



# THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors

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## Abstract

The Concise Guide to PHARMACOLOGY 2019/20 is the fourth in this series of biennial publications. The Concise Guide provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands ([www.guidetopharmacology.org](http://www.guidetopharmacology.org)), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.14748>. G protein-coupled receptors are one of the six major pharmacological targets into which the Guide is divided, with the others being: ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2019, and supersedes data presented in the 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

## Conflict of interest

The authors state that there are no conflicts of interest to disclose.

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**Overview:** 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) [1479]. The remaining 350 non-sensory GPCRs mediate 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 [1642, 1772], although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs [1129] 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" [1890] 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<sub>B</sub> receptors, as well as three taste type 1 receptors and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man [1479].

**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 and five pheromone receptors (V1 receptors).

**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 evolutionary ancient motif also found in polycystic kidney disease 1 (PKD1)-like proteins, which has been suggested to be both required and sufficient for autoproteolysis [1743].

**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)) [811].

#### GPCR families

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

<sup>a</sup>Numbers in brackets refer to orphan receptors for which an endogenous ligand has been proposed in at least one publication, see [455]; <sup>b</sup>[1634]; <sup>c</sup>[1479]; <sup>d</sup>[2109].

Much of our current understanding of the structure and function of GPCRs is the result of pioneering work on the visual pigment rhodopsin and on the  $\beta_2$  adrenoceptor, the latter culminating in the award of the 2012 Nobel Prize in chemistry to Robert Lefkowitz and Brian Kobilka [1121, 1244].

#### Pseudogenes

Below is a curated list of pseudogenes that in humans are non-coding for receptor protein. In some cases these have a shared ancestry with genes that encode functional receptors in rats and mice.

*ADGRE4P*, *GNRHR2*, *GPR79*, *HTR5BP*, *NPY6R*, *TAAR3P*, *TAAR4P*, *TAAR7P*, *TAS2R12P*, *TAS2R15P*, *TAS2R18P*, *TAS2R2P*, *TAS2R62P*, *TAS2R63P*, *TAS2R64P*, *TAS2R67P*, *TAS2R68P*, *TAS2R6P*. A more detailed listing containing further information can be viewed [here](#).

#### Olfactory receptors

Olfactory receptors are also seven-transmembrane spanning G protein-coupled receptors, responsible for the detection of odorants. These are not currently included as they are not yet associated with extensive pharmacological data but are curated in the following databases: The gene list of olfactory receptors at [HGNC](#), and curated by [HORDE](#) and [ORDB](#).

### Further reading on G protein-coupled receptors

- Kenakin T. (2018) Is the Quest for Signaling Bias Worth the Effort? *Mol. Pharmacol.* **93**: 266-269 [PMID:29348268]
- Michel MC *et al.* (2018) Biased Agonism in Drug Discovery-Is It Too Soon to Choose a Path? *Mol. Pharmacol.* **93**: 259-265 [PMID:29326242]
- Roth BL *et al.* (2017) Discovery of new GPCR ligands to illuminate new biology. *Nat. Chem. Biol.* **13**: 1143-1151 [PMID:29045379]
- Sriram K *et al.* (2018) G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs? *Mol. Pharmacol.* **93**: 251-258 [PMID:29298813]

### Family structure

S23	Orphan and other 7TM receptors	S68	Corticotropin-releasing factor receptors	S100	Neuropeptide S receptor
S24	Class A Orphans	S69	Dopamine receptors	S101	Neuropeptide W/neuropeptide B receptors
-	Class B Orphans	S71	Endothelin receptors	S102	Neuropeptide Y receptors
S33	Class C Orphans	S72	G protein-coupled estrogen receptor	S103	Neurotensin receptors
-	Opsin receptors	S73	Formylpeptide receptors	S104	Opioid receptors
S33	Taste 1 receptors	S74	Free fatty acid receptors	S106	Orexin receptors
S34	Taste 2 receptors	S76	GABA <sub>B</sub> receptors	S107	Oxoglutarate receptor
S35	Other 7TM proteins	S78	Galanin receptors	S108	P2Y receptors
S36	5-Hydroxytryptamine receptors	S79	Ghrelin receptor	S110	Parathyroid hormone receptors
S39	Acetylcholine receptors (muscarinic)	S80	Glucagon receptor family	S111	Platelet-activating factor receptor
S41	Adenosine receptors	S81	Glycoprotein hormone receptors	S112	Prokineticin receptors
S42	Adhesion Class GPCRs	S82	Gonadotrophin-releasing hormone receptors	S113	Prolactin-releasing peptide receptor
S45	Adrenoceptors	S83	GPR18, GPR55 and GPR119	S114	Prostanoid receptors
S48	Angiotensin receptors	S84	Histamine receptors	S116	Proteinase-activated receptors
S50	Apelin receptor	S86	Hydroxycarboxylic acid receptors	S117	QRFP receptor
S51	Bile acid receptor	S87	Kisspeptin receptor	S118	Relaxin family peptide receptors
S51	Bombesin receptors	S88	Leukotriene receptors	S120	Somatostatin receptors
S53	Bradykinin receptors	S89	Lysophospholipid (LPA) receptors	S121	Succinate receptor
S54	Calcitonin receptors	S90	Lysophospholipid (S1P) receptors	S122	Tachykinin receptors
S56	Calcium-sensing receptor	S92	Melanin-concentrating hormone receptors	S123	Thyrotropin-releasing hormone receptors
S57	Cannabinoid receptors	S93	Melanocortin receptors	S124	Trace amine receptor
S58	Chemerin receptors	S94	Melatonin receptors	S125	Urotensin receptor
S59	Chemokine receptors	S95	Metabotropic glutamate receptors	S126	Vasopressin and oxytocin receptors
S63	Cholecystokinin receptors	S97	Motilin receptor	S127	VIP and PACAP receptors
S64	Class Frizzled GPCRs	S98	Neuromedin U receptors		
S67	Complement peptide receptors	S99	Neuropeptide FF/neuropeptide AF receptors		

## Orphan and other 7TM receptors

G protein-coupled receptors → Orphan and other 7TM receptors

**Overview:** This set contains 'orphan' G protein coupled receptors where the endogenous ligand(s) is not known, and other 7TM receptors.

## Class A Orphans

G protein-coupled receptors → Orphan and other 7TM receptors → Class A Orphans

**Overview:** Table 1 lists a number of putative GPCRs identified by **NC-IUPHAR [612]**, for which preliminary evidence for an endogenous ligand has been published, or for which there exists a potential link to a disease, or disorder. These GPCRs have recently been reviewed in detail [455]. 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.

**Table 1:** Class A orphan GPCRs with putative endogenous ligands

<i>GPR3</i>	<i>GPR4</i>	<i>GPR6</i>	<i>GPR12</i>	<i>GPR15</i>	<i>GPR17</i>	<i>GPR20</i>
<i>GPR22</i>	<i>GPR26</i>	<i>GPR31</i>	<i>GPR34</i>	<i>GPR35</i>	<i>GPR37</i>	<i>GPR39</i>
<i>GPR50</i>	<i>GPR63</i>	<i>GRP65</i>	<i>GPR68</i>	<i>GPR75</i>	<i>GPR84</i>	<i>GPR87</i>
<i>GPR88</i>	<i>GPR132</i>	<i>GPR149</i>	<i>GPR161</i>	<i>GPR183</i>	<i>LGR4</i>	<i>LGR5</i>
<i>LGR6</i>	<i>MAS1</i>	<i>MRGPRD</i>	<i>MRGPRX1</i>	<i>MRGPRX2</i>	<i>P2RY10</i>	<i>TAAR2</i>

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 (*GPR18*, *GPR55* and *GPR119*).

Nomenclature	<i>GPR3</i>	<i>GPR4</i>	<i>GPR6</i>
HGNC, UniProt	<i>GPR3</i> , P46089	<i>GPR4</i> , P46093	<i>GPR6</i> , P46095
Agonists	diphenyleiiodonium chloride [2388]	–	–
Endogenous ligands	–	Protons	–
Comments	<i>Sphingosine 1-phosphate</i> was reported to be an endogenous agonist [2168], but this finding was not replicated in subsequent studies [2389]. Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> [545]. Gene disruption results in premature ovarian ageing [1234], reduced β-amyloid deposition [2112] and hypersensitivity to thermal pain [1837] in mice. First small molecule inverse agonist [993] and agonists identified [2386]	An initial report suggesting activation by <i>lysophosphatidylcholine</i> and <i>sphingosylphosphorylcholine</i> [2440] has been retracted [1597]. <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 [455, 1932]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [2377]. Negative allosteric modulators of <i>GPR4</i> have been reported [2137].	An initial report that <i>sphingosine 1-phosphate</i> (S1P) was a high-affinity ligand (EC <sub>50</sub> value of 39nM) [941, 2168] was not repeated in arrestin-based assays [2015, 2389]. Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> and to be located intracellularly [1644]. <i>GPR6</i> -deficient mice showed reduced striatal cyclic AMP production <i>in vitro</i> and selected alterations in instrumental conditioning <i>in vivo</i> . [1309].

Nomenclature	<a href="#">GPR12</a>	<a href="#">GPR15</a>	<a href="#">GPR17</a>
HGNC, UniProt	<a href="#">GPR12, P47775</a>	<a href="#">GPR15, P49685</a>	<a href="#">GPR17, Q13304</a>
Endogenous agonists	–	–	UDP-glucose [143, 395], LTC <sub>4</sub> [395], UDP-galactose [143, 395], uridine diphosphate [143, 395], LTD <sub>4</sub> [395]
Comments	Reports that <a href="#">sphingosine 1-phosphate</a> is a ligand of GPR12 [940, 2168] have not been replicated in arrestin-based assays [2015, 2389]. Gene disruption results in dyslipidemia and obesity [170].	Reported to act as a co-receptor for HIV [541]. In an infection-induced colitis model, <i>Gpr15</i> knockout mice were more prone to tissue damage and inflammatory cytokine expression [1089].	Reported to be a dual leukotriene and <a href="#">uridine diphosphate</a> receptor [395]. Another group instead proposed that GPR17 functions as a negative regulator of the CysLT <sub>1</sub> receptor response to leukotriene D <sub>4</sub> (LTD <sub>4</sub> ). For further discussion, see [455]. Reported to antagonize CysLT <sub>1</sub> receptor signalling <i>in vivo</i> and <i>in vitro</i> [1350]. See reviews [280] and [455].

Nomenclature	<a href="#">GPR19</a>	<a href="#">GPR20</a>	<a href="#">GPR21</a>	<a href="#">GPR22</a>	<a href="#">GPR25</a>	<a href="#">GPR26</a>	<a href="#">GPR27</a>
HGNC, UniProt	<a href="#">GPR19, Q15760</a>	<a href="#">GPR20, Q99678</a>	<a href="#">GPR21, Q99679</a>	<a href="#">GPR22, Q99680</a>	<a href="#">GPR25, O00155</a>	<a href="#">GPR26, Q8NDV2</a>	<a href="#">GPR27, Q9NS67</a>
Agonists	<a href="#">adropin</a> ( <a href="#">ENHO</a> , <a href="#">Q6UWT2</a> ) [1770]	–	–	–	–	–	–
Comments	–	Reported to inhibit adenylyl cyclase constitutively through G <sub>i/o</sub> [817]. GPR20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [230].	<i>Gpr21</i> knockout mice were resistant to diet-induced obesity, exhibiting an increase in glucose tolerance and insulin sensitivity, as well as a modest lean phenotype [1639].	Gene disruption results in increased severity of functional decompensation following aortic banding [10]. Identified as a susceptibility locus for osteoarthritis [574, 1072, 2187].	–	Has been reported to activate adenylyl cyclase constitutively through G <sub>s</sub> [1016]. <i>Gpr26</i> knockout mice show increased levels of anxiety and depression-like behaviours [2421].	Knockdown of <i>Gpr27</i> reduces endogenous mouse insulin promoter activity and glucose-stimulated insulin secretion [1160].

Nomenclature	<a href="#">GPR31</a>	<a href="#">GPR32</a>	<a href="#">GPR33</a>	<a href="#">GPR34</a>
HGNC, UniProt	<a href="#">GPR31, O00270</a>	<a href="#">GPR32, O75388</a>	<a href="#">GPR33, Q49SQ1</a>	<a href="#">GPR34, Q9UPC5</a>
Potency order of endogenous ligands	–	<a href="#">resolvin D1</a> > <a href="#">LXA<sub>4</sub></a>	–	–
Endogenous agonists	<a href="#">12S-HETE</a> [769] – Mouse	<a href="#">resolvin D1</a> [1153], <a href="#">LXA<sub>4</sub></a> [1153]	–	<a href="#">lysophosphatidylserine</a> [1107, 2054]
Labelled ligands	–	[ <sup>3</sup> H] <a href="#">resolvin D1</a> (Agonist) [1153]	–	–
Comments	See [455] for discussion of pairing.	<a href="#">Resolvin D1</a> has been demonstrated to activate GPR32 in two publications [366, 1153]. The pairing was not replicated in a recent study based on arrestin recruitment [2015]. <i>GPR32</i> is a pseudogene in mice and rats. See reviews [280] and [455].	<i>GPR33</i> is a pseudogene in most individuals, containing a premature stop codon within the coding sequence of the second intracellular loop [1845].	<a href="#">Lysophosphatidylserine</a> has been reported to be a ligand of GPR34 in several publications, but the pairing was not replicated in a recent study based on arrestin recruitment [2015]. Fails to respond to a variety of lipid-derived agents [2389]. Gene disruption results in an enhanced immune response [1277]. Characterization of agonists at this receptor is discussed in [945] and [455].

Nomenclature	<a href="#">GPR35</a>	<a href="#">GPR37</a>
HGNC, UniProt	<a href="#">GPR35, Q9HC97</a>	<a href="#">GPR37, O15354</a>
Endogenous agonists	<a href="#">2-oleoyl-LPA</a> [1626], <a href="#">kynurenic acid</a> [2015, 2253]	–
Agonists	–	<a href="#">neuropeptide head activator</a> [1795]
Comments	Several studies have shown that <a href="#">kynurenic acid</a> is an agonist of GPR35 but it remains controversial whether the proposed endogenous ligand reaches sufficient tissue concentrations to activate the receptor [1162]. <a href="#">2-oleoyl-LPA</a> has also been proposed as an endogenous ligand [1626] but these results were not replicated in an arrestin assay [2015]. The phosphodiesterase inhibitor <a href="#">zaprinast</a> [2105] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signalling [2105]. GPR35 is also activated by the pharmaceutical adjunct <a href="#">pamoic acid</a> [2432]. See reviews [455] and [502].	Reported to associate and regulate the dopamine transporter [1382] and to be a substrate for parkin [1380]. Gene disruption results in altered striatal signalling [1381]. The peptides <a href="#">prosaptide</a> and <a href="#">prosaposin</a> are proposed as endogenous ligands for GPR37 and GPR37L1 [1438].

Nomenclature	<a href="#">GPR37L1</a>	<a href="#">GPR39</a>	<a href="#">GPR45</a>	<a href="#">GPR50</a>
HGNC, UniProt	<a href="#">GPR37L1</a> , <a href="#">O60883</a>	<a href="#">GPR39</a> , <a href="#">O43194</a>	<a href="#">GPR45</a> , <a href="#">Q9Y5Y3</a>	<a href="#">GPR50</a> , <a href="#">Q13585</a>
Endogenous agonists	–	<a href="#">Zn<sup>2+</sup></a> [898]	–	–
Comments	The peptides <a href="#">prosapptide</a> and <a href="#">prosaposin</a> are proposed as endogenous ligands for <a href="#">GPR37</a> and <a href="#">GPR37L1</a> [1438].	<a href="#">Zn<sup>2+</sup></a> has been reported to be a potent and efficacious agonist of human, mouse and rat <a href="#">GPR39</a> [2383]. <a href="#">Obestatin</a> ( <a href="#">GHRH</a> , <a href="#">Q9UBU3</a> ), a fragment from the ghrelin precursor, was reported initially as an endogenous ligand, but subsequent studies failed to reproduce these findings. <a href="#">GPR39</a> has been reported to be down-regulated in adipose tissue in obesity-related diabetes [315]. Gene disruption results in obesity and altered adipocyte metabolism [1696]. Reviewed in [455].	–	<a href="#">GPR50</a> is structurally related to <a href="#">MT<sub>1</sub></a> and <a href="#">MT<sub>2</sub></a> melatonin receptors, with which it heterodimerises constitutively and specifically [1265]. <a href="#">Gpr50</a> knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [126].

Nomenclature	<a href="#">GPR52</a>	<a href="#">GPR61</a>	<a href="#">GPR62</a>	<a href="#">GPR63</a>
HGNC, UniProt	<a href="#">GPR52</a> , <a href="#">Q9Y2T5</a>	<a href="#">GPR61</a> , <a href="#">Q9BZJ8</a>	<a href="#">GPR62</a> , <a href="#">Q9BZJ7</a>	<a href="#">GPR63</a> , <a href="#">Q9BZJ6</a>
Comments	First small molecule agonist reported [1931].	<a href="#">GPR61</a> deficient mice exhibit obesity associated with hyperphagia [1545]. Although no endogenous ligands have been identified, 5-(nonyloxy)tryptamine has been reported to be a low affinity inverse agonist [2092].	–	<a href="#">Sphingosine 1-phosphate</a> and <a href="#">dioleoylphosphatidic acid</a> have been reported to be low affinity agonists for <a href="#">GPR63</a> [1584] but this finding was not replicated in an arrestin-based assay [2389].

Nomenclature	<a href="#">GPR65</a>	<a href="#">GPR68</a>
HGNC, UniProt	<a href="#">GPR65</a> , <a href="#">Q8IYL9</a>	<a href="#">GPR68</a> , <a href="#">Q15743</a>
Endogenous ligands	Protons	Protons
Allosteric modulators	–	<a href="#">ogerin</a> (Positive) (pK <sub>B</sub> 5) [925], <a href="#">lorazepam</a> (Positive) [925]
Comments	<a href="#">GPR4</a> , <a href="#">GPR65</a> , <a href="#">GPR68</a> and <a href="#">GPR132</a> are now thought to function as proton-sensing receptors detecting acidic pH [455, 1932]. Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease [1145].	<a href="#">GPR68</a> was previously identified as a receptor for <a href="#">sphingosylphosphorylcholine</a> (SPC) [2358], but the original publication has been retracted [2357]. <a href="#">GPR4</a> , <a href="#">GPR65</a> , <a href="#">GPR68</a> and <a href="#">GPR132</a> are now thought to function as proton-sensing receptors detecting acidic pH [455, 1932]. A family of 3,5-disubstituted isoxazoles were identified as agonists of <a href="#">GPR68</a> [1839].

Nomenclature	<a href="#">GPR75</a>	<a href="#">GPR78</a>	<a href="#">GPR79</a>	<a href="#">GPR82</a>
HGNC, UniProt	<a href="#">GPR75</a> , <a href="#">O95800</a>	<a href="#">GPR78</a> , <a href="#">Q96P69</a>	<a href="#">GPR79</a> , –	<a href="#">GPR82</a> , <a href="#">Q96P67</a>
Comments	<a href="#">CCL5</a> ( <a href="#">CCL5</a> , <a href="#">P13501</a> ) was reported to be an agonist of <a href="#">GPR75</a> [ <a href="#">942</a> ], but the pairing could not be repeated in an arrestin assay [ <a href="#">2015</a> ].	<a href="#">GPR78</a> has been reported to be constitutively active, coupled to elevated cAMP production [ <a href="#">1016</a> ].	–	Mice with <i>Gpr82</i> knockout have a lower body weight and body fat content associated with reduced food intake, decreased serum triglyceride levels, as well as higher insulin sensitivity and glucose tolerance [ <a href="#">558</a> ].

Nomenclature	<a href="#">GPR83</a>	<a href="#">GPR84</a>	<a href="#">GPR85</a>	<a href="#">GPR87</a>	<a href="#">GPR88</a>	<a href="#">GPR101</a>
HGNC, UniProt	<a href="#">GPR83</a> , <a href="#">Q9NYM4</a>	<a href="#">GPR84</a> , <a href="#">Q9NQSS</a>	<a href="#">GPR85</a> , <a href="#">P60893</a>	<a href="#">GPR87</a> , <a href="#">Q9BY21</a>	<a href="#">GPR88</a> , <a href="#">Q9GZN0</a>	<a href="#">GPR101</a> , <a href="#">Q96P66</a>
Endogenous agonists	–	–	–	<a href="#">LPA</a> [ <a href="#">1523</a> , <a href="#">2076</a> ]	–	–
Agonists	<a href="#">PEN</a> {Mouse} [ <a href="#">719</a> ] – Mouse, <a href="#">Zn<sup>2+</sup></a> [ <a href="#">1531</a> ] – Mouse	<a href="#">decanoic acid</a> [ <a href="#">2015</a> , <a href="#">2254</a> ], <a href="#">undecanoic acid</a> [ <a href="#">2254</a> ], <a href="#">lauric acid</a> [ <a href="#">2254</a> ]	–	–	–	–
Comments	One isoform has been implicated in the induction of CD4(+) CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [ <a href="#">803</a> ]. The extracellular N-terminal domain is reported as an intramolecular inverse agonist [ <a href="#">1532</a> ].	Medium chain free fatty acids with carbon chain lengths of 9-14 activate <a href="#">GPR84</a> [ <a href="#">2064</a> , <a href="#">2254</a> ]. A surrogate ligand for <a href="#">GPR84</a> , <a href="#">6-n-octylaminouracil</a> has also been proposed [ <a href="#">2064</a> ]. See review [ <a href="#">455</a> ] for discussion of classification. Mutational analysis and molecular modelling of <a href="#">GPR84</a> has been reported [ <a href="#">1588</a> ].	Proposed to regulate hippocampal neurogenesis in the adult, as well as neurogenesis-dependent learning and memory [ <a href="#">352</a> ].	–	Gene disruption results in altered striatal signalling [ <a href="#">1312</a> ]. Small molecule agonists have been reported [ <a href="#">163</a> ].	Mutations in <a href="#">GPR101</a> have been linked to gigantism and acromegaly [ <a href="#">2154</a> ].



Nomenclature	<a href="#">GPR132</a>	<a href="#">GPR135</a>	<a href="#">GPR139</a>	<a href="#">GPR141</a>	<a href="#">GPR142</a>	<a href="#">GPR146</a>
HGNC, UniProt	<a href="#">GPR132, Q9UNW8</a>	<a href="#">GPR135, Q8IZ08</a>	<a href="#">GPR139, Q6DWJ6</a>	<a href="#">GPR141, Q7Z602</a>	<a href="#">GPR142, Q7Z601</a>	<a href="#">GPR146, Q96CH1</a>
Endogenous ligands	Protons	–	–	–	–	–
Comments	GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [455, 1932]. Reported to respond to <a href="#">lysophosphatidylcholine</a> [1027], but later retracted [2321].	–	Peptide agonists have been reported [953].	–	Small molecule agonists have been reported [2138, 2407].	Yosten <i>et al.</i> demonstrated inhibition of <a href="#">proinsulin C-peptide (INS, P01308)</a> -induced stimulation of cFos expression following knockdown of GPR146 in KATO III cells, suggesting proinsulin C-peptide as an endogenous ligand of the receptor [2404].

Nomenclature	<a href="#">GPR148</a>	<a href="#">GPR149</a>	<a href="#">GPR150</a>	<a href="#">GPR151</a>	<a href="#">GPR152</a>	<a href="#">GPR153</a>	<a href="#">GPR160</a>
HGNC, UniProt	<a href="#">GPR148, Q8TDV2</a>	<a href="#">GPR149, Q86SP6</a>	<a href="#">GPR150, Q8NGU9</a>	<a href="#">GPR151, Q8TDV0</a>	<a href="#">GPR152, Q8TDT2</a>	<a href="#">GPR153, Q6NV75</a>	<a href="#">GPR160, Q9UJ42</a>
Comments	–	<i>Gpr149</i> knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [542].	–	GPR151 responded to galanin with an EC <sub>50</sub> value of 2 $\mu$ M, suggesting that the endogenous ligand shares structural features with <a href="#">galanin (GAL, P22466)</a> [939].	–	–	–

Nomenclature	<a href="#">GPR161</a>	<a href="#">GPR162</a>	<a href="#">GPR171</a>	<a href="#">GPR173</a>
HGNC, UniProt	<a href="#">GPR161, Q8N6U8</a>	<a href="#">GPR162, Q16538</a>	<a href="#">GPR171, O14626</a>	<a href="#">GPR173, Q9NS66</a>
Comments	A C-terminal truncation (deletion) mutation in Gpr161 causes congenital cataracts and neural tube defects in the vacuolated lens (vl) mouse mutant [1403]. The mutated receptor is associated with cataract, spina bifida and white belly spot phenotypes in mice [1140]. Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish [1261].	–	GPR171 has been shown to be activated by the endogenous peptide <a href="#">BigLEN</a> (Mouse). This receptor-peptide interaction is believed to be involved in regulating feeding and metabolism responses [718].	–

Nomenclature	<a href="#">GPR174</a>	<a href="#">GPR176</a>	<a href="#">GPR182</a>	<a href="#">GPR183</a>
HGNC, UniProt	<a href="#">GPR174, Q9BXC1</a>	<a href="#">GPR176, Q14439</a>	<a href="#">GPR182, O15218</a>	<a href="#">GPR183, P32249</a>
Endogenous agonists	<a href="#">lysophosphatidylserine</a> [949]	–	–	<a href="#">7<math>\alpha</math>,25-dihydroxycholesterol</a> [799, 1301], <a href="#">7<math>\alpha</math>,27-dihydroxycholesterol</a> [1301], <a href="#">7<math>\beta</math>, 25-dihydroxycholesterol</a> [1301], <a href="#">7<math>\beta</math>, 27-dihydroxycholesterol</a> [1301]
Comments	See [945] which discusses characterization of agonists at this receptor.	–	Rat GPR182 was first proposed as the adrenomedullin receptor [1041]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [1070] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [831].	Two independent publications have shown that <a href="#">7<math>\alpha</math>,25-dihydroxycholesterol</a> is an agonist of GPR183 and have demonstrated by mass spectrometry that this oxysterol is present endogenously in tissues [799, 1301]. Gpr183-deficient mice show a reduction in the early antibody response to a T-dependent antigen. GPR183-deficient B cells fail to migrate to the outer follicle and instead stay in the follicle centre [1062, 1685].

Nomenclature	<a href="#">LGR4</a>	<a href="#">LGR5</a>	<a href="#">LGR6</a>
HGNC, UniProt	<a href="#">LGR4, Q9BXB1</a>	<a href="#">LGR5, O75473</a>	<a href="#">LGR6, Q9HBX8</a>
Endogenous agonists	<a href="#">R-spondin-2 (RSPO2, Q6UXX9)</a> [305], <a href="#">R-spondin-1 (RSPO1, Q2MKA7)</a> [305], <a href="#">R-spondin-3 (RSPO3, Q9BXY4)</a> [305], <a href="#">R-spondin-4 (RSPO4, Q2I0M5)</a> [305]	<a href="#">R-spondin-2 (RSPO2, Q6UXX9)</a> [305], <a href="#">R-spondin-1 (RSPO1, Q2MKA7)</a> [305], <a href="#">R-spondin-3 (RSPO3, Q9BXY4)</a> [305], <a href="#">R-spondin-4 (RSPO4, Q2I0M5)</a> [305]	<a href="#">R-spondin-1 (RSPO1, Q2MKA7)</a> [305, 467], <a href="#">R-spondin-2 (RSPO2, Q6UXX9)</a> [305, 467], <a href="#">R-spondin-3 (RSPO3, Q9BXY4)</a> [305, 467], <a href="#">R-spondin-4 (RSPO4, Q2I0M5)</a> [305, 467]
Comments	LGR4 does not couple to heterotrimeric G proteins or recruit arrestins when stimulated by the R-spondins, indicating a unique mechanism of action. R-spondins bind to LGR4, which specifically associates with Frizzled and LDL receptor-related proteins (LRPs) that are activated by the extracellular Wnt molecules and then trigger canonical Wnt signalling to increase gene expression [305, 467, 1834]. Gene disruption leads to multiple developmental disorders [1002, 1329, 2011, 2284].	The four R-spondins can bind to LGR4, LGR5, and LGR6, which specifically associate with Frizzled and LDL receptor-related proteins (LRPs), proteins that are activated by extracellular Wnt molecules and which then trigger canonical Wnt signalling to increase gene expression [305, 467].	–

Nomenclature	<a href="#">MAS1</a>	<a href="#">MAS1L</a>
HGNC, UniProt	<a href="#">MAS1, P04201</a>	<a href="#">MAS1L, P35410</a>
Agonists	<a href="#">angiotensin-(1-7) (AGT, P01019)</a> [707] – Mouse	–

Nomenclature	<a href="#">MRGPRD</a>	<a href="#">MRGPRE</a>	<a href="#">MRGPRF</a>	<a href="#">MRGPRG</a>
HGNC, UniProt	<a href="#">MRGPRD, Q8TDS7</a>	<a href="#">MRGPRE, Q86SM8</a>	<a href="#">MRGPRF, Q96AM1</a>	<a href="#">MRGPRG, Q86SM5</a>
Endogenous agonists	<a href="#">β-alanine</a> [1958, 2015]	–	–	–
Comments	An endogenous peptide with a high degree of sequence similarity to <a href="#">angiotensin-(1-7) (AGT, P01019)</a> , <a href="#">alamandine (AGT)</a> , was shown to promote NO release in MRGPRD-transfected cells. The binding of alamandine to MRGPRD to was shown to be blocked by D-Pro <sup>7</sup> -angiotensin-(1-7), <a href="#">β-alanine</a> and <a href="#">PD123319</a> [1208]. Genetic ablation of MRGPRD+ neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [322]. See reviews [455] and [2009].	See reviews [455] and [2009].	MRGPRF has been reported to respond to stimulation by angiotensin metabolites [678]. See reviews [455] and [2009].	See reviews [455] and [2009].

Nomenclature	<a href="#">MRGPRX1</a>	<a href="#">MRGPRX2</a>	<a href="#">MRGPRX3</a>	<a href="#">MRGPRX4</a>	<a href="#">P2RY8</a>	<a href="#">P2RY10</a>
HGNC, UniProt	<a href="#">MRGPRX1, Q96LB2</a>	<a href="#">MRGPRX2, Q96LB1</a>	<a href="#">MRGPRX3, Q96LB0</a>	<a href="#">MRGPRX4, Q96LA9</a>	<a href="#">P2RY8, Q86VZ1</a>	<a href="#">P2RY10, O00398</a>
Endogenous agonists	bovine adrenal medulla peptide 8-22 ( <a href="#">PENK, P01210</a> ) [ <a href="#">347, 1253, 2015</a> ]	PAMP-20 ( <a href="#">ADM, P35318</a> ) [ <a href="#">1035</a> ]	–	–	–	sphingosine 1-phosphate [ <a href="#">1523</a> ], LPA [ <a href="#">1523</a> ]
Agonists	–	cortistatin-14 {Mouse, Rat} [ <a href="#">1035, 1202, 1815, 2015</a> ]	–	–	–	–
Selective agonists	–	PAMP-12 (human) [ <a href="#">1035</a> ]	–	–	–	–
Comments	Reported to mediate the sensation of itch [ <a href="#">1305, 1969</a> ]. Reports that bovine adrenal medulla peptide 8-22 ( <a href="#">PENK, P01210</a> ) 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 [ <a href="#">1253</a> ] were replicated in an independent study using an arrestin recruitment assay [ <a href="#">2015</a> ]. See reviews [ <a href="#">455</a> ] and [ <a href="#">2009</a> ].	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 [ <a href="#">1815</a> ], also confirmed in an independent study using an arrestin recruitment assay [ <a href="#">2015</a> ]. See reviews [ <a href="#">455</a> ] and [ <a href="#">2009</a> ].	–	See reviews [ <a href="#">455</a> ] and [ <a href="#">2009</a> ].	–	–

Nomenclature	<a href="#">TAAR2</a>	<a href="#">TAAR3</a>	<a href="#">TAAR4P</a>	<a href="#">TAAR5</a>	<a href="#">TAAR6</a>	<a href="#">TAAR8</a>	<a href="#">TAAR9</a>
HGNC, UniProt	<a href="#">TAAR2, Q9P1P5</a>	<a href="#">TAAR3P, Q9P1P4</a>	<a href="#">TAAR4P, –</a>	<a href="#">TAAR5, O14804</a>	<a href="#">TAAR6, Q96R18</a>	<a href="#">TAAR8, Q969N4</a>	<a href="#">TAAR9, Q96R19</a>
Potency order of endogenous ligands	$\beta$ -phenylethylamine > tryptamine [ <a href="#">205</a> ]	–	–	–	–	–	–
Comments	Probable pseudogene in 10–15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [ <a href="#">455</a> ].	TAAR3 is thought to be a pseudogene in man though functional in rodents [ <a href="#">455</a> ].	Pseudogene in man but functional in rodents [ <a href="#">455</a> ].	Trimethylamine is reported as an agonist [ <a href="#">2242</a> ] and 3-iodothyronamine an inverse agonist [ <a href="#">499</a> ].	–	–	TAAR9 appears to be functional in most individuals but has a polymorphic premature stop codon at amino acid 61 (rs2842899) with an allele frequency of 10–30% in different populations [ <a href="#">2202</a> ].

### Further reading on Class A Orphans

McNeil BD *et al.* (2015) Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* **519**: 237-41 [[PMID:25517090](#)]

## Class C Orphans

G protein-coupled receptors → Orphan and other 7TM receptors → Class C Orphans

**Overview:** This set contains class C 'orphan' G protein coupled receptors where the endogenous ligand(s) is not known.

Nomenclature	<i>GPR156</i>	<i>GPR158</i>	<i>GPR179</i>	<i>GPRC5A</i>	<i>GPRC5B</i>	<i>GPRC5C</i>	<i>GPRC5D</i>	GPRC6 receptor
HGNC, UniProt	<i>GPR156</i> , <i>Q8NFN8</i>	<i>GPR158</i> , <i>Q5T848</i>	<i>GPR179</i> , <i>Q6PRD1</i>	<i>GPRC5A</i> , <i>Q8NFJ5</i>	<i>GPRC5B</i> , <i>Q9NZH0</i>	<i>GPRC5C</i> , <i>Q9NQ84</i>	<i>GPRC5D</i> , <i>Q9NZD1</i>	<i>GPRC6A</i> , <i>Q5T6X5</i>
Comments	–	–	–	–	–	–	–	GPRC6 is a G <sub>q</sub> -coupled receptor which responds to basic amino acids [2282].

### Further reading on Class C Orphans

Harpse K *et al.* (2017) Structural insight to mutation effects uncover a common allosteric site in class C GPCRs. *Bioinformatics* **33**: 1116–1120 [PMID:28011766]

## Taste 1 receptors

G protein-coupled receptors → Orphan and other 7TM receptors → 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 involvement of PLCβ2 [2429], TRPM5 [2429] and IP3 [883] receptors in post-receptor signalling of taste receptors. Although predominantly associated with the oral cavity, taste receptors are also located elsewhere, including further down the gastrointestinal system, in the lungs and in the brain.

**Sweet/Umami:** T1R3 acts as an obligate partner in T1R1/T1R3 and T1R2/T1R3 heterodimers, which sense umami or sweet, respectively. T1R1/T1R3 heterodimers respond to *L*-glutamic acid and may be positively allosterically modulated by 5'-nucleoside monophosphates, such as 5'-GMP [1272]. T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin [1564].

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

**Comments:** Positive allosteric modulators of T1R2/T1R3 have been reported [2363]. Such compounds enhance the sweet taste of sucrose mediated by these receptors, but are tasteless on their own.

### Further reading on Taste 1 receptors

Palmer RK. (2019) A Pharmacological Perspective on the Study of Taste. *Pharmacol. Rev.* **71**: 20-48  
[\[PMID:30559245\]](#)

## Taste 2 receptors

[G protein-coupled receptors](#) → [Orphan and other 7TM receptors](#) → [Taste 2 receptors](#)

**Overview:** 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 [334], while T2R14 responded to at least eight different bitter tastants, including (-)-[α-thujone](#) and [picrotoxinin](#) [133].

Specialist database [BitterDB](#) contains additional information on bitter compounds and receptors [2306].

Nomenclature	<a href="#">TAS2R1</a>	<a href="#">TAS2R3</a>	<a href="#">TAS2R4</a>	<a href="#">TAS2R5</a>	<a href="#">TAS2R7</a>	<a href="#">TAS2R8</a>	<a href="#">TAS2R9</a>
HGNC, UniProt	<a href="#">TAS2R1, Q9NYW7</a>	<a href="#">TAS2R3, Q9NYW6</a>	<a href="#">TAS2R4, Q9NYW5</a>	<a href="#">TAS2R5, Q9NYW4</a>	<a href="#">TAS2R7, Q9NYW3</a>	<a href="#">TAS2R8, Q9NYW2</a>	<a href="#">TAS2R9, Q9NYW1</a>

Nomenclature	<a href="#">TAS2R10</a>	<a href="#">TAS2R13</a>	<a href="#">TAS2R14</a>	<a href="#">TAS2R16</a>	<a href="#">TAS2R19</a>	<a href="#">TAS2R20</a>	<a href="#">TAS2R30</a>
HGNC, UniProt	<a href="#">TAS2R10, Q9NYW0</a>	<a href="#">TAS2R13, Q9NYV9</a>	<a href="#">TAS2R14, Q9NYV8</a>	<a href="#">TAS2R16, Q9NYV7</a>	<a href="#">TAS2R19, P59542</a>	<a href="#">TAS2R20, P59543</a>	<a href="#">TAS2R30, P59541</a>

Nomenclature	<a href="#">TAS2R31</a>	<a href="#">TAS2R38</a>	<a href="#">TAS2R39</a>	<a href="#">TAS2R40</a>
HGNC, UniProt	<a href="#">TAS2R31, P59538</a>	<a href="#">TAS2R38, P59533</a>	<a href="#">TAS2R39, P59534</a>	<a href="#">TAS2R40, P59535</a>
Antagonists	<a href="#">6-methoxysakuranetin</a> (pIC <sub>50</sub> 5.6) [1098], <a href="#">GIV3727</a> (pIC <sub>50</sub> 5.1–5.2) [1984]	–	–	–

Nomenclature	<a href="#">TAS2R41</a>	<a href="#">TAS2R42</a>	<a href="#">TAS2R43</a>	<a href="#">TAS2R45</a>	<a href="#">TAS2R46</a>	<a href="#">TAS2R50</a>	<a href="#">TAS2R60</a>
HGNC, UniProt	<a href="#">TAS2R41</a> , <a href="#">P59536</a>	<a href="#">TAS2R42</a> , <a href="#">Q7RTR8</a>	<a href="#">TAS2R43</a> , <a href="#">P59537</a>	<a href="#">TAS2R45</a> , <a href="#">P59539</a>	<a href="#">TAS2R46</a> , <a href="#">P59540</a>	<a href="#">TAS2R50</a> , <a href="#">P59544</a>	<a href="#">TAS2R60</a> , <a href="#">P59551</a>

### Further reading on Taste 2 receptors

Palmer RK. (2019) A Pharmacological Perspective on the Study of Taste. *Pharmacol. Rev.* **71**: 20-48  
[\[PMID:30559245\]](#)

## Other 7TM proteins

G protein-coupled receptors → Orphan and other 7TM receptors → Other 7TM proteins

Nomenclature	<a href="#">GPR107</a>	<a href="#">GPR137</a>	<a href="#">TPRA1</a>	<a href="#">GPR143</a>	<a href="#">GPR157</a>
HGNC, UniProt	<a href="#">GPR107</a> , <a href="#">Q5VW38</a>	<a href="#">GPR137</a> , <a href="#">Q96N19</a>	<a href="#">TPRA1</a> , <a href="#">Q86W33</a>	<a href="#">GPR143</a> , <a href="#">P51810</a>	<a href="#">GPR157</a> , <a href="#">Q5UAW9</a>
Endogenous agonists	–	–	–	<a href="#">levodopa</a> [1316]	–
Comments	GPR107 is a member of the LUSTR family of proteins found in both plants and animals, having similar topology to G protein-coupled receptors [540]	–	TPRA1 shows no homology to known G protein-coupled receptors.	Loss-of-function mutations underlie ocular albinism type 1 [117].	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 on Orphan and other 7TM receptors

- Davenport AP *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**: 967-86 [\[PMID:23686350\]](#)
- Gilissen J *et al.* (2016) Insight into SUCNR1 (GPR91) structure and function. *Pharmacol. Ther.* **159**: 56-65 [\[PMID:26808164\]](#)
- Insel PA *et al.* (2015) G Protein-Coupled Receptor (GPCR) Expression in Native Cells: "Novel" endoGPCRs as Physiologic Regulators and Therapeutic Targets. *Mol. Pharmacol.* **88**: 181-7 [\[PMID:25737495\]](#)
- Khan MZ *et al.* (2017) Neuro-psychopharmacological perspective of Orphan receptors of Rhodopsin (class A) family of G protein-coupled receptors. *Psychopharmacology (Berl.)* **234**: 1181-1207 [\[PMID:28289782\]](#)
- Mackenzie AE *et al.* (2017) The emerging pharmacology and function of GPR35 in the nervous system. *Neuropharmacology* **113**: 661-671 [\[PMID:26232640\]](#)
- Ngo T *et al.* (2016) Identifying ligands at orphan GPCRs: current status using structure-based approaches. *Br. J. Pharmacol.* **173**: 2934-51 [\[PMID:26837045\]](#)

## 5-Hydroxytryptamine receptors

G protein-coupled receptors → 5-Hydroxytryptamine receptors

**Overview:** 5-HT receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-HT receptors [914] and subsequently revised [816]**) are, with the exception of the ionotropic 5-HT<sub>3</sub> class, GPCRs where the endogenous agonist is **5-hydroxytryptamine**. The diversity of metabotropic 5-HT recep-

tors is increased by alternative splicing that produces isoforms of the 5-HT<sub>2A</sub> (non-functional), 5-HT<sub>2C</sub> (non-functional), 5-HT<sub>4</sub>, 5-HT<sub>6</sub> (non-functional) and 5-HT<sub>7</sub> receptors. Unique amongst the GPCRs, RNA editing produces 5-HT<sub>2C</sub> receptor isoforms that differ in function, such as efficiency and specificity of coupling to

G<sub>q/11</sub> and also pharmacology [181, 2291]. Most 5-HT receptors (except 5-HT<sub>1e</sub> and 5-HT<sub>5b</sub>) play specific roles mediating functional responses in different tissues (reviewed by [1765, 2219]).

