but less than 5.3 for human TA₁ [1682].

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Urotensin receptor

Overview: The urotensin-II (U-II) receptor (UT, nomenclature as agreed by NC-IUPHAR, [1691,1694]) is activated by the endogenous dodecapeptide U-II (*UTS2*, O95399), originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [1685]. 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* [1689,1700,1702–1703]. Human U-II (*UTS2*, O95399), an 11-amino-acid peptide [1689], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding [1686,1696]. This sequence is also conserved in the deduced amino-acid sequence of rat U-II (14 amino-acids) and mouse U-II (14 amino-acids), although the N-terminal is more divergent from the human sequence [1688].

A second endogenous ligand for UT has been discovered in rat [1707]. The urotensin II-related peptide (URP (*UTS2B*, Q765I0)), 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 (*UTS2B*, Q765I0) are predicted for the mature mouse and human peptides.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK _i)	Selective agonists (pK _i)	Selective antagonists (pK _i)	Radioligands (K _d)
UT receptor	<i>UTS2R</i> , Q9UKP6	G _{q/11}	U-II (8.6) [1692–1693,1695]	[Pen5]-U (4–11) (human) (9.7) [1695], U-II-(4–11) (human) (9.6) [1695], AC-7954 (6.6) [1690,1698], FL104 (pEC ₅₀ 5.8 – 7.5) [1697,1699]	urantide (8.3) [1704], SB-706375 (8.0) [1692], SB-611812 (6.6) [1705], palosuran (pIC ₅₀ 7.1) [1687]	[¹²⁵ I]U-II (human) (Agonist, Full agonist) (4×10 ⁻¹⁰ – 2.4×10 ⁻¹⁰ M) [1684,1701]

Comments: In human vasculature, human U-II (*UTS2*, O95399) elicits both vasoconstrictor (pD₂ 9.3–10.1, [1701]) and vasodilator (pIC₅₀ 10.3–10.4, [1706]) responses.

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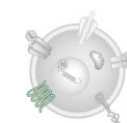
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Vasopressin and oxytocin receptors

Overview: Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytocin receptors) are activated by the endogenous cyclic nonapeptides AVP (AVP, P01178) and oxytocin (OXT, P01178) (OT). These peptides are derived from precursors which also produce neurophysins (neurophysin I for OT; neurophysin II for AVP).

