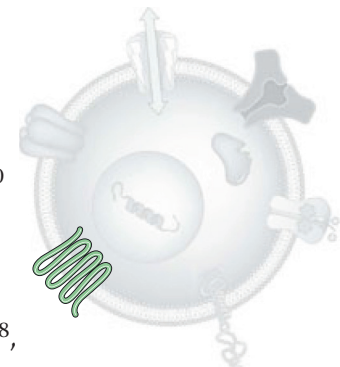


# The Concise Guide to PHARMACOLOGY 2023/24: G protein-coupled receptors

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## Abstract

The Concise Guide to PHARMACOLOGY 2023/24 is the sixth in this series of biennial publications. The Concise Guide provides concise overviews, mostly in tabular format, of the key properties of approximately 1800 drug targets, and about 6000 interactions with about 3900 ligands. There is an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (<https://www.guidetopharmacology.org>), which provides more detailed views of target and ligand properties. Although the Concise Guide constitutes almost 500 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/bph.16177>. 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-2023, and supersedes data presented in the 2021/22, 2019/20, 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (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) [1771]. 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 [1966, 2141], although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs [1329] 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" [2294] 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 [1771].

**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 [2088].

**Frizzled family** consists of 10 Frizzled proteins (FZD<sub>1-10</sub>) 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)) [949].

**GPCR families**

Family	Class A	Class B (Secretin)	Class C (Glutamate)	Adhesion	Frizzled
Receptors with known ligands	197	15	12	0	11
Orphans	87 (54) <sup>a</sup>	-	8 (1) <sup>a</sup>	26 (6) <sup>a</sup>	0
Sensory (olfaction)	390 <sup>b,c</sup>	-	-	-	-
Sensory (vision)	10 <sup>d</sup> opsins	-	-	-	-
Sensory (taste)	30 <sup>c</sup> taste 2	-	3 <sup>c</sup> taste 1	-	-
Sensory (pheromone)	5 <sup>c</sup> vomeronasal 1	-	-	-	-
Total	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 [532]; <sup>b</sup>[1950]; <sup>c</sup>[1771]; <sup>d</sup>[2556].

**Pseudogenes**

A number of pseudogenes have been identified in the human genome, which, in some cases, have a shared ancestry with functional G protein-coupled receptors in other species, including rats and mice.

A curated list includes:

[ADGRE4P](#), [GNHR2](#), [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](#).

**Odorant receptors**

Odorant receptors are G protein-coupled receptors responsible for the detection of generally volatile compounds associated with olfaction. 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](#).

**Family structure**

S26	Orphan and other 7TM receptors	S72	Corticotropin-releasing factor receptors	S100	Neuropeptide S receptor
S27	Class A Orphans	S72	Dopamine receptors	S101	Neuropeptide W/neuropeptide B receptors
-	Class B Orphans	S74	Endothelin receptors	S101	Neuropeptide Y receptors
S34	Class C Orphans	S75	G protein-coupled estrogen receptor	S103	Neurotensin receptors
S35	Opsin receptors	S76	Formylpeptide receptors	S103	Opioid receptors
S35	Taste 1 receptors	S77	Free fatty acid receptors	S105	Orexin receptors
S36	Taste 2 receptors	S78	GABA <sub>B</sub> receptors	S107	Oxoglutarate receptor
S38	Other 7TM proteins	S80	Galanin receptors	S107	P2Y receptors
S39	5-Hydroxytryptamine receptors	S81	Ghrelin receptor	S109	Parathyroid hormone receptors
S41	Acetylcholine receptors (muscarinic)	S82	Glucagon receptor family	S110	Platelet-activating factor receptor
S44	Adenosine receptors	S83	Glycoprotein hormone receptors	S110	Prokineticin receptors
S45	Adhesion Class GPCRs	S84	Gonadotrophin-releasing hormone receptors	S111	Prolactin-releasing peptide receptor
S49	Adrenoceptors	S85	GPR18, GPR55 and GPR119	S112	Prostanoid receptors
S53	Angiotensin receptors	S86	Histamine receptors	S114	Proteinase-activated receptors
S54	Apelin receptor	S87	Hydroxycarboxylic acid receptors	S115	QRFP receptor
S55	Bile acid receptor	S88	Kisspeptin receptor	S116	Relaxin family peptide receptors
S56	Bombesin receptors	S89	Leukotriene receptors	S117	Somatostatin receptors
S57	Bradykinin receptors	S90	Lysophospholipid (LPA) receptors	S118	Succinate receptor
S58	Calcitonin receptors	S92	Lysophospholipid (S1P) receptors	S119	Tachykinin receptors
S59	Calcium-sensing receptor	S93	Melanin-concentrating hormone receptors	S120	Thyrotropin-releasing hormone receptors
S60	Cannabinoid receptors	S93	Melanocortin receptors	S121	Trace amine receptor
S61	Chemerin receptors	S94	Melatonin receptors	S121	Urotensin receptor
S62	Chemokine receptors	S95	Metabotropic glutamate receptors	S122	Vasopressin and oxytocin receptors
S66	Cholecystokinin receptors	S97	Motilin receptor	S124	VIP and PACAP receptors
S68	Class Frizzled GPCRs	S98	Neuromedin U receptors		
S70	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.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16177/full>

Orphan and other 7TM receptors S26

## Class A Orphans

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

**Overview:** Table 11 lists a number of putative GPCRs identified by **NC-IUPHAR** [712], 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 [532]. The GPCRs in Table 11 are all Class A, rhodopsin-like GPCRs. Class A orphan GPCRs not listed in Table 11 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>GPR65</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>
HGNC, UniProt	<i>GPR3</i> , P46089	<i>GPR4</i> , P46093
Endogenous ligands	–	Protons
Agonists	diphenylethylamine [2880]	–
Comments	Sphingosine 1-phosphate was reported to be an endogenous agonist [2629], but this finding was not replicated in subsequent studies [2885]. Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> [638]. Gene disruption results in premature ovarian ageing [1449], reduced β-amyloid deposition [2561] and hypersensitivity to thermal pain [2229] in mice. First small molecule inverse agonist [1161] and agonists identified [2880].	An initial report suggesting activation by lysophosphatidylcholine and sphingosylphosphorylcholine [2955] has been retracted [1908]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [532, 2344]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [2869]. Negative allosteric modulators of GPR4 have been reported [2587].

Nomenclature	<i>GPR6</i>	<i>GPR12</i>	<i>GPR15</i>
HGNC, UniProt	<i>GPR6</i> , P46095	<i>GPR12</i> , P47775	<i>GPR15</i> , P49685
Comments	An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC <sub>50</sub> value of 39nM) [1097, 2629] was not repeated in arrestin-based assays [2436, 2885]. Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> and to be located intracellularly [1971]. GPR6-deficient mice showed reduced striatal cyclic AMP production in vitro and selected alterations in instrumental conditioning in vivo. [1557].	Reports that sphingosine 1-phosphate is a ligand of GPR12 [1096, 2629] have not been replicated in arrestin-based assays [2436, 2885]. Gene disruption results in dyslipidemia and obesity [206].	Reported to act as a co-receptor for HIV [633]. In an infection-induced colitis model, Gpr15 knock-out mice were more prone to tissue damage and inflammatory cytokine expression [1276].

Nomenclature	<a href="#">GPR17</a>	<a href="#">GPR19</a>	<a href="#">GPR20</a>	<a href="#">GPR21</a>
HGNC, UniProt	<a href="#">GPR17, Q13304</a>	<a href="#">GPR19, Q15760</a>	<a href="#">GPR20, Q99678</a>	<a href="#">GPR21, Q99679</a>
Endogenous agonists	<a href="#">UDP-glucose [177, 461]</a> , <a href="#">LTC<sub>4</sub> [461]</a> , <a href="#">UDP-galactose [177, 461]</a> , <a href="#">UDP [177, 461]</a> , <a href="#">LTD<sub>4</sub> [461]</a>	–	–	–
Agonists	–	<a href="#">adropin (ENHO, Q6UWT2) [2138]</a>	–	–
Comments	Reported to be a dual leukotriene and UDP receptor [461]. 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 [532]. Reported to antagonize CysLT <sub>1</sub> receptor signalling in vivo and in vitro [1612]. See reviews [110] and [532].	–	Reported to inhibit adenylyl cyclase constitutively through G <sub>i/o</sub> [955]. GPR20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [274].	Gpr21 knockout mice were resistant to diet-induced obesity, exhibiting an increase in glucose tolerance and insulin sensitivity, as well as a modest lean phenotype [1961].

Nomenclature	<a href="#">GPR22</a>	<a href="#">GPR25</a>	<a href="#">GPR26</a>	<a href="#">GPR27</a>	<a href="#">GPR31</a>	<a href="#">GPR32</a>	<a href="#">GPR33</a>
HGNC, UniProt	<a href="#">GPR22, Q99680</a>	<a href="#">GPR25, O00155</a>	<a href="#">GPR26, Q8NDV2</a>	<a href="#">GPR27, Q9NS67</a>	<a href="#">GPR31, O00270</a>	<a href="#">GPR32, O75388</a>	<a href="#">GPR33, Q49SQ1</a>
Potency order of endogenous ligands	–	–	–	–	–	<a href="#">resolvin D1 &gt; LXA<sub>4</sub></a>	–
Endogenous agonists	–	–	–	–	<a href="#">12S-HETE [901]</a> – Mouse	<a href="#">resolvin D1 [1359]</a> , <a href="#">LXA<sub>4</sub> [1359]</a>	–
Labelled ligands	–	–	–	–	–	<a href="#">[<sup>3</sup>H]resolvin D1 (Agonist) [1359]</a>	–
Comments	Gene disruption results in increased severity of functional decompensation following aortic banding [13]. Identified as a susceptibility locus for osteoarthritis [668, 1253, 2648].	–	Has been reported to activate adenylyl cyclase constitutively through G <sub>s</sub> [1186]. Gpr26 knockout mice show increased levels of anxiety and depression-like behaviours [2927].	Knockdown of Gpr27 reduces endogenous mouse insulin promoter activity and glucose-stimulated insulin secretion [1365].	See [532] for discussion of pairing.	<a href="#">Resolvin D1</a> has been demonstrated to activate GPR32 in two publications [427, 1359]. The pairing was not replicated in a recent study based on arrestin recruitment [2436]. GPR32 is a pseudogene in mice and rats. See reviews [110] and [532].	GPR33 is a pseudogene in most individuals, containing a premature stop codon within the coding sequence of the second intracellular loop [2204].

Nomenclature	<a href="#">GPR34</a>	<a href="#">GPR35</a>
HGNC, UniProt	<a href="#">GPR34, Q9UPC5</a>	<a href="#">GPR35, Q9HC97</a>
Endogenous agonists	<a href="#">lysophosphatidylserine [1297, 2483]</a>	<a href="#">2-oleoyl-LPA [1941]</a> , <a href="#">kynurenic acid [2436, 2725]</a>

Comments	Lysophosphatidylserine has been reported to be a ligand of GPR34 in several publications, but the pairing was not replicated in a recent study based on arrestin recruitment [2436]. Fails to respond to a variety of lipid-derived agents [2885]. Gene disruption results in an enhanced immune response [1512]. Characterization of agonists at this receptor is discussed in [1102] and [532].	Several studies have shown that kynurenic acid is an agonist of GPR35 but it remains controversial whether the proposed endogenous ligand reaches sufficient tissue concentrations to activate the receptor [1366]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [1941] but these results were not replicated in an arrestin assay [2436]. The phosphodiesterase inhibitor zaprinast [2550] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signalling [2550]. GPR35 is also activated by the pharmaceutical adjunct pamoic acid [2943]. See reviews [532] and [590].
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Nomenclature	<a href="#">GPR37</a>	<a href="#">GPR37L1</a>	<a href="#">GPR39</a>
HGNC, UniProt	<a href="#">GPR37, O15354</a>	<a href="#">GPR37L1, O60883</a>	<a href="#">GPR39, O43194</a>
Endogenous agonists	–	–	Zn <sup>2+</sup> [1043]
Agonists	<a href="#">neuropeptide head activator</a> [2170]	–	–
Comments	Reported to associate and regulate the dopamine transporter [1649] and to be a substrate for parkin [1647]. Gene disruption results in altered striatal signalling [1648]. The peptides prosaptide and prosaposin are proposed as endogenous ligands for GPR37 and GPR37L1 [1715].	The peptides prosaptide and prosaposin are proposed as endogenous ligands for GPR37 and GPR37L1 [1715].	Zn <sup>2+</sup> has been reported to be a potent and efficacious agonist of human, mouse and rat GPR39 [2877]. <a href="#">Obestatin</a> (GHRL, Q9UBU3), a fragment from the ghrelin precursor, was reported initially as an endogenous ligand, but subsequent studies failed to reproduce these findings. GPR39 has been reported to be down-regulated in adipose tissue in obesity-related diabetes [360]. Gene disruption results in obesity and altered adipocyte metabolism [2034]. Reviewed in [532].

Nomenclature	<a href="#">GPR45</a>	<a href="#">GPR50</a>	<a href="#">GPR52</a>	<a href="#">GPR61</a>	<a href="#">GPR62</a>	<a href="#">GPR63</a>
HGNC, UniProt	<a href="#">GPR45, Q9Y5Y3</a>	<a href="#">GPR50, Q13585</a>	<a href="#">GPR52, Q9Y2T5</a>	<a href="#">GPR61, Q9BZJ8</a>	<a href="#">GPR62, Q9BZJ7</a>	<a href="#">GPR63, Q9BZJ6</a>
Comments	–	GPR50 is structurally related to MT <sub>1</sub> and MT <sub>2</sub> melatonin receptors, with which it heterodimerises constitutively and specifically [1490]. Gpr50 knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [153].	First small molecule agonist reported [2343].	GPR61 deficient mice exhibit obesity associated with hyperphagia [1852]. Although no endogenous ligands have been identified, 5-(nonyloxy)tryptamine has been reported to be a low affinity inverse agonist [2529].	–	<a href="#">Sphingosine 1-phosphate</a> and <a href="#">dioleoylphosphatidic acid</a> have been reported to be low affinity agonists for GPR63 [1894] but this finding was not replicated in an arrestin-based assay [2885].

Nomenclature	<a href="#">GPR65</a>	<a href="#">GPR68</a>	<a href="#">GPR75</a>	<a href="#">GPR78</a>	<a href="#">GPR79</a>
HGNC, UniProt	<a href="#">GPR65, Q8IYL9</a>	<a href="#">GPR68, Q15743</a>	<a href="#">GPR75, O95800</a>	<a href="#">GPR78, Q96P69</a>	<a href="#">GPR79, –</a>
Endogenous ligands	Protons	Protons	–	–	–
Allosteric modulators (Positive)	–	<a href="#">ogerin</a> (pK <sub>B</sub> 5) [1078], <a href="#">lorazepam</a> (lorazepam characterised as a non-selective GPR68 positive allosteric modulator for the agonist proton in cAMP production) [1078]	–	–	–
Comments	GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [532, 2344]. Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease [1345].	GPR68 was previously identified as a receptor for <a href="#">sphingosyl-phosphorylcholine</a> (SPC) [2844], but the original publication has been retracted [1]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [532, 2344]. A family of 3,5-disubstituted isoxazoles were identified as agonists of GPR68 [2231].	<a href="#">CCL5</a> ( <a href="#">CCL5, P13501</a> ) was reported to be an agonist of GPR75 [1098], but the pairing could not be repeated in an arrestin assay [2436].	GPR78 has been reported to be constitutively active, coupled to elevated cAMP production [1186].	–

Nomenclature	<a href="#">GPR82</a>	<a href="#">GPR83</a>	<a href="#">GPR84</a>	<a href="#">GPR85</a>	<a href="#">GPR87</a>
HGNC, UniProt	<a href="#">GPR82, Q96P67</a>	<a href="#">GPR83, Q9NYM4</a>	<a href="#">GPR84, Q9NQ55</a>	<a href="#">GPR85, P60893</a>	<a href="#">GPR87, Q9BY21</a>
Endogenous agonists	–	–	–	–	<a href="#">LPA</a> [1832, 2510]
Agonists	–	<a href="#">PEN</a> {Mouse} [838] – Mouse, <a href="#">Zn<sup>2+</sup></a> [1823] – Mouse	<a href="#">decanoic acid</a> [2436, 2727], <a href="#">undecanoic acid</a> [2727], <a href="#">lauric acid</a> [2727], <a href="#">6-nonylpyridine-2,4-diol</a> (ortho-steric) [1655], <a href="#">DL-175</a> (ortho-steric) [1655], <a href="#">Embelin</a> (ortho-steric) [1655], <a href="#">PSB-16434</a> (ortho-steric) [1655], <a href="#">ZQ-16</a> (ortho-steric) [1655]	–	–
Allosteric modulators	–	–	<a href="#">DIM</a> (Agonist) [1655]	–	–
Comments	Mice with Gpr82 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 [652].	One isoform has been implicated in the induction of CD4(+) CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [939]. The extracellular N-terminal domain is reported as an intramolecular inverse agonist [1824].	Medium chain free fatty acids with carbon chain lengths of 9-14 activate GPR84 [2498, 2727]. A surrogate ligand for GPR84, <a href="#">6-n-octylaminouracil</a> has also been proposed [2498]. See review [532] for discussion of classification. Mutational analysis and molecular modelling of GPR84 has been reported [1897].	Proposed to regulate hippocampal neurogenesis in the adult, as well as neurogenesis-dependent learning and memory [406].	–



Nomenclature	<a href="#">GPR88</a>	<a href="#">GPR101</a>	<a href="#">GPR132</a>	<a href="#">GPR135</a>	<a href="#">GPR139</a>	<a href="#">GPR141</a>	<a href="#">GPR142</a>
HGNC, UniProt	<a href="#">GPR88, Q9GZNO</a>	<a href="#">GPR101, Q96P66</a>	<a href="#">GPR132, Q9UNW8</a>	<a href="#">GPR135, Q8IZO8</a>	<a href="#">GPR139, Q6DWJ6</a>	<a href="#">GPR141, Q7Z602</a>	<a href="#">GPR142, Q7Z601</a>
Endogenous ligands	–	–	Protons	–	–	–	–
Comments	Gene disruption results in altered striatal signalling [1560]. Small molecule agonists have been reported [198].	Mutations in GPR101 have been linked to gigantism and acromegaly [2613].	GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [532, 2344]. Reported to respond to lysophosphatidylcholine [1197], but later retracted [2800].	–	Peptide agonists have been reported [1115].	–	Small molecule agonists have been reported [2588, 2904].

Nomenclature	<a href="#">GPR146</a>	<a href="#">GPR148</a>	<a href="#">GPR149</a>	<a href="#">GPR150</a>	<a href="#">GPR151</a>	<a href="#">GPR152</a>	<a href="#">GPR153</a>
HGNC, UniProt	<a href="#">GPR146, Q96CH1</a>	<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>
Comments	Yosten <i>et al.</i> demonstrated inhibition of proinsulin C-peptide (INS, P01308)-induced stimulation of cFos expression following knockdown of GPR146 in KATO III cells, suggesting proinsulin C-peptide as an endogenous ligand of the receptor [2900]. Reviewed in [1531].	–	Gpr149 knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [635].	–	GPR151 responded to galanin with an EC <sub>50</sub> value of 2 µM, suggesting that the endogenous ligand shares structural features with galanin (GAL, P22466) [1095].	–	–

Nomenclature	<a href="#">GPR160</a>	<a href="#">GPR161</a>	<a href="#">GPR162</a>	<a href="#">GPR171</a>	<a href="#">GPR173</a>	<a href="#">GPR174</a>
HGNC, UniProt	<a href="#">GPR160, Q9UJ42</a>	<a href="#">GPR161, Q8N6U8</a>	<a href="#">GPR162, Q16538</a>	<a href="#">GPR171, O14626</a>	<a href="#">GPR173, Q9NS66</a>	<a href="#">GPR174, Q9BXC1</a>
Endogenous agonists	–	–	–	–	–	lysophosphatidylserine [1108]
Comments	–	A C-terminal truncation (deletion) mutation in Gpr161 causes congenital cataracts and neural tube defects in the vacuolated lens (vl) mouse mutant [1677]. The mutated receptor is associated with cataract, spina bifida and white belly spot phenotypes in mice [1340]. Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish [1485].	–	GPR171 has been shown to be activated by the endogenous peptide BigLEN (Mouse). This receptor-peptide interaction is believed to be involved in regulating feeding and metabolism responses [837].	–	See [1102] which discusses characterization of agonists at this receptor.

Nomenclature	<a href="#">GPR176</a>	<a href="#">GPR182</a>	<a href="#">GPR183</a>
HGNC, UniProt	<a href="#">GPR176, Q14439</a>	<a href="#">GPR182, O15218</a>	<a href="#">GPR183, P32249</a>
Endogenous agonists	–	–	<a href="#">7<math>\alpha</math>,25-dihydroxycholesterol</a> [935, 1545], <a href="#">7<math>\alpha</math>,27-dihydroxycholesterol</a> [1545], <a href="#">7<math>\beta</math>, 25-dihydroxycholesterol</a> [1545], <a href="#">7<math>\beta</math>, 27-dihydroxycholesterol</a> [1545]
Comments	–	Rat GPR182 was first proposed as the adrenomedullin receptor [1215]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [1249] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [971].	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 [935, 1545]. 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 [1240, 2021].

Nomenclature	<a href="#">LGR4</a>	<a href="#">LGR5</a>
HGNC, UniProt	<a href="#">LGR4, Q9BXB1</a>	<a href="#">LGR5, O75473</a>
Endogenous agonists	<a href="#">R-spondin-2 (RSPO2, Q6UXX9)</a> [349], <a href="#">R-spondin-1 (RSPO1, Q2MKA7)</a> [349], <a href="#">R-spondin-3 (RSPO3, Q9BXY4)</a> [349], <a href="#">R-spondin-4 (RSPO4, Q2I0M5)</a> [349]	<a href="#">R-spondin-2 (RSPO2, Q6UXX9)</a> [349], <a href="#">R-spondin-1 (RSPO1, Q2MKA7)</a> [349], <a href="#">R-spondin-3 (RSPO3, Q9BXY4)</a> [349], <a href="#">R-spondin-4 (RSPO4, Q2I0M5)</a> [349]
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 [349, 546, 2225]. Gene disruption leads to multiple developmental disorders [1172, 1580, 2432, 2763].	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 [349, 546].

Nomenclature	<a href="#">LGR6</a>	<a href="#">MAS1</a>	<a href="#">MAS1L</a>	<a href="#">MRGPRD</a>	<a href="#">MRGPRE</a>	<a href="#">MRGPRF</a>
HGNC, UniProt	<a href="#">LGR6, Q9HBX8</a>	<a href="#">MAS1, P04201</a>	<a href="#">MAS1L, P35410</a>	<a href="#">MRGPRD, Q8TDS7</a>	<a href="#">MRGPRE, Q86SM8</a>	<a href="#">MRGPRF, Q96AM1</a>
Endogenous agonists	<a href="#">R-spondin-1 (RSPO1, Q2MKA7)</a> [349, 546], <a href="#">R-spondin-2 (RSPO2, Q6UXX9)</a> [349, 546], <a href="#">R-spondin-3 (RSPO3, Q9BXY4)</a> [349, 546], <a href="#">R-spondin-4 (RSPO4, Q2I0M5)</a> [349, 546]	–	–	<a href="#"><math>\beta</math>-alanine</a> [2373, 2436]	–	–
Agonists	–	<a href="#">angiotensin-(1-7) (AGT, P01019)</a> [825] – Mouse	–	–	–	–

Comments	–	–	–	An endogenous peptide with a high degree of sequence similarity to <a href="#">angiotensin-(1-7)</a> ( <a href="#">ACT</a> , <a href="#">P01019</a> ), <a href="#">alamandine</a> ( <a href="#">ACT</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> [ <a href="#">1420</a> ]. Genetic ablation of MRGPRD+ neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [ <a href="#">368</a> ]. See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</a> ].	See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</a> ].	MRGPRF has been reported to respond to stimulation by angiotensin metabolites [ <a href="#">791</a> ]. See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</a> ].
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Nomenclature	<a href="#">MRGPRG</a>	<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="#">MRGPRG</a> , <a href="#">Q86SM5</a>	<a href="#">MRGPRX1</a> , <a href="#">Q96LB2</a>	<a href="#">MRGPRX2</a> , <a href="#">Q96LB1</a>	<a href="#">MRGPRX3</a> , <a href="#">Q96LB0</a>	<a href="#">MRGPRX4</a> , <a href="#">Q96LA9</a>	<a href="#">P2RY8</a> , <a href="#">Q86VZ1</a>	<a href="#">P2RY10</a> , <a href="#">O00398</a>
Endogenous agonists	–	bovine adrenal medulla peptide 8-22 ( <a href="#">PENK</a> , <a href="#">P01210</a> ) [ <a href="#">400</a> , <a href="#">1472</a> , <a href="#">2436</a> ]	<a href="#">PAMP-20</a> ( <a href="#">ADM</a> , <a href="#">P35318</a> ) [ <a href="#">1207</a> ]	–	–	–	<a href="#">sphingosine 1-phosphate</a> [ <a href="#">1832</a> ], <a href="#">LPA</a> [ <a href="#">1832</a> ]
Agonists	–	–	<a href="#">cortistatin-14</a> (Mouse, Rat) [ <a href="#">1207</a> , <a href="#">1413</a> , <a href="#">2193</a> , <a href="#">2436</a> ]	–	–	–	–
Selective agonists	–	–	<a href="#">PAMP-12</a> (human) [ <a href="#">1207</a> ]	–	–	–	–
Comments	See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</a> ].	Reported to mediate the sensation of itch [ <a href="#">1550</a> , <a href="#">2384</a> ]. Reports that <a href="#">bovine adrenal medulla peptide 8-22</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="#">1472</a> ] were replicated in an independent study using an arrestin recruitment assay [ <a href="#">2436</a> ]. See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</a> ].	A diverse range of substances has been reported to be agonists of MRGPRX2, with <a href="#">cortistatin 14</a> the highest potency agonist in assays of calcium mobilisation [ <a href="#">2193</a> ], also confirmed in an independent study using an arrestin recruitment assay [ <a href="#">2436</a> ]. See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</a> ].	–	See reviews [ <a href="#">532</a> ] and [ <a href="#">2430</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, Q96RI8</a>	<a href="#">TAAR8, Q969N4</a>	<a href="#">TAAR9, Q96RI9</a>
Potency order of endogenous ligands	$\beta$ -phenylethylamine > tryptamine [244]	–	–	–	–	–	–
Comments	Probable pseudogene in 10–15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [532].	TAAR3 is thought to be a pseudogene in man though functional in rodents [532].	Pseudogene in man but functional in rodents [532].	Trimethylamine is reported as an agonist [2711] and 3-iodothyronamine an inverse agonist [587].	–	–	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 [2668].

**Further reading on Class A Orphans**

Akbari P *et al.* (2021) Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity. *Science* **373**: [PMID:34210852]  
 McNeil BD *et al.* (2015) Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* **519**: 237-41 [PMID:25517090]

Wirthgen E *et al.* (2017) Kynurenic Acid: The Janus-Faced Role of an Immunomodulatory Tryptophan Metabolite and Its Link to Pathological Conditions. *Front Immunol* **8**: 1957 [PMID:29379504]

## 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	<a href="#">GPR156</a>	<a href="#">GPR158</a>	<a href="#">GPR179</a>	<a href="#">GPCR5A</a>	<a href="#">GPCR5B</a>	<a href="#">GPCR5C</a>	<a href="#">GPCR5D</a>	<a href="#">GPCR6 receptor</a>
HGNC, UniProt	<a href="#">GPR156, Q8NFN8</a>	<a href="#">GPR158, Q5T848</a>	<a href="#">GPR179, Q6PRD1</a>	<a href="#">GPCR5A, Q8NFI5</a>	<a href="#">GPCR5B, Q9NZH0</a>	<a href="#">GPCR5C, Q9NQ84</a>	<a href="#">GPCR5D, Q9NZD1</a>	<a href="#">GPCR6A, Q5T6X5</a>
Comments	–	–	–	–	–	–	–	GPCR6 is a related G <sub>q</sub> -coupled receptor which responds to basic amino acids [2760].

**Further reading on Class C Orphans**

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

## Opsin receptors

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

Nomenclature	<a href="#">OPN3</a>	<a href="#">OPN4</a>	<a href="#">OPN5</a>
HGNC, UniProt	<a href="#">OPN3</a> , <a href="#">Q9H1Y3</a>	<a href="#">OPN4</a> , <a href="#">Q9UHM6</a>	<a href="#">OPN5</a> , <a href="#">Q6U736</a>
Comments	–	–	Evidence indicates that UV light triggers OPN5 to activate G <sub>i</sub> -mediated signalling in mammalian tissues [1327].

## 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 [2938], TRPM5 [2938] and IP3 [1025] 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** [1501]. T1R2/T1R3 heterodimers respond to sugars, such as **sucrose**, and artificial sweeteners, such as **saccharin** [1874].

Nomenclature	<a href="#">TAS1R1</a>	<a href="#">TAS1R2</a>	<a href="#">TAS1R3</a>
HGNC, UniProt	<a href="#">TAS1R1</a> , <a href="#">Q7RTX1</a>	<a href="#">TAS1R2</a> , <a href="#">Q8TE23</a>	<a href="#">TAS1R3</a> , <a href="#">Q7RTX0</a>

**Comments:** Positive allosteric modulators of T1R2/T1R3 have been reported [2848]. Such compounds enhance the sweet taste of sucrose mediated by these receptors, but are tasteless on their own.

### Further reading on Taste 1 receptors

- Behrens M *et al.* (2020) Structure-Function Analyses of Human Bitter Taste Receptors-Where Do We Stand? *Molecules* **25**: 4423 [PMID:32993119]
- 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:** Taste 2 receptors or Bitter taste receptors (TAS2Rs) are G protein-coupled receptors expressed in oral sensory cells and a variety of non-gustatory tissues. The ~25 human TAS2Rs share low amino acid sequence identities with other GPCR families and are classified as broadly tuned "generalist" receptors with numerous, chemically diverse bitter agonists, as narrowly

tuned "specialist" receptors with very few activators, as intermediately tuned receptors with an average number of agonists, or receptors specialized to interact with chemically defined activators [1717]. The number of functional bitter taste receptor genes varies among species and orthologues might not be functionally conserved. Due to their expression in various tissues, the signal

transduction of TAS2Rs is complex. Some TAS2Rs interact with drugs such as analgesic, anti-inflammatory, and antibacterial compounds. The specialist database [BitterDB](#) contains additional information on bitter compounds and receptors [516].