Nomenclature	5-HT <sub>1A</sub> receptor	5-HT <sub>1B</sub> receptor
HGNC, UniProt	<i>HTR1A</i> , P08908	<i>HTR1B</i> , P28222
Agonists	U92016A [1416], vilazodone (Partial agonist) [463], vortioxetine (Partial agonist) [105]	L-694,247 [738], naratriptan (Partial agonist) [1548], eletriptan [1548], frovatriptan [2359], zolmitriptan (Partial agonist) [1548], vortioxetine (Partial agonist) [105], rizatriptan (Partial agonist) [1548]
Selective agonists	8-OH-DPAT [473, 791, 1032, 1251, 1452, 1575, 1577, 1578], NLX-101 [1576]	CP94253 [1122]
Antagonists	(S)-UH 301 (pK <sub>i</sub> 7.9) [1575]	–
Selective antagonists	WAY-100635 (pK <sub>i</sub> 7.9–9.2) [1575, 1577], robalzotan (pK <sub>i</sub> 9.2) [1007]	SB 224289 (Inverse agonist) (pK <sub>i</sub> 8.2–8.6) [670, 1573, 1924], SB236057 (Inverse agonist) (pK <sub>i</sub> 8.2) [1445], GR-55562 (pK <sub>B</sub> 7.4) [915]
Labelled ligands	[ <sup>3</sup> H]robalzotan (Antagonist) (pK <sub>d</sub> 9.8) [994], [ <sup>3</sup> H]WAY100635 (Antagonist) (pK <sub>d</sub> 9.5) [1075], [ <sup>3</sup> H]8-OH-DPAT (Agonist) [174, 1032, 1574, 1577], [ <sup>3</sup> H]NLX-112 (Agonist) [864], [ <sup>11</sup> C]WAY100635 (Antagonist) [2161], p-[ <sup>18</sup> F]MPPF (Antagonist) [418]	[ <sup>3</sup> H]N-methyl-AZ10419369 (Agonist, Partial agonist) [1356], [ <sup>3</sup> H]GR 125,743 (Selective Antagonist) (pK <sub>d</sub> 8.6–9.2) [738, 2350], [ <sup>3</sup> H]alniditan (Agonist) [1260], [ <sup>125</sup> I]GTI (Agonist) [213, 256] – Rat, [ <sup>3</sup> H]eletriptan (Agonist, Partial agonist) [1548], [ <sup>3</sup> H]sumatriptan (Agonist, Partial agonist) [1548], [ <sup>11</sup> C]AZ10419369 (Agonist, Partial agonist) [2207]



Nomenclature	5-HT <sub>1D</sub> receptor	5-HT <sub>1e</sub> receptor	5-HT <sub>1F</sub> receptor
HGNC, UniProt	<i>HTR1D</i> , P28221	<i>HTR1E</i> , P28566	<i>HTR1F</i> , P30939
Agonists	dihydroergotamine [790, 1260, 1267], ergotamine [711], L-694,247 [2340], naratriptan [506, 1548, 1794], zolmitriptan [1548], frovatriptan [2359], rizatriptan [1548]	BRL-54443 [250]	BRL-54443 [250], eletriptan [1548], sumatriptan [12, 13, 1548, 2236]
Selective agonists	PNU109291 [564] – Gorilla, eletriptan [1548]	–	lasmiditan [1563], LY334370 [2236], 5-BODMT [1113], LY344864 [1702]
Selective antagonists	SB 714786 (pK <sub>i</sub> 9.1) [2264]	–	–
Labelled ligands	[ <sup>3</sup> H]eletriptan (Agonist) [1548], [ <sup>3</sup> H]alniditan (Agonist) [1260], [ <sup>125</sup> I]GTI (Selective Agonist) [213, 256] – Rat, [ <sup>3</sup> H]GR 125,743 (Selective Antagonist) (pK <sub>d</sub> 8.6) [2350], [ <sup>3</sup> H]sumatriptan (Agonist) [1548]	[ <sup>3</sup> H]5-HT (Agonist) [1413, 1657]	[ <sup>3</sup> H]LY334370 (Agonist) [2236], [ <sup>125</sup> I]LSD (Agonist) [48] – Mouse

Nomenclature	5-HT <sub>2A</sub> receptor	5-HT <sub>2B</sub> receptor	5-HT <sub>2C</sub> receptor
HGNC, UniProt	<i>HTR2A</i> , P28223	<i>HTR2B</i> , P41595	<i>HTR2C</i> , P28335
Agonists	DOI [227, 1562, 1986]	methysergide (Partial agonist) [1117, 1827, 2237], DOI [1179, 1562, 1883]	DOI [544, 1562, 1883], Ro 60-0175 [1097, 1117]
Selective agonists	–	BW723C86 [124, 1117, 1883], Ro 60-0175 [1117]	WAY-163909 [533], lorcaserin [2125]
Antagonists	risperidone (Inverse agonist) (pK <sub>i</sub> 9.3–10) [1131, 1156, 1901], mianserin (pK <sub>i</sub> 7.7–9.6) [1117, 1146, 1452], ziprasidone (pK <sub>i</sub> 8.8–9.5) [1131, 1156, 1901, 1939], volinanserin (pIC <sub>50</sub> 6.5–9.3) [1117, 1317, 1782], blonanserin (pK <sub>i</sub> 9.1) [1611], clozapine (Inverse agonist) (pK <sub>i</sub> 7.6–9) [1117, 1156, 1449, 1901, 2201], H05 (pIC <sub>50</sub> 7.2) [2356]	mianserin (pK <sub>i</sub> 7.9–8.8) [200, 1117, 2237]	mianserin (Inverse agonist) (pK <sub>i</sub> 8.3–9.2) [607, 1117, 1452], methysergide (pK <sub>i</sub> 8.6–9.1) [544, 1117], ziprasidone (Inverse agonist) (pK <sub>i</sub> 7.9–9) [858, 1156, 1939], olanzapine (Inverse agonist) (pK <sub>i</sub> 8.1–8.4) [858, 1156, 1939], loxapine (Inverse agonist) (pK <sub>i</sub> 7.8–8) [858, 1156]
Selective antagonists	compound 3b (pK <sub>i</sub> 10.6) [603], ketanserin (pK <sub>i</sub> 8.1–9.7) [261, 1117, 1771], pimavanserin (Inverse agonist) (pK <sub>i</sub> 9.3) [659, 2201]	BF-1 (pK <sub>i</sub> 10.1) [1895], RS-127445 (pK <sub>i</sub> 9–9.5) [200, 1117], EGIS-7625 (pK <sub>i</sub> 9) [1146]	FR260010 (pK <sub>i</sub> 9) [807], SB 242084 (pK <sub>i</sub> 8.2–9) [1071, 1117], RS-102221 (pK <sub>i</sub> 8.3–8.4) [201, 1117]
Labelled ligands	[ <sup>3</sup> H]fananserin (Antagonist) (pK <sub>d</sub> 9.9) [1362] – Rat, [ <sup>3</sup> H]ketanserin (Antagonist) (pK <sub>d</sub> 8.6–9.7) [1117, 1771], [ <sup>11</sup> C]volinanserin (Antagonist) [784], [ <sup>18</sup> F]altanserin (Antagonist) [1823]	[ <sup>3</sup> H]LSD (Agonist) [1771], [ <sup>3</sup> H]5-HT (Agonist) [2235] – Rat, [ <sup>3</sup> H]mesulergine (Antagonist, Inverse agonist) (pK <sub>d</sub> 7.9) [1117], [ <sup>125</sup> I]DOI (Agonist)	[ <sup>3</sup> H]mesulergine (Antagonist, Inverse agonist) (pK <sub>d</sub> 8.7–9.3) [607, 1771], [ <sup>125</sup> I]DOI (Agonist) [607], [ <sup>3</sup> H]LSD (Agonist)

Nomenclature	5-HT <sub>4</sub> receptor	5-HT <sub>5A</sub> receptor	5-HT <sub>5B</sub> receptor
HGNC, UniProt	<i>HTR4</i> , Q13639	<i>HTR5A</i> , P47898	<i>HTR5BP</i> , –
Agonists	cisapride (Partial agonist) [89, 141, 690, 1440, 1441, 2190]		
Selective agonists	TD-8954 [1427], ML 10302 (Partial agonist) [152, 178, 1440, 1441, 1442], RS67506 [842] – Rat, relenopride (Partial agonist) [702], velusetrag [1314, 1994], BIMU 8 [398]	–	–
Selective antagonists	RS 100235 (pK <sub>i</sub> 8.7–12.2) [398, 1809], SB 204070 (pK <sub>i</sub> 9.8–10.4) [141, 1440, 1441, 2192], GR 113808 (pK <sub>i</sub> 9.3–10.3) [89, 141, 178, 398, 1401, 1809, 2190]	SB 699551 (pK <sub>i</sub> 8.2) [416]	–
Labelled ligands	[ <sup>3</sup> H]GR 113808 (Antagonist) (pK <sub>d</sub> 9.7–10.3) [89, 141, 1442, 2190], [ <sup>125</sup> I]SB 207710 (Antagonist) (pK <sub>d</sub> 10.1) [251] – Pig, [ <sup>3</sup> H]RS 57639 (Selective Antagonist) (pK <sub>d</sub> 9.7) [199] – Guinea pig, [ <sup>11</sup> C]SB207145 (Antagonist) (pK <sub>d</sub> 8.6) [1344]	[ <sup>125</sup> I]LSD (Agonist) [737], [ <sup>3</sup> H]5-CT (Agonist) [737]	[ <sup>125</sup> I]LSD (Agonist) [1404] – Mouse, [ <sup>3</sup> H]5-CT (Agonist) [2233] – Mouse

Nomenclature	5-HT <sub>6</sub> receptor	5-HT <sub>7</sub> receptor
HGNC, UniProt	<i>HTR6</i> , P50406	<i>HTR7</i> , P34969
Selective agonists	WAY-181187 [1887], E6801 (Partial agonist) [893], WAY-208466 [151], EMD-386088 [1405]	LP-12 [1257], LP-44 [1257], LP-211 [1258] – Rat, AS-19 [1091], E55888 [229]
Antagonists	–	lurasidone (pK <sub>i</sub> 9.3) [954], pimozone (pK <sub>i</sub> 9.3) [1826] – Rat, vortioxetine (pK <sub>i</sub> 6.3) [105]
Selective antagonists	SB399885 (pK <sub>i</sub> 9) [882], SB 271046 (pK <sub>i</sub> 8.9) [247], cerlapirdine (pK <sub>i</sub> 8.9) [407], SB357134 (pK <sub>i</sub> 8.5) [248], Ro 63-0563 (pK <sub>i</sub> 7.9–8.4) [184, 1985]	SB269970 (pK <sub>i</sub> 8.6–8.9) [2119], SB656104 (pK <sub>i</sub> 8.7) [613], DR-4004 (pK <sub>i</sub> 8.7) [710, 1082], JNJ-18038683 (pK <sub>i</sub> 8.2) [197], SB 258719 (Inverse agonist) (pK <sub>i</sub> 7.5) [2120]
Labelled ligands	[ <sup>11</sup> C]GSK215083 (Antagonist) (pK <sub>i</sub> 9.8) [1656], [ <sup>125</sup> I]SB258585 (Selective Antagonist) (pK <sub>d</sub> 9) [882], [ <sup>3</sup> H]LSD (Agonist) [183], [ <sup>3</sup> H]Ro 63-0563 (Antagonist) (pK <sub>d</sub> 8.3) [184], [ <sup>3</sup> H]5-CT (Agonist)	[ <sup>3</sup> H]5-CT (Agonist) [2119], [ <sup>3</sup> H]5-HT (Agonist) [107, 2026], [ <sup>3</sup> H]SB269970 (Selective Antagonist) (pK <sub>d</sub> 8.9) [2119], [ <sup>3</sup> H]LSD (Agonist) [2026]

**Comments:** Tabulated pK<sub>i</sub> and K<sub>D</sub> values refer to binding to human 5-HT receptors unless indicated otherwise. The nomenclature of 5-HT<sub>1B</sub>/5-HT<sub>1D</sub> receptors has been revised [816]. Only the non-rodent form of the receptor was previously called 5-HT<sub>1D</sub>: the human 5-HT<sub>1B</sub> receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors [800]. Wang *et al.* (2013) report X-ray structures which reveal the binding modality of ergotamine and dihydroergotamine (DHE) to the 5-HT<sub>1B</sub> receptor in comparison with the structure of the 5-HT<sub>2B</sub> receptor [2249]; some of these drugs adopt rather different conformations depending on the target receptor [1681]. Various

5-HT receptors have multiple partners in addition to G proteins, which may affect function and pharmacology [1384]. NAS181 is a selective antagonist of the rodent 5-HT<sub>1B</sub> receptor. Fananserlin (LSD) and ketanserin bind with high affinity to dopamine D4 and histamine H<sub>1</sub> receptors respectively, and ketanserin is a potent α1 adrenoceptor antagonist, in addition to blocking 5-HT<sub>2A</sub> receptors. Lysergic acid (LSD) and ergotamine show a strong preference for arrestin recruitment over G protein coupling at the 5-HT<sub>2B</sub> receptor, with no such preference evident at 5-HT<sub>1B</sub> receptors, and they also antagonise 5-HT<sub>7A</sub> receptors [2231]. DHE (dihydroergocryptine), pergolide and cabergoline also show significant preference for arrestin recruitment over G protein cou-

pling at 5-HT<sub>2B</sub> receptors [2231]. The 5-HT<sub>2B</sub> (and other 5-HT) receptors interact with immunocompetent cells [1645]. The serotonin antagonist mesulergine was key to the discovery of the 5-HT<sub>2C</sub> receptor [1672], initially known as 5-HT<sub>1C</sub> [83]. The human 5-HT<sub>5A</sub> receptor may couple to several signal transduction pathways when stably expressed in C6 glioma cells [1599] and rodent prefrontal cortex (layer V pyramidal neurons) [724]. The human orthologue of the mouse 5-HT<sub>5B</sub> receptor is non-functional (stop codons); the 5-HT<sub>1E</sub> receptor has not been cloned from mouse, or rat, impeding definition of its function [800]. In addition to accepted receptors, an 'orphan' receptor, unofficially termed 5-HT<sub>1P</sub>, has been described [695].

### Further reading on 5-Hydroxytryptamine receptors

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## Acetylcholine receptors (muscarinic)

G protein-coupled receptors → Acetylcholine receptors (muscarinic)

**Overview:** Muscarinic acetylcholine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Muscarinic Acetylcholine Receptors [318]**) are GPCRs of the Class A, rhodopsin-like family where the endogenous agonist is **acetylcholine**. In addition to the agents listed in the table, **AC-42**, its structural analogues **AC-260584** and **77-LH-28-1**, **N-desmethylozapine**, **TBPB** and **LuAE51090** have been described as functionally selective agonists of the M<sub>1</sub> receptor subtype *via* binding in a mode distinct from that utilized by non-selective agonists [82, 1014, 1198, 1199, 1408, 1859, 2018, 2019, 2061]. There are two pharmacologically characterised allosteric sites on muscarinic receptors, one defined by its binding **gallamine**, **strychnine** and **brucine**, and the other defined by the binding of **KT 5720**, **WIN 62,577**, **WIN 51,708** and **staurosporine** [1215, 1216].

Nomenclature	M <sub>1</sub> receptor	M <sub>2</sub> receptor
HGNC, UniProt	<i>CHRM1</i> , P11229	<i>CHRM2</i> , P08172
Agonists	carbachol [385, 976, 2326], pilocarpine (Partial agonist) [976], bethanechol [976]	carbachol [358, 976, 1147], bethanechol [976]
Selective agonists	SPP1 [242]	–
Antagonists	glycopyrrolate (pIC <sub>50</sub> 9.9) [2037], AE9C90CB (pK <sub>i</sub> 9.7) [1979], atropine (pK <sub>i</sub> 8.5–9.6) [385, 636, 878, 923, 1683, 1993], tiotropium (pK <sub>i</sub> 9.6) [501], 4-DAMP (pK <sub>i</sub> 9.2) [537]	tiotropium (pK <sub>i</sub> 9.9) [501], glycopyrrolate (pIC <sub>50</sub> 9.3) [2037], atropine (pK <sub>i</sub> 7.8–9.2) [265, 358, 878, 923, 1147, 1561, 1683], AE9C90CB (pK <sub>i</sub> 8.6) [1979], tolterodine (Inverse agonist) (pK <sub>i</sub> 8.4–8.6) [704, 1561, 1979]
Selective antagonists	biperiden (pK <sub>d</sub> 9.3) [190], VU0255035 (pK <sub>i</sub> 7.8) [1943], guanylpirenzepine (pK <sub>i</sub> 7.3–7.6) [25, 2234] – Rat	tripitramine (pK <sub>i</sub> 9.6) [1351]
Allosteric modulators	muscarinic toxin 7 (Negative) (pK <sub>i</sub> 11–11.1) [1606], benzoquinazolinone 12 (Positive) (pK <sub>B</sub> 6.6) [4], KT 5720 (Positive) (pK <sub>d</sub> 6.4) [1215], brucine (Positive) (pK <sub>d</sub> 4.5–5.8) [976, 1214], BQCA (Positive) (pK <sub>B</sub> 4–4.8) [4, 5, 296, 1336], VU0029767 (Positive) [1385], VU0090157 (Positive) [1385]	W-84 (Negative) (pK <sub>d</sub> 6–7.5) [1470, 2155], C <sub>7</sub> /3-phth (Negative) (pK <sub>d</sub> 7.1) [386], alcuronium (Negative) (pK <sub>d</sub> 6.1–6.9) [976, 2155], gallamine (Negative) (pK <sub>d</sub> 5.9–6.3) [399, 1212], LY2119620 (Positive) (pK <sub>d</sub> 5.7) [437, 1158], LY2033298 (Positive) (pK <sub>d</sub> 4.4) [2185]
Labelled ligands	[ <sup>3</sup> H]QNB (Antagonist) (pK <sub>d</sub> 10.6–10.8) [387, 1683], Cy3B-telenzepine (Antagonist) (pK <sub>d</sub> 10.5) [856], [ <sup>3</sup> H]N-methyl scopolamine (Antagonist) (pK <sub>d</sub> 9.4–10.3) [324, 385, 387, 878, 976, 977, 1011, 1074, 1212], [ <sup>3</sup> H](+)-telenzepine (Antagonist) (pK <sub>i</sub> 9.4) [580] – Rat, Alexa-488-telenzepine (Antagonist) (pK <sub>d</sub> 9.3) [856], [ <sup>3</sup> H]pirenzepine (Antagonist) (pK <sub>d</sub> 7.9) [2273]	[ <sup>3</sup> H]QNB (Antagonist) (pK <sub>d</sub> 10.1–10.6) [1683], Cy3B-telenzepine (Antagonist) (pK <sub>i</sub> 10.4) [1568], [ <sup>3</sup> H]tiotropium (Antagonist) (pK <sub>d</sub> 10.3) [1856], [ <sup>3</sup> H]N-methyl scopolamine (Antagonist) (pK <sub>d</sub> 9.3–9.9) [324, 358, 878, 976, 977, 1011, 1074, 1212, 2261], Alexa-488-telenzepine (Antagonist) (pK <sub>i</sub> 8.8) [1568], [ <sup>3</sup> H]acetylcholine (Agonist) [1213], [ <sup>3</sup> H]oxotremorine-M (Agonist) [153], [ <sup>3</sup> H]dimethyl-W84 (Allosteric modulator, Positive) (pK <sub>d</sub> 8.5) [2154], [ <sup>18</sup> F]FP-TZTP (Agonist) [975] – Mouse

Nomenclature	<b>M<sub>3</sub> receptor</b>	<b>M<sub>4</sub> receptor</b>	<b>M<sub>5</sub> receptor</b>
HGNC, UniProt	<a href="#">CHRM3</a> , <a href="#">P20309</a>	<a href="#">CHRM4</a> , <a href="#">P08173</a>	<a href="#">CHRM5</a> , <a href="#">P08912</a>
Agonists	<a href="#">pilocarpine</a> (Partial agonist) [ <a href="#">976</a> ], <a href="#">carbachol</a> [ <a href="#">358</a> , <a href="#">976</a> , <a href="#">2326</a> ], <a href="#">bethanechol</a> [ <a href="#">976</a> ]	<a href="#">pilocarpine</a> (Partial agonist) [ <a href="#">976</a> ], <a href="#">carbachol</a> [ <a href="#">976</a> , <a href="#">2326</a> ], <a href="#">bethanechol</a> [ <a href="#">976</a> ]	<a href="#">pilocarpine</a> (Partial agonist) [ <a href="#">740</a> ], <a href="#">carbachol</a> [ <a href="#">2326</a> ]
Antagonists	<a href="#">tiotropium</a> (pK <sub>i</sub> 9.5–11.1) [ <a href="#">501</a> , <a href="#">519</a> ], <a href="#">AE9C90CB</a> (pK <sub>i</sub> 9.9) [ <a href="#">1979</a> ], <a href="#">atropine</a> (pK <sub>i</sub> 8.9–9.8) [ <a href="#">265</a> , <a href="#">519</a> , <a href="#">878</a> , <a href="#">923</a> , <a href="#">1683</a> , <a href="#">1993</a> ], <a href="#">ipratropium</a> (pK <sub>i</sub> 9.3–9.8) [ <a href="#">519</a> , <a href="#">878</a> ], <a href="#">aclidinium</a> (pIC <sub>50</sub> 9.8) [ <a href="#">1733</a> ]	<a href="#">glycopyrrolate</a> (pIC <sub>50</sub> 9.8) [ <a href="#">2037</a> ], <a href="#">AE9C90CB</a> (pK <sub>i</sub> 9.5) [ <a href="#">1979</a> ], <a href="#">4-DAMP</a> (pK <sub>i</sub> 8.9) [ <a href="#">537</a> ], <a href="#">oxybutynin</a> (pK <sub>i</sub> 8.7) [ <a href="#">1979</a> ], <a href="#">biperiden</a> (pK <sub>d</sub> 8.6) [ <a href="#">190</a> ], <a href="#">UH-AH 37</a> (pK <sub>i</sub> 8.3–8.4) [ <a href="#">704</a> , <a href="#">2292</a> ]	<a href="#">glycopyrrolate</a> (pIC <sub>50</sub> 9.7) [ <a href="#">2037</a> ], <a href="#">AE9C90CB</a> (pK <sub>i</sub> 9.5) [ <a href="#">1979</a> ], <a href="#">4-DAMP</a> (pK <sub>i</sub> 9) [ <a href="#">537</a> ], <a href="#">tolterodine</a> (pK <sub>i</sub> 8.5–8.8) [ <a href="#">704</a> , <a href="#">1979</a> ], <a href="#">darifenacin</a> (pK <sub>i</sub> 7.9–8.6) [ <a href="#">704</a> , <a href="#">841</a> , <a href="#">878</a> , <a href="#">1979</a> ]
Selective antagonists	–	–	<a href="#">ML381</a> (pK <sub>i</sub> 6.3) [ <a href="#">684</a> ]
Allosteric modulators	<a href="#">WIN 62,577</a> (Positive) (pK <sub>d</sub> 5.1) [ <a href="#">1216</a> ], <a href="#">N-chloromethyl-brucine</a> (Positive) (pK <sub>d</sub> 3.3) [ <a href="#">1214</a> ]	<a href="#">muscarinic toxin 3</a> (Negative) (pK <sub>i</sub> 8.7) [ <a href="#">1011</a> , <a href="#">1635</a> ], <a href="#">VU0152100</a> (Positive) (pEC <sub>50</sub> 6.4) [ <a href="#">224</a> ] – Rat, <a href="#">VU0152099</a> (Positive) (pEC <sub>50</sub> 6.4) [ <a href="#">224</a> ] – Rat, <a href="#">LY2119620</a> (Positive) (pK <sub>d</sub> 5.7) [ <a href="#">437</a> ], <a href="#">thiochrome</a> (Positive) (pK <sub>d</sub> 4) [ <a href="#">1213</a> ], <a href="#">LY2033298</a> (Positive) [ <a href="#">333</a> ]	<a href="#">ML380</a> (Positive) (pEC <sub>50</sub> 6.7) [ <a href="#">149</a> , <a href="#">686</a> ]
Selective allosteric modulators	–	–	<a href="#">ML375</a> (Negative) (pIC <sub>50</sub> 6.5) [ <a href="#">685</a> ]
Labelled ligands	<a href="#">[<sup>3</sup>H]tiotropium</a> (Antagonist) (pK <sub>d</sub> 10.7) [ <a href="#">1856</a> ], <a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) (pK <sub>d</sub> 10.4) [ <a href="#">1683</a> ], <a href="#">[<sup>3</sup>H]N-methyl scopolamine</a> (Antagonist) (pK <sub>d</sub> 9.7–10.2) [ <a href="#">324</a> , <a href="#">358</a> , <a href="#">878</a> , <a href="#">923</a> , <a href="#">976</a> , <a href="#">1011</a> , <a href="#">1074</a> , <a href="#">1212</a> ], <a href="#">[<sup>3</sup>H]darifenacin</a> (Antagonist) (pK <sub>d</sub> 9.5) [ <a href="#">1993</a> ]	<a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) (pK <sub>d</sub> 9.7–10.5) [ <a href="#">387</a> , <a href="#">1683</a> ], <a href="#">[<sup>3</sup>H]N-methyl scopolamine</a> (Antagonist) (pK <sub>d</sub> 9.9–10.2) [ <a href="#">324</a> , <a href="#">358</a> , <a href="#">387</a> , <a href="#">878</a> , <a href="#">976</a> , <a href="#">1011</a> , <a href="#">1074</a> , <a href="#">1212</a> , <a href="#">1635</a> , <a href="#">2261</a> ], <a href="#">[<sup>3</sup>H]acetylcholine</a> (Agonist) [ <a href="#">1213</a> ]	<a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) (pK <sub>d</sub> 10.2–10.7), <a href="#">[<sup>3</sup>H]N-methyl scopolamine</a> (Antagonist) (pK <sub>d</sub> 9.3–9.7) [ <a href="#">324</a> , <a href="#">358</a> , <a href="#">878</a> , <a href="#">1011</a> , <a href="#">1074</a> , <a href="#">2261</a> ]

**Comments:** The crystal structures of the M<sub>1</sub>–M<sub>4</sub> receptor subtypes have been reported [[777](#), [2111](#), [2382](#)]. Direct activation *via* an allosteric site has been reported for M<sub>1</sub> receptors ([BQCA](#), [PF-06767832](#)) and M<sub>4</sub> receptors ([LY2033298](#)) [[462](#), [1225](#), [1227](#), [1336](#), [1550](#), [1551](#)]. The allosteric site for [gallamine](#) and [strychnine](#) on M<sub>2</sub> receptors can be labelled by [\[<sup>3</sup>H\]dimethyl-W84](#) [[2155](#)]. [McN-A-343](#) is a functionally selective partial agonist that appears

to interact in a bitopic mode with both the orthosteric and an allosteric site on the M<sub>2</sub> muscarinic receptor [[2186](#)]. [THRX160209](#), hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M<sub>2</sub> receptors by binding both to the orthosteric and a nearby allosteric site [[59](#), [2028](#)].

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. It should be noted that the measured affinities of antagonists (and agonists) in radioligand binding studies are sensitive to ionic strength and can increase over 10-fold at low ionic strength compared to their values at physiological ionic strengths [[167](#)].

### Further reading on Acetylcholine receptors (muscarinic)

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# Adenosine receptors

G protein-coupled receptors → Adenosine receptors

**Overview:** Adenosine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Adenosine Receptors [624]**) are activated by the endogenous ligand **adenosine** (potentially **inosine** also at A<sub>3</sub> receptors). Crystal structures for the

antagonist-bound [410, 964, 1307, 1922], agonist-bound [1232, 1233, 2354] and G protein-bound A<sub>2A</sub> adenosine receptors [307] have been described. The structures of an antagonist-bound A1 receptor [712] and an adenosine-bound A1 receptor-G<sub>i</sub> complex

[521] have been resolved by cryo-electronmicroscopy. Another structure of an antagonist-bound A1 receptor obtained with X-ray crystallography has also been reported [361].

Nomenclature	A <sub>1</sub> receptor	A <sub>2A</sub> receptor	A <sub>2B</sub> receptor	A <sub>3</sub> receptor
HGNC, UniProt	<i>ADORA1</i> , P30542	<i>ADORA2A</i> , P29274	<i>ADORA2B</i> , P29275	<i>ADORA3</i> , P0DMS8
Endogenous agonists	adenosine [2369]	adenosine [2369]	adenosine [2369]	adenosine [2369]
Agonists	NECA [658, 1005, 1813, 2151, 2369]	NECA [209, 500, 658, 1088, 1173, 2369]	NECA [160, 209, 995, 1289, 2033, 2203, 2369]	NECA [209, 658, 971, 1858, 2204, 2369]
Selective agonists	cyclopentyladenosine [442, 469, 658, 848, 968, 1005, 1813], 5-Cl-5-deoxy-(±)-ENBA [620], TCPA [162], CCPA [968, 1609], MRS7469 [2148]	apadenoson [1674], UK-432,097 [768, 2354], AZD4635 [410], CGS 21680 [209, 500, 658, 968, 1088, 1115, 1173, 1609], regadenoson [968]	BAY 60-6583 [539]	piclidenoson [592, 647, 1115, 2204], CI-IB-MECA [225, 971, 1085], MRS5698 [2147]
Antagonists	CGS 15943 (pK <sub>i</sub> 8.5) [1636], xanthine amine congener (pK <sub>d</sub> 7.5) [620]	CGS 15943 (pK <sub>i</sub> 7.7–9.4) [500, 1088, 1115, 1636], xanthine amine congener (pK <sub>i</sub> 8.4–9) [500, 1115]	xanthine amine congener (pK <sub>i</sub> 6.9–8.8) [160, 995, 996, 1115, 1289, 2033], CGS 15943 (pK <sub>i</sub> 6–8.1) [76, 995, 996, 1115, 1636, 2033]	CGS 15943 (pK <sub>i</sub> 7–7.9) [1093, 1115, 1636, 2204], xanthine amine congener (pK <sub>i</sub> 7–7.4) [1115, 1858, 2204]
Selective antagonists	PSB36 (pK <sub>i</sub> 9.9) [6] – Rat, DPCPX (pK <sub>i</sub> 7.4–9.2) [469, 950, 1609, 1813, 2295], derenofylline (pK <sub>i</sub> 9) [1033], WRC-0571 (pK <sub>i</sub> 8.8) [1387], DU172 (pK <sub>i</sub> 7.4) [712]	SCH442416 (pK <sub>i</sub> 8.4–10.3) [1957, 2139], ZM-241385 (pK <sub>i</sub> 8.8–9.1) [1636]	PSB-0788 (pK <sub>i</sub> 9.4) [208], PSB603 (pK <sub>i</sub> 9.3) [208], MRS1754 (pK <sub>i</sub> 8.8) [995, 1092], PSB1115 (pK <sub>i</sub> 7.3) [832]	MRS1220 (pK <sub>i</sub> 8.2–9.2) [971, 1093, 2055, 2384], VUF5574 (pK <sub>i</sub> 8.4) [2193], MRS1523 (pK <sub>i</sub> 7.7) [1268], MRS1191 (pK <sub>i</sub> 7.5) [971, 998, 1273]
Allosteric modulators	PD81723 (Positive) [258]	–	–	LUF6000 (Positive) [772], LUF6096 (Positive) [847]
Labelled ligands	[ <sup>3</sup> H]CCPA (Agonist) [1115, 1813], [ <sup>3</sup> H]DPCPX (Antagonist) (pK <sub>d</sub> 8.4–9.2) [442, 592, 1115, 1636, 1813, 2151]	[ <sup>3</sup> H]ZM 241385 (Antagonist) (pK <sub>d</sub> 8.7–9.1) [39, 656], [ <sup>3</sup> H]CGS 21680 (Agonist) [983, 2246]	[ <sup>3</sup> H]MRS1754 (Antagonist) (pK <sub>d</sub> 9.8) [995]	[ <sup>125</sup> I]AB-MECA (Agonist) [1636, 2204]

**Comments:** Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A<sub>2B</sub> adenosine receptor (*ADORA2BP1*) with 79% identity to the A<sub>2B</sub> adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor [972]. DPCPX also exhibits antagonism at A<sub>2B</sub> receptors (pK<sub>i</sub> ca. 7, [37, 1115]). An-

tagonists at A<sub>3</sub> receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A<sub>3</sub> receptor. In the absence of other adenosine receptors, [<sup>3</sup>H]DPCPX and [<sup>3</sup>H]ZM 241385 can also be used to label A<sub>2B</sub> receptors (K<sub>D</sub> ca. 30 and 60 nM respectively). [<sup>125</sup>I]AB-MECA also binds to A<sub>1</sub> receptors [1115]. [<sup>3</sup>H]CGS 21680 is relatively selective for A<sub>2A</sub> re-

ceptors, but may also bind to other sites in cerebral cortex [438, 1006]. [<sup>3</sup>H]NECA binds to other non-receptor elements, which also recognise adenosine [1318]. XAC-BY630 has been described as a fluorescent antagonist for labelling A<sub>1</sub> adenosine receptors in living cells, although activity at other adenosine receptors was not examined [234].

### Further reading on Adenosine receptors

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## Adhesion Class GPCRs

G protein-coupled receptors → 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 GPCR autoproteolysis-inducing (GAIN) domain [60] containing a GPCR proteolytic site. The N-terminus often shares structural homology with adhesive domains (e.g. cadherins, immunoglobulin, lectins) facilitating inter- and matricellular interactions and leading to the term adhesion GPCR [626, 2397]. Several receptors have been suggested to function as mechanosensors [219, 1697, 1900, 2310]. **The nomenclature of these receptors was revised in 2015 as recommended by NC-IUPHAR and the Adhesion GPCR Consortium [788].**

Nomenclature	<a href="#">ADGRA1</a>	<a href="#">ADGRA2</a>	<a href="#">ADGRA3</a>	<a href="#">ADGRB1</a>	<a href="#">ADGRB2</a>	<a href="#">ADGRB3</a>
HGNC, UniProt	<a href="#">ADGRA1, Q86SQ6</a>	<a href="#">ADGRA2, Q96PE1</a>	<a href="#">ADGRA3, Q8IWK6</a>	<a href="#">ADGRB1, O14514</a>	<a href="#">ADGRB2, O60241</a>	<a href="#">ADGRB3, O60242</a>
Endogenous agonists	–	–	–	phosphatidylserine [1655]	–	–
Comments	–	Required to assemble higher-order Reck/Gpr124/Frizzled/Lrp5/6 complexes [573, 1726, 2188, 2200, 2436].	–	Reported to mediate phagocytosis through binding of phosphatidylserine [1655] and lipopolysaccharide [447].	–	Reported to bind C1q-like molecules [194].

Nomenclature	<a href="#">CELSR1</a>	<a href="#">CELSR2</a>	<a href="#">CELSR3</a>	<a href="#">ADGRD1</a>	<a href="#">ADGRD2</a>
HGNC, UniProt	<a href="#">CELSR1, Q9NYQ6</a>	<a href="#">CELSR2, Q9HCU4</a>	<a href="#">CELSR3, Q9NYQ7</a>	<a href="#">ADGRD1, Q6QNK2</a>	<a href="#">ADGRD2, Q7Z7M1</a>
Comments	–	Mutated in Joubert syndrome patients [2218].	High-confidence risk gene for Tourette syndrome [2260].	Is a G <sub>s</sub> protein-coupled receptor [186, 1278] and highly expressed in glioblastoma [122].	–

Nomenclature	<a href="#">ADGRE1</a>	<a href="#">ADGRE2</a>	<a href="#">ADGRE3</a>	<a href="#">ADGRE4P</a>	<a href="#">ADGRES</a>
HGNC, UniProt	<a href="#">ADGRE1, Q14246</a>	<a href="#">ADGRE2, Q9UHX3</a>	<a href="#">ADGRE3, Q9BY15</a>	<a href="#">ADGRE4P, Q86SQ3</a>	<a href="#">ADGRES, P48960</a>
Comments	–	A mutation destabilizing the GAIN domain sensitizes mast cells to IgE-independent vibration-induced degranulation [219]. Reported to bind chondroitin sulfate B [2024].	–	–	Reported to bind CD55 [789], chondroitin sulfate B [2024], $\alpha_5\beta_1$ and $\alpha\gamma\beta_3$ integrins [2262], and CD90 [2248].

Nomenclature	<a href="#">ADGRF1</a>	<a href="#">ADGRF2</a>	<a href="#">ADGRF3</a>	<a href="#">ADGRF4</a>	<a href="#">ADGRF5</a>
HGNC, UniProt	<a href="#">ADGRF1, Q5T601</a>	<a href="#">ADGRF2, Q8IZF7</a>	<a href="#">ADGRF3, Q8IZF5</a>	<a href="#">ADGRF4, Q8IZF3</a>	<a href="#">ADGRF5, Q8IZF2</a>
Comments	Synaptamide is an agonist at ADGRF1 supporting neurogenesis [1240] and couples to G <sub>s</sub> and G <sub>q</sub> pathways [482, 2041].	ADGRF2 is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [1744].	ADGRF3 is highly expressed in gastrointestinal neuroendocrine tumors [308, 308].	ADGRF4 couples to G <sub>q/11</sub> proteins [482], is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [1744].	ADGRF5 controls alveolar surfactant secretion via G <sub>q/11</sub> pathway [253].

Nomenclature	<a href="#">ADGRG1</a>	<a href="#">ADGRG2</a>	<a href="#">ADGRG3</a>	<a href="#">ADGRG4</a>	<a href="#">ADGRG5</a>	<a href="#">ADGRG6</a>	<a href="#">ADGRG7</a>
HGNC, UniProt	<a href="#">ADGRG1, Q9Y653</a>	<a href="#">ADGRG2, Q8IZP9</a>	<a href="#">ADGRG3, Q86Y34</a>	<a href="#">ADGRG4, Q8IZF6</a>	<a href="#">ADGRG5, Q8IZF4</a>	<a href="#">ADGRG6, Q86SQ4</a>	<a href="#">ADGRG7, Q96K78</a>
Comments	Reported to bind tissue transglutaminase 2 [2355] and collagen, which activates the G <sub>12/13</sub> pathway [1330].	ADGRG2 is coupled to G <sub>q</sub> and G <sub>s</sub> pathways [481] and gene deficiency causes congenital obstructive azoospermia [1663].	ADGRG3 is expressed in immune cells [1947, 2255] and couples to G <sub>o</sub> proteins [770].	ADGRG4 is highly expressed in enterochromaffin cells and gastrointestinal neuroendocrine tumors [1250].	ADGRG5 is a constitutively active G <sub>s</sub> protein-coupled receptor [770, 2310], highly expressed in eosinophils and NK cells [1682].	ADGRG6 is a key regulator of Schwann cell-mediated myelination [1481], and couples to G <sub>s</sub> and G <sub>i/o</sub> pathways [1468].	ADGRG7 is expressed in intestine and involved in intestine contractility regulation [1580].

Nomenclature	<a href="#">ADGRL1</a>	<a href="#">ADGRL2</a>	<a href="#">ADGRL3</a>	<a href="#">ADGRL4</a>	<a href="#">ADGRV1</a>
HGNC, UniProt	<a href="#">ADGRL1, O94910</a>	<a href="#">ADGRL2, O95490</a>	<a href="#">ADGRL3, Q9HAR2</a>	<a href="#">ADGRL4, Q9HBW9</a>	<a href="#">ADGRV1, Q8WXG9</a>
Comments	Couples to G <sub>s</sub> and G <sub>q</sub> pathways [ <a href="#">1252</a> , <a href="#">1533</a> ].	–	A LPHN3 gene variant in humans is associated with attention-deficit-hyperactivity disorder [ <a href="#">62</a> , <a href="#">2313</a> ].	–	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [ <a href="#">973</a> ].

### Further reading on Adhesion Class GPCRs

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# Adrenoceptors

G protein-coupled receptors → Adrenoceptors

**Overview: The nomenclature of the Adrenoceptors has been agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [277], see also [869].**

## Adrenoceptors, $\alpha_1$

$\alpha_1$ -Adrenoceptors are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Phenylephrine, methoxamine and cirazoline are agonists and prazosin and cirazoline antagonists considered selective for  $\alpha_1$ - relative to  $\alpha_2$ -adrenoceptors. [<sup>3</sup>H]prazosin and [<sup>125</sup>I]HEAT (BE2254) are

relatively selective radioligands. S(+)-niguldipine also has high affinity for L-type Ca<sup>2+</sup> channels. Fluorescent derivatives of prazosin (Bodipy PLprazosin- QAPB) are used to examine cellular localisation of  $\alpha_1$ -adrenoceptors. Selective  $\alpha_1$ -adrenoceptor agonists are used as nasal decongestants; antagonists to treat hypertension (doxazosin, prazosin) and benign prostatic hyperplasia

(alfuzosin, tamsulosin). The  $\alpha_1$ - and  $\beta_2$ -adrenoceptor antagonist carvedilol is used to treat congestive heart failure, although the contribution of  $\alpha_1$ -adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs are  $\alpha_1$ -adrenoceptor antagonists contributing to side effects such as orthostatic hypotension and extrapyramidal effects.

Nomenclature	$\alpha_{1A}$ -adrenoceptor	$\alpha_{1B}$ -adrenoceptor	$\alpha_{1D}$ -adrenoceptor
HGNC, UniProt	ADRA1A, P35348	ADRA1B, P35368	ADRA1D, P25100
Endogenous agonists	(-)-adrenaline [904, 1948], (-)-noradrenaline [904, 1948, 2104]	–	(-)-noradrenaline [904, 1948], (-)-adrenaline [904, 1948]
Agonists	oxymetazoline [904, 1610, 1948, 2104], phenylephrine [2104], methoxamine [1948, 2104]	phenylephrine [614, 1459]	–
Selective agonists	A61603 [614, 1116], dabuzalgron [179]	–	–
Antagonists	prazosin (Inverse agonist) (pK <sub>i</sub> 9–9.9) [335, 443, 614, 1948, 2312], doxazosin (pK <sub>i</sub> 9.3) [795], terazosin (pK <sub>i</sub> 8.7) [1436], phentolamine (pK <sub>i</sub> 8.6) [1948], alfuzosin (pK <sub>i</sub> 8.1) [867]	prazosin (Inverse agonist) (pK <sub>i</sub> 9.6–9.9) [614, 1948, 2312], tamsulosin (Inverse agonist) (pK <sub>i</sub> 9.5–9.7) [614, 1948, 2312], doxazosin (pK <sub>i</sub> 9.1) [795], alfuzosin (pK <sub>i</sub> 8.6) [868], terazosin (pK <sub>i</sub> 8.6) [1436], phentolamine (pK <sub>i</sub> 7.5) [1948]	prazosin (Inverse agonist) (pK <sub>i</sub> 9.5–10.2) [614, 1948, 2312], tamsulosin (pK <sub>i</sub> 9.8–10.2) [614, 1948, 2312], doxazosin (pK <sub>i</sub> 9.1) [795], terazosin (pK <sub>i</sub> 9.1) [1436], alfuzosin (pK <sub>i</sub> 8.4) [867], dapiprazole (pK <sub>i</sub> 8.4) [79], phentolamine (Inverse agonist) (pK <sub>i</sub> 8.2) [1948], RS-100329 (pK <sub>i</sub> 7.9) [2312], labetalol (pK <sub>i</sub> 6.6) [79]
Selective antagonists	tamsulosin (pK <sub>i</sub> 10–10.7) [335, 443, 614, 1948, 2312], silodosin (pK <sub>i</sub> 10.4) [1948], S(+)-niguldipine (pK <sub>i</sub> 9.1–10) [614, 1948], RS-100329 (pK <sub>i</sub> 9.6) [2312], SNAP5089 (pK <sub>i</sub> 8.8–9.4) [867, 1256, 2294], <i>p</i> -Da1a (pK <sub>i</sub> 9.2–9.3) [1412, 1755], RS-17053 (pK <sub>i</sub> 9.2–9.3) [335, 443, 611, 614]	Rec 15/2615 (pK <sub>i</sub> 9.5) [2110], L-765314 (pK <sub>i</sub> 7.7) [1662], AH 11110 (pK <sub>i</sub> 7.5) [1875]	BMY-7378 (pK <sub>i</sub> 8.7–9.1) [310, 2403]

**Comments:** The  $\alpha_{1C}$ -adrenoceptor corresponds to the pharmacologically defined  $\alpha_{1A}$ -adrenoceptor [869]. Some tissues possess  $\alpha_{1A}$ -adrenoceptors ( $\alpha_{1L}$ -adrenoceptors [614, 1501]) that display relatively low affinity in functional and binding assays for prazosin indicative of different receptor states or locations.  $\alpha_{1A}$ -adrenoceptor C-terminal splice variants form homo- and heterodimers, but fail to generate a functional  $\alpha_{1L}$ -adrenoceptor

[1768].  $\alpha_{1D}$ -Adrenoceptors form heterodimers with  $\alpha_{1B}$ - or  $\beta_2$ -adrenoceptors that show increased cell-surface expression [2164]. Recombinant  $\alpha_{1D}$ -adrenoceptors have been shown in some heterologous systems to be mainly located intracellularly but cell-surface localization is encouraged by truncation of the N-terminus, or by co-expression of  $\alpha_{1B}$ - or  $\beta_2$ -adrenoceptors [779, 2164]. In blood vessels all three  $\alpha_1$ -adrenoceptor subtypes are located on the surface and intracellularly [1433, 1434]. Signalling is

predominantly via G<sub>q/11</sub> but  $\alpha_1$ -adrenoceptors also couple to G<sub>i/o</sub>, G<sub>s</sub> and G<sub>12/13</sub>. Several  $\alpha_{1A}$ -adrenoceptor agonists display ligand directed signalling bias relative to noradrenaline [575]. There are also differences between subtypes in coupling efficiency to different pathways. In vascular smooth muscle, the potency of agonists is related to the predominant subtype,  $\alpha_{1D}$ -conveying greater agonist sensitivity than  $\alpha_{1A}$ -adrenoceptors [609].

**Adrenoceptors,  $\alpha_2$** 

$\alpha_2$ -Adrenoceptors are activated by (-)-adrenaline and with lower potency by (-)-noradrenaline. **Brimonidine** and **talipexole** are agonists and **rauwolscine** and **yohimbine** antagonists selective for  $\alpha_2$ - relative to  $\alpha_1$ -adrenoceptors. [<sup>3</sup>H]rauwolscine, [<sup>3</sup>H]brimonidine and [<sup>3</sup>H]RX821002 are relatively selective radioligands. There is species variation in the pharmacology of

the  $\alpha_{2A}$ -adrenoceptor. Multiple mutations of  $\alpha_2$ -adrenoceptors have been described, some associated with alterations in function. Presynaptic  $\alpha_2$ -adrenoceptors regulate many functions in the nervous system. The  $\alpha_2$ -adrenoceptor agonists **clonidine**, **guanabenz** and **brimonidine** affect central baroreflex control (hypotension and bradycardia), induce hypnotic effects and analgesia, and modulate seizure activity and platelet aggregation. **Clonidine** is an anti-hypertensive and counteracts opioid with-

drawal. **Dexmedetomidine** (also **xylazine**) is used as a sedative and analgesic in human and veterinary medicine with sympatholytic and anxiolytic properties. The  $\alpha_2$ -adrenoceptor antagonist **yohimbine** has been used to treat erectile dysfunction and **mirtazapine** as an anti-depressant. The  $\alpha_{2B}$  subtype appears to be involved in neurotransmission in the spinal cord and  $\alpha_{2C}$  in regulating catecholamine release from adrenal chromaffin cells.

Nomenclature	$\alpha_{2A}$ -adrenoceptor	$\alpha_{2B}$ -adrenoceptor	$\alpha_{2C}$ -adrenoceptor
HGNC, UniProt	<i>ADRA2A</i> , P08913	<i>ADRA2B</i> , P18089	<i>ADRA2C</i> , P18825
Endogenous agonists	(-)-adrenaline [985, 1704], (-)-noradrenaline [985, 1704]	(-)-noradrenaline (Partial agonist) [985, 1704], (-)-adrenaline [985]	(-)-noradrenaline [985, 1704], (-)-adrenaline [985]
Agonists	dexmedetomidine (Partial agonist) [985, 1339, 1678, 1704], clonidine (Partial agonist) [985, 1678, 1704], brimonidine [985, 1339, 1678, 1704], apraclonidine [1519], guanabenz [79], guanfacine (Partial agonist) [985, 1342]	dexmedetomidine [985, 1339, 1678, 1704], clonidine (Partial agonist) [985, 1678, 1704], brimonidine (Partial agonist) [985, 1678, 1704], guanabenz [79], guanfacine [985]	dexmedetomidine [985, 1678, 1704], brimonidine (Partial agonist) [985, 1339, 1678, 1704], apraclonidine [1519], guanfacine (Partial agonist) [985], guanabenz [79]
Selective agonists	oxymetazoline (Partial agonist) [985, 1339, 2169]	–	–
Antagonists	yohimbine (pK <sub>i</sub> 8.4–9.2) [276, 487, 2169]	yohimbine (pK <sub>i</sub> 7.9–8.9) [276, 487, 2169], phenoxybenzamine (pK <sub>i</sub> 8.5) [2280], tolazoline (pK <sub>i</sub> 5.5) [985]	yohimbine (pK <sub>i</sub> 8.5–9.5) [276, 487, 2169], WB 4101 (pK <sub>i</sub> 8.4–9.4) [276, 487, 2169], spiroxatrine (pK <sub>i</sub> 9) [2169], mirtazapine (pK <sub>i</sub> 7.7) [593], tolazoline (pK <sub>i</sub> 5.4) [985]
Selective antagonists	BRL 44408 (pK <sub>i</sub> 8.2–8.8) [2169, 2405]	imiloxan (pK <sub>i</sub> 7.3) [1443] – Rat	JP1302 (pK <sub>B</sub> 7.8) [1855]
Labelled ligands	–	–	[ <sup>3</sup> H]MK-912 (Antagonist) (pK <sub>d</sub> 10.1) [2169]

**Comments:** **ARC-239** and **prazosin** show selectivity for  $\alpha_{2B}$ - and  $\alpha_{2C}$ -adrenoceptors over  $\alpha_{2A}$ -adrenoceptors. **Oxymetazoline** is a reduced efficacy imidazoline agonist but also binds to non-GPCR binding sites for imidazolines, classified as I<sub>1</sub>, I<sub>2</sub> and I<sub>3</sub> sites [444]; catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands evoking hypotensive effects *in vivo*. I<sub>1</sub>-imidazoline receptors cause central inhibition of sympathetic

tone, I<sub>2</sub>-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I<sub>3</sub>-imidazoline receptors regulate insulin secretion from pancreatic  $\beta$ -cells.  $\alpha_{2A}$ -adrenoceptor stimulation reduces insulin secretion from  $\beta$ -islets [2375], with a polymorphism in the 5'-UTR of the *ADRA2A* gene being associated with increased receptor expression in  $\beta$ -islets and heightened susceptibility to diabetes [1821].  $\alpha_{2A}$ - and  $\alpha_{2C}$ -adrenoceptors form homodimers [1990]. Heterodimers between  $\alpha_{2A}$ - and either the

$\alpha_{2C}$ -adrenoceptor or  $\mu$  opioid peptide receptor exhibit altered signalling and trafficking properties compared to the individual receptors [1990, 2099, 2217]. Signalling by  $\alpha_2$ -adrenoceptors is primarily via G<sub>i/o</sub>, although the  $\alpha_{2A}$ -adrenoceptor also couples to G<sub>s</sub> [538]. Imidazoline compounds display bias relative to each other at the  $\alpha_{2A}$ -adrenoceptor [1670]. The noradrenaline reuptake inhibitor desipramine acts directly on the  $\alpha_{2A}$ -adrenoceptor to promote internalisation *via* recruitment of arrestin [421].