Nomenclature	V _{1A} receptor	V _{1B} receptor	V ₂ receptor	OT receptor
HGNC, UniProt	AVPR1A, P37288	AVPR1B, P47901	AVPR2, P30518	OXTR, P30559
Principal transduction	G _{q/11}	G _{q/11}	G _s	G _{q/11} , G _{i/o}
Rank order of potency	AVP > oxytocin	AVP > oxytocin	AVP > oxytocin	oxytocin > AVP
Selective agonists (pK _i)	F180 (pK _d 7.9 – 8.3) [1711,1719]	d[Leu ⁴]LVP (9.8) [1731], d[Cha ⁴]AVP (9.0 – 9.7) [1721,1726], d[D-Pal ²]AVP (7.9) [1715,1721]	d[Val ⁴ ,DArg ⁸]VP, OPC-51803 (7.0) [1730], VNA932 (pIC ₅₀ 7.1) [1723]	[Thr ⁴ ,Gly ⁷]OT (8.2 – 8.4) [1718,1722,1727]
Selective antagonists (pK _i)	d(CH ₂) ₅ [Tyr(Me) ² ,Arg ⁸]VP (9.0), SR 49059 (8.1 – 9.3) [1708,1719, 1726,1732,1735,1738,1740–1742], conivaptan (8.2 – 8.4) [1738–1739]	SSR149415 (8.4 – 9.3) [1725–1726,1737]	tolvaptan (9.37) [1743], lixivaptan (Inverse agonist) (8.9 – 9.2) [1710,1735], SR 121463A (8.4 – 9.3) [1708,1719–1720,1734–1735,1738, 1742], d(CH ₂) ₅ [D-Ile ² ,Ile ⁴]AVP (6.9 – 8.4) [1735], OPC-31260 (Inverse antagonist) (7.6) [1744]	SSR126768A (8.82 – 9.05) [1736], L-371,257 (8.8) [1726], desGlyNH ₂ - d(CH ₂) ₅ [Tyr(Me) ² ,Thr ⁴ ,Orn ⁸]OT (8.5), L-372662 (8.4) [1712]
Radioligands (K _d)	[³ H]SR49059 (Antagonist), [¹²⁵ I]OH-LVA (Antagonist) (3.99x10 ⁻¹¹ – 5x10 ⁻¹¹ M) [1717,1719,1732], [³ H]AVP (Agonist, Full agonist) (2.51x10 ⁻⁹ – 6.3x10 ⁻¹¹ M) [1714,1717,1719–1720,1730, 1732,1733,1738–1743], [³ H]d(CH ₂) ₅ [Tyr(Me) ²]AVP (Antagonist) (1.1x10 ⁻⁹ M)	[³ H]SSR149415 (Antagonist), [³ H]AVP (Agonist, Full agonist) (2.51x10 ⁻⁹ – 2.5x10 ⁻¹⁰ M) [1714,1717,1719–1720,1730, 1732,1733,1738–1743]	[³ H]AVP (Agonist, Full agonist) (3.98x10 ⁻⁹ – 3.99x10 ⁻¹⁰ M) [1717,1719–1720,1730,1733, 1738–1739,1741–1743], [³ H]SR 121463A (Antagonist, Inverse agonist) (4.1x10 ⁻⁹ – 5x10 ⁻¹⁰ M) [1720,1734], [³ H]desGly- NH ₂ [D-Ile ² ,Ile ⁴]VP (2.8x10 ⁻⁹ M), [³ H]dDAVP (Agonist, Full agonist) (6.3x10 ⁻⁸ – 8x10 ⁻¹⁰ M) [1717,1720,1741]	[³⁵ S]non-peptide OT antagonist (Antagonist) (4.2x10 ⁻¹¹ M) [1729], [¹²⁵ I]d(CH ₂) ₅ [Tyr(Me) ² ,Thr ⁴ ,Orn ⁸ ,Tyr-NH ₂ ⁹]OVT (Antagonist) (9x10 ⁻¹¹ M), [³ H]OT (human, mouse, rat) (Agonist, Full agonist) [1717,1724,1727–1728], [¹¹¹ In]DOTA-dLVT (4.5x10 ⁻⁹ M) [1716]

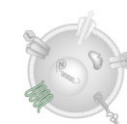
Comments: The V₂ receptor exhibits marked species differences, such that many ligands (d(CH₂)₅[D-Ile²,Ile⁴]AVP and [³H]desGly-NH₂[D-Ile²,Ile⁴]VP) exhibit low affinity at human V₂ receptors [1709]. Similarly, [³H]d[D-Arg⁸]VP is V₂ selective in the rat, not in the human [1733]. The gene encoding the V₂ receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [1713]. d[Cha⁴]AVP is selective only for the human and bovine V_{1B} receptors [1721], while d[Leu⁴]LVP has high affinity for the rat V_{1B} receptor [1731].

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Vasopressin and oxytocin receptors 1561

VIP and PACAP receptors

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, [1749]) are activated by the endogenous peptides VIP (*VIP*, P01282), PACAP-38 (*ADCYAP1*, P18509), PACAP-27 (*ADCYAP1*, P18509), peptide histidine isoleucineamide (PHI), peptide histidine methionineamide (PHM (*VIP*, P01282)) and peptide histidine valine (PHV (*VIP*, P01282)). “PACAP type II receptors” (VPAC₁ and VPAC₂ recep-

tors) display comparable affinity for PACAP and VIP (*VIP*, P01282), whereas PACAP-27 (*ADCYAP1*, P18509) and PACAP-38 (*ADCYAP1*, P18509) are >100 fold more potent than VIP (*VIP*, P01282) as agonists of most isoforms of the PAC₁ receptor. However, one splice variant of the human PAC₁ receptor has been reported to respond to PACAP-38 (*ADCYAP1*, P18509), PACAP-27 (*ADCYAP1*, P18509) and VIP (*VIP*, P01282) with comparable affinity [1745]. PG 99-465 [1752] has been used as a selective VPAC₂ receptor antagonist in a number of physiological studies,

but has been reported to have significant activity at VPAC₁ and PAC₁ receptors [1746]. The selective PAC₁ receptor agonist maxadilan, was extracted from the salivary glands of sand flies (*Lutzomyia longipalpis*) and has no sequence homology to VIP (*VIP*, P01282) or PACAP [1753]. Two deletion variants of maxadilan, M65 [1758] and Max.d.4 [1754] have been reported to be PAC₁ receptor antagonists, but these peptides have not been extensively characterised.