Nomenclature	<i>TAS2R1</i>	<i>TAS2R3</i>	<i>TAS2R4</i>	<i>TAS2R5</i>	<i>TAS2R7</i>	<i>TAS2R8</i>	<i>TAS2R9</i>
HGNC, UniProt	<i>TAS2R1</i> , Q9NYW7	<i>TAS2R3</i> , Q9NYW6	<i>TAS2R4</i> , Q9NYW5	<i>TAS2R5</i> , Q9NYW4	<i>TAS2R7</i> , Q9NYW3	<i>TAS2R8</i> , Q9NYW2	<i>TAS2R9</i> , Q9NYW1
Agonists	cohumulone [1110], L-Phe-Phe-Phe [2638], L-Trp-Trp-Trp [1323], dextromethorphan [1717]	chloroquine [1717]	L-Trp-Trp-Trp [1323], azithromycin [1141], stevioside [990], colchicine [1717]	epigallocatechin-3-gallate [2421], Procyanidin C2 [2420], 1,10-Phenanthroline [1717]	grandinin [2421], malvidin-3-glucoside [2420], cromoglicic acid [1717]	oleuropein [511], andrographolide [718], chloramphenicol [1717], parthenolide [1717]	ofloxacin [607], pirenzepine [607], procainamide [607]
Antagonists	–	–	abscisic acid (pIC <sub>50</sub> 4.5) [2103]	–	–	S6821 (pIC <sub>50</sub> 7.7) [718], S7958 (pIC <sub>50</sub> 7.2) [718]	–
Comments	–	–	–	–	Aluminum sulfate and magnesium sulfate act as TAS2R7 agonists; EC <sub>50</sub> values are 29 μM [2739] and 14900 μM [166] respectively.	–	–

Nomenclature	<i>TAS2R10</i>	<i>TAS2R13</i>	<i>TAS2R14</i>	<i>TAS2R16</i>
HGNC, UniProt	<i>TAS2R10</i> , Q9NYW0	<i>TAS2R13</i> , Q9NYV9	<i>TAS2R14</i> , Q9NYV8	<i>TAS2R16</i> , Q9NYV7
Agonists	bergapten [1633], cucurbitacin B [243], strychnine [1717], denatonium [243], haloperidol [1717]	denatonium [1717], diphenidol [1717]	flufenamic acid [576], aristolochic acid [1917], lupulone [1110], nobiletin [164], luteolin [2201], santonin [1917], daticsetin [2201], parthenolide [1917], (-)-α-thujone [163], picrotoxinin [163], N-octanoyl-L-homoserine lactone [1142], phloretin [2201], resveratrol [2201], tributyrin [1489], eriodictyol chalcone [2201], (±)-Equol [2202], silibinin [2201], (+/-)-Eriodictyol [2201], genistein [1917], homoeriodictyol [2201], coumestrol [2202], vanillin [1801], L-Trp-Trp-Trp [1323], quinine [1717]	4-Nitrophenyl-β-D-mannopyranoside [2567], Phenyl-β-D-glucopyranoside [313], salicin [313], beta-gentiobiose [2250], D-(-)-Amygdalin [313], sinigrin [1717]
Antagonists	–	–	–	probenecid (pIC <sub>50</sub> 3.5) [869]

Nomenclature	<i>TAS2R19</i>	<i>TAS2R20</i>	<i>TAS2R30</i>	<i>TAS2R31</i>	<i>TAS2R38</i>	<i>TAS2R39</i>
HGNC, UniProt	<i>TAS2R19</i> , P59542	<i>TAS2R20</i> , P59543	<i>TAS2R30</i> , P59541	<i>TAS2R31</i> , P59538	<i>TAS2R38</i> , P59533	<i>TAS2R39</i> , P59534
Agonists	–	ritanserin [1633], methoxsalen [1633], cromoglicic acid [1717], tobramycin [1141], vanillin [1801], diphenidol [1717]	denatonium [1717], absinthin [1717], amarogentin [2215]	aristolochic acid [1370], saccharin [1370], acesulfame [1370], famotidine [1717]	phenylthiocarbamide [312], propylthiouracil [312], goitrin [2808], methimazole [165], sinigrin [1717]	theaflavin-3'-O-gallate [2857], theaflavin [2857], luteolin [2201], epicatechin gallate [2857], naringenin [2201], scutellarein [2201], datsicetin [2201], phloretin [2201], genistein [2202], (±)-Equol [2202], epigallocatechin [1857], (-)-Epicatechin [1857], vanillin [1801], L-Trp-Trp-Trp [1323]
Antagonists	–	–	–	GIV3727 (pIC <sub>50</sub> 5.5) [2401], sakuranetin (pIC <sub>50</sub> 5.3) [710], cyclamate (pIC <sub>50</sub> 1.8) [161]	probenecid (pIC <sub>50</sub> 3.7) [869]	6-Methylflavone (pIC <sub>50</sub> 4.7) [2200]
Comments	–	–	–	–	Of the two main variants of <i>TAS2R38</i> , only the taster-variant ( <i>TAS2R38</i> -PAV) is exquisitely sensitive to the listed agonists as well as to structurally related bitter substances from cruciferous vegetables. The non-taster variant ( <i>TAS2R38</i> -AVI) is non-functional [312, 1278].	–

Nomenclature	<i>TAS2R40</i>	<i>TAS2R41</i>	<i>TAS2R42</i>	<i>TAS2R43</i>
HGNC, UniProt	<i>TAS2R40</i> , P59535	<i>TAS2R41</i> , P59536	<i>TAS2R42</i> , Q7RTR8	<i>TAS2R43</i> , P59537
Agonists	cohumulone [1110], dapson (Threshold=30 μM) [1717], quinine [1717]	chloramphenicol [2560]	–	aristolochic acid [1370], lactucopicrin [1406], aloin [2090], Cyclolinopeptide 1-Mso,3-Met-CL6 [1407], bengalensol [1408], grosheimin [2215], amarogentin [1717], saccharin [1370], acesulfame [1370]
Antagonists	GIV3727 (pIC <sub>50</sub> 5.2) [2401]	–	–	GIV3727 (pIC <sub>50</sub> 4.9) [2401], 3-methylhexanal (pIC <sub>50</sub> 4.1) [2479], citronellal (pIC <sub>50</sub> 4.1) [2479], cyclamate (pIC <sub>50</sub> 2.3) [161]

Nomenclature	<i>TAS2R45</i>	<i>TAS2R46</i>	<i>TAS2R50</i>	<i>TAS2R60</i>
HGNC, UniProt	<i>TAS2R45</i> , P59539	<i>TAS2R46</i> , P59540	<i>TAS2R50</i> , P59544	<i>TAS2R60</i> , P59551
Agonists	–	lactucopicrin [1406], strychnine [288], grosheimin [2215], absinthin [288], bengalensol [1408], andrographolide [2215], amarogentin [2215], picrotoxinin [288], denatonium [1717], colchicine [1717], L-Trp-Trp-Trp [1323]	andrographolide [162], amarogentin [162]	–
Antagonists	–	3β-hydroxydihydrocostunolide (pIC <sub>50</sub> 5.3) [289]	–	–

**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

**Overview:** These proteins are predicted to have 7TM domains, but functional studies have yet to confirm them as G protein-coupled receptors.

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, Q5VW38</a>	<a href="#">GPR137, Q96N19</a>	<a href="#">TPRA1, Q86W33</a>	<a href="#">GPR143, P51810</a>	<a href="#">GPR157, Q5UAW9</a>
Endogenous agonists	–	–	–	<a href="#">levodopa [1565]</a>	–
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 [632]	–	TPRA1 shows no homology to known G protein-coupled receptors.	Loss-of-function mutations underlie ocular albinism type 1 [143].	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 [1063] and subsequently revised [954]**) 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 [218, 2770]. 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 [2129, 2686]).

Nomenclature	5-HT <sub>1A</sub> receptor	5-HT <sub>1B</sub> receptor	5-HT <sub>1D</sub> receptor	5-HT <sub>1e</sub> receptor	5-HT <sub>1F</sub> receptor
HGNC, UniProt	<i>HTR1A</i> , P08908	<i>HTR1B</i> , P28222	<i>HTR1D</i> , P28221	<i>HTR1E</i> , P28566	<i>HTR1F</i> , P30939
Agonists	U92016A [1690], vilazodone (Partial agonist) [541], vortioxetine (Partial agonist) [127]	L-694,247 [863], naratriptan (Partial agonist) [1856], eletriptan [1856], frovatriptan [2845], zolmitriptan (Partial agonist) [1856], vortioxetine (Partial agonist) [127], rizatriptan (Partial agonist) [1856]	dihydroergotamine [924, 1482, 1492], ergotamine [829], L-694,247 [2824], naratriptan [595, 1856, 2169], zolmitriptan [1856], frovatriptan [2845], rizatriptan [1856]	BRL-54443 [296]	BRL-54443 [296], eletriptan [1856], sumatriptan [15, 16, 1856, 2705]
Selective agonists	8-OH-DPAT [553, 925, 1204, 1470, 1736, 1885, 1887, 1888], NLX-101 [1886]	CP94253 [1316]	PNU109291 [658] – Gorilla, eletriptan [1856]	–	lasmiditan [1873], LY334370 [2705], 5-BODMT [1306], LY344864 [2042]
Antagonists	(S)-UH 301 (pK <sub>i</sub> 7.9) [1885]	–	–	–	–
Selective antagonists	WAY-100635 (pK <sub>i</sub> 7.9–9.2) [1885, 1887], robalzotan (pK <sub>i</sub> 9.2) [1177]	SB 224289 (Inverse agonist) (pK <sub>i</sub> 8.2–8.6) [782, 1883, 2336], SB236057 (Inverse agonist) (pK <sub>i</sub> 8.2) [1728], GR-55562 (pK <sub>B</sub> 7.4) [1064]	SB 714786 (pK <sub>i</sub> 9.1) [2742]	–	–
Labelled ligands	[ <sup>3</sup> H]robalzotan (Antagonist) (pK <sub>d</sub> 9.8) [1163], [ <sup>3</sup> H]WAY100635 (Antagonist) (pK <sub>d</sub> 9.5) [1257], [ <sup>3</sup> H]8-OH-DPAT (Agonist) [211, 1204, 1884, 1887], [ <sup>3</sup> H]NLX-112 (Agonist) [1007], [ <sup>11</sup> C]WAY100635 (Antagonist) [2620], p-[ <sup>18</sup> F]MPPF (Antagonist) [490]	[ <sup>3</sup> H]N-methyl-AZ10419369 (Agonist, Partial agonist) [1617], [ <sup>3</sup> H]GR 125,743 (Selective Antagonist) (pK <sub>d</sub> 8.6–9.2) [863, 2834], [ <sup>3</sup> H]alniditan (Agonist) [1482], [ <sup>125</sup> I]GTI (Agonist) [253, 303] – Rat, [ <sup>3</sup> H]eletriptan (Agonist, Partial agonist) [1856], [ <sup>3</sup> H]sumatriptan (Agonist, Partial agonist) [1856], [ <sup>11</sup> C]AZ10419369 (Agonist, Partial agonist) [2673]	[ <sup>3</sup> H]eletriptan (Agonist) [1856], [ <sup>3</sup> H]alniditan (Agonist) [1482], [ <sup>125</sup> I]GTI (Selective Agonist) [253, 303] – Rat, [ <sup>3</sup> H]GR 125,743 (Selective Antagonist) (pK <sub>d</sub> 8.6) [2834], [ <sup>3</sup> H]sumatriptan (Agonist) [1856]	[ <sup>3</sup> H]5-HT (Agonist) [1686, 1988]	[ <sup>3</sup> H]LY334370 (Agonist) [2705], [ <sup>125</sup> I]LSD (Agonist) [55] – Mouse

Nomenclature	5-HT <sub>2A</sub> receptor	5-HT <sub>2B</sub> receptor	5-HT <sub>2C</sub> receptor
HGNC, UniProt	<a href="#">HTR2A</a> , <a href="#">P28223</a>	<a href="#">HTR2B</a> , <a href="#">P41595</a>	<a href="#">HTR2C</a> , <a href="#">P28335</a>
Agonists	<a href="#">DOI</a> [ <a href="#">268</a> , <a href="#">1872</a> , <a href="#">2403</a> ]	<a href="#">methysergide</a> (Partial agonist) [ <a href="#">1311</a> , <a href="#">2214</a> , <a href="#">2706</a> ], <a href="#">DOI</a> [ <a href="#">1386</a> , <a href="#">1872</a> , <a href="#">2287</a> ]	<a href="#">DOI</a> [ <a href="#">637</a> , <a href="#">1872</a> , <a href="#">2287</a> ], <a href="#">Ro 60-0175</a> [ <a href="#">1286</a> , <a href="#">1311</a> ]
Selective agonists	–	<a href="#">BW723C86</a> [ <a href="#">151</a> , <a href="#">1311</a> , <a href="#">2287</a> ], <a href="#">Ro 60-0175</a> [ <a href="#">1311</a> ]	<a href="#">WAY-163909</a> [ <a href="#">627</a> ], <a href="#">lorcaserin</a> [ <a href="#">2576</a> ]
Antagonists	<a href="#">risperidone</a> (Inverse agonist) (pK <sub>i</sub> 9.3–10) [ <a href="#">1331</a> , <a href="#">1362</a> , <a href="#">2307</a> ], <a href="#">mianserin</a> (pK <sub>i</sub> 7.7–9.6) [ <a href="#">1311</a> , <a href="#">1346</a> , <a href="#">1736</a> ], <a href="#">ziprasidone</a> (pK <sub>i</sub> 8.8–9.5) [ <a href="#">1331</a> , <a href="#">1362</a> , <a href="#">2307</a> , <a href="#">2350</a> ], <a href="#">volinanserin</a> (pIC <sub>50</sub> 6.5–9.3) [ <a href="#">1311</a> , <a href="#">1566</a> , <a href="#">2155</a> ], <a href="#">blonanserin</a> (pK <sub>i</sub> 9.1) [ <a href="#">1925</a> ], <a href="#">clozapine</a> (Inverse agonist) (pK <sub>i</sub> 7.6–9) [ <a href="#">1311</a> , <a href="#">1362</a> , <a href="#">1733</a> , <a href="#">2307</a> , <a href="#">2667</a> ], <a href="#">H05</a> (pIC <sub>50</sub> 7.2) [ <a href="#">2843</a> ]	<a href="#">mianserin</a> (pK <sub>i</sub> 7.9–8.8) [ <a href="#">238</a> , <a href="#">1311</a> , <a href="#">2706</a> ]	<a href="#">mianserin</a> (Inverse agonist) (pK <sub>i</sub> 8.3–9.2) [ <a href="#">707</a> , <a href="#">1311</a> , <a href="#">1736</a> ], <a href="#">methysergide</a> (pK <sub>i</sub> 8.6–9.1) [ <a href="#">637</a> , <a href="#">1311</a> ], <a href="#">ziprasidone</a> (Inverse agonist) (pK <sub>i</sub> 7.9–9) [ <a href="#">1000</a> , <a href="#">1362</a> , <a href="#">2350</a> ], <a href="#">olanzapine</a> (Inverse agonist) (pK <sub>i</sub> 8.1–8.4) [ <a href="#">1000</a> , <a href="#">1362</a> , <a href="#">2350</a> ], <a href="#">loxapine</a> (Inverse agonist) (pK <sub>i</sub> 7.8–8) [ <a href="#">1000</a> , <a href="#">1362</a> ]
Selective antagonists	<a href="#">compound 3b</a> (pK <sub>i</sub> 10.6) [ <a href="#">703</a> ], <a href="#">ketanserin</a> (pK <sub>i</sub> 8.1–9.7) [ <a href="#">308</a> , <a href="#">1311</a> , <a href="#">2140</a> ], <a href="#">pimavanserin</a> (Inverse agonist) (pK <sub>i</sub> 9.3) [ <a href="#">769</a> , <a href="#">2667</a> ]	<a href="#">BF-1</a> (pK <sub>i</sub> 10.1) [ <a href="#">2300</a> ], <a href="#">RS-127445</a> (pK <sub>i</sub> 9–9.5) [ <a href="#">238</a> , <a href="#">1311</a> ], <a href="#">EGIS-7625</a> (pK <sub>i</sub> 9) [ <a href="#">1346</a> ]	<a href="#">FR260010</a> (pK <sub>i</sub> 9) [ <a href="#">944</a> ], <a href="#">SB 242084</a> (pK <sub>i</sub> 8.2–9) [ <a href="#">1250</a> , <a href="#">1311</a> ], <a href="#">RS-102221</a> (pK <sub>i</sub> 8.3–8.4) [ <a href="#">239</a> , <a href="#">1311</a> ]
Labelled ligands	<a href="#">[<sup>3</sup>H]fananserin</a> (Antagonist) (pK <sub>d</sub> 9.9) [ <a href="#">1623</a> ] – Rat, <a href="#">[<sup>3</sup>H]ketanserin</a> (Antagonist) (pK <sub>d</sub> 8.6–9.7) [ <a href="#">1311</a> , <a href="#">2140</a> ], <a href="#">[<sup>11</sup>C]volinanserin</a> (Antagonist) [ <a href="#">918</a> ], <a href="#">[<sup>18</sup>F]altanserin</a> (Antagonist) [ <a href="#">2210</a> ]	<a href="#">[<sup>3</sup>H]LSD</a> (Agonist) [ <a href="#">2140</a> ], <a href="#">[<sup>3</sup>H]5-HT</a> (Agonist) [ <a href="#">2704</a> ] – Rat, <a href="#">[<sup>3</sup>H]mesulergine</a> (Antagonist, Inverse agonist) (pK <sub>d</sub> 7.9) [ <a href="#">1311</a> ], <a href="#">[<sup>125</sup>I]DOI</a> (Agonist)	<a href="#">[<sup>3</sup>H]mesulergine</a> (Antagonist, Inverse agonist) (pK <sub>d</sub> 8.7–9.3) [ <a href="#">707</a> , <a href="#">2140</a> ], <a href="#">[<sup>125</sup>I]DOI</a> (Agonist) [ <a href="#">707</a> ], <a href="#">[<sup>3</sup>H]LSD</a> (Agonist)

Nomenclature	5-HT <sub>4</sub> receptor	5-HT <sub>5A</sub> receptor	5-ht <sub>5b</sub> receptor
HGNC, UniProt	<a href="#">HTR4</a> , <a href="#">Q13639</a>	<a href="#">HTR5A</a> , <a href="#">P47898</a>	<a href="#">HTR5BP</a> , –
Agonists	<a href="#">cisapride</a> (Partial agonist) [ <a href="#">106</a> , <a href="#">175</a> , <a href="#">803</a> , <a href="#">1719</a> , <a href="#">1720</a> , <a href="#">2653</a> ]	–	–
Selective agonists	<a href="#">TD-8954</a> [ <a href="#">1700</a> ], <a href="#">ML 10302</a> (Partial agonist) [ <a href="#">187</a> , <a href="#">215</a> , <a href="#">1719</a> , <a href="#">1720</a> , <a href="#">1721</a> ], <a href="#">RS67506</a> [ <a href="#">983</a> ] – Rat, <a href="#">relenopride</a> (Partial agonist) [ <a href="#">816</a> ], <a href="#">velusetrag</a> [ <a href="#">1562</a> , <a href="#">2411</a> ], <a href="#">BIMU 8</a> [ <a href="#">465</a> ]	–	–
Selective antagonists	<a href="#">RS 100235</a> (pK <sub>i</sub> 8.7–12.2) [ <a href="#">465</a> , <a href="#">2186</a> ], <a href="#">SB 204070</a> (pK <sub>i</sub> 9.8–10.4) [ <a href="#">175</a> , <a href="#">1719</a> , <a href="#">1720</a> , <a href="#">2653</a> ], <a href="#">GR 113808</a> (pK <sub>i</sub> 9.3–10.3) [ <a href="#">106</a> , <a href="#">175</a> , <a href="#">215</a> , <a href="#">465</a> , <a href="#">1720</a> , <a href="#">2186</a> , <a href="#">2653</a> ]	<a href="#">SB 699551</a> (pK <sub>i</sub> 8.2) [ <a href="#">487</a> ]	–
Labelled ligands	<a href="#">[<sup>3</sup>H]GR 113808</a> (Antagonist) (pK <sub>d</sub> 9.7–10.3) [ <a href="#">106</a> , <a href="#">175</a> , <a href="#">1721</a> , <a href="#">2653</a> ], <a href="#">[<sup>123</sup>I]SB 207710</a> (Antagonist) (pK <sub>d</sub> 10.1) [ <a href="#">297</a> ] – Pig, <a href="#">[<sup>3</sup>H]RS 57639</a> (Selective Antagonist) (pK <sub>d</sub> 9.7) [ <a href="#">237</a> ] – Guinea pig, <a href="#">[<sup>11</sup>C]SB207145</a> (Antagonist) (pK <sub>d</sub> 8.6) [ <a href="#">1604</a> ]	<a href="#">[<sup>125</sup>I]LSD</a> (Agonist) [ <a href="#">862</a> ], <a href="#">[<sup>3</sup>H]5-CT</a> (Agonist) [ <a href="#">862</a> ]	<a href="#">[<sup>125</sup>I]LSD</a> (Agonist) [ <a href="#">1678</a> ] – Mouse, <a href="#">[<sup>3</sup>H]5-CT</a> (Agonist) [ <a href="#">2703</a> ] – Mouse

Nomenclature	5-HT <sub>6</sub> receptor	5-HT <sub>7</sub> receptor
HGNC, UniProt	<a href="#">HTR6</a> , <a href="#">P50406</a>	<a href="#">HTR7</a> , <a href="#">P34969</a>
Selective agonists	<a href="#">WAY-181187</a> [2291], <a href="#">E6801</a> (Partial agonist) [1036], <a href="#">WAY-208466</a> [186], <a href="#">EMD-386088</a> [1679]	<a href="#">LP-12</a> [1476], <a href="#">LP-44</a> [1476], <a href="#">LP-211</a> [1477] – Rat, <a href="#">AS-19</a> [1279], <a href="#">E55888</a> [272]
Antagonists	–	<a href="#">lurasidone</a> (pK <sub>i</sub> 9.3) [1116], <a href="#">pimozide</a> (pK <sub>i</sub> 9.3) [2213] – Rat, <a href="#">vortioxetine</a> (pK <sub>i</sub> 6.3) [127]
Selective antagonists	<a href="#">SB399885</a> (pK <sub>i</sub> 9) [1024], <a href="#">SB 271046</a> (pK <sub>i</sub> 8.9) [293], <a href="#">cerlapirdine</a> (pK <sub>i</sub> 8.9) [476], <a href="#">SB357134</a> (pK <sub>i</sub> 8.5) [294], <a href="#">Ro 63-0563</a> (pK <sub>i</sub> 7.9–8.4) [221, 2402]	<a href="#">SB269970</a> (pK <sub>i</sub> 8.6–8.9) [2569], <a href="#">SB656104</a> (pK <sub>i</sub> 8.7) [713], <a href="#">DR-4004</a> (pK <sub>i</sub> 8.7) [828, 1266], <a href="#">JNJ-18038683</a> (pK <sub>i</sub> 8.2) [234], <a href="#">SB 258719</a> (Inverse agonist) (pK <sub>i</sub> 7.5) [2570]
Labelled ligands	[ <sup>11</sup> C]GSK215083 (Antagonist) (pK <sub>i</sub> 9.8) [1987], [ <sup>125</sup> I]SB258585 (Selective Antagonist) (pK <sub>d</sub> 9) [1024], [ <sup>3</sup> H]LSD (Agonist) [220], [ <sup>3</sup> H]Ro 63-0563 (Antagonist) (pK <sub>d</sub> 8.3) [221], [ <sup>3</sup> H]5-CT (Agonist)	[ <sup>3</sup> H]5-CT (Agonist) [2569], [ <sup>3</sup> H]5-HT (Agonist) [130, 2450], [ <sup>3</sup> H]SB269970 (Selective Antagonist) (pK <sub>d</sub> 8.9) [2569], [ <sup>3</sup> H]LSD (Agonist) [2450]

**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 [954]. 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 [936]. 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 [2719]; some of these drugs adopt rather different conformations depending on the target receptor [2017].

Various 5-HT receptors have multiple partners in addition to G proteins, which may affect function and pharmacology [1652]. [NAS181](#) is a selective antagonist of the rodent 5-HT<sub>1B</sub> receptor. [Fananserin](#) (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 [2701]. DHE ([dihydroergocryptine](#)), [pergolide](#) and [cabergoline](#) also show significant preference for arrestin recruitment over G

protein coupling at 5-HT<sub>2B</sub> receptors [2701]. The 5-HT<sub>2B</sub> (and other 5-HT) receptors interact with immunocompetent cells [1972]. The serotonin antagonist [mesulegine](#) was key to the discovery of the 5-HT<sub>2C</sub> receptor [2006], initially known as 5-HT<sub>1C</sub> [100]. The human 5-HT<sub>5A</sub> receptor may couple to several signal transduction pathways when stably expressed in C6 glioma cells [1910] and rodent prefrontal cortex (layer V pyramidal neurons) [845]. 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 [936]. In addition to accepted receptors, an 'orphan' receptor, unofficially termed 5-HT<sub>1p</sub>, has been described [808].

### Further reading on 5-Hydroxytryptamine receptors

Bockaert J *et al.* (2011) 5-HT(4) receptors, a place in the sun: act two. *Curr Opin Pharmacol* **11**: 87-93 [PMID:21342787]

Hayes DJ *et al.* (2011) 5-HT receptors and reward-related behaviour: a review. *Neurosci Biobehav Rev* **35**: 1419-49 [PMID:21402098]

Hoyer D *et al.* (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev* **46**: 157-203 [PMID:7938165]

Leopoldo M *et al.* (2011) Serotonin 5-HT7 receptor agents: Structure-activity relationships and potential therapeutic applications in central nervous system disorders. *Pharmacol Ther* **129**: 120-48 [PMID:20923682]

Meltzer HY *et al.* (2011) The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol* **11**: 59-67 [PMID:21420906]

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## Acetylcholine receptors (muscarinic)

G protein-coupled receptors → Acetylcholine receptors (muscarinic)

**Overview:** Muscarinic acetylcholine receptors (mAChRs) (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Muscarinic Acetylcholine Receptors** [364]) are activated by the endogenous agonist [acetylcholine](#). All five (M1-M5) mAChRs are ubiquitously expressed in the human body

and are therefore attractive targets for many disorders. Functionally, M<sub>1</sub>, M<sub>3</sub>, and M<sub>5</sub> mAChRs preferentially couple to G<sub>q/11</sub> proteins, whilst M<sub>2</sub> and M<sub>4</sub> mAChRs predominantly couple to G<sub>i/o</sub> proteins. Both agonists and antagonists of mAChRs are clinically approved drugs, including [pilocarpine](#) for the treatment

of elevated intra-ocular pressure and glaucoma, and [atropine](#) for the treatment of bradycardia and poisoning by muscarinic agents such as organophosphates. Of note, it has been observed that mAChRs dimerise reversibly [998] and that dimerisation/oligomerisation can be affected by ligands [1506, 1656].