**Adrenoceptors,  $\beta$** 

$\beta$ -Adrenoceptors are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Isoprenaline is selective for  $\beta$ -adrenoceptors relative to  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors, while **propranolol** (pK<sub>i</sub> 8.2–9.2) and **cyanopindolol** (pK<sub>i</sub> 10.0–11.0) are relatively  $\beta_1$  and  $\beta_2$  adrenoceptor-selective antagonists. (-)-noradrenaline, **xamoterol** and (-)-Ro 363 show selectivity for  $\beta_1$ - relative to  $\beta_2$ -adrenoceptors. Pharmacological differences ex-

ist between human and mouse  $\beta_3$ -adrenoceptors, and the 'rodent selective' agonists **BRL 37344** and **CL316243** have low efficacy at the human  $\beta_3$ -adrenoceptor whereas **CGP 12177** and **L 755507** activate human  $\beta_3$ -adrenoceptors [88].  $\beta_3$ -Adrenoceptors are resistant to blockade by **propranolol**, but can be blocked by high concentrations of **bupranolol**. **SR59230A** has reasonably high affinity at  $\beta_3$ -adrenoceptors, but does not discriminate well between the three  $\beta$ - subtypes whereas **L 755507** is

more selective. [<sup>125</sup>I]-cyanopindolol, [<sup>125</sup>I]-hydroxy benzylpindolol and [<sup>3</sup>H]-alprenolol are high affinity radioligands that label  $\beta_1$ - and  $\beta_2$ - adrenoceptors and  $\beta_3$ -adrenoceptors can be labelled with higher concentrations (nM) of [<sup>125</sup>I]-cyanopindolol together with  $\beta_1$ - and  $\beta_2$ -adrenoceptor antagonists. [<sup>3</sup>H]-L-748337 is a  $\beta_3$ -selective radioligand [2197]. Fluorescent ligands such as BODIPY-TMR-CGP12177 can be used to track  $\beta$ -adrenoceptors at the cellular level [8]. Somewhat selective  $\beta_1$ -

adrenoceptor agonists (**denopamine**, **dobutamine**) are used short term to treat cardiogenic shock but, chronically, reduce survival.  $\beta_1$ -Adrenoceptor-preferring antagonists are used to treat hypertension (**atenolol**, **betaxolol**, **bisoprolol**, **metoprolol** and **nebivolol**), cardiac arrhythmias (**atenolol**, **bisoprolol**, **esmolol**) and cardiac

failure (**metoprolol**, **nebivolol**). Cardiac failure is also treated with **carvedilol** that blocks  $\beta_1$ - and  $\beta_2$ -adrenoceptors, as well as  $\alpha_1$ -adrenoceptors. Short (**salbutamol**, **terbutaline**) and long (**formoterol**, **salmeterol**) acting  $\beta_2$ -adrenoceptor-selective agonists are powerful bronchodilators used to treat respiratory disorders.

Many first generation  $\beta$ -adrenoceptor antagonists (**propranolol**) block both  $\beta_1$ - and  $\beta_2$ -adrenoceptors and there are no  $\beta_2$ -adrenoceptor-selective antagonists used therapeutically. The  $\beta_3$ -adrenoceptor agonist **mirabegron** is used to control overactive bladder syndrome.

Nomenclature	$\beta_1$ -adrenoceptor	$\beta_2$ -adrenoceptor	$\beta_3$ -adrenoceptor
HGNC, UniProt	<i>ADRB1</i> , P08588	<i>ADRB2</i> , P07550	<i>ADRB3</i> , P13945
Potency order of endogenous ligands	(-)-noradrenaline > (-)-adrenaline	(-)-adrenaline > (-)-noradrenaline	(-)-noradrenaline = (-)-adrenaline
Endogenous agonists	(-)-adrenaline [633, 891], (-)-noradrenaline [633, 891], noradrenaline [633]	(-)-adrenaline [633, 891, 982], (-)-noradrenaline [633, 891]	(-)-noradrenaline [891, 1720, 2044], (-)-adrenaline [891]
Agonists	<b>pindolol</b> (Partial agonist) [1159], <b>isoprenaline</b> [633, 1874], <b>dobutamine</b> (Partial agonist) [956]	<b>pindolol</b> (Partial agonist) [1159], <b>arformoterol</b> [40], <b>isoprenaline</b> [1874], <b>ephedrine</b> (Partial agonist) [982]	<b>carazolol</b> [1431]
Selective agonists	(-)-Ro 363 [1472], <b>xamoterol</b> (Partial agonist) [956], <b>denopamine</b> (Partial agonist) [956, 2066]	<b>formoterol</b> [94], <b>salmeterol</b> [94], <b>zinterol</b> [94], <b>vilanterol</b> [1737], <b>procaterol</b> [94], <b>indacaterol</b> [123], <b>fenoterol</b> [65], <b>salbutamol</b> (Partial agonist) [96, 956], <b>terbutaline</b> (Partial agonist) [96], <b>orciprenaline</b> [2014]	L 755507 [94], L742791 [2277], <b>mirabegron</b> [2089], CGP 12177 (Partial agonist) [177, 1319, 1431, 1472], SB251023 [936] – Mouse, BRL 37344 [177, 505, 891, 1431], CL316243 [2372]
Antagonists	<b>carvedilol</b> (pK <sub>i</sub> 9.5) [297], <b>bupranolol</b> (pK <sub>i</sub> 7.3–9) [297, 1319], <b>SR59230A</b> (pK <sub>i</sub> 8.6) [297], <b>levobunolol</b> (pK <sub>i</sub> 8.4) [79], <b>labetalol</b> (pK <sub>i</sub> 8.2) [79], <b>metoprolol</b> (pK <sub>i</sub> 7–7.6) [96, 297, 891, 1319], <b>esmolol</b> (pK <sub>i</sub> 6.9) [79], <b>nadolol</b> (pK <sub>i</sub> 6.9) [297], <b>practolol</b> (pK <sub>i</sub> 6.1–6.8) [96, 1319], <b>propafenone</b> (pK <sub>i</sub> 6.7) [79], <b>sotalol</b> (pK <sub>i</sub> 6.1) [79]	<b>carvedilol</b> (pK <sub>i</sub> 9.4–9.9) [96, 297], <b>timolol</b> (pK <sub>i</sub> 9.7) [96], <b>propranolol</b> (pK <sub>i</sub> 9.1–9.5) [96, 99, 956, 1319], <b>SR59230A</b> (pK <sub>i</sub> 9.3) [297], <b>levobunolol</b> (pK <sub>i</sub> 9.3) [79], <b>bupranolol</b> (pK <sub>i</sub> 8.3–9.1) [297, 1319], <b>alprenolol</b> (pK <sub>i</sub> 9) [96], <b>nadolol</b> (pK <sub>i</sub> 7–8.6) [96, 297], <b>labetalol</b> (pK <sub>i</sub> 8) [79], <b>propafenone</b> (pK <sub>i</sub> 7.4) [79], <b>sotalol</b> (pK <sub>i</sub> 6.5) [79]	<b>SR59230A</b> (pK <sub>i</sub> 6.9–8.4) [297, 471, 891], <b>bupranolol</b> (pK <sub>i</sub> 6.8–7.3) [177, 297, 1319, 1431], <b>propranolol</b> (pK <sub>i</sub> 6.3–7.2) [1319, 1720], <b>levobunolol</b> (pK <sub>i</sub> 6.8) [1720]
Selective antagonists	CGP 20712A (pK <sub>i</sub> 8.5–9.2) [96, 297, 1319], <b>levobetaxolol</b> (pK <sub>i</sub> 9.1) [1942], <b>betaxolol</b> (pK <sub>i</sub> 8.8) [1319], <b>nebivolol</b> (pI <sub>C</sub> <sub>50</sub> 8.1–8.7) [1669] – Rabbit, <b>atenolol</b> (pK <sub>i</sub> 6.7–7.6) [96, 1021, 1319], <b>acebutolol</b> (pK <sub>i</sub> 6.4) [79]	ICI 118551 (Inverse agonist) (pK <sub>i</sub> 9.2–9.5) [96, 99, 1319]	L-748337 (pK <sub>i</sub> 8.4) [297], L748328 (pK <sub>i</sub> 8.4) [297]
Labelled ligands	[ <sup>125</sup> I]ICYP (Antagonist) (pK <sub>D</sub> 10.4–11.3) [956, 1319, 1874]	[ <sup>125</sup> I]ICYP (Antagonist) (pK <sub>D</sub> 11.1) [1319, 1874]	[ <sup>125</sup> I]ICYP (Agonist, Partial agonist) [1319, 1472, 1720, 1874, 2044]
Comments	The agonists indicated have less than two orders of magnitude selectivity [94].	–	Agonist SB251023 has a pEC <sub>50</sub> of 6.9 for the splice variant of the mouse $\beta_3$ receptor, $\beta_{3b}$ [936].

**Comments:** [<sup>125</sup>I]ICYP can be used to define  $\beta_1$ - or  $\beta_2$ -adrenoceptors when conducted in the presence of a  $\beta_1$ - or  $\beta_2$ -adrenoceptor-selective antagonist. A fluorescent analogue of CGP 12177 can be used to study  $\beta_2$ -adrenoceptors in living cells [97]. [<sup>125</sup>I]ICYP at higher (nM) concentrations can be used to label  $\beta_3$ -adrenoceptors in systems with few if any other  $\beta$ -adrenoceptor subtypes. The  $\beta_3$ -adrenoceptor has an intron in the coding region, but splice variants have only been described for the mouse [576], where the isoforms display different signalling characteris-

tics [936]. There are 3  $\beta$ -adrenoceptors in turkey (termed the  $\beta$ ,  $\beta_{3c}$  and  $\beta_{4c}$ ) that have a pharmacology that differs from the human  $\beta$ -adrenoceptors [95]. Numerous polymorphisms have been described for the  $\beta$ -adrenoceptors; some are associated with signalling and trafficking, altered susceptibility to disease and/or altered responses to pharmacotherapy [1279]. All  $\beta$ -adrenoceptors couple to G<sub>s</sub> (activating adenylyl cyclase and elevating cAMP levels), but also activate G<sub>i</sub> and  $\beta$ -arrestin-mediated signalling. Many  $\beta_1$ - and  $\beta_2$ -adrenoceptor antagonists are agonists at  $\beta_3$ -

adrenoceptors (CL316243, CGP 12177 and **carazolol**). Many ‘antagonists’ of cAMP accumulation, for example **carvedilol** and **bucindolol**, weakly activate MAP kinase pathways [98, 577, 644, 645, 1872, 1873] and thus display ‘protean agonism’. **Bupranolol** acts as a neutral antagonist in most systems so far examined. Agonists also display biased signalling at the  $\beta_2$ -adrenoceptor via G<sub>s</sub> or arrestins [520]. X-ray crystal structures have been described of the agonist bound [2265] and antagonist bound forms of the  $\beta_1$ - [2266], agonist-bound [363] and antagonist-bound forms of the

$\beta_2$ -adrenoceptor [1773, 1820], as well as a fully active agonist-bound,  $G_s$  protein-coupled  $\beta_2$ -adrenoceptor [1774]. Carvedilol and bucindolol bind to a site on the  $\beta_1$ -adrenoceptor involving contacts in TM2, 3, and 7 and extracellular loop 2 that may facilitate coupling to arrestins [2266]. Compounds displaying arrestin-

biased signalling at the  $\beta_2$ -adrenoceptor have a greater effect on the conformation of TM7, whereas full agonists for  $G_s$  coupling promote movement of TM5 and TM6 [1302]. Recent studies using NMR spectroscopy demonstrate significant conformational flexibility in the  $\beta_2$ -adrenoceptor that is stabilized by both agonist

and G proteins highlighting the dynamic nature of interactions with both ligand and downstream signalling partners [1090, 1372, 1605]. Such flexibility likely has consequences for our understanding of biased agonism, and for the future therapeutic exploitation of this phenomenon.

### Further reading on Adrenoceptors

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## Angiotensin receptors

G protein-coupled receptors → Angiotensin receptors

**Overview:** The actions of **angiotensin II (AGT, P01019)** (Ang II) are mediated by  $AT_1$  and  $AT_2$  receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Angiotensin receptors [465, 1045]**), which have around 30% sequence similarity. The decapeptide **angiotensin I (AGT, P01019)**, the octapeptide **angiotensin II (AGT, P01019)** and the heptapeptide **angiotensin III (AGT, P01019)** are endogenous ligands. **Losartan**, **candesartan**, **telmisartan**, etc. are clinically used  $AT_1$  receptor blockers.

Nomenclature	$AT_1$ receptor	$AT_2$ receptor
HGNC, UniProt	<i>AGTR1</i> , P30556	<i>AGTR2</i> , P50052
Endogenous agonists	angiotensin II (AGT, P01019) [466, 2199], angiotensin III (AGT, P01019) [466], angiotensin IV (AGT, P01019) (Partial agonist) [1222]	angiotensin III (AGT, P01019) [432, 466, 2298], angiotensin II (AGT, P01019) [466, 2000, 2298], angiotensin-(1-7) (AGT, P01019) [210]
Agonists	[Sar <sup>1</sup> ,Cha <sup>4</sup> ]Ang-II [896, 1464] – Rat	–
Selective agonists	L-162,313 [1687], L-163,101 [2175]	CGP42112 [210], [p-aminoPhe <sup>6</sup> ]ang II [466, 2021] – Rat, compound 21 [2214]
Antagonists	saprisartan (p <i>K</i> <sub>i</sub> 9.1) [870] – Rat, 5-oxo-1-2-4-oxadiazol biphenyl (p <i>C</i> <sub>50</sub> 8.8) [1583] – Rat, 5-butyl-methyl imidazole carboxylate 30 (p <i>C</i> <sub>50</sub> 8.5) [16], LY303336 (p <i>C</i> <sub>50</sub> 8.3) [2198], TRV120027 (p <i>K</i> <sub>d</sub> 7.7) [2220]	saralasin (p <i>C</i> <sub>50</sub> 9) [371] – Rat
Selective antagonists	candesartan (p <i>C</i> <sub>50</sub> 9.5–9.7) [2199], eprosartan (p <i>C</i> <sub>50</sub> 8.4–8.8) [543], losartan (p <i>C</i> <sub>50</sub> 7.4–8.7) [466, 2135], telmisartan (p <i>C</i> <sub>50</sub> 8.4) [1417], olmesartan (p <i>C</i> <sub>50</sub> 8.1) [1127]	PD123177 (p <i>C</i> <sub>50</sub> 8.5–9.5) [337, 371, 529] – Rat, EMA401 (p <i>C</i> <sub>50</sub> 8.5–9.3) [599, 1800, 1998], PD123319 (p <i>K</i> <sub>d</sub> 8.7–9.2) [466, 528, 2308]
Labelled ligands	[ <sup>3</sup> H]candesartan (Antagonist) (p <i>K</i> <sub>d</sub> 10.3) [594], [ <sup>125</sup> I][Sar <sup>1</sup> ]Ang-II (Agonist) [591] – Rat, [ <sup>125</sup> I][Sar <sup>1</sup> ,Ile <sup>8</sup> ]Ang-II (Agonist, Partial agonist) [591] – Rat, [ <sup>3</sup> H]eprosartan (Antagonist) (p <i>K</i> <sub>d</sub> 9.1) [24] – Rat, [ <sup>3</sup> H]losartan (Antagonist) (p <i>K</i> <sub>d</sub> 8.2) [341] – Rat	[ <sup>125</sup> I]CGP42112 (Agonist) [466, 2298, 2299], [ <sup>125</sup> I][Sar <sup>1</sup> ,Ile <sup>8</sup> ]Ang-II (Agonist) [2097] – Rat
Comments	Telmisartan and candesartan are also reported to be agonists of PPAR $\gamma$ [2040].	–

**Comments:** AT<sub>1</sub> receptors are predominantly coupled to G<sub>q/11</sub>, however they are also linked to arrestin recruitment and stimulate G protein-independent arrestin signalling [1332]. Most species express a single *AGTR1* gene, but two related *agtr1a* and *agtr1b* receptor genes are expressed in rodents. The AT<sub>2</sub> receptor counteracts several of the growth responses initiated by the AT<sub>1</sub> receptors. The AT<sub>2</sub> receptor is much less abundant than the AT<sub>1</sub> receptor in adult

tissues and is upregulated in pathological conditions. AT<sub>1</sub> receptor antagonists bearing substituted 4-phenylquinoline moieties have been synthesized, which bind to AT<sub>1</sub> receptors with nanomolar affinity and are slightly more potent than losartan in functional studies [300]. The antagonist activity of CGP42112 at the AT<sub>2</sub> receptor has also been reported [1596]. The AT<sub>1</sub> and bradykinin B<sub>2</sub> receptors have been proposed to form a heterodimeric complex

[3]. β-Arrestin1 prevents AT<sub>1</sub>-B<sub>2</sub> receptor heteromerization[1756]. There is also evidence for an AT<sub>4</sub> receptor that specifically binds angiotensin IV (*AGT*, P01019) and is located in the brain and kidney. An additional putative endogenous ligand for the AT<sub>4</sub> receptor has been described (LVV-hemorphin (*HBB*, P68871), a globin decapeptide) [1467].

### Further reading on Angiotensin receptors

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# Apelin receptor

G protein-coupled receptors → Apelin receptor

**Overview:** The apelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the apelin receptor [1713]**) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. **Apelin-36** (*APLN*, *Q9ULZ1*), **apelin-13**

(*APLN*, *Q9ULZ1*) and [**Pyr**<sup>1</sup>]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 [2106]. A second family of peptides discovered independently and named Elabela [372] or Toddler, that

has little sequence similarity to apelin, is present, and functional at the apelin receptor in the adult cardiovascular system [1668, 2379]. Structure-activity relationship Elabela analogues have been described [1528].

Nomenclature	apelin receptor
HGNC, UniProt	<i>APLNR</i> , P35414
Potency order of endogenous ligands	[ <b>Pyr</b> <sup>1</sup> ]apelin-13 ( <i>APLN</i> , <i>Q9ULZ1</i> ) ≥ apelin-13 ( <i>APLN</i> , <i>Q9ULZ1</i> ) > apelin-36 ( <i>APLN</i> , <i>Q9ULZ1</i> ) [584, 2106]
Endogenous agonists	apelin-13 ( <i>APLN</i> , <i>Q9ULZ1</i> ) [584, 909, 1428], apelin receptor early endogenous ligand ( <i>APELA</i> , <i>PODMC3</i> ) [483], apelin-17 ( <i>APLN</i> , <i>Q9ULZ1</i> ) [547, 1428], [ <b>Pyr</b> <sup>1</sup> ]apelin-13 ( <i>APLN</i> , <i>Q9ULZ1</i> ) [1056, 1428], Elabela/Toddler-21 ( <i>APELA</i> , <i>PODMC3</i> ) [2378], Elabela/Toddler-32 ( <i>APELA</i> , <i>PODMC3</i> ) [2378], apelin-36 ( <i>APLN</i> , <i>Q9ULZ1</i> ) [584, 909, 1056, 1428], Elabela/Toddler-11 ( <i>APELA</i> , <i>PODMC3</i> ) [2378]
Selective agonists	CMF-019 (Biased agonist) [1781], MM07 (Biased agonist) [226]
Antagonists	MM54 (pK <sub>i</sub> 8.2) [1338]
Labelled ligands	[ <sup>125</sup> I][Nle <sup>75</sup> , Tyr <sup>77</sup> ]apelin-36 (human) (Agonist) [1056], [ <sup>125</sup> I][Glp <sup>65</sup> Nle <sup>75</sup> , Tyr <sup>77</sup> ]apelin-13 (Agonist) [909], [ <sup>125</sup> I]( <b>Pyr</b> <sup>1</sup> )apelin-13 (Agonist) [1050], [ <sup>125</sup> I]apelin-13 (Agonist) [584], [ <sup>3</sup> H]( <b>Pyr</b> <sup>1</sup> )[Met(0)11]-apelin-13 (Agonist) [1428]

**Comments:** Potency order determined for heterologously expressed human apelin receptor (pD<sub>2</sub> values range from 9.5 to 8.6). The apelin receptor may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this

function [323]. A modified apelin-13 peptide, **apelin-13(F13A)** was reported to block the hypotensive response to apelin in rat *in vivo* [1238], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant apelin receptor [584]. The

apelin receptor antagonist, MM54, was reported to suppress tumour growth and increase survival in an intracranial xenograft mouse model of glioblastoma [809].

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## Bile acid receptor

G protein-coupled receptors → 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	GPBA receptor
HGNC, UniProt	GPBAR1, Q8TDU6
Potency order of endogenous ligands	lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid [1055, 1392]
Selective agonists	S-EMCA [1676] – Mouse, betulinic acid [680], oleanolic acid [1871]

**Comments:** The triterpenoid natural product **betulinic acid** has also been reported to inhibit inflammatory signalling through the NF $\kappa$ B pathway [2081]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [2209]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [1313].

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## Bombesin receptors

G protein-coupled receptors → Bombesin receptors

**Overview:** Mammalian bombesin (Bn) receptors comprise 3 subtypes: BB<sub>1</sub>, BB<sub>2</sub>, BB<sub>3</sub> (**nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, [990]**). BB<sub>1</sub> and BB<sub>2</sub> are activated by the endogenous ligands **gastrin-releasing peptide (GRP, P07492)** (GRP), **neuromedin B (NMB, P08949)** (NMB) and **GRP-(18-27) (GRP, P07492)**. **Bombesin** is a tetradecapeptide, originally derived from amphibians. The three Bn receptor subtypes couple primarily to the G<sub>q/11</sub> and G<sub>12/13</sub> family of G proteins [990]. Each of these receptors is widely distributed in the CNS and peripheral tissues [723, 990, 1721, 1766, 1866, 2420]. Activation of BB<sub>1</sub> and BB<sub>2</sub> receptors causes a wide range of physiological/pathophysiological actions, including the stimulation of normal and neoplastic tissue growth, smooth-muscle contraction, feeding behavior, secretion and many central nervous system effects including regulation of circadian rhythm and mediation of pruritus [990, 991, 992, 1359, 1489, 1766]. A physiological role for the BB<sub>3</sub> receptor has yet to be fully defined although recently studies suggest an important role in glucose and insulin regulation, metabolic homeostasis, feeding, regulation of body temperature, obesity, diabetes mellitus and growth of normal/neoplastic tissues [723, 1360, 1619, 2345].

Nomenclature	<b>BB<sub>1</sub> receptor</b>	<b>BB<sub>2</sub> receptor</b>	<b>BB<sub>3</sub> receptor</b>
HGNC, UniProt	<i>NMBR</i> , P28336	<i>GRPR</i> , P30550	<i>BRS3</i> , P32247
Endogenous agonists	neuromedin B ( <i>NMB</i> , P08949) [990, 1766, 2166]	neuromedin C [2166], gastrin releasing peptide(14-27) (human) [2166]	–
Selective agonists	–	–	compound 9g [1398], MK-7725 [373], MK-5046 [1494, 1915], [D-Tyr <sup>6</sup> ,Apa-4Cl <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ]bombesin-(6-14) [1376], compound 17c [1397], bag-1 [759], compound 22e [836]
Antagonists	D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH <sub>2</sub> (pIC <sub>50</sub> 6.2–6.6) [722]	–	–
Selective antagonists	PD 176252 (pIC <sub>50</sub> 9.3–9.8) [722], PD 168368 (pIC <sub>50</sub> 9.3–9.6) [722], dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH <sub>2</sub>	[D-Phe <sup>6</sup> , Leu <sup>13</sup> , Cpa <sup>14</sup> , $\psi$ 13-14]bombesin-(6-14) (pK <sub>i</sub> 9.8) [722], JMV641 (pIC <sub>50</sub> 9.3) [2140] – Mouse, [(3-Ph-Pr <sup>6</sup> ), His <sup>7</sup> ,D-Ala <sup>11</sup> ,D-Pro <sup>13</sup> , $\psi$ 13-14],Phe <sup>14</sup> ]bombesin-(6-14) (pIC <sub>50</sub> 9.2) [722, 1231], JMV594 (pIC <sub>50</sub> 8.9) [1308, 2140] – Mouse, [D-Tpi <sup>6</sup> , Leu <sup>13</sup> $\psi$ (CH <sub>2</sub> NH)-Leu <sup>14</sup> ]bombesin-(6-14) (pIC <sub>50</sub> 8.9) [722]	bantag-1 (pIC <sub>50</sub> 8.6–8.7) [759, 1494], ML-18 (pIC <sub>50</sub> 5.3) [1488]
Labelled ligands	[ <sup>125</sup> I]BH-NMB (human, mouse, rat) (Agonist), [ <sup>125</sup> I][Tyr <sup>4</sup> ]bombesin (Agonist)	[ <sup>125</sup> I][D-Tyr <sup>6</sup> ]bombesin-(6-13)-methyl ester (Selective Antagonist) (pK <sub>d</sub> 9.3) [1375] – Mouse, [ <sup>125</sup> I][Tyr <sup>4</sup> ]bombesin (Agonist) [144], [ <sup>125</sup> I]GRP (human) (Agonist)	[ <sup>3</sup> H]bag-2 (Agonist) [759] – Mouse, [ <sup>125</sup> I][D-Tyr <sup>6</sup> , $\beta$ -Ala <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ]bombesin-(6-14) (Agonist) [1377, 1494]

**Comments:** All three human subtypes may be activated by [D-Phe<sup>6</sup>, $\beta$ -Ala<sup>11</sup>,Phe<sup>13</sup>,Nle<sup>14</sup>]bombesin-(6-14) [1377]. [D-Tyr<sup>6</sup>,Apa-4Cl<sup>11</sup>,Phe<sup>13</sup>,Nle<sup>14</sup>]bombesin-(6-14) has more than 200-fold selectivity for BB<sub>3</sub> receptors over BB<sub>1</sub> and BB<sub>2</sub> [1376, 1377, 1766, 1767].

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## Bradykinin receptors

G protein-coupled receptors → Bradykinin receptors

**Overview:** Bradykinin (or kinin) receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Bradykinin (kinin) Receptors [1243]**) are activated by the endogenous peptides bradykinin (*KNG1*, P01042) (BK), [des-Arg<sup>9</sup>]bradykinin (*KNG1*, P01042), Lys-BK (kallidin (*KNG1*, P01042)), [des-Arg<sup>10</sup>]kallidin (*KNG1*, P01042), [Phospho-Ser<sup>6</sup>]-Bradykinin, T-kinin (*KNG1*, P01042) (Ile-Ser-BK), [Hyp<sup>3</sup>]bradykinin (*KNG1*, P01042) and Lys-[Hyp<sup>3</sup>]-bradykinin (*KNG1*, P01042). Variation in pharmacology and activity of B<sub>1</sub> and B<sub>2</sub> receptor antagonists at species orthologs has been documented. Icatibant (Hoe140, Firazir) is approved in North America and Europe for the treatment of acute attacks of hereditary angioedema.

Nomenclature	B <sub>1</sub> receptor	B <sub>2</sub> receptor
HGNC, UniProt	<i>BDKRB1</i> , P46663	<i>BDKRB2</i> , P30411
Potency order of endogenous ligands	[des-Arg <sup>10</sup> ]kallidin ( <i>KNG1</i> , P01042) > [des-Arg <sup>9</sup> ]bradykinin ( <i>KNG1</i> , P01042) = kallidin ( <i>KNG1</i> , P01042) > bradykinin ( <i>KNG1</i> , P01042)	kallidin ( <i>KNG1</i> , P01042) > bradykinin ( <i>KNG1</i> , P01042) ≫ [des-Arg <sup>9</sup> ]bradykinin ( <i>KNG1</i> , P01042), [des-Arg <sup>10</sup> ]kallidin ( <i>KNG1</i> , P01042)
Endogenous agonists	[des-Arg <sup>10</sup> ]kallidin ( <i>KNG1</i> , P01042) [80, 118, 714, 1012]	bradykinin ( <i>KNG1</i> , P01042)
Selective agonists	NG29 [1879], [Sar,D-Phe <sup>8</sup> ,des-Arg <sup>9</sup> ]bradykinin [1012]	NG291 [282, 1880], [Hyp <sup>3</sup> ,Tyr(Me) <sup>8</sup> ]BK, [Phe <sup>8</sup> ,ψ(CH <sub>2</sub> -NH)Arg <sup>9</sup> ]BK, labradimil [282, 1880]
Selective antagonists	B-9958 (pK <sub>i</sub> 9.2–10.3) [689, 1784], [Leu <sup>9</sup> ,des-Arg <sup>10</sup> ]kallidin (pK <sub>i</sub> 9.1–9.3) [80, 118], SSR240612 (pK <sub>i</sub> 9.1–9.2) [732], R-954 (pA <sub>2</sub> 8.6) [715], R-715 (pA <sub>2</sub> 8.5) [713]	icatibant (pK <sub>i</sub> 10.2) [43], FR173657 (pA <sub>2</sub> 8.2) [1814], anitibant (pK <sub>i</sub> 8.2) [1742]
Labelled ligands	[ <sup>125</sup> I]Hpp-desArg <sup>10</sup> HOE140 (pK <sub>d</sub> 10), [ <sup>3</sup> H]Lys-[des-Arg <sup>9</sup> ]BK (Agonist), [ <sup>3</sup> H]Lys-[Leu <sup>8</sup> ][des-Arg <sup>9</sup> ]BK (Antagonist)	[ <sup>3</sup> H]BK (human, mouse, rat) (Agonist) [2318] – Mouse, [ <sup>3</sup> H]NPC17731 (Antagonist) (pK <sub>d</sub> 9.1–9.4) [2423, 2424], [ <sup>125</sup> I][Tyr <sup>8</sup> ]bradykinin (Agonist)

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# Calcitonin receptors

G protein-coupled receptors → Calcitonin receptors

**Overview:** This receptor family comprises a group of receptors for the calcitonin/CGRP family of peptides. The calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors [830, 1732]**) are generated by the genes *CALCR* (which codes for the CT receptor) 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 proteins), 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 the CT receptor; these in turn produce variants of the AMY receptor [1732], some of which can be potentially activated by CGRP. The endogenous agonists are the peptides **calcitonin** (*CALCA*, P01258),  **$\alpha$ -CGRP** (*CALCA*, P06881) (formerly known as CGRP-I),  **$\beta$ -CGRP** (*CALCB*, P10092) (formerly known as CGRP-II), **amylin** (*IAPP*, P10997) (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), **adrenomedullin** (*ADM*, P35318) and **adrenomedullin 2/intermedin** (*ADM2*, Q7Z4H4). There are species differences in peptide sequences, particularly for the CTs. **CTR-stimulating peptide** [Pig] (CRSP) is another mem-

ber of the family with selectivity for the CT receptor but it is not expressed in humans [1047]. **Olcegepant** (also known as BIBN4096BS, pKi10.5) and **telcagepant** (also known as MK0974, pKi9) are the most selective antagonists available, showing selectivity for CGRP receptors, with a particular preference for those of primate origin. CLR (calcitonin receptor-like receptor) by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, adrenomedullin and adrenomedullin 2/intermedin.

Nomenclature	CT receptor	AMY <sub>1</sub> receptor	AMY <sub>2</sub> receptor	AMY <sub>3</sub> receptor
HGNC, UniProt	<i>CALCR</i> , P30988	–	–	–
Subunits	–	RAMP1 (Accessory protein), CT receptor	CT receptor, RAMP2 (Accessory protein)	CT receptor, RAMP3 (Accessory protein)
Potency order of endogenous ligands	calcitonin (salmon) ≥ calcitonin ( <i>CALCA</i> , P01258) ≥ amylin ( <i>IAPP</i> , P10997), $\alpha$ -CGRP ( <i>CALCA</i> , P06881), $\beta$ -CGRP ( <i>CALCB</i> , P10092) > adrenomedullin ( <i>ADM</i> , P35318), adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4)	calcitonin (salmon) ≥ amylin ( <i>IAPP</i> , P10997) ≥ $\alpha$ -CGRP ( <i>CALCA</i> , P06881), $\beta$ -CGRP ( <i>CALCB</i> , P10092) > adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) ≥ calcitonin ( <i>CALCA</i> , P01258) > adrenomedullin ( <i>ADM</i> , P35318)	Poorly defined	calcitonin (salmon) ≥ amylin ( <i>IAPP</i> , P10997) > $\alpha$ -CGRP ( <i>CALCA</i> , P06881), $\beta$ -CGRP ( <i>CALCB</i> , P10092) ≥ adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) ≥ calcitonin ( <i>CALCA</i> , P01258) > adrenomedullin ( <i>ADM</i> , P35318)
Endogenous agonists	calcitonin ( <i>CALCA</i> , P01258) [35, 68, 827, 1183, 1263, 1517]	$\alpha$ -CGRP ( <i>CALCA</i> , P06881) [827, 1182, 1183, 1263, 2241], amylin ( <i>IAPP</i> , P10997) [705], $\beta$ -CGRP ( <i>CALCB</i> , P10092)	amylin ( <i>IAPP</i> , P10997) [705]	amylin ( <i>IAPP</i> , P10997) [705]
Sub/family-selective agonists	pramlintide [705]	pramlintide [705]	–	pramlintide [705]
Sub/family-selective antagonists	CT-(8-32) (salmon) (pK <sub>d</sub> 9) [874], AC187 (pK <sub>i</sub> 7.2) [827]	AC187 (pK <sub>i</sub> 8) [827], CT-(8-32) (salmon) (pK <sub>i</sub> 7.8) [827], olcegepant (pK <sub>d</sub> 7.2) [2241]	–	CT-(8-32) (salmon) (pK <sub>i</sub> 7.9) [827], AC187 (pK <sub>i</sub> 7.7) [827]
Labelled ligands	[ <sup>125</sup> I]CT (human) (Agonist), [ <sup>125</sup> I]CT (salmon) (Agonist)	[ <sup>125</sup> I] $\alpha$ CGRP (human) (Agonist), [ <sup>125</sup> I]BH-AMY (rat, mouse) (Agonist)	[ <sup>125</sup> I]BH-AMY (rat, mouse) (Agonist)	[ <sup>125</sup> I]BH-AMY (rat, mouse) (Agonist)

Nomenclature	calcitonin receptor-like receptor	CGRP receptor	AM <sub>1</sub> receptor	AM <sub>2</sub> receptor
HGNC, UniProt	<a href="#">CALCRL, Q16602</a>	–	–	–
Subunits	–	calcitonin receptor-like receptor, RAMP1 (Accessory protein)	calcitonin receptor-like receptor, RAMP2 (Accessory protein)	calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Potency order of endogenous ligands	–	$\alpha$ -CGRP ( <a href="#">CALCA, P06881</a> ), $\beta$ -CGRP ( <a href="#">CALCB, P10092</a> ) > adrenomedullin ( <a href="#">ADM, P35318</a> ) $\geq$ adrenomedullin 2/intermedin ( <a href="#">ADM2, Q7Z4H4</a> ) > amylin ( <a href="#">IAPP, P10997</a> ) $\geq$ calcitonin (salmon)	adrenomedullin ( <a href="#">ADM, P35318</a> ) > adrenomedullin 2/intermedin ( <a href="#">ADM2, Q7Z4H4</a> ) > $\alpha$ -CGRP ( <a href="#">CALCA, P06881</a> ), $\beta$ -CGRP ( <a href="#">CALCB, P10092</a> ), amylin ( <a href="#">IAPP, P10997</a> ) > calcitonin (salmon)	adrenomedullin ( <a href="#">ADM, P35318</a> ) $\geq$ adrenomedullin 2/intermedin ( <a href="#">ADM2, Q7Z4H4</a> ) $\geq$ $\alpha$ -CGRP ( <a href="#">CALCA, P06881</a> ), $\beta$ -CGRP ( <a href="#">CALCB, P10092</a> ) > amylin ( <a href="#">IAPP, P10997</a> ) > calcitonin (salmon)
Endogenous agonists	–	$\beta$ -CGRP ( <a href="#">CALCB, P10092</a> ) [23, 1426], $\alpha$ -CGRP ( <a href="#">CALCA, P06881</a> ) [23, 1426]	adrenomedullin ( <a href="#">ADM, P35318</a> ) [23, 1426]	adrenomedullin ( <a href="#">ADM, P35318</a> ) [23, 623]
Antagonists	–	olcegepant (pK <sub>i</sub> 10.7–11) [512, 828, 829, 1022, 1368], telcagepant (pK <sub>i</sub> 9.1) [1857]	–	–
Selective antagonists	–	–	AM-(22-52) (human) (pK <sub>i</sub> 7–7.8) [829]	AM-(22-52) (human)
Labelled ligands	–	[ <sup>125</sup> I] $\alpha$ CGRP (human) (Agonist), [ <sup>125</sup> I] $\alpha$ CGRP (mouse, rat) (Agonist)	[ <sup>125</sup> I]AM (rat) (Agonist)	[ <sup>125</sup> I]AM (rat) (Agonist)

**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 calcitonin ([CALCA, P01258](#)) has low affinity for <sup>125</sup>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 [388, 827, 828]. The major human CTR splice variant (hCT<sub>(a)</sub>), which does not contain an insert) with RAMP1 (*i.e.* the AMY<sub>1(a)</sub> recep-

tor) has a high affinity for CGRP [2241], unlike hCT<sub>(a)</sub>-RAMP3 (*i.e.* AMY<sub>3(a)</sub> receptor) [388, 827]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [1495, 1750, 2134]. Emerging data suggests that AMY<sub>1</sub> could be a second CGRP receptor [826].

The ligands described have limited selectivity. Adrenomedullin has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM<sub>2</sub> receptors. Adrenomedullin 2/intermedin also has high affinity for the AM<sub>2</sub> receptor [903]. CGRP-(8-37) acts as an antagonist of CGRP (pK<sub>i</sub> 8) and inhibits some AM and AMY responses (pK<sub>i</sub> 6-7). It is weak at CT receptors. Human AM-(22-52) has some selectivity towards AM

receptors, but with modest potency (pK<sub>i</sub> 7), limiting its use [829]. Olcegepant shows the greatest selectivity between receptors but still has significant affinity for AMY<sub>1</sub> receptors [2241].

G<sub>s</sub> is a prominent route for effector coupling for CLR and CTR but other pathways (*e.g.* Ca<sup>2+</sup>, ERK, Akt), and G proteins can be activated [2240]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, [ASL \(P04424\)](#)) is important for the coupling of CLR to adenylyl cyclase [578].

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

### Further reading on Calcitonin receptors

- Hay DL *et al.* (2018) Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. *Br. J. Pharmacol.* **175**: 3-17 [PMID:29059473]
- Hay DL *et al.* (2016) Receptor Activity-Modifying Proteins (RAMPs): New Insights and Roles. *Annu. Rev. Pharmacol. Toxicol.* **56**: 469-87 [PMID:26514202]
- Kato J *et al.* (2015) Bench-to-bedside pharmacology of adrenomedullin. *Eur. J. Pharmacol.* **764**: 140-8 [PMID:26144371]
- Russell FA *et al.* (2014) Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol. Rev.* **94**: 1099-142 [PMID:25287861]
- Russo AF. (2015) Calcitonin gene-related peptide (CGRP): a new target for migraine. *Annu. Rev. Pharmacol. Toxicol.* **55**: 533-52 [PMID:25340934]

# Calcium-sensing receptor

G protein-coupled receptors → Calcium-sensing receptor

**Overview:** The calcium-sensing receptor (CaS, **provisional nomenclature as recommended by NC-IUPHAR [612]**) responds to multiple endogenous ligands, including extracellular calcium and other divalent/trivalent cations, polyamines and polycationic peptides, L-amino acids (particularly L-Trp and L-Phe), glutathione and various peptide analogues, ionic

strength and extracellular pH (reviewed in [1228]). While divalent/trivalent cations, polyamines and polycations are CaS receptor agonists [252, 1754], L-amino acids, glutamyl peptides, ionic strength and pH are allosteric modulators of agonist function [411, 612, 885, 1752, 1753]. Indeed, L-amino acids have been identified as "co-agonists", with both concomitant calcium and

L-amino acid binding required for full receptor activation [682, 2416]. The sensitivity of the CaS receptor to primary agonists is increased by elevated extracellular pH [295] or decreased extracellular ionic strength [1753]. This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

Nomenclature	CaS receptor
HGNC, UniProt	CASR, P41180
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) [411]
Cation rank order of potency	Gd <sup>3+</sup> > Ca <sup>2+</sup> > Mg <sup>2+</sup> [252]
Glutamyl peptide rank order of potency	S-methylglutathione ≈ γGlu-Val-Gly > glutathione > γGlu-Cys [243, 1621, 2256]
Polyamine rank order of potency	spermine > spermidine > putrescine [1754]
Allosteric modulators	ATF 936 (Negative) (pIC <sub>50</sub> 8.9) [2302], encaleret (Negative) (pIC <sub>50</sub> 7.9) [1956], SB-423562 (Negative) (pIC <sub>50</sub> 7.1) [1176], ronacaleret (Negative) (pIC <sub>50</sub> 6.5–6.8) [101], NPS 2143 (Negative) (pK <sub>B</sub> 6.2–6.7) [459, 1226, 1229], cinacalcet (Positive) (pK <sub>B</sub> 5.9–6.6) [414, 459, 1226, 1229], tecalcet (Positive) (pK <sub>B</sub> 6.2–6.6) [414, 459], AC265347 (Positive) (pK <sub>B</sub> 6.3–6.4) [414, 1226], calhex 231 (Negative) (pIC <sub>50</sub> 6.4) [1699], calindol (Positive) (pK <sub>B</sub> 6.3) [414]

**Comments:** The CaS receptor has a number of physiological functions, but it is best known for its central role in parathyroid and renal regulation of extracellular calcium homeostasis [798]. This is seen most clearly in patients with loss-of-function CaS receptor mutations who develop familial hypocalcaemic hyperparathyroidism (heterozygous mutations) or neonatal severe hyperparathyroidism (heterozygous, compound heterozygous or homozygous mutations) [798] and in *Casr* null mice [339, 885], which exhibit similar increases in PTH secretion and blood calcium levels. Gain-of-function CaS mutations are associated with autosomal dominant hypocalcaemia and Bartter syndrome type V [798].

The CaS receptor primarily couples to G<sub>q/11</sub>, G<sub>12/13</sub> and G<sub>i/o</sub> [459, 693, 922, 2124], but in some cell types can couple to G<sub>s</sub> [1370]. However, the CaS receptor can form heteromers with Class C GABA<sub>B</sub> [340, 362] and mGlu1/5 receptors [651], which may introduce further complexity in its signalling capabilities.

Multiple other small molecule chemotypes are positive and negative allosteric modulators of the CaS receptor [1078, 1565]. Further, **etelcalcetide** is a novel peptide positive allosteric modulator of the receptor [2243]. Agonists and positive allosteric modulators of the CaS receptor are termed Type I and II calcimimetics, respectively, and can suppress parathyroid hormone (PTH

(PTH, P01270)) secretion [1567]. Negative allosteric modulators are called calcilytics and can act to increase PTH (PTH, P01270) secretion [1566].

Where functional pK<sub>B</sub> values are provided for allosteric modulators, this refers to ligand affinity determined in an assay that measures a functional readout of receptor activity (*i.e.* a receptor signalling assay), as opposed to affinity determined in a radioligand binding assay. The functional pK<sub>B</sub> may differ depending on the signalling pathway studied. Consult the 'More detailed page' for the assay description, as well as other functional readouts.

## Further reading on Calcium-sensing receptor

- Brown EM. (2013) Role of the calcium-sensing receptor in extracellular calcium homeostasis. *Best Pract. Res. Clin. Endocrinol. Metab.* **27**: 333-43 [PMID:23856263]
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- Hannan FM *et al.* (2018) The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. *Nat Rev Endocrinol* **15**: 33-51 [PMID:30443043]
- Nemeth EF *et al.* (2018) Discovery and Development of Calcimimetic and Calcilytic Compounds. *Prog Med Chem* **57**: 1-86 [PMID:29680147]

# Cannabinoid receptors

G protein-coupled receptors → Cannabinoid receptors

**Overview:** Cannabinoid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Cannabinoid Receptors [1692]**) are activated by endogenous ligands that include N-arachidonylethanolamine (anandamide), N-homo- $\gamma$ -linolenylethanolamine, N-docosatetra-7,10,13,16-enylethanolamine and 2-arachidonoylglycerol. Potency determinations of endogenous

agonists at these receptors are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion [38].

There are currently three licenced cannabinoid medicines each of which contains a compound that can activate CB<sub>1</sub> and CB<sub>2</sub> receptors [1690]. Two of these medicines were developed to sup-

press nausea and vomiting produced by chemotherapy. These are nabilone (Cesamet<sup>®</sup>), a synthetic CB<sub>1</sub>/CB<sub>2</sub> receptor agonist, and synthetic  $\Delta^9$ -tetrahydrocannabinol (Marinol<sup>®</sup>; dronabinol), which can also be used as an appetite stimulant. The third medicine, Sativex<sup>®</sup>, contains mainly  $\Delta^9$ -tetrahydrocannabinol and cannabidiol, both extracted from cannabis, and is used to treat multiple sclerosis and cancer pain.

Nomenclature	CB <sub>1</sub> receptor	CB <sub>2</sub> receptor
HGNC, UniProt	CNR1, P21554	CNR2, P34972
Agonists	HU-210 [590, 1960], CP55940 [590, 1824, 1960], WIN55212-2 [590, 1959, 1960], $\Delta^9$ -tetrahydrocannabinol (Partial agonist) [590, 1960], cannabiniol (Partial agonist) [590, 1960]	HU-210 [590, 1796, 1960], WIN55212-2 [590, 1959, 1960], CP55940 [590, 1824, 1960], $\Delta^9$ -tetrahydrocannabinol (Partial agonist) [121, 590, 1796, 1960]
Selective agonists	arachidonyl-2-chloroethylamide [872] – Rat, arachidonylcyclopropylamide [872] – Rat, O-1812 [489] – Rat, R-(+)-methanandamide [1073] – Rat	JWH-133 [930, 1691], L-759,633 [663, 1824], AM1241 [2381], L-759,656 [663, 1824], HU-308 [806]
Selective antagonists	rimonabant (pK <sub>i</sub> 7.9–8.7) [589, 590, 1804, 1835, 1960], AM6545 (pK <sub>i</sub> 8.5) [217], AM251 (pK <sub>i</sub> 8.1) [1196] – Rat, AM281 (pK <sub>i</sub> 7.9) [1195] – Rat, LY320135 (pK <sub>i</sub> 6.9) [589]	SR144528 (pK <sub>i</sub> 8.3–9.2) [1805, 1824], AM-630 (pK <sub>i</sub> 7.5) [1824]
Allosteric modulators	GAT100 (Negative) (pEC <sub>50</sub> 7.7) [1172], ZCZ011 (Positive) (pEC <sub>50</sub> 6.3) [943] – Mouse, GAT211 (Positive) [1205], cannabidiol (Negative) [1204]	pepcan-12 (Positive) (pK <sub>i</sub> ~7.3) [1701], compound C2 (Positive) [643]
Labelled ligands	[ <sup>3</sup> H]rimonabant (Antagonist) (pK <sub>d</sub> 8.9–10) [228, 880, 1025, 1698, 1806, 1972, 2118] – Rat –	

**Comments:** Both CB<sub>1</sub> and CB<sub>2</sub> receptors may be labelled with [<sup>3</sup>H]CP55940 (0.5 nM; [1960]) and [<sup>3</sup>H]WIN55212-2 (2–2.4 nM; [1987, 2013]). Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [1608, 2444]. There is evidence for an

allosteric site on the CB<sub>1</sub> receptor [1735]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [1692]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have

been identified [1692]. Moreover, GPR18, GPR55 and GPR119, although showing little structural similarity to CB<sub>1</sub> and CB<sub>2</sub> receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands [1692].

### Further reading on Cannabinoid receptors

- Howlett AC *et al.* (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev.* **54**: 161-202 [PMID:12037135]
- Pertwee RG *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB<sub>1</sub> and CB<sub>2</sub>. *Pharmacol. Rev.* **62**: 588-631 [PMID:21079038]
- Pertwee RG. (2010) Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Curr. Med. Chem.* **17**: 1360-81 [PMID:20166927]

## Chemerin receptors

G protein-coupled receptors → Chemerin receptors

**Overview:** Nomenclature for the chemerin receptors is presented as **recommended by NC-IUPHAR [455, 1065]**. The chemoattractant protein and adipokine, **chemerin (RARRES2, Q99969)**, has been shown to be the endogenous ligand for both chemerin family receptors. Chemerin<sub>1</sub> was the founding family member, and when *GPR1* was de-orphanised it was re-named Chemerin<sub>2</sub> [1065]. Chemerin<sub>1</sub> is also activated by the lipid-derived, anti-inflammatory ligand **resolvin E1 (RvE1)**, which is formed *via* the sequential metabolism of **EPA** by aspirin-modified cyclooxygenase and lipoxygenase [66, 67]. In addition, two GPCRs for **resolvin D1 (RvD1)** have been identified: FPR2/ALX, the lipoxin A<sub>4</sub> receptor, and GPR32, an orphan receptor [1153].