Nomenclature	VPAC ₁ receptor	VPAC ₂ receptor	PAC ₁ receptor
HGNC, UniProt	<i>VIPR1</i> , P32241	<i>VIPR2</i> , P41587	<i>ADCYAP1R1</i> , P41586
Principal transduction	G _s	G _s	G _s
Rank order of potency	VIP, PACAP-27, PACAP-38 >> GHRH (<i>GHRH</i> , P01286), PHI, secretin (<i>SCT</i> , P09683)	VIP, PACAP-38, PACAP-27 > PHI >> GHRH (<i>GHRH</i> , P01286), secretin (<i>SCT</i> , P09683)	PACAP-27, PACAP-38 >> VIP
Selective agonists (pK _i)	[Ala ^{11,22,28}]VIP (8.1) [1755], [Lys ¹⁵ ,Arg ¹⁶ ,Leu ²⁷]VIP-(1–7)/GRF-(8–27)-NH ₂ (pEC ₅₀ 8.3) [1751]	Ro 25-1392 (8.0) [1760], Ro 25-1553 (pEC ₅₀ 8.7) [1751], Ro 25-1553 (pEC ₅₀ 8.3) [1750], Ro 25-1553 (pIC ₅₀ 9.5) [1748], Ro 25-1553 (pIC ₅₀ 8.8) [1750], Ro 25-1553 (pIC ₅₀ 7.8) [1751]	maxadilan (pEC ₅₀ 10.3) [1746], maxadilan (pEC ₅₀ 6.2) [1746]
Selective antagonists (pK _i)	PG 97-269 (pIC ₅₀ 8.7) [1747], PG 97-269 (pIC ₅₀ 8.7) [1750], PG 97-269 (pIC ₅₀ 8.7) [1750], PG 97-269 (pIC ₅₀ 8.0) [1746], PG 97-269 (pIC ₅₀ 7.1) [1746]	–	–
Radioligands (K _d)	[¹²⁵ I]PACAP-27 (Agonist), [¹²⁵ I]VIP (Agonist) (4×10 ^{–10} M) [1755]	[¹²⁵ I]PACAP-27 (Agonist), [¹²⁵ I]VIP (Agonist) (7×10 ^{–10} M) [1755]	[¹²⁵ I]PACAP-27 (Agonist) (8.7×10 ^{–10} M) [1756]

Comments: Subtypes of PAC₁ receptors have been proposed based on tissue differences in the potencies of PACAP-27 (*ADCYAP1*, P18509) and PACAP-38 (*ADCYAP1*, P18509); these might result from differences in G protein coupling and second messenger mechanisms [1759], or from alternative splicing of PAC₁ receptor mRNA [1757].

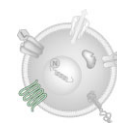
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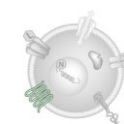
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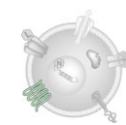


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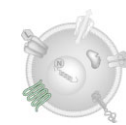
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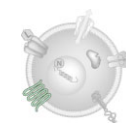
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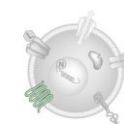
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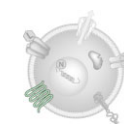
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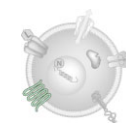
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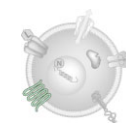
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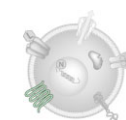
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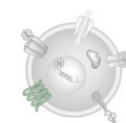
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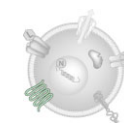
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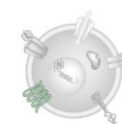
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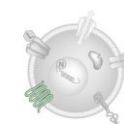
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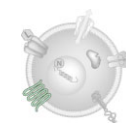
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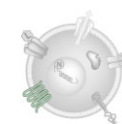
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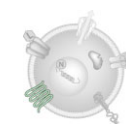
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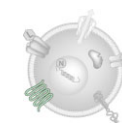
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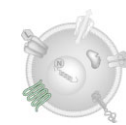
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