Nomenclature	<b>M<sub>1</sub> receptor</b>	<b>M<sub>2</sub> receptor</b>
HGNC, UniProt	<i>CHRM1</i> , P11229	<i>CHRM2</i> , P08172
Endogenous agonists	acetylcholine [1143, 1252]	acetylcholine [419, 1143, 1252]
Agonists	xanomeline (Partial agonist) [452, 2077, 2751, 2806], methacholine [2008, 2178] – Rat, arecoline [1143, 1969, 2178], oxotremorine (Partial agonist) [1143, 2178], carbachol [452, 1143, 2806], pilocarpine (Partial agonist) [1143, 2178], bethanechol [1143, 2178], iperoxo [2308]	iperoxo [2308, 2309], xanomeline [2077, 2751, 2806], methacholine [2008, 2178] – Rat, oxotremorine [1143, 2178], arecoline [1143, 1969, 2178], pilocarpine (Partial agonist) [1143, 2178], bethanechol [1143, 2178]
Antagonists	tiotropium (pK <sub>i</sub> 9.6–10.7) [589, 2080, 2508, 2551], aclidinium (pIC <sub>50</sub> 10.1–10.2) [2080, 2551], glycopyrrolate (pIC <sub>50</sub> 9.6–10.1) [2462, 2508], ipratropium (pK <sub>i</sub> 9.3–9.8) [1021, 2080], atropine (pK <sub>i</sub> 8.5–9.6) [452, 742, 1021, 1075, 2019, 2410], biperiden (pK <sub>d</sub> 9.3) [227], 4-DAMP (pK <sub>i</sub> 9.3) [606], darifenacin (pK <sub>i</sub> 8.9–9.1) [819, 1021, 2396], scopolamine (pK <sub>i</sub> 9) [509, 1075], oxybutynin (pK <sub>i</sub> 8.6) [559, 2396], tolterodine (pK <sub>i</sub> 8.4–8.5) [819, 2396], droxidopa (pK <sub>i</sub> 7.1) [509]	tiotropium (pK <sub>i</sub> 9.9–10.7) [589, 2080, 2508, 2551], aclidinium (pIC <sub>50</sub> 10.1) [2080, 2551], ipratropium (pK <sub>i</sub> 9.3–9.8) [1021, 2080], glycopyrrolate (pIC <sub>50</sub> 8.7–9.5) [2462, 2508], atropine (pK <sub>i</sub> 7.8–9.2) [509, 1021, 1075, 2019], scopolamine (pK <sub>i</sub> 8.7) [227, 1075], tolterodine (Inverse agonist) (pK <sub>i</sub> 8.4–8.5) [819, 2396], 4-DAMP (pK <sub>i</sub> 8.4) [606], biperiden (pK <sub>d</sub> 8.2) [227], oxybutynin (pK <sub>i</sub> 7.9–8.1) [559, 2396], darifenacin (Inverse agonist) (pK <sub>i</sub> 7.2–7.3) [819, 1021, 2396], tropicamide (pK <sub>i</sub> 7.2) [509]
Selective antagonists	pirenzepine (pK <sub>i</sub> 7.6–8.3) [311, 606, 982, 1075, 1181, 2771], VU0255035 (pK <sub>i</sub> 7.8) [2356]	AFDX384 (pK <sub>i</sub> 8.1–8.2) [509, 606]
Allosteric modulators (Positive)	benzoquinazolinone 12 (pK <sub>B</sub> 6.6) [6], KT 5720 (pK <sub>d</sub> 6.4) [1427], brucine (pK <sub>d</sub> 4.5–5.8) [203, 1143, 1426], BQCA (pK <sub>B</sub> 4–4.8) [6, 7, 341, 1590], VU0029767 [1654], VU0090157 [1654]	LY2119620 (pK <sub>d</sub> 5.5–5.7) [510, 1364], LY2033298 (pK <sub>d</sub> 4.4) [2646]
Allosteric modulators (Negative)	muscarinic toxin 7 (pK <sub>i</sub> 11–11.1) [742, 1858, 1953]	gallamine (pK <sub>i</sub> 5.8–7.6) [1347, 1780, 2609], W-84 (pK <sub>d</sub> 6–7.5) [1762, 2609], C7/3-phth (pK <sub>d</sub> 7.1) [98, 453], alcuronium (pK <sub>d</sub> 6.1–6.9) [98, 1143, 2609], gallamine (pK <sub>d</sub> 5.9–6.3) [466, 1424]
Labelled ligands	[ <sup>3</sup> H]QNB (Antagonist) (pK <sub>d</sub> 10.6–10.8) [1144, 2019], [ <sup>3</sup> H]N-methyl scopolamine (Antagonist) (pK <sub>d</sub> 9.4–10.3) [370, 452, 454, 1021, 1143, 1145, 1181, 1256, 1424], [ <sup>3</sup> H]darifenacin (Selective Antagonist) (pK <sub>d</sub> 8.8) [2410], [ <sup>3</sup> H]iperoxo (Agonist) [2308], [ <sup>3</sup> H]pirenzepine (Selective Antagonist) (pK <sub>d</sub> 7.9) [374, 2284, 2651, 2752], [ <sup>3</sup> H]acetylcholine (Agonist)	[ <sup>3</sup> H]QNB (Antagonist) (pK <sub>d</sub> 10.1–10.6) [1144, 2019], [ <sup>3</sup> H]iperoxo (Agonist) [2308], [ <sup>3</sup> H]N-methyl scopolamine (Antagonist) (pK <sub>d</sub> 9.3–9.9) [370, 1021, 1144, 1145, 1256, 1424, 2736], [ <sup>3</sup> H]AFDX-384 (Selective Antagonist) (pK <sub>d</sub> 9) [374, 1742, 2651], [ <sup>3</sup> H]acetylcholine (Agonist) [1425]
Comments	Atypical agonists: AC-42 [99, 1409, 1410, 2256, 2439, 2440], 77-LH-28-1 [99, 1409], N-desmethylyclozapine [2256, 2439, 2495], TBPB [1184, 1252, 2256], McN-A-343 [1143, 2178]	Atypical agonists: AC-42 [1409, 1682], 77-LH-28-1 [1409, 1682], N-desmethylyclozapine [2495], McN-A-343 [1143, 1682, 2178]

Nomenclature	<b>M<sub>3</sub> receptor</b>	<b>M<sub>4</sub> receptor</b>	<b>M<sub>5</sub> receptor</b>
HGNC, UniProt	<i>CHRM3</i> , P20309	<i>CHRM4</i> , P08173	<i>CHRM5</i> , P08912
Endogenous agonists	acetylcholine [419, 1143, 1252]	acetylcholine [1143, 1252]	acetylcholine [419]
Agonists	xanomeline (Partial agonist) [2077, 2751, 2806], methacholine [2008, 2178] – Rat, arecoline [1143, 1969, 2178], oxotremorine [1143, 2178], pilocarpine (Partial agonist) [1143, 2178], carbachol [419, 1143, 2806], bethanechol [1143, 2178], iperoxo [2308]	xanomeline (Partial agonist) [1694, 2077, 2751, 2806], methacholine [2008, 2178] – Rat, arecoline [1143, 1969, 2178], oxotremorine [1143, 2178], pilocarpine (Partial agonist) [1143, 2178], carbachol [1143, 2806], bethanechol [1143, 2178], iperoxo [2308]	xanomeline (Partial agonist) [866, 2077, 2751, 2806], pilocarpine (Partial agonist) [184, 599, 866], carbachol [184, 866, 2806], arecoline [1969, 2178], bethanechol [2178], iperoxo [2308], methacholine [2178]

Antagonists	<a href="#">tiotropium</a> (pK <sub>i</sub> 9.5–11.1) [589, 610, 2080, 2508, 2551], <a href="#">acridinium</a> (pK <sub>i</sub> 10.1–10.2) [2080, 2551], <a href="#">atropine</a> (pK <sub>i</sub> 8.5–9.8) [509, 1021, 1075, 2019], <a href="#">glycopyrrolate</a> (pIC <sub>50</sub> 9.6–9.8) [2462, 2508], <a href="#">ipratropium</a> (pK <sub>i</sub> 9.3–9.8) [610, 1021, 2080], <a href="#">scopolamine</a> (pK <sub>i</sub> 9.4) [227, 1075], <a href="#">4-DAMP</a> (pK <sub>i</sub> 9.3) [606], <a href="#">darifenacin</a> (pK <sub>i</sub> 8.9–9.1) [819, 1021, 2396], <a href="#">oxybutynin</a> (pK <sub>i</sub> 8.8) [559, 2396], <a href="#">tolterodine</a> (pK <sub>i</sub> 8.4–8.5) [819, 2396], <a href="#">biperiden</a> (pK <sub>d</sub> 8.4) [227], <a href="#">tropicamide</a> (pK <sub>i</sub> 7) [509]	<a href="#">tiotropium</a> (pK <sub>i</sub> 10.2–10.6) [2508, 2551], <a href="#">acridinium</a> (pK <sub>i</sub> 10) [2551], <a href="#">glycopyrrolate</a> (pK <sub>i</sub> 9.1–10) [2462, 2508], <a href="#">atropine</a> (pK <sub>i</sub> 8.7–9.5) [509, 1021, 1075, 2019], <a href="#">scopolamine</a> (pK <sub>i</sub> 9.1–9.5) [227, 1075], <a href="#">ipratropium</a> (pK <sub>i</sub> 9.2) [1021], <a href="#">4-DAMP</a> (pK <sub>i</sub> 8.9) [606], <a href="#">oxybutynin</a> (pK <sub>i</sub> 8.4–8.7) [559, 2396], <a href="#">biperiden</a> (pK <sub>d</sub> 8.6) [227], <a href="#">tolterodine</a> (pK <sub>i</sub> 8.3–8.4) [819, 2396], <a href="#">darifenacin</a> (pK <sub>i</sub> 7.3–8.1) [819, 1021, 2396], <a href="#">tropicamide</a> (pK <sub>i</sub> 6.9) [352]	<a href="#">tiotropium</a> (pK <sub>i</sub> 9.8–10.2) [2508, 2551], <a href="#">acridinium</a> (pK <sub>i</sub> 9.9) [2551], <a href="#">glycopyrrolate</a> (pK <sub>i</sub> 8.9–9.9) [2462, 2508], <a href="#">atropine</a> (pK <sub>i</sub> 8.3–9.3) [509, 1021, 1803], <a href="#">4-DAMP</a> (pK <sub>i</sub> 9) [606], <a href="#">ipratropium</a> (pK <sub>i</sub> 8.8) [1021], <a href="#">tolterodine</a> (pK <sub>i</sub> 8.5–8.8) [819, 2396], <a href="#">scopolamine</a> (pK <sub>i</sub> 8.7) [227], <a href="#">darifenacin</a> (pK <sub>i</sub> 7.9–8.6) [819, 1021, 2396], <a href="#">biperiden</a> (pK <sub>d</sub> 8.2) [227], <a href="#">oxybutynin</a> (pK <sub>i</sub> 7.9) [559, 2396], <a href="#">tropicamide</a> (pK <sub>i</sub> 6.4) [509]
Selective antagonists	–	<a href="#">PCS1055</a> (pK <sub>i</sub> 8.2) [509], <a href="#">AFDX384</a> (pK <sub>i</sub> 7.3–8) [509, 606], <a href="#">PD 102807</a> (pK <sub>i</sub> 7.4–7.6) [509, 1954]	<a href="#">ML381</a> (pK <sub>i</sub> 6.3) [797]
Allosteric modulators (Positive)	<a href="#">WIN 62,577</a> (pK <sub>d</sub> 5.1) [1428], <a href="#">N-chloromethyl-brucine</a> (pK <sub>d</sub> 3.3) [1426]	<a href="#">VU0152100</a> (pEC <sub>50</sub> 6.4) [265] – Rat, <a href="#">VU0152099</a> (pEC <sub>50</sub> 6.4) [265] – Rat, <a href="#">LY2033298</a> (pK <sub>B</sub> 4.9–5.5) [381, 2495], <a href="#">LY2119620</a> (pK <sub>d</sub> 5.5) [510], <a href="#">thiochrome</a> (pK <sub>d</sub> 4) [1425]	<a href="#">amiodarone</a> (pK <sub>B</sub> 7.2) [2448], <a href="#">ML380</a> (pK <sub>B</sub> 4.8) [184, 799]
Allosteric modulators (Negative)	–	<a href="#">muscarinic toxin 3</a> (pK <sub>i</sub> 8.7) [1181, 1952]	–
Selective allosteric modulators	–	–	<a href="#">ML375</a> (Negative) (pK <sub>B</sub> 6.2–6.6) [184, 319, 798]
Labelled ligands	<a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) (pK <sub>d</sub> 10.4) [1144, 2019], <a href="#">[<sup>3</sup>H]N-methyl scopolamine</a> (Antagonist) (pK <sub>d</sub> 9.7–10.2) [370, 1021, 1143, 1144, 1256, 1424], <a href="#">[<sup>3</sup>H]darifenacin</a> (Selective Antagonist) (pK <sub>d</sub> 9.5) [2410], <a href="#">[<sup>3</sup>H]4-DAMP</a> (Selective Antagonist) (pK <sub>i</sub> 8.8–9.4) [374, 1162], <a href="#">[<sup>3</sup>H]jiperoxo</a> (Agonist) [2308], <a href="#">[<sup>3</sup>H]acetylcholine</a> (Agonist)	<a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) <a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) (pK <sub>d</sub> 9.7–10.5) [1144, 2018], <a href="#">[<sup>3</sup>H]N-methyl scopolamine</a> (Antagonist) (pK <sub>d</sub> 9.9–10.2) [370, 1143, 1144, 1256, 1424, 2736], <a href="#">[<sup>3</sup>H]jiperoxo</a> (Agonist) [2308], <a href="#">[<sup>3</sup>H]AF DX-384</a> (Selective Antagonist) (pK <sub>d</sub> 8.7) [374, 1742, 2651], <a href="#">[<sup>3</sup>H]acetylcholine</a> (Agonist) [1425]	<a href="#">[<sup>3</sup>H]QNB</a> (Antagonist) (pK <sub>d</sub> 10.2–10.7) [1144], <a href="#">[<sup>3</sup>H]N-methyl scopolamine</a> (Antagonist) (pK <sub>d</sub> 9.3–9.7) [370, 419, 1021, 1144, 1256, 2699, 2736], <a href="#">[<sup>3</sup>H]jiperoxo</a> (Agonist) [2308], <a href="#">[<sup>3</sup>H]acetylcholine</a> (Agonist)
Comments	Atypical agonists: <a href="#">AC-42</a> [1409], <a href="#">77-LH-28-1</a> [1409], <a href="#">N-desmethylozapine</a> [2495], <a href="#">McN-A-343</a> [1143, 2178]	Atypical agonists: <a href="#">AC-42</a> [1409], <a href="#">77-LH-28-1</a> [1409], <a href="#">N-desmethylozapine</a> [2495], <a href="#">McN-A-343</a> [1143, 2178]	Atypical agonists: <a href="#">AC-42</a> [1409], <a href="#">77-LH-28-1</a> [1409], <a href="#">McN-A-343</a> [2178]

**Comments:** Atomic structures for all five mAChRs bound to antagonists have been determined [910, 2494, 2559, 2699, 2876]. Structures of agonist-bound M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, and M<sub>4</sub> mAChRs [1364, 2726, 2840, 2929] and β<sub>2</sub>-arrestin-bound M<sub>2</sub> mAChR have been reported [2451]. These structures show that the orthosteric binding site of this family of receptor is absolutely conserved and, as a consequence, explain why highly selective orthosteric ligand binding to any specific mAChR has been notoriously difficult to achieve. As such, it is common to assess the rank order of affinity for a range of antagonists with limited selectivity (e.g., [4-DAMP](#), [darifenacin](#), [pirenzepine](#), [AFDX384](#)) to identify the involvement of particular subtypes- although caution should be used in the design and interpretation of such experiments due to the lack of absolute ligand subtype selectivity [1839]. Some ligands may display selectivity at the level of function

(e.g., [xanomeline](#)) or binding kinetics (e.g., [tiotropium](#)) [2077, 2351, 2553]. In addition, structures of the M<sub>3</sub> and M<sub>4</sub> mAChR DREADDS (designer receptors exclusively activated by designer drugs) have been reported providing insights into orthosteric ligand selectivity for these chemogenetic tools [2929].

Structures of the M<sub>1</sub> and M<sub>2</sub> and M<sub>4</sub> mAChRs in complex with allosteric modulators [1364, 1611, 2726] have validated numerous pharmacological studies that indicated the presence of a common mAChR allosteric site located at the extracellular entrance to these receptors. In addition, a structure of the M<sub>1</sub> mAChR with muscarinic toxin 7 (MT7) bound to the common allosteric site has provided insight into the extreme subtype selectivity of MT7 [1611]. Allosteric ligands proposed to bind to this common allosteric site include [gallamine](#), [strychnine](#), [C<sub>7</sub>/3-](#)

[phth](#), [brucine](#) and [LY2033298](#). Additionally, a second allosteric site has been proposed on the mAChRs based on pharmacological analyses of the actions of compounds such as [KT 5720](#), [WIN 62,577](#), [WIN 51,708](#), [staurosporine](#) and [amiodarone](#) [319, 1427, 1428, 2448]. In the presence of the orthosteric ligand, allosteric modulators can exert positive, negative, or neutral cooperativity with that ligand. Direct receptor activation *via* an allosteric site has been reported for a number of allosteric ligands of the mAChRs [540, 1438, 1441, 1590, 1861, 1862]. ‘Atypical agonists’ are ligands that have been suggested to have bitopic binding modes for at least one subtype whereby the agonist occupies both the orthosteric and allosteric sites [99, 1251, 2647]. Several mAChR PET radioligands have been reported, but their utility for subtype selectivity measurements in the human brain has yet to be confirmed [1968].

**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 [729]**) are activated by the endogenous ligand **adenosine** (potentially **inosine** also at A<sub>3</sub> receptors). Crystal structures for the antagonist-bound [480, 1129, 1553, 2334], agonist-bound

[1446, 1447, 2839] and G protein-bound A<sub>2A</sub> adenosine receptors [351] have been described. The structures of an antagonist-bound A<sub>1</sub> receptor [830] and an adenosine-bound A<sub>1</sub> receptor-G<sub>i</sub> complex [612] have been resolved by cryo-electron microscopy. Another structure of an antagonist-bound A<sub>1</sub> receptor obtained

with X-ray crystallography has also been reported [422]. The structure of the A<sub>2B</sub> receptor has also been elucidated [413]. **Caffeine** is a nonselective antagonist for adenosine receptors, while **istradefylline**, a selective A<sub>2A</sub> receptor antagonist, is on the market for the treatment of Parkinson's disease.

Nomenclature	A <sub>1</sub> receptor	A <sub>2A</sub> receptor	A <sub>2B</sub> receptor	A <sub>3</sub> receptor
HGNC, UniProt	ADORA1, P30542	ADORA2A, P29274	ADORA2B, P29275	ADORA3, PODMS8
Endogenous agonists	adenosine [2859]	adenosine [727, 728, 2859]	adenosine [727, 728, 2859]	adenosine [727, 728, 2859]
Agonists	NECA [767, 1175, 2190, 2607, 2859]	NECA [248, 588, 767, 1274, 1378, 2859]	NECA [194, 248, 1164, 1529, 2458, 2669, 2859]	NECA [248, 767, 1137, 2255, 2670, 2859]
Selective agonists	cyclopentyladenosine [518, 548, 767, 989, 1134, 1175, 2190], 5-Cl-5-deoxy-(±)-ENBA [722], TCPA [196], CCPA [1134, 1923], MRS7469 [2602]	apadenoson [2009], UK-432,097 [900, 2839], compound 4g [480], CGS 21680 [248, 588, 767, 1134, 1274, 1308, 1378, 1923], regadenoson [1134]	BAY 60-6583 [631]	piclidenoson [691, 756, 1308, 2670], CI-IB-MECA [266, 1137, 1271], MRS5698 [2601]
Antagonists	CGS 15943 (pK <sub>i</sub> 8.5) [1957], xanthine amine congener (pK <sub>d</sub> 7.5) [722]	CGS 15943 (pK <sub>i</sub> 7.7–9.4) [588, 1274, 1308, 1957], xanthine amine congener (pK <sub>i</sub> 8.4–9) [588, 1308]	xanthine amine congener (pK <sub>i</sub> 6.9–8.8) [194, 1164, 1165, 1308, 1529, 2458], CGS 15943 (pK <sub>i</sub> 6–8.1) [89, 1164, 1165, 1308, 1957, 2458]	CGS 15943 (pK <sub>i</sub> 7–7.9) [1281, 1308, 1957, 2670], xanthine amine congener (pK <sub>i</sub> 7–7.4) [1308, 2255, 2670]
Selective antagonists	PSB36 (pK <sub>i</sub> 9.9) [8] – Rat, DPCPX (pK <sub>i</sub> 7.4–9.2) [548, 1111, 1923, 2190, 2775], derenofylline (pK <sub>i</sub> 9) [1205], WRC-0571 (pK <sub>i</sub> 8.8) [1659], DU172 (pK <sub>i</sub> 7.4) [830]	SCH442416 (pK <sub>i</sub> 8.4–10.3) [2372, 2589], ZM-241385 (pK <sub>i</sub> 8.8–9.1) [1957]	PSB-0788 (pK <sub>i</sub> 9.4) [247], PSB603 (pK <sub>i</sub> 9.3) [247], MRS1754 (pK <sub>i</sub> 8.8) [1164, 1280], PSB1115 (pK <sub>i</sub> 7.3) [972]	MRS1220 (pK <sub>i</sub> 8.2–9.2) [1137, 1281, 2484, 2878], VUF5574 (pK <sub>i</sub> 8.4) [2657], MRS1523 (pK <sub>i</sub> 7.7) [1493], MRS1191 (pK <sub>i</sub> 7.5) [1137, 1168, 1507]
Allosteric modulators (Positive)	PD81723 [305]	–	–	LUF6000 [834], LUF6096 [988], MRS8054 [676]
Labelled ligands	[ <sup>3</sup> H]CCPA (Agonist) [1308, 2190], [ <sup>3</sup> H]DPCPX (Antagonist) (pK <sub>d</sub> 8.4–9.2) [518, 691, 1308, 1957, 2190, 2607]	[ <sup>3</sup> H]ZM 241385 (Antagonist) (pK <sub>d</sub> 8.7–9.1) [44, 765], [ <sup>3</sup> H]CGS 21680 (Agonist) [1152, 2716]	[ <sup>3</sup> H]MRS1754 (Antagonist) (pK <sub>d</sub> 9.8) [1164]	[ <sup>125</sup> I]AB-MECA (Agonist) [1957, 2670]

**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 [1138]. *DPCPX* also exhibits antagonism at A<sub>2B</sub> receptors (pK<sub>i</sub> ca.

7, [42, 1308]). Antagonists at A<sub>3</sub> receptors exhibit marked species differences, such that only *MRS1523* and *MRS1191* are selective at the rat A<sub>3</sub> receptor. In the absence of other adenosine receptors, [<sup>3</sup>H]*DPCPX* and [<sup>3</sup>H]*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 [1308]. [<sup>3</sup>H]*CGS 21680* is relatively

selective for A<sub>2A</sub> receptors, but may also bind to other sites in cerebral cortex [512, 1176]. [<sup>3</sup>H]*NECA* binds to other non-receptor elements, which also recognise adenosine [1567]. *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 [278].

### 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 [69] containing a GPCR proteolysis site (GPS). The N-terminal extracellular region often shares

structural homology with adhesive domains (e.g. cadherins, immunoglobulin, lectins) facilitating inter- and matricellular interactions and leading to the term adhesion GPCR [731, 2894]. Several receptors have been suggested to function as mechanosensors [259, 2035, 2305, 2789]. Cryo-EM structures of the

7-transmembrane domain of several adhesion GPCRs have been determined recently [136, 1525, 2053, 2054, 2107, 2110, 2833, 2956]. **The nomenclature of these receptors was revised in 2015 as recommended by NC-IUPHAR and the Adhesion GPCR Consortium** [922].

Nomenclature	ADGRA1	ADGRA2	ADGRA3
HGNC, UniProt	ADGRA1, Q865Q6	ADGRA2, Q96PE1	ADGRA3, Q81WK6
Comments	–	Required to assemble higher-order Reck/Gpr124/Frizzled/Lrp5/6 complexes [667, 2072, 2650, 2666, 2950]. Interacts with Reck [436, 667, 2666], Syndecan-1, -2 [440], Integrin- $\alpha$ v $\beta$ 3 [2649] and heparin [2649]. Principal signal transduction involves Dishevelled [667], $\beta$ -catenin [2072] and Cdc42 [384]. Required for CNS vascularization and blood-brain barrier formation [384, 1658, 2666].	ADGRA3 is a stem and progenitor cell marker in the male reproductive tract [2326]. It controls fluid homeostasis, sperm maturation and storage in the male reproductive tract [1918]. Principal signal transduction involves Dishevelled [1500].

Nomenclature	<a href="#">ADGRB1</a>	<a href="#">ADGRB2</a>	<a href="#">ADGRB3</a>	<a href="#">CELSR1</a>	<a href="#">CELSR2</a>
Systematic nomenclature	–	–	–	ADGRC1	ADGRC2
HGNC, UniProt	<a href="#">ADGRB1</a> , <a href="#">O14514</a>	<a href="#">ADGRB2</a> , <a href="#">O60241</a>	<a href="#">ADGRB3</a> , <a href="#">O60242</a>	<a href="#">CELSR1</a> , <a href="#">Q9NYQ6</a>	<a href="#">CELSR2</a> , <a href="#">Q9HCU4</a>
Endogenous agonists	<a href="#">phosphatidylserine</a> [1986]	–	–	–	–
Comments	Reported to mediate phagocytosis through binding of phosphatidylserine [1986] and lipopolysaccharide [524]. Suppresses medulloblastoma formation [2951] and is involved in dendrite development [625]. A recent study disputes the previously reported expression of ADGRB1 by macrophages [1068].	Principal signal transduction involves $G\alpha_2$ [2099]. A R1465W mutation confers increased coupling to $G\alpha_i$ [2099].	Reported to bind C1q-like molecules [231]. Promotes myoblast fusion in vertebrates [927].	Principal signal transduction involves Rho kinase [1903]. Interacts with Vangl-2 [571, 1467], Frizzled-6 [571] and LRRK2 [2252].	Mutated in Joubert syndrome patients [2685]. Signal transduction is potentially mediated through $G\alpha_{q/11}$ [2365]. Interacts homomerically with CELSR2/ADGRC2 [2365].

Nomenclature	<a href="#">CELSR3</a>	<a href="#">ADGRD1</a>	<a href="#">ADGRD2</a>	<a href="#">ADGRE1</a>
Systematic nomenclature	ADGRC3	–	–	–
HGNC, UniProt	<a href="#">CELSR3</a> , <a href="#">Q9NYQ7</a>	<a href="#">ADGRD1</a> , <a href="#">Q6QNK2</a>	<a href="#">ADGRD2</a> , <a href="#">Q7Z7M1</a>	<a href="#">ADGRE1</a> , <a href="#">Q14246</a>
Endogenous agonists	–	Peptides derived from the Stachel sequence: THLTNFAILMQVV; PLXDC2 is an activating ligand for mouse ADGRD1. [199, 1513]	–	–
Comments	High-confidence risk gene for Tourette syndrome [2735]. Signal transduction is potentially mediated through $G\alpha_{q/11}$ [2365]. Interacts with Frizzled-3 [2558], Dystroglycan [1530] and homomerically with CELSR3/ADGRC3 [2365].	Is a $G_s$ protein-coupled receptor [223, 1513] and highly expressed in glioblastoma [149]. Couples also to $G_i$ proteins [1514]. Strong association with body height [1275, 1283, 2596]. Associated with bone mineral density [2243]. Regulates oviductal fluid flow in mice [199]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2054, 2110].	–	–



Nomenclature	<a href="#">ADGRE2</a>	<a href="#">ADGRE3</a>	<a href="#">ADGRE4P</a>	<a href="#">ADGRES</a>
HGNC, UniProt	<a href="#">ADGRE2</a> , <a href="#">Q9UHX3</a>	<a href="#">ADGRE3</a> , <a href="#">Q9BY15</a>	<a href="#">ADGRE4P</a> , <a href="#">Q86SQ3</a>	<a href="#">ADGRES</a> , <a href="#">P48960</a>
Comments	A mutation destabilizing the GAIN domain sensitizes mast cells to IgE-independent vibration-induced degranulation [259]. Reported to bind chondroitin sulfate B [2447]. Principal signal transduction involves G protein-coupling [197] and the phospholipase C pathway [1112]. Interacts with FHR1 [1112].	–	–	Reported to bind CD55 [923], chondroitin sulfate B [2447], $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins [2737], and CD90 [2718]. Expression levels on leukocytes are regulated by shear stress-dependent interaction with CD55 on red blood cells [1220]. Promotes the retention of blood-exposed dendritic cells in the spleen by interaction with CD55 on red blood cells [1546].

Nomenclature	<a href="#">ADGRF1</a>	<a href="#">ADGRF2</a>	<a href="#">ADGRF3</a>	<a href="#">ADGRF4</a>
HGNC, UniProt	<a href="#">ADGRF1</a> , <a href="#">Q5T601</a>	<a href="#">ADGRF2P</a> , <a href="#">Q8IZF7</a>	<a href="#">ADGRF3</a> , <a href="#">Q8IZF5</a>	<a href="#">ADGRF4</a> , <a href="#">Q8IZF3</a>
Endogenous agonists	Peptides derived from the Stachel sequence TSFSI LMSFPVPTIFPVVKWIT [563, 2467]	–	–	Peptides derived from the ADGRF5 (GPR116) Stachel sequence: TSFISILMSPDSD [563]
Comments	N-Docosahexaenoylethanolamine is an agonist at ADGRF1 supporting neurogenesis [1456] and couples to $G_s$ and $G_q$ pathways [563, 2467]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2110, 2956]. Furthermore, the domain structure of the N terminus (SEA, HormR, GAIN) has been solved by X-ray crystallography [2722].	ADGRF2 is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [2089].	ADGRF3 is highly expressed in gastrointestinal neuroendocrine tumors [353].	ADGRF4 couples to $G_{q/11}$ proteins [563], is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [2089]. ADGRF4 is required for enamel mineralization mediated by ameloblasts [429].

Nomenclature	<a href="#">ADGRF5</a>	<a href="#">ADGRG1</a>
HGNC, UniProt	<a href="#">ADGRF5</a> , <a href="#">Q8IZF2</a>	<a href="#">ADGRG1</a> , <a href="#">Q9Y653</a>
Endogenous agonists	Peptides derived from the Stachel sequence: TSFISILMSPDSD [563]	Peptides derived from the Stachel sequence: TYFAVLM [2467]
Comments	ADGRF5 controls alveolar surfactant secretion via $G_{q/11}$ pathway [299, 563, 1310, 2546]. ADGRF5 deficiency leads to dysregulation of lung surfactant homeostasis [279, 749, 2870].	ADGRG1 is a collagen-responsive platelet receptor sensing shear forces [2884]. Reported to bind tissue transglutaminase 2 [2841] and collagen, which activates the $G_{12/13}$ pathway [1581]. Interacts with heparin [428]. Couples to G13 proteins [2467]. 3- $\alpha$ -acetoxydihydrodeoxygedunin is a partial agonist [2468], dihydromunduletone, a rotenoid derivative, is an antagonist [2466]. Negatively regulates immediate effector functions in human NK cells [383]. Deficiency leads to dysregulation of central and peripheral myelination [11, 814] and ADGRG1 deficiency in humans lead to bilateral frontoparietal polymicrogyria [2044]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [136].

Nomenclature	<a href="#">ADGRG2</a>	<a href="#">ADGRG3</a>	<a href="#">ADGRG4</a>
HGNC, UniProt	<a href="#">ADGRG2, Q8IZP9</a>	<a href="#">ADGRG3, Q86Y34</a>	<a href="#">ADGRG4, Q8IZF6</a>
Endogenous agonists	Peptides derived from the Stachel sequence: TSFGVLLDLSRTSLPP [562]	–	–
Comments	ADGRG2 is coupled to G <sub>q</sub> and G <sub>s</sub> pathways [562, 2922] and gene deficiency causes congenital obstructive azoospermia [1994]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [1525, 2833].	ADGRG3 couples to G <sub>o</sub> proteins [902], G <sub>α<sub>s</sub></sub> and G <sub>α<sub>o/i</sub></sub> signaling [1067]. Binds to exogenous ligands beclomethasone dipropionate and cortisol [902, 2053], and the 7-helix transmembrane domain structure has been determined by cryo-EM [2053].	ADGRG4 is highly expressed in enterochromaffin cells and gastrointestinal neuroendocrine tumors [1469]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2833].