Nomenclature	<a href="#">chemerin receptor 1</a>	<a href="#">chemerin receptor 2</a>
Common abbreviation	Chemerin <sub>1</sub>	Chemerin <sub>2</sub>
HGNC, UniProt	<a href="#">CMKLR1, Q99788</a>	<a href="#">GPR1, P46091</a>
Potency order of endogenous ligands	<a href="#">resolvin E1</a> > <a href="#">chemerin C-terminal peptide</a> > <a href="#">18R-HEPE</a> > <a href="#">EPA</a> [66]	–
Endogenous agonists	–	<a href="#">chemerin (RARRES2, Q99969)</a> [109]
Selective agonists	<a href="#">resolvin E1</a>	–
Labelled ligands	<a href="#">[<sup>3</sup>H]resolvin E1</a> (Agonist) [66, 67]	–
Comments	–	Reported to act as a co-receptor for HIV [1952]. See review [455] for discussion of pairing with chemerin.

**Comments:** CCX832 (structure not disclosed) is a selective antagonist, pK<sub>i</sub>=9.2 [1066].

### Further reading on Chemerin receptors

- Kennedy AJ *et al.* (2018) International Union of Basic and Clinical Pharmacology CIII: Chemerin Receptors CMKLR1 (Chemerin1) and GPR1 (Chemerin2) Nomenclature, Pharmacology, and Function. *Pharmacol. Rev.* **70**: 174-196 [PMID:29279348]
- Shin WJ *et al.* (2018) Mechanisms and Functions of Chemerin in Cancer: Potential Roles in Therapeutic Intervention. *Front Immunol* **9**: 2772 [PMID:30555465]

# Chemokine receptors

G protein-coupled receptors → Chemokine receptors

**Overview:** Chemokine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Chemokine Receptors [90, 1524, 1525]**) 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. Additional hematopoietic and non-hematopoietic roles have been identified for many chemokines in the areas of embryonic development, immune cell proliferation, activation and death, viral infection, and as antibiotics, among others. 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 [90].

Chemokines in turn can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as  $\beta$ -chemokines;  $n=28$ ), CXC (also known as  $\alpha$ -chemokines;  $n=17$ ) 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 recep-

tor 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 [91]. 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 [2401] and aliases.

Nomenclature	CCR1	CCR2	CCR3
HGNC, UniProt	CCR1, P32246	CCR2, P41597	CCR3, P51677
Endogenous agonists	CCL3 (CCL3, P10147) [375, 406, 862, 2443], CCL23 (CCL23, P55773) [375], CCL5 (CCL5, P13501) [406, 862], CCL7 (CCL7, P80098) [375, 775], CCL15 (CCL15, Q16663) [423], CCL14 (CCL14, Q16627) [375], CCL13 (CCL13, Q99616), CCL8 (CCL8, P80075)	CCL2 (CCL2, P13500) [423, 1335, 1461, 1658, 2167], CCL13 (CCL13, Q99616) [1335, 2167], CCL7 (CCL7, P80098) [423, 1335, 2167], CCL11 (CCL11, P51671) (Partial agonist) [1335, 1658], CCL16 (CCL16, O15467)	CCL13 (CCL13, Q99616) [1505, 2167], CCL24 (CCL24, O00175) [1505, 1658], CCL5 (CCL5, P13501) [449], CCL7 (CCL7, P80098) [449], CCL11 (CCL11, P51671) [531, 1108, 1505, 1849, 2167], CCL26 (CCL26, Q9Y258) [1108, 1505, 1658], CCL15 (CCL15, Q16663) [423], CCL28 (CCL28, Q9NRJ3), CCL8 (CCL8, P80075)
Agonists	–	–	CCL11 (Mouse) [449]
Endogenous antagonists	CCL4 (CCL4, P13236) (pK <sub>i</sub> 7.1–7.8) [375, 406]	CCL26 (CCL26, Q9Y258) (pIC <sub>50</sub> 8.5) [1658]	CXCL10 (CXCL10, P02778), CXCL11 (CXCL11, O14625), CXCL9 (CXCL9, Q07325)
Selective antagonists	BX 471 (pK <sub>i</sub> 8.2–9) [1274], compound 2b-1 (pIC <sub>50</sub> 8.7) [1552], UCB35625 (pIC <sub>50</sub> 8) [1849], CP-481,715 (pK <sub>d</sub> 8) [708]	GSK Compound 34 (pK <sub>i</sub> 7.6)	banyu (I) (Inverse agonist) (pK <sub>i</sub> 8.5) [2247], SB328437 (pK <sub>i</sub> 8.4), BMS compound 87b (pK <sub>i</sub> 8.1) [2232]
Labelled ligands	[ <sup>125</sup> I]CCL7 (human) (Agonist) [140], [ <sup>125</sup> I]CCL3 (human) (Agonist) [140, 720, 1870], [ <sup>125</sup> I]CCL5 (human) (Agonist) [1870]	[ <sup>125</sup> I]CCL2 (human) (Agonist), [ <sup>125</sup> I]CCL7 (human) (Agonist)	[ <sup>125</sup> I]CCL11 (human) (Antagonist) (pK <sub>d</sub> 8.3) [2247], [ <sup>125</sup> I]CCL5 (human) (Agonist), [ <sup>125</sup> I]CCL7 (human) (Agonist)

Nomenclature	CCR4	CCR5	CCR6	CCR7	CCR8	CCR9	CCR10
HGNC, UniProt	CCR4, P51679	CCR5, P51681	CCR6, P51684	CCR7, P32248	CCR8, P51685	CCR9, P51686	CCR10, P46092
Endogenous agonists	CCL22 (CCL22, O00626) [947], CCL17 (CCL17, Q92583) [947]	CCL5 (CCL5, P13501) [87, 1547, 1833], CCL4 (CCL4, P13236) [1547, 1833], CCL8 (CCL8, P80075) [1833], CCL3 (CCL3, P10147) [1547, 1833, 2443], CCL11 (CCL11, P51671) [175], CCL2 (CCL2, P13500) [1547], CCL14 (CCL14, Q16627) [1547], CCL16 (CCL16, O15467)	CCL20 (CCL20, P78556) [22, 86, 1730], beta-defensin 4A (DEFB4A DEFB4B, O15263) [2373]	CCL21 (CCL21, O00585) [2399], CCL19 (CCL19, Q99731) [1640, 2398, 2399]	CCL1 (CCL1, P22362) [441, 819, 948], CCL8 {Mouse}	CCL25 (CCL25, O15444)	CCL27 (CCL27, Q9Y4X3) [901], CCL28 (CCL28, Q9NRJ3)
Agonists	vMIP-III	RS-HIV-1 gp120	–	–	vMIP-I [441, 948]	–	–
Endogenous antagonists	–	CCL7 (CCL7, P80098) (pK <sub>i</sub> 7.5) [1547]	–	–	–	–	–
Antagonists	–	vicriviroc (pK <sub>i</sub> 9.1) [2043], ancriviroc (pK <sub>i</sub> 7.8–8.7) [1348, 1647, 2043]	–	–	–	–	–
Selective antagonists	compound 8ic (pIC <sub>50</sub> 7.7) [2396]	E913 (pIC <sub>50</sub> 8.7) [1349], aplaviroc (pK <sub>i</sub> 8.5) [1348], maraviroc (pIC <sub>50</sub> 8.1) [1547], TAK-779 (pK <sub>i</sub> 7.5) [1348], MRK-1 [1175] – Rat	–	–	vMCC-I (pIC <sub>50</sub> 9.4) [441]	–	–
Selective allosteric modulators	–	–	–	–	–	vercirnon (Antagonist) (pIC <sub>50</sub> 8.2) [2244]	–
Antibodies	mogamulizumab (Inhibition) [58, 1962]	–	–	–	–	–	–
Labelled ligands	[ <sup>125</sup> I]CCL17 (human) (Agonist), [ <sup>125</sup> I]CCL27 (human) (Agonist)	[ <sup>125</sup> I]CCL4 (human) (Agonist) [1547], [ <sup>125</sup> I]CCL3 (human) (Agonist), [ <sup>125</sup> I]CCL5 (human) (Agonist), [ <sup>125</sup> I]CCL8 (human) (Agonist)	[ <sup>125</sup> I]CCL20 (human) (Agonist) [742]	[ <sup>125</sup> I]CCL19 (human) (Agonist), [ <sup>125</sup> I]CCL21 (human) (Agonist) [989]	[ <sup>125</sup> I]CCL1 (human) (Agonist) [948, 1819]	[ <sup>125</sup> I]CCL25 (human) (Agonist)	–



Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6	CX <sub>3</sub> CR1
HGNC, UniProt	<a href="#">CXCR1</a> , <a href="#">P25024</a>	<a href="#">CXCR2</a> , <a href="#">P25025</a>	<a href="#">CXCR3</a> , <a href="#">P49682</a>	<a href="#">CXCR4</a> , <a href="#">P61073</a>	<a href="#">CXCR5</a> , <a href="#">P32302</a>	<a href="#">CXCR6</a> , <a href="#">O00574</a>	<a href="#">CX3CR1</a> , <a href="#">P49238</a>
Endogenous agonists	<a href="#">CXCL8</a> ( <a href="#">CXCL8</a> , <a href="#">P10145</a> ) [ <a href="#">157</a> , <a href="#">783</a> , <a href="#">1239</a> , <a href="#">2316</a> , <a href="#">2336</a> ], <a href="#">CXCL6</a> ( <a href="#">CXCL6</a> , <a href="#">P80162</a> ) [ <a href="#">2341</a> ]	<a href="#">CXCL1</a> ( <a href="#">CXCL1</a> , <a href="#">P09341</a> ) [ <a href="#">783</a> , <a href="#">1239</a> , <a href="#">2336</a> ], <a href="#">CXCL8</a> ( <a href="#">CXCL8</a> , <a href="#">P10145</a> ) [ <a href="#">157</a> , <a href="#">783</a> , <a href="#">1239</a> , <a href="#">2316</a> , <a href="#">2336</a> ], <a href="#">CXCL7</a> ( <a href="#">PPBP</a> , <a href="#">P02775</a> ) [ <a href="#">20</a> ], <a href="#">CXCL3</a> ( <a href="#">CXCL3</a> , <a href="#">P19876</a> ) [ <a href="#">20</a> ], <a href="#">CXCL2</a> ( <a href="#">CXCL2</a> , <a href="#">P19875</a> ) [ <a href="#">20</a> ], <a href="#">CXCL5</a> ( <a href="#">CXCL5</a> , <a href="#">P42830</a> ) [ <a href="#">20</a> ], <a href="#">CXCL6</a> ( <a href="#">CXCL6</a> , <a href="#">P80162</a> ) [ <a href="#">2341</a> ]	<a href="#">CXCL11</a> ( <a href="#">CXCL11</a> , <a href="#">O14625</a> ) [ <a href="#">845</a> ], <a href="#">CXCL10</a> ( <a href="#">CXCL10</a> , <a href="#">P02778</a> ) [ <a href="#">845</a> , <a href="#">2285</a> ], <a href="#">CXCL9</a> ( <a href="#">CXCL9</a> , <a href="#">Q07325</a> ) [ <a href="#">845</a> , <a href="#">2285</a> ]	<a href="#">CXCL12<math>\alpha</math></a> ( <a href="#">CXCL12</a> , <a href="#">P48061</a> ) [ <a href="#">861</a> , <a href="#">1311</a> ], <a href="#">CXCL12<math>\beta</math></a> ( <a href="#">CXCL12</a> , <a href="#">P48061</a> ) [ <a href="#">861</a> ]	<a href="#">CXCL13</a> ( <a href="#">CXCL13</a> , <a href="#">O43927</a> ) [ <a href="#">111</a> ]	<a href="#">CXCL16</a> ( <a href="#">CXCL16</a> , <a href="#">Q9H2A7</a> ) [ <a href="#">2309</a> ]	<a href="#">CX<sub>3</sub>CL1</a> ( <a href="#">CX<sub>3</sub>CL1</a> , <a href="#">P78423</a> ) [ <a href="#">664</a> ]
Agonists	<a href="#">vCXCL1</a> [ <a href="#">1334</a> ], <a href="#">HIV-1 matrix protein p17</a> [ <a href="#">698</a> ]	<a href="#">vCXCL1</a> [ <a href="#">1334</a> ], <a href="#">HIV-1 matrix protein p17</a> [ <a href="#">698</a> ]	–	–	–	–	–
Selective agonists	–	–	–	<a href="#">ALX40-4C</a> (Partial agonist) [ <a href="#">2426</a> ], <a href="#">X4-HIV-1 gp120</a>	–	–	–
Endogenous antagonists	–	–	<a href="#">CCL11</a> ( <a href="#">CCL11</a> , <a href="#">P51671</a> ) ( $pK_i$ 7.2) [ <a href="#">2285</a> ], <a href="#">CCL7</a> ( <a href="#">CCL7</a> , <a href="#">P80098</a> ) ( $pK_i$ 6.6) [ <a href="#">2285</a> ]	–	–	–	–
Antagonists	–	–	–	<a href="#">plerixafor</a> ( $pK_i$ 7) [ <a href="#">2426</a> ]	–	–	–
Selective antagonists	–	<a href="#">navarixin</a> ( $pI_{C_{50}}$ 10.3) [ <a href="#">90</a> , <a href="#">535</a> ], <a href="#">danirixin</a> ( $pI_{C_{50}}$ 7.9) [ <a href="#">1457</a> ], <a href="#">SB 225002</a> ( $pI_{C_{50}}$ 7.7) [ <a href="#">2296</a> ], <a href="#">elubirixin</a> ( $pI_{C_{50}}$ 7.7) [ <a href="#">90</a> ], <a href="#">SX-517</a> ( $pI_{C_{50}}$ 7.2) [ <a href="#">1347</a> ]	–	<a href="#">T134</a> ( $pI_{C_{50}}$ 8.4) [ <a href="#">2096</a> ], <a href="#">mavorixafor</a> ( $pI_{C_{50}}$ 7.9) [ <a href="#">1980</a> ], <a href="#">HIV-Tat</a>	–	–	–
Allosteric modulators	<a href="#">reparixin</a> (Negative) ( $pI_{C_{50}}$ 9) [ <a href="#">157</a> ]	<a href="#">reparixin</a> (Negative) ( $pI_{C_{50}}$ 6.4) [ <a href="#">157</a> ]	–	–	–	–	–
Labelled ligands	[ <sup>125</sup> I] <a href="#">CXCL8</a> (human) (Agonist) [ <a href="#">783</a> , <a href="#">1802</a> ]	[ <sup>125</sup> I] <a href="#">CXCL8</a> (human) (Agonist) [ <a href="#">783</a> , <a href="#">1802</a> ], [ <sup>125</sup> I] <a href="#">CXCL1</a> (human) (Agonist), [ <sup>125</sup> I] <a href="#">CXCL5</a> (human) (Agonist), [ <sup>125</sup> I] <a href="#">CXCL7</a> (human) (Agonist)	[ <sup>125</sup> I] <a href="#">CXCL10</a> (human) (Agonist), [ <sup>125</sup> I] <a href="#">CXCL11</a> (human) (Agonist)	[ <sup>125</sup> I] <a href="#">CXCL12<math>\alpha</math></a> (human) (Agonist) [ <a href="#">491</a> , <a href="#">861</a> ]	[ <sup>125</sup> I] <a href="#">CXCL13</a> (mouse) (Agonist) [ <a href="#">245</a> ] – Mouse	[ <sup>125</sup> I] <a href="#">CXCL16</a> (human) (Agonist)	[ <sup>125</sup> I] <a href="#">CX<sub>3</sub>CL1</a> (human) (Agonist)

Nomenclature	<a href="#">XCR1</a>	<a href="#">ACKR1</a>	<a href="#">ACKR2</a>	<a href="#">ACKR3</a>	<a href="#">ACKR4</a>	<a href="#">CCRL2</a>
HGNC, UniProt	<a href="#">XCR1, P46094</a>	<a href="#">ACKR1, Q16570</a>	<a href="#">ACKR2, O00590</a>	<a href="#">ACKR3, P25106</a>	<a href="#">ACKR4, Q9NBP9</a>	<a href="#">CCRL2, O00421</a>
Endogenous ligands	–	<a href="#">CXCL5 (CXCL5, P42830)</a> , <a href="#">CXCL6 (CXCL6, P80162)</a> , <a href="#">CXCL8 (CXCL8, P10145)</a> , <a href="#">CXCL11 (CXCL11, O14625)</a> , <a href="#">CCL2 (CCL2, P13500)</a> , <a href="#">CCL5 (CCL5, P13501)</a> , <a href="#">CCL7 (CCL7, P80098)</a> , <a href="#">CCL11 (CCL11, P51671)</a> , <a href="#">CCL14 (CCL14, Q16627)</a> , <a href="#">CCL17 (CCL17, Q92583)</a>	–	–	–	<a href="#">chemerin C-terminal peptide</a> , <a href="#">CCL19 (CCL19, Q99731)</a> [109]
Endogenous agonists	<a href="#">XCL1 (XCL1, P47992)</a> [619], <a href="#">XCL2 (XCL2, Q9UBD3)</a> [619]	–	<a href="#">CCL2 (CCL2, P13500)</a> , <a href="#">CCL3 (CCL3, P10147)</a> , <a href="#">CCL4 (CCL4, P13236)</a> , <a href="#">CCL5 (CCL5, P13501)</a> , <a href="#">CCL7 (CCL7, P80098)</a> , <a href="#">CCL8 (CCL8, P80075)</a> , <a href="#">CCL11 (CCL11, P51671)</a> , <a href="#">CCL13 (CCL13, Q99616)</a> , <a href="#">CCL14 (CCL14, Q16627)</a> , <a href="#">CCL17 (CCL17, Q92583)</a> , <a href="#">CCL22 (CCL22, O00626)</a>	<a href="#">CXCL12<math>\alpha</math> (CXCL12, P48061)</a> [741, 2015], <a href="#">CXCL11 (CXCL11, O14625)</a>	<a href="#">CCL19 (CCL19, Q99731)</a> [2276], <a href="#">CCL25 (CCL25, O15444)</a> [2276], <a href="#">CCL21 (CCL21, O00585)</a> [2276]	–
Comments	XCL1 cannot be iodinated, but a secreted alkaline phosphatase (SEAP)-XCL1 fusion peptide can be used as a probe at XCR1.	ACKR1 is used by <i>Plasmodium vivax</i> and <i>Plasmodium knowlsei</i> for entering erythrocytes.	–	Several lines of evidence have suggested that CGRP and adrenomedullin could be ligands for ACKR3; however, classical direct binding to the receptor has not yet been convincingly demonstrated [2074].	–	–

**Comments:** Specific chemokine receptors facilitate cell entry by microbes, such as ACKR1 for *Plasmodium vivax*, and CCR5 and CXCR4 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 gamma-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. Three chemokine receptor antagonists have now been approved by the FDA: 1) the CCR5 antagonist [maraviroc](#) (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and 2) the CXCR4 antagonist [plerixafor](#) (Sanofi) for hematopoi-

etic stem cell mobilization with [G-CSF \(CSF3, P09919\)](#) in patients undergoing transplantation in the context of chemotherapy for Hodgkins' Disease and multiple myeloma; and 3) the CCR4 blocking antibody [Poteligeo](#) (mogamulizumab-kpkc, Kyowa Kirin, Inc.) for mycosis fungoides or Sezary syndrome.

### Further reading on Chemokine receptors

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## Cholecystokinin receptors

G protein-coupled receptors → Cholecystokinin receptors

**Overview:** Cholecystokinin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CCK receptors [1598]**) are activated by the endogenous peptides cholecystokinin-8 (CCK-8 (CCK, P06307)), CCK-33 (CCK, P06307), CCK-58 (CCK, P06307) and gastrin (gastrin-17 (GAST, P01350)). There are only two distinct subtypes of CCK receptors, CCK<sub>1</sub> and CCK<sub>2</sub> receptors [1139, 2263], with some alternatively spliced forms most often identified in neoplastic cells. The CCK receptor subtypes are distinguished by their peptide selectivity, with the CCK<sub>1</sub> receptor requiring the carboxyl-terminal heptapeptide-amide that includes a sulfated tyrosine for high affinity and potency, while the CCK<sub>2</sub> receptor requires only the carboxyl-terminal tetrapeptide shared by each 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 <sub>1</sub> receptor	CCK <sub>2</sub> receptor
HGNC, UniProt	CCKAR, P32238	CCKBR, P32239
Potency order of endogenous ligands	CCK-8 (CCK, P06307), CCK-58 (CCK, P06307), CCK-39 (CCK), CCK-33 (CCK, P06307) >> gastrin-17 (GAST, P01350), desulfated cholecystokinin-8 > CCK-4 (CCK, P06307)	CCK-8 (CCK, P06307), CCK-39 (CCK), CCK-33 (CCK, P06307), CCK-58 (CCK, P06307) ≥ gastrin-17 (GAST, P01350), desulfated cholecystokinin-8, CCK-4 (CCK, P06307)
Endogenous agonists	CCK-33 (CCK, P06307), CCK-39 (CCK), CCK-58 (CCK, P06307), CCK-8 (CCK, P06307)	desulfated cholecystokinin-8 [1242], gastrin-17 (GAST, P01350) [931] – Mouse, CCK-4 (CCK, P06307) [957], desulfated gastrin-14 (GAST, P01350), desulfated gastrin-17 (GAST, P01350), desulfated gastrin-34 (GAST, P01350), desulfated gastrin-71 (GAST, P01350), gastrin-14 (GAST, P01350), gastrin-34 (GAST, P01350), gastrin-71 (GAST, P01350)
Selective agonists	A-71623 [74] – Rat, JMV180 [1068], GW-5823 [851]	RB-400 [138] – Rat, PBC-264 [974] – Rat
Antagonists	linitript (pIC <sub>50</sub> 8.3) [733]	–
Selective antagonists	devazepide (pIC <sub>50</sub> 9.7) [931] – Rat, T-0632 (pIC <sub>50</sub> 9.6) [2103] – Rat, PD-140548 (pIC <sub>50</sub> 8.6) [1977] – Rat, lorglumide (pIC <sub>50</sub> 6.7–8.2) [931, 963] – Rat	YF-476 (pIC <sub>50</sub> 9.7) [218, 2094], GV150013 (pIC <sub>50</sub> 9.4) [2180], L-740093 (pIC <sub>50</sub> 9.2) [1590], YM-022 (pIC <sub>50</sub> 9.2) [1590], JNJ-26070109 (pIC <sub>50</sub> 8.5) [1510], L-365260 (pIC <sub>50</sub> 8.4) [1242], RP73870 (pIC <sub>50</sub> 8) [1291] – Rat, LY262691 (pIC <sub>50</sub> 7.5) [1773] – Rat
Labelled ligands	[ <sup>3</sup> H]devazepide (Antagonist) (pK <sub>d</sub> 9.7) [338], [ <sup>125</sup> I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [1731]	[ <sup>3</sup> H]PD140376 (Antagonist) (pK <sub>i</sub> 9.7–10) [935] – Guinea pig, [ <sup>125</sup> I]PD142308 (Antagonist) (pK <sub>d</sub> 9.6) [905] – Guinea pig, [ <sup>125</sup> I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [1731], [ <sup>125</sup> I]gastrin (Agonist), [ <sup>3</sup> H]gastrin (Agonist), [ <sup>3</sup> H]L365260 (Antagonist) (pK <sub>d</sub> 8.2–8.5) [1590], [ <sup>125</sup> I]-BDZ <sub>2</sub> (Antagonist) (pK <sub>i</sub> 8.4) [27]

**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 CCK<sub>2</sub> receptor in which intron 4 is retained, adding 69 amino acids to the intracel-

lular loop 3 (ICL3) region, has been described to be present particularly in certain neoplasms where mRNA mis-splicing has been commonly observed [1995], but it is not clear that this receptor splice form plays a special role in carcinogenesis. Another alternative splicing event for the CCK<sub>2</sub> receptor was reported [2012],

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.

### Further reading on Cholecystokinin receptors

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## Class Frizzled GPCRs

G protein-coupled receptors → Class Frizzled GPCRs

**Overview:** Receptors of the Class Frizzled (FZD, **nomenclature as agreed by the NC-IUPHAR subcommittee on the Class Frizzled GPCRs [1902]**), are GPCRs originally identified in *Drosophila* [332], which are highly conserved across species. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it mediates effects in the Hedgehog signaling pathway [1902]. 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  $\beta$ -catenin (*CTNNB1*, P35222) or being  $\beta$ -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  $\beta$ -catenin and subsequently its translocation to the nucleus.  $\beta$ -Catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors.  $\beta$ -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 heterotrimeric G proteins [496, 1694, 1903], the elevation of intracellular calcium [1989], activation of cGMP-specific PDE6 [21] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [802]. Novel resonance energy transfer-based tools have allowed the study of the GPCR-like nature of FZDs in greater detail. Upon ligand stimulation, FZDs undergo conformational changes and signal *via*

heterotrimeric G proteins [2332, 2333]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling. Importantly, FZDs exist in at least two distinct conformational states that regulate the pathway selection [2333]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [354], as well as for  $\beta$ -catenin-dependent [262] and -independent [263, 1084] 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 (DKK)), as well as modulatory (co)-receptors with *Ryk*, *ROR1*, *ROR2* and Kremen, which may also function as independent signalling proteins.

Nomenclature	FZD <sub>1</sub>	FZD <sub>2</sub>	FZD <sub>3</sub>	FZD <sub>4</sub>	FZD <sub>5</sub>
HGNC, UniProt	<a href="#">FZD1, Q9UP38</a>	<a href="#">FZD2, Q14332</a>	<a href="#">FZD3, Q9NPG1</a>	<a href="#">FZD4, Q9ULV1</a>	<a href="#">FZD5, Q13467</a>
Allosteric modulators	–	–	–	FzM1.8 (Negative) (pIC <sub>50</sub> 5.5–7.8) [679], FzM1.8 (Positive) (pEC <sub>50</sub> 6.4) [1799], FzM1 (Negative) (pIC <sub>50</sub> 6.2) [679, 1799]	–
Antibodies	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~9.1) [771]	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~9) [771]	–	–	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~9) [771]
Comments	–	–	–	–	IgG-2919 and IgG-2921 are FZD <sub>5</sub> antibodies that have exhibited antitumour activities <i>in vitro</i> and <i>in vivo</i> (inhibiting the growth of RNF43-mutant pancreatic ductal adenocarcinoma cells/xenograft tumours), by blocking autocrine Wnt-β-catenin signalling in these mutant, FZD <sub>5</sub> -dependent cells [2029].

Nomenclature	FZD <sub>6</sub>	FZD <sub>7</sub>	FZD <sub>8</sub>	FZD <sub>9</sub>	FZD <sub>10</sub>
HGNC, UniProt	<a href="#">FZD6, O60353</a>	<a href="#">FZD7, O75084</a>	<a href="#">FZD8, Q9H461</a>	<a href="#">FZD9, O00144</a>	<a href="#">FZD10, Q9ULW2</a>
Selective antagonists	–	Fz7-21 (pIC <sub>50</sub> 7) [1589]	–	–	–
Antibodies	–	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~9) [771]	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~8) [771]	–	–
Comments	–	–	FZD8-Fc/OMP-54F28 is a FZD <sub>8</sub> antagonist [477].	–	Radio-labelled murine monoclonal antibody MAb 92-13 has been used to demonstrate the therapeutic potential of targeting FZD <sub>10</sub> -positive tumours [639].

Nomenclature	SMO
HGNC, UniProt	SMO, Q99835
Agonists	SMO agonist (SAC) [350] – Mouse, purmorphamine [1978]
Antagonists	MRT-92 (pK <sub>d</sub> 9.5) [890], SANT-1 (pK <sub>i</sub> 7.7) [350] – Mouse, cyclopamine-KAAD (pIC <sub>50</sub> 7.7) [2080] – Mouse, cyclopamine (pIC <sub>50</sub> ~7) [2162] – Mouse
Selective antagonists	vismodegib (pK <sub>i</sub> 7.8) [2252]
Allosteric modulators	GSA-10 (Positive) (pEC <sub>50</sub> 5.9) [726]
Comments	SANT-3 and SANT-4 are SMO antagonists [350].

**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 FZD and SMO coupling to G proteins is incomplete, but progress have been made [72, 496, 1083, 1374, 1808, 1945, 2229, 2332]. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships [1081]. Development of pharmacological tools for SMO has been facilitated by successful crystalization of several SMO structures [278, 924, 2250, 2251, 2279, 2427]. The recently solved FZD4 in apo state has provided first insight into FZD transmembranous organization [2380].

#### 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) (pEC<sub>50</sub> 7.7-8.9 [2332]), 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-4 (RSPO4, Q210M5), sFRP-1 (SFRP1, Q8N474), sFRP-2 (SERP2, Q96HF1), sFRP-3 (ERZB, Q92765), sFRP-4 (SFRP4, Q6FHJ7), sFRP-5 (SFRP5, Q6FHJ7).

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

**Small exogenous ligands:** Foxy-5 [2075], Box-5 [988], UM206 [1189], and XWnt8 (P28026) also known as mini-Wnt8.

**Ligands associated with SMO signalling:** cholesterol, oxysterols [278, 1325, 1761].

#### Further reading on Class Frizzled GPCRs

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## Complement peptide receptors

G protein-coupled receptors → Complement peptide receptors

**Overview:** Complement peptide receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Complement peptide receptors [1114]**) are activated by the endogenous 75 amino-acid anaphylatoxin polypeptides C3a (C3, P01024) and C5a (C5, P01031), generated upon stimulation of the complement cascade. C3a and C5a exert their functions through binding to their receptors (C3aR and C5aR), causing cell activation and triggering cellular degranulation that contributes to the local inflammation.

Nomenclature	C3a receptor	C5a <sub>1</sub> receptor	C5a <sub>2</sub> receptor
HGNC, UniProt	C3AR1, Q16581	C5AR1, P21730	C5AR2, Q9P296
Potency order of endogenous ligands	C3a (C3, P01024) > C5a (C5, P01031) [45]	C5a (C5, P01031), C5a des-Arg (C5) > C3a (C3, P01024) [45]	–
Endogenous agonists	–	ribosomal protein S19 (RPS19, P39019) [2363]	–
Agonists	compound 17 [1786], compound 21 [1785], casoxin C [2082, 2402], albutensin A [2086, 2402], oryzatensin [1003, 2083, 2402]	NDT9513727 (Inverse agonist) [244], N-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO <sub>2</sub> H [1054, 1136], lactomedin 1 [2276, 2402]	–
Selective agonists	–	–	P59 (Biased agonist) [434], P32 (Biased agonist) [434]
Antagonists	SB290157 (pIC <sub>50</sub> 7.6) [44], compound 4 (pIC <sub>50</sub> 5.9) [1785]	avacopan (pIC <sub>50</sub> 9.7) [134], W54011 (pK <sub>i</sub> 8.7) [2056], DF2593A (pIC <sub>50</sub> 8.3) [1499], AcPhe-Orn-Pro-D-Cha-Trp-Arg (pIC <sub>50</sub> 7.9) [2323], N-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO <sub>2</sub> H (pIC <sub>50</sub> 7.2) [1136]	–
Labelled ligands	[ <sup>125</sup> I]C3a (human) (Agonist) [342]	[ <sup>125</sup> I]C5a (human) (Agonist) [929]	[ <sup>125</sup> I]C5a (human) (Agonist)
Comments	C3a-C3aR signalling plays a crucial role in inhibiting neural progenitor cell proliferation during neurodevelopment, playing a critical role in the normal development of the mammalian brain [426].	–	–

**Comments:** SB290157 has also been reported to have agonist properties at the C3a receptor [1396]. The putative chemoattractant receptor termed C5a<sub>2</sub> (also known as GPR77, C5L2) binds [<sup>125</sup>I]C5a with no clear signalling function, but has a putative role opposing inflammatory responses [291, 655, 673]. Binding to this site may be displaced with the rank order C5a des-Arg (C5) > C5a (C5, P01031) [291, 1631] while there is controversy over the abil-

ity of C3a (C3, P01024) and C3a des Arg (C3, P01024) to compete [902, 1029, 1030, 1631]. C5a<sub>2</sub> appears to lack G protein signalling and has been termed a decoy receptor [1910]. However, C5a<sub>2</sub> does recruit arrestin after ligand binding, which might provide a signalling pathway for this receptor [103, 2192], and forms heteromers with C5a<sub>1</sub>. C5a, but not C5a-des Arg, induces upregulation of heteromer formation between complement C5a receptors C5a<sub>1</sub> and

C5a<sub>2</sub> [433]. There are also reports of pro-inflammatory activity of C5a<sub>2</sub>, mediated by HMGB1, but the signaling pathway that underlies this is currently unclear (reviewed in [1271]). More recently, work in T cells has shown that C5a<sub>1</sub> and C5a<sub>2</sub> act in opposition to each other and that altering the equilibrium between the two receptors, by differential expression or production of C5a-des Arg (which favours C5a<sub>2</sub>), can affect the final cellular response [61].

### Further reading on Complement peptide receptors

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## Corticotropin-releasing factor receptors

G protein-coupled receptors → Corticotropin-releasing factor receptors

**Overview:** Corticotropin-releasing factor (CRF, **nomenclature as agreed by the NC-IUPHAR subcommittee on Corticotropin-releasing Factor Receptors [824]**) receptors are activated by the endogenous peptides **corticotrophin-releasing hormone (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. CRF<sub>1</sub> and CRF<sub>2</sub> receptors are activated non-selectively by CRH and UCN. CRF<sub>2</sub> receptors are selectively activated by UCN2 and UCN3. Binding to CRF receptors can be conducted using radioligands [<sup>125</sup>I]Tyr<sup>0</sup>-CRF or [<sup>125</sup>I]Tyr<sup>0</sup>-sauvagine with K<sub>d</sub> values of 0.1-0.4 nM. CRF<sub>1</sub> and CRF<sub>2</sub> receptors are non-selectively antagonized by  $\alpha$ -helical CRF, **D-Phe-CRF-(12-41)** and **astressin**. CRF<sub>1</sub> receptors are selectively antagonized by small molecules **NBI27914**, **R121919**, **antalarmin**, **CP 154,526**, **CP 376,395**. CRF<sub>2</sub> receptors are selectively antagonized by **antisauvagine** and **astressin 2B**.

Nomenclature	CRF <sub>1</sub> receptor	CRF <sub>2</sub> receptor
HGNC, UniProt	CRHR1, P34998	CRHR2, Q13324
Endogenous agonists	urocortin 1 (UCN, P55089) [451, 453, 508], corticotrophin-releasing hormone (CRH, P06850) [353, 450, 453, 508, 1648, 2212]	urocortin 2 (UCN2, Q96RP3) [451], urocortin 3 (UCN3, Q969E3) [451]
Antagonists	SSR125543A (pK <sub>i</sub> 8.7) [766], <b>astressin</b> (pK <sub>i</sub> 8.7) [1812]	<b>astressin</b> (pIC <sub>50</sub> 9.2) [1810]
Selective antagonists	<b>CP 154,526</b> (pIC <sub>50</sub> 9.3–10.4) [1328] – Rat, <b>DMP696</b> (pK <sub>i</sub> 8.3–9) [835], <b>NBI27914</b> (pK <sub>i</sub> 8.3–9) [346], <b>R121919</b> (pK <sub>i</sub> 8.3–9) [2442], <b>antalarmin</b> (pK <sub>i</sub> 8.3–9) [2278], <b>CP 376,395</b> (pIC <sub>50</sub> 8.3) [355] – Rat, <b>CRA1000</b> (pIC <sub>50</sub> 6.4–7.1) [330]	<b>antisauvagine</b> (pK <sub>d</sub> 8.8–9.6) [453], <b>K41498</b> (pK <sub>i</sub> 9.2) [1211], <b>astressin 2B</b> (pIC <sub>50</sub> 8.9) [1810], <b>K31440</b> (pK <sub>i</sub> 8.7–8.8) [1846]

**Comments:** A CRF binding protein has been identified (**CRHBP, P24387**) to which both **corticotrophin-releasing hormone (CRH, P06850)** and **urocortin 1 (UCN, P55089)** bind with high affinities, which has been suggested to bind and inactivate circulating **corticotrophin-releasing hormone (CRH, P06850)** [1686].

### Further reading on Corticotropin-releasing factor receptors

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Corticotropin-releasing factor receptors S68



## Dopamine receptors

G protein-coupled receptors → Dopamine receptors

**Overview:** Dopamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Dopamine Receptors [1906]**) are commonly divided into D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) families, where the endogenous agonist is [dopamine](#).

Nomenclature	D <sub>1</sub> receptor	D <sub>2</sub> receptor
HGNC, UniProt	<a href="#">DRD1</a> , <a href="#">P21728</a>	<a href="#">DRD2</a> , <a href="#">P14416</a>
Sub/family-selective labelled ligands	<a href="#">[<sup>125</sup>I]SCH23982</a> (Antagonist) (pK <sub>d</sub> 9.5) [ <a href="#">478</a> ], <a href="#">[<sup>3</sup>H]SCH-23390</a> (Antagonist) (pK <sub>d</sub> 9.5) [ <a href="#">2435</a> ]	<a href="#">[<sup>3</sup>H]spiperone</a> (Antagonist) (pK <sub>d</sub> 10.2) [ <a href="#">266</a> , <a href="#">888</a> , <a href="#">2433</a> ] – Rat
Endogenous agonists	<a href="#">dopamine</a> [ <a href="#">2060</a> , <a href="#">2132</a> ]	<a href="#">dopamine</a> [ <a href="#">272</a> , <a href="#">628</a> , <a href="#">1876</a> ]
Agonists	<a href="#">fenoldopam</a> [ <a href="#">2132</a> ]	<a href="#">rotigotine</a> [ <a href="#">497</a> ], <a href="#">cabergoline</a> (Partial agonist) [ <a href="#">1451</a> ], <a href="#">aripiprazole</a> (Partial agonist) [ <a href="#">2410</a> ], <a href="#">bromocriptine</a> [ <a href="#">628</a> , <a href="#">1451</a> , <a href="#">1876</a> ], <a href="#">MLS1547</a> (Biased agonist) [ <a href="#">627</a> ], <a href="#">ropinirole</a> [ <a href="#">843</a> ], <a href="#">apomorphine</a> (Partial agonist) [ <a href="#">272</a> , <a href="#">628</a> , <a href="#">1451</a> , <a href="#">1876</a> , <a href="#">2006</a> ], <a href="#">pramipexole</a> [ <a href="#">1446</a> , <a href="#">1876</a> ], <a href="#">benzquinamide</a> [ <a href="#">744</a> ]
Sub/family-selective agonists	<a href="#">A68930</a> [ <a href="#">1569</a> ], <a href="#">SKF-38393</a> (Partial agonist) [ <a href="#">2060</a> , <a href="#">2132</a> ]	<a href="#">quinpirole</a> [ <a href="#">272</a> , <a href="#">1446</a> , <a href="#">1665</a> , <a href="#">2006</a> , <a href="#">2008</a> , <a href="#">2196</a> ]
Selective agonists	<a href="#">SKF-83959</a> (Biased agonist) [ <a href="#">413</a> ], <a href="#">A77636</a> [ <a href="#">1844</a> ], <a href="#">SKF-81297</a> [ <a href="#">50</a> ] – Rat	<a href="#">sumanirole</a> [ <a href="#">1415</a> ]
Antagonists	<a href="#">flupentixol</a> (pK <sub>i</sub> 7–8.4) [ <a href="#">2060</a> , <a href="#">2132</a> ]	<a href="#">blonanserin</a> (pK <sub>i</sub> 9.9) [ <a href="#">1611</a> ], <a href="#">pipotiazine</a> (pK <sub>i</sub> 9.7) [ <a href="#">2007</a> ], <a href="#">perphenazine</a> (pK <sub>i</sub> 8.9–9.6) [ <a href="#">1156</a> , <a href="#">1920</a> ], <a href="#">risperidone</a> (pK <sub>i</sub> 9.4) [ <a href="#">70</a> ], <a href="#">perospirone</a> (pK <sub>i</sub> 9.2) [ <a href="#">1919</a> ], <a href="#">trifluoperazine</a> (pK <sub>i</sub> 8.9–9) [ <a href="#">1156</a> , <a href="#">1920</a> ], <a href="#">quetiapine</a> (pK <sub>i</sub> 7.2) [ <a href="#">70</a> ]
Sub/family-selective antagonists	<a href="#">SCH-23390</a> (pK <sub>i</sub> 7.4–9.5) [ <a href="#">2060</a> , <a href="#">2132</a> ], <a href="#">SKF-83566</a> (pK <sub>i</sub> 9.5) [ <a href="#">2060</a> ], <a href="#">ecopipam</a> (pK <sub>i</sub> 8.3) [ <a href="#">2133</a> ]	<a href="#">haloperidol</a> (pK <sub>i</sub> 7.4–8.8) [ <a href="#">628</a> , <a href="#">1341</a> , <a href="#">1446</a> , <a href="#">2006</a> , <a href="#">2133</a> ]
Selective antagonists	–	<a href="#">L-741,626</a> (pK <sub>i</sub> 7.9–8.5) [ <a href="#">755</a> , <a href="#">1171</a> ], <a href="#">domperidone</a> (pK <sub>i</sub> 7.9–8.4) [ <a href="#">628</a> , <a href="#">2006</a> ], <a href="#">raclopride</a> (pK <sub>i</sub> 8) [ <a href="#">1453</a> ], <a href="#">ML321</a> (pK <sub>i</sub> 7) [ <a href="#">2347</a> , <a href="#">2348</a> ]
Labelled ligands	–	<a href="#">[<sup>3</sup>H]raclopride</a> (Antagonist) (pK <sub>d</sub> 8.9) [ <a href="#">1184</a> ] – Rat

Nomenclature	<b>D<sub>3</sub> receptor</b>	<b>D<sub>4</sub> receptor</b>	<b>D<sub>5</sub> receptor</b>
HGNC, UniProt	<i>DRD3</i> , P35462	<i>DRD4</i> , P21917	<i>DRD5</i> , P21918
Sub/family-selective labelled ligands	–	[ <sup>3</sup> H]spiperone (Antagonist) (pK <sub>d</sub> 9.5) [866, 2196]	[ <sup>3</sup> H]SCH-23390 (Antagonist) (pK <sub>d</sub> 9.2) [1797]
Endogenous agonists	dopamine [272, 628, 1876, 2008]	dopamine [2196]	dopamine [2060]
Agonists	pramipexole [1446, 1876], bromocriptine (Partial agonist) [628, 1451, 1876], ropinirole [843], apomorphine (Partial agonist) [272, 628, 1451, 1876, 2006]	apomorphine (Partial agonist) [1451]	–
Sub/family-selective agonists	quinpirole [272, 1446, 1453, 1665, 1876, 2006, 2008, 2196]	quinpirole [1451, 1665, 2196]	A68930 [1569]
Selective agonists	PD 128907 [1745, 1876]	PD168,077 (Partial agonist) [1141] – Rat, A412997 [1491] – Rat, A412997 [1491]	–
Antagonists	perospirone (pK <sub>i</sub> 9.6) [2006], sertindole (pK <sub>i</sub> 8–8.8) [70, 1901, 1920], prochlorperazine (pK <sub>i</sub> 8.4) [79], (-)-sulpiride (pK <sub>i</sub> 6.7–7.7) [628, 2006, 2102], loxapine (pK <sub>i</sub> 7.7) [1920], domperidone (pK <sub>i</sub> 7.1–7.6) [628, 2006], promazine (pK <sub>i</sub> 6.8) [273]	perospirone (pK <sub>i</sub> 10.1) [1921], sertindole (pK <sub>i</sub> 7.8–9.1) [273, 1920, 1920, 1921], sonopiprazole (pK <sub>i</sub> 8.9) [1892], loxapine (pK <sub>i</sub> 8.1) [1920]	–
Sub/family-selective antagonists	haloperidol (pK <sub>i</sub> 7.5–8.6) [628, 1939, 2006, 2133]	haloperidol (pK <sub>i</sub> 8.7–8.8) [1191, 1939, 2133]	SCH-23390 (pK <sub>i</sub> 7.5–9.5) [2060], SKF-83566 (pK <sub>i</sub> 9.4) [2060], ecopipam (pK <sub>i</sub> 8.3) [2060]
Selective antagonists	S33084 (pK <sub>i</sub> 9.6) [1450], nafadotride (pK <sub>i</sub> 9.5) [1877], PG01037 (pK <sub>i</sub> 9.2) [756], NGB 2904 (pK <sub>i</sub> 8.8) [2343], SB 277011-A (pK <sub>i</sub> 8) [1783], (+)-S-14297 (pK <sub>i</sub> 6.9–7.9) [1448, 1453]	L745870 (pK <sub>i</sub> 9.4) [1171], A-381393 (pK <sub>i</sub> 8.8) [1543], L741742 (pK <sub>i</sub> 8.5) [1831], ML398 (pK <sub>i</sub> 7.4) [154]	–
Selective allosteric modulators	SB269652 (Negative) (pK <sub>i</sub> ~9) [642]	–	–
Labelled ligands	[ <sup>3</sup> H]spiperone (Antagonist) (pK <sub>d</sub> 9.9) [888, 2433] – Rat, [ <sup>3</sup> H]7-OH-DPAT (Agonist) [1798], [ <sup>3</sup> H]PD128907 (Agonist) [29]	[ <sup>125</sup> I]L750667 (Antagonist) (pK <sub>d</sub> 9.8) [1665], [ <sup>3</sup> H]NGD941 (Antagonist) (pK <sub>d</sub> 8.3) [1736]	[ <sup>125</sup> I]SCH23982 (Antagonist) (pK <sub>d</sub> 9.1)

**Comments:** The selectivity of many of these agents is less than two orders of magnitude. [<sup>3</sup>H]raclopride exhibits similar high affinity for D<sub>2</sub> and D<sub>3</sub> receptors (low affinity for D<sub>4</sub>), but has been used to label D<sub>2</sub> receptors in the presence of a D<sub>3</sub>-selective antago-

nist. [<sup>3</sup>H]7-OH-DPAT has similar affinity for D<sub>2</sub> and D<sub>3</sub> receptors, but labels only D<sub>3</sub> receptors in the absence of divalent cations. The pharmacological profile of the D<sub>5</sub> receptor is similar to, yet distinct from, that of the D<sub>1</sub> receptor. The splice variants of the

D<sub>2</sub> receptor are commonly termed D<sub>2S</sub> and D<sub>2L</sub> (short and long). The *DRD4* gene encoding the D<sub>4</sub> receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

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## Endothelin receptors

G protein-coupled receptors → Endothelin receptors

**Overview:** Endothelin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Endothelin Receptors [454]**) are activated by the endogenous 21 amino-acid peptides endothelins 1-3 (**endothelin-1 (EDN1, P05305)**, **endothelin-2 (EDN2, P20800)** and **endothelin-3 (EDN3, P14138)**).

Nomenclature	ET <sub>A</sub> receptor	ET <sub>B</sub> receptor
HGNC, UniProt	EDNRA, P25101	EDNRB, P24530
Potency order of endogenous ligands	endothelin-1 (EDN1, P05305) = endothelin-2 (EDN2, P20800) > endothelin-3 (EDN3, P14138) [1353]	endothelin-1 (EDN1, P05305) = endothelin-2 (EDN2, P20800), endothelin-3 (EDN3, P14138) [1854]
Selective agonists	–	sarafotoxin S6c [1163, 1838], BQ 3020 [1793], [Ala <sup>1,3,11,15</sup> ]ET-1 [1471], IRL 1620 [2268]
Antagonists	SB209670 (pK <sub>B</sub> 9.4) [553] – Rat, TAK 044 (pA <sub>2</sub> 8.4) [2271] – Rat, bosentan (pA <sub>2</sub> 7.2) [403] – Rat	SB209670 (pK <sub>B</sub> 9.4) [553] – Rat, TAK 044 (pA <sub>2</sub> 8.4) [2271] – Rat, bosentan (pK <sub>i</sub> 7.1) [1527]
Selective antagonists	macitentan (pIC <sub>50</sub> 9.3) [192], sitaxsentan (pA <sub>2</sub> 8) [2334], FR139317 (Inverse agonist) (pIC <sub>50</sub> 7.3–7.9) [1353], BQ123 (pA <sub>2</sub> 6.9–7.4) [1353], ambrisentan (pA <sub>2</sub> 7.1) [193]	K-8794 (pIC <sub>50</sub> 8.2) [1951], A192621 (pK <sub>d</sub> 8.1) [2226], BQ788 (pK <sub>d</sub> 7.9–8) [1838], IRL 2500 (pK <sub>d</sub> 7.2) [1838], Ro 46-8443 (pIC <sub>50</sub> 7.2) [232]
Labelled ligands	[ <sup>125</sup> I]PD164333 (Antagonist) (pK <sub>d</sub> 9.6–9.8) [457], [ <sup>3</sup> H]S0139 (Antagonist) (pK <sub>d</sub> 9.2), [ <sup>125</sup> I]PD151242 (Antagonist) (pK <sub>d</sub> 9–9.1) [458], [ <sup>3</sup> H]BQ123 (Antagonist) (pK <sub>d</sub> 8.5) [944]	[ <sup>125</sup> I]IRL1620 (Agonist) [1544], [ <sup>125</sup> I]BQ3020 (Agonist) [810, 1471, 1693], [ <sup>125</sup> I][Ala <sup>1,3,11,15</sup> ]ET-1 (Agonist) [1471]

**Comments:** Splice variants of the ET<sub>A</sub> receptor have been identified in rat pituitary cells; one of these, ET<sub>A</sub>R-C13, appeared to show loss of function with comparable plasma membrane expression to wild type receptor [822]. Subtypes of the ET<sub>B</sub> receptor have been proposed, although gene disruption studies in mice suggest that only a single gene product exists [1465]. Crystal structures of the ET<sub>B</sub> receptor bound to the antagonist bosentan and ET<sub>B</sub> selective analogue K-8794 [1951] and selective ET<sub>B</sub> agonists endothelin-3 (EDN3, P14138) and IRL 1620 [1950] have been reported.

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## G protein-coupled estrogen receptor

G protein-coupled receptors → G protein-coupled estrogen receptor

**Overview:** The G protein-coupled estrogen receptor (GPER, nomenclature as agreed by the **NC-IUPHAR Subcommittee on the G protein-coupled estrogen receptor [1740]**) was identified following observations of estrogen-evoked cyclic AMP signalling in breast cancer cells [71], which mirrored the differential expression of an orphan 7-transmembrane recep-

tor GPR30 [304]. There are observations of both cell-surface and intracellular expression of the GPER receptor [1789, 2123]. Selective agonist/ antagonists for GPER have been characterized [1740]. Antagonists of the nuclear estrogen receptor, such as fulvestrant [596], tamoxifen [1789, 2123] and raloxifene [1700], as well as the flavonoid 'phytoestrogens' genistein and quercetin [1352], are

agonists of GPER. A complete review of GPER pharmacology has been recently published [1740]. The roles of GPER in physiological systems throughout the body (cardiovascular, metabolic, endocrine, immune, reproductive) and in cancer have also been reviewed [595, 1203, 1437, 1740, 1741].

Nomenclature	GPER
HGNC, UniProt	GPER1, Q99527
Agonists	fulvestrant [2123], raloxifene [1700], 4-hydroxytamoxifen [1789]
Selective agonists	G-1 [195]
Selective antagonists	G36 (pIC <sub>50</sub> 6.8–6.9) [485], G15 (pIC <sub>50</sub> 6.7) [484]
Labelled ligands	[ <sup>3</sup> H]17β-estradiol (Agonist) [2123]

**Comments:** Antagonists at the nuclear estrogen receptor, such as fulvestrant, tamoxifen [596] and raloxifene [1700], as well as the flavonoid 'phytoestrogens' genistein and quercetin [1352], are agonists at GPER receptors. A complete review of GPER pharmacology has been recently published [1740].

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## Formylpeptide receptors

G protein-coupled receptors → Formylpeptide receptors

**Overview:** The [formylpeptide receptors](#) (nomenclature agreed by the [NC-IUPHAR Subcommittee on the formylpeptide receptor family \[2387\]](#)) 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  $\beta$ 42, serum amyloid A and [spinorphin](#), derived from  [\$\beta\$ -haemoglobin \(HBB, P68871\)](#).

Nomenclature	<a href="#">FPR1</a>	<a href="#">FPR2/ALX</a>	<a href="#">FPR3</a>
HGNC, UniProt	<a href="#">FPR1, P21462</a>	<a href="#">FPR2, P25090</a>	<a href="#">FPR3, P25089</a>
Potency order of endogenous ligands	<a href="#">fMet-Leu-Phe</a> > <a href="#">cathepsin G (CTSG, P08311)</a> > <a href="#">annexin I (ANXA1, P04083)</a> [1224, 2058]	<a href="#">LXA<sub>4</sub></a> = aspirin triggered lipoxin A4 = <a href="#">ATLa2</a> = <a href="#">resolvin D1</a> > <a href="#">LTC<sub>4</sub></a> = <a href="#">LTD<sub>4</sub></a> $\gg$ <a href="#">15-deoxy-LXA4</a> $\gg$ <a href="#">fMet-Leu-Phe</a> [401, 600, 602, 750, 2086]	–
Endogenous agonists	–	<a href="#">LXA<sub>4</sub></a> [1153], <a href="#">resolvin D1</a> [1153], aspirin-triggered <a href="#">resolvin D1</a> [1152], aspirin triggered lipoxin A4	<a href="#">F2L (HEBP1, Q9NRV9)</a> [1447]
Agonists	<a href="#">fMet-Leu-Phe</a> [630, 1963]	–	–
Selective agonists	–	<a href="#">ATLa2</a> [765]	–
Endogenous antagonists	<a href="#">spinorphin</a> (pIC <sub>50</sub> 4.3) [1275, 1526]	–	–
Antagonists	<a href="#">t-Boc-FLFLF</a> (pK <sub>i</sub> 6–6.5) [2288]	–	–
Selective antagonists	<a href="#">cyclosporin H</a> (pK <sub>i</sub> 6.1–7.1) [2288, 2370]	<a href="#">WRWWWW</a> (pIC <sub>50</sub> 6.6) [92], <a href="#">t-Boc-FLFLF</a> (pIC <sub>50</sub> 4.3–6) [629, 2030, 2245]	–
Labelled ligands	<a href="#">[<sup>3</sup>H]fMet-Leu-Phe</a> (Agonist) [1137]	<a href="#">[<sup>3</sup>H]LXA<sub>4</sub></a> (Agonist) [600, 601]	–
Comments	A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [833].	–	–

**Comments:** Note that the data for FPR2/ALX are also reproduced on the [leukotriene](#) receptor page.

### Further reading on Formylpeptide receptors

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## Free fatty acid receptors

G protein-coupled receptors → Free fatty acid receptors

**Overview:** Free fatty acid receptors (FFA, **nomenclature as agreed by the NC-IUPHAR Subcommittee on free fatty acid receptors [455, 2039]**) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (including C14.0 (myristic acid), C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (linoleic acid), C18:3, ( $\alpha$ -linolenic acid), C20:4 (arachidonic acid), C20:5,n-3 (EPA) and C22:6,n-3 (docosahexaenoic acid)) activate FFA1 [239, 958, 1144] and FFA4 receptors [876, 938, 1617], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA2 [249, 1223, 1591] and FFA3 [249, 1223] receptors. The crystal structure for agonist bound FFA1 has been described [2023].

Nomenclature	FFA1 receptor	FFA2 receptor
HGNC, UniProt	<i>FFAR1</i> , O14842	<i>FFAR2</i> , O15552
Endogenous agonists	docosahexaenoic acid [239, 958], $\alpha$ -linolenic acid [239, 958, 1144], oleic acid [239, 958, 1144], myristic acid [239, 958, 1144]	propanoic acid [249, 1223, 1591, 1894], acetic acid [249, 1223, 1591, 1894], butyric acid [249, 1223, 1591, 1894], <i>trans</i> -2-methylcrotonic acid [1894], 1-methylcyclopropanecarboxylic acid [1894]
Selective agonists	AMG-837 [1286], compound 4 [381], TUG-770 [380], TUG-905 [379], GW9508 (Partial agonist) [238], fasiglifam [1028, 1558, 2023, 2157]	TUG-1375 [801]
Selective antagonists	GW1100 (pIC <sub>50</sub> 6) [238, 2038]	GLPG0974 (pIC <sub>50</sub> 8.1) [1546, 1715], CATPB (pIC <sub>50</sub> 6.5) [927]
Comments	A wide range of both saturated and unsaturated fatty acids containing from 6 to 22 carbons have been shown to act as agonists at FFA1 [239, 958, 1144]. Antagonist GW1100 is also an oxytocin receptor antagonist [238]. Fasiglifam, TUG-770 and GW9508 are approximately 100 fold selective for FFA1 over FFA4 [238, 380, 1558]. AMG-837 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 [1286, 2353].	

Nomenclature	FFA3 receptor	FFA4 receptor	GPR42
HGNC, UniProt	FFAR3, O14843	FFAR4, Q5NUL3	GPR42, O15529
Endogenous agonists	propanoic acid [249, 1223, 1894, 2352], butyric acid [249, 1223, 1894, 2352], 1-methylcyclopropanecarboxylic acid [1894]	$\alpha$ -linolenic acid [1955], myristic acid [2275], $\alpha$ -linolenic acid [2100] – Rat, oleic acid [2275]	–
Agonists	acetic acid [249, 1223, 1894, 2352]	–	–
Selective agonists	–	compound A [1616], TUG-891 [1955], NCG21 [2065]	–
Comments	Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [1095]. A range of FFA3 selective molecules with agonist and antagonist properties, but which bind at sites distinct from the short chain fatty acid binding site ( <i>i.e.</i> allosteric modulators), have been described [196, 926, 1337].	A wide range of both saturated and unsaturated fatty acids containing from 6 to 22 carbons have been shown to act as agonists at FFA4 [382] with a small subset listed above. Compound A [PMID 24997608] exhibits more than 1000 fold selectivity [1616], and TUG-891 50-1000 fold selectivity for FFA4 over FFA1 [1955], dependent on the assay. NCG21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [2057].	–

**Comments:** Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [1490], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [2275]. The long FFA4 splice variant has not been identified in other primates or rodents to date [876, 1490]. *GPR42* was originally described as a pseudogene within the family (ENSM0025000002583), but the discovery of several polymorphisms suggests that some versions of GPR42 may be functional [1276]. *GPR84* is a structurally-unrelated G protein-coupled receptor which has been found to respond to medium chain fatty acids [2254].

### Further reading on Free fatty acid receptors

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# GABA<sub>B</sub> receptors

G protein-coupled receptors → GABA<sub>B</sub> receptors

**Overview:** Functional GABA<sub>B</sub> receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on GABA<sub>B</sub> receptors** [215, 1710]) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub> [215, 557, 1709, 1710, 2173]. GABA<sub>B</sub> receptors are widespread in the CNS and regulate both pre- and postsynaptic activity. The GABA<sub>B1</sub> subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10–100-fold less than for the native receptor. Co-expression of GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits allows transport of GABA<sub>B1</sub> to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca<sup>2+</sup> channels (Ca<sub>v</sub>2.1, Ca<sub>v</sub>2.2), or inwardly rectifying potassium channels (Kir3) [159, 215, 216]. The GABA<sub>B1</sub> subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) versus flytrap module (VTM), whereas the GABA<sub>B2</sub> subunit mediates G protein-coupled signalling [215, 681, 683, 1709]. The two

subunits interact by direct allosteric coupling [1485], such that GABA<sub>B2</sub> increases the affinity of GABA<sub>B1</sub> for agonists and reciprocally GABA<sub>B1</sub> facilitates the coupling of GABA<sub>B2</sub> to G proteins [681, 1161, 1709]. GABA<sub>B1</sub> and GABA<sub>B2</sub> 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<sub>B1</sub> subunit but other domains of the proteins also contribute to their heteromerization [159, 270, 1709]. Recent evidence indicates that higher order assemblies of GABA<sub>B</sub> receptor comprising dimers of heterodimers occur in recombinant expression systems and *in vivo* and that such complexes exhibit negative functional cooperativity between heterodimers [409, 1708]. Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA<sub>B2</sub> subunit to impart altered signalling kinetics and agonist potency to the receptor complex [116, 1907, 2160] and are re-

viewed by [1711]. The molecular complexity of GABA<sub>B</sub> receptors is further increased through association with trafficking and effector proteins [Schwenk *et al.*, 2016, *Nature Neuroscience* 19(2): 233–42] and reviewed by [1707]. Four isoforms of the human GABA<sub>B1</sub> subunit have been cloned. The predominant GABA<sub>B1a</sub> and GABA<sub>B1b</sub> isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA<sub>B1a</sub>-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA<sub>B1b</sub>-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [1749, 2216]. Only the 1a and 1b variants are identified as components of native receptors [215]. Additional GABA<sub>B1</sub> subunit isoforms have been described in rodents and humans [1236] and reviewed by [159].

Nomenclature	GABA <sub>B</sub> receptor
Subunits	GABA <sub>B1</sub> , GABA <sub>B2</sub> , kctd12b (Accessory protein), KCTD16 (Accessory protein), KCTD12 (Accessory protein), KCTD8 (Accessory protein)
Agonists	CGP 44532 [635] – Rat, (-)-baclofen [635] – Rat, 3-APPA [881], baclofen [881, 2327], 3-APMPA [2327]
Antagonists	CGP 62349 (pK <sub>i</sub> 8.5–8.9) [881, 2327], CGP 55845 (pK <sub>i</sub> 7.8) [2327], SCH 50911 (pK <sub>i</sub> 5.5–6) [881, 2327], CGP 35348 (pK <sub>i</sub> 4.4) [2327], 2-hydroxy-saclofen (pIC <sub>50</sub> 4.1) [1052] – Rat
Allosteric modulators	rac-BHFF (Positive) (pEC <sub>50</sub> 6.6) [1366], GS39783 (Positive) (pK <sub>B</sub> 4.7) [849, 2182], compound 14 (Negative) (pIC <sub>50</sub> 4.4) [351], CGP7930 (Positive) [2181]
Labelled ligands	[ <sup>3</sup> H]CGP 54626 (Antagonist) (pK <sub>i</sub> 9.1) [1015] – Rat, [ <sup>3</sup> H]CGP 62349 (Antagonist) (pK <sub>d</sub> 9.1) [1060] – Rat, [ <sup>125</sup> I]CGP 64213 (Antagonist) (pK <sub>d</sub> 9) [650] – Rat, [ <sup>125</sup> I]CGP 71872 (Antagonist) (pK <sub>d</sub> 9) [1052] – Rat, [ <sup>3</sup> H](R)-(-)-baclofen (Agonist)

## Subunits

Nomenclature	GABA <sub>B1</sub>	GABA <sub>B2</sub>
HGNC, UniProt	GABBR1, Q9UBSS	GABBR2, O75899



**Comments:** Potencies of agonists and antagonists listed in the table, quantified as IC<sub>50</sub> values for the inhibition of [<sup>3</sup>H]CGP27492 binding to rat cerebral cortex membranes, are from [215, 634, 635]. Radioligand K<sub>D</sub> values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the GABA<sub>B1</sub> subunit [137]. CGP27492 (3-APPA), CGP35024 (3-APMPA) and CGP 44532 act as antagonists at human GABA<sub>A</sub> ρ1 receptors, with potencies in the low micromolar range [634]. In addition to the ligands listed in the table, Ca<sup>2+</sup> binds to the VTm of the GABA<sub>B1</sub>

subunit to act as a positive allosteric modulator of GABA [650]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 [2223] and (+)-BHF [9, 159, 166, 634]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA<sub>B2</sub> subunit [534, 1709]. In the presence of CGP7930 or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [634]. A negative allosteric modulator of GABA<sub>B</sub> activity has been reported [351]. Knock-out of the GABA<sub>B1</sub> subunit in C57B mice causes

the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA<sub>B1</sub><sup>-/-</sup> BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but not familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety [563, 2184]. A similar phenotype has been found for GABA<sub>B2</sub><sup>-/-</sup> BALB/c mice [669].

### Further reading on GABA<sub>B</sub> receptors

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# Galanin receptors

G protein-coupled receptors → Galanin receptors

**Overview:** Galanin receptors (**provisional nomenclature as recommended by NC-IUPHAR [612]**) 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 [579]; 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 [155] and porcine galanin-5–29 [1970]) and N-terminally extended forms (*e.g.* N-terminally seven and nine residue elongated forms of porcine galanin [156, 1970]) have been reported.

Nomenclature	<i>GAL</i> <sub>1</sub> receptor	<i>GAL</i> <sub>2</sub> receptor	<i>GAL</i> <sub>3</sub> receptor
HGNC, UniProt	<i>GALR1</i> , P47211	<i>GALR2</i> , O43603	<i>GALR3</i> , O60755
Potency order of endogenous ligands	galanin ( <i>GAL</i> , P22466) > galanin-like peptide ( <i>GALP</i> , Q9UBC7) [1623]	galanin-like peptide ( <i>GALP</i> , Q9UBC7) ≥ galanin ( <i>GAL</i> , P22466) [1623]	galanin-like peptide ( <i>GALP</i> , Q9UBC7) > galanin ( <i>GAL</i> , P22466) [1197]
Agonists	–	galanin(2-29) (rat/mouse) [1651, 2257, 2258, 2259] – Rat	–
Selective agonists	–	[D-Trp <sup>2</sup> ]galanin-(1-29) [1996] – Rat	–
Selective antagonists	2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC <sub>50</sub> 5.6) [1914]	M871 (pK <sub>i</sub> 7.9) [2010]	SNAP 398299 (pK <sub>i</sub> 8.3) [1132, 1133, 2069], SNAP 37889 (pK <sub>i</sub> 7.8–7.8) [1132, 1133, 2069]
Selective allosteric modulators	–	CYM2503 (Positive) (pEC <sub>50</sub> 9.2) [1322] – Rat	–
Labelled ligands	[ <sup>125</sup> I][Tyr <sup>26</sup> ]galanin (human) (Agonist) [608], [ <sup>125</sup> I][Tyr <sup>26</sup> ]galanin (human) (Agonist) [608]	[ <sup>125</sup> I][Tyr <sup>26</sup> ]galanin (human) (Agonist) [2258] – Rat	[ <sup>125</sup> I][Tyr <sup>26</sup> ]galanin (pig) (Agonist) [207, 1997]
Comments	–	The CYM2503 PAM potentiates the anticonvulsant activity of endogenous galanin in mouse seizure models [1322].	–

**Comments:** Galanin-(1-11) is a high-affinity agonist at *GAL*<sub>1</sub>/*GAL*<sub>2</sub> (pK<sub>i</sub> 9), and galanin(2-11) is selective for *GAL*<sub>2</sub> and *GAL*<sub>3</sub> compared with *GAL*<sub>1</sub> [1321]. [<sup>125</sup>I]-[Tyr<sup>26</sup>]galanin binds to all three subtypes with K<sub>d</sub> values generally reported to range from 0.05 to 1 nM, depending on the assay conditions used [608, 1982, 1996, 1997, 2258]. Porcine galanin-(3-29) does not bind to cloned *GAL*<sub>1</sub>, *GAL*<sub>2</sub> or *GAL*<sub>3</sub> receptors, but a receptor that is functionally activated by porcine galanin-(3–29) has been reported in pituitary

and gastric smooth muscle cells [758, 2342]. 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 [2171], spinal cord [2307], locus coeruleus, hippocampus [114] and hypothalamus [115, 1249], but exhibit agonist activity at some peripheral sites [115, 758]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at *GAL*<sub>1</sub> receptors expressed endogenously in Bowes

human melanoma cells [1623], and at heterologously expressed recombinant *GAL*<sub>1</sub>, *GAL*<sub>2</sub> and *GAL*<sub>3</sub> receptors [608, 1996, 1997]. Recent studies have described the synthesis of a series of novel, systemically-active, galanin analogues, with modest preferential binding at the *GAL*<sub>2</sub> 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 [1847].

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

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full>

# Ghrelin receptor

G protein-coupled receptors → Ghrelin receptor

**Overview:** The ghrelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [456]**) is 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 preproghrelin, although the mature peptides from rat and human differ by only two amino acids [1399]. Alternative splicing results

in the formation of a second peptide, [*des-Gln*<sup>14</sup>]ghrelin (*GHRL*, *Q9UBU3*) with equipotent biological activity [907]. A unique post-translational modification (octanoylation of Ser<sup>3</sup>, catalysed by ghrelin *O*-acyltransferase (*MBOAT4*, *Q96T53*) [2374] occurs in both peptides, essential for full activity in binding to ghrelin receptors in the hypothalamus and pituitary, and for the release of growth hormone from the pituitary [1128]. Structure activity studies showed the first five N-terminal amino acids to be

the minimum required for binding [131], 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 [899]. In cell systems, the ghrelin receptor is constitutively active [900], 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 [1652].

Nomenclature	ghrelin receptor
HGNC, UniProt	<i>GHSR</i> , <i>Q92847</i>
Potency order of endogenous ligands	ghrelin ( <i>GHRL</i> , <i>Q9UBU3</i> ) = [ <i>des-Gln</i> <sup>14</sup> ]ghrelin ( <i>GHRL</i> , <i>Q9UBU3</i> ) [130, 1399]
Antagonists	liver enriched antimicrobial peptide 2 ( <i>LEAP2</i> , <i>Q969E1</i> ) (pIC <sub>50</sub> 8.2) [675]
Selective antagonists	<i>GSK1614343</i> (pIC <sub>50</sub> 8.4) [1848], <i>GSK1614343</i> (pK <sub>B</sub> 8) [1684] – Rat
Labelled ligands	[ <sup>125</sup> I][His <sup>9</sup> ]ghrelin (human) (Agonist) [1051], [ <sup>125</sup> I][Tyr <sup>4</sup> ]ghrelin (human) (Agonist) [1515]

**Comments:** [*des-octanoyl*]ghrelin (*GHRL*, *Q9UBU3*) has been shown to bind (as [<sup>125</sup>I]Tyr<sup>4</sup>-*des-octanoyl*-ghrelin) and have effects in the cardiovascular system [130], which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been

identified ([D-Arg<sup>1</sup>,D-Phe<sup>5</sup>,D-Trp<sup>7,9</sup>,Leu<sup>11</sup>]substance P, pD<sub>2</sub> 8.3; [897]). Ulimorelin, described as a ghrelin receptor agonist (pK<sub>i</sub> 7.8 and pD<sub>2</sub> 7.5 at human recombinant ghrelin receptors), has been shown to stimulate ghrelin receptor mediated food intake and gastric emptying but not elicit release of growth hormone, or modify ghrelin stimulated growth hormone release, thus pharmacolog-

ically discriminating the orexigenic and gastrointestinal actions of ghrelin (*GHRL*, *Q9UBU3*) from the release of growth hormone [622]. A number of selective antagonists have been reported, including peptidomimetic [1514] and non-peptide small molecules including *GSK1614343* [1684, 1848].

## Further reading on Ghrelin receptor

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# Glucagon receptor family

G protein-coupled receptors → Glucagon receptor family

**Overview:** The glucagon family of receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the Glucagon receptor family [1410]**) are activated by the endogenous peptide (27-44 aa) hormones **glucagon** (*GCG*, P01275), **glucagon-like peptide 1** (*GCG*, P01275), **glucagon-like peptide 2** (*GCG*, P01275), **glucose-dependent insulinotropic polypeptide** (also known as **gastric inhibitory polypeptide** (*GIP*, P09681)), **GHRH** (*GHRH*, P01286) and **secretin** (*SCT*, P09683). One common precursor (*GCG*) generates **glucagon** (*GCG*, P01275), **glucagon-like peptide 1** (*GCG*, P01275) and **glucagon-like peptide 2** (*GCG*, P01275) peptides [952]. For a recent review on review the current understanding of the structures of GLP-1 and GLP-1R, the molecular basis of their interaction, and the signaling events associated with it, see de Graaf et al, 2016 [736].

Nomenclature	GHRH receptor	GIP receptor	GLP-1 receptor
HGNC, UniProt	<i>GHRHR</i> , Q02643	<i>GIPR</i> , P48546	<i>GLP1R</i> , P43220
Endogenous agonists	GHRH ( <i>GHRH</i> , P01286)	gastric inhibitory polypeptide ( <i>GIP</i> , P09681) [2225]	glucagon-like peptide 1-(7-36) amide ( <i>GCG</i> , P01275) [1020], glucagon-like peptide 1-(7-37) ( <i>GCG</i> , P01275) [498]
Agonists	Jl-38 [289], sermorelin	–	liraglutide [11199], lixisenatide [2290], WB4-24 [583]
Selective agonists	BIM28011 [431], tesamorelin	–	semaglutide [1206], exendin-4 [1460], exendin-4 [1020], exendin-3 (P20394) [1776]
Selective antagonists	JV-1-36 (pK <sub>i</sub> 10.1–10.4) [1886, 2205, 2206] – Rat, JV-1-38 (pK <sub>i</sub> 10.1) [1886, 2205, 2206] – Rat	[Pro <sup>3</sup> ]GIP [672] – Mouse	exendin-(9-39) (pK <sub>i</sub> 8.1) [1020], GLP-1-(9-36) (pIC <sub>50</sub> 6.9) [1486] – Rat, T-0632 (pIC <sub>50</sub> 4.7) [2131]
Labelled ligands	[ <sup>125</sup> I]GHRH (human) (Agonist) [212] – Rat	[ <sup>125</sup> I]GIP (human) (Agonist) [648] – Rat	[ <sup>125</sup> I]GLP-1-(7-36)-amide (Agonist) [1020], [ <sup>125</sup> I]exendin-(9-39) (Antagonist) (pK <sub>d</sub> 8.3) [1020], [ <sup>125</sup> I]GLP-1-(7-37) (human) (Agonist)

Nomenclature	GLP-2 receptor	glucagon receptor	secretin receptor
HGNC, UniProt	<i>GLP2R</i> , O95838	<i>GCCR</i> , P47871	<i>SCTR</i> , P47872
Endogenous agonists	glucagon-like peptide 2 ( <i>GCG</i> , P01275) [2128]	glucagon ( <i>GCG</i> , P01275) [1718]	secretin ( <i>SCT</i> , P09683) [376]
Agonists	teduglutide [1423]	NNC1702 [2418]	–
Selective antagonists	–	L-168,049 (pIC <sub>50</sub> 8.4) [312], adomeglivant (pK <sub>i</sub> 8.2) [1059, 1063], des-His <sup>1</sup> -[Glu <sup>9</sup> ]glucagon-NH <sub>2</sub> (pA <sub>2</sub> 7.2) [2176, 2177] – Rat, NNC 92-1687 (pK <sub>i</sub> 5) [1345], BAY27-9955 [1695]	[(CH <sub>2</sub> NH) <sup>4,5</sup> ]secretin (pK <sub>i</sub> 5.3) [776]
Labelled ligands	–	[ <sup>125</sup> I]glucagon (human, mouse, rat) (Agonist)	[ <sup>125</sup> I](Tyr <sup>10</sup> )secretin-27 (rat) (Agonist) [2172] – Rat

**Comments:** The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically **RAMP2**, in heterologous expression systems [384], although the physiological significance of this has yet to be established.

### Further reading on Glucagon receptor family

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## Glycoprotein hormone receptors

G protein-coupled receptors → Glycoprotein hormone receptors

**Overview:** Glycoprotein hormone receptors (**provisional nomenclature [612]**) are activated by a non-covalent heterodimeric glycoprotein made up of a common  $\alpha$  chain (glycoprotein hormone common alpha subunit (CGA, P01215) CGA, P01215), with a unique  $\beta$  chain that confers the biological specificity to FSH (CGA FSHB, P01215 P01225), LH (CGA LHB, P01215 P01229), hCG (CGA CGB3, P01215 P01233) or TSH (CGA TSHB, P01215 P01222). 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 [1850].

Nomenclature	FSH receptor	LH receptor	TSH receptor
HGNC, UniProt	FSHR, P23945	LHCGR, P22888	TSHR, P16473
Potency order of endogenous ligands	FSH (CGA FSHB, P01215 P01225)	LH (CGA LHB, P01215 P01229), hCG (CGA CGB3, P01215 P01233) [997, 1534]	TSH (CGA TSHB, P01215 P01222)
Labelled ligands	[ <sup>125</sup> I]FSH (human) (Agonist)	[ <sup>125</sup> I]LH (Agonist), [ <sup>125</sup> I]chorionic gonadotropin (human) (Agonist)	[ <sup>125</sup> I]TSH (human) (Agonist)

### Further reading on Glycoprotein hormone receptors

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# Gonadotrophin-releasing hormone receptors

G protein-coupled receptors → Gonadotrophin-releasing hormone receptors

**Overview:** GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors (**provisonal nomenclature [612]**, also called Type I and Type II GnRH receptor, respectively [1456]) have been cloned from numerous species, most of which express two or three types of GnRH receptor [1455, 1456, 1971]. GnRH I (*GNRH1*, P01148) (p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH<sub>2</sub>) is a hypothalamic decapeptide also known as luteinizing hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin or simply as GnRH. It is a member of a family of similar peptides found in many species [1455, 1456, 1971] including GnRH II (*GNRH2*, O43555) (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-

Pro-Gly-NH<sub>2</sub> (which is also known as chicken GnRH-II). Receptors for three forms of GnRH exist in some species but only GnRH I and GnRH II and their cognate receptors have been found in mammals [1455, 1456, 1971]. GnRH<sub>1</sub> receptors are expressed by pituitary gonadotrophs, where they mediate the effects of GnRH on gonadotropin hormone synthesis and secretion that underpin central control of mammalian reproduction. GnRH analogues are used in assisted reproduction and to treat steroid hormone-dependent conditions [1079]. Notably, agonists cause desensitization of GnRH-stimulated gonadotropin secretion and the con-

sequent reduction in circulating sex steroids is exploited to treat hormone-dependent cancers of the breast, ovary and prostate [1079]. GnRH<sub>1</sub> receptors are selectively activated by GnRH I and all lack the COOH-terminal tails found in other GPCRs. GnRH<sub>2</sub> receptors do have COOH-terminal tails and (where tested) are selective for GnRH II over GnRH I. GnRH<sub>2</sub> receptors are expressed by some primates but not by humans [1496]. Phylogenetic classifications divide GnRH receptors into three [1456] or five groups [2311] and highlight examples of gene loss through evolution, with humans retaining only one ancient gene.

Nomenclature	GnRH <sub>1</sub> receptor	GnRH <sub>2</sub> receptor
HGNC, UniProt	<i>GNRHR</i> , P30968	<i>GNRHR2</i> , Q96P88
Potency order of endogenous ligands	GnRH I ( <i>GNRH1</i> , P01148) > GnRH II ( <i>GNRH2</i> , O43555) [1456]	GnRH II ( <i>GNRH2</i> , O43555) > GnRH I ( <i>GNRH1</i> , P01148) (Monkey) [1454]
Endogenous agonists	GnRH I ( <i>GNRH1</i> , P01148) [1323], GnRH II ( <i>GNRH2</i> , O43555) [606, 1323, 2032]	GnRH II ( <i>GNRH2</i> , O43555) [1454] – Monkey, GnRH I ( <i>GNRH1</i> , P01148) [1454, 1456] – Monkey
Selective agonists	buserelin [1555], buserelin [1554], buserelin [1554], triptorelin [127], leuprolide [2045], goserelin, histrelin, nafarelin	–
Antagonists	itirelix (pK <sub>i</sub> 9.5) [1811]	–
Selective antagonists	cetrorelix (pK <sub>i</sub> 9.3–10) [128, 129, 2045], abarelix (pK <sub>i</sub> 9.1–9.5) [2045], degarelix (pK <sub>i</sub> 8.8) [2194], ganirelix	trptorelix-1 [1357] – Monkey
Labelled ligands	[ <sup>125</sup> I]cetrorelix (Antagonist) (pK <sub>d</sub> 9.7) [892], [ <sup>125</sup> I]triptorelin (Agonist) [480] – Rat, [ <sup>125</sup> I]buserelin (Agonist) [1178] – Rat, [ <sup>125</sup> I]GnRH I (human, mouse, rat) (Agonist)	–

**Comments:** GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors couple primarily to G<sub>q/11</sub> [752] but coupling to G<sub>s</sub> and G<sub>i</sub> is evident in some systems [1157, 1178]. GnRH<sub>2</sub> receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [319]. 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 [357, 814, 1284, 1885]. In some human cancer cell models GnRH II (*GNRH2*, O43555) is more potent than GnRH I (*GNRH1*, P01148), implying mediation by GnRH<sub>2</sub> receptors [757], but GnRH<sub>2</sub> receptors are not expressed

by humans because the human *GNRHR2* gene contains a frame shift and internal stop codon [1496]. The possibility remains that this gene generates GnRH<sub>2</sub> receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (*GNRH2*, O43555) (see [1560]). Alternatively, evidence for multiple active GnRH receptor conformations [319, 320, 597, 1407, 1456] raises the possibility that GnRH<sub>1</sub> receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon a conformation that couples to G<sub>i</sub> rather than G<sub>q/11</sub> proteins as in pituitary cells [320, 1407]. Loss-of-function mutations in the GnRH<sub>1</sub> 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' GnRH<sub>1</sub> receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists [1230]. Human GnRH<sub>1</sub> receptors are poorly expressed at the cell surface because of failure to meet structural quality control criteria for endoplasmic reticulum exit [598, 1232], and this increases susceptibility to point mutations that further impair trafficking [598, 1230]. GnRH receptor signalling may require receptor oligomerisation [412, 1155].

### Further reading on Gonadotrophin-releasing hormone receptors

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## GPR18, GPR55 and GPR119

G protein-coupled receptors → GPR18, GPR55 and GPR119

**Overview:** GPR18, GPR55 and GPR119 (**provisional nomenclature**), although showing little structural similarity to CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands [1692]. Although there are multiple reports to indicate that GPR18, GPR55 and GPR119 can be activated *in vitro* by N-arachidonoylglycine, lysophosphatidylinositol and N-oleoylethanolamide, respectively, there is a lack of evidence for activation by these lipid messengers *in vivo*. As such, therefore, these receptors retain their orphan status.

Nomenclature	GPR18	GPR55	GPR119
HGNC, UniProt	GPR18, Q14330	GPR55, Q9Y2T6	GPR119, Q8TDV5
Potency order of endogenous ligands	–	–	N-oleoylethanolamide, N-palmitoylethanolamine > SEA (anandamide is ineffective) [1643]
Endogenous agonists	N-arachidonoylglycine [1126]	lysophosphatidylinositol [852, 1625, 2015], 2-arachidonoylglycerolphosphoinositol [1627]	N-oleoylethanolamide [389, 1643, 2015], N-palmitoylethanolamine, SEA
Selective agonists	–	AM251 [852, 1042, 1843]	AS1269574 [2400], PSN632408 [1643], PSN375963 [1643]
Selective antagonists	–	CID16020046 (apparent pA <sub>2</sub> ) (pA <sub>2</sub> 7.3) [1044], ML193 (pIC <sub>50</sub> 6.7) [865]	–
Comments	The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on arrestin assays [2015, 2389]. See [455] for discussion.	See reviews [455] and [1961].	In addition to those shown above, further small molecule agonists have been reported [793].

**Comments:** GPR18 failed to respond to a variety of lipid-derived agents in an *in vitro* screen [2389], but has been reported to be activated by Δ<sup>9</sup>-tetrahydrocannabinol [1422]. GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB<sub>1</sub> receptor antagonists/inverse agonists [1692]. It has been reported that lysophosphatidylinositol acts at other sites in addition to GPR55 [2367]. N-Arachidonoylserine has been suggested to act as a low efficacy agonist/antagonist at GPR18 *in vitro* [1420]. It has also been suggested oleoyl-lysophosphatidylcholine acts, at least in part, through GPR119 [1592]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleoylethanolamide-mediated responses suggests additional mechanisms of action [1592].

### Further reading on GPR18, GPR55 and GPR119

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## Histamine receptors

G protein-coupled receptors → Histamine receptors

**Overview:** Histamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors [871, 1653]**) are activated by the endogenous ligand **histamine**. Marked species differences exist between histamine receptor orthologues [871]. The human and rat H<sub>3</sub> receptor genes are subject to significant splice variance [100]. The potency order of his-

tamine at histamine receptor subtypes is H<sub>3</sub> = H<sub>4</sub> > H<sub>2</sub> > H<sub>1</sub> [1653]. Some agonists at the human H<sub>3</sub> receptor display significant ligand bias [1803]. Antagonists of all 4 histamine receptors have clinical uses: H<sub>1</sub> antagonists for allergies (*e.g.* **cetirizine**), H<sub>2</sub> antagonists for acid-reflux diseases (*e.g.* **ranitidine**), H<sub>3</sub> antagonists for narcolepsy (*e.g.* **pitolisant**/WAKIX; Registered) and

H<sub>4</sub> antagonists for atopic dermatitis (*e.g.* **ZPL-3893787**; Phase IIa) [1653] and vestibular neuritis (AUV) (SENS-111 (Seliforant, previously UR-63325), entered and completed vestibular neuritis (AUV) Phase IIa efficacy and safety trials, respectively) [75, 2213].

Nomenclature	H <sub>1</sub> receptor	H <sub>2</sub> receptor
HGNC, UniProt	<i>HRH1</i> , P35367	<i>HRH2</i> , P25021
Selective agonists	methylhistaprodifen [1923], histaprodifen [1283]	amthamine [1149]
Antagonists	cyproheptadine (pK <sub>i</sub> 10.2) [1469], promethazine (pK <sub>i</sub> 9.6) [697], mepyramine (Inverse agonist) (pK <sub>i</sub> 8.7–9) [204, 1775], cetirizine (Inverse agonist) (pK <sub>i</sub> 8.2) [1469], diphenhydramine (pK <sub>i</sub> 7.9) [204]	–
Selective antagonists	clemastine (pK <sub>i</sub> 10.3) [79], desloratadine (pK <sub>i</sub> 9) [1266], triprolidine (pK <sub>i</sub> 8.5–9) [204, 1469], azelastine (pK <sub>i</sub> 8.9) [1738], astemizole (pK <sub>i</sub> 8.5) [1673]	tiotidine (pK <sub>i</sub> 7.5) [161] – Rat, ranitidine (pK <sub>i</sub> 7.1) [1262], cimetidine (pK <sub>i</sub> 6.8) [299]
Labelled ligands	[ <sup>3</sup> H]pyrilamine (Antagonist, Inverse agonist) (pK <sub>d</sub> 8.4–9.1) [464, 1469, 1901, 1923], [ <sup>11</sup> C]doxepin (Antagonist) (pK <sub>d</sub> 9) [955], [ <sup>11</sup> C]pyrilamine (Antagonist, Inverse agonist)	[ <sup>125</sup> I]iodoaminopotentidine (Antagonist) (pK <sub>d</sub> 8.7) [1185] – Rat, [ <sup>3</sup> H]tiotidine (Antagonist) (pK <sub>d</sub> 7.7–8.7) [1480]



Nomenclature	<a href="#">H<sub>3</sub> receptor</a>	<a href="#">H<sub>4</sub> receptor</a>
HGNC, UniProt	<a href="#">HRH3</a> , <a href="#">Q9Y5N1</a>	<a href="#">HRH4</a> , <a href="#">Q9H3N8</a>
Selective agonists	<a href="#">immethridine</a> [1110], <a href="#">methimepip</a> [1109], <a href="#">MK-0249</a> (Inverse agonist) [1536]	<a href="#">clobenpropit</a> (Partial agonist) [570, 1283, 1298, 1299, 1509], <a href="#">4-methylhistamine</a> [674, 1283], <a href="#">ST-1006</a> [1653], <a href="#">VUF 8430</a> [1282]
Antagonists	<a href="#">iodophenpropit</a> (p <i>K</i> <sub>i</sub> 8.2–8.7) [2305, 2338]	–
Selective antagonists	<a href="#">pitolisant</a> (p <i>K</i> <sub>i</sub> 8.1–8.6) [1653, 2447], <a href="#">A331440</a> (p <i>K</i> <sub>i</sub> 8.5) [794], <a href="#">conessine</a> (p <i>K</i> <sub>i</sub> 8.3) [1653], <a href="#">MK-0249</a> (p <i>K</i> <sub>i</sub> 8.2) [1653], <a href="#">thioperamide</a> (Selective for H <sub>3</sub> /H <sub>4</sub> compared to H <sub>1</sub> and H <sub>3</sub> .) (p <i>K</i> <sub>i</sub> 7.1–7.7) [404, 569, 570, 1280, 1320, 2305, 2338], <a href="#">ciproxifan</a> (p <i>K</i> <sub>i</sub> 6.7–7.3) [404, 569, 570, 1280, 1653, 2338]	<a href="#">ZPL-3893787</a> (p <i>K</i> <sub>i</sub> 8.3) [1653], <a href="#">INCB-38579</a> (p <i>K</i> <sub>i</sub> 8.3) [1653], <a href="#">JNJ 7777120</a> (p <i>K</i> <sub>i</sub> 7.8–8.3) [1283, 2001, 2129], <a href="#">JNJ-39758979</a> (p <i>K</i> <sub>i</sub> 7.9) [1653, 1878], <a href="#">thioperamide</a> (Selective for H <sub>3</sub> /H <sub>4</sub> compared to H <sub>1</sub> and H <sub>3</sub> .) (p <i>K</i> <sub>i</sub> 6.3–7.6) [569, 570, 1298, 1299, 1509, 2441]
Labelled ligands	<a href="#">[<sup>123</sup>I]iodoproxyfan</a> (Antagonist) (p <i>K</i> <sub>d</sub> 10.2) [1280], <a href="#">[<sup>125</sup>I]iodophenpropit</a> (Antagonist) (p <i>K</i> <sub>d</sub> 9.2) [980] – Rat, <a href="#">[<sup>3</sup>H](R)-α-methylhistamine</a> (Agonist) [1298], <a href="#">N-[<sup>3</sup>H]α-methylhistamine</a> (Agonist) [349] – Mouse	<a href="#">[<sup>3</sup>H]JNJ 7777120</a> (Antagonist) (p <i>K</i> <sub>d</sub> 8.4) [2129]

**Comments:** [Histaprodifen](#) and [methylhistaprodifen](#) are reduced efficacy agonists. The H<sub>4</sub> receptor appears to exhibit broadly similar pharmacology to the H<sub>3</sub> receptor for imidazole-containing ligands, although [\(R\)-α-methylhistamine](#) and [N-α-methylhistamine](#) are less potent, while [clobenpropit](#) acts as a reduced efficacy agonist at the H<sub>4</sub> receptor and an antagonist at the H<sub>3</sub> receptor [1298, 1542, 1579, 1612, 2441]. Moreover, [4-methylhistamine](#) is identified as a high affinity, full agonist for the human H<sub>4</sub> receptor [1283]. [\[<sup>3</sup>H\]histamine](#) has been used to label the H<sub>4</sub> receptor in heterologous expression systems.

#### Further reading on Histamine receptors

- Gbahou F *et al.* (2012) The histamine autoreceptor is a short isoform of the H<sub>3</sub> receptor. *Br. J. Pharmacol.* **166**: 1860-71 [PMID:22356432]
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- van Rijn RM *et al.* (2008) Cloning and characterization of dominant negative splice variants of the human histamine H<sub>4</sub> receptor. *Biochem. J.* **414**: 121-31 [PMID:18452403]

# Hydroxycarboxylic acid receptors

G protein-coupled receptors → Hydroxycarboxylic acid receptors

**Overview:** The hydroxycarboxylic acid family of receptors (ENSM00500000271913, nomenclature as agreed by the NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors [455, 1614]) 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 [2004, 2159, 2320]. These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA<sub>2</sub> receptors only and is unlikely to be the natural ligand [2159, 2320].

Nomenclature	HCA <sub>1</sub> receptor	HCA <sub>2</sub> receptor	HCA <sub>3</sub> receptor
HGNC, UniProt	<i>HCAR1</i> , Q9BXC0	<i>HCAR2</i> , Q8TDS4	<i>HCAR3</i> , P49019
Potency order of endogenous ligands	–	β-D-hydroxybutyric acid > butyric acid	–
Endogenous agonists	L-lactic acid [18, 290, 1300, 2015]	β-D-hydroxybutyric acid [2077], butyric acid	3-hydroxyoctanoic acid [17]
Agonists	compound 2 [1853], 3,5-dihydroxybenzoic acid [1297]	SCH 900271 [1646], GSK256073 [2022]	–
Selective agonists	–	MK 6892 [1946], MK 1903 [180], nicotinic acid [2004, 2159, 2320], acipimox [2004, 2320], monomethyl fumarate [2101]	compound 6o [1981], IBC 293 [1925]
Labelled ligands	–	[ <sup>3</sup> H]nicotinic acid (Agonist) [2004, 2159, 2320]	–

**Comments:** Further closely-related GPCRs include the 5-oxoeicosanoid receptor (*OXER1*, Q8TDS5) and *GPR31* (O00270). Lactate activates HCA<sub>1</sub> on adipocytes in an autocrine manner. It inhibits lipolysis and thereby promotes anabolic effects. HCA<sub>2</sub> and HCA<sub>3</sub> regulate adipocyte lipolysis and immune functions under conditions of increased FFA formation through lipolysis (e.g., during fasting). HCA<sub>2</sub> agonists acting mainly through the receptor on immune cells exert antiatherogenic and anti-inflammatory effects. HCA<sub>2</sub> is also a receptor for butyrate and mediates some of the beneficial effects of short-chain fatty acids produced by gut microbiota. HCA<sub>3</sub> has been shown to be activated by aromatic D-amino acids.

## Further reading on Hydroxycarboxylic acid receptors

- Boatman PD *et al.* (2008) Nicotinic acid receptor agonists. *J. Med. Chem.* **51**: 7653-62 [PMID:18983141]
- Graff EC *et al.* (2016) Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. *Metab. Clin. Exp.* **65**: 102-13 [PMID:26773933]
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- Offermanns S *et al.* (2015) Nutritional or pharmacological activation of HCA(2) ameliorates neuroinflammation. *Trends Mol Med* **21**: 245-55 [PMID:25766751]

## Kisspeptin receptor

G protein-coupled receptors → Kisspeptin receptor

**Overview:** The kisspeptin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the kisspeptin receptor [1102]**), like neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) re-

sponds 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. Kisspeptins have roles in, for example, cancer metastasis, fertility/puberty regulation and glucose homeostasis.