Nomenclature	<a href="#">ADGRG5</a>	<a href="#">ADGRG6</a>
HGNC, UniProt	<a href="#">ADGRG5, Q8IZF4</a>	<a href="#">ADGRG6, Q86SQ4</a>
Endogenous agonists	Peptides derived from the Stachel sequence: TYFAVLMQLSG DPVPAEL [2466, 2789]	Peptides derived from the Stachel sequence: THFGVLMDLPRASQL; Progesterone and 17-hydroxyprogesterone seem to activate Gi signaling via GPR126 (ADGRG6). [56, 1513]
Comments	ADGRG5 is a constitutively active G <sub>s</sub> protein-coupled receptor [902, 2466, 2789]. Dihydrumunduletone is an antagonist [2466]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2054].	ADGRG6 is a key regulator of Schwann cell-mediated myelination [1773], and couples to G <sub>s</sub> and G <sub>i/o</sub> pathways [1513, 1760, 2035]. Apomorphine hydrochloride is an exogenous agonist [263]. Binds to Laminin-211 [2035]. ADGRG6 is essential for normal differentiation of promyelinating Schwann cells and for normal myelination of axons [1760, 1773, 1774, 2035], normal placenta development [2598], and for proper heart development [1999, 2710]. Furthermore, conditional deletion of <i>Adgrg6</i> revealed that this adhesion GPCR is involved in regulation of body length and bone mass [2486] and intervertebral disc function [1555]. Involved in arthrogyrposis multiplex congenita (lethal congenital contracture syndrome-9) [2147].

Nomenclature	<a href="#">ADGRG7</a>	<a href="#">ADGRL1</a>	<a href="#">ADGRL2</a>	<a href="#">ADGRL3</a>	<a href="#">ADGRL4</a>	<a href="#">ADGRV1</a>	
HGNC, UniProt	<a href="#">ADGRG7, Q96K78</a>	<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	ADGRG7 is expressed in intestine and involved in regulation of intestinal contractility [1890].	Couples to G <sub>s</sub> and G <sub>q</sub> pathways [1471, 1825]. Principal signal transduction involves G <sub>α<sub>s</sub></sub> [1825], G <sub>α<sub>o</sub></sub> [1471, 2122] and G <sub>α<sub>q</sub></sub> [2122]. Interacts with Tenascin-2 [2386], FLRT-1, -3 [1921], Neurexin-1 $\alpha$ , -1 $\beta$ , -2 $\beta$ , -3 $\beta$ [251], Contactin-6 [2963], Shank [1357] and TRIP8b [2064, 2065].	–	A LPHN3 gene variant in humans is associated with attention-deficit-hyperactivity disorder [72, 2792]. Principal signal transduction involves G <sub>α<sub>12/13</sub></sub> [1667] and G <sub>α<sub>q</sub></sub> [1667]. Interacts with Tenascin-3 [1921], FLRT-1, -3 [1921] and UNC5A [1131].	–	–	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [1139]. Interacts with Harmonin [2160] and Whirlin [2662].

**Further reading on Adhesion Class GPCRs**

Bassilana F *et al.* (2019) Adhesion G protein-coupled receptors: opportunities for drug discovery. *Nat Rev Drug Discov* **18**: 869-884 [PMID:31462748]

Hamann J *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors. *Pharmacol Rev* **67**: 338-67 [PMID:25713288]

Langenhan T *et al.* (2013) Sticky signaling—adhesion class G protein-coupled receptors take the stage. *Sci Signal* **6**: re3 [PMID:23695165]

Liebscher I *et al.* (2016) Tethered Agonism: A Common Activation Mechanism of Adhesion GPCRs. *Handb Exp Pharmacol* **234**: 111-125 [PMID:27832486]

Monk KR *et al.* (2015) Adhesion G Protein-Coupled Receptors: From In Vitro Pharmacology to In Vivo Mechanisms. *Mol Pharmacol* **88**: 617-23 [PMID:25956432]

Purcell RH *et al.* (2018) Adhesion G Protein-Coupled Receptors as Drug Targets. *Annu Rev Pharmacol Toxicol* **58**: 429-449 [PMID:28968187]

# Adrenoceptors

G protein-coupled receptors → Adrenoceptors

**Overview: The nomenclature of the Adrenoceptors has been agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [328, 1012].****Adrenoceptors,  $\alpha_1$** 

The three  $\alpha_1$ -adrenoceptor subtypes  $\alpha_{1A}$ ,  $\alpha_{1B}$  and  $\alpha_{1D}$  are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. (-)-phenylephrine, methoxamine and cirazoline are agonists and prazosin and doxazosin 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. Flu-

orescent derivatives of prazosin (Bodipy FLprazosin- QAPB) are used to examine cellular localisation of  $\alpha_1$ -adrenoceptors.  $\alpha_1$ -Adrenoceptor agonists are used as nasal decongestants; antagonists to treat symptoms of benign prostatic hyperplasia (alfuzosin, doxazosin, terazosin, tamsulosin and silodosin, with the last two compounds being  $\alpha_{1A}$ -adrenoceptor selective and claiming to relax bladder neck tone with less hypotension); and to a lesser

extent hypertension (doxazosin, terazosin). 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.

Nomenclature	$\alpha_{1A}$ -adrenoceptor	$\alpha_{1B}$ -adrenoceptor	$\alpha_{1D}$ -adrenoceptor
HGNC, UniProt	ADRA1A, P35348	ADRA1B, P35368	ADRA1D, P25100
Endogenous agonists	(-)-adrenaline [1052, 2095, 2360], (-)-noradrenaline [515, 669, 1052, 2095, 2360, 2549]	(-)-adrenaline [2360], (-)-noradrenaline [2360]	(-)-noradrenaline [1052, 2095, 2360], (-)-adrenaline [1052, 2095, 2360]
Agonists	phenylephrine [2549], methoxamine [2360, 2549]	phenylephrine [715, 1746]	methoxamine [2095, 2360, 2549], phenylephrine [2095, 2549]
Selective agonists	A61603 [715, 1309], oxymetazoline [1052, 1924, 2360, 2549], dabuzalgron [216]	–	–
Antagonists	prazosin (Inverse agonist) (pK <sub>i</sub> 9–9.9) [382, 519, 715, 2096, 2360, 2791], doxazosin (pK <sub>i</sub> 8.6–9.3) [931, 2096], terazosin (pK <sub>i</sub> 7.9–8.7) [1713, 2096], phentolamine (pK <sub>i</sub> 8.2–8.6) [2096, 2360], alfuzosin (pK <sub>i</sub> 7.8–8.1) [1010, 2096]	prazosin (Inverse agonist) (pK <sub>i</sub> 8.7–9.9) [715, 2096, 2360, 2791], tamsulosin (Inverse agonist) (pK <sub>i</sub> 8.1–9.7) [715, 2096, 2360, 2791], doxazosin (pK <sub>i</sub> 8.5–9.1) [931, 2096], alfuzosin (pK <sub>i</sub> 7.6–8.6) [1011, 2096], terazosin (pK <sub>i</sub> 8–8.6) [1713, 2096], phentolamine (pK <sub>i</sub> 6.6–7.5) [2096, 2360]	prazosin (Inverse agonist) (pK <sub>i</sub> 9.1–10.2) [715, 2096, 2360, 2791], tamsulosin (pK <sub>i</sub> 9.2–10.2) [715, 2096, 2360, 2791], doxazosin (pK <sub>i</sub> 8.3–9.1) [931, 2096], terazosin (pK <sub>i</sub> 7.7–9.1) [1713, 2096], alfuzosin (pK <sub>i</sub> 7.7–8.4) [1010, 2096], dapiprazole (pK <sub>i</sub> 8.4) [93, 2096], phentolamine (Inverse agonist) (pK <sub>i</sub> 6.8–8.2) [2096, 2360], RS-100329 (pK <sub>i</sub> 7.6–7.9) [2096, 2791], labetalol (pK <sub>i</sub> 6.1–6.6) [93, 2096]
Selective antagonists	tamsulosin (pK <sub>i</sub> 9.7–10.7) [382, 519, 715, 2096, 2360, 2791], silodosin (pK <sub>i</sub> 9.6–10.4) [2096, 2360], S(+)-niguldipine (pK <sub>i</sub> 9.1–10) [715, 2096, 2360], RS-100329 (pK <sub>i</sub> 9.6) [2096, 2791], SNAP5089 (pK <sub>i</sub> 8.8–9.4) [1010, 1475, 2096, 2774], r-Da1a (pK <sub>i</sub> 9.2–9.3) [1618, 2116], RS-17053 (pK <sub>i</sub> 8.3–9.3) [382, 519, 714, 715, 2096]	Rec 15/2615 (pK <sub>i</sub> 9.5) [2557], L-765314 (pK <sub>i</sub> 7.7) [1993], AH 11110 (pK <sub>i</sub> 7.5) [2277]	BMY-7378 (pK <sub>i</sub> 8.6–9.1) [355, 2096, 2899]

**Comments:** The three  $\alpha_1$ -adrenoceptor subtypes are  $\alpha_{1A}$ ,  $\alpha_{1B}$  and  $\alpha_{1D}$ . The previously described  $\alpha_{1C}$ -adrenoceptor is a species homologue that corresponds to the pharmacologically defined  $\alpha_{1A}$ -adrenoceptor [1012]. Some tissues possess  $\alpha_{1A}$ -adrenoceptors (termed  $\alpha_{11}$ -adrenoceptors [715, 1802]) 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, and

do not generate a functional  $\alpha_{1L}$ -adrenoceptor [2135]. 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 and formation of heterodimers of with  $\alpha_{1B}$ - $\alpha_{1B}$  or  $\beta_2$ - $\beta_2$ -adrenoceptors [912, 2623]. In blood vessels all three  $\alpha_1$ -adrenoceptor subtypes are located both at the cell surface and intracellularly [1711, 1712]. Signalling is predominantly

via  $G_{q/11}$  but  $\alpha_1$ -adrenoceptors also couple to  $G_{i/o}$ ,  $G_s$  and  $G_{12/13}$ . Several  $\alpha_{1A}$ -adrenoceptor agonists display ligand directed signalling bias relative to noradrenaline [669] although some bias appears to relate to off-target activity [515]. 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 compared to  $\alpha_{1A}$ -adrenoceptors [709].

## Adrenoceptors, $\alpha_2$

The three  $\alpha_2$ -adrenoceptor subtypes  $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_{2C}$  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. [ $^3$ H]rauwolscine, [ $^3$ H]brimonidine and [ $^3$ H]RX821002 are relatively selective radioligands. There are species variations 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 (relatively little used) and counteracts opioid withdrawal. **Dexmedetomidine** (also **xylozine**) is

increasingly used as a sedative and analgesic in human [132] and veterinary medicine and has sympatholytic and anxiolytic properties. The  $\alpha_2$ -adrenoceptor antagonist **mirtazapine** is used 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. Although subtype-selective antagonists have been developed, none are used clinically and they remain experimental tools.

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 [1154, 2045, 2093], (-)-noradrenaline [1154, 2045, 2093]	(-)-noradrenaline (Partial agonist) [1154, 2045, 2093], (-)-adrenaline [1154, 2093]	(-)-noradrenaline [1154, 1385, 2045, 2093], (-)-adrenaline [1154, 2093]
Agonists	dexmedetomidine (Partial agonist) [1154, 1598, 2013, 2045, 2093], clonidine (Partial agonist) [1154, 2013, 2045, 2093], brimonidine [1154, 1598, 2013, 2045, 2093], apraclonidine [1827], guanabenz [93, 2093], guanfacine (Partial agonist) [1154, 1602, 2093], moxonidine [2093], tizanidine [2093]	dexmedetomidine [1154, 1598, 2013, 2045, 2093], clonidine (Partial agonist) [1154, 2013, 2045, 2093], brimonidine (Partial agonist) [1154, 2013, 2045, 2093], guanabenz [93, 2093], guanfacine [1154, 2093], oxymetazoline (Partial agonist) [1154, 2093, 2628], moxonidine [2093], tizanidine [2093]	dexmedetomidine [1154, 2013, 2045, 2093], brimonidine (Partial agonist) [1154, 1598, 2013, 2045, 2093], apraclonidine [1827, 2093], oxymetazoline (Partial agonist) [1154, 1385, 2093, 2628], guanfacine (Partial agonist) [1154], guanabenz [93, 2093], moxonidine [2093]
Selective agonists	oxymetazoline (Partial agonist) [1154, 1598, 2093, 2628]	–	–
Antagonists	RX821002 (pK <sub>i</sub> 8.1–9.2) [2094, 2628], yohimbine (pK <sub>i</sub> 8.4–9.2) [327, 570, 2094, 2628], atipamezole (pK <sub>i</sub> 8.5) [2094], idazoxan (pK <sub>i</sub> 7.2) [2094]	lisuride (pK <sub>i</sub> 8.5–9.9) [1735, 2094], yohimbine (pK <sub>i</sub> 7.9–8.9) [327, 570, 2094, 2628], phenoxybenzamine (pK <sub>i</sub> 8.5) [2758], RX821002 (pK <sub>i</sub> 7.5–8.4) [2094, 2628], atipamezole (pK <sub>i</sub> 7.9) [2094], idazoxan (pK <sub>i</sub> 6.4) [2094], tolazoline (pK <sub>i</sub> 5.5) [1154]	MK-912 (pK <sub>i</sub> 9.8–10) [2094], lisuride (pK <sub>i</sub> 9.3–9.9) [1598, 1735, 2094], yohimbine (pK <sub>i</sub> 8.5–9.5) [327, 570, 2094, 2628], WB 4101 (pK <sub>i</sub> 8.2–9.4) [327, 570, 2094, 2628], spiroxatrine (pK <sub>i</sub> 8.7–9) [2094, 2628], RX821002 (pK <sub>i</sub> 8.1–8.7) [2094, 2253, 2628], atipamezole (pK <sub>i</sub> 8.5) [2094], mirtazapine (pK <sub>i</sub> 7.7) [692], idazoxan (pK <sub>i</sub> 7.2) [2094], tolazoline (pK <sub>i</sub> 5.4) [1154]
Selective antagonists	BRL 44408 (pK <sub>i</sub> 8.2–8.8) [2628, 2901]	ARC-239 (pK <sub>i</sub> 6.8–8.6) [327, 570, 2094, 2628], imiloxan (pK <sub>i</sub> 7.3) [1724] – Rat	JP1302 (pK <sub>B</sub> 6.9–7.8) [2094, 2253]
Labelled ligands	–	–	[ $^3$ H]MK-912 (Antagonist) (pK <sub>d</sub> 10.1) [2628]

**Comments:** The three  $\alpha_2$ -adrenoceptor subtypes are termed  $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_{2C}$ . **ARC-239** and **prazosin** show some selectivity for  $\alpha_{2B}$ - and  $\alpha_{2C}$ -adrenoceptors over  $\alpha_{2A}$ -adrenoceptors. **Oxymetazoline** is an imidazoline partial agonist that also binds to non-GPCR binding sites for imidazolines, classified as  $I_1$ ,  $I_2$  and  $I_3$  [521] at which catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands with hypotensive effects *in vivo*.  $I_1$ -imidazoline recognition sites cause central inhibition of sympathetic tone,  $I_2$ -imidazoline sites are an allosteric binding site on monoamine oxidase B, and  $I_3$ -imidazoline sites regulate insulin secretion from pancreatic

### Adrenoceptors, $\beta$

The three  $\beta$ -adrenoceptor subtypes  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  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** ( $pK_i$  8.2-9.2) and **cyanopindolol** ( $pK_i$  10.0-11.0) are relatively selective antagonists for  $\beta_1$ - and  $\beta_2$ - relative to  $\beta_3$ -adrenoceptors. (-)-noradrenaline, **xamoterol** and (-)-Ro 363 show selectivity for  $\beta_1$ - relative to  $\beta_2$ -adrenoceptors. Pharmacological differences exist between human and mouse  $\beta_3$ -adrenoceptors, and the 'rodent selective' agonists **BRL 37344** and **CL316243** have low efficacy at the human  $\beta_3$ -adrenoceptor whereas **CGP 12177** (low potency) 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**

$\beta$ -cells.  $\alpha_{2A}$ -adrenoceptor stimulation reduces insulin secretion from  $\beta$ -islets [2867], 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 [2208]. The  $\alpha_{2A}$ - and  $\alpha_{2C}$ -adrenoceptors form homodimers [2407]. 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 [2407, 2537, 2684]. Signalling by  $\alpha_2$ -adrenoceptors is primarily via  $G_{i/o}$ , although the  $\alpha_{2A}$ -adrenoceptor also couples to  $G_s$  [630]. Imidazoline compounds display bias relative to each other at the

has reasonably high affinity at  $\beta_3$ -adrenoceptors, but does not discriminate between the three  $\beta$ - subtypes [1727] whereas **L-748337** is more selective. [ $^{125}I$ ]-cyanopindolol, [ $^{125}I$ ]-hydroxy benzylpindolol and [ $^3H$ ]-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 [ $^{125}I$ ]-cyanopindolol together with  $\beta_1$ - and  $\beta_2$ -adrenoceptor antagonists. 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 cardiac arrhythmias (**atenolol**, **bisoprolol**, **esmolol**) and cardiac failure (**metoprolol**, **nebivolol**) but also in combination

$\alpha_{2A}$ -adrenoceptor [2003]. The noradrenaline reuptake inhibitor desipramine acts directly on  $\alpha_{2A}$ -adrenoceptors to promote internalisation *via* recruitment of  $\beta$ -arrestin [493]. The structure of the  $\alpha_{2B}$ -adrenoceptor has recently been determined by cryo-EM in complex with dexmedetomidine and  $G_{\alpha_o}$  at a resolution of 2.9 Å providing insights into the structural requirements required for interactions with  $\alpha_2$ -adrenoceptor agonists [2905].

with other treatments to treat hypertension (**atenolol**, **betaxolol**, **bisoprolol**, **metoprolol** and **nebivolol**) [2802]. 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. There is evidence to suggest that  $\beta$ -adrenoceptor antagonists can reduce metastasis in certain types of cancer [1016].

Nomenclature	$\beta_1$ -adrenoceptor	$\beta_2$ -adrenoceptor
HGNC, UniProt	<b>ADRB1</b> , <b>P08588</b>	<b>ADRB2</b> , <b>P07550</b>
Potency order of endogenous ligands	(-)-noradrenaline > (-)-adrenaline	(-)-adrenaline > (-)-noradrenaline
Endogenous agonists	(-)-adrenaline [739, 1033], (-)-noradrenaline [739, 1033], noradrenaline [739]	(-)-adrenaline [739, 1033, 1150], (-)-noradrenaline [739, 1033]
Agonists	isoprenaline [739, 2276], dobutamine (Partial agonist) [1118], cimaterol [114], fenoterol [114]	arformoterol [45], indacaterol [147, 150], fenoterol [75, 121, 549], isoprenaline [2276], cimaterol [114]
Selective agonists	(-)-Ro 363 [1764], xamoterol (Partial agonist) [1118], denopamine (Partial agonist) [1118, 2500]	formoterol [114], olodaterol [254], salmeterol [114], zinterol [114], vilanterol [2085], abediterol [68], procaterol [114], clenbuterol [114, 121, 1254], salbutamol (Partial agonist) [115, 1118], terbutaline (Partial agonist) [115], orciprenaline [2435]
Antagonists	carvedilol ( $pK_i$ 8.8-9.5) [115, 342], bupranolol ( $pK_i$ 7.3-9) [115, 342, 1568], (-)-propranolol ( $pK_i$ 7.9-8.9) [115, 1191, 1568, 2422], <b>SR59230A</b> ( $pK_i$ 7.5-8.6) [115, 342], levobunolol ( $pK_i$ 8.4) [93], labetalol (Partial agonist) ( $pK_i$ 7.6-8.2) [93, 115, 118], metoprolol ( $pK_i$ 7-7.9) [115, 118, 342, 1033, 1568], esmolol ( $pK_i$ 6.7-6.9) [93, 1859], nadolol ( $pK_i$ 6.9) [342], practolol ( $pK_i$ 6.1-6.8) [115, 1568], propafenone ( $pK_i$ 6.7) [93], sotalol ( $pK_i$ 6.1) [93]	carvedilol ( $pK_i$ 9.4-9.9) [115, 342], timolol ( $pK_i$ 9.7) [115], propranolol ( $pK_i$ 9.1-9.5) [115, 119, 1118, 1568], <b>SR59230A</b> ( $pK_i$ 8.5-9.3) [115, 342], levobunolol ( $pK_i$ 9.3) [93], bupranolol ( $pK_i$ 8.3-9.1) [115, 342, 1568], alprenolol (Partial agonist) ( $pK_i$ 9) [115], nadolol ( $pK_i$ 7-8.6) [115, 342], labetalol (Partial agonist) ( $pK_i$ 8) [93], propafenone ( $pK_i$ 7.4) [93], sotalol ( $pK_i$ 6.3-6.5) [93, 115]

Selective antagonists	CGP 20712A (pK <sub>i</sub> 7.9–9.2) [115, 342, 1568, 2275, 2422], nebivolol (pK <sub>i</sub> 9.2) [114, 726], levobetaxolol (pK <sub>i</sub> 8.2–9.1) [2354], NDD-825 (pK <sub>i</sub> 8.3–9) [117], ICI-89406 (Partial agonist) (pK <sub>i</sub> 8.8) [1749], betaxolol (pK <sub>i</sub> 8.8) [1568], nebivolol (pI <sub>C<sub>50</sub></sub> 8.1–8.7) [2002] – Rabbit, NDD-713 (pK <sub>i</sub> 7.8–8.5) [117], bisoprolol (pK <sub>i</sub> 8) [117]	ICI 118551 (Inverse agonist) (pK <sub>i</sub> 9.2–9.5) [115, 119, 1568]
Allosteric modulators	–	AS408 [1554]
Labelled ligands	[ <sup>125</sup> I]ICYP (Antagonist) (pK <sub>d</sub> 10.4–11.3) [1118, 1568, 2276]	[ <sup>125</sup> I]ICYP (Antagonist) (pK <sub>d</sub> 11.1) [1568, 2276]
Comments	The agonists indicated have less than two orders of magnitude selectivity [114].	–

Nomenclature	β <sub>3</sub> -adrenoceptor
HGNC, UniProt	ADRB3, P13945
Potency order of endogenous ligands	(-)-noradrenaline = (-)-adrenaline
Endogenous agonists	(-)-noradrenaline [1033, 2066, 2471], (-)-adrenaline [1033]
Agonists	carazolol (Partial agonist) [114, 1707], isoprenaline [114, 1033, 1707, 1764, 2066, 2276, 2471], fenoterol [114]
Selective agonists	L 755507 [114], vibegron [302, 578, 634], L742791 [2755], solabegron [1093, 1726, 2626], mirabegron [2523], SB251023 [1090] – Mouse, rodent selective BRL 37344 [214, 594, 1033, 1707], rodent selective CL316243 [2864]
Antagonists	SR59230A (pK <sub>i</sub> 6.9–8.4) [114, 342, 550, 1033], bupranolol (pK <sub>i</sub> 6.8–7.3) [214, 342, 1568, 1707], propranolol (pK <sub>i</sub> 6.3–7.2) [1568, 2066], levobunolol (pK <sub>i</sub> 6.8) [2066]
Selective antagonists	L748328 (pK <sub>i</sub> 8.4–8.6) [114, 342], L-748337 (pK <sub>i</sub> 8–8.4) [114, 342]
Labelled ligands	[ <sup>125</sup> I]ICYP (Agonist, Partial agonist) [1568, 1764, 2066, 2276, 2471], [ <sup>3</sup> H]CGP12177 (Agonist, Partial agonist) [115]
Comments	Agonist SB251023 has a pEC <sub>50</sub> of 6.9 for the splice variant of the mouse β <sub>3</sub> receptor, β <sub>3b</sub> [1090]. [ <sup>3</sup> H] L-748337 is a selective antagonist that is used to label β <sub>3</sub> -AR [2661].

**Comments:** The three β-adrenoceptors are termed β<sub>1</sub>, β<sub>2</sub> and β<sub>3</sub>. [<sup>125</sup>I]ICYP can be used to define either β<sub>1</sub>- or β<sub>2</sub>-adrenoceptors when conducted in the presence of a β<sub>1</sub>- or a β<sub>2</sub>-adrenoceptor-selective antagonist. A fluorescent analogue of CGP 12177 is used to study β-adrenoceptors in living cells [120]. [<sup>125</sup>I]ICYP at higher (nM) concentrations has been used to label β<sub>3</sub>-adrenoceptors in systems with few if any other β-adrenoceptor subtypes. The β<sub>3</sub>-adrenoceptor has an intron in the coding region, but splice variants have only been described for the mouse [670], where the isoforms display different signalling characteristics [1090]. There are three β-adrenoceptors in turkey (termed the tβ, tβ3c and tβ4c) with pharmacology that differs from the human β-adrenoceptors [116]. Numerous polymorphisms have been described for the β-adrenoceptors; some are associated with altered signalling and trafficking, susceptibility to disease and/or altered responses to pharmacotherapy [1515]. All β-adrenoceptors couple to G<sub>s</sub> (activating adenylyl cyclase and elevating cAMP levels),

but the β<sub>2</sub>- and β<sub>3</sub>-adrenoceptors in particular can also activate G<sub>i</sub> and the β<sub>2</sub>-adrenoceptor activates β-arrestin-mediated signalling. Many β<sub>1</sub>- and β<sub>2</sub>-adrenoceptor antagonists are agonists at β<sub>3</sub>-adrenoceptors (CL316243, CGP 12177 and carazolol). Many ‘antagonists’ of cAMP accumulation, for example carvedilol and bucindolol, weakly activate MAP kinase pathways [118, 671, 753, 754, 2273, 2274] and thus display biased agonism. Bupranolol acts as a neutral antagonist in most systems so far examined. Agonists also display biased signalling at the β<sub>2</sub>-adrenoceptor *via* G<sub>s</sub> or arrestins [611]. X-ray crystal structures have been described of the agonist bound [2743] and antagonist bound forms of the β<sub>1</sub>- [2744], agonist-bound [424] and antagonist-bound forms of the β<sub>2</sub>-adrenoceptor [2142, 2207], as well as a fully active agonist-bound, G<sub>s</sub> protein-coupled β<sub>2</sub>-adrenoceptor [2143], as well as providing insights into the structural requirements for agonist, partial agonist, antagonist, G protein and β-arrestin coupling [2759]. Structures have also been described

for negative allosteric modulators of the β<sub>2</sub>-adrenoceptor [1554]. Cryo-EM studies have also been recently described that provide a structural framework for agonist mediated signal transduction [2474]. The agonists carvedilol and bucindolol bind to a site on the β<sub>1</sub>-adrenoceptor involving contacts in TM2, 3, and 7 and extracellular loop 2 that may facilitate coupling to arrestins [2744]. Compounds displaying β-arrestin-biased signalling at the β<sub>2</sub>-adrenoceptor have a greater effect on the conformation of TM7, whereas full agonists for G<sub>s</sub> coupling promote movement of TM5 and TM6 [1547]. Recent studies using NMR spectroscopy demonstrate significant conformational flexibility in the β<sub>2</sub>-adrenoceptor that is stabilized by both agonist and G proteins highlighting the dynamic nature of interactions with both ligand and downstream signalling partners [1277, 1635, 1919]. Such flexibility likely has consequences for our understanding of allostereism and biased agonism, and for the future therapeutic exploitation of these phenomena.

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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<sub>1</sub> and AT<sub>2</sub> receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Angiotensin receptors** [544, 1219]), 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**, **olmesartan**, **telmisartan**, *etc.* are clinically used AT<sub>1</sub> receptor blockers.

Nomenclature	AT <sub>1</sub> receptor	AT <sub>2</sub> receptor
HGNC, UniProt	<i>AGTR1</i> , P30556	<i>AGTR2</i> , P50052
Endogenous agonists	angiotensin II ( <i>AGT</i> , P01019) [545, 2664], angiotensin III ( <i>AGT</i> , P01019) [545], angiotensin IV ( <i>AGT</i> , P01019) (Partial agonist) [1435]	angiotensin III ( <i>AGT</i> , P01019) [504, 545, 2778], angiotensin II ( <i>AGT</i> , P01019) [545, 2418, 2778], angiotensin-(1-7) ( <i>AGT</i> , P01019) [249]
Agonists	[Sar <sup>1</sup> ,Cha <sup>4</sup> ]Ang-II [1041, 1753] – Rat	–
Selective agonists	L-162,313 [2024], L-163,101 [2635]	CGP42112 [249], [p-aminoPhe <sup>6</sup> ]ang II [545, 2443] – Rat, compound 21 [2681]
Antagonists	saprisartan (pK <sub>i</sub> 9.1) [1013] – Rat, 5-oxo-1-2-4-oxadiazol biphenyl (pIC <sub>50</sub> 8.8) [1893] – Rat, 5-butyl-methyl imidazole carboxylate 30 (pIC <sub>50</sub> 8.5) [19], LY303336 (pIC <sub>50</sub> 8.3) [2665], TRV027 (pK <sub>d</sub> 7.7) [2688]	saralasin (pIC <sub>50</sub> 9) [434] – Rat
Selective antagonists	candesartan (pIC <sub>50</sub> 9.5–9.7) [2664], eprosartan (pIC <sub>50</sub> 8.4–8.8) [636], losartan (pIC <sub>50</sub> 7.4–8.7) [545, 2585], telmisartan (pIC <sub>50</sub> 8.4) [1691], olmesartan (pIC <sub>50</sub> 8.1) [1326]	PD123177 (pIC <sub>50</sub> 8.5–9.5) [386, 434, 622] – Rat, olodanrigan (pIC <sub>50</sub> 8.5–9.3) [699, 2175, 2416], PD123319 (pK <sub>d</sub> 8.7–9.2) [545, 621, 2787]
Labelled ligands	[ <sup>3</sup> H]candesartan (Antagonist) (pK <sub>d</sub> 10.3) [694], [ <sup>125</sup> I][Sar <sup>1</sup> ]Ang-II (Agonist) [690] – Rat, [ <sup>125</sup> I][Sar <sup>1</sup> ,Ile <sup>8</sup> ]Ang-II (Agonist, Partial agonist) [690] – Rat, [ <sup>3</sup> H]eprosartan (Antagonist) (pK <sub>d</sub> 9.1) [28] – Rat, [ <sup>3</sup> H]losartan (Antagonist) (pK <sub>d</sub> 8.2) [390] – Rat	[ <sup>125</sup> I]CGP42112 (Agonist) [545, 2778, 2779], [ <sup>125</sup> I][Sar <sup>1</sup> ,Ile <sup>8</sup> ]Ang-II (Agonist) [2535] – Rat
Comments	Telmisartan and candesartan are also reported to be agonists of PPAR <sub>γ</sub> [2465].	Compounds have been generated with enhanced AT <sub>2</sub> receptor selectivity and proteolytic stability by imposing conformational constraints at position 6 of Angiotensin II [2605].