Nomenclature	kisspeptin receptor
HGNC, UniProt	<i>KISS1R</i> , Q969F8
Endogenous agonists	kisspeptin-10 ( <i>KISS1</i> ) [1142, 1624], kisspeptin-54 ( <i>KISS1</i> , Q15726) [1142, 1624], kisspeptin-14 ( <i>KISS1</i> , Q15726) [1142], kisspeptin-13 ( <i>KISS1</i> , Q15726) [1142]
Selective agonists	4-fluorobenzoyl-FGLRW-NH <sub>2</sub> [2143], [d-Yr] <sup>1</sup> KP-10 [439] – Mouse, TAK-448 [1593]
Selective antagonists	peptide 234 [1822]
Labelled ligands	[ <sup>125</sup> I]Tyr <sup>45</sup> -kisspeptin-15 (Agonist) [1624], [ <sup>125</sup> I]kisspeptin-13 (human) (Agonist) [1427], [ <sup>125</sup> I]kisspeptin-10 (human) (Agonist) [1142], [ <sup>125</sup> I]kisspeptin-14 (human) (Agonist) [1427], [d-Tyr- <sup>14</sup> C]TAK-448 (Agonist) [1502]

**Comments:** 2-acylamino-4,6-diphenylpyridine derivatives have been described and are the first small molecule kisspeptin receptor antagonists reported with potential for treatment of sex-hormone dependent diseases such as prostate cancer and endometriosis [1120].

### Further reading on Kisspeptin receptor

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- Kanda S *et al.* (2013) Structure, synthesis, and phylogeny of kisspeptin and its receptor. *Adv. Exp. Med. Biol.* **784**: 9–26 [PMID:23550000]
- Kirby HR *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. *Pharmacol. Rev.* **62**: 565–78 [PMID:21079036]
- Oakley AE *et al.* (2009) Kisspeptin signaling in the brain. *Endocr. Rev.* **30**: 713–43 [PMID:19770291]
- Pasquier J *et al.* (2014) Molecular evolution of GPCRs: Kisspeptin/kisspeptin receptors. *J. Mol. Endocrinol.* **52**: T101–17 [PMID:24577719]

# Leukotriene receptors

G protein-coupled receptors → Leukotriene receptors

**Overview:** The leukotriene receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene Receptors [279, 280]**) are activated by the endogenous ligands leukotrienes (LT), synthesized from lipoxygenase metabolism of arachidonic acid. The human BLT<sub>1</sub> receptor is the high affinity LTB<sub>4</sub> receptor whereas the BLT<sub>2</sub> receptor in addition to being a low-affinity LTB<sub>4</sub> receptor also binds several other lipoxygenase-products, such as **12S-HETE, 12S-HPETE, 15S-HETE**, and the thromboxane synthase product

**12-hydroxyheptadecatrienoic acid**. The BLT receptors mediate chemotaxis and immunomodulation in several leukocyte populations and are in addition expressed on non-myeloid cells, such as vascular smooth muscle and endothelial cells. In addition to BLT receptors, LTB<sub>4</sub> has been reported to bind to the peroxisome proliferator activated receptor (PPAR)  $\alpha$  [1288] and the vanilloid TRPV1 ligand-gated nonselective cation channel [1421]. The receptors for the cysteinyl-leukotrienes (*i.e.* LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>) are termed CysLT<sub>1</sub> and CysLT<sub>2</sub> and exhibit distinct expression pat-

terns in human tissues, mediating for example smooth muscle cell contraction, regulation of vascular permeability, and leukocyte activation. There is also evidence in the literature for additional CysLT receptor subtypes, derived from functional in vitro studies, radioligand binding and in mice lacking both CysLT<sub>1</sub> and CysLT<sub>2</sub> receptors [280]. Cysteinyl-leukotrienes have also been suggested to signal through the P2Y<sub>12</sub> receptor [625, 1600, 1659], GPR17 [395] and GPR99 [1036].

Nomenclature	BLT <sub>1</sub> receptor	BLT <sub>2</sub> receptor	CysLT <sub>1</sub> receptor	CysLT <sub>2</sub> receptor	OXE receptor	FPR2/ALX
HGNC, UniProt	<i>LTBR</i> , Q15722	<i>LTBR2</i> , Q9NPC1	<i>CYSLTR1</i> , Q9Y271	<i>CYSLTR2</i> , Q9NS75	<i>OXER1</i> , Q8TDS5	<i>FPR2</i> , P25090
Potency order of endogenous ligands	LTB <sub>4</sub> > 20-hydroxy-LTB <sub>4</sub> >> 12R-HETE [2395]	12-hydroxyheptadecatrienoic acid > LTB <sub>4</sub> > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE > 20-hydroxy-LTB <sub>4</sub> [1633, 2395]	LTD <sub>4</sub> > LTC <sub>4</sub> > LTE <sub>4</sub> [1333, 1867]	LTC <sub>4</sub> ≥ LTD <sub>4</sub> >> LTE <sub>4</sub> [844, 1604, 2087]	5-oxo-EETE, 5-oxo-C20:3, 5-oxo-ODE > 5-oxo-15-HETE > 5S-HPETE > 5S-HETE [739, 908, 1013, 1607, 1664, 1729, 1908]	LXA <sub>4</sub> = aspirin triggered lipoxin A4 = ATLa2 = resolvin D1 > LTC <sub>4</sub> = LTD <sub>4</sub> >> 15-deoxy-LXA4 >> fMet-Leu-Phe [401, 600, 602, 750, 2086]
Endogenous agonists	–	–	–	–	–	LXA <sub>4</sub> [1153], resolvin D1 [1153], aspirin-triggered resolvin D1 [1152], aspirin triggered lipoxin A4
Selective agonists	–	–	–	–	–	ATLa2 [765]
Endogenous antagonists	–	–	–	–	5-oxo-12-HETE (pIC <sub>50</sub> 6.3) [1728]	–
Antagonists	–	–	pranlukast (pK <sub>i</sub> 7.1–8.8) [301, 1777], pobilukast (pK <sub>i</sub> 7.1) [303]	pranlukast (pA <sub>2</sub> 7.1) [302], pobilukast (pA <sub>2</sub> 6.2) [302]	–	–
Selective antagonists	BIIL 260 (pK <sub>i</sub> 8.8) [168, 536], CP105696 (pIC <sub>50</sub> 8.1) [1964], U75302 (pK <sub>i</sub> 6.4) [189]	LY255283 (pIC <sub>50</sub> 6–7.1) [859, 2395]	ICI198615 (pK <sub>i</sub> 9.7) [646] – Guinea pig, zafirlukast (zafirlukast is only about 100-fold selective for CysLT <sub>1</sub> ) (pK <sub>i</sub> 8.9) [301, 1777], montelukast (pK <sub>i</sub> 8.6) [1777], MK-571 (pIC <sub>50</sub> 8) [1333]	BayCysLT <sub>2</sub> (pA <sub>2</sub> 8.4) [306], BayCysLT <sub>2</sub> (pA <sub>2</sub> 8.3) [306], HAMI3379 (pIC <sub>50</sub> 7.4) [2339]	–	WRWWWW (pIC <sub>50</sub> 6.6) [92], t-Boc-FLFLF (pIC <sub>50</sub> 4.3–6) [629, 2030, 2245]
Labelled ligands	[ <sup>3</sup> H]LTB <sub>4</sub> (Agonist) [2394], [ <sup>3</sup> H]CGS23131 (Antagonist) (pK <sub>d</sub> 7.9) [965]	[ <sup>3</sup> H]LTB <sub>4</sub> (pK <sub>d</sub> 7.6–9.7)	[ <sup>3</sup> H]LTD <sub>4</sub> (Agonist), [ <sup>3</sup> H]ICI-198615 (Antagonist) (pK <sub>d</sub> 10.6) [1830]	[ <sup>3</sup> H]LTD <sub>4</sub> (Agonist) [844]	[ <sup>3</sup> H]5-oxo-EETE (Agonist) [1607]	[ <sup>3</sup> H]LXA <sub>4</sub> (Agonist) [600, 601]

**Comments:** The FPR2/ALX receptor (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene and Lipoxin Receptors [280]**) is activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A<sub>4</sub> (LXA<sub>4</sub>) and 15-epi-LXA<sub>4</sub> (aspirin triggered lipoxin A<sub>4</sub>, ATL). The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide [365] as well as **annexin I (ANXA1, P04083)** (ANXA1) and its N-terminal peptides [415, 1688]. 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 [1788]. Furthermore, FPR2/ALX has been suggested to act as a receptor mediating the proinflammatory actions of the acute-phase reactant, serum amyloid A [2002, 2047]. The agonist activity of the lipid mediators described has been questioned [804, 1716], which may derive from batch-to-batch differences, partial agonism or biased agonism. Results from Cooray *et al.* (2013) [415] have addressed this issue and the role of homodimers and heterodimers in intracellular signaling. A receptor selective for LXB<sub>4</sub> has been suggested from functional studies [64, 1343, 1818]. Note that the data for FPR2/ALX are also

reproduced on the [Formylpeptide receptor pages](#).

Oxoecosanoid receptors (OXE, **nomenclature agreed by the NC-IUPHAR subcommittee on Oxoecosanoid Receptors [236]**) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-E<sub>2</sub>E the most potent agonist identified for this receptor. Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as **docosahexaenoic acid** and **EPA**, acted as receptor antagonists [908].

### Further reading on Leukotriene receptors

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Bäck M *et al.* (2011) International Union of Basic and Clinical Pharmacology. LXXXIV: leukotriene receptor nomenclature, distribution, and pathophysiological functions. *Pharmacol. Rev.* **63**: 539-84 [PMID:21771892]

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## Lysophospholipid (LPA) receptors

G protein-coupled receptors → Lysophospholipid (LPA) receptors

**Overview:** Lysophosphatidic acid (LPA) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid Receptors [455, 1080]**) are activated by the endogenous phospholipid LPA. The first receptor, LPA<sub>1</sub>, was identified as *ventricular zone gene-1 (vzg-1)* [840], leading to deorphanisation of members of the endothelial differentiation gene (*edg*) family as other LPA receptors along with sphingosine 1-phosphate (S1P) receptors. Additional LPA receptor GPCRs were later identified. Gene names have been codified as *LPAR1*, *etc.* to reflect the receptor function of proteins. The crystal structure of LPA<sub>1</sub> was solved and demonstrates extracellular LPA access to the

binding pocket, consistent with proposed delivery *via* autotaxin [378]. These studies have also implicated cross-talk with endocannabinoids *via* phosphorylated intermediates that can also activate these receptors. 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. Binding affinities of unlabeled, natural LPA and AEAp to LPA<sub>1</sub> were measured using backscattering interferometry (pK<sub>d</sub> = 9) [1466]. Binding affinities were 77-fold lower than values obtained using radioactivity [2371]. 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 TGFα "shedding" assay [949]. LPA has also been described as an agonist for the transient receptor potential (Trp) ion channel TRPV1 [1586] and TRPA1 [1111]. LPA was originally proposed to be a ligand for GPCR35, but data show that in fact it is a receptor for **CXCL17 (CXCL17, Q6UXB2)** [1379]. All of these proposed non-GPCR receptor identities require confirmation and are not currently recognized as *bona fide* LPA receptors.

Nomenclature	LPA <sub>1</sub> receptor	LPA <sub>2</sub> receptor	LPA <sub>3</sub> receptor	LPA <sub>4</sub> receptor	LPA <sub>5</sub> receptor	LPA <sub>6</sub> receptor
HGNC, UniProt	<a href="#">LPAR1</a> , <a href="#">Q92633</a>	<a href="#">LPAR2</a> , <a href="#">Q9HBW0</a>	<a href="#">LPAR3</a> , <a href="#">Q9UBY5</a>	<a href="#">LPAR4</a> , <a href="#">Q99677</a>	<a href="#">LPAR5</a> , <a href="#">Q9H1C0</a>	<a href="#">LPAR6</a> , <a href="#">P43657</a>
Selective agonists	–	dodecylphosphate [2221], decyl dihydrogen phosphate [2221], <a href="#">GRI977143</a> [1106]	<a href="#">OMPT</a> [818]	–	–	–
Antagonists	<a href="#">Ki16425</a> (pIC <sub>50</sub> 6.6–6.9) [1622] – Mouse, <a href="#">VPC12249</a> (pK <sub>i</sub> 5.2–6.9) [846] – Mouse, <a href="#">VPC32179</a> [839]	–	<a href="#">VPC12249</a> (pK <sub>i</sub> 6.4) [846], <a href="#">VPC32179</a> [839]	–	–	–
Sub/family-selective antagonists	–	–	<a href="#">Ki16425</a> (pK <sub>i</sub> 6.4) [1622]	–	–	–
Selective antagonists	<a href="#">BMS-986020</a> (pIC <sub>50</sub> 8.9), <a href="#">AM966</a> (pIC <sub>50</sub> 6.7–7.8) [2068], <a href="#">ONO-7300243</a> (pIC <sub>50</sub> 6.8) [2108], <a href="#">AM095</a> (pIC <sub>50</sub> 6–6.1) [2068]	–	<a href="#">dioctanoylglycerol pyrophosphate</a> (pK <sub>i</sub> 5.5–7) [604, 1622]	–	<a href="#">AS2717638</a> (pIC <sub>50</sub> 7.4) [1521], <a href="#">TCLPA5</a> (pIC <sub>50</sub> 6.1) [1148]	–

**Comments:** [Ki16425](#) [1622], [VPC12249](#) [846] and [VPC32179](#) [839] have dual antagonist activity at LPA<sub>1</sub> and LPA<sub>3</sub> receptors. There is growing evidence for *in vivo* efficacy of these chemical antagonists in several disorders, including fetal hydrocephalus [2408], fetal hypoxia [857], lung fibrosis [1618], systemic sclerosis [1618] and atherosclerosis progression [1154]. The LPA<sub>2</sub> selective agonist, [GRI977143](#), also shows efficacy in an animal model of multiple sclerosis [1896]. The LPA<sub>5</sub> selective antagonist, [AS2717638](#), is effective in pain models [1058].

### Further reading on Lysophospholipid (LPA) receptors

Chun J *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol. Rev.* **62**: 579–87 [PMID:21079037]  
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## Lysophospholipid (S1P) receptors

G protein-coupled receptors → Lysophospholipid (S1P) receptors

**Overview:** Sphingosine 1-phosphate (S1P) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors [1080]**) are activated by the endogenous lipid [sphingosine 1-phosphate](#) (S1P). Originally cloned as orphan members of the endothelial differentiation gene (*edg*) family, current gene names have been designated as S1P<sub>1</sub>R through S1P<sub>5</sub>R [884]. S1PRs, particularly S1P<sub>1</sub>, are expressed throughout all mammalian organ systems. Ligand delivery occurs *via* two known carriers (or "chaperones"): albumin and HDL-bound apolipoprotein M (ApoM), the latter of which elicits biased agonist signaling by S1P<sub>1</sub> in multiple cell types [173, 649]. The five S1PRs, two chaperones, and active cellular metabolism have complicated analyses of receptor ligand binding in native systems. Signaling pathways and physiological roles have been characterized through radioligand binding in heterologous expression sys-

tems, targeted deletion of the different S1PRs, and most recently, mouse models that report *in vivo* S1PR1 activation [1134, 1135]. A crystal structure of an S1P<sub>1</sub>-T4 fusion protein confirmed aspects of ligand binding, specificity, and receptor activation determined

previously through biochemical and genetic studies [172, 805]. **Fingolimod** (FTY720), the first drug to target any of the lysophospholipid receptors, binds to four of the five S1PRs, and was the first oral therapy for multiple sclerosis [390]. The mechanisms of

action of fingolimod and other S1PR modulating drugs in development include binding S1PRs in multiple organ systems, *e.g.*, immune and nervous systems, although the precise nature of their receptor interactions requires clarification [405, 753, 754, 1739].

Nomenclature	S1P <sub>1</sub> receptor	S1P <sub>2</sub> receptor	S1P <sub>3</sub> receptor	S1P <sub>4</sub> receptor	S1P <sub>5</sub> receptor
HGNC, UniProt	<i>S1PR1</i> , P21453	<i>S1PR2</i> , O95136	<i>S1PR3</i> , Q99500	<i>S1PR4</i> , O95977	<i>S1PR5</i> , Q9H228
Potency order of endogenous ligands	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate [49, 1628]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate [49, 1628]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate [1628]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate [2189]	sphingosine 1-phosphate > dihydro sphingosine 1-phosphate [946]
Agonists	fingolimod-phosphate [237, 615], siponimod [709, 1649], etrasimod [275]	–	fingolimod-phosphate [237, 615], fingolimod-phosphate [237, 615]	fingolimod-phosphate [237, 615, 1650, 1864, 2362], etrasimod [274, 275]	fingolimod-phosphate [237, 615, 1650], siponimod [671, 694, 2178], etrasimod [275]
Selective agonists	RP-001 [288], ponesimod [191], cenerimod [1703], CYM5442 [721], SEW2871 [1864] – Mouse	–	CYM-5541 [1004]	CYM-50308 [2179]	A-971432 [490, 889]
Antagonists	VPC23019 (pK <sub>i</sub> 7.9) [460], VPC03090-P (pK <sub>i</sub> 7.6–7.7) [1069], VPC44116 (pIC <sub>50</sub> 7.6) [616]	–	VPC44116 (pK <sub>i</sub> 6.5) [616], VPC23019 (pK <sub>i</sub> 5.9) [460]	–	–
Selective antagonists	NIBR-0213 (pIC <sub>50</sub> 8.6) [1751], W146 (pK <sub>i</sub> 7.1) [1865]	JTE-013 (pIC <sub>50</sub> 7.8) [1638]	TY-52156 (pK <sub>i</sub> 7) [1522]	CYM-50358 (pIC <sub>50</sub> 7.6) [325, 761]	–

**Comments:** The FDA-approved immunomodulator **fingolimod** (FTY720) is phosphorylated *in vivo* [33] to generate an agonist with activity at S1P<sub>1</sub>, S1P<sub>3</sub>, S1P<sub>4</sub> and S1P<sub>5</sub> receptors [237, 1371]. Many of the physiological consequences of **fingolimod-phosphate** ad-

ministration, as well as those of other currently described S1P<sub>1</sub> agonists, may involve functional antagonism *via* ubiquitination and subsequent degradation of S1P<sub>1</sub> [1637]. Additionally, receptor specificities of the different compounds may depend on the

functional assay system utilized and from which species the receptor sequence originated.

### Further reading on Lysophospholipid (S1P) receptors

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Pyne NJ *et al.* (2017) Sphingosine 1-Phosphate Receptor 1 Signaling in Mammalian Cells. *Molecules* **22**: [PMID:28241498]  
 Rosen H *et al.* (2013) Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. *Annu. Rev. Biochem.* **82**: 637–62 [PMID:23527695]  
 Yanagida K *et al.* (2017) Vascular and Immunobiology of the Circulatory Sphingosine 1-Phosphate Gradient. *Annu. Rev. Physiol.* **79**: 67–91 [PMID:27813829]

## Melanin-concentrating hormone receptors

G protein-coupled receptors → Melanin-concentrating hormone receptors

**Overview:** Melanin-concentrating hormone (MCH) receptors (**provisional nomenclature as recommended by NC-IUPHAR [612]**) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRPCWQV; mammalian MCH) generated from a precursor (*PMCH*, P20382), which also produces **neuropeptide EI** (*PMCH*, P20382) and **neuropeptide GE** (*PMCH*, P20382).

Nomenclature	MCH <sub>1</sub> receptor	MCH <sub>2</sub> receptor
HGNC, UniProt	<i>MCHR1</i> , Q99705	<i>MCHR2</i> , Q969V1
Selective antagonists	GW803430 (pIC <sub>50</sub> 9.3) [860], SNAP-7941 (pA <sub>2</sub> 9.2) [206], T-226296 (pIC <sub>50</sub> 8.3) [2093], ATC0175 (pIC <sub>50</sub> 7.9–8.1) [329]	–
Labelled ligands	[ <sup>125</sup> I]S36057 (Antagonist) (pK <sub>d</sub> 9.2–9.5) [77], [ <sup>125</sup> I][Phe <sup>13</sup> , Tyr <sup>19</sup> ]MCH (Agonist) [269], [ <sup>3</sup> H]MCH (human, mouse, rat) (Agonist) [269]	–

**Comments:** The MCH<sub>2</sub> receptor appears to be a non-functional pseudogene in rodents [2098].

### Further reading on Melanin-concentrating hormone receptors

- Chung S *et al.* (2011) Recent updates on the melanin-concentrating hormone (MCH) and its receptor system: lessons from MCH1R antagonists. *J. Mol. Neurosci.* **43**: 115–21 [PMID:20582487]
- Eberle AN *et al.* (2010) Cellular models for the study of the pharmacology and signaling of melanin-concentrating hormone receptors. *J. Recept. Signal Transduct. Res.* **30**: 385–402 [PMID:21083507]
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- Takase K *et al.* (2014) Meta-analysis of melanin-concentrating hormone signaling-deficient mice on behavioral and metabolic phenotypes. *PLoS ONE* **9**: e99961 [PMID:24924345]



# Melanocortin receptors

G protein-coupled receptors → Melanocortin receptors

**Overview:** Melanocortin receptors (**provisional nomenclature as recommended by NC-IUPHAR [612]**) are activated by members of the melanocortin family ( $\alpha$ -MSH (*POMC*, P01189),  $\beta$ -MSH (*POMC*, P01189) and  $\gamma$ -MSH (*POMC*, P01189) forms;  $\delta$  form is not found in mammals) and adrenocorticotrophin (*ACTH* (*POMC*, P01189)). Endogenous antagonists include agouti (*ASIP*, P42127) and agouti-related protein (*AGRP*, O00253). *ACTH*(1-24) was approved by the US FDA as a diagnostic agent for adrenal function test, whilst NDP-MSH was approved by EMA for the treatment of erythropoietic protoporphyria. Several synthetic melanocortin receptor agonists are under clinical development.

Nomenclature	MC <sub>1</sub> receptor	MC <sub>2</sub> receptor	MC <sub>3</sub> receptor	MC <sub>4</sub> receptor	MC <sub>5</sub> receptor
HGNC, UniProt	<i>MC1R</i> , Q01726	<i>MC2R</i> , Q01718	<i>MC3R</i> , P41968	<i>MC4R</i> , P32245	<i>MC5R</i> , P33032
Potency order of endogenous agonists	$\alpha$ -MSH ( <i>POMC</i> , P01189) > $\beta$ -MSH ( <i>POMC</i> , P01189) > <i>ACTH</i> ( <i>POMC</i> , P01189), $\gamma$ -MSH ( <i>POMC</i> , P01189)	<i>ACTH</i> ( <i>POMC</i> , P01189)	$\gamma$ -MSH ( <i>POMC</i> , P01189), $\beta$ -MSH ( <i>POMC</i> , P01189) > <i>ACTH</i> ( <i>POMC</i> , P01189), $\alpha$ -MSH ( <i>POMC</i> , P01189)	$\beta$ -MSH ( <i>POMC</i> , P01189) > $\alpha$ -MSH ( <i>POMC</i> , P01189), <i>ACTH</i> ( <i>POMC</i> , P01189) > $\gamma$ -MSH ( <i>POMC</i> , P01189)	$\alpha$ -MSH ( <i>POMC</i> , P01189) > $\beta$ -MSH ( <i>POMC</i> , P01189) > <i>ACTH</i> ( <i>POMC</i> , P01189) > $\gamma$ -MSH ( <i>POMC</i> , P01189)
Selective agonists	–	corticotropin zinc hydroxide	[D-Trp <sup>8</sup> ] $\gamma$ -MSH [745]	THIQ [1916]	–
Antagonists	–	–	PG-106 (pIC <sub>50</sub> 6.7) [746]	–	–
Selective antagonists	–	–	–	MBP10 (pIC <sub>50</sub> 10) [132], HS014 (pK <sub>i</sub> 8.5) [1891]	–
Labelled ligands	[ <sup>125</sup> I]NDP-MSH (Agonist) [1138]	[ <sup>125</sup> I] <i>ACTH</i> -(1-24) (Agonist)	[ <sup>125</sup> I]NDP-MSH (Agonist) [1138], [ <sup>125</sup> I]SHU9119 (Antagonist) [1581]	[ <sup>125</sup> I]SHU9119 (Antagonist) (pK <sub>d</sub> 9.2) [1581], [ <sup>125</sup> I]NDP-MSH (Agonist) [1138, 1889]	[ <sup>125</sup> I]NDP-MSH (Agonist) [1138]

**Comments:** Polymorphisms of the MC<sub>1</sub> receptor have been linked to variations in skin pigmentation. Defects of the MC<sub>2</sub> receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC<sub>4</sub> receptor have been linked to obesity [328, 586].

## Further reading on Melanocortin receptors

- Caruso V *et al.* (2014) Synaptic changes induced by melanocortin signalling. *Nat. Rev. Neurosci.* **15**: 98-110 [PMID:24588018]
- Renquist BJ *et al.* (2011) Physiological roles of the melanocortin MC<sub>3</sub> receptor. *Eur. J. Pharmacol.* **660**: 13-20 [PMID:21211527]
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# Melatonin receptors

G protein-coupled receptors → Melatonin receptors

**Overview:** Melatonin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Melatonin Receptors [525]**) are activated by the endogenous ligands **melatonin** and clinically used drugs like **ramelteon**, **agomelatine** and **tasimelteon**.

Nomenclature	<b>MT<sub>1</sub> receptor</b>	<b>MT<sub>2</sub> receptor</b>
HGNC, UniProt	<b><i>MTNR1A</i>, P48039</b>	<b><i>MTNR1B</i>, P49286</b>
Endogenous agonists	<b>melatonin [78, 524, 526]</b>	<b>melatonin [78, 524, 526]</b>
Agonists	<b>ramelteon [1049], agomelatine [78, 146], tasimelteon [1759]</b>	<b>agomelatine [78, 146], ramelteon [1049, 1778], tasimelteon [1759]</b>
Selective agonists	–	<b>UCM1014 [2016], IIK7 [587, 2051], 5-methoxy-luzindole (Partial agonist) [526]</b>
Selective antagonists	–	<b>4P-PDOT (pK<sub>i</sub> 8.8–9.4) [78, 526, 527], K185 (pK<sub>i</sub> 9.3) [587, 2051], DH97 (pK<sub>i</sub> 8) [2107]</b>
Labelled ligands	<b>[<sup>125</sup>I]SD6 (Agonist) [1245], 2-[<sup>125</sup>I]melatonin (Agonist) [78, 526], [<sup>3</sup>H]melatonin (Agonist) [254]</b>	<b>[<sup>125</sup>I]SD6 (Agonist) [1245], 2-[<sup>125</sup>I]melatonin (Agonist) [78, 526], [<sup>125</sup>I]DIV880 (Agonist, Partial agonist) [1245], [<sup>3</sup>H]melatonin (Agonist) [254]</b>

**Comments:** **Melatonin**, **2-iodo-melatonin**, **agomelatine**, **GR 196429**, **LY 156735** and **ramelteon [1049]** are nonselective agonists for MT<sub>1</sub> and MT<sub>2</sub> receptors. (-)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT<sub>1</sub> receptors (see **AMMTC** for structure) [2136]. **Luzindole** is an MT<sub>1</sub>/MT<sub>2</sub> non-selective competitive melatonin receptor antagonist with about 15–25 fold selectivity for the MT<sub>2</sub> receptor [527]. MT<sub>1</sub>/MT<sub>2</sub> heterodimers present different pharmacological profiles from MT<sub>1</sub> and MT<sub>2</sub> receptors [84].

The MT<sub>3</sub> binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML<sub>2</sub> receptor, binds selectively **2-iodo-[<sup>125</sup>I]5MCA-NAT [1473]**. Pharmacological investigations of MT<sub>3</sub> binding sites have primarily been conducted in hamster tissues. At this site, The endogenous ligand **N-acetylserotonin [546, 1324, 1473, 1719]** and **5MCA-NAT [1719]** appear to function as agonists, while **prazosin [1324]** functions as an antagonist. The MT<sub>3</sub> binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase

**2 (NQO2, P16083 [1601, 1602])**. The MT<sub>3</sub> binding site activated by **5MCA-NAT** in eye ciliary body is positively coupled to adenylyl cyclase and regulates chloride secretion [928]. *Xenopus* melanophores and chick brain express a distinct receptor (x420, P49219; c346, P49288, initially termed Mel<sub>1C</sub>) coupled to the G<sub>i/o</sub> family of G proteins, for which GPR50 has recently been suggested to be a mammalian counterpart [530] although **melatonin** does not bind to GPR50 receptors. Several variants of the **MTNR1B** gene have been associated with increased type 2 diabetes risk [1043].

## Further reading on Melatonin receptors

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- Liu J *et al.* (2016) MT1 and MT2 Melatonin Receptors: A Therapeutic Perspective. *Annu. Rev. Pharmacol. Toxicol.* **56**: 361–83 [PMID:26514204]
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# Metabotropic glutamate receptors

G protein-coupled receptors → Metabotropic glutamate receptors

**Overview:** Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [1899]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate. The mGlu family is composed of eight members (named mGlu1 to mGlu8) which are divided in three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I (mGlu<sub>1</sub> and mGlu<sub>5</sub>), Group-II (mGlu<sub>2</sub> and mGlu<sub>3</sub>) and Group-III (mGlu<sub>4</sub>, mGlu<sub>6</sub>, mGlu<sub>7</sub> and mGlu<sub>8</sub>) (see Further reading).

Structurally, mGlu are composed of three juxtaposed domains: a core G protein-activating seven-transmembrane domain (TM), common to all GPCRs, is linked via a rigid cysteine-rich domain (CRD) to the Venus Flytrap domain (VFTD), a large bi-lobed extracellular domain where glutamate binds. The structures of the

VFTD of mGlu<sub>1</sub>, mGlu<sub>2</sub>, mGlu<sub>3</sub>, mGlu<sub>5</sub> and mGlu<sub>7</sub> have been solved [1177, 1482, 1530, 2156]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organization similar to that of other GPCRs, although the helices appear more compacted [383, 515, 2335]. mGlu form constitutive dimers crosslinked by a disulfide bridge. Recent studies revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [518]. Although well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [1493, 2393].

The endogenous ligands of mGlu are **L-glutamic acid**, **L-serine-O-phosphate**, N-acetylaspartylglutamate (**NAAG**) and **L-cysteine sulphinic acid**. Group-I mGlu receptors may be ac-

tivated by **3,5-DHPG** and **(S)-3HPG** [221] and antagonized by **(S)-hexylhomoibotenic acid** [1346]. Group-II mGlu receptors may be activated by **LY389795** [1483], **LY379268** [1483], **eglumegad** [1898 2337], **DCG-IV** and **(2R,3R)-APDC** [1899, and antagonised by **eGlu** [979] and **LY307452** [571, 2289]. Group-III mGlu receptors may be activated by **L-AP4** and **(R,S)-4-PPG** [666]. An example of an antagonist selective for mGlu receptors is **LY341495**, which blocks mGlu<sub>2</sub> and mGlu<sub>3</sub> at low nanomolar concentrations, mGlu<sub>8</sub> at high nanomolar concentrations, and mGlu<sub>4</sub>, mGlu<sub>5</sub>, and mGlu<sub>7</sub> in the micromolar range [1099]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that bind within the TM domain have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Nomenclature	mGlu <sub>1</sub> receptor	mGlu <sub>2</sub> receptor	mGlu <sub>3</sub> receptor	mGlu <sub>4</sub> receptor	mGlu <sub>5</sub> receptor
HGNC, UniProt	<i>GRM1</i> , Q13255	<i>GRM2</i> , Q14416	<i>GRM3</i> , Q14832	<i>GRM4</i> , Q14833	<i>GRM5</i> , P41594
Endogenous agonists	L-glutamic acid [1705]	L-glutamic acid [1705]	L-glutamic acid [1705], NAAG [1906]	L-glutamic acid [1705]	L-glutamic acid [1705]
Agonists	–	–	–	L-AP4 [2337], L-serine-O-phosphate [2337]	–
Selective agonists	–	–	–	LSP4-2022 [731]	(S)-(+)-CBPG (Partial agonist) [1373] – Rat, CHPG [1529]
Antagonists	LY367385 (pIC <sub>50</sub> 5.1) [400]	–	–	MAP4 (pK <sub>i</sub> 4.6) [792] – Rat	–
Selective antagonists	3-MATIDA (pIC <sub>50</sub> 5.2) [1506] – Rat, (S)-(+)-CBPG (pIC <sub>50</sub> 4.2) [1373] – Rat, (S)-TBPG (pIC <sub>50</sub> 4.2) [417] – Rat, AIDA (pA <sub>2</sub> 4.2) [1507]	PCCG-4 (pIC <sub>50</sub> 5.1) [1677] – Rat	–	–	ACDPP (pIC <sub>50</sub> 6.9) [202]
Allosteric modulators	–	CBIPES (Positive) (pEC <sub>50</sub> 7) [1010], 4-MPPTS (Positive) (pIC <sub>50</sub> 5.8) [108, 1009, 1010, 1884]	MNI-137 (Negative) (pIC <sub>50</sub> 7.7) [850] – Rat, VU0650786 (Negative) (pIC <sub>50</sub> 6.4) [560]	SIB-1893 (Positive) (pEC <sub>50</sub> 6.3–6.8) [1395], MPEP (Positive) (pEC <sub>50</sub> 6.3–6.6) [1395], PHCCC (Positive) (pEC <sub>50</sub> 4.5) [1358]	alloswitch-1 (Negative) (pIC <sub>50</sub> 8.1) [1714] – Rat, CDPBP (Positive) (pEC <sub>50</sub> 7.6–8) [1100, 1290], MTEP (Negative) (pK <sub>i</sub> 7.8) [246], MPEP (Negative) (pIC <sub>50</sub> 7.4–7.7) [665, 667], fenobam (Negative) (pIC <sub>50</sub> 7.2) [1723]
Selective allosteric modulators	BAY 367620 (Negative) (pK <sub>i</sub> 9.5) [309] – Rat, JNJ16259685 (Negative) (pIC <sub>50</sub> 8.9) [1210], Ro01-6128 (Positive) (pK <sub>i</sub> 7.5–7.7) [1118] – Rat, LY456236 (Negative) (pIC <sub>50</sub> 6.9) [1270], CPCCOEt (Negative) (pIC <sub>50</sub> 5.2–5.8) [1293]	Ro64-5229 (Negative) (pIC <sub>50</sub> 7) [1130] – Rat, biphenylindanone A (Positive) (pEC <sub>50</sub> 7) [203]	ML337 (Negative) (pIC <sub>50</sub> 6.2) [2286] – Rat	VU0361737 (Positive) (pEC <sub>50</sub> 6.6) [559], VU0155041 (Positive) (pEC <sub>50</sub> 6.1) [1595]	VU-1545 (Positive) (pEC <sub>50</sub> 8) [470]

Nomenclature	<a href="#">mGlu<sub>6</sub> receptor</a>	<a href="#">mGlu<sub>7</sub> receptor</a>	<a href="#">mGlu<sub>8</sub> receptor</a>
HGNC, UniProt	<a href="#">GRM6</a> , <a href="#">O15303</a>	<a href="#">GRM7</a> , <a href="#">Q14831</a>	<a href="#">GRM8</a> , <a href="#">O00222</a>
Endogenous agonists	<a href="#">L-glutamic acid</a> [ <a href="#">1705</a> ]	<a href="#">L-glutamic acid</a> [ <a href="#">1705</a> ]	<a href="#">L-serine-O-phosphate</a> [ <a href="#">1365</a> , <a href="#">2337</a> ], <a href="#">L-glutamic acid</a> [ <a href="#">1705</a> ]
Agonists	–	<a href="#">LSP4-2022</a> [ <a href="#">731</a> ], <a href="#">L-serine-O-phosphate</a> [ <a href="#">2337</a> ], <a href="#">L-AP4</a> [ <a href="#">2337</a> ]	<a href="#">(S)-3,4-DCPG</a> [ <a href="#">2122</a> ], <a href="#">L-AP4</a> [ <a href="#">1365</a> ]
Selective agonists	<a href="#">1-benzyl-APDC</a> [ <a href="#">2158</a> ] – Rat, <a href="#">homo-AMPA</a> [ <a href="#">264</a> ]	–	–
Antagonists	<a href="#">MAP4</a> (pIC <sub>50</sub> 3.5) [ <a href="#">1706</a> ] – Rat, <a href="#">THPG</a> [ <a href="#">2126</a> ]	–	<a href="#">MPPG</a> (pIC <sub>50</sub> 4.3) [ <a href="#">2337</a> ]
Allosteric modulators	–	<a href="#">MMPPIP</a> (Negative) (pIC <sub>50</sub> 6.1–7.6) [ <a href="#">1594</a> , <a href="#">2063</a> ] – Rat, <a href="#">ADX71743</a> (Negative) (pIC <sub>50</sub> 7.2) [ <a href="#">1031</a> ], <a href="#">AMN082</a> (Positive) (pEC <sub>50</sub> 6.5–6.8) [ <a href="#">1463</a> ], <a href="#">XAP044</a> (Negative) (pIC <sub>50</sub> 5.6) [ <a href="#">676</a> ]	<a href="#">VU0422288</a> (Positive) (pK <sub>B</sub> 6.7) [ <a href="#">978</a> ], <a href="#">VU0155094</a> (Positive) (pK <sub>B</sub> 5) [ <a href="#">978</a> ]

**Comments:** The activity of [NAAG](#) as an agonist at mGlu<sub>3</sub> receptors was questioned on the basis of contamination with glutamate [[374](#), [631](#)], but this has been refuted [[1553](#)].

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [<sup>3</sup>H][R214127](#) [[1209](#)] and [<sup>3</sup>H][YM298198](#) [[1125](#)] at mGlu<sub>1</sub> receptors and [<sup>3</sup>H][M-MPEP](#) [[665](#)] and [<sup>3</sup>H][methoxymethyl-MTEP](#) [[51](#)] at mGlu<sub>5</sub> receptors; [<sup>3</sup>H][LY341495](#) and [<sup>3</sup>H][eglumegad](#) for mGlu<sub>2</sub> and mGlu<sub>3</sub> receptors [[1008](#), [1906](#)]). Although a number of radioligands have been used to examine binding in native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes

of mGlu receptors and may have unappreciated biased or neutral activity at other subtypes [[849](#)]. Potential differences linked to the species (*e.g.* human *versus* rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

[\(S\)-\(+\)-CBPG](#) is an antagonist at mGlu<sub>1</sub>, but is an agonist (albeit of reduced efficacy) at mGlu<sub>5</sub> receptors. [DCG-IV](#) also exhibits agonist activity at NMDA glutamate receptors [[2183](#)], and is an antagonist at all Group-III mGluRs with an IC<sub>50</sub> of 30 μM. A potential novel metabotropic glutamate receptor coupled to phospho-

inositide turnover has been observed in rat brain; it is activated by [4-methylhomoibotenic acid](#) (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but is resistant to [LY341495](#) [[392](#)]. 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 [[1112](#), [1675](#)]

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.

### Further reading on Metabotropic glutamate receptors

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# Motilin receptor

G protein-coupled receptors → Motilin receptor

**Overview:** Motilin receptors (**provisional nomenclature**) are activated by **motilin** (*MLN*, P12872), a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a **motilin-associated peptide** (*MLN*, P12872). These receptors promote gastrointestinal motility and are 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	motilin receptor
HGNC, UniProt	<i>MLNR</i> , O43193
Endogenous agonists	motilin ( <i>MLN</i> , P12872) [422, 1400, 1401, 1402]
Agonists	alemcinal [2117], erythromycin [588, 2117], azithromycin [241]
Selective agonists	camicinal [113, 1863], mitemcinal [1123, 2085] – Rabbit
Selective antagonists	MA-2029 (pA <sub>2</sub> 9.2) [2048], GM-109 (pIC <sub>50</sub> 8) [808] – Rabbit
Labelled ligands	[ <sup>125</sup> I]motilin (human) (Agonist) [588]

**Comments:** In terms of structure, the motilin receptor has closest homology with the ghrelin receptor. Thus, the human motilin receptor shares 52% overall amino acid identity with the ghrelin receptor and 86% in the transmembrane regions [834, 2085, 2117]. However, differences between the N-terminus regions of these receptors means that their cognate peptide ligands do not readily activate each other [448, 1863]. In laboratory rodents, the gene encoding the motilin precursor appears to be absent, while the receptor appears to be a pseudogene [834, 1861]. Functions of **motilin** (*MLN*, P12872) are not usually detected in rodents, al-

though brain and other responses to motilin and the macrolide **alemcinal** have been reported and the mechanism of these actions is obscure [1424, 1587]. Notably, in some non-laboratory rodents (*e.g.* the North American kangaroo rat (*Dipodomys*) and mouse (*Microdipodops*) a functional form of motilin may exist but the motilin receptor is non-functional [1269]. Marked differences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [1862]. Note that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other ac-

tions are possible (*e.g.* P2X inhibition by erythromycin; [2430]). Small molecule motilin receptor agonists are now described [1269, 1863, 2293]. The motilin receptor does not appear to have constitutive activity [897]. Although not proven, the existence of biased agonism at the receptor has been suggested [1402, 1462, 1860]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [588]. Receptor dimerisation has not been reported.

## Further reading on Motilin receptor

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- Marrinan SL *et al.* (2018) A randomized, double-blind, placebo-controlled trial of camicinal in Parkinson's disease. *Mov. Disord.* **33**: 329-332 [PMID:29278279]
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## Neuromedin U receptors

G protein-coupled receptors → Neuromedin U receptors

**Overview:** Neuromedin U receptors (**provisional nomenclature as recommended by NC-IUPHAR [612]**) are activated by the endogenous 25 amino acid peptide neuromedin U (**neuromedin U-25 (NMU, P48645)**, NmU-25), a peptide originally isolated from pig spinal cord [1458]. 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 lev-

els 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 (**neuromedin S-33 (NMS, Q5H8A3)**)

has also been identified as an endogenous agonist [1497]. 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	NMUR1, Q9HB89	NMUR2, Q9GZQ4
Antagonists	–	R-PSOP (p <i>K</i> <sub>B</sub> 7) [1303]

**Comments:** NMU1 and NMU2 couple predominantly to G<sub>q/11</sub> although there is evidence of good coupling to G<sub>i/o</sub> [235, 910, 918]. NMU1 and NMU2 can be labelled with [<sup>125</sup>I]-NmU and [<sup>125</sup>I]-NmS (of various species, *e.g.* [1432]), BODIPY<sup>®</sup> TMR-NMU or Cy3B-NMU-8 [235]. A range of radiolabelled (<sup>125</sup>I-), fluorescently labelled (*e.g.* Cy3, Cy5, rhodamine and FAM) and biotin labelled versions of **neuromedin U-25 (NMU, P48645)** and **neuromedin S-33 (NMS, Q5H8A3)** are now commercially available.

### Further reading on Neuromedin U receptors

- Brighton PJ *et al.* (2004) Neuromedin U and its receptors: structure, function, and physiological roles. *Pharmacol. Rev.* **56**: 231-48 [PMID:15169928]
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- Mitchell JD *et al.* (2009) Emerging pharmacology and physiology of neuromedin U and the structurally related peptide neuromedin S. *Br. J. Pharmacol.* **158**: 87-103 [PMID:19519756]
- Novak CM. (2009) Neuromedin S and U. *Endocrinology* **150**: 2985-7 [PMID:19549882]

## Neuropeptide FF/neuropeptide AF receptors

G protein-coupled receptors → Neuropeptide FF/neuropeptide AF receptors

**Overview:** The Neuropeptide FF receptor family contains two subtypes, NPFF1 and NPFF2 (**provisional nomenclature [612]**), which exhibit high affinities for neuropeptide FF (NPFF, O15130) and RFamide related peptides (RFRP: precursor gene symbol NPVF, Q9HCQ7). NPFF1 is broadly distributed in the central nervous system with the highest levels found in the limbic system and the hypothalamus. NPFF2 is present in high density in the superficial layers of the mammalian spinal cord where it is involved in nociception and modulation of opioid functions.

Nomenclature	NPFF1 receptor	NPFF2 receptor
HGNC, UniProt	NPFFR1, Q9GZQ6	NPFFR2, Q9Y5X5
Potency order of endogenous ligands	RFRP-1 (NPVF, Q9HCQ7) > RFRP-3 (NPVF, Q9HCQ7) > FMRFneuropeptide FF (NPFF, O15130) > neuropeptide AF (NPFF, O15130) > neuropeptide SF (NPFF, O15130), QRFP43 (QRFP, P83859), PrRP-31 (PRLH, P81277) [728]	neuropeptide AF (NPFF, O15130), neuropeptide FF (NPFF, O15130) > PrRP-31 (PRLH, P81277) > FMRF, QRFP43 (QRFP, P83859) > neuropeptide SF (NPFF, O15130) [728]
Endogenous agonists	neuropeptide FF (NPFF, O15130) [728, 729, 1476], RFRP-3 (NPVF, Q9HCQ7) [729, 730, 1476]	neuropeptide FF (NPFF, O15130) [729, 1475]
Selective agonists	–	dNPA [1829], AC263093 [1194]
Antagonists	RF9 (pK <sub>i</sub> 7.2) [1974]	–
Selective antagonists	AC262620 (pK <sub>i</sub> 7.7–8.1) [1194], AC262970 (pK <sub>i</sub> 7.4–8.1) [1194]	–
Labelled ligands	[ <sup>125</sup> I]Y-RFRP-3 (Agonist) [729], [ <sup>3</sup> H]NPVF (Agonist) [2095], [ <sup>125</sup> I]NPFF (Agonist) [728]	[ <sup>125</sup> I]EYF (Agonist) [1476], [ <sup>3</sup> H]EYF (Agonist) [2095], [ <sup>125</sup> I]NPFF (Agonist) [728]

**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<sub>i</sub> 7.1 and 7.2, respectively, [1974]).

### Further reading on Neuropeptide FF/neuropeptide AF receptors

- Moulédous L *et al.* (2010) Opioid-modulating properties of the neuropeptide FF system. *Biofactors* **36**: 423-9 [PMID:20803521]
- Vyas N *et al.* (2006) Structure-activity relationships of neuropeptide FF and related peptidic and non-peptidic derivatives. *Peptides* **27**: 990-6 [PMID:16490282]
- Yang HY *et al.* (2008) Modulatory role of neuropeptide FF system in nociception and opiate analgesia. *Neuropeptides* **42**: 1-18 [PMID:17854890]

## Neuropeptide S receptor

G protein-coupled receptors → Neuropeptide S receptor

**Overview:** The neuropeptide S receptor (NPS, **provisional nomenclature** [612]) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (NPS, POCOP6).

Nomenclature	NPS receptor
HGNC, UniProt	<i>NPSR1</i> , Q6W5P4
Endogenous agonists	neuropeptide S (NPS, POCOP6) [2360]
Selective agonists	PWT1-NPS [1840] – Mouse
Selective antagonists	NCGC 84 (pA <sub>2</sub> 9) [2127], SHA 68 (pA <sub>2</sub> 8.1) [1841] – Mouse, RTI-118 [2428]
Labelled ligands	[ <sup>125</sup> I]Tyr <sup>10</sup> NPS (human) (Agonist) [2360]

**Comments:** Multiple single-nucleotide polymorphisms (SNP) and several splice variants have been identified in the human NPS receptor. The most interesting of these is an Asn-Ile exchange at position 107 (Asn<sup>107</sup>Ile). The human NPS receptor Asn<sup>107</sup>Ile displayed similar binding affinity but higher NPS potency (by approx. 10-fold) than human NPS receptor Asn107 [1787]. Several epidemiological studies reported an association between Asn<sup>107</sup>Ile receptor variant and susceptibility to panic disorders [507, 510, 1629, 1758]. The SNP Asn<sup>107</sup>Ile has also been linked to sleep behavior [727], inflammatory bowel disease [440], schizophrenia [1254], increased impulsivity and ADHD symptoms [1186]. Interestingly, a carboxy-terminal splice variant of human NPS receptor was found to be overexpressed in asthmatic patients [1193].

### Further reading on Neuropeptide S receptor

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## Neuropeptide W/neuropeptide B receptors

G protein-coupled receptors → Neuropeptide W/neuropeptide B receptors

**Overview:** The neuropeptide BW receptor 1 (NPBW1, **provisional nomenclature [612]**) is activated by two 23-amino-acid peptides, neuropeptide W (**neuropeptide W-23 (NPW, Q8N729)**) and neuropeptide B (**neuropeptide B-23 (NPB, Q8NG41)**) [638, 1953]. C-terminally extended forms of the peptides (**neuropeptide W-30 (NPW, Q8N729)** and **neuropeptide B-29**

(**NPB, Q8NG41**)) also activate NPBW1 [233]. Unique to both forms of neuropeptide B is the N-terminal bromination of the first tryptophan residue, and it is from this post-translational modification that the nomenclature NPB is derived. These peptides were first identified from bovine hypothalamus and therefore are classed as neuropeptides. Endogenous variants of the peptides with-

out the N-terminal bromination, **des-Br-neuropeptide B-23 (NPB, Q8NG41)** and **des-Br-neuropeptide B-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 neuropeptide W and neuropeptide B [233].

Nomenclature	NPBW1 receptor	NPBW2 receptor
HGNC, UniProt	<i>NPBWR1</i> , P48145	<i>NPBWR2</i> , P48146
Potency order of endogenous ligands	neuropeptide B-29 ( <i>NPB</i> , Q8NG41) > neuropeptide B-23 ( <i>NPB</i> , Q8NG41) > neuropeptide W-23 ( <i>NPW</i> , Q8N729) > neuropeptide W-30 ( <i>NPW</i> , Q8N729) [233]	neuropeptide W-23 ( <i>NPW</i> , Q8N729) > neuropeptide W-30 ( <i>NPW</i> , Q8N729) > neuropeptide B-29 ( <i>NPB</i> , Q8NG41) > neuropeptide B-23 ( <i>NPB</i> , Q8NG41) [233]
Selective agonists	Ava3 [1038], Ava5 [1038]	–
Labelled ligands	[ <sup>125</sup> I]NPW-23 (human) (Agonist) [1976]	[ <sup>125</sup> I]NPW-23 (human) (Agonist) [1953]

**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<sup>-/-</sup> mice show changes in social behavior, suggesting that the NPBW1 pathway may have an important role in the emotional responses of social interaction [1537].

For a review of the contribution of neuropeptide B/W to social dominance, see Watanabe and Yamamoto, 2015 [2270]. It has been reported that neuropeptide W may have a key role in the gating of stressful stimuli when mice are exposed to novel environments [1512].

Two antagonists have been discovered and reported to have affin-

ity for NPBW1, ML181 and ML250, the latter exhibiting improved selectivity (100 fold) for NPBW1 compared to MCH1 receptors [762, 763]. Computational insights into the binding of antagonists to this receptor have also been described [1667].

### Further reading on Neuropeptide W/neuropeptide B receptors

Sakurai T. (2013) NPBWR1 and NPBWR2: Implications in Energy Homeostasis, Pain, and Emotion. *Front Endocrinol (Lausanne)* **4**: 23 [PMID:23515889] Singh G *et al.* (2006) Neuropeptide B and W: neurotransmitters in an emerging G-protein-coupled receptor system. *Br. J. Pharmacol.* **148**: 1033–41 [PMID:16847439]

# Neuropeptide Y receptors

G protein-coupled receptors → Neuropeptide Y receptors

**Overview:** Neuropeptide Y (NPY) receptors (**nomenclature agreed by the NC-IUPHAR Subcommittee on Neuropeptide Y Receptors [1444]**) are activated by the endogenous peptides **neuropeptide Y (NPY, P01303)**, **neuropeptide Y-(3-36)**, **peptide YY (PYY, P10082)**, **PYY-(3-36)** and **pancreatic polypeptide (PPY, P01298)** (PP). The receptor originally identified as the Y3 receptor has been identified as the **CXCR4 chemokine receptor**

(originally named LESTR, [1310]). 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 [743]. Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the potency of PP is greater at the rat Y<sub>4</sub> receptor than at the human receptor [566]. In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [<sup>125</sup>I]-PYY or [<sup>125</sup>I]-NPY can be used to label Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>5</sub> and y<sub>6</sub> subtypes non-selectively, while [<sup>125</sup>I][cPP(1-7), NPY(19-23), Ala<sup>31</sup>, Aib<sup>32</sup>, Gln<sup>34</sup>]hPP may be used to label Y<sub>5</sub> receptors preferentially (note that cPP denotes chicken peptide sequence and hPP is the human sequence).

ity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [<sup>125</sup>I]-PYY or [<sup>125</sup>I]-NPY can be used to label Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>5</sub> and y<sub>6</sub> subtypes non-selectively, while [<sup>125</sup>I][cPP(1-7), NPY(19-23), Ala<sup>31</sup>, Aib<sup>32</sup>, Gln<sup>34</sup>]hPP may be used to label Y<sub>5</sub> receptors preferentially (note that cPP denotes chicken peptide sequence and hPP is the human sequence).

Nomenclature	Y <sub>1</sub> receptor	Y <sub>2</sub> receptor	Y <sub>4</sub> receptor	Y <sub>5</sub> receptor	y <sub>6</sub> receptor
HGNC, UniProt	<i>NPY1R</i> , P25929	<i>NPY2R</i> , P49146	<i>NPY4R</i> , P50391	<i>NPY5R</i> , Q15761	<i>NPY6R</i> , Q99463
Potency order of endogenous ligands	neuropeptide Y = peptide YY ≫ pancreatic polypeptide	peptide YY = peptide YY(3-36) = neuropeptide Y = neuropeptide Y(3-36) ≫ pancreatic polypeptide	pancreatic polypeptide ≫ neuropeptide Y = peptide YY	neuropeptide Y > peptide YY > pancreatic polypeptide	neuropeptide Y = peptide YY > pancreatic polypeptide
Endogenous agonists	neuropeptide Y ( <i>NPY</i> , P01303), peptide YY ( <i>PYY</i> , P10082)	<i>PYY</i> -(3-36) ( <i>PYY</i> , P10082) [677, 692], neuropeptide Y ( <i>NPY</i> , P01303), neuropeptide Y-(3-36) ( <i>NPY</i> , P01303), peptide YY ( <i>PYY</i> , P10082)	pancreatic polypeptide ( <i>PPY</i> , P01298) [106, 1327, 2149, 2368]	–	–
Agonists	[Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY [430], [Leu <sup>31</sup> ,Pro <sup>34</sup> ]PYY (human), [Pro <sup>34</sup> ]NPY, [Pro <sup>34</sup> ]PYY (human)	–	–	–	–
Selective agonists	–	–	–	[Ala <sup>31</sup> ,Aib <sup>32</sup> ]NPY (pig) [287]	–
Selective antagonists	BIBO3304 (pIC <sub>50</sub> 9.5) [2303], BIBP3226 (pK <sub>i</sub> 8.1–9.3) [513, 2304]	BIIIE0246 (pIC <sub>50</sub> 8.5) [511], JNJ-5207787 (pIC <sub>50</sub> 6.9–7.1) [198]	–	L-152,804 (pK <sub>i</sub> 7.6) [1037]	–
Selective allosteric modulators	–	–	niclosamide (Positive) [1988]	–	–
Labelled ligands	[ <sup>3</sup> H]BIBP3226 (Antagonist) (pK <sub>d</sub> 8.7), [ <sup>125</sup> I][Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY (Agonist)	[ <sup>125</sup> I]PYY-(3-36) (human) (Agonist)	[ <sup>125</sup> I]PP (human) (Agonist)	[ <sup>125</sup> I][cPP(1-7), NPY(19-23), Ala <sup>31</sup> , Aib <sup>32</sup> , Gln <sup>34</sup> ]hPP (Agonist) [532] – Rat	–
Comments	Note that Pro <sup>34</sup> -containing NPY and PYY can also bind Y <sub>4</sub> and Y <sub>5</sub> receptors, so strictly speaking are not selective, but are the 'preferred' agonists.	–	–	–	–

**Comments:** The Y<sub>1</sub> agonists indicated are selective relative to Y<sub>2</sub> receptors. BIBP3226 is selective relative to Y<sub>2</sub>, Y<sub>4</sub> and Y<sub>5</sub> receptors [691]. NPY-(13-36) is Y<sub>2</sub> selective relative to Y<sub>1</sub> and Y<sub>5</sub> receptors. PYY-(3-36) is Y<sub>2</sub> selective relative to Y<sub>1</sub> receptors. Note that Pro34-containing NPY and PYY can also bind Y<sub>4</sub> and Y<sub>5</sub>, thus they are selective only relative to Y<sub>2</sub>. The y<sub>6</sub> receptor is a pseudogene in humans, but is functional in mouse, rabbit and some other mammals.

### Further reading on Neuropeptide Y receptors

Bowers ME *et al.* (2012) Neuropeptide regulation of fear and anxiety: Implications of cholecystokinin, endogenous opioids, and neuropeptide Y. *Physiol. Behav.* **107**: 699-710 [PMID:22429904]

Michel MC *et al.* (1998) XVI. International Union of Pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY and pancreatic polypeptide receptors. *Pharmacol. Rev.* **50**: 143-150 [PMID:9549761]

Pedragosa-Badia X *et al.* (2013) Neuropeptide Y receptors: how to get subtype selectivity. *Front Endocrinol (Lausanne)* **4**: 5 [PMID:23382728]

Zhang L *et al.* (2011) The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. *Pharmacol. Ther.* **131**: 91-113 [PMID:21439311]

## Neurotensin receptors

G protein-coupled receptors → Neurotensin receptors

**Overview:** Neurotensin receptors (nomenclature as recommended by NC-IUPHAR [612]) 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, 30990), which also generates neuromedin N, an agonist at the NTS<sub>2</sub> receptor. [<sup>3</sup>H]neurotensin (human, mouse, rat) and [<sup>125</sup>I]neurotensin (human, mouse, rat) may be used to label NTS<sub>1</sub> and NTS<sub>2</sub> receptors at 0.1-0.3 and 3-5 nM concentrations respectively.

Nomenclature	NTS <sub>1</sub> receptor	NTS <sub>2</sub> receptor
HGNC, UniProt	NTSR1, P30989	NTSR2, O95665
Potency order of endogenous ligands	neurotensin (NTS, P30990) > neuromedin N {Mouse, Rat} [855]	neurotensin (NTS, P30990) = neuromedin N {Mouse, Rat} [1411]
Selective agonists	JMV449 [1983] – Rat	levocabastine [1411, 1801]
Selective antagonists	meclizant (pIC <sub>50</sub> 7.5–8.2) [767]	–
Labelled ligands	[ <sup>3</sup> H]meclizant (Antagonist) (pK <sub>d</sub> 8.5) [1188] – Rat	–

**Comments:** Neurotensin (NTS, P30990) appears to be a low-efficacy agonist at the NTS<sub>2</sub> receptor [2222], while the NTS<sub>1</sub> receptor antagonist meclizant is an agonist at NTS<sub>2</sub> receptors [2222]. An additional protein, provisionally termed NTS<sub>3</sub> (also known as

NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation [1585]. It has been reported to interact with the NTS<sub>1</sub> receptor [1388] and the NTS<sub>2</sub> receptor [283], and has been implicated in hormone traf-

ficking and/or neurotensin uptake. A splice variant of the NTS<sub>2</sub> receptor bearing 5 transmembrane domains has been identified in mouse [211] and later in rat [1689].

### Further reading on Neurotensin receptors

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Ouyang Q *et al.* (2017) Oncogenic role of neurotensin and neurotensin receptors in various cancers. *Clin. Exp. Pharmacol. Physiol.* **44**: 841-846 [PMID:28556374]

# Opioid receptors

G protein-coupled receptors → 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),  $\beta$ -endorphin (*POMC*, P01189) ( $\beta$ -end),  $\alpha$ -neodynorphin (*PDYN*, P01213), dynorphin A (*PDYN*, P01213) (dynA), dynorphin B (*PDYN*, P01213) (dynB), big dynorphin (*PDYN*, P01213) (Big dyn), nociceptin/orphanin FQ (*PNO*, Q13519) (N/OFQ);

endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter nomenclature for the opioid receptors,  $\mu$ ,  $\delta$  and  $\kappa$ , is well established, and **NC-IUPHAR** considers this nomenclature appropriate, along with the symbols spelled out (mu, delta, and kappa), and the acronyms, MOP, DOP, and KOP. [428, 488, 612]. The human N/OFQ receptor, NOP, is considered 'opioid-related' rather than opioid because,

while it exhibits a high degree of structural homology with the conventional opioid receptors [1478], it displays a distinct pharmacology. Currently there are numerous clinically used drugs, such as morphine and many other opioid analgesics, as well as antagonists such as naloxone, however only for the  $\mu$  receptor.

Nomenclature	$\delta$ receptor	$\kappa$ receptor
HGNC, UniProt	<i>OPRD1</i> , P41143	<i>OPRK1</i> , P41145
Principal endogenous agonists	$\beta$ -endorphin ( <i>POMC</i> , P01189), [Leu]enkephalin ( <i>PENK</i> , P01210), [Met]enkephalin ( <i>PENK</i> , P01210)	big dynorphin ( <i>PDYN</i> , P01213), dynorphin A ( <i>PDYN</i> , P01213)
Agonists	DADLE [2142], etorphine [2142], ethylketocyclazocine [2142]	–
Sub/family-selective agonists	BU08028 (Partial agonist) [1076]	BU08028 [1076]
Selective agonists	UFP-512 [2215], BW373U86 [1220], ADL5859 [1220], DPDPE [1511, 2142], [D-Ala <sup>2</sup> ]deltorphin II [568], ADL5747 [1221], SNC80 [292, 1757]	U50488 [345, 1671, 1973, 2142, 2230, 2437, 2439], enadoline [934, 1571], U69593 [1192, 2142], salvinorin A [281, 1825]
Antagonists	UFP-505 (pK <sub>i</sub> 9.8) [494, 495], naltrexone (pK <sub>i</sub> 8) [2142], naloxone (pK <sub>i</sub> 7.2) [2142]	buprenorphine (pK <sub>i</sub> 9.1–10.2) [2142, 2439], nalmefene (pK <sub>i</sub> 9.5) [2142], naltrexone (pK <sub>i</sub> 8.4–9.4) [1671, 1973, 2142], naloxone (pK <sub>i</sub> 7.6–8.6) [1671, 1973, 2142, 2437, 2439]
Sub/family-selective antagonists	AT-076 (pK <sub>i</sub> 7.7) [2142, 2412]	AT-076 (pK <sub>i</sub> 8.9) [2142, 2413]
Selective antagonists	naltriben (pK <sub>i</sub> 10) [2003, 2142], naltrindole (pK <sub>i</sub> 9.7) [1725, 2142], TIPP $\psi$ (Inverse agonist) (pK <sub>i</sub> 9) [1888, 2142]	nor-binaltorphimine (pK <sub>i</sub> 8.9–11) [1671, 1724, 1973, 2142, 2437, 2439], 5'-guanidinonaltrindole (pK <sub>i</sub> 9.7–9.9) [1017, 1671, 2031], JD <sub>Tic</sub> (pK <sub>i</sub> 9–9.4) [1520, 2121, 2413]
Labelled ligands	[ <sup>3</sup> H]naltrindole (Antagonist) (pK <sub>d</sub> 10.4) [2364] – Rat, [ <sup>3</sup> H][D-Ala <sup>2</sup> ]deltorphin I (Selective Agonist) [2027], [ <sup>3</sup> H]diprenorphine (Agonist) [56, 2142], [ <sup>3</sup> H]DPDPE (Agonist) [28], [ <sup>3</sup> H]deltorphin II (Agonist) [284], [ <sup>3</sup> H]naltriben (Antagonist) [1264]	[ <sup>3</sup> H]diprenorphine (Antagonist) (pK <sub>d</sub> 9.1) [56, 1973], [ <sup>3</sup> H]U69593 (Agonist) [1192, 1671, 1973], [ <sup>3</sup> H]enadoline (Agonist) [1975]

Nomenclature	$\mu$ receptor	NOP receptor
HGNC, UniProt	<i>OPRM1</i> , P35372	<i>OPRL1</i> , P41146
Potential endogenous agonists	endomorphin-1, endomorphin-2	–
Principal endogenous agonists	$\beta$ -endorphin ( <i>POMC</i> , P01189), [Met]enkephalin ( <i>PENK</i> , P01210), [Leu]enkephalin ( <i>PENK</i> , P01210)	–
Endogenous agonists	–	nociceptin/orphanin FQ ( <i>PNOC</i> , Q13519) [11, 165, 1630]
Agonists	levorphanol [797], hydromorphone [2287], fentanyl [2142], buprenorphine (Partial agonist) [2142], methadone [1727], UFP-505 [494, 495], codeine [2142], tapentadol [2163], pethidine [1727]	–
Sub/family-selective agonists	BU08028 (Partial agonist) [1076]	cebranopadol [1292], BU08028 (Partial agonist) [1076]
Selective agonists	sufentanil [2224], DAMGO [796, 2142], loperamide [356], morphine [717, 2142], PL017 [336, 2142]	N/OFG-(1-13)-NH <sub>2</sub> [165, 764, 1418, 1630], Ac-RYYRWK-NH <sub>2</sub> (Partial agonist) [514, 1418], SCH221510 [2208], Ro64-6198 [987, 2301], AT-403 [63]
Antagonists	naltrexone (pK <sub>i</sub> 9.1–9.7) [1061, 2142], nalmefene (pK <sub>i</sub> 9.5) [2142], nalorphine (pK <sub>i</sub> 8.9) [2142], naloxone (pK <sub>i</sub> 8.9) [2142], methylnaltrexone (pK <sub>i</sub> 8.7) [2287]	–
Sub/family-selective antagonists	AT-076 (pK <sub>i</sub> 8.8) [2142, 2413]	AT-076 (pK <sub>i</sub> 8.8) [2413]
Selective antagonists	alvimopan (pK <sub>i</sub> 9.3) [1219], levallorphan (pK <sub>i</sub> 8.8–9.3) [1361], CTAP (pK <sub>i</sub> 8.6) [336, 2142]	UFP-101 (pK <sub>i</sub> 10.2) [294], LY2940094 (pK <sub>i</sub> 10) [2141], compound 24 (pK <sub>i</sub> 9.6) [605], SB 612111 (pK <sub>i</sub> 9.2–9.5) [2017, 2411], J-113397 (pI <sub>C50</sub> 8.3) [1057]
Allosteric modulators	BMS-986123 (Neutral) (pK <sub>B</sub> 6) [267], BMS-986121 (Positive) (pK <sub>B</sub> 5.7) [267], BMS-986124 (Neutral) (pK <sub>B</sub> 5.7) [267], BMS-986122 (Positive) (pK <sub>B</sub> 5.3) [267]	–
Labelled ligands	[ <sup>3</sup> H]diprenorphine (Antagonist) (pK <sub>d</sub> 10.1) [1780] – Mouse, [ <sup>3</sup> H]DAMGO (Agonist) [1780] – Rat, [ <sup>3</sup> H]PL017 (Agonist) [825] – Rat	[ <sup>3</sup> H]N/OFG (Agonist) [514, 1477]

**Comments:** Three naloxone-sensitive opioid receptor genes have been identified in humans, and while the  $\mu$ -receptor in particular may be subject to extensive alternative splicing [1660], these putative isoforms have not been correlated with any of the subtypes of receptor proposed in years past. Opioid receptors may heterodimerize with each other or with other 7TM receptors [1019], and give rise to complexes with a unique pharmacology, however, evidence for such heterodimers in native cells is equivocal and the consequences of this heterodimerization for signalling remains largely unknown. For  $\mu$ -opioid receptors at least, dimerization does not seem to be required for signalling [1180]. 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 [2409].

endomorphin-1 and endomorphin-2 have been identified as highly selective, putative endogenous agonists for the  $\mu$ -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  $\mu$ -receptors [1613] and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists

[255]. Pathway bias for agonists makes general rank orders of potency and efficacy somewhat obsolete, so these do not appear in 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.

The richness of opioid receptor pharmacology has been enhanced with the recent discovery of allosteric modulators of  $\mu$  and  $\delta$  receptors, notably the positive allosteric modulators and silent allosteric "antagonists" outlined in [267, 268]. Negative allosteric modulation of opioid receptors has been previously suggested [1048], whether all compounds are acting at a similar site remains to be established.

**Further reading on Opioid receptors**

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- Pradhan AA *et al.* (2011) The delta opioid receptor: an evolving target for the treatment of brain disorders. *Trends Pharmacol. Sci.* **32**: 581–90 [PMID:21925742]
- Williams JT *et al.* (2013) Regulation of  $\mu$ -opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol. Rev.* **65**: 223–54 [PMID:23321159]

# Orexin receptors

G protein-coupled receptors → Orexin receptors

**Overview:** Orexin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Orexin receptors [612]**) 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 and some typical peptide modifications [1852]. Currently the only orexin receptor ligand in clinical use is **suvorexant**, which is used as a hypnotic. Orexin receptor crystal structures have been solved [2390, 2392].

Nomenclature	<b>OX<sub>1</sub> receptor</b>	<b>OX<sub>2</sub> receptor</b>
HGNC, UniProt	<i>HCRT1</i> , <b>O43613</b>	<i>HCRT2</i> , <b>O43614</b>
Potency order of endogenous ligands	<b>orexin-A</b> ( <i>HCRT</i> , <b>O43612</b> ) > <b>orexin-B</b> ( <i>HCRT</i> , <b>O43612</b> )	<b>orexin-A</b> ( <i>HCRT</i> , <b>O43612</b> ) = <b>orexin-B</b> ( <i>HCRT</i> , <b>O43612</b> )
Selective agonists	–	[Ala <sup>11</sup> , D-Leu <sup>15</sup> ]orexin-B [73, 1748], Nag 26 [1535, 1807], YNT-185 [951, 1535]
Antagonists	<b>SB-649868</b> (pK <sub>i</sub> 9.3–9.6) [293, 429], <b>suvorexant</b> (pK <sub>i</sub> 8.7–9.3) [293, 429, 1513], <b>filorexant</b> (pK <sub>i</sub> 8.4–9.1) [293, 429, 2319], <b>TCS 1102</b> (pK <sub>i</sub> 8.5) [148], <b>almorexant</b> (pK <sub>i</sub> 7.8–8.5) [293, 581, 1363, 1364, 1367], <b>Cp-1</b> (pK <sub>i</sub> 7.6–8) [1363, 1364]	<b>SB-649868</b> (pK <sub>i</sub> 8.9–9.8) [293, 429], <b>TCS 1102</b> (pK <sub>i</sub> 9.7) [148], <b>suvorexant</b> (pK <sub>i</sub> 8.9–9.5) [293, 429, 1513], <b>Cp-1</b> (pK <sub>i</sub> 8.5–9.3) [1363, 1364], <b>filorexant</b> (pK <sub>i</sub> 8.9–9.1) [293, 429, 2319]
Selective antagonists	<b>SB-674042</b> (70–300-fold selective) (pK <sub>i</sub> 8.7–9.3) [1200, 1363, 1364, 1367], <b>SB-334867</b> (50–150-fold selective) (pK <sub>i</sub> 7.2–7.9) [1200, 1363, 1364, 1722, 1746, 1991], <b>SB-408124</b> (60–80-fold selective) (pK <sub>i</sub> 7.2–7.9) [1200, 1364, 1513]	<b>EMPA</b> (300–3000-fold selective) (pK <sub>i</sub> 8.4–9.2) [1363, 1364, 1367, 1513, 2152], <b>JNJ-10397049</b> (200–800-fold selective) (pK <sub>i</sub> 7.7–8.4) [429, 1414, 2152], <b>TCS-OX2-29</b> (pK <sub>i</sub> 6.9–7.5) [148, 879]
Labelled ligands	[ <sup>3</sup> H] <b>SB-674042</b> (Antagonist) (pK <sub>d</sub> 8.3–9.1) [1200, 1364, 1367], [ <sup>3</sup> H] <b>almorexant</b> (Antagonist) (pK <sub>d</sub> 8.6–8.9) [1364, 1367], [ <sup>125</sup> I]- <b>orexin-A</b> (Agonist) [1168, 1747, 1852]	[ <sup>3</sup> H] <b>almorexant</b> (Selective Antagonist) (pK <sub>d</sub> 8.9–9.8) [1364, 1367], [ <sup>3</sup> H] <b>Cp-1</b> (Selective Antagonist) (pK <sub>d</sub> 9.2–9.4) [1364], [ <sup>3</sup> H] <b>EMPA</b> (Selective Antagonist) (pK <sub>d</sub> 8.6–9) [1363, 1367], [ <sup>125</sup> I]- <b>orexin-A</b> (Agonist) [1168, 1747, 1852]

**Comments:** The primary coupling of orexin receptors to G<sub>q/11</sub> proteins is rather speculative and based on the strong activation of phospholipase C, though recent studies in recombinant cells also stress the importance of G<sub>q/11</sub> [1167]. Coupling of both receptors to G<sub>i/o</sub> and G<sub>s</sub> has also been reported [1046, 1170, 1255, 1769]. For most native cellular responses observed, the G protein pathway is unknown. The relative potency order of endogenous ligands depends on the cellular signal transduction machinery

[1166]. Similarly, [Ala<sup>11</sup>, D-Leu<sup>15</sup>]orexin-B, Nag 26 and YNT-185 may show variable selectivity for OX<sub>2</sub> receptors and are also likely to activate OX<sub>1</sub> receptors [1748, 1807]. Many antagonists and radioligands are not well-characterized, and thus the affinities are uncertain. Among radioligands, [<sup>3</sup>H]**SB-674042**, [<sup>3</sup>H]**EMPA** and [<sup>3</sup>H]-**almorexant** are commercially available. [<sup>3</sup>H]-**TCS 1102** (pK<sub>d/OX1</sub> 8.2, pK<sub>d/OX2</sub> 9.0) [293] and Rhodamine Green-orexin-A [445] are also useful radioligand tools. Orexin receptors have

been reported to be able to form complexes with each other and some other GPCRs as well as  $\sigma$ 1 receptors, which might affect the signaling and pharmacology [1169, 1549]. Loss-of-function mutations in the gene encoding the OX<sub>2</sub> receptor underlie canine hereditary narcolepsy [1287]. Antagonists of the orexin receptors are the focus of major drug discovery efforts for their potential to treat insomnia and other disorders of wakefulness [1816], while agonists would likely be useful in human narcolepsy.

### Further reading on Orexin receptors

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- Burdakov D. (2018) Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons. *Neuropharmacology* [PMID:30347195]
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## Oxoglutarate receptor

G protein-coupled receptors → Oxoglutarate receptor

Overview: Nomenclature as recommended by [NC-IUPHAR](#) [455].

Nomenclature	oxoglutarate receptor
HGNC, UniProt	<a href="#">OXGR1</a> , <a href="#">Q96P68</a>
Endogenous agonists	<a href="#">α-ketoglutaric acid</a> [838, 2015]

### Further reading on Oxoglutarate receptor

- Davenport AP *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**: 967–86 [PMID:23686350]
- Grimm PR and Welling PA (2017) alpha-Ketoglutarate drives electroneutral NaCl reabsorption in intercalated cells by activating a G-protein coupled receptor. *Oxgr1. Curr. Opin. Nephrol. Hypertens.* **26**: 426–433 [PMID:28771454]

## P2Y receptors

G protein-coupled receptors → P2Y receptors

**Overview:** P2Y receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on P2Y Receptors [1, 2]**) are activated by the endogenous ligands **ATP**, **ADP**, **uridine triphosphate**, **uridine diphosphate** and **UDP-glucose**. The relationship of many of the cloned receptors to endogenously ex-

pressed receptors is not yet established and so it might be appropriate to use wording such as 'uridine triphosphate-preferring (or ATP-, etc.) P2Y receptor' or 'P2Y<sub>1</sub>-like', etc., until further, as yet undefined, corroborative criteria can be applied [271, 567, 966, 2227, 2281].

Clinically used drugs acting on these receptors include the dinucleoside polyphosphate **diquafosol**, agonist of the P2Y<sub>2</sub> receptor subtype, approved in Japan for the management of dry eye disease [1207], and the P2Y<sub>12</sub> receptor antagonists **prasugrel**, **ticagrelor** and **cangrelor**, all approved as antiplatelet drugs [298, 1734].

Nomenclature	P2Y <sub>1</sub> receptor	P2Y <sub>2</sub> receptor	P2Y <sub>4</sub> receptor	P2Y <sub>6</sub> receptor
HGNC, UniProt	<i>P2RY1</i> , P47900	<i>P2RY2</i> , P41231	<i>P2RY4</i> , P51582	<i>P2RY6</i> , Q15077
Potency order of endogenous ligands	ADP > ATP	uridine triphosphate > ATP [1217]	uridine triphosphate > ATP (at rat recombinant receptors, UTP = ATP)	uridine diphosphate ≫ uridine triphosphate > ADP
Endogenous agonists	–	uridine triphosphate [1087, 1217]	–	–
Agonists	ADPβS [2088], 2MeSADP [1882, 2238]	–	–	–
Sub/family-selective agonists	–	diquafosol [1680], denufosol [1218, 1680, 2388], UTPγS [1217]	diquafosol [259], denufosol [2388], UTPγS [1218]	–
Selective agonists	MRS2365 [364], 2-Cl-ADP(α-BH <sub>3</sub> ) [85]	MRS2698 [960], 2-thioUTP [549], PSB1114 (EC <sub>50</sub> value determined using an IP <sub>3</sub> functional assay) [549, 550, 959]	MRS4062 [1390], MRS2927 [1390], (N)methanocarba-UTP [1087]	Rp-5-OMe-UDPαB [706, 774], MRS2957 [1389], MRS2693 [158]
Antagonists	suramin (pK <sub>i</sub> 5.3) [2238], PPADS (pK <sub>i</sub> 5.2) [2238]	–	–	–
Sub/family-selective antagonists	–	reactive blue-2 (pIC <sub>50</sub> 6) [981], suramin (pIC <sub>50</sub> 4.3) [981, 1882]	PPADS (pEC <sub>50</sub> 2–5) [969], reactive blue-2 (pIC <sub>50</sub> 4.7) [185] – Rat	reactive blue-2 (pK <sub>B</sub> 6) [2228], PPADS (pK <sub>B</sub> 4) [2228], suramin (pK <sub>B</sub> 4) [2228]
Selective antagonists	MRS2500 (pK <sub>i</sub> 8.8–9.1) [316, 1086], MRS2279 (pK <sub>i</sub> 7.9) [2238], MRS2179 (pK <sub>i</sub> 7–7.1) [220, 2238]	AR-C118925XX (pIC <sub>50</sub> ~6) [1064], AR-C126313 (pEC <sub>50</sub> 6) [960], PSB-416 (pIC <sub>50</sub> 4.7) [873]	ATP (pK <sub>d</sub> 6.2) [1067]	MRS2578 (pIC <sub>50</sub> 7.4) [1369], MRS2567 (pIC <sub>50</sub> 6.9) [1369]
Selective allosteric modulators	BMS compound 16 (Negative) (pK <sub>i</sub> 6.9) [2417], 2,2'-pyridylisatogen tosylate (Negative) (pIC <sub>50</sub> 6.8) [657]	–	–	–
Labelled ligands	[ <sup>3</sup> H]MRS2279 (Antagonist) (pK <sub>d</sub> 8.1) [2238], [ <sup>3</sup> H]2MeSADP (Agonist) [2088], [ <sup>35</sup> S]ADPβS (Agonist)	–	–	MRS4162 (Selective Antagonist) (pEC <sub>50</sub> 7.6) [986]



Nomenclature	P2Y <sub>11</sub> receptor	P2Y <sub>12</sub> receptor	P2Y <sub>13</sub> receptor	P2Y <sub>14</sub> receptor
HGNC, UniProt	<i>P2RY11</i> , Q96G91	<i>P2RY12</i> , Q9H244	<i>P2RY13</i> , Q9BPV8	<i>P2RY14</i> , Q15391
Potency order of endogenous ligands	ATP > ADP	ADP > ATP	ADP ≫ ATP	uridine diphosphate = UDP-glucose [311]
Endogenous agonists	–	ADP [854]	–	–
Sub/family-selective agonists	–	2MeSADP [854], ADPβS [2088]	2MeSADP [1386], 2MeSATP [1386], ADPβS [1386]	–
Selective agonists	AR-C67085 [102, 408], NF546 [1430], ATPγS [408]	–	–	α,β-methylene-2-thio-UDP [446], MRS2905 [967], 2-thio-UDP [446]
Antagonists	–	cangrelor (pIC <sub>50</sub> 9.4) [970], Ap <sub>4</sub> A (pIC <sub>50</sub> 6) [1386], 2MeSAMP (pIC <sub>50</sub> 5.4) [2088]	cangrelor (pIC <sub>50</sub> 8.3) [1386], Ap <sub>4</sub> A (pIC <sub>50</sub> 6.7) [1386], 2MeSAMP (pIC <sub>50</sub> 5.6) [1386]	–
Sub/family-selective antagonists	suramin (pIC <sub>50</sub> 4.8–6) [408], reactive blue-2 (pIC <sub>50</sub> 5) [408]	–	–	–
Selective antagonists	NF157 (pK <sub>i</sub> 7.3) [2170], NF340 (pIC <sub>50</sub> 6.4–7.1) [1430]	AZD1283 (pK <sub>i</sub> 8) [88, 2419], ARL66096 (pIC <sub>50</sub> 7.9) [932, 933], ticagrelor (pK <sub>i</sub> 7.8) [2414]	MRS2603 (pIC <sub>50</sub> 6.2) [1094], MRS2211 (pIC <sub>50</sub> 6) [1094]	PPTN (pK <sub>i</sub> 10.1) [110]
Labelled ligands	–	[ <sup>3</sup> H]2MeSADP (Agonist) [2088], [ <sup>3</sup> H]PSB-0413 (Antagonist) (pK <sub>d</sub> 8.3–8.5) [548, 1620]	[ <sup>33</sup> P]2MeSADP (Agonist) [1386]	MRS4174 (Selective Antagonist) (pK <sub>i</sub> 10.1) [1105], MRS4183 (Selective Agonist) [1104]

**Comments:** A series of 4-alkoxyimino derivatives of uridine-5'-triphosphate which could be useful for derivatization as fluorescent P2Y<sub>2/4/6</sub> receptor probes has been recently synthesized [986].

Single nucleotide polymorphisms of the P2Y<sub>1</sub> gene have been associated to different platelet reactivity to ADP ADP [863]. Three frequent nonsynonymous P2Y<sub>2</sub> receptor polymorphisms have been identified, one of which was significantly more common in cystic fibrosis patients. This polymorphism is linked to increases in Ca<sup>2+</sup> influx in transfected cells, and might therefore play a role in disease development [286]. Although uridine triphosphate

(UTP) was also shown to be a biased agonist at P2Y<sub>11</sub>, this is still under debate [1508, 2297]. A group of single nucleotide polymorphisms in the P2Y<sub>12</sub> gene, forming the so called P2Y<sub>12</sub> H2 haplotype, has been associated with increased platelet responsiveness to ADP, increased risk of peripheral arterial disease and with coronary artery disease [321]. The platelet-type bleeding disorder due to P2Y<sub>12</sub> receptor defects is an autosomal recessive condition characterized by mild to moderate mucocutaneous bleeding and excessive bleeding after surgery or trauma. The defect is due to the inability of ADP to induce platelet aggregation [317]. The P2Y<sub>13</sub>

receptor Met-158-Thr polymorphism, which is in linkage disequilibrium with the P2Y<sub>12</sub> locus, is not associated with acute myocardial infarction, diabetes mellitus or related risk factors [47]. The P2Y<sub>14</sub> receptor was previously considered to exclusively bind sugar nucleotides such as UDP-glucose and UDP-galactose [331]. However, more recent evidence with several cell lines has demonstrated that uridine diphosphate (UDP) is 5-fold more potent than UDP-glucose [311]. UDP was also shown to competitively antagonise the UDP-glucose response at the human recombinant P2Y<sub>14</sub> receptor [632].

#### Further reading on P2Y receptors

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## Parathyroid hormone receptors

G protein-coupled receptors → Parathyroid hormone receptors

**Overview:** The parathyroid hormone receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Parathyroid Hormone Receptors [662]**) are family B G protein-coupled receptors. 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 (PTHLH, P12272) (141 amino-acids) and related peptides (PTH-(1-34), PTHrP-(1-36) (PTHLH, P12272)). The parathyroid hormone 2 receptor (PTH2 receptor) is activated by the precursor-derived peptide TIP39 (PTH2, Q96A98) (39 amino acids). [<sup>125</sup>I]PTH may be used to label both PTH1 and PTH2 receptors.

Nomenclature	PTH1 receptor	PTH2 receptor
HGNC, UniProt	PTH1R, Q03431	PTH2R, P49190
Potency order of endogenous ligands	PTH (PTH, P01270) = PTHrP (PTHLH, P12272)	TIP39 (PTH2, Q96A98), PTH (PTH, P01270) ≫ PTHrP (PTHLH, P12272)
Agonists	teriparatide [660]	TIP39 (PTH2, Q96A98) [725, 887]
Selective agonists	PTHrP-(1-34) (human) [661] – Rat	–

**Comments:** The parathyroid hormone type 1 receptor (PTHR) is the canonical GPCR for PTH and PTHrP. It is coupled to G<sub>s</sub> and G<sub>q</sub> and regulates the development of bone, heart, mammary glands and other tissues in response to PTHrP, and blood concentrations of calcium and phosphate ions, as well as vitamin D, in response to PTH. Another important action of the PTH/PTHR system is to stimulate bone formation when the hormone is intermittently administered (daily injection).

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 [1018].

### Further reading on Parathyroid hormone receptors

- Cheloha RW *et al.* (2015) PTH receptor-1 signalling-mechanistic insights and therapeutic prospects. *Nat Rev Endocrinol* **11**: 712-24 [PMID:26303600]
- Vilardaga JP *et al.* (2014) Endosomal generation of cAMP in GPCR signaling. *Nat. Chem. Biol.* **10**: 700-6 [PMID:25271346]
- Gardella TJ *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCIII. The Parathyroid Hormone Receptors-Family B G Protein-Coupled Receptors. *Pharmacol. Rev.* **67**: 310-37 [PMID:25713287]

## Platelet-activating factor receptor

G protein-coupled receptors → 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 recommended by NC-IUPHAR [612]**) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1378] and lysophosphatidylcholine [1615]. It may also be activated by bacterial lipopolysaccharide [1540].

Nomenclature	PAF receptor
HGNC, UniProt	<a href="#">PTAFR</a> , <a href="#">P25105</a>
Selective agonists	<a href="#">methylcarbamyl PAF</a>
Selective antagonists	<a href="#">foropafant</a> (p <i>K</i> <sub>i</sub> 10.3) [853], <a href="#">ABT-491</a> (p <i>K</i> <sub>i</sub> 9.2) [32], <a href="#">CV-6209</a> (p <i>C</i> <sub>50</sub> 8.1–8.3) [716, 1539], <a href="#">L659989</a> (p <i>K</i> <sub>i</sub> 7.8) [937], <a href="#">apafant</a> (p <i>K</i> <sub>i</sub> 5.2–7.5) [1654, 2067]
Labelled ligands	<a href="#">[<sup>3</sup>H]PAF</a> (Agonist) [640, 1539]

**Comments:** Note that a previously recommended radioligand ([\[<sup>3</sup>H\]apafant](#); *K*<sub>d</sub> 44.6 nM) is currently unavailable.

### Further reading on Platelet-activating factor receptor

- Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-288 [PMID:15914470]
- Prescott SM *et al.* (2000) Platelet-activating factor and related lipid mediators. *Annu. Rev. Biochem.* **69**: 419-45 [PMID:10966465]
- Ishii S *et al.* (2000) Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice. *Prog. Lipid Res.* **39**: 41-82 [PMID:10729607]

## Prokineticin receptors

G protein-coupled receptors → Prokineticin receptors

**Overview:** Prokineticin receptors, PKR<sub>1</sub> and PKR<sub>2</sub> (**provisional nomenclature as recommended by NC-IUPHAR [612]**) 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, [1905]) is a potent, non-selective agonist at prokineticin receptors [1393], while Bv8, an orthologue of PROK2 from amphibians (*Bombina sp.*, [1474]), is equipotent at recombinant PKR<sub>1</sub> and PKR<sub>2</sub> [1559], and has high potency in macrophage chemotaxis assays, which are lost in PKR<sub>1</sub>-null mice.

Nomenclature	PKR <sub>1</sub>	PKR <sub>2</sub>
HGNC, UniProt	<a href="#">PROKR1</a> , <a href="#">Q8TCW9</a>	<a href="#">PROKR2</a> , <a href="#">Q8NFJ6</a>
Potency order of endogenous ligands	prokineticin-2 ( <a href="#">PROK2, Q9HC23</a> ) > prokineticin-1 ( <a href="#">PROK1, Q9HC23</a> ) > prokineticin-2β ( <a href="#">PROK2</a> ) [348, 1285, 1393, 2005]	prokineticin-2 ( <a href="#">PROK2, Q9HC23</a> ) > prokineticin-1 ( <a href="#">PROK1, Q9HC23</a> ) > prokineticin-2β ( <a href="#">PROK2</a> ) [348, 1285, 1393, 2005]
Agonists	<a href="#">MIT1</a> [1393]	<a href="#">MIT1</a> [1393]
Selective agonists	<a href="#">IS20</a> [668], <a href="#">IS1</a> [668]	–
Labelled ligands	<a href="#">[<sup>125</sup>I]BH-MIT1</a> (Agonist) [1393]	<a href="#">[<sup>125</sup>I]BH-MIT1</a> (Agonist) [1393]

**Comments:** Genetic mutations in *PROKR1* are associated with Hirschsprung's disease [1836], while genetic mutations in *PROKR2* are associated with hypogonadotropic hypogonadism with anosmia [504], hypopituitarism with pituitary stalk interruption [1792] and Hirschsprung's disease [1836]. PKR<sub>2</sub> has been recently identified as a receptor for *T. cruzi* natural infection [1077].

### Further reading on Prokineticin receptors

- Boulberdaa M *et al.* (2011) Prokineticin receptor 1 (PKR1) signalling in cardiovascular and kidney functions. *Cardiovasc. Res.* **92**: 191-8 [PMID:21856786]
- Negri L *et al.* (2018) The Prokineticins: Neuromodulators and Mediators of Inflammation and Myeloid Cell-Dependent Angiogenesis. *Physiol. Rev.* **98**: 1055-1082 [PMID:29537336]
- Negri L *et al.* (2012) Bv8/PK2 and prokineticin receptors: a druggable pronociceptive system. *Curr Opin Pharmacol* **12**: 62-6 [PMID:22136937]
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- Ngan ES *et al.* (2008) Prokineticin-signaling pathway. *Int. J. Biochem. Cell Biol.* **40**: 1679-84 [PMID:18440852]

## Prolactin-releasing peptide receptor

G protein-coupled receptors → Prolactin-releasing peptide receptor

**Overview:** The precursor (*PRLH*, P81277) for PrRP generates 31 and 20-amino-acid versions. *QRFP43* (*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 [875] derived from a FMRamide-related peptide precursor (*NPVF*, Q9HCQ7), which is cleaved to generate neuropeptide SF (*NPVF*, O15130), neuropeptide RFRP-1 (*NPVF*, Q9HCQ7), neuropeptide RFRP-2 (*NPVF*, Q9HCQ7) and neuropeptide RFRP-3 (*NPVF*, Q9HCQ7) (neuropeptide NPVF).

Nomenclature	PrRP receptor
HGNC, UniProt	<i>PRLHR</i> , P49683
Potency order of endogenous ligands	PrRP-20 ( <i>PRLH</i> , P81277) = PrRP-31 ( <i>PRLH</i> , P81277) [1201]
Endogenous agonists	PrRP-20 ( <i>PRLH</i> , P81277) [561, 1201], PrRP-31 ( <i>PRLH</i> , P81277) [561, 1201]
Endogenous antagonists	neuropeptide Y ( <i>NPY</i> , P01303) (pK <sub>i</sub> 5.4) [1190]
Labelled ligands	[ <sup>125</sup> I]PrRP-20 (human) (Agonist) [1201], [ <sup>125</sup> I]PrRP31 (Agonist) [552]

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

### Further reading on Prolactin-releasing peptide receptor

Samson WK *et al.* (2006) Prolactin releasing peptide (PrRP): an endogenous regulator of cell growth. *Peptides* **27**: 1099-103 [PMID:16500730] Takayanagi Y *et al.* (2010) Roles of prolactin-releasing peptide and RFamide related peptides in the control of stress and food intake. *FEBS J.* **277**: 4998-5005 [PMID:21126313]

## Prostanoid receptors

G protein-coupled receptors → Prostanoid receptors

**Overview:** Prostanoid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors [2329]**) are activated by the endogenous ligands prostaglandins  $\text{PGD}_2$ ,  $\text{PGE}_1$ ,  $\text{PGE}_2$ ,  $\text{PGF}_{2\alpha}$ ,  $\text{PGH}_2$ , prostacyclin [ $\text{PGI}_2$ ] and thromboxane  $\text{A}_2$ . Measurement of the potency of  $\text{PGI}_2$  and thromboxane  $\text{A}_2$  is hampered by their instability in physiological salt solution; they are often replaced by **cicaprost** and **U46619**, respectively, in receptor characterization studies.