**Comments:** AT<sub>1</sub> receptors are predominantly coupled to G<sub>q/11</sub> [544, 1219], however they also recruit β-arrestins and stimulate G protein-independent β-arrestin signaling [1151, 1585, 2912]. Most species express a single *AGTR1* gene located on chromosome 3, but two related *Agtr1a* and *Agtr1b* receptor genes are expressed in rodents. Expression of the X chromosome-linked *AGTR2* gene is higher in females than males. AT<sub>1</sub> receptor antagonists bearing substituted biphenyl tetrazolium moieties are clinically used to treat hypertension and other cardiovascular disorders. They bind to AT<sub>1</sub> receptors with nanomolar affinity and are more potent than losartan in functional studies [1219]. High-resolution crystal structures of AT<sub>1</sub> receptor bound to non-

peptide antagonists (PDB id: 4ZUD, 4YAY) and peptide agonists (PDB id: 6DO1, 6OS0, 6OS1, 6OS2) are deposited in the protein structure database [2393]. The AT<sub>1</sub> and bradykinin B2 receptors have been proposed to form a heterodimeric complex [5]. β-arrestin1 prevents AT<sub>1</sub>-B2 receptor heteromerization [2117]. The AT<sub>2</sub> receptor counteracts several of the growth responses initiated by 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. Agonist activation of AT<sub>2</sub> receptors promotes anti-fibrotic tissue protection in cardiovascular and renal diseases [2738]. AT<sub>2</sub> receptors are involved in pain modulation [57, 2175] and AT<sub>2</sub> receptor antagonists relieve peripheral

neuropathic pain in chronic diseases such as diabetes [2175, 2415]. High-resolution structures of the AT<sub>2</sub> receptor bound to non-peptide antagonists (PDB id: 5UNF, 7JNI) and peptide agonists (PDB id: 5XJM, 6JOD) are available in the protein structure database [2393]. An AT<sub>3</sub> receptor was proposed based on cDNA isolated from a neuroblastoma cell line, but existence of a genuine *AGTR3* gene and AT<sub>3</sub> receptor are not confirmed at this time. However, there is evidence for an AT<sub>4</sub> receptor that specifically binds **angiotensin IV** (*AGT*, P01019) (*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) [*HBB*, P68871], a globin decapeptide) [1759].

### 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 [2056] and subsequently updated [2154]**) 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 endoge-

nous ligands which are cleaved from a 77 amino-acid precursor peptide (*APLN*, Q9ULZ1) [2552]. A second family of peptides discovered independently and named Elabela [435] or Toddler, that has little sequence similarity to apelin, is present, and functional at the apelin receptor in the adult cardiovascular system [2001, 2872]. The enzymatic pathways generating biologically

active apelin and Elabela isoforms have not been determined but both propeptides include sites for potential proprotein convertase processing [2370]. Structure-activity relationship Elabela analogues have been described [1836, 2608]. The stoichiometry of apelin receptor-heterotrimeric G protein complexes has been studied using cryogenic-electron microscopy [2907].

Nomenclature	apelin receptor
HGNC, UniProt	<i>APLNR</i> , P35414
Potency order of endogenous ligands	[ <b>Pyr</b> <sup>1</sup> ] <b>apelin-13</b> ( <i>APLN</i> , Q9ULZ1) ≥ <b>apelin-13</b> ( <i>APLN</i> , Q9ULZ1) > <b>apelin-36</b> ( <i>APLN</i> , Q9ULZ1) [678, 2552]
Endogenous agonists	apelin-13 ( <i>APLN</i> , Q9ULZ1) [678, 1057, 1704], apelin receptor early endogenous ligand ( <i>APELA</i> , P0DMC3) [564], apelin-17 ( <i>APLN</i> , Q9ULZ1) [641, 1704], [ <b>Pyr</b> <sup>1</sup> ] <b>apelin-13</b> ( <i>APLN</i> , Q9ULZ1) [1231, 1704], Elabela/Toddler-21 ( <i>APELA</i> , P0DMC3) [2871], Elabela/Toddler-32 ( <i>APELA</i> , P0DMC3) [2871], <b>apelin-36</b> ( <i>APLN</i> , Q9ULZ1) [678, 1057, 1231, 1704], Elabela/Toddler-11 ( <i>APELA</i> , P0DMC3) [2871]
Selective agonists	CMF-019 (Biased agonist) [2153], MM07 (Biased agonist) [267], azelaprag [87, 405]
Antagonists	MM54 (pK <sub>i</sub> 8.2) [1597]
Labelled ligands	[ <sup>125</sup> I][Nle <sup>75</sup> , Tyr <sup>77</sup> ] <b>apelin-36</b> (human) (Agonist) [1231], [ <sup>125</sup> I][Glp <sup>65</sup> Nle <sup>75</sup> , Tyr <sup>77</sup> ] <b>apelin-13</b> (Agonist) [1057], [ <sup>125</sup> I] <b>[Pyr</b> <sup>1</sup> ] <b>apelin-13</b> (Agonist) [1225], [ <sup>125</sup> I] <b>apelin-13</b> (Agonist) [678], [ <sup>3</sup> H] <b>[Pyr</b> <sup>1</sup> ] <b>[Met(0)11]-apelin-13</b> (Agonist) [1704]



**Comments:** Potency order determined for heterologously expressed human apelin receptor ( $pD_2$  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 [369]. A modified apelin-13 peptide, **apelin-13(F13A)** was reported to block the hypotensive response to apelin in rat *in vivo* [1453], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant

apelin receptor [678]. The apelin receptor antagonist, MM54, was reported to suppress tumour growth and increase survival in an intracranial xenograft mouse model of glioblastoma [946].

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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 [1230, 1664]
Selective agonists	S-EMCA [2011] – Mouse, betulinic acid [793], oleanolic acid [2271]

**Comments:** The triterpenoid natural product **betulinic acid** has also been reported to inhibit inflammatory signalling through the NFκB pathway [2516]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [2675]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [1561].

### Further reading on Bile acid receptor

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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**, [41, 1160]). BB<sub>1</sub> and BB<sub>2</sub> are activated by the endogenous ligands **neuromedin B (NMB, P08949)** (NMB), **gastrin-releasing peptide (GRP, P07492)** (GRP), and **GRP-(18-27) (GRP, P07492)**. **Bombesin** is a tetra-decapeptide, originally derived from amphibians and structurally closely related to GRP. The three Bn receptor subtypes couple primarily to the G<sub>q/11</sub> and G<sub>12/13</sub> family of G proteins [1160]. Each of these receptors is widely distributed in the CNS and peripheral tissues [842, 1159, 1160,

1595, 1596, 2067, 2133, 2265, 2926]. 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, respiration, gastrointestinal motility, feeding behavior, secretion and many central nervous system effects including regulation of circadian rhythm, body temperature control, sighing, behavioral disorders and mediation of pruritus [411, 417, 752, 1160, 1497, 1784, 1793, 1795, 2111, 2133, 2490, 2715]. BB<sub>3</sub> is an orphan receptor, although some propose it is constitutively active [2541]. BB<sub>3</sub> receptor knockout studies show it has important roles in glucose and

insulin regulation, metabolic homeostasis, feeding, regulation of body temperature, obesity, diabetes mellitus and growth of normal/neoplastic tissues [842, 1496, 1622, 1791, 1934, 2829]. Bn receptors are one of the most frequently overexpressed receptors in cancers and are receiving increased attention for their roles in tumor growth, as well as for tumour imaging and for receptor-targeted cytotoxicity [128, 1387, 1619, 1640, 1641, 1782, 1793, 2257]. Bn receptors are also receiving attention because they are one of the primary neurotransmitters for pruritus [411, 417, 1263, 2490].

Nomenclature	BB <sub>1</sub> receptor	BB <sub>2</sub> receptor	BB <sub>3</sub> receptor
HGNC, UniProt	<i>NMBR</i> , P28336	<i>GRPR</i> , P30550	<i>BRS3</i> , P32247
Endogenous agonists	neuromedin B ( <i>NMB</i> , P08949) [1160, 2133, 2625]	neuromedin C [2625], gastrin releasing peptide(14-27) (human) [2625], gastrin-releasing peptide ( <i>GRP</i> , P07492) [178, 2237, 2625]	–
Selective agonists	–	[D-Tyr <sup>6</sup> ,β-Ala <sup>11</sup> ,N-Me-Ala <sup>13</sup> ,Nle <sup>14</sup> ]bombesin-(6-14) [1050]	compound 9g [1672, 2131, 2134], MK-7725 [438], MK-5046 [1792, 2327], [D-Tyr <sup>6</sup> ,A-pa-4Cl <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ]bombesin-(6-14) [1643], compound 17c [1671], bag-1 [888], compound 22e [977]
Antagonists	D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH <sub>2</sub> (pIC <sub>50</sub> 6.2–6.6) [841]	–	–
Selective antagonists	PD 176252 (pIC <sub>50</sub> 9.3–9.8) [841], PD 168368 (pIC <sub>50</sub> 9.3–9.6) [841], 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> ,ψ13-14]bombesin-(6-14) (pK <sub>d</sub> 9.8) [841], JMV641 (pIC <sub>50</sub> 9.3) [2590] – Mouse, [(3-Ph-Pr <sup>6</sup> ), His <sup>7</sup> ,D-Ala <sup>11</sup> ,D-Pro <sup>13</sup> ,y13-14],Phe <sup>14</sup> ]bombesin-(6-14) (pIC <sub>50</sub> 9.2) [841, 1445], JMV594 (pIC <sub>50</sub> 8.9) [1556, 2590] – Mouse, [D-Tpi <sup>6</sup> , Leu <sup>13</sup> y(CH <sub>2</sub> NH)-Leu <sup>14</sup> ]bombesin-(6-14) (pIC <sub>50</sub> 8.9) [841], [D-Phe <sup>6</sup> , Stat <sup>13</sup> , Leu <sup>14</sup> Bn(6-14) (pIC <sub>50</sub> 8.1) [1641]	bantag-1 (pIC <sub>50</sub> 8.6–8.7) [888, 1792, 2132], ML-18 (pIC <sub>50</sub> 5.3) [1783]
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) [1642] – Mouse, BAY86-7548 (Antagonist) (pIC <sub>50</sub> 8.6) [1199, 2625], [ <sup>125</sup> I][Tyr <sup>4</sup> ]bombesin (Agonist) [178], BAY86-7548 (Selective Antagonist) (pIC <sub>50</sub> 8.1) [1387, 1640, 1641], [ <sup>125</sup> I]GRP (human) (Agonist)	[ <sup>125</sup> I]bantag-1 (Selective Antagonist) (pK <sub>d</sub> 9.6) [2132], [ <sup>3</sup> H]bag-2 (Agonist) [888] – Mouse, [ <sup>125</sup> I][D-Tyr <sup>6</sup> ,b-Ala <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ]bombesin-(6-14) (Agonist) [1644, 1792]

**Comments:** All three human subtypes may be activated by [D-Phe<sup>6</sup>,β-Ala<sup>11</sup>,Phe<sup>13</sup>,Nle<sup>14</sup>]bombesin-(6-14) [1644]. The Agonist [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> [1643,

1644, 2133, 2133, 2134]. A recent study [2131] shows MK-5046 is functioning as an allosteric agonist for hBRS-3 (the first for any BnR). A further recent study reports for the first time, the active crystal structure of hGRPR (BB<sub>2</sub>) as well as two active state

GRPR structures bound to GRP or [D-Phe<sup>6</sup>,β-Ala<sup>11</sup>,Phe<sup>13</sup>,Nle<sup>14</sup>]bombesin-(6-14) [2016].

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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 [1460]**) 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 (Hoe 140,

Firazir) is approved in North America and Europe for the treatment of acute attacks of hereditary angioedema. Inhibition of bradykinin with icatibant in COVID-19 infection is under clinical evaluation, with trial NCT05407597 expected to complete in mid 2023.

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) [95, 144, 832, 1182]	bradykinin ( <i>KNG1</i> , P01042) [70, 1003]
Selective agonists	NG29 [2281], [Sar,D-Phe <sup>8</sup> ,des-Arg <sup>9</sup> ]bradykinin [90, 1182]	NG291 [168], labradimil [2282], [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
Selective antagonists	B-9958 (pK <sub>i</sub> 9.2–10.3) [802, 2157], deucricitabant (pK <sub>i</sub> 9.3) [1480, 1481], [Leu <sup>9</sup> ,des-Arg <sup>10</sup> ]kallidin (pK <sub>i</sub> 9.1–9.3) [95, 144], SSR240612 (pK <sub>i</sub> 9.1–9.2) [857], R-954 (pA <sub>2</sub> 8.6) [833], R-715 (pA <sub>2</sub> 8.5) [831]	icatibant (pK <sub>i</sub> 10.2) [49], deucricitabant (pK <sub>i</sub> 9.3) [1480, 1481], FR173657 (pA <sub>2</sub> 8.2) [2191], anantibant (pK <sub>i</sub> 8.2) [2097]
Labelled ligands	[ <sup>125</sup> I]Hpp-desArg <sup>10</sup> HOE140 (Antagonist) (pK <sub>d</sub> 10), [ <sup>125</sup> I]Hpp-desArg <sup>10</sup> HOE140 (Antagonist) (pK <sub>d</sub> 10) [551, 1956], [ <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) [2797] – Mouse, [ <sup>3</sup> H]NPC17731 (Antagonist) (pK <sub>d</sub> 9.1–9.4) [2933, 2934], [ <sup>125</sup> I]HPP-HOE140 (Antagonist) [551, 1956], [ <sup>125</sup> I][Tyr <sup>8</sup> ]bradykinin (Agonist) [1564]

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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 [968, 970, 2079]**) are generated by the genes *CALCA* (which codes for the CT receptor, CTR) and *CALCL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying proteins), which are single TM domain proteins of ca. 150 amino

acids, identified as a family of three members; RAMP1, RAMP2 and RAMP3. There are splice variants of the CTR; these in turn produce variants of AMY receptors [2079], 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 member of the family with selectivity for the CTR but it is not expressed in humans [1222]. 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. There are several approved drugs that target this receptor family, such as pramlintide, erenumab, and the "gepant" class of CGRP receptor antagonists. There are also species differences in agonist pharmacology; for example, CGRP displays potent activity at multiple rat and mouse receptors [113, 774]. The summary table only reflects human receptor pharmacology.

## Complexes

Nomenclature	AMY <sub>1</sub> receptor	AMY <sub>2</sub> receptor	AMY <sub>3</sub> receptor	CGRP receptor	AM <sub>1</sub> receptor	AM <sub>2</sub> receptor
Subunits	CT receptor, RAMP1 (Accessory protein)	CT receptor, RAMP2 (Accessory protein)	CT receptor, RAMP3 (Accessory protein)	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	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	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)	$\alpha$ -CGRP ( <i>CALCA</i> , P06881), $\beta$ -CGRP ( <i>CALCB</i> , P10092) > adrenomedullin ( <i>ADM</i> , P35318) ≥ adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) > amylin ( <i>IAPP</i> , P10997)	adrenomedullin ( <i>ADM</i> , P35318) > adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) > $\alpha$ -CGRP ( <i>CALCA</i> , P06881), $\beta$ -CGRP ( <i>CALCB</i> , P10092), amylin ( <i>IAPP</i> , P10997)	adrenomedullin ( <i>ADM</i> , P35318) ≥ adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) ≥ $\alpha$ -CGRP ( <i>CALCA</i> , P06881), $\beta$ -CGRP ( <i>CALCB</i> , P10092) > amylin ( <i>IAPP</i> , P10997)
Endogenous agonists	$\alpha$ -CGRP ( <i>CALCA</i> , P06881) [966, 1390, 1391, 1487, 2709], amylin ( <i>IAPP</i> , P10997) [823], $\beta$ -CGRP ( <i>CALCB</i> , P10092)	amylin ( <i>IAPP</i> , P10997) [823]	amylin ( <i>IAPP</i> , P10997) [823]	$\beta$ -CGRP ( <i>CALCB</i> , P10092) [27, 1701], $\alpha$ -CGRP ( <i>CALCA</i> , P06881) [27, 1701]	adrenomedullin ( <i>ADM</i> , P35318) [27, 1701], adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) [968]	adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4) [968], adrenomedullin ( <i>ADM</i> , P35318) [27, 725]
Agonists	pramlintide [823], calcitonin (salmon)	–	pramlintide [823], calcitonin (salmon)	–	–	–
Antagonists	rimegepant (pK <sub>B</sub> 8.1) [1976], AC187 (pK <sub>B</sub> 8) [966], CT-(8-32) (salmon) (pK <sub>i</sub> 7.8) [966], olcegepant (pK <sub>B</sub> 7.5) [967]	–	CT-(8-32) (salmon) (pK <sub>B</sub> 7.9) [966], AC187 (pK <sub>B</sub> 7.7) [966]	olcegepant (pK <sub>i</sub> 10.7–11) [602, 967, 969, 1192, 1630], ubrogepant (pK <sub>B</sub> 10.8) [1785], rimegepant (pK <sub>B</sub> 9.6) [1976], telcagepant (pK <sub>i</sub> 9.1) [2254]	AM-(22-52) (human) (pK <sub>i</sub> 7–7.8) [969]	AM-(22-52) (human)
Labelled ligands	[ <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)	[ <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)

## Receptors and Subunits

Nomenclature	CT receptor	calcitonin receptor-like receptor
HGNC, UniProt	<i>CALCR</i> , P30988	<i>CALCRL</i> , Q16602
Potency order of endogenous ligands	calcitonin ( <i>CALCA</i> , P01258) ≥ amylin ( <i>IAPP</i> , P10997), α-CGRP ( <i>CALCA</i> , P06881), β-CGRP ( <i>CALCB</i> , P10092) > adrenomedullin ( <i>ADM</i> , P35318), adrenomedullin 2/intermedin ( <i>ADM2</i> , Q7Z4H4)	–
Endogenous agonists	calcitonin ( <i>CALCA</i> , P01258) [39, 78, 966, 1391, 1487, 1820]	–
Agonists	calcitonin (salmon) [39, 473, 850, 2041], pramlintide [823]	–
Antagonists	CT-(8-32) (salmon) (pK <sub>B</sub> 8.2) [966], AC187 (pK <sub>B</sub> 7.2) [966]	–
Labelled ligands	[ <sup>125</sup> I]CT (human) (Agonist), [ <sup>125</sup> I]CT (salmon) (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 [455, 966, 967]. 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> receptor) has a high affinity for CGRP

[2709], unlike hCT<sub>(a)</sub>-RAMP3 (*i.e.* AMY<sub>3(a)</sub> receptor) [455, 966]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [1794, 2104, 2584]. Emerging data suggests that AMY<sub>1</sub> could be a second CGRP receptor [2232]. 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 [968]. 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 [969]. Olcegepant (also known as BIBN4096BS, pK<sub>i</sub> ~10.5) and

telcagepant (also known as MK0974, pK<sub>i</sub> ~9) are examples of the "gepant" class of small molecule antagonists. These are selective for the CGRP receptor over the AM receptors but depending on the compound, have variable affinity for the AMY<sub>1</sub> receptor [775]. These antagonists tend to have higher affinity at primate receptors, compared to rodent receptors [1786, 2709]. 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 [2232]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, *ASL* (P04424) is important for the coupling of CLR to adenylyl cyclase [672]. [<sup>125</sup>I]-Salmon CT is the most common radioligand for CTR but it has high affinity for AMY receptors and is also poorly reversible.

**Further reading on Calcitonin receptors**

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## Calcium-sensing receptor

G protein-coupled receptors → Calcium-sensing receptor

**Overview:** The calcium-sensing receptor (CaS, **provisional nomenclature as recommended by NC-IUPHAR [712] and subsequently updated [1440]**) 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 extracellu-

lar pH (reviewed in [1442]). While divalent/trivalent cations, polyamines and polycations are CaS receptor agonists [298, 2115], L-amino acids, glutamyl peptides, ionic strength and pH are allosteric modulators of agonist function [482, 712, 1027, 2113, 2114]. Indeed, L-amino acids have been identified as "co-agonists", with both concomitant calcium and L-amino acid binding required for full receptor activation [795, 2918]. The

sensitivity of the CaS receptor to primary agonists is increased by elevated extracellular pH [340] or decreased extracellular ionic strength [2114] while sensitivity is decreased by pathophysiological phosphate concentrations [372]. 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) [482]
Cation rank order of potency	Gd <sup>3+</sup> > Ca <sup>2+</sup> > Mg <sup>2+</sup> [298]
Glutamyl peptide rank order of potency	S-methylglutathione ≈ $\gamma$ Glu-Val-Gly > glutathione > $\gamma$ Glu-Cys [287, 1936, 2730]
Polyamine rank order of potency	spermine > spermidine > putrescine [2115]
Allosteric modulators (Positive)	upacalcet (pIC <sub>50</sub> 8.1) [2272], evocalcet (pEC <sub>50</sub> 7) [1755], cinacalcet (pK <sub>B</sub> 5.9–6.6) [485, 536, 1439, 1443], tecalcet (pK <sub>B</sub> 6.2–6.6) [485, 536], AC265347 (pK <sub>B</sub> 6.3–6.4) [485, 1439], calindol (pK <sub>B</sub> 6.3) [485], etelcalcetide (pEC <sub>50</sub> 4.6) [2712]
Allosteric modulators (Negative)	ATF936 (pIC <sub>50</sub> 8.9) [2782], encaleret (pIC <sub>50</sub> 7.9) [2371], SB-423562 (pIC <sub>50</sub> 7.1) [1382], ronacaleret (pIC <sub>50</sub> 6.5–6.8) [123], NPS 2143 (pK <sub>B</sub> 6.2–6.7) [536, 1439, 1443], calhex 231 (pIC <sub>50</sub> 6.4) [2037]

**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 [934]. This is seen most clearly in patients with loss-of-function CaS receptor mutations who develop familial hypocalcaemic hypercalcaemia (heterozygous mutations) or neonatal severe hyperparathyroidism (heterozygous, compound heterozygous or homozygous mutations) [934] and in *Casr* null mice [388, 1027], 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 [934].

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The CaS receptor primarily couples to G<sub>q/11</sub>, G<sub>12/13</sub> and G<sub>i/o</sub> [536, 806, 1074, 2575], but in some cell types can couple to G<sub>s</sub> [1632]. The CaS receptor acts as a homodimer [2918]. However, the CaS receptor can also form heteromers with Class C GABA<sub>B</sub> [389, 423] and mGlu1/5 receptors [760], which may introduce further complexity in its signalling capabilities. Multiple other small molecule chemotypes are positive and negative allosteric modulators of the CaS receptor [1261, 1876]. Further, etelcalcetide is a novel peptide positive allosteric modulator of the receptor, that also displays weak agonist activity [2712]. 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 [1878]. Negative allosteric modulators are called calcilytics and can act to increase PTH (PTH, P01270) secretion [1877]. 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.

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## Cannabinoid receptors

G protein-coupled receptors → Cannabinoid receptors

**Overview:** Cannabinoid receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Cannabinoid Receptors [2029]) 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 [43].

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 [2027]. Two of these medicines were developed to suppress nausea and vomiting produced by chemotherapy. These

are nabilone (Cesamet®), a synthetic CB<sub>1</sub>/CB<sub>2</sub> receptor agonist, and synthetic  $\Delta^9$ -tetrahydrocannabinol (Marinol®; dronabinol), which can also be used as an appetite stimulant. The third medicine, Sativex®, 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 [685, 2377], CP55940 [685, 2211, 2377], WIN55212-2 [685, 2374, 2377], Δ <sup>9</sup> -tetrahydrocannabinol (Partial agonist) [685, 2377], cannabitol (Partial agonist) [685, 2377]	HU-210 [685, 2171, 2377], WIN55212-2 [685, 2374, 2377], CP55940 [685, 2211, 2377], Δ <sup>9</sup> -tetrahydrocannabinol (Partial agonist) [148, 685, 2171, 2377]
Selective agonists	arachidonyl-2-chloroethylamide [1015] – Rat, arachidonylcyclopropylamide [1015] – Rat, O-1812 [574] – Rat, R-(+)-methanandamide [1255] – Rat	JWH-133 [1083, 2028], L-759,633 [773, 2211], AM1241 [2875], L-759,656 [773, 2211], onternabez [942], GW405833 (Partial agonist) [1653]
Selective antagonists	JD5037 (pK <sub>i</sub> 9.5) [2533], rimonabant (pK <sub>i</sub> 7.9–8.7) [684, 685, 2181, 2227, 2377], AM6545 (pK <sub>i</sub> 8.5) [257], AM251 (pK <sub>i</sub> 8.1) [1404] – Rat, AM281 (pK <sub>i</sub> 7.9) [1403] – Rat, LY320135 (pK <sub>i</sub> 6.9) [684]	SR144528 (pK <sub>i</sub> 8.3–9.2) [2182, 2211], AM-630 (pK <sub>i</sub> 7.5) [2211]
Allosteric modulators (Positive)	ZCZ011 (pEC <sub>50</sub> 6.3) [1099] – Mouse, GAT211 [1417]	pepcan-12 (pK <sub>i</sub> ~7.3) [2040], compound C2 [751]
Allosteric modulators (Negative)	GAT100 (pEC <sub>50</sub> 7.7) [1377], cannabidiol [1416]	–
Labelled ligands	[ <sup>3</sup> H]rimonabant (Antagonist) (pK <sub>d</sub> 8.9–10) [271, 1022, 1195, 2036, 2183, 2388, 2568] – 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; [2377]) and [<sup>3</sup>H]WIN55212-2 (2–2.4 nM; [2405, 2434]). Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [1922, 2964]. There is evidence for an

allosteric site on the CB<sub>1</sub> receptor [2082]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [2029]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119

have been identified [2029]. 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 [2029].

### 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. (2010) Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Curr Med Chem* **17**: 1360–81 [PMID:20166927]

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]

## Chemerin receptors

G protein-coupled receptors → Chemerin receptors

**Overview:** Nomenclature for the chemerin receptors is presented as **recommended by NC-IUPHAR** [532, 1243]. 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> [1243]. 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 [76, 77]. 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 [1359].

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="#">CMKLR2, 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> [76]	–
Endogenous agonists	–	<a href="#">chemerin</a> ( <a href="#">RARRES2, Q99969</a> ) [133]
Selective agonists	<a href="#">resolvin E1</a>	–
Labelled ligands	<a href="#">[<sup>3</sup>H]resolvin E1</a> (Agonist) [76, 77]	–
Comments	–	Reported to act as a co-receptor for HIV [2366]. See review [532] for discussion of pairing with chemerin.

**Comments:** CCX832 (structure not disclosed) is a selective antagonist, pK<sub>i</sub>=9.2 [1245].

### 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** [107, 1833, 1834]) 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 antibacterials, 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 [107].

Chemokines in turn can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as β-chemokines; *n*= 28), CXC (also known as α-chemokines; *n*= 17) and CX3C (*n*= 1) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines respectively. C chemokines (*n*= 2) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high-affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. G protein-coupled chemokine receptors are named according

to the class of chemokines bound, whereas ACKR is the root acronym for atypical chemokine receptors [108]. 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 [2960] and aliases.



Nomenclature	CCR1	CCR2	CCR3
HGNC, UniProt	CCR1, P32246	CCR2, P41597	CCR3, P51677
Endogenous agonists	CCL3 (CCL3, P10147) [442, 475, 1005, 2962], CCL23 (CCL23, P55773) [442], CCL5 (CCL5, P13501) [475, 1005], CCL7 (CCL7, P80098) [442, 906], CCL15 (CCL15, Q16663) [495], CCL14 (CCL14, Q16627) [442], CCL13 (CCL13, Q99616), CCL8 (CCL8, P80075)	CCL2 (CCL2, P13500) [495, 1584, 1748, 1989, 2627], CCL13 (CCL13, Q99616) [1584, 2627], CCL7 (CCL7, P80098) [495, 1584, 2627], CCL11 (CCL11, P51671) (Partial agonist) [1584, 1989], CCL16 (CCL16, O15467)	CCL13 (CCL13, Q99616) [1807, 2627], CCL24 (CCL24, O00175) [1807, 1989], CCL5 (CCL5, P13501) [526], CCL7 (CCL7, P80098) [526], CCL11 (CCL11, P51671) [624, 1298, 1807, 2244, 2627], CCL26 (CCL26, Q9Y258) [1298, 1807, 1989], CCL15 (CCL15, Q16663) [495], CCL28 (CCL28, Q9NRJ3), CCL8 (CCL8, P80075)
Agonists	–	–	CCL11 (Mouse) [526]
Endogenous antagonists	CCL4 (CCL4, P13236) (pK <sub>i</sub> 7.1–7.8) [442, 475]	CCL26 (CCL26, Q9Y258) (pIC <sub>50</sub> 8.5) [1989]	CXCL10 (CXCL10, P02778), CXCL11 (CXCL11, O14625), CXCL9 (CXCL9, Q07325)
Selective antagonists	BX 471 (pK <sub>i</sub> 8.2–9) [1508], compound 2b-1 (pIC <sub>50</sub> 8.7) [1863], UCB35625 (pIC <sub>50</sub> 8) [2244], CP-481,715 (pK <sub>d</sub> 8) [826]	GSK Compound 34 (pK <sub>i</sub> 7.6)	banyu (I) (Inverse agonist) (pK <sub>i</sub> 8.5) [2717], SB328437 (pK <sub>i</sub> 8.4), BMS compound 87b (pK <sub>i</sub> 8.1) [2702]
Labelled ligands	[ <sup>125</sup> I]CCL7 (human) (Agonist) [174], [ <sup>125</sup> I]CCL3 (human) (Agonist) [174, 840, 2270], [ <sup>125</sup> I]CCL5 (human) (Agonist) [2270]	[ <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) [2717], [ <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) [1105], CCL17 (CCL17, Q92583) [1105]	CCL5 (CCL5, P13501) [104, 1855, 2224], CCL4 (CCL4, P13236) [1855, 2224], CCL8 (CCL8, P80075) [2224], CCL3 (CCL3, P10147) [1855, 2224, 2962], CCL11 (CCL11, P51671) [212], CCL2 (CCL2, P13500) [1855], CCL14 (CCL14, Q16627) [1855], CCL16 (CCL16, O15467)	CCL20 (CCL20, P78556) [26, 103, 2076], beta-defensin 4A (DEFB4A DEFB4B, O15263) [2865]	CCL21 (CCL21, O00585) [2896], CCL19 (CCL19, Q99731) [1963, 2895, 2896]	CCL1 (CCL1, P22362) [517, 957, 1107], CCL8 (CCL8, P80075)	CCL25 (CCL25, O15444)	CCL27 (CCL27, Q9Y4X3) [1046], CCL28 (CCL28, Q9NRJ3)
Agonists	vMIP-III	R5-HIV-1 gp120	–	–	vMIP-I [517, 1107]	–	–
Endogenous antagonists	–	CCL7 (CCL7, P80098) (pK <sub>i</sub> 7.5) [1855] vMIP-II (pIC <sub>50</sub> 8.3) [1304]	–	–	–	–	–
Antagonists	–	vMIP-II (pIC <sub>50</sub> 8.3) [1304]	–	–	vMIP-II (pIC <sub>50</sub> 8.1) [517]	–	–

Selective antagonists	<a href="#">compound 8ic</a> (pIC <sub>50</sub> 7.7) [2893]	<a href="#">vicriviroc</a> (pK <sub>i</sub> 9.1) [2470], <a href="#">E913</a> (pIC <sub>50</sub> 8.7) [1609], <a href="#">ancriviroc</a> (pK <sub>i</sub> 7.8–8.7) [1608, 1974, 2470], <a href="#">aplaviroc</a> (pK <sub>i</sub> 8.5) [1608], <a href="#">maraviroc</a> (pIC <sub>50</sub> 8.1) [1855], <a href="#">TAK-779</a> (pK <sub>i</sub> 7.5) [1608], <a href="#">MRK-1</a> [1381] – Rat	–	–	–	–	–
Selective allosteric modulators	–	–	–	–	–	<a href="#">vercirnon</a> (Antagonist) (pIC <sub>50</sub> 8.2) [2713]	–
Antibodies	<a href="#">mogamulizumab</a> (Inhibition) [67, 2375]	<a href="#">leronlimab</a> (Binding) [1955]	–	–	–	–	–
Labelled ligands	<a href="#">[<sup>125</sup>I]CCL17</a> (human) (Agonist), <a href="#">[<sup>125</sup>I]CCL27</a> (human) (Agonist)	<a href="#">[<sup>125</sup>I]CCL4</a> (human) (Agonist) [1855], <a href="#">[<sup>125</sup>I]CCL3</a> (human) (Agonist), <a href="#">[<sup>125</sup>I]CCL5</a> (human) (Agonist), <a href="#">[<sup>125</sup>I]CCL8</a> (human) (Agonist)	<a href="#">[<sup>125</sup>I]CCL20</a> (human) (Agonist) [868]	<a href="#">[<sup>125</sup>I]CCL19</a> (human) (Agonist), <a href="#">[<sup>125</sup>I]CCL21</a> (human) (Agonist) [1158]	<a href="#">[<sup>125</sup>I]CCL1</a> (human) (Agonist) [1107, 2206]	<a href="#">[<sup>125</sup>I]CCL25</a> (human) (Agonist)	–

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6	CX <sub>3</sub> CR1
HGNC, UniProt	<a href="#">CXCR1</a> , P25024	<a href="#">CXCR2</a> , P25025	<a href="#">CXCR3</a> , P49682	<a href="#">CXCR4</a> , P61073	<a href="#">CXCR5</a> , P32302	<a href="#">CXCR6</a> , O00574	<a href="#">CX3CR1</a> , P49238
Endogenous agonists	<a href="#">CXCL8</a> ( <a href="#">CXCL8</a> , P10145) [191, 917, 1455, 2795, 2819], <a href="#">CXCL6</a> ( <a href="#">CXCL6</a> , P80162) [2825]	<a href="#">CXCL1</a> ( <a href="#">CXCL1</a> , P09341) [917, 1455, 2819], <a href="#">CXCL8</a> ( <a href="#">CXCL8</a> , P10145) [191, 917, 1455, 2795, 2819], <a href="#">CXCL7</a> ( <a href="#">PPBP</a> , P02775) [24], <a href="#">CXCL3</a> ( <a href="#">CXCL3</a> , P19876) [24], <a href="#">CXCL2</a> ( <a href="#">CXCL2</a> , P19875) [24], <a href="#">CXCL5</a> ( <a href="#">CXCL5</a> , P42830) [24], <a href="#">CXCL6</a> ( <a href="#">CXCL6</a> , P80162) [2825]	<a href="#">CXCL11</a> ( <a href="#">CXCL11</a> , O14625) [986], <a href="#">CXCL10</a> ( <a href="#">CXCL10</a> , P02778) [986, 2764], <a href="#">CXCL9</a> ( <a href="#">CXCL9</a> , Q07325) [986, 2764]	<a href="#">CXCL12α</a> ( <a href="#">CXCL12</a> , P48061) [1004, 1559], <a href="#">CXCL12β</a> ( <a href="#">CXCL12</a> , P48061) [1004]	<a href="#">CXCL13</a> ( <a href="#">CXCL13</a> , O43927) [137]	<a href="#">CXCL16</a> ( <a href="#">CXCL16</a> , Q9H2A7) [2788]	<a href="#">CX<sub>3</sub>CL1</a> ( <a href="#">CX3CL1</a> , P78423) [776]
Agonists	<a href="#">vCXCL1</a> [1583]	<a href="#">vCXCL1</a> [1583], <a href="#">HIV-1 matrix protein p17</a> [811]	–	–	–	–	–
Selective agonists	–	–	–	<a href="#">ALX40-4C</a> (Partial agonist) [2936], <a href="#">X4-HIV-1 gp120</a>	–	–	–

Endogenous antagonists	–	–	CCL11 (CCL11, P51671) (pK <sub>i</sub> 7.2) [2764], CCL7 (CCL7, P80098) (pK <sub>i</sub> 6.6) [2764]	–	–	–	–
Antagonists	–	–	–	–	–	–	–
Selective antagonists	–	–	–	–	–	–	–
			navarixin (pIC <sub>50</sub> 10.3) [107, 629], danirixin (pIC <sub>50</sub> 7.9) [1741], SB 225002 (pIC <sub>50</sub> 7.7) [2776], elubirixin (pIC <sub>50</sub> 7.7) [107], SX-517 (pIC <sub>50</sub> 7.2) [1607]	–	–	–	–
Allosteric modulators (Negative)	–	–	–	–	–	–	–
			reparixin (pIC <sub>50</sub> 6.4) [191]				
Labelled ligands	[ <sup>125</sup> I]CXCL8 (human) (Agonist) [917, 2179]	[ <sup>125</sup> I]CXCL8 (human) (Agonist) [917, 2179], [ <sup>125</sup> I]CXCL1 (human) (Agonist), [ <sup>125</sup> I]CXCL5 (human) (Agonist), [ <sup>125</sup> I]CXCL7 (human) (Agonist)	[ <sup>125</sup> I]CXCL10 (human) (Agonist), [ <sup>125</sup> I]CXCL11 (human) (Agonist)	[ <sup>125</sup> I]CXCL12α (human) (Agonist) [577, 1004]	[ <sup>125</sup> I]CXCL13 (mouse) (Agonist) [291] – Mouse	[ <sup>125</sup> I]CXCL16 (human) (Agonist)	[ <sup>125</sup> I]CX <sub>3</sub> CL1 (human) (Agonist)

Nomenclature	XCR1	ACKR1	ACKR2	ACKR3	ACKR4
HGNC, UniProt	XCR1, P46094	ACKR1, Q16570	ACKR2, O00590	ACKR3, P25106	ACKR4, Q9NPB9
Endogenous ligands	–	CXCL5 (CXCL5, P42830), CXCL6 (CXCL6, P80162), CXCL8 (CXCL8, P10145), CXCL11 (CXCL11, O14625), CCL2 (CCL2, P13500), CCL5 (CCL5, P13501), CCL7 (CCL7, P80098), CCL11 (CCL11, P51671), CCL14 (CCL14, Q16627), CCL17 (CCL17, Q92583)	–	–	–

Endogenous agonists	XCL1 (XCL1, P47992) [721], XCL2 (XCL2, Q9UBD3) [721]	–	CCL2 (CCL2, P13500), CCL3 (CCL3, P10147), CCL4 (CCL4, P13236), CCL5 (CCL5, P13501), CCL7 (CCL7, P80098), CCL8 (CCL8, P80075), CCL11 (CCL11, P51671), CCL13 (CCL13, Q99616), CCL14 (CCL14, Q16627), CCL17 (CCL17, Q92583), CCL22 (CCL22, O00626)	CXCL12 $\alpha$ (CXCL12, P48061) [867, 2436], CXCL11 (CXCL11, O14625)	CCL19 (CCL19, Q99731) [2754], CCL25 (CCL25, O15444) [2754], CCL21 (CCL21, O00585) [2754]
Selective antagonists	–	–	–	LIH383 (pEC <sub>50</sub> 9.2) [1718]	–
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 knowlesi</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 [2509].	–

**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 he-

matopoietic 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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 Scholten DJ *et al.* (2012) Pharmacological modulation of chemokine receptor function. *Br J Pharmacol* **165**: 1617-43 [PMID:21699506]

## Cholecystokinin receptors

G protein-coupled receptors → Cholecystokinin receptors

**Overview:** Cholecystokinin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CCK receptors [1909]**) 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 [1339, 2741], 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 [1458], gastrin-17 (GAST, P01350) [1085] – Mouse, CCK-4 (CCK, P06307) [1120], 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 [86] – Rat, JMV180 [1247], GW-5823 [994]	RB-400 [172] – Rat, PBC-264 [1140] – Rat
Antagonists	linitript (pIC <sub>50</sub> 8.3) [858]	–
Selective antagonists	devazepide (pIC <sub>50</sub> 9.7) [1085] – Rat, T-0632 (pIC <sub>50</sub> 9.6) [2547] – Rat, PD-140548 (pIC <sub>50</sub> 8.6) [2394] – Rat, lorglumide (pIC <sub>50</sub> 6.7–8.2) [1085, 1126] – Rat	YF-476 (pIC <sub>50</sub> 9.7) [258, 2531], GV150013 (pIC <sub>50</sub> 9.4) [2641], L-740093 (pIC <sub>50</sub> 9.2) [1899], YM-022 (pIC <sub>50</sub> 9.2) [1899], JNJ-26070109 (pIC <sub>50</sub> 8.5) [1813], L-365260 (pIC <sub>50</sub> 8.4) [1458], RP73870 (pIC <sub>50</sub> 8) [1533] – Rat, LY262691 (pIC <sub>50</sub> 7.5) [2142] – Rat
Labelled ligands	[ <sup>3</sup> H]devazepide (Antagonist) (pK <sub>d</sub> 9.7) [387], [ <sup>125</sup> I]DTyr-Gly-[(Nle28,31) CCK-26-33 (Agonist) [2078]	[ <sup>3</sup> H]PD140376 (Antagonist) (pK <sub>i</sub> 9.7–10) [1089] – Guinea pig, [ <sup>125</sup> I]PD142308 (Antagonist) (pK <sub>d</sub> 9.6) [1053] – Guinea pig, [ <sup>125</sup> I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [2078], [ <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) [1899], [ <sup>125</sup> I]-BDZ2 (Antagonist) (pK <sub>i</sub> 8.4) [31]

**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 intracellular loop 3 (ICL3) region, has been described to be present particularly in certain neoplasms where mRNA mis-splicing has been commonly observed [2412], 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 [2433], 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 [2312]**), are GPCRs originally identified in *Drosophila* [380], which are highly conserved across species. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it is involved in the Hedgehog signaling pathway [2312]. SMO exerts its effects by activating heterotrimeric G proteins or stabilization of GLI by sequestering catalytic PKA subunits [83, 943, 2358]. While SMO itself is bound by sterols and oxysterols [488, 1288], 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 cooper-

ation 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. WNT/ $\beta$ -catenin-dependent signalling can also be activated by FZD subtype-specific WNT surrogates [1722].  $\beta$ -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 [584, 2032, 2313], the elevation of intracellular calcium [2406], activation of cGMP-specific PDE6 [25] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [938]. 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

[1349, 1353, 2292, 2813, 2814]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling towards planar-cell-polarity-like pathways. Importantly, FZDs exist in at least two distinct conformational states that regulate pathway selection [2814]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [410], as well as for  $\beta$ -catenin-dependent [309] and -independent [310, 1270] 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	<i>FZD1</i> , Q9UP38	<i>FZD2</i> , Q14332	<i>FZD3</i> , Q9NPG1	<i>FZD4</i> , Q9ULV1	<i>FZD5</i> , Q13467
Allosteric modulators (Positive)	–	–	–	<b>FzM1.8</b> (pEC <sub>50</sub> 6.4) [2174]	–
Allosteric modulators (Negative)	–	–	–	<b>FzM1.8</b> (pIC <sub>50</sub> 5.5–7.8) [792], <b>FzM1</b> (pIC <sub>50</sub> 6.2) [792, 2174]	–
Antibodies	<b>vantictumab</b> (Antagonist) (pIC <sub>50</sub> ~9.1) [903]	<b>vantictumab</b> (Antagonist) (pIC <sub>50</sub> ~9) [903]	–	–	<b>vantictumab</b> (Antagonist) (pIC <sub>50</sub> ~9) [903]
Comments	–	–	–	–	IgG-2919 and IgG-2921 are FZD <sub>5</sub> antibodies that have exhibited antitumour activities in vitro and in vivo (inhibiting the growth of RNF43-mutant pancreatic ductal adenocarcinoma cells/xenograft tumours), by blocking autocrine Wnt- $\beta$ -catenin signalling in these mutant, FZD <sub>5</sub> -dependent cells [2453].

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</a> , <a href="#">O60353</a>	<a href="#">FZD7</a> , <a href="#">O75084</a>	<a href="#">FZD8</a> , <a href="#">Q9H461</a>	<a href="#">FZD9</a> , <a href="#">O00144</a>	<a href="#">FZD10</a> , <a href="#">Q9ULW2</a>
Selective antagonists	–	<a href="#">Fz7-21</a> (pIC <sub>50</sub> 7) [1898]	–	–	–
Allosteric modulators (Negative)	–	–	<a href="#">carbamazepine</a> (pK <sub>d</sub> 4.8) [2945]	–	–
Antibodies	–	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~9) [903]	<a href="#">vantictumab</a> (Antagonist) (pIC <sub>50</sub> ~8) [903]	–	–
Comments	SAG1.3 and pumorphamine have been described as weak partial agonists with varying potencies depending on a read-out [1353].	–	FZD8-Fc/OMP-54F28 is a FZD <sub>8</sub> antagonist [556].	–	Radio-labelled murine monoclonal antibody MAb 92-13 has been used to demonstrate the therapeutic potential of targeting FZD <sub>10</sub> -positive tumours [745].

Nomenclature	<a href="#">SMO</a>
HGNC, UniProt	<a href="#">SMO</a> , <a href="#">Q99835</a>
Agonists	<a href="#">SAG1.3</a> [403] – Mouse, <a href="#">pumorphamine</a> [2395]
Antagonists	<a href="#">MRT-92</a> (pK <sub>d</sub> 9.5) [1032], <a href="#">SANT-1</a> (pK <sub>i</sub> 7.7) [403] – Mouse, <a href="#">cyclopamine-KAAD</a> (pIC <sub>50</sub> 7.7) [2514] – Mouse, <a href="#">cyclopamine</a> (pIC <sub>50</sub> 6.97) [2621] – Mouse
Selective antagonists	<a href="#">vismodegib</a> (pK <sub>i</sub> 7.8) [2724]
Allosteric modulators (Positive)	<a href="#">GSA-10</a> (pEC <sub>50</sub> 5.9) [851]
Comments	SANT-3 and SANT-4 are SMO antagonists [403]. Cyclopamine-KAAD can act as an inverse agonist [2814].

**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 [82, 568, 584, 1267, 1639, 2105, 2106, 2185, 2358, 2697, 2813]. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships [1265]. However, progress in understanding WNT-FZD interactions has been initiated with generation of eGFP-tagged WNT-3A and its use in BRET-based binding assays [1352, 2515, 2772]. Development of pharmacological tools [1351] for SMO has been facilitated by successful determination of several SMO structures [329, 568, 1076, 1288, 2105, 2106, 2720, 2721, 2757, 2924, 2937]. The recently solved FZD<sub>4</sub> and FZD<sub>5</sub> structures in apo state, as well as the structure of FZD<sub>7</sub> bound to a heterotri-

meric Gs protein, have provided first insights into FZD transmembrane organization [2616, 2842, 2873].

#### 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 [2813]), [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](#) ([SFRP2](#), [Q96HF1](#)), [sFRP-3](#) ([FRZB](#), [Q92765](#)), [sFRP-4](#) ([SFRP4](#), [Q6FHJ7](#)), [sFRP-5](#) ([SFRP5](#), [Q6FHJ7](#)).

**Extracellular proteins that interact with WNTs or LRP5:** [Dickkopf 1](#) ([DKK1](#), [O94907](#)), [WIF1](#) ([Q9Y5W5](#)), [sclerostin](#) ([SOST](#), [Q9BQB4](#)), [kremen 1](#) ([KREMEN1](#), [Q96MU8](#)) and [kremen 2](#) ([KREMEN2](#), [Q8NCW0](#))

**Small exogenous ligands:** [Foxy-5](#) [2245], [Box-5](#) [1157], [UM206](#) [1395], and [XWnt8](#) ([P28026](#)) also known as mini-Wnt8.

**Ligands associated with SMO signalling:** [cholesterol](#), [oxysterols](#) [329, 1574, 2125].

**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 [1307]**) 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 (C3a receptor, C5a receptor 1 and C5a receptor 2), causing cell recruitment and triggering cellular degranulation that contributes to local inflammation.

Nomenclature	C3a receptor
HGNC, UniProt	C3AR1, Q16581
Potency order of endogenous ligands	C3a (C3, P01024) > C5a (C5, P01031) [51]
Agonists	E7 [53, 648, 2325], compound 17 [2159], compound 21 [2158], casoxin C [2517, 2898], albutensin A [1933, 2898], oryzatensin [1173, 2518, 2898]
Antagonists	JR14a (pIC <sub>50</sub> 8) [2220], SB290157 (SB290157 has also been reported to have agonist properties at the C3a receptor, and act as a weak C5aR2 activator) (pIC <sub>50</sub> 7.6) [50, 1503]
Labelled ligands	[ <sup>125</sup> I]C3a (human) (Agonist) [391], Eu-DTPA-hC3a (Agonist) [520]
Comments	Dual pro- and anti-inflammatory roles of C3a receptor have been reported in pathological conditions [498]. In particular, C3 and the C3a receptor have been identified as being involved in regulating the intestinal immune response during chronic colitis [2492, 2762]. Protective roles of the C3a receptor were reported for traumatic spinal cord injury [273], melanoma [1840] and systemic lupus erythematosus [1268]. C3a-C3a receptor signalling inhibits neural progenitor cell proliferation during neurodevelopment, playing a critical role in the normal development of the mammalian brain [408]. Inactivation of C3a receptor leads to decreased cytotoxic NK-cell infiltration into tumors [1854]. Moreover, a protective role for C3a receptor is described in experimental chronic pyelonephritis [2944].

Nomenclature	C5a <sub>1</sub> receptor	C5a <sub>2</sub> receptor
HGNC, UniProt	CSAR1, P21730	CSAR2, Q9P296
Potency order of endogenous ligands	C5a (C5, P01031), C5a des-Arg (C5) > C3a (C3, P01024) [51]	–
Endogenous agonists	C5a des-Arg (C5) (Partial agonist) [334], ribosomal protein S19 (RPS19, P39019) [2852]	C5a (C5, P01031) [334], C5a des-Arg (C5) [334, 1947]
Agonists	BM221 [848], NDT9513727 (Inverse agonist) [290], N-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO <sub>2</sub> H [1229, 1336], BM213 [848], lactomedin 1 [1980, 2898]	C5a <sup>pep</sup> (Partial agonist) [1980]
Selective agonists	–	P59 (Biased agonist) [506], P32 (Biased agonist) [506]



Antagonists	<a href="#">avacopan</a> (pIC <sub>50</sub> 9.7) [167], <a href="#">W54011</a> (pK <sub>i</sub> 8.7) [2485], <a href="#">DF2593A</a> (pIC <sub>50</sub> 8.3) [1799], <a href="#">ACT-1014-6470</a> (pIC <sub>50</sub> 8) [926], <a href="#">AcPhe-Orn-Pro-D-Cha-Trp-Arg</a> (pIC <sub>50</sub> 7.9) [2803], <a href="#">PMX205</a> (pIC <sub>50</sub> 7.5) [1505, 1650], <a href="#">DF3016A</a> (pIC <sub>50</sub> 7.3) [269], <a href="#">N-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO2H</a> (pIC <sub>50</sub> 7.2) [1336]	<a href="#">A8Δ71-3</a> (pIC <sub>50</sub> ~6) [1964] – Mouse
Labelled ligands	<a href="#">[125]IC5a (human)</a> (Agonist) [1082], <a href="#">Eu-DTPA-[Ser<sup>27</sup>, Nle<sup>70</sup>]hC5a</a> (Agonist) [849]	<a href="#">Eu-DTPA-[Ser<sup>27</sup>, Nle<sup>70</sup>]hC5a</a> (Agonist) [847], <a href="#">[125]IC5a (human)</a> (Agonist)
Comments	The C5a <sub>1</sub> receptor is currently referred to as C5aR1 in the literature. C5a <sub>1</sub> has been an attractive target for pharmacological inhibition to treat a myriad of inflammatory and neurodegenerative diseases. Several C5a <sub>1</sub> antagonists have been reported that have progressed to various stages of clinical development [965, 1505, 1775], although none are yet approved for use in humans. The non-peptide C5aR1 inhibitor CXC168 (Avacopan®), developed by ChemoCentryx/Amgen, is currently the most clinically advanced C5aR1 inhibitor [167]. The drug was approved by the FDA in October 2021, as an adjunctive treatment in adults for severe active ANCA-associated vasculitis (specifically microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA)) in combination with standard therapy including glucocorticoids [1451]. Considering the potential benefits of blocking the C5a-C5a <sub>1</sub> axis to limit myeloid infiltration and prevent excessive lung inflammation in Coronavirus disease 2019 (COVID-19) [357], the two anti-C5a/C5a <sub>1</sub> blocking antibodies, <a href="#">avdoralimab</a> (IPH5401) and <a href="#">vilobelimab</a> (IFX-1), were studied in patients with COVID-19 severe pneumonia (NCT04371367 and NCT04333420) [2691].	The C5a <sub>2</sub> receptor is commonly referred to as C5L2 and C5aR2 in the literature. C5a <sub>2</sub> was traditionally recognized as a decoy receptor for C5a, as it has no reported G protein signalling capacity. New research however, shows C5a <sub>2</sub> is capable of mediating its own set of signalling events and immunomodulatory actions, not only towards C5a <sub>1</sub> but also other complement, chemokine and pattern recognition receptors [1502].

**Comments:** [SB290157](#) has also been reported to have agonist properties at the C3a receptor [1503, 1670]. The chemoattractant receptor C5a<sub>2</sub> (also known as GPR77, C5L2) binds C5a and has putative roles in either opposing or promoting inflammatory responses [334, 764, 785, 1504, 1981]. Binding to this site may be displaced with the rank order [C5a des-Arg \(C5\)](#) > [C5a \(C5, P01031\)](#) [334, 1947] while there is controversy over the ability of [C3a \(C3, P01024\)](#) and [C3a des Arg \(C3, P01024\)](#) to compete [1047, 1201, 1202, 1947]. C5a<sub>2</sub> appears to lack G protein signalling and has been termed a decoy receptor [2320]. However, C5a<sub>2</sub> does recruit β-arrestin 2 after ligand binding,

which might provide a signalling pathway for this receptor [125, 2656], and forms heteromers with C5a<sub>1</sub>. A recent study has identified p90RSK (90 kDa ribosomal s6 kinase) phosphorylation as a potential signalling pathway for C5a<sub>2</sub> [1979]. C5a, but not C5a-des Arg, induces upregulation of heterodimer formation between complement C5a receptors C5a<sub>1</sub> and C5a<sub>2</sub> [505]. There are also reports of pro-inflammatory activity of C5a<sub>2</sub>, mediated by HMGB1, likely through AKT and MAPK signalling pathways (reviewed in [1498, 2935]). In T cells it has been 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 [71]. In human macrophages, C5a<sub>2</sub> was observed to modulate multiple complement and chemokine receptor-mediated signalling and pattern recognition-induced cytokine responses, independent of C5a<sub>1</sub> [1502]. In addition, C5a<sub>2</sub> is reported to act as a C5a transporter on endothelial cells, and is required for the transport of C5a into the vessel lumen and the subsequent neutrophil arrest in arthritis [1754].