Nomenclature	DP <sub>1</sub> receptor	DP <sub>2</sub> receptor
HGNC, UniProt	<i>PTGDR</i> , Q13258	<i>PTGDR2</i> , Q9Y5Y4
Potency order of endogenous ligands	$\text{PGD}_2 > \text{PGE}_1 \gg \text{PGE}_2 > \text{PGF}_{2\alpha} > \text{PGI}_2$ , thromboxane $\text{A}_2$	$\text{PGD}_2 \gg \text{PGF}_{2\alpha}$ , $\text{PGE}_2 > \text{PGI}_2$ , thromboxane $\text{A}_2$
Agonists	treprostinil [2071, 2300]	–
Selective agonists	BW 245C [188, 2330, 2331], L-644,698 [2330, 2331]	15(R)-15-methyl-PGD <sub>2</sub> [821, 1484, 2052]
Antagonists	–	fevipiprant (p <i>K<sub>d</sub></i> 9) [2072, 2073], ramatroban (p <i>K<sub>i</sub></i> 7.4) [2052]
Selective antagonists	laropiprant (p <i>K<sub>i</sub></i> 10.1) [2046], BWA868C (p <i>K<sub>i</sub></i> 8.6–9.3) [188, 701, 2330], ONO-AE3-237 (p <i>K<sub>i</sub></i> 7.7) [877, 2144, 2146]	CAY 10471 (p <i>C</i> <sub>50</sub> 8.9) [1832, 2174]
Labelled ligands	[ <sup>3</sup> H]PGD <sub>2</sub> (Agonist) [2314, 2330]	[ <sup>3</sup> H]PGD <sub>2</sub> (Agonist) [1394, 1949]

Nomenclature	EP <sub>1</sub> receptor	EP <sub>2</sub> receptor	EP <sub>3</sub> receptor	EP <sub>4</sub> receptor
HGNC, UniProt	<i>PTGER1</i> , P34995	<i>PTGER2</i> , P43116	<i>PTGER3</i> , P43115	<i>PTGER4</i> , P35408
Potency order of endogenous ligands	$\text{PGE}_2 > \text{PGE}_1 > \text{PGF}_{2\alpha}$ , $\text{PGI}_2 > \text{PGD}_2$ , thromboxane $\text{A}_2$	$\text{PGE}_2 = \text{PGE}_1 > \text{PGF}_{2\alpha}$ , $\text{PGI}_2 > \text{PGD}_2$ , thromboxane $\text{A}_2$	$\text{PGE}_2$ , $\text{PGE}_1 > \text{PGF}_{2\alpha}$ , $\text{PGI}_2 > \text{PGD}_2$ , thromboxane $\text{A}_2$	$\text{PGE}_2 = \text{PGE}_1 > \text{PGF}_{2\alpha}$ , $\text{PGI}_2 > \text{PGD}_2$ , thromboxane $\text{A}_2$
Endogenous agonists	–	$\text{PGE}_2$ [7, 2034, 2314]	$\text{PGE}_2$ (EP <sub>3</sub> -III isoform) [7]	–
Agonists	17-phenyl- $\omega$ -trinor-PGE <sub>2</sub> [1940]	treprostinil [2071, 2300], PGE <sub>1</sub> [119]	misoprostol (methyl ester) (EP <sub>3</sub> -III isoform) [7]	17-phenyl- $\omega$ -trinor-PGE <sub>2</sub> [2113]
Selective agonists	ONO-DI-004 [2062] – Mouse	ONO-AE1-259 [2062] – Mouse, omidenepag [1103], butaprost (free acid form) [7, 2034]	sulprostone (EP <sub>3</sub> -III isoform) [7], ONO-AE-248 [617, 1315]	L902688 [618, 1235], ONO-AE1-329 [617, 618]
Antagonists	–	–	–	EP <sub>4</sub> A (p <i>K<sub>i</sub></i> 7.6–8.5) [1340, 2406]
Selective antagonists	ONO-8711 (p <i>K<sub>i</sub></i> 9.2) [2269], SC-51322 (p <i>K<sub>i</sub></i> 7.9) [7]	PF-04418948 (PF-04418948 has weaker affinity at the EP <sub>2</sub> -receptor in guinea-pigs) (p <i>K<sub>B</sub></i> 8.3) [14, 169], TG6-129 (p <i>K<sub>B</sub></i> 8.1) [654]	L-826266 (EP <sub>3</sub> -III isoform (p <i>K<sub>i</sub></i> =8.04 in the presence of HSA)) (p <i>K<sub>i</sub></i> 9.1) [1026], ONO-AE3-240 (p <i>C</i> <sub>50</sub> 8.8) [42] – Mouse, DG-041 (p <i>K<sub>i</sub></i> 8.4) [1024]	ONO-AE3-208 (p <i>K<sub>i</sub></i> 8.5), GW 627368 (p <i>K<sub>i</sub></i> 7–7.1) [2314, 2315]
Labelled ligands	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [7, 1940, 2314]	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [7, 2314]	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [7, 2314]	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [7, 461, 2300, 2314]

Nomenclature	FP receptor	IP receptor	TP receptor
HGNC, UniProt	<a href="#">PTGFR</a> , P43088	<a href="#">PTGIR</a> , P43119	<a href="#">TBXA2R</a> , P21731
Potency order of endogenous ligands	PGF <sub>2α</sub> > PGD <sub>2</sub> > PGE <sub>2</sub> > PGI <sub>2</sub> , thromboxane A <sub>2</sub>	PGI <sub>2</sub> ≫ PGE <sub>1</sub> > PGD <sub>2</sub> , PGF <sub>2α</sub> > thromboxane A <sub>2</sub>	thromboxane A <sub>2</sub> = PGH <sub>2</sub> ≫ PGD <sub>2</sub> , PGE <sub>2</sub> , PGF <sub>2α</sub> , PGI <sub>2</sub>
Endogenous agonists	–	PGI <sub>2</sub> [1965], PGE <sub>1</sub> [1391, 2036]	–
Agonists	<a href="#">ONO-9054</a> [2366]	<a href="#">iloprost</a> [7, 2314], <a href="#">treprostinil</a> [2300]	–
Selective agonists	<a href="#">fluprostenol</a> [7], <a href="#">latanoprost (free acid form)</a> [7]	<a href="#">cicaprost</a> [7], <a href="#">MRE-269</a> [145, 1181]	<a href="#">U46619</a> [7]
Antagonists	–	–	<a href="#">ramatroban</a> (pK <sub>i</sub> 8) [2114]
Selective antagonists	<a href="#">AS604872</a> (pK <sub>i</sub> 7.5) [397]	<a href="#">RO1138452</a> (pK <sub>i</sub> 8.7) [176], <a href="#">RO3244794</a> (pA <sub>2</sub> 8.5) [176]	<a href="#">vapiprost</a> (pK <sub>i</sub> 8.3–9.4) [69, 1326], <a href="#">SQ-29548</a> (pK <sub>i</sub> 8.1–9.1) [7, 2070, 2314]
Labelled ligands	[ <sup>3</sup> H]PGF <sub>2α</sub> (Agonist) [7, 8, 2314], [ <sup>3</sup> H](+)-fluprostenol (Agonist)	[ <sup>3</sup> H]iloprost (Agonist) [7, 187, 2300, 2314]	[ <sup>125</sup> I]SAP (Antagonist) (pK <sub>d</sub> 7.7–9.3) [1538], [ <sup>125</sup> I]BOP (Agonist) [1500], [ <sup>3</sup> H]SQ-29548 (Antagonist) (pK <sub>d</sub> 7.4–8.2) [7, 2314]

**Comments:** Whilst [cicaprost](#) is selective for IP receptors, it does exhibit moderate agonist potency at EP<sub>4</sub> receptors [7]. Apart from IP receptors, [iloprost](#) also binds to EP<sub>1</sub> receptors.

The EP<sub>1</sub> agonist [17-phenyl-ω-trinor-PGE<sub>2</sub>](#) also shows agonist activity at EP<sub>3</sub> and EP<sub>4</sub> receptors [617, 2113]. [Butaprost](#) and [SC46275](#) may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1281] and TP receptors [1151, 1779]. mRNA for the EP<sub>3</sub> receptor undergoes alternative splicing to produce variants which can interfere with signalling [1632] or generate complex patterns of G-protein (G<sub>i/o</sub>, G<sub>q/11</sub>, G<sub>s</sub> and G<sub>12,13</sub>) coupling (*e.g.* [1143, 1557]). The number of

EP<sub>3</sub> receptor (protein) variants are variable depending on species, with five in human, three in rat and three in mouse. Putative receptor(s) for prostamide F (which as yet lack molecular correlates) and which preferentially recognize [PGF<sub>2</sub>-1-ethanolamide](#) and its analogues (*e.g.* [Bimatoprost](#)) have been identified, together with moderate-potency antagonists (*e.g.* [AGN 211334](#)) [2328].

The free acid form of AL-12182, [AL12180](#), used in *in vitro* studies, has a EC<sub>50</sub> of 15nM which is the concentration of the compound giving half-maximal stimulation of inositol phosphate turnover in HEK-293 cells expressing the human FP receptor [1941].

References given alongside the TP receptor agonists [I-BOP](#) [1409] and [STA<sub>2</sub>](#) [69] use human platelets as the source of TP receptors for competition radio-ligand binding assays to determine the indicated activity values.

Pharmacological evidence for a second IP receptor, denoted IP<sub>2</sub>, in the central nervous system [2091, 2272] and in the BEAS-2B human airway epithelial cell line [2317] is available. This receptor is selectively activated by 15R-17,18,19,20-tetranor-16-m-tolyl-isocarbacyclin ([15R-TIC](#)) and 15R-Deoxy 17,18,19,20-tetranor-16-m-tolyl-isocarbacyclin ([15-deoxy-TIC](#)). However, molecular biological evidence for an IP<sub>2</sub> subtype is currently lacking.

### Further reading on Prostanoid receptors

Woodward DF *et al.* (2011) International union of basic and clinical pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress. *Pharmacol. Rev.* **63**: 471-538 [PMID:21752876]

## Proteinase-activated receptors

G protein-coupled receptors → Proteinase-activated receptors

**Overview:** Proteinase-activated receptors (PARs, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Proteinase-activated Receptors [894]**) 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 **SFLLRN-NH<sub>2</sub>**, **SLIGKV-NH<sub>2</sub>**, **TFRGAP-NH<sub>2</sub>** and **GYPGQV-NH<sub>2</sub>**, respectively. With the exception of PAR3, synthetic peptides with these 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 Gα<sub>q</sub>-coupled calcium signalling, thereby preventing

activation by activating proteinases but not by agonist peptides. Neutrophil elastase (NE) cleavage of PAR1 and PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [1764]. PAR2 activation by NE regulates inflammation and pain responses [1518, 2431] and triggers mucin secretion from airway epithelial cells [2434].

Nomenclature	PAR1	PAR2	PAR3	PAR4
HGNC, UniProt	<a href="#">F2R</a> , <a href="#">P25116</a>	<a href="#">F2RL1</a> , <a href="#">P55085</a>	<a href="#">F2RL2</a> , <a href="#">O00254</a>	<a href="#">F2RL3</a> , <a href="#">Q96R10</a>
Agonist proteases	thrombin ( <a href="#">F2</a> , <a href="#">P00734</a> ), activated protein C ( <a href="#">PROC</a> , <a href="#">P04070</a> ), matrix metalloproteinase 1 ( <a href="#">MMP1</a> , <a href="#">P45452</a> ), matrix metalloproteinase 13 ( <a href="#">MMP13</a> , <a href="#">P45452</a> ) [81]	Trypsin, tryptase, TF/VIIa, Xa; elastase, neutrophil expressed; cathepsin S [1001, 1762]	thrombin ( <a href="#">F2</a> , <a href="#">P00734</a> )	thrombin ( <a href="#">F2</a> , <a href="#">P00734</a> ), trypsin, cathepsin G ( <a href="#">CTSG</a> , <a href="#">P08311</a> )
Agonists	<a href="#">F16357</a>	–	–	–
Selective agonists	<a href="#">TFLLR-NH<sub>2</sub></a> [391]	<a href="#">AY77</a> [2385], <a href="#">GB110</a> [112], 2-furoyl-LIGRLO-amide [1419], <a href="#">SLIGKV-NH<sub>2</sub></a> [1241], <a href="#">SLIGRL-NH<sub>2</sub></a> [1241]	–	<a href="#">AYPGKF-NH<sub>2</sub></a> , <a href="#">GYPGKF-NH<sub>2</sub></a> , <a href="#">GYPGQV-NH<sub>2</sub></a>
Selective antagonists	<a href="#">vorapaxar</a> (p <i>K<sub>i</sub></i> ; 8.1) [327], <a href="#">atopaxar</a> (p <i>C</i> <sub>50</sub> 7.7) [1124], <a href="#">RWJ-56110</a> (p <i>C</i> <sub>50</sub> 6.4) [52]	<a href="#">I-191</a> (p <i>C</i> <sub>50</sub> 7.1) [1000], <a href="#">AZ8838</a> (p <i>K<sub>d</sub></i> 6.5) [360], <a href="#">GB88</a> (p <i>C</i> <sub>50</sub> 5.7) [2050], <a href="#">P2pal18s</a> [1933]	–	<a href="#">BMS-986120</a> (p <i>K<sub>d</sub></i> 10) [2325], <a href="#">YD-3</a> (p <i>C</i> <sub>50</sub> 6.9) [2283], <a href="#">ML354</a> (p <i>C</i> <sub>50</sub> 6.8) [2283], <a href="#">P4pal-10</a> [427], <a href="#">RAG8</a> (Agonist) [1763]
Allosteric modulators	–	<a href="#">AZ3451</a> (Negative) (p <i>C</i> <sub>50</sub> 7.6) [360]	–	–
Labelled ligands	<a href="#">[<sup>3</sup>H]haTRAP</a> (Agonist) [19]	2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH <sub>2</sub> (Agonist) [895], 2-furoyl-LIGRL[N[ <sup>3</sup> H]propionyl]-O-NH <sub>2</sub> (Agonist) [895], [ <sup>3</sup> H]2-furoyl-LIGRL-NH <sub>2</sub> (Selective Agonist) [1040], <a href="#">trans-cinnamoyl-LIGRLO [N-[<sup>3</sup>H]propionyl]-NH<sub>2</sub></a> (Agonist) [30]	–	–
Comments	<a href="#">TFLLR-NH<sub>2</sub></a> is selective relative to the PAR <sub>2</sub> receptor [171, 1053].	2-Furoyl-LIGRLO-NH <sub>2</sub> activity was measured via calcium mobilisation in HEK 293 cells which constitutively coexpress human PAR <sub>1</sub> and PAR <sub>2</sub> .	–	–

**Comments:** 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 ([TMPRSS15](#), [P98073](#)) on pancreatic-derived trypsinogen ([PRSSI](#), [P07477](#)); tryptase, a family of enzymes ( $\alpha/\beta 1$  [TPSAB1](#), [Q15661](#);  $\gamma 1$  [TPSG1](#), [Q9NRR2](#);  $\delta 1$  [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](#)).



### Further reading on Proteinase-activated receptors

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## QRFP receptor

G protein-coupled receptors → QRFP receptor

**Overview:** The human gene encoding the QRFP receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the QRFP receptor [1259]**; QRFP, formerly known as the Peptide P518 receptor), previously designated as an orphan GPCR receptor was identified in 2001 by Lee *et al.* from a hypothalamus cDNA library [1237]. However, the reported cDNA (AF411117) is a chimera with bases 1-127 derived from chromosome 1 and bases 155-1368 derived from chromosome 4. When corrected, QRFP (also referred to as SP9155 or AQ27) encodes a 431 amino acid protein that shares sequence similarities in the transmembrane spanning regions with other peptide receptors. These include neuropeptide FF2 (38%), neuropeptide Y<sub>2</sub> (37%) and galanin Gal<sub>1</sub> (35%) receptors.

Nomenclature	QRFP receptor
HGNC, UniProt	QRFP, Q96P65
Endogenous agonists	QRFP26 (QRFP) [343, 999]
Agonists	LV-2186 [41], LV-2172 [1572]
Selective antagonists	compound 25e (pIC <sub>50</sub> 7.3) [687, 688]
Labelled ligands	[ <sup>125</sup> I]QRFP43 (human) (Agonist) [641, 1164, 2090], [ <sup>125</sup> I]26RFa (human) (Agonist) [260]

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

### Further reading on QRFP receptor

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# Relaxin family peptide receptors

G protein-coupled receptors → Relaxin family peptide receptors

**Overview:** Relaxin family peptide receptors (RXFP, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Relaxin family peptide receptors** [120, 785]) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are heterodimeric peptide hormones structurally related to insulin: **relaxin-1** (*RLN1*, P04808), **relaxin** (*RLN2*, P04090), **relaxin-3** (*RLN3*, Q8WXF3) (also known as INSL7), insulin-like peptide 3 (*INSL3* (*INSL3*, P51460)) and *INSL5* (*INSL5*,

Q9Y5Q6). Species homologues of relaxin have distinct pharmacology and **relaxin** (*RLN2*, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [1912]. **Relaxin-3** (*RLN3*, Q8WXF3) is the ligand for RXFP3 but it also binds to RXFP1 and RXFP4 and has differential affinity for RXFP2 between species [1911]. *INSL5* (*INSL5*, Q9Y5Q6) is the ligand for RXFP4 but is a weak antagonist of RXFP3. **Relaxin** (*RLN2*, P04090) and *INSL3* (*INSL3*, P51460) have

multiple complex binding interactions with RXFP1 [1930] and RXFP2 [886] which direct the N-terminal LDL $\alpha$  modules of the receptors together with a linker domain to act as a tethered ligand to direct receptor signaling [1913]. *INSL5* (*INSL5*, Q9Y5Q6) and **relaxin-3** (*RLN3*, Q8WXF3) interact with their receptors using distinct residues in their B-chains for binding, and activation, respectively [921, 2324].

Nomenclature	RXFP1	RXFP2	RXFP3	RXFP4
HGNC, UniProt	<i>RXFP1</i> , Q9HBX9	<i>RXFP2</i> , Q8WXD0	<i>RXFP3</i> , Q9NSD7	<i>RXFP4</i> , Q8TDU9
Potency order of endogenous ligands	relaxin ( <i>RLN2</i> , P04090) = relaxin-1 ( <i>RLN1</i> , P04808) > relaxin-3 ( <i>RLN3</i> , Q8WXF3) [2049]	<i>INSL3</i> ( <i>INSL3</i> , P51460) > relaxin ( <i>RLN2</i> , P04090) >> relaxin-3 ( <i>RLN3</i> , Q8WXF3) [1174, 2049]	relaxin-3 ( <i>RLN3</i> , Q8WXF3) > relaxin-3 (B chain) ( <i>RLN3</i> , Q8WXF3) > relaxin ( <i>RLN2</i> , P04090) [1296]	<i>INSL5</i> ( <i>INSL5</i> , Q9Y5Q6) = relaxin-3 ( <i>RLN3</i> , Q8WXF3) > relaxin-3 (B chain) ( <i>RLN3</i> , Q8WXF3) [1294, 1295]
Endogenous antagonists	–	–	<i>INSL5</i> ( <i>INSL5</i> , Q9Y5Q6) (p <i>K<sub>i</sub></i> 7) [2438]	–
Antagonists	B-R13/17K H2 relaxin (pEC <sub>50</sub> 5.7–6.7) [913, 1570]	–	R3(B $\Delta$ 23-27)R/I5 chimeric peptide (pIC <sub>50</sub> 9.2) [1165]	R3(B $\Delta$ 23-27)R/I5 chimeric peptide (pIC <sub>50</sub> 8–8.6) [823, 1165]
Selective antagonists	–	A(9-26) <i>INSL3</i> (p <i>K<sub>i</sub></i> 9.1) [912], A(10-24) <i>INSL3</i> (p <i>K<sub>i</sub></i> 8.7) [912], A(C10/15S) <i>INSL3</i> (p <i>K<sub>i</sub></i> 8.6) [2422], <i>INSL3</i> B chain dimer analogue 8 (p <i>K<sub>i</sub></i> 8.5) [1938], A( $\Delta$ 10/15C) <i>INSL3</i> (p <i>K<sub>i</sub></i> 8.3) [2422], cyclic <i>INSL3</i> B-chain analogue 6 (p <i>K<sub>i</sub></i> 6.7) [1936], <i>INSL3</i> B-chain analogue (p <i>K<sub>i</sub></i> 5.1) [479], (des 1-8) A-chain <i>INSL3</i> analogue [285]	minimised relaxin-3 analogue 3 (p <i>K<sub>i</sub></i> 7.6) [1934], R3-B1-22R (p <i>K<sub>i</sub></i> 7.4) [823]	minimised relaxin-3 analogue 3 (pIC <sub>50</sub> 6.6) [1934]
Allosteric modulators	ML290 (Agonist) (pEC <sub>50</sub> 7) [2346, 2349]	–	–	–
Labelled ligands	[ <sup>33</sup> P]relaxin (human) (Agonist) [786, 2049], europium-labelled relaxin (Agonist) [1935], [ <sup>125</sup> I]relaxin (human) (Agonist)	[ <sup>125</sup> I] <i>INSL3</i> (human) (Agonist) [1516], [ <sup>33</sup> P]relaxin (human) (Agonist) [786, 2049]	[ <sup>125</sup> I]relaxin-3 (human) (Agonist) [1296], [ <sup>125</sup> I]relaxin-3-B/ <i>INSL5</i> A chimera (Agonist) [1294], europium-labelled relaxin-3-B/ <i>INSL5</i> A chimera (Agonist) [823]	[ <sup>125</sup> I]relaxin-3 (human) (Agonist) [1295], [ <sup>125</sup> I]relaxin-3-B/ <i>INSL5</i> A chimera (Agonist) [1294], europium-labelled mouse <i>INSL5</i> (Agonist) [135], europium-labelled relaxin-3-B/ <i>INSL5</i> A chimera (Agonist) [823], europium-labelled <i>INSL5</i> (p <i>K<sub>d</sub></i> 8.3) [823]
Comments	–	Europium-labelled <i>INSL3</i> is a fluorescent ligand for this receptor ( <i>K<sub>d</sub></i> =1 nM) [1937].	–	–

**Comments:** Relaxin (*RLN2*, P04090) is the cognate peptide ligand for RXFP1 and is in extended Phase III clinical trials for the treatment of acute heart failure [1435]. Relaxin has vasodilatory, anti-fibrotic, angiogenic, anti-apoptotic and anti-inflammatory effects. A small molecule allosteric agonist ML290 has been developed [1944, 2349], and a relaxin B-chain mimetic peptide B7-33 has been developed which has cell specific signaling properties [911]. The antifibrotic actions of relaxin are dependent on the angiotensin receptor AT<sub>2</sub> [377]. *INSL3* (*INSL3*, P51460) is the cognate peptide for RXFP2 and is a circulating hormone that in males is essential for testicular descent *in utero* [1556] and in females has important roles in ovarian follicle function [961]. In adults, *INSL3*

has potential roles in testicular function [962] and the musculoskeletal system [472]. RXFP2 is also present in brain, associated with cortico-thalamic motor circuits [1917]. cAMP elevation is the major signalling pathway for both RXFP1 and RXFP2 [919, 920], but RXFP1 also activates MAP kinases, nitric oxide signalling, and tyrosine kinase phosphorylation; and relaxin can interact with glucocorticoid receptors [787]. Receptor expression profiles suggest that RXFP3 is a brain neuropeptide receptor and RXFP4 a gut hormone receptor. The brain relaxin-3/RXFP3 system modulates feeding [652, 653, 823, 1934, 1992] *via* effects in hypothalamus [475, 652, 1039], anxiety [1842, 2415], reward and motivated, goal-directed behaviours [906, 1842, 2239], and spatial and so-

cial memory [34, 780]. Of the other relaxin peptides, relaxin-3 (*RLN3*, Q8WXF3) is an agonist at RXFP3 and RXFP4 whereas *INSL5* (*INSL5*, Q9Y5Q6) is an agonist at RXFP4 and a weak antagonist at RXFP3. *INSL5* (*INSL5*, Q9Y5Q6) is secreted from enteroendocrine L cells and the *INSL5*/RXFP4 system affects food intake [751] and glucose homeostasis [1331]. RXFP3 and RXFP4 couple to G<sub>i/o</sub> and inhibit adenylyl cyclase [1296, 2191], and also cause Erk1/2 phosphorylation [2191]. RXFP4 also causes phosphorylation of p38MAPK, Akt and S6RP [55] and GLP-1 secretion *in vitro* [54]. There is evidence that at RXFP3, relaxin (*RLN2*, P04090) is a biased ligand compared to the cognate ligand relaxin-3 (*RLN3*, Q8WXF3) [2191].

### Further reading on Relaxin family peptide receptors

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## Somatostatin receptors

G protein-coupled receptors → Somatostatin receptors

**Overview:** Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (SST<sub>1</sub>-SST<sub>5</sub>; **nomenclature as agreed by the NC-IUPHAR Subcommittee on Somatostatin Receptors [773]**). Activation of these receptors produces a wide range of physiological effects throughout the body including the inhibition of secretion of many hormones. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14 (SST, P61278)) and somatostatin-28 (SRIF-28 (SST, P61278)). Cortistatin-14 {Mouse, Rat} has also been suggested to be an endogenous ligand for somatostatin receptors [468].

Nomenclature	SST <sub>1</sub> receptor	SST <sub>2</sub> receptor	SST <sub>3</sub> receptor	SST <sub>4</sub> receptor	SST <sub>5</sub> receptor
HGNC, UniProt	SSTR1, P30872	SSTR2, P30874	SSTR3, P32745	SSTR4, P31391	SSTR5, P35346
Agonists	pasireotide [1893]	pasireotide [1893], veldoreotide [15]	pasireotide [1893]	NNC269100 [1306], veldoreotide [15]	pasireotide [1893], veldoreotide [15]
Selective agonists	L-797,591 [1817], Des-Ala <sup>1,2,5</sup> -[D-Trp <sup>8</sup> ,IAmP <sup>9</sup> ]SRIF [565]	L-054,522 [2376], BIM 23027 [313], L-779,976 [1817], octreotide [257, 1666, 1966, 1967, 1968, 2376], lanreotide [257, 1666, 1966, 1967, 1968]	L-796,778 [1817]	L-803,087 [1817], J-2156 [562]	BIM 23052 [1439, 1966, 1967, 1968], L-817,818 [1817]
Selective antagonists	SRA880 (pK <sub>d</sub> 8–8.1) [916]	DOTA- <sub>JR11</sub> [326]	MK-4256 (pIC <sub>50</sub> 9.2) [837], ACQ090 (pK <sub>i</sub> 7.9) [917]	–	SSA1 (pK <sub>i</sub> 9.3) [585]

**Comments:** [<sup>125</sup>I]Tyr<sup>11</sup>-SRIF-14, [<sup>125</sup>I]LTT-SRIF-28, [<sup>125</sup>I]CGP 23996 and [<sup>125</sup>I]Tyr<sup>10</sup>-CST14 may be used to label somatostatin receptors nonselectively. A number of nonpeptide subtype-selective agonists have been synthesised [1817]. Octreotide and lanreotide are being used in the treatment of SST<sub>2</sub>-expressing neuroendocrine tumors and pasireotide for SST<sub>5</sub>-expressing neuroendocrine tumors. A novel peptide somatostatin analogue, veldoreotide (COR-005), has affinity for SST<sub>2</sub>, SST<sub>4</sub> and SST<sub>5</sub> receptors and is a potent inhibitor of GH secretion [1717, 1954].

### Further reading on Somatostatin receptors

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## Succinate receptor

G protein-coupled receptors → Succinate receptor

**Overview: Nomenclature as recommended by NC-IUPHAR [455].** The Succinate receptor has been identified as being activated by physiological levels of the Krebs cycle intermediate succinate and other dicarboxylic acids such as maleate in 2004. Since its pairing with its endogenous ligand, the receptor has been the focus of intensive research and its role has been evidenced in various (patho)physiological processes such as regulation of renin production, retinal angiogenesis, inflammation or immune response.

Nomenclature	<a href="#">succinate receptor</a>
HGNC, UniProt	<a href="#">SUCNR1</a> , <a href="#">Q9BXA5</a>
Endogenous agonists	<a href="#">succinic acid</a> [838, 2015], <a href="#">maleic acid</a> [696]
Agonists	<a href="#">compound 31</a> (Partial agonist) [1791], <a href="#">cis-epoxysuccinic acid</a> [2153], <a href="#">compound 130</a> (Partial agonist) [2153], <a href="#">cis-epoxysuccinic acid</a> [696], <a href="#">maleic acid</a> [703], <a href="#">maleic acid</a> [838]

**Comments:** In humans, there is the possibility of two open-reading frames (ORFs) for *SUCNR1*, one giving a protein of 330 amino acids (AA) and the other one 334-AA. Wittenberger *et al.* [2322] noted that the 330-AA protein was more likely to be expressed given the Kozak sequence surrounding the second ATG. Some databases report *SUCNR1* as being 334-AA long.

### Further reading on Succinate receptor

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# Tachykinin receptors

G protein-coupled receptors → Tachykinin receptors

**Overview:** Tachykinin receptors (**provisional nomenclature as recommended by NC-IUPHAR [612]**) are activated by the endogenous peptides **substance P** (*TAC1*, P20366) (SP), **neurokinin A** (*TAC1*, P20366) (NKA; previously known as substance K, neurokinin  $\alpha$ , neuromedin L), **neurokinin B** (*TAC3*, Q9UHF0) (NKB; previously known as neurokinin  $\beta$ , neuromedin

K), **neuropeptide K** (*TAC1*, P20366) and **neuropeptide  $\gamma$**  (*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. Antagonists such as **aprepitant** and **fosaprepitant** were approved by FDA and EMA, in combination with other antiemetic agents, for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

	NK <sub>1</sub> receptor	NK <sub>2</sub> receptor	NK <sub>3</sub> receptor
Nomenclature	NK <sub>1</sub> receptor	NK <sub>2</sub> receptor	NK <sub>3</sub> receptor
HGNC, UniProt	<i>TACR1</i> , P25103	<i>TACR2</i> , P21452	<i>TACR3</i> , P29371
Potency order of endogenous ligands	substance P ( <i>TAC1</i> , P20366) > neurokinin A ( <i>TAC1</i> , P20366) > neurokinin B ( <i>TAC3</i> , Q9UHF0)	neurokinin A ( <i>TAC1</i> , P20366) > neurokinin B ( <i>TAC3</i> , Q9UHF0) $\gg$ substance P ( <i>TAC1</i> , P20366)	neurokinin B ( <i>TAC3</i> , Q9UHF0) > neurokinin A ( <i>TAC1</i> , P20366) > substance P ( <i>TAC1</i> , P20366)
Agonists	substance P-OMe [2130]	–	–
Selective agonists	[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP [2130], septide [139, 820], [Pro <sup>9</sup> ]SP [2145] – Rat	[Lys <sup>5</sup> ,Me-Leu <sup>9</sup> ,Nle <sup>10</sup> ]NKA-(4-10) [1406] – Rat, GR64349 [476] – Rat, [ $\beta$ Ala <sup>8</sup> ]neurokinin A-(4-10) [556]	[Phe(Me) <sup>7</sup> ]neurokinin B [1868, 1869], senktide [1868, 1869, 2130]
Antagonists	L760735 (pIC <sub>50</sub> 9.7) [815]	–	–
Selective antagonists	aprepitant (pK <sub>i</sub> 10.1) [781, 782], CP 99994 (pK <sub>i</sub> 9.3–9.7) [57, 1869], RP67580 (pIC <sub>50</sub> 7.7) [610]	GR94800 (pK <sub>i</sub> 9.8) [223], saredutant (pK <sub>i</sub> 9.4–9.7) [57, 556, 1869], GR 159897 (pK <sub>d</sub> 7.8–9.5) [147, 556, 1999], MEN10627 (pK <sub>i</sub> 9.2) [699], nepadutant (pK <sub>i</sub> 8.5–8.7) [314, 394]	osanetant (pK <sub>i</sub> 8.4–9.7) [57, 125, 393, 555, 1034, 1641, 1868, 1869, 2130], talnetant (pK <sub>i</sub> 7.4–9) [142, 700, 1868, 1869], PD157672 (pIC <sub>50</sub> 7.8–7.9) [182, 2130]
Labelled ligands	[ <sup>125</sup> I]L703,606 (Antagonist) (pK <sub>d</sub> 9.5) [621], [ <sup>125</sup> I]BH-[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP (Agonist) [2150] – Rat, [ <sup>3</sup> H]SP (human, mouse, rat) (Agonist) [93], [ <sup>125</sup> I]SP (human, mouse, rat) (Agonist), [ <sup>18</sup> F]SPA-RQ (Antagonist) [367]	[ <sup>3</sup> H]saredutant (Antagonist) (pK <sub>d</sub> 9.7) [749] – Rat, [ <sup>125</sup> I]NKA (human, mouse, rat) (Agonist) [2267], [ <sup>3</sup> H]GR100679 (Antagonist) (pK <sub>d</sub> 9.2) [778]	[ <sup>3</sup> H]osanetant (Antagonist) (pK <sub>d</sub> 9.9), [ <sup>3</sup> H]senktide (Agonist) [760] – Guinea pig, [ <sup>125</sup> I][MePhe <sup>7</sup> ]NKB (Agonist)

**Comments:** The NK<sub>1</sub> receptor has also been described to couple to G proteins other than G<sub>q/11</sub> [1828]. The crystal structure of the human NK<sub>1</sub> receptor in complex with antagonists has been determined [1909, 2391]. The hexapeptide agonist sep-

ptide appears to bind to an overlapping but non-identical site to **substance P** (*TAC1*, P20366) on the NK<sub>1</sub> receptor. There are additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK<sub>3</sub> receptor was

found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells [509, 1150].

### Further reading on Tachykinin receptors

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## Thyrotropin-releasing hormone receptors

G protein-coupled receptors → Thyrotropin-releasing hormone receptors

**Overview:** Thyrotropin-releasing hormone (TRH) receptors (**provisional nomenclature as recommended by NC-IUPHAR [612]**) are activated by the endogenous tripeptide TRH (TRH, P20396) (pGlu-His-ProNH<sub>2</sub>). TRH (TRH, P20396) and TRH analogues fail to distinguish TRH<sub>1</sub> and TRH<sub>2</sub> receptors [2059]. [<sup>3</sup>H]TRH (human, mouse, rat) is able to label both TRH<sub>1</sub> and TRH<sub>2</sub> receptors with K<sub>d</sub> values of 13 and 9 nM respectively. Synthesis and biology of ring-modified L-Histidine containing TRH analogues has been reported [1429].

Nomenclature	TRH <sub>1</sub> receptor	TRH <sub>2</sub> receptor
HGNC, UniProt	TRHR, P34981	–
Antagonists	diazepam (pK <sub>i</sub> 5.2) [522] – Rat	–
Selective antagonists	midazolam (pK <sub>i</sub> 5.5) [522] – Rat, chlordiazepoxide (pK <sub>i</sub> 4.8) [522] – Rat, chlordiazepoxide (pK <sub>i</sub> 4.7) [2042] – Mouse	–
Comments	–	A class A G protein-coupled receptor: not present in man

### Further reading on Thyrotropin-releasing hormone receptors

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## Trace amine receptor

G protein-coupled receptors → Trace amine receptor

**Overview:** Trace amine-associated receptors were discovered from a search for novel 5-HT receptors [205], where 15 mammalian orthologues were identified and divided into two families. The TA<sub>1</sub> receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Trace amine receptor**

[1355]) has affinity for the endogenous trace amines tyramine, β-phenylethylamine and octopamine in addition to the classical amine dopamine [205]. Emerging evidence suggests that TA<sub>1</sub> is a modulator of monoaminergic activity in the brain [2351] with TA<sub>1</sub> and dopamine D<sub>2</sub> receptors shown to form constitu-

tive heterodimers when co-expressed [572]. In addition to trace amines, receptors can be activated by amphetamine-like psychostimulants, and endogenous thyronamines.

Nomenclature	TA <sub>1</sub> receptor
HGNC, UniProt	TAAR1, Q96RJO
Potency order of endogenous ligands	tyramine > β-phenylethylamine > octopamine = dopamine [205]
Agonists	RO5166017 [1790]
Antagonists	EPPTB (Inverse agonist) (pIC <sub>50</sub> 5.1) [222]
Labelled ligands	[ <sup>3</sup> H]tyramine (Agonist) [205]

**Comments:** In addition to TA<sub>1</sub>, in man there are up to 5 functional TAAR genes (TAAR2,5,6,8,9). See [205] for detailed discussion. The product of the gene TAAR2 (also known as GPR58) appears to respond to β-phenylethylamine > tyramine and to couple through G<sub>s</sub> [205].

TAAR3, in some individuals, and TAAR4 are pseudogenes in man, although functional in rodents. The signalling characteristics and pharmacology of TAAR<sub>5</sub> (PNR, Putative Neurotransmitter Receptor: TAAR5, O14804), TAAR<sub>6</sub> (Trace amine receptor 4, TaR-4: TAAR6, 96RI8), TAAR<sub>8</sub> (Trace amine receptor 5, GPR102: TAAR8, Q969N4) and TAAR<sub>9</sub> (trace amine associated receptor 9: TAAR9,

96RI9) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have affinity for rodent cloned trace amine receptors, including TA<sub>1</sub> [1881]. An antagonist EPPTB has recently been described with a pK<sub>i</sub> of 9.1 at the mouse TA<sub>1</sub> but >5.3 for human TA<sub>1</sub> [2025].

### Further reading on Trace amine receptor

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# Urotensin receptor

G protein-coupled receptors → Urotensin receptor

**Overview:** The urotensin-II (U-II) receptor (UT, **nomenclature as agreed by the NC-IUPHAR Subcommittee on the Urotensin receptor** [516, 612, 2211]) is activated by the endogenous dodecapeptide **urotensin-II** (*UTS2*, O95399), originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [150, 2210]. 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 pre-

dicted receptor encoded by the rat gene *gpr14* [425, 1304, 1498, 1603]. Human **urotensin-II** (*UTS2*, O95399), an 11-amino-acid peptide [425], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding [240, 1101]. This sequence is also conserved in the deduced amino-acid sequence of rat **urotensin-II** {Rat} (14 amino-acids) and mouse **urotensin-II** {Mouse} (14 amino-acids), although the N-terminal is more divergent from the human sequence [424]. A second endogenous

ligand for the UT has been discovered in rat [2053]. This is the **urotensin II-related peptide** (*UTS2B*, Q76510), an octapeptide that is derived from a different gene, but shares the C-terminal sequence (CFWKYCV) common to U-II from other species. Identical sequences to rat **urotensin II-related peptide** (*UTS2B*, Q76510) are predicted for the mature mouse and human peptides [523]. UT exhibits relatively high sequence identity with somatostatin, opioid and galanin receptors [2211].

Nomenclature	UT receptor
HGNC, UniProt	<i>UTS2R</i> , Q9UKP6
Endogenous agonists	<b>urotensin II-related peptide</b> ( <i>UTS2B</i> , Q76510) [523, 1354], <b>urotensin-II</b> ( <i>UTS2</i> , O95399) [517, 554, 747]
Selective agonists	[Pen <sup>5</sup> ]U-(4-11) (human) [747], U-II-(4-11) (human) [747], [3-iodo-Tyr <sup>6</sup> ]U-II-(4-11) (human) [1187], Urolinin [104], FL104 [1246, 1248], AC-7954 [436, 1247]
Selective antagonists	urantide (pK <sub>i</sub> 8.3) [1661], [Orn <sup>5</sup> ]URP (pK <sub>i</sub> 7.2) [492] – Rat, palosuran (pIC <sub>50</sub> 7.1) [402], SB-611812 (pK <sub>i</sub> 6.6) [1760], [Cha <sup>6</sup> ]U-II-(4-11) (pK <sub>i</sub> 6.4) [344] – Rat
Labelled ligands	[ <sup>125</sup> I]U-II (human) (Agonist) [46, 214, 344, 1354], [ <sup>125</sup> I]N-biotin-[Ahx <sup>0</sup> , Bpa <sup>3</sup> ]U-II (human) [503]

**Comments:** In the human vasculature, human **urotensin-II** (*UTS2*, O95399) elicits both vasoconstrictor (pD<sub>2</sub> 9.3-10.1, [1354]) and vasodilator (pIC<sub>50</sub> 10.3-10.4, [2035]) responses.

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## Vasopressin and oxytocin receptors

G protein-coupled receptors → Vasopressin and oxytocin receptors

**Overview:** Vasopressin (AVP) and oxytocin (OT) receptors (**nomenclature as recommended by NC-IUPHAR [612]**) are activated by the endogenous cyclic nonapeptides **vasopressin (AVP, P01185)** and **oxytocin (OXT, P01178)**. These peptides are derived from precursors which also produce neurophysins (neurophysin I for oxytocin; neurophysin II for vasopressin). Vasopressin and oxytocin differ at only 2 amino acids (positions 3 and 8). There are metabolites of these neuropeptides that may be biologically active [474].

Nomenclature	V <sub>1A</sub> receptor	V <sub>1B</sub> receptor
HGNC, UniProt	AVPR1A, P37288	AVPR1B, P47901
Potency order of endogenous ligands	vasopressin (AVP, P01185) > oxytocin (OXT, P01178) [26, 359, 419, 1541, 1851, 2078, 2115]	vasopressin (AVP, P01185) > oxytocin (OXT, P01178) [26, 359, 486, 748, 1541, 1851, 2078, 2116]
Selective agonists	F180 [53, 419]	d[Leu <sup>4</sup> ]LVP [1679], d[Cha <sup>4</sup> ]AVP [486, 748]
Antagonists	conivaptan (pK <sub>i</sub> 8.2–8.4) [2078, 2079]	nelivaptan (pK <sub>i</sub> 8.4–9.3) [748, 1929]
Selective antagonists	relcovaptan (pK <sub>i</sub> 8.1–9.3) [26, 419, 748, 2078, 2115], d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> ,Arg <sup>8</sup> ]VP (pK <sub>i</sub> 9)	–
Labelled ligands	[ <sup>125</sup> I]OH-LVA (Antagonist) (pK <sub>d</sub> 10.3–10.4) [369, 419], [ <sup>3</sup> H]AVP (human, mouse, rat) (Agonist) [231, 369, 2078, 2079, 2115], [ <sup>3</sup> H]d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> ]AVP (Antagonist) (pK <sub>d</sub> 9)	[ <sup>3</sup> H]AVP (human, mouse, rat) (Agonist) [486, 1851, 2078, 2079, 2116]

Nomenclature	V <sub>2</sub> receptor	OT receptor
HGNC, UniProt	AVPR2, P30518	OXT, P30559
Potency order of endogenous ligands	vasopressin (AVP, P01185) > oxytocin (OXT, P01178) [26, 359, 369, 1679, 1927, 2078, 2365]	oxytocin (OXT, P01178) > vasopressin (AVP, P01185) [26, 369, 370, 396, 748, 984, 1096]
Selective agonists	VNA932 [582], OPC-51803 [1541], d[Val <sup>4</sup> ,DArg <sup>8</sup> ]VP	[Thr <sup>4</sup> ,Gly <sup>7</sup> ]OT [370, 551, 984]
Antagonists	–	L-371,257 (pK <sub>i</sub> 8.8) [748]
Selective antagonists	conivaptan (pK <sub>i</sub> 9.4) [435], tolvaptan (pK <sub>i</sub> 9.4) [2365], satavaptan (pK <sub>i</sub> 8.4–9.3) [26, 420, 1926, 1927, 2078], lixivaptan (Inverse agonist) (pK <sub>i</sub> 8.9–9.2) [36, 1927], d(CH <sub>2</sub> ) <sub>5</sub> [D-Ile <sup>2</sup> ,Ile <sup>4</sup> ]AVP (pK <sub>i</sub> 6.9–8.4) [420, 1927], mozavaptan (Inverse agonist) (pK <sub>i</sub> 7.4–8.1) [420, 1927, 2078, 2116, 2365]	SSR126768A (pK <sub>i</sub> 8.8–9.1) [1928], desGlyNH <sub>2</sub> -d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> ,Thr <sup>4</sup> ,Orn <sup>8</sup> ]OT (pK <sub>i</sub> 8.5), L-372662 (pK <sub>i</sub> 8.4) [136]
Labelled ligands	[ <sup>3</sup> H]AVP (human, mouse, rat) (Agonist) [420, 1541, 2078, 2079, 2365], [ <sup>3</sup> H]dDAVP (Agonist) [1383], [ <sup>3</sup> H]desGly-NH <sub>2</sub> [D-Ile <sup>2</sup> ,Ile <sup>4</sup> ]VP (pK <sub>d</sub> 8.6)	[ <sup>125</sup> I]d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sup>2</sup> ,Thr <sup>4</sup> ,Orn <sup>8</sup> ,Tyr-NH <sub>2</sub> <sup>9</sup> ]OVT (Antagonist) (pK <sub>d</sub> 10), [ <sup>3</sup> H]OT (human, mouse, rat) (Agonist) [369, 637, 984, 1098], [ <sup>111</sup> In]DOTA-dLVT (pK <sub>d</sub> 8.3) [368]

**Comments:** Vasopressin and oxytocin receptors have a characteristic and sometimes overlapping distribution in a number of tissues including brain. There are phylogenetic, ontogenetic and sex-specific differences in the levels and distribution of these receptors, particularly in the brain. The V<sub>2</sub> receptor exhibits marked species differences, such that many ligands

(d(CH<sub>2</sub>)<sub>5</sub>[D-Ile<sup>2</sup>,Ile<sup>4</sup>]AVP and [<sup>3</sup>H]desGly-NH<sub>2</sub>[D-Ile<sup>2</sup>,Ile<sup>4</sup>]VP) exhibit low affinity at human V<sub>2</sub> receptors [31]. Similarly, DAVP is more V<sub>2</sub> selective in the rat than in the human [1851]. The gene encoding the V<sub>2</sub> receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [164]. D[Cha<sup>4</sup>]AVP is selective only for the human and bovine V<sub>1B</sub> receptors [486], while

d[Leu<sup>4</sup>]LVP has high affinity for the rat V<sub>1B</sub> receptor [1679]. Knockouts of vasopressin and oxytocin receptors have system-specific defects (e.g., impaired ability to concentrate urine in V<sub>2</sub> receptor knockouts) which include behavioural deficits (principally in V<sub>1A</sub>, V<sub>1B</sub> and OT receptor knockouts).

### Further reading on Vasopressin and oxytocin receptors

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## VIP and PACAP receptors

G protein-coupled receptors → VIP and PACAP receptors

**Overview:** Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors [812, 813]**) are activated by the endogenous peptides VIP (VIP, P01282), PACAP-38 (ADCYAP1, P18509), PACAP-27 (ADCYAP1, P18509), peptide histidine isoleucineamide (PHI {Mouse, Rat}), peptide histidine methionineamide (PHM (VIP, P01282)) and peptide histidine valine (PHV (VIP, P01282)). VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors dis-

play comparable affinity for the PACAP peptides, PACAP-27 (ADCYAP1, P18509) and PACAP-38 (ADCYAP1, P18509), 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 PAC<sub>1</sub> receptor. However, one splice variant of the human PAC<sub>1</sub> receptor has been reported to respond to PACAP-38 (ADCYAP1, P18509), PACAP-27 (ADCYAP1, P18509) and VIP (VIP, P01282) with comparable affinity [452]. PG 99-465 [1492] has been used as a selec-

tive VPAC<sub>2</sub> receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC<sub>1</sub> and PAC<sub>1</sub> receptors [493]. The selective PAC<sub>1</sub> receptor agonist maxadilan, was extracted from the salivary glands of sand flies (*Lutzomyia longipalpis*) and has no sequence homology to VIP (VIP, P01282) or the PACAP peptides [1503]. Two deletion variants of maxadilan, M65 [2165] and Max.d.4 [1504] have been reported to be PAC<sub>1</sub> receptor antagonists, but these peptides have not been extensively characterised.

Nomenclature	PAC <sub>1</sub> receptor	VPAC <sub>1</sub> receptor	VPAC <sub>2</sub> receptor
HGNC, UniProt	<i>ADCYAP1R1</i> , P41586	<i>VIPR1</i> , P32241	<i>VIPR2</i> , P41587
Potency order of endogenous ligands	PACAP-27 ( <i>ADCYAP1</i> , P18509), PACAP-38 ( <i>ADCYAP1</i> , P18509) ≫ VIP ( <i>VIP</i> , P01282)	VIP ( <i>VIP</i> , P01282), PACAP-27 ( <i>ADCYAP1</i> , P18509), PACAP-38 ( <i>ADCYAP1</i> , P18509) ≫ GHRH ( <i>GHRH</i> , P01286), PHI {Pig}, secretin ( <i>SCT</i> , P09683)	VIP ( <i>VIP</i> , P01282), PACAP-38 ( <i>ADCYAP1</i> , P18509), PACAP-27 ( <i>ADCYAP1</i> , P18509) > PHI {Pig} ≫ GHRH ( <i>GHRH</i> , P01286), secretin ( <i>SCT</i> , P09683)
Selective agonists	maxadilan [493], maxadilan [493]	[Lys <sup>15</sup> , Arg <sup>16</sup> , Leu <sup>27</sup> ]VIP-(1-7)/GRF-(8-27)-NH <sub>2</sub> [1487], [Ala <sup>11,22,28</sup> ]VIP [1582]	Ro 25-1553 [735, 1023, 1487], Ro 25-1392 [2344]
Selective antagonists	–	PG 97-269 (pIC <sub>50</sub> 8.7) [734, 1023]	–
Labelled ligands	[ <sup>125</sup> I]PACAP-27 (Agonist) [1712]	[ <sup>125</sup> I]VIP (human, mouse, rat) (Agonist) [1582], [ <sup>125</sup> I]PACAP-27 (Agonist)	[ <sup>125</sup> I]VIP (human, mouse, rat) (Agonist) [1582], [ <sup>125</sup> I]PACAP-27 (Agonist)

**Comments:** Subtypes of PAC<sub>1</sub> 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 [2195], or from alternative splicing of PAC<sub>1</sub> receptor mRNA [2020].

#### Further reading on VIP and PACAP receptors

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