### 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 [964]**) 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	<i>CRHR1</i> , P34998	<i>CRHR2</i> , Q13324
Endogenous agonists	urocortin 1 ( <i>UCN</i> , P55089) [528, 530, 597], corticotrophin-releasing hormone ( <i>CRH</i> , P06850) [407, 527, 530, 597, 1975, 2678]	urocortin 2 ( <i>UCN2</i> , Q96RP3) [528], urocortin 3 ( <i>UCN3</i> , Q969E3) [528]
Antagonists	SSR125543A (pK <sub>i</sub> 8.7) [896], <b>astressin</b> (pK <sub>i</sub> 8.7) [2189]	<b>astressin</b> (pIC <sub>50</sub> 9.2) [2187]
Selective antagonists	<b>CP 154,526</b> (pIC <sub>50</sub> 9.3–10.4) [1579] – Rat, <b>DMP696</b> (pK <sub>i</sub> 8.3–9) [976], <b>NBI27914</b> (pK <sub>i</sub> 8.3–9) [397], <b>R121919</b> (pK <sub>i</sub> 8.3–9) [2961], <b>antalarmin</b> (pK <sub>i</sub> 8.3–9) [2756], <b>NBI-35965</b> (pK <sub>i</sub> 8.4) [1744] – Rat, <b>CP 376,395</b> (pIC <sub>50</sub> 8.3) [415] – Rat, <b>CRA1000</b> (pIC <sub>50</sub> 6.4–7.1) [378]	<b>antisauvagine</b> (pK <sub>d</sub> 8.8–9.6) [530], <b>K41498</b> (pK <sub>i</sub> 9.2) [1423], <b>astressin 2B</b> (pIC <sub>50</sub> 8.9) [2187], <b>K31440</b> (pK <sub>i</sub> 8.7–8.8) [2226]

**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) [537, 2023].

## Further reading on Corticotropin-releasing factor receptors

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# Dopamine receptors

G protein-coupled receptors → Dopamine receptors

**Overview:** Dopamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Dopamine Receptors [2314]**) 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	<b>D<sub>1</sub> receptor</b>	<b>D<sub>2</sub> receptor</b>
HGNC, UniProt	<i>DRD1</i> , P21728	<i>DRD2</i> , P14416
Endogenous agonists	dopamine [2491, 2582]	dopamine [320, 733, 2278]
Agonists	fenoldopam [2582]	rotigotine [585], cabergoline (Partial agonist) [1735], aripiprazole (Partial agonist) [2911], bromocriptine [733, 1735, 2278], <i>MLS1547</i> (Biased agonist) [732], ropinirole [984], apomorphine (Partial agonist) [320, 733, 1735, 2278, 2427], pramipexole [1729, 2278], benzquinamide [871]
Sub/family-selective agonists	A68930 [1879], <i>SKF-38393</i> (Partial agonist) [2491, 2582]	quinpirole [320, 1729, 1996, 2427, 2429, 2660]
Selective agonists	<i>SKF-83959</i> (Biased agonist) [484], <i>A77636</i> [2239], <i>SKF-81297</i> [59] – Rat	sumanirole [1689]
Antagonists	flupentixol (pK <sub>i</sub> 7–8.4) [2491, 2582]	blonanserin (pK <sub>i</sub> 9.9) [1925], pipotiazine (pK <sub>i</sub> 9.7) [2428], perphenazine (pK <sub>i</sub> 8.9–9.6) [1362, 2330], risperidone (pK <sub>i</sub> 9.4) [80], perospirone (pK <sub>i</sub> 9.2) [2331], trifluoperazine (pK <sub>i</sub> 8.9–9) [1362, 2332], quetiapine (pK <sub>i</sub> 7.2) [80]
Sub/family-selective antagonists	<i>SCH-23390</i> (pK <sub>i</sub> 7.4–9.5) [2491, 2582], <i>SKF-83566</i> (pK <sub>i</sub> 9.5) [2491], <i>ecopipam</i> (pK <sub>i</sub> 8.3) [2583]	haloperidol (pK <sub>i</sub> 7.4–8.8) [733, 1601, 1729, 2427, 2583]
Selective antagonists	–	L-741,626 (pK <sub>i</sub> 7.9–8.5) [885, 1376], domperidone (pK <sub>i</sub> 7.9–8.4) [733, 2427], raclopride (pK <sub>i</sub> 8) [1737], <i>ML321</i> (pK <sub>i</sub> 7) [2830, 2831]
Sub/family-selective labelled ligands	[ <sup>125</sup> I] <i>SCH23982</i> (Antagonist) (pK <sub>d</sub> 9.5) [557], [ <sup>3</sup> H] <i>SCH-23390</i> (Antagonist) (pK <sub>d</sub> 9.5) [2949]	[ <sup>3</sup> H]spiperone (Antagonist) (pK <sub>d</sub> 10.2) [315, 1030, 2947] – Rat
Labelled ligands	–	[ <sup>3</sup> H]raclopride (Antagonist) (pK <sub>d</sub> 8.9) [1324] – 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
Endogenous agonists	dopamine [320, 733, 2278, 2429]	dopamine [2660]	dopamine [2491]
Agonists	cariprazine (Partial agonist) [1295], pramipexole [1729, 2278], bromocriptine (Partial agonist) [733, 1735, 2278], ropinirole [984], apomorphine (Partial agonist) [320, 733, 1735, 2278, 2427]	apomorphine (Partial agonist) [1735]	–
Sub/family-selective agonists	quinpirole [320, 1729, 1737, 1996, 2278, 2427, 2429, 2660]	quinpirole [1735, 1996, 2660]	A68930 [1879]
Selective agonists	<i>PD 128907</i> [2098, 2278]	<i>PD168,077</i> (Partial agonist) [1341] – Rat, <i>A412997</i> [1788] – Rat, <i>A412997</i> [1788]	–
Antagonists	perospirone (pK <sub>i</sub> 9.6) [2427], sertindole (pK <sub>i</sub> 8–8.8) [80, 2307, 2330], prochlorperazine (pK <sub>i</sub> 8.4) [93], (-)-sulpiride (pK <sub>i</sub> 6.7–7.7) [733, 2427, 2542], loxapine (pK <sub>i</sub> 7.7) [2330], domperidone (pK <sub>i</sub> 7.1–7.6) [733, 2427], promazine (pK <sub>i</sub> 6.8) [321]	perospirone (pK <sub>i</sub> 10.1) [2333], sertindole (pK <sub>i</sub> 7.8–9.1) [321, 2330, 2332, 2333], sonepiprazole (pK <sub>i</sub> 8.9) [2297], loxapine (pK <sub>i</sub> 8.1) [2332]	–
Sub/family-selective antagonists	haloperidol (pK <sub>i</sub> 7.5–8.6) [733, 2350, 2427, 2583]	haloperidol (pK <sub>i</sub> 8.7–8.8) [1397, 2350, 2583]	<i>SCH-23390</i> (pK <sub>i</sub> 7.5–9.5) [2491], <i>SKF-83566</i> (pK <sub>i</sub> 9.4) [2491], <i>ecopipam</i> (pK <sub>i</sub> 8.3) [2491]

Selective antagonists	S33084 (pK <sub>i</sub> 9.6) [1734], nafadotride (pK <sub>i</sub> 9.5) [2279], PG01037 (pK <sub>i</sub> 9.2) [886], NGB 2904 (pK <sub>i</sub> 8.8) [2827], SB 277011-A (pK <sub>i</sub> 8) [2156], (+)-S-14297 (pK <sub>i</sub> 6.9–7.9) [1732, 1737]	L745870 (pK <sub>i</sub> 9.4) [1376], A-381393 (pK <sub>i</sub> 8.8) [1850], L741742 (pK <sub>i</sub> 8.5) [2221], ML398 (pK <sub>i</sub> 7.4) [188]	–
Selective allosteric modulators	SB269652 (Negative) (pK <sub>i</sub> -9) [750]	–	–
Sub/family-selective labelled ligands	–	[ <sup>3</sup> H]spiperone (Antagonist) (pK <sub>d</sub> 9.5) [1009, 2660]	[ <sup>3</sup> H]SCH-23390 (Antagonist) (pK <sub>d</sub> 9.2) [2172]
Labelled ligands	[ <sup>3</sup> H]spiperone (Antagonist) (pK <sub>d</sub> 9.9) [1030, 2947] – Rat, [ <sup>3</sup> H]7-OH-DPAT (Agonist) [2173], [ <sup>3</sup> H]PD128907 (Agonist) [33]	[ <sup>125</sup> I]L750667 (Antagonist) (pK <sub>d</sub> 9.8) [1996], [ <sup>3</sup> H]NGD941 (Antagonist) (pK <sub>d</sub> 8.3) [2084]	[ <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

antagonist. [<sup>3</sup>H]7-OH-DPAT has similar affinity for D<sub>2</sub> and D<sub>3</sub> receptors, but labels only D<sub>3</sub> receptors in the absence of divalent cations. The pharmacological profile of the D<sub>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.

### Further reading on Dopamine receptors

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Urs NM *et al.* (2017) New Concepts in Dopamine D<sub>2</sub> Receptor Biased Signaling and Implications for Schizophrenia Therapy. *Biol Psychiatry* **81**: 78-85 [PMID:27832841]

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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 [531]**) 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	<i>EDNRA</i> , P25101	<i>EDNRB</i> , P24530
Potency order of endogenous ligands	endothelin-1 ( <i>EDN1</i> , P05305) = endothelin-2 ( <i>EDN2</i> , P20800) > endothelin-3 ( <i>EDN3</i> , P14138) [1614]	endothelin-1 ( <i>EDN1</i> , P05305) = endothelin-2 ( <i>EDN2</i> , P20800), endothelin-3 ( <i>EDN3</i> , P14138) [2251]
Selective agonists	–	sarafotoxin S6c [1367, 2230], BQ 3020 [2168], [Ala <sup>1,3,11,15</sup> ]ET-1 [1763], sovateptide [2137, 2746]
Antagonists	SB209670 (pKB 9.4) [647] – Rat, TAK 044 (pA <sub>2</sub> 8.4) [2749] – Rat, bosentan (pA <sub>2</sub> 7.2) [471] – Rat, apocitentan (pA <sub>2</sub> 6.7) [1094]	SB209670 (pKB 9.4) [647] – Rat, TAK 044 (pA <sub>2</sub> 8.4) [2749] – Rat, bosentan (pK <sub>i</sub> 7.1) [471], apocitentan (pA <sub>2</sub> 5.5) [1094]
Selective antagonists	clazosentan (pA <sub>2</sub> 9.5) [2218], macitentan (pIC <sub>50</sub> 9.3) [229], atrasentan (pA <sub>2</sub> 9.2) [1959], zibotentan (pIC <sub>50</sub> 8.3) [1810], sitaxsentan (pA <sub>2</sub> 8) [2815], FR139317 (Inverse agonist) (pIC <sub>50</sub> 7.3–7.9) [1614], BQ123 (pA <sub>2</sub> 6.9–7.4) [1614], ambrisentan (pA <sub>2</sub> 7.1) [230]	K-8794 (pIC <sub>50</sub> 8.2) [2364], A192621 (pK <sub>d</sub> 8.1) [2695], BQ788 (pK <sub>d</sub> 7.9–8) [2230], IRL 2500 (pK <sub>d</sub> 7.2) [2230], Ro 46-8443 (pIC <sub>50</sub> 7.2) [276]

Labelled ligands	<sup>125</sup> I]PD164333 (Antagonist) (pKd 9.6–9.8) [534], [ <sup>3</sup> H]S0139 (Antagonist) (pKd 9.2) [1731], [ <sup>125</sup> I]PD151242 (Antagonist) (pKd 9–9.1) [535], [ <sup>3</sup> H]BQ123 (Antagonist) (pKd 8.5) [1100]	<sup>125</sup> I]IRL1620 (Agonist) [1851], [ <sup>125</sup> I]BQ3020 (Agonist) [948, 1763, 2030], [ <sup>125</sup> I][Ala <sup>1,3,11,15</sup> ]ET-1 (Agonist) [1763]
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**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 [960]. 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 [1756].

Cryogenic-electron microscopy structures of ET<sub>A</sub> and ET<sub>B</sub> bound to endothelin-1 (*EDN1*, P05305) and ET<sub>B</sub> bound to *sovateptide* (IRL1620) [1166] and crystal structures of the ET<sub>B</sub> receptor complexed with non-selective agonists endothelin-1 (*EDN1*, P05305) [2363] and *sarafotoxin S6b* [1128], ET<sub>B</sub> selective agonists endothelin-3 (*EDN3*, P14138) and *sovateptide* (IRL1620) [2362],

inverse agonist *IRL 2500* [1844], and clinically relevant non-selective antagonist *bosentan* and the ET<sub>B</sub> selective analogue *K-8794* [2364] have been reported. *Sparsentan* is a combined ET<sub>A</sub> and AT<sub>1</sub> receptor antagonist [1348].

### Further reading on Endothelin receptors

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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 [2091]) was identified following observations of estrogen-evoked cyclic AMP signalling in breast cancer cells [81], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [348]. There are observations of both cell-surface and

intracellular expression of the GPER receptor [2163, 2573]. Selective agonist/antagonists for GPER have been characterized [2091]. Antagonists of the nuclear estrogen receptor, such as *fulvestrant* [696], *tamoxifen* [2163, 2573] and *raloxifene* [2039], as well as the flavonoid 'phytoestrogens' *genistein* and *quercetin* [1613], are agonists of GPER. Reviews of GPER pharmacology have been published [2091]. The roles of GPER in (patho)physio-

logical systems throughout the body (cardiovascular, metabolic, endocrine, immune, reproductive) and in cancer have also been reviewed [695, 1415, 1714, 2091, 2092]. The GPER-selective agonist G-1 is currently in Phase I/II clinical trials for cancer (NCT04130516).

Nomenclature	GPER
HGNC, UniProt	GPER1, Q99527
Endogenous agonists	17β-estradiol [2163, 2573]
Agonists	fulvestrant [2573], raloxifene [2039], 4-hydroxytamoxifen [2163]
Selective agonists	G-1 [232]
Selective antagonists	G36 (pIC <sub>50</sub> 6.8–6.9) [566], G15 (pIC <sub>50</sub> 6.7) [565]
Labelled ligands	[ <sup>3</sup> H]17β-estradiol (Agonist) [2573]

**Further reading on G protein-coupled estrogen receptor**

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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 [2882]) respond to exogenous ligands such as the bacterial product fMet-Leu-Phe (fMLP)

and endogenous ligands such as lipoxin A<sub>4</sub> (LXA<sub>4</sub>), 15-*epi*-lipoxin A<sub>4</sub>, annexin I (ANXA1, P04083), cathepsin G (CTSG, P08311), amyloid β<sub>42</sub>, serum amyloid A and spinorphin, derived from β-haemoglobin (HBB, P68871). FPR1 also serves as a plague recep-

tor for selective destruction of human immune cells by *Y. pestis* [1962]. The FPR1/2 agonists 'compound 17b' and 'compound 43' have shown cardiac protective functions [768, 2108].

Nomenclature	FPR1	FPR2/ALX	FPR3
HGNC, UniProt	FPR1, P21462	FPR2, P25090	FPR3, P25089
Potency order of endogenous and other ligands	–	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 [469, 700, 702, 879, 2520]	–
Potency order of endogenous ligands	fMet-Leu-Phe > cathepsin G (CTSG, P08311) > annexin I (ANXA1, P04083) [1437, 2488]	–	–
Endogenous agonists	–	LXA <sub>4</sub> [1359], resolvin D1 [1359], aspirin-triggered resolvin D1 [1358], aspirin triggered lipoxin A4	F2L (HEBP1, Q9NRV9) [1730]
Agonists	fMet-Leu-Phe [735, 2378]	–	–
Selective agonists	–	ATLa2 [895]	–
Endogenous antagonists	spinorphin (pIC <sub>50</sub> 4.3) [1509, 1835]	–	–
Antagonists	t-Boc-FLFLF (pK <sub>i</sub> 6–6.5) [2767]	–	–
Selective antagonists	cyclosporin H (pK <sub>i</sub> 6.1–7.1) [2767, 2860]	WRWWWW (pIC <sub>50</sub> 6.6) [111], t-Boc-FLFLF (pIC <sub>50</sub> 4.3–6) [734, 2454, 2714]	–
Labelled ligands	[ <sup>3</sup> H]fMet-Leu-Phe (Agonist) [1337]	[ <sup>3</sup> H]LXA <sub>4</sub> (Agonist) [700, 701]	–
Comments	A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [974].	–	–

**Comments:** Note that the data for FPR2/ALX are also reproduced on the [leukotriene](#) receptor page. FPR1 has been reported to be the plague receptor on host immune cells [1962]. By interacting with LcrV, the needle cap protein of the type III secretion system of *Y. pestis*, FPR1 serves to promote translocation of virulent factors of the bacteria. The R190W mutation of FPR1 confers resistance to this function of *Y. pestis*. Several FPR1/2 agonists including compound 17b'

and 'compound 43' have been shown to display cardiac protective functions in mouse models of myocardial ischemia-reperfusion injury [768, 2108]. Studies have been conducted to explore the mechanisms by which FPR2 mediates both inflammatory and anti-inflammatory signaling in a ligand-dependent manner. The status of FPR2 dimerization is a determining factor for ligand-specific conformational changes leading to biased signaling [486]. There is also a report on ligand concentration-

dependent dual modulation of FPR2 by lipoxin A<sub>4</sub> for receptor-activation vs. anti-inflammatory activities [788]. Some FPR2 ligands may display allosteric modulatory effects that cause changes in FPR2 conformational states and receptor signaling [2928]. The 3-D structure of FPR2 has been solved by the use of cryo-electron microscopy [2958] and receptor protein crystallization [409]. The FPR2 structure reveals a large binding pocket that can accommodate several ligands of different shapes and sizes.

### 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** [532, 2464]) 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, ( $\beta$ -linolenic acid), C20:4 (arachidonic acid), C20:5,n-3 (EPA) and C22:6,n-3 (docosahexaenoic acid)) activate FFA1 [284, 1121, 1344] and FFA4 receptors [1019, 1092, 1931], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid))

activate FFA2 [295, 1436, 1900] and FFA3 [295, 1436] receptors. The crystal structure for agonist bound FFA1 has been described [2446].

Nomenclature	FFA1 receptor	FFA2 receptor
HGNC, UniProt	FFAR1, O14842	FFAR2, O15552
Endogenous agonists	docosahexaenoic acid [284, 1121], $\alpha$ -linolenic acid [284, 1121, 1344], oleic acid [284, 1121, 1344], myristic acid [284, 1121, 1344]	propanoic acid [295, 1436, 1900, 2299], acetic acid [295, 1436, 1900, 2299], butyric acid [295, 1436, 1900, 2299], trans-2-methylcrotonic acid [2299], 1-methylcyclopropanecarboxylic acid [2299]
Agonists	HWL-088 [412]	–
Selective agonists	AMG-837 [1522], compound 4 [448], TUG-770 [447], TUG-905 [446], GW9508 (Partial agonist) [283], fasiglifam [1200, 1869, 2446, 2615]	TUG-1375 [937]
Selective antagonists	GW1100 (pIC <sub>50</sub> 6) [283, 2463]	GLPG0974 (pIC <sub>50</sub> 8.1) [1853, 2058], CATPB (pIC <sub>50</sub> 6.5) [1080]

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 [284, 1121, 1344]. Antagonist GW1100 is also an oxytocin receptor antagonist [283]. Fasiglifam, TUG-770 and GW9508 are approximately 100 fold selective for FFA1 over FFA4 [283, 447, 1869]. 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 [1522, 2838].	–
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Nomenclature	FFA3 receptor	FFA4 receptor
HGNC, UniProt	FFAR3, O14843	FFAR4, Q5NUL3
Endogenous agonists	propanoic acid [295, 1436, 2299, 2837], butyric acid [295, 1436, 2299, 2837], 1-methylcyclopropanecarboxylic acid [2299]	$\alpha$ -linolenic acid [2369], myristic acid [2753], $\alpha$ -linolenic acid [2538] – Rat, oleic acid [2753]
Agonists	acetic acid [295, 1436, 2299, 2837]	–
Selective agonists	–	compound A [1930], TUG-891 [2369], NCG21 [2499]
Comments	Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [1284]. 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.e. allosteric modulators), have been described [233, 1079, 1591].	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 [449] with a small subset listed above. Compound A [PMID 24997608] exhibits more than 1000 fold selectivity [1930], and TUG-891 50-1000 fold selectivity for FFA4 over FFA1 [2369], dependent on the assay. NCG21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [2487].

**Comments:** Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [1787], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [2753]. The long FFA4

splice variant has not been identified in other primates or rodents to date [1019, 1787].

*GPR42* was originally described as a pseudogene within the family (ENSMF0025000002583), but the discovery of several

polymorphisms suggests that some versions of GPR42 may be functional [1510]. *GPR84* is a structurally-unrelated G protein-coupled receptor which has been found to respond to medium chain fatty acids [2727].

### 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 [255, 2051]**) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub>

[255, 651, 2050, 2051, 2633]. 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) [193, 255, 256]. The GABA<sub>B1</sub> subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA<sub>B2</sub> subunit mediates G protein-coupled signalling [255, 794, 796, 2050]. The cryo-electron microscopy structures of the human full-length GABA<sub>B1</sub>-GABA<sub>B2</sub> heterodimer have been solved in the inactive apo state, two intermediate agonist-bound forms

and an active state in which the heterodimer is bound to an agonist and a positive allosteric modulator [2355]. The positive allosteric modulator binds to the transmembrane dimerization interface and stabilizes the active state. 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 [479, 2048]. 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 [142, 2317, 2619] and are reviewed by [2052]. The molecular complexity of GABA<sub>B</sub> receptors is further increased through

association with trafficking and effector proteins [2318] and reviewed by [2047]. 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 [2022, 2683]. Amyloid precursor protein (APP) and soluble APP (sAPP) bind to the N-terminal sushi domain of the GABA<sub>B1a</sub> isoform to regulate axonal trafficking of GABA<sub>B</sub> receptors and release of neurotransmitters [2176].

### Complexes

Nomenclature	GABA <sub>B</sub> receptor
Subunits	GABA <sub>B1</sub> , GABA <sub>B2</sub> , KCTD8 (Accessory protein), KCTD12 (Accessory protein), <i>kctd12b</i> (Accessory protein), KCTD16 (Accessory protein)
Agonists	CGP 44532 [741] – Rat, (-)-baclofen [741] – Rat, 3-APPA [1023], baclofen [1023, 2807], 3-APMPA [2807]
Antagonists	CGP 62349 (pKi 8.5–8.9) [1023, 2807], CGP 55845 (pKi 7.8) [2807], SCH 50911 (pKi 5.5–6) [1023, 2807], CGP 35348 (pKi 4.4) [2807], 2-hydroxy-saclofen (pIC <sub>50</sub> 4.1) [1227] – Rat
Allosteric modulators (Positive)	rac-BHFF (pEC <sub>50</sub> 6.6) [1627], GS39783 (pKB 4.7) [992, 2643], CGP7930 [2642]
Allosteric modulators (Negative)	compound 14 (pIC <sub>50</sub> 4.4) [404]
Labelled ligands	[ <sup>3</sup> H]CGP 54626 (Antagonist) (pKi 9.1) [1185] – Rat, [ <sup>3</sup> H]CGP 62349 (Antagonist) (pKd 9.1) [1236] – Rat, [ <sup>125</sup> I]CGP 64213 (Antagonist) (pKd 9) [759] – Rat, [ <sup>125</sup> I]CGP 71872 (Antagonist) (pKd 9) [1227] – Rat, [ <sup>3</sup> H](R)-(-)-baclofen (Agonist)

### Subunits

Nomenclature	GABA <sub>B1</sub>	GABA <sub>B2</sub>
HGNC, UniProt	GABBR1, Q9UBS5	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 [255, 740, 741]. 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 [171]. 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 [740]. 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 [759]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 [2692] and (+)-BHFF [12, 193, 202, 740]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA<sub>B2</sub> subunit [628, 2050]. In the presence of CGP7930 or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [740]. A negative allosteric modulator of GABA<sub>B</sub> activity has been reported [404]. 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 [657, 2645]. A similar phenotype has been found for GABA<sub>B2</sub><sup>-/-</sup> BALB/c mice [781].

**Further reading on GABAB receptors**

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# Galanin receptors

G protein-coupled receptors → Galanin receptors

**Overview:** Galanin receptors (**provisional nomenclature as recommended by NC-IUPHAR [712]**) 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 [673]; 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, amphibians and fish. Shorter peptide species (*e.g.* human galanin-1-19 [189] and porcine galanin-5-29 [2385]) and N-terminally extended forms (*e.g.* N-terminally seven and nine residue elongated

forms of porcine galanin [190, 2385]) have been reported. More recently, the newly-identified peptide, spexin (SPX), has been reported to activate human GAL2 and GAL3 (but not GAL1) receptors in heterologous expression systems; and to alter GAL2/3 receptor-related behaviours in animals [1269].

Nomenclature	<b>GAL<sub>1</sub> receptor</b>	<b>GAL<sub>2</sub> receptor</b>	<b>GAL<sub>3</sub> receptor</b>
HGNC, UniProt	<i>GALR1</i> , P47211	<i>GALR2</i> , O43603	<i>GALR3</i> , O60755
Potency order of endogenous ligands	<b>galanin</b> ( <i>GAL</i> , P22466) > <b>galanin-like peptide</b> ( <i>GALP</i> , Q9UBC7) [1938]	<b>galanin-like peptide</b> ( <i>GALP</i> , Q9UBC7) ≥ <b>galanin</b> ( <i>GAL</i> , P22466) [1938]	<b>galanin-like peptide</b> ( <i>GALP</i> , Q9UBC7) > <b>galanin</b> ( <i>GAL</i> , P22466) [1405]
Endogenous agonists	–	<b>spexin-1</b> ( <i>SPX</i> , Q9BT56) [1269]	<b>spexin-1</b> ( <i>SPX</i> , Q9BT56) [1269]
Agonists	–	<b>galanin(2-29)</b> (rat/mouse) [1982, 2732, 2733, 2734] – Rat	–
Selective agonists	–	<b>[D-Trp<sup>2</sup>]galanin-(1-29)</b> [2413] – Rat, <b>Qu-SPX</b> [1459]	–
Selective antagonists	<b>2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide</b> (pIC <sub>50</sub> 5.6) [2324]	<b>M871</b> (pK <sub>i</sub> 7.9) [2431]	<b>SNAP 398299</b> (pK <sub>i</sub> 8.3) [1332, 1333, 2503], <b>SNAP 37889</b> (pK <sub>i</sub> 7.8–7.8) [1332, 1333, 2503]
Selective allosteric modulators	–	<b>CYM2503</b> (Positive) (pEC <sub>50</sub> 9.2) [1571] – Rat	–
Labelled ligands	<b>[<sup>125</sup>I][Tyr<sup>26</sup>]galanin (human)</b> (Agonist) [708], <b>[<sup>125</sup>I][Tyr<sup>26</sup>]galanin (human)</b> (Agonist) [708]	<b>[<sup>125</sup>I][Tyr<sup>26</sup>]galanin (human)</b> (Agonist) [2733] – Rat, <b>[<sup>125</sup>I]spexin-1</b> (Agonist) [1269]	<b>[<sup>125</sup>I][Tyr<sup>26</sup>]galanin (pig)</b> (Agonist) [246, 2414], <b>[<sup>125</sup>I]spexin-1</b> (Agonist) [1269]
Comments	–	The CYM2503 PAM potentiates the anticonvulsant activity of endogenous galanin in mouse seizure models [1571]. Activation and binding potency of spexin at human GAL <sub>2</sub> receptor is less than galanin ( <i>GAL</i> ) [1269].	Activation and binding potency of spexin at human GAL <sub>3</sub> receptor is higher than galanin ( <i>GAL</i> ) [1269].

**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> [1570]. [<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 [708, 2399, 2413, 2414, 2733]. 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 [887, 2826]. 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 [2631], spinal cord [2786], locus coeruleus, hippocampus [140] and hypothalamus [141, 1468], but exhibit agonist activity

at some peripheral sites [141, 887]. The chimeric peptides **M15**, **M32**, **M35**, **M40** and **C7** are agonists at GAL<sub>1</sub> receptors expressed endogenously in Bowes human melanoma cells [1938], and at heterologously expressed recombinant GAL<sub>1</sub>, GAL<sub>2</sub> and GAL<sub>3</sub> receptors [708, 2413, 2414]. Further studies 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 [2241]. More recent studies have identified

synthetic spexin (SPX)-based peptides that are selective GAL<sub>2</sub> receptor agonists [1459, 2166].

### Further reading on Galanin receptors

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## Ghrelin receptor

G protein-coupled receptors → Ghrelin receptor

**Overview:** The ghrelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [533]**) 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 prepro-ghrelin, although the mature peptides from rat and human differ by only two amino acids [1673]. Alternative splicing results in the formation of a second peptide, [*des-Gln*<sup>14</sup>]*ghrelin* (*GHRL*, *Q9UBU3*) with equipotent biological activity [1055]. A unique

post-translational modification (octanoylation of Ser<sup>3</sup>, catalysed by ghrelin O-acyltransferase (*MBOAT4*, *Q96T53*) [2866] 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 [1328]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [158], 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 [1044]. An endogenous antagonist

and inverse agonist called Liver enriched antimicrobial peptide 2 (Leap2), expressed primarily in hepatocytes and in enterocytes of the proximal intestine [787, 1588] inhibits ghrelin receptor-induced GH secretion and food intake [787]. The secretion of Leap2 and ghrelin is inversely regulated under various metabolic conditions [1637]. In cell systems, the ghrelin receptor is constitutively active [1045], 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 [1983].

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> ] <i>ghrelin</i> ( <i>GHRL</i> , <i>Q9UBU3</i> ) [157, 1673]
Antagonists	liver enriched antimicrobial peptide 2 ( <i>LEAP2</i> , <i>Q969E1</i> ) (pIC <sub>50</sub> 8.2) [787]
Selective antagonists	GSK1614343 (pIC <sub>50</sub> 8.4) [2242], GSK1614343 (pK <sub>b</sub> 8) [2020] – Rat
Labelled ligands	[ <sup>125</sup> I][His <sup>9</sup> ] <i>ghrelin</i> (human) (Agonist) [1226], [ <sup>125</sup> I][Tyr <sup>4</sup> ] <i>ghrelin</i> (human) (Agonist) [1818]

**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 [157], 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; [1042]). 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 pharmacologically discriminating the orexigenic and gastrointestinal actions of *ghrelin* (*GHRL*, *Q9UBU3*) from the release of growth hormone [724]. Similar discrimination

of ghrelin receptor mediated physiological functions can be obtained by activation of distinct signaling pathways [1708]. A number of selective antagonists have been reported, including peptidomimetic [1817] and non-peptide small molecules including GSK1614343 [2004, 2020, 2242].

**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 [1684]**) 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 [1114]. For a recent review on the current understanding of the structures of GLP-1 and GLP-1R, the molecular basis of their interaction, and the associated signaling events see de Graaf *et al.*, 2016 [861].

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) [2694]	glucagon-like peptide 1-(7-36) amide ( <i>GCG</i> , P01275) [1190], glucagon-like peptide 1-(7-37) ( <i>GCG</i> , P01275) [586]
Agonists	Jl-38 [332], sermorelin	–	liraglutide [1313], lixisenatide [2769], WB4-24 [677]
Selective agonists	BIM28011 [503], tesamorelin	–	semaglutide [1418], exendin-4 [1747], exendin-4 [1190], exendin-3 (P20394) [2145]
Selective antagonists	JV-1-36 (pK <sub>i</sub> 10.1–10.4) [2290, 2671, 2672] – Rat, JV-1-38 (pK <sub>i</sub> 10.1) [2290, 2671, 2672] – Rat	[Pro <sup>3</sup> ]GIP [784] – Mouse	exendin-(9-39) (pK <sub>i</sub> 8.1) [1190], GLP-1-(9-36) (pIC <sub>50</sub> 6.9) [1779] – Rat, T-0632 (pIC <sub>50</sub> 4.7) [2581]
Labelled ligands	[ <sup>125</sup> I]GHRH (human) (Agonist) [252] – Rat	[ <sup>125</sup> I]GIP (human) (Agonist) [757] – Rat	[ <sup>125</sup> I]GLP-1-(7-36)-amide (Agonist) [1190], [ <sup>125</sup> I]exendin-(9-39) (Antagonist) (pK <sub>d</sub> 8.3) [1190], [ <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>GCGR</i> , P47871	<i>SCTR</i> , P47872
Endogenous agonists	glucagon-like peptide 2 ( <i>GCG</i> , P01275) [2578]	glucagon ( <i>GCG</i> , P01275) [2061]	secretin ( <i>SCT</i> , P09683) [443]
Agonists	teduglutide [1699]	NNC1702 [2923]	–
Selective agonists	apraglutide [947, 2404]	–	–

Selective antagonists	–	L-168,049 (pIC <sub>50</sub> 8.4) [358], adomeglivant (pKi 8.2) [1235, 1241], des-His1-[Glu9]glucagon-NH <sub>2</sub> (pA <sub>2</sub> 7.2) [2636, 2637] – Rat, NNC 92-1687 (pKi 5) [1605], BAY27-9955 [2033]	[(CH <sub>2</sub> NH) <sup>4-5</sup> ]secretin (pKi 5.3) [908]
Labelled ligands	–	[ <sup>125</sup> I]glucagon (human, mouse, rat) (Agonist)	[ <sup>125</sup> I](Tyr <sup>10</sup> )secretin-27 (rat) (Agonist) [2632] – Rat

**Comments:** The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically **RAMP2**, in heterologous expression systems [451], 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** [712]) 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 [537, 2246].

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) [1167, 1826]	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

Jiang X *et al.* (2012) Structure of follicle-stimulating hormone in complex with the entire ecto-domain of its receptor. *Proc Natl Acad Sci USA* **109**: 12491-6 [PMID:22802634]  
 Kleinau G *et al.* *Thyroid Disease Manager*. Accessed on 2017-02-23.

Tao YX *et al.* (2009) Follicle stimulating hormone receptor mutations and reproductive disorders. *Prog Mol Biol Transl Sci* **89**: 115-31 [PMID:20374735]  
 Troppmann B *et al.* (2013) Structural and functional plasticity of the luteinizing hormone/choriogonadotropin receptor. *Hum Reprod Update* **19**: 583-602 [PMID:23686864]

# Gonadotrophin-releasing hormone receptors

G protein-coupled receptors → Gonadotrophin-releasing hormone receptors

**Overview:** GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors (**provisional nomenclature** [712], also called Type I and Type II GnRH receptor, respectively [1740]) have been cloned from numerous species, most of which express two or three types of GnRH receptor [1739, 1740, 2387]. 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 [1739, 1740, 2387] 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 [1739, 1740, 2387]. 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 [1262]. Notably, agonists cause desensitization of GnRH-stimulated gonadotropin secretion and the consequent reduction in circulating sex steroids is exploited to treat

hormone-dependent cancers of the breast, ovary and prostate [1262]. 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 [1796]. Phylogenetic classifications divide GnRH receptors into three [1740] or five groups [2790] and highlight examples of gene loss through evolution, with humans retaining only one ancient gene. The structure of the GnRH<sub>1</sub> receptor in complex with **elagolix** has been elucidated [2861].

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) [1740]	GnRH II ( <i>GNRH2</i> , O43555) > GnRH I ( <i>GNRH1</i> , P01148) (Monkey) [1738]
Endogenous agonists	GnRH I ( <i>GNRH1</i> , P01148) [1572], GnRH II ( <i>GNRH2</i> , O43555) [706, 1572, 2457]	GnRH II ( <i>GNRH2</i> , O43555) [1738] – Monkey, GnRH I ( <i>GNRH1</i> , P01148) [1738, 1740] – Monkey
Selective agonists	buserelin [1865, 1866], triptorelin [154], leuprolide [2472], goserelin, histrelin, nafarelin	–
Antagonists	iturelix (pK <sub>i</sub> 9.5) [2188]	–
Selective antagonists	cetrorelix (pK <sub>i</sub> 9.3–10) [155, 156, 2472], abarelix (pK <sub>i</sub> 9.1–9.5) [2472], elagolix (pK <sub>i</sub> 9.1) [398, 1401], degarelix (pK <sub>i</sub> 8.8) [2658], ganirelix	trptorelix-1 [1620] – Monkey
Labelled ligands	[ <sup>125</sup> I]cetrorelix (Antagonist) (pK <sub>d</sub> 9.7) [1034], [ <sup>125</sup> I]triptorelin (Agonist) [561] – Rat, [ <sup>125</sup> I]buserelin (Agonist) [1384] – 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> [881] but coupling to G<sub>s</sub> and G<sub>i</sub> is evident in some systems [1363, 1384]. GnRH<sub>2</sub> receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [365]. 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 [418, 952, 1520, 2289]. 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 [884], but

GnRH<sub>2</sub> receptors are not expressed by humans because the human *GNRHR2* gene contains a frame shift and internal stop codon [1796]. 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 [1871]). Alternatively, evidence for multiple active GnRH receptor conformations [365, 366, 697, 1681, 1740] 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 [366, 1681]. 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 [1444]. 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 [698, 1444], and this increases susceptibility to point mutations that further impair trafficking [698, 1444]. GnRH receptor signalling may require receptor oligomerisation [483, 1361].

**Further reading on Gonadotrophin-releasing hormone receptors**

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Millar RP *et al.* (2004) Gonadotropin-releasing hormone receptors. *Endocr Rev* **25**: 235-75 [PMID:15082521]  
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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 [2029]. 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) [1967]
Endogenous agonists	N-arachidonoylglycine [1325]	lysophosphatidylinositol [995, 1940, 2436], 2-arachidonoylglycerolphosphoinositol [1942]	N-oleoylethanolamide [456, 1967, 2436], N-palmitoylethanolamine, SEA
Selective agonists	–	AM251 [995, 1216, 2238]	AS1269574 [2897], PSN632408 [1967], PSN375963 [1967]
Selective antagonists	–	CID16020046 (apparent pA <sub>2</sub> ) (pA <sub>2</sub> 7.3) [1218], ML193 (pIC <sub>50</sub> 6.7) [1008]	–
Comments	The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on arrestin assays [2436, 2885]. See [532] for discussion.	See reviews [532] and [2376].	In addition to those shown above, further small molecule agonists have been reported [929].

**Comments:** GPR18 failed to respond to a variety of lipid-derived agents in an *in vitro* screen [2885], but has been reported to be activated by Δ<sup>9</sup>-tetrahydrocannabinol [1698]. GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB<sub>1</sub> receptor

antagonists/inverse agonists [2029]. It has been reported that lysophosphatidylinositol acts at other sites in addition to GPR55 [2856]. N-Arachidonoylserine has been suggested to act as a low efficacy agonist/antagonist at GPR18 *in vitro* [1696]. It has also been suggested oleoyl-lysophosphatidylcholine acts, at

least in part, through GPR119 [1901]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleoylethanolamide-mediated responses suggests additional mechanisms of action [1901].

**Further reading on GPR18, GPR55 and GPR119**

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]

Hassing HA *et al.* (2016) Biased signaling of lipids and allosteric actions of synthetic molecules for GPR119. *Biochem Pharmacol* **119**: 66-75 [PMID:27569424]

Liu B *et al.* (2015) GPR55: from orphan to metabolic regulator? *Pharmacol Ther* **145**: 35-42 [PMID:24972076]

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]

## Histamine receptors

G protein-coupled receptors → Histamine receptors

**Overview:** Histamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors [1014, 1984]**) are activated by the endogenous ligand **histamine**. Marked species differences exist between histamine receptor orthologues [1014]. The human and rat H<sub>3</sub> receptor genes are subject to significant splice variance [122].

The potency order of histamine at histamine receptor subtypes is H<sub>3</sub> = H<sub>4</sub> > H<sub>2</sub> > H<sub>1</sub> [1984]. Some agonists at the human H<sub>3</sub> receptor display significant ligand bias [2180]. 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.* **adriforant**; Phase IIa) [1984] and vestibular neuritis (AUV) (SENS-111 (Seliforant, previously UR-63325), entered and completed vestibular neuritis (AUV) Phase IIa efficacy and safety trials, respectively) [88, 2679].

Nomenclature	H <sub>1</sub> receptor	H <sub>2</sub> receptor
HGNC, UniProt	<i>HRH1</i> , P35367	<i>HRH2</i> , P25021
Selective agonists	<b>methylhistaprodifen</b> [2335], <b>histaprodifen</b> [1519]	<b>amthamine</b> [1354]
Antagonists	<b>cyproheptadine</b> (pK <sub>i</sub> 10.2) [1761], <b>promethazine</b> (pK <sub>i</sub> 9.6) [810], <b>mepyramine</b> (Inverse agonist) (pK <sub>i</sub> 8.7–9) [242, 2144], <b>cetirizine</b> (Inverse agonist) (pK <sub>i</sub> 8.2) [1761], <b>diphenhydramine</b> (pK <sub>i</sub> 7.9) [242]	–
Selective antagonists	<b>clemastine</b> (pK <sub>i</sub> 10.3) [93], <b>desloratadine</b> ((pK <sub>i</sub> 9) [1491], <b>triprolidine</b> (pK <sub>i</sub> 8.5–9) [242, 1761], <b>azelastine</b> (pK <sub>i</sub> 8.9) [2086], <b>astemizole</b> (pK <sub>i</sub> 8.5) [2007]	<b>tiotidine</b> (pK <sub>i</sub> 7.5) [195] – Rat, <b>ranitidine</b> ((pK <sub>i</sub> 7.1) [1486], <b>cimetidine</b> ((pK <sub>i</sub> 6.8) [344]
Labelled ligands	[ <sup>3</sup> H]pyrilamine (Antagonist, Inverse agonist) (pK <sub>d</sub> 8.4–9.1) [543, 1761, 2307, 2335], [ <sup>11</sup> C]doxepin (Antagonist) (pK <sub>d</sub> 9) [1117], [ <sup>11</sup> C]pyrilamine (Antagonist, Inverse agonist)	[ <sup>125</sup> I]iodoaminopotentidine (Antagonist) (pK <sub>d</sub> 8.7) [1369] – Rat, [ <sup>3</sup> H]tiotidine (Antagonist) (pK <sub>d</sub> 7.7–8.7) [1772]

Nomenclature	H <sub>3</sub> receptor	H <sub>4</sub> receptor
HGNC, UniProt	<i>HRH3</i> , Q9Y5N1	<i>HRH4</i> , Q9H3N8
Selective agonists	<b>GSK-189254</b> (Inverse agonist) [1703], <b>immethridine</b> [1302], <b>methimepip</b> [1301], <b>MK-0249</b> (Inverse agonist) [1842]	<b>clobpropit</b> (Partial agonist) [663, 1519, 1542, 1543, 1812], <b>4-methylhistamine</b> [786, 1519], <b>ST-1006</b> [1984], <b>VUF 8430</b> [1518]
Antagonists	<b>iodophenpropit</b> (pK <sub>i</sub> 8.2–8.7) [2785, 2822]	<b>SENS-111</b> [2038]



Selective antagonists	<a href="#">pitolisant</a> (pK <sub>i</sub> 8.1–8.6) [1431, 1984], <a href="#">A331440</a> (pK <sub>i</sub> 8.5) [930], <a href="#">conessine</a> (pK <sub>i</sub> 8.3) [1984], <a href="#">MK-0249</a> (pK <sub>i</sub> 8.2) [1984], <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> .) (pK <sub>i</sub> 7.1–7.7) [472, 662, 663, 1516, 1569, 2785, 2822], <a href="#">ciproxifan</a> (pK <sub>i</sub> 6.7–7.3) [472, 662, 663, 1516, 1984, 2822]	<a href="#">adriforant</a> (pK <sub>i</sub> 8.3) [1984], <a href="#">INCB-38579</a> (pK <sub>i</sub> 8.3) [1984], <a href="#">JNJ 7777120</a> (pK <sub>i</sub> 7.8–8.3) [1519, 2419, 2579], <a href="#">JNJ-39758979</a> (pK <sub>i</sub> 7.9) [1984, 2280], <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> .) (pK <sub>i</sub> 6.3–7.6) [662, 663, 1542, 1543, 1812, 2957]
Labelled ligands	<a href="#">[<sup>123</sup>I]iodoproxyfan</a> (Antagonist) (pK <sub>d</sub> 10.2) [1516], <a href="#">[<sup>125</sup>I]iodophenpropit</a> (Antagonist) (pK <sub>d</sub> 9.2) [1148] – Rat, <a href="#">[<sup>3</sup>H](R)-α-methylhistamine</a> (Agonist) [1542], <a href="#">N-[<sup>3</sup>H]α-methylhistamine</a> (Agonist) [402] – Mouse	<a href="#">[<sup>3</sup>H]JNJ 7777120</a> (Antagonist) (pK <sub>d</sub> 8.4) [2579]

**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 [1542, 1849, 1889, 1926, 2957]. Moreover, [4-methylhistamine](#) is identified as a high affinity, full agonist for

the human H<sub>4</sub> receptor [1519]. [<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

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 Nieto-Alamilla G *et al.* (2016) The Histamine H<sub>3</sub> Receptor: Structure, Pharmacology, and Function. *Mol Pharmacol* **90**: 649-673 [PMID:27563055]

Panula P *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCVIII. Histamine Receptors. *Pharmacol Rev* **67**: 601-55 [PMID:26084539]  
 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** [532, 1928]) 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** [2425, 2618, 2799]. 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 [2618, 2799].

Nomenclature	HCA <sub>1</sub> receptor	HCA <sub>2</sub> receptor	HCA <sub>3</sub> receptor
HGNC, UniProt	<a href="#">HCAR1</a> , <a href="#">Q9BXC0</a>	<a href="#">HCAR2</a> , <a href="#">Q8TDS4</a>	<a href="#">HCAR3</a> , <a href="#">P49019</a>
Potency order of endogenous ligands	–	β-D-hydroxybutyric acid > butyric acid	–
Endogenous agonists	<a href="#">L-lactic acid</a> [21, 333, 1544, 2436]	β-D-hydroxybutyric acid [2511], <a href="#">butyric acid</a>	<a href="#">3-hydroxyoctanoic acid</a> [20]
Agonists	<a href="#">compound 2</a> [2249], <a href="#">3,5-dihydroxybenzoic acid</a> [1541]	<a href="#">SCH 900271</a> [1973], <a href="#">GSK256073</a> [2445]	<a href="#">D-phenyllactic acid</a> [2031]
Selective agonists	–	<a href="#">MK 6892</a> [2359], <a href="#">MK 1903</a> [217], <a href="#">nicotinic acid</a> [2425, 2618, 2799], <a href="#">acipimox</a> [2425, 2799], <a href="#">monomethyl fumarate</a> [2540]	<a href="#">compound 6o</a> [2398], <a href="#">IBC 293</a> [2337]
Labelled ligands	–	<a href="#">[<sup>3</sup>H]nicotinic acid</a> (Agonist) [2425, 2618, 2799]	–

**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, and by D-phenyllactic acid, a metabolite of gut lactic acid bacteria [*2031*].

#### Further reading on Hydroxycarboxylic acid receptors

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Graff EC *et al.* (2016) Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. *Metab Clin Exp* **65**: 102-13 [*PMID:26773933*]

Kamanna VS *et al.* (2013) Recent advances in niacin and lipid metabolism. *Curr Opin Lipidol* **24**: 239-45 [*PMID:23619367*]

Kennedy L *et al.* (2022) Lactate receptor HCAR1 regulates neurogenesis and microglia activation after neonatal hypoxia-ischemia. *Elife* **11**: [*PMID:35942676*]

Offermanns S. (2017) Hydroxy-Carboxylic Acid Receptor Actions in Metabolism. *Trends Endocrinol Metab* **28**: 227-236 [*PMID:28087125*]

Offermanns S *et al.* (2011) International Union of Basic and Clinical Pharmacology. LXXXII: Nomenclature and Classification of Hydroxy-carboxylic Acid Receptors (GPR81, GPR109A, and GPR109B). *Pharmacol Rev* **63**: 269-90 [*PMID:21454438*]

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** [*1291*]), like neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomen-

clature) responds to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. **Kisspeptin-54** (*KISS1*, *Q15726*) (KP54, originally named metastin), **kisspeptin-13** (*KISS1*, *Q15726*) (KP13) and **kisspeptin-10** (*KISS1*) (KP10) are

biologically-active peptides cleaved from the *KISS1* (*Q15726*) gene product. Kisspeptins have roles in, for example, cancer metastasis, fertility/puberty regulation and glucose homeostasis.

Nomenclature	kisspeptin receptor
HGNC, UniProt	<i>KISS1R</i> , <i>Q969F8</i>
Endogenous agonists	kisspeptin-10 ( <i>KISS1</i> ) [ <i>1342</i> , <i>1939</i> ], kisspeptin-54 ( <i>KISS1</i> , <i>Q15726</i> ) [ <i>1342</i> , <i>1939</i> ], kisspeptin-14 ( <i>KISS1</i> , <i>Q15726</i> ) [ <i>1342</i> ], kisspeptin-13 ( <i>KISS1</i> , <i>Q15726</i> ) [ <i>1342</i> ]
Selective agonists	4-fluorobenzoyl-FGLRW-NH <sub>2</sub> [ <i>2595</i> ], [dY] <sup>1</sup> KP-10 [ <i>513</i> ] – Mouse, TAK-448 [ <i>1904</i> ]
Selective antagonists	peptide 234 [ <i>2209</i> ]
Labelled ligands	[ <sup>125</sup> I]Tyr <sup>45</sup> -kisspeptin-15 (Agonist) [ <i>1939</i> ], [ <sup>125</sup> I]kisspeptin-13 (human) (Agonist) [ <i>1702</i> ], [ <sup>125</sup> I]kisspeptin-10 (human) (Agonist) [ <i>1342</i> ], [ <sup>125</sup> I]kisspeptin-14 (human) (Agonist) [ <i>1702</i> ], [d-Tyr- <sup>14</sup> C]TAK-448 (Agonist) [ <i>1804</i> ]

**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 [*537*, *1314*].

#### Further reading on Kisspeptin receptor

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# Leukotriene receptors

G protein-coupled receptors → Leukotriene receptors

**Overview:** The leukotriene receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene Receptors [109, 110]**) 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-hydroxyheptadecatrienic 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) α [1526] and the vanilloid TRPV1 ligand-gated nonselective cation channel [1697]. The crystal structure of the BLT<sub>1</sub> receptor was initially determined in complex with selective antagonists [1051, 1723] and has recently been extended to the cryo-electron microscopy structure of LTB<sub>4</sub>-bound human BLT<sub>1</sub> receptor at 2.91 Å resolution [2731]. 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 patterns in human

tissues, mediating for example smooth muscle cell contraction, regulation of vascular permeability, and leukocyte activation. Quite recently, the the crystal structures of both receptors have been solved, the CysLT<sub>1</sub> in complex with **zafirlukast** and **pranlukast** [1575] and the CysLT<sub>2</sub> in complex with three dual CysLT<sub>1</sub>/CysLT<sub>2</sub> antagonists [904]. 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 [110]. Cysteinyl-leukotrienes have also been suggested to signal through the P2Y<sub>12</sub> receptor [730, 1911, 1990], GPR17 [461] and GPR99 [1208].

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> , Q8TD55	<i>FPR2</i> , P25090
Potency order of endogenous and other ligands	–	–	–	–	–	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 [469, 700, 702, 879, 2520]
Potency order of endogenous ligands	LTB <sub>4</sub> > 20-hydroxy-LTB <sub>4</sub> >> 12R-HETE [2892]	12-hydroxyheptadecatrienic acid > LTB <sub>4</sub> > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE > 20-hydroxy-LTB <sub>4</sub> [1949, 2892]	LTD <sub>4</sub> > LTC <sub>4</sub> > LTE <sub>4</sub> [1587, 2267]	LTC <sub>4</sub> ≥ LTD <sub>4</sub> >> LTE <sub>4</sub> [985, 1916, 2521]	5-oxo-EETE, 5-oxo-C20:3, 5-oxo-ODE > 5-oxo-15-HETE > 5S-HPETE > 5S-HETE [865, 1056, 1183, 1920, 1995, 2075, 2319]	–
Endogenous agonists	–	–	–	–	–	LXA <sub>4</sub> [1359], resolvin D1 [1359], aspirin-triggered resolvin D1 [1358], aspirin triggered lipoxin A4
Selective agonists	–	–	–	–	–	ATLa2 [895]
Endogenous antagonists	–	–	–	–	5-oxo-12-HETE (pIC <sub>50</sub> 6.3) [2074]	–
Antagonists	–	–	pranlukast (pKi 7.1–8.8) [345, 2146], pobilukast (pKi 7.1) [347]	pranlukast (pA <sub>2</sub> 7.1) [346], pobilukast (pA <sub>2</sub> 6.2) [346]	S-Y048 (pIC <sub>50</sub> 10.7) [2881]	–

Selective antagonists	<b>BIIL 260</b> (pK <sub>i</sub> 8.8) [204, 580], <b>CP105696</b> (pIC <sub>50</sub> 8.1) [2379], <b>U75302</b> (pK <sub>i</sub> 6.4) [226]	<b>LY255283</b> (pIC <sub>50</sub> 6–7.1) [1001, 2892]	<b>ICI198615</b> (pKi 9.7) [755] – Guinea pig, <b>zafirlukast</b> (zafirlukast is only about 100-fold selective for CysLT1) (pKi 8.9) [345, 2146], <b>montelukast</b> (pKi 8.6) [2146], <b>MK-571</b> (pIC <sub>50</sub> 8) [1587]	<b>BayCysLT<sub>2</sub></b> (pA <sub>2</sub> 8.4) [350], <b>BayCysLT<sub>2</sub></b> (pA <sub>2</sub> 8.3) [350], <b>HAMI3379</b> (pIC <sub>50</sub> 7.4) [2823]	–	<b>WRWWWW</b> (pIC <sub>50</sub> 6.6) [111], <b>t-Boc-FLFL</b> (pIC <sub>50</sub> 4.3–6) [734, 2454, 2714]
Labelled ligands	<b>[<sup>3</sup>H]LTB<sub>4</sub></b> (Agonist) [2891], [ <sup>3</sup> H] <b>CGS23131</b> (Antagonist) (pK <sub>d</sub> 7.9) [1130]	<b>[<sup>3</sup>H]LTB<sub>4</sub></b> (pK <sub>d</sub> 7.6–9.7)	<b>[<sup>3</sup>H]LTD<sub>4</sub></b> (Agonist), [ <sup>3</sup> H] <b>ICI-198615</b> (Antagonist) (pK <sub>d</sub> 10.6) [2219]	<b>[<sup>3</sup>H]LTD<sub>4</sub></b> (Agonist) [985]	<b>[<sup>3</sup>H]5-oxo-ETE</b> (Agonist) [1920]	<b>[<sup>3</sup>H]LXA<sub>4</sub></b> (Agonist) [700, 701]

**Comments:** The FPR2/ALX receptor (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene and Lipoxin Receptors [110]**) 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 [426] as well as **annexin I (ANXA1, P04083)** (ANXA1) and its N-terminal peptides [486, 2025]. 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 [2162]. Furthermore, FPR2/ALX has been suggested to act as a receptor mediating the proinflammatory actions of the

acute-phase reactant, serum amyloid A [2423, 2475]. FPR2/ALX has also been reported to be activated by **resolvin D1** [1875]. The agonist activity of the lipid mediators described has been questioned [940, 2059], which may derive from batch-to-batch differences, partial agonism or biased agonism. Results from Cooray *et al.* (2013) [486] have addressed this issue and the role of homodimers and heterodimers in intracellular signaling. ATL-induced conformational changes of recombinant human ALX was demonstrated using FRET analysis [788]; ATL gives a bell-shaped concentration-response relationship, inducing maximal conformational changes of ALX at 0.1–1 nM. In addition, the crystal structure of ALX was reported at 2.8 Å resolution [409]. A receptor selective for **LXB<sub>4</sub>** has been suggested from functional

studies [74, 1603, 2203]. 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 Leukotriene receptors [281]**) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with **5-oxo-ETE** the most potent agonist identified for this receptor. Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as **docosahexaenoic acid** and **EPA**, acted as receptor antagonists [1056].

### Further reading on Leukotriene receptors

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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 [532, 1264, 1757, 2863]**) are activated by the endogenous phospholipid LPA. The first receptor, LPA<sub>1</sub>, was identified as *ventricular zone gene-1* (*vzg-1*) [981]. This discovery represented the beginning of the de-orphanisation of members of the endothelial differentiation

gene (*edg*) family, as other LPA and sphingosine 1-phosphate (S1P) receptors were found. Five additional LPA receptors (LPA<sub>2,3,4,5,6</sub>) have since been identified [1757] and their gene nomenclature codified for human *LPAR1*, *LPAR2*, *etc.* (HUGO Gene Nomenclature Committee, HGNC) and *Lpar1*, *Lpar2*, *etc.* for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function of their corresponding proteins.

The crystal structure of LPA<sub>1</sub> [29, 445, 1551] and LPA<sub>6</sub> [2548] are solved and indicate that LPA accesses the extracellular binding pocket, consistent with its proposed delivery via autotaxin [445]. These studies have also implicated cross-talk with endocannabinoids *via* phosphorylated intermediates that can also activate these receptors. The binding affinities to LPA<sub>1</sub> of unlabeled, natural LPA and anandamide phosphate (AEA<sub>p</sub>) were measured

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Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16177/full>

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using backscattering interferometry ( $pK_d = 9$ ) [1758, 2150]. Utilization of this method indicated affinities that were 77-fold lower than when measured using radioactivity-based protocols [2862]. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. Multiple groups have independently published validation

of all six LPA receptors described in these tables, and further validation was achieved using a distinct read-out via a novel  $TGF\alpha$  "shedding" assay [1108]. LPA has been proposed to be a ligand for GPR35 [1941], supported by a study revealing that LPA modulates macrophage function through GPR35 [1234]. However chemokine (C-X-C motif) ligand 17 (CXCL17 (CXCL17,

Q6UXB2)) is reported to be a ligand for GPR35/CXCR8 [1646]. Moreover, LPA has also been described as an agonist for the transient receptor potential (Trp) ion channels TRPV1 [1896] and TRPA1 [1303]. 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	<i>LPAR1</i> , Q92633	<i>LPAR2</i> , Q9HBW0	<i>LPAR3</i> , Q9UBY5	<i>LPAR4</i> , Q99677	<i>LPAR5</i> , Q9H1C0	<i>LPAR6</i> , P43657
Agonists	UCM-05194 [844]	–	–	–	–	–
Selective agonists	–	dodecylphosphate [2689], decyl dihydrogen phosphate [2689], GRI977143 [1296]	OMPT [956]	–	–	–
Antagonists	Ki16425 (pIC <sub>50</sub> 6.6–6.9) [1937] – Mouse, VPC12249 (pKi 5.2–6.9) [987] – Mouse, VPC32179 [980]	–	VPC12249 (pKi 6.4) [987], VPC32179 [980]	–	compound 66 (pIC <sub>50</sub> 7.5) [2919], compound 65 (pIC <sub>50</sub> 7.2) [2919]	–
Sub/family-selective antagonists	–	–	Ki16425 (pKi 6.4) [1937]	–	–	–
Selective antagonists	BMS-986020 (pIC <sub>50</sub> 8.9), AM966 (pIC <sub>50</sub> 6.7–7.8) [2502], ONO-7300243 (pIC <sub>50</sub> 6.8) [2555], AM095 (pIC <sub>50</sub> 6–6.1) [2502]	H2L5186303 (pIC <sub>50</sub> 8.1) [686, 687], UCM-14216 (pIC <sub>50</sub> 5.7) [1258]	dioctanoylglycerol pyrophosphate (pKi 5.5–7) [704, 1937]	–	AS2717638 (pIC <sub>50</sub> 7.4) [1830], TCLPA5 (pIC <sub>50</sub> 6.1) [1350]	–

**Comments:** Ki16425 [1937], VPC12249 [987] and VPC32179 [980] 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 [2909], fetal hypoxia [999], lung fibrosis [1932], systemic sclero-

sis [1932] and atherosclerosis progression [1360]. LPA<sub>2</sub> selective antagonist SAR100842 [1448], and LPA<sub>1</sub> selective agonist UCM-05194 [844], are proposed for therapy of systemic sclerosis and neuropathic pain, respectively. The LPA<sub>2</sub> selective agonist, GRI977143, shows efficacy in an animal model of multiple

sclerosis [2301]. The LPA<sub>5</sub> selective antagonist, AS2717638, is effective in pain models [1233]. Antidepressants, amitriptyline, clomipramine, and mianserin, are reported to show profibrotic responses *via* LPA<sub>1</sub> [1951].

#### Further reading on Lysophospholipid (LPA) receptors

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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 [1264]**) are activated by the endogenous lipid **sphingosine 1-phosphate** (S1P). Originally cloned as orphan members of the endothelial differentiation gene (*edg*) family [208, 1757], the receptors are currently designated as S1P<sub>1</sub>R through S1P<sub>5</sub>R [208, 1026, 1757]. Their gene nomenclature has been codified as human *S1PR1*, *S1PR2*, *etc.* (HUGO Gene Nomenclature Committee, HGNC) and *S1pr1*, *S1pr2*, *etc.* for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function. All S1P receptors (S1PRs) have been knocked-out in mice constitutively and in some cases, conditionally.

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 [210, 758]. 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 systems, targeted deletion of the different S1PRs, and most recently, mouse models that report *in vivo* S1P<sub>1</sub>R activation [1334, 1335]. The structures of S1P<sub>1</sub> [941, 1551, 2847, 2903], S1P<sub>2</sub> [399], S1P<sub>3</sub> [1610, 2939], and S1P<sub>5</sub> [1586, 2906] are solved, and confirmed aspects of ligand binding, specificity, and receptor activation, determined previously through biochemical and genetic studies [209, 941]. **Fingolimod** (FTY720), the first FDA-approved drug to target any of the lysophospholipid receptors,

binds as a phosphorylated metabolite to four of the five S1PRs, and was the first oral therapy for multiple sclerosis (MS) [457]. Second-generation S1PR modulators **siponimod**, **ozanimod**, and **ponesimod** that target S1P<sub>1</sub> and S1P<sub>5</sub> are also FDA approved for the treatment of various MS forms [208, 1757]. In 2021, ozanimod became the first S1PR modulator to be FDA approved for the treatment of ulcerative colitis [2258]. The mechanisms of action of fingolimod and other S1PR-modulating drugs now 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 [474, 882, 883, 2087].

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> , O9S136	<i>S1PR3</i> , Q99500	<i>S1PR4</i> , O9S977	<i>S1PR5</i> , Q9H228
Potency order of endogenous ligands	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [58, 1943]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [58, 1943]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [1943]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [2652]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [1104]
Agonists	fingolimod-phosphate [282, 716], siponimod [827, 1977], BMS-986166 (Partial agonist) [822], BMS-986104 derivative 12 (Biased agonist) [821], BMS-986104 derivative 24 (Biased agonist) [821], etrasimod [325], SAR247799 (Biased agonist) [2062], ST-2191 [2455], ST-1478 [1106], ST-1505 [1106]	S1P d20:1 (Partial agonist) [2700]	fingolimod-phosphate [282, 716], fingolimod-phosphate [282, 716]	fingolimod-phosphate [282, 716, 1978, 2263, 2851], etrasimod [324, 325]	fingolimod-phosphate [282, 716, 1978], siponimod [783, 807, 2639], etrasimod [325]
Selective agonists	RP-001 [331], cenerimod [2043], CYM5442 [843], ponesimod [228], SEW2871 [2263] – Mouse	–	CYM-5541 [1174]	CYM-50308 [2640], SLB736 [1049]	A-971432 [575, 1031]
Antagonists	VPC23019 (pKi 7.9) [538], VPC03090-P (pKi 7.6–7.7) [1248], VPC44116 (pIC <sub>50</sub> 7.6) [717]	–	VPC44116 (pKi 6.5) [717], VPC23019 (pKi 5.9) [538]	–	–
Selective antagonists	NIBR-0213 (pIC <sub>50</sub> 8.6) [2112], W146 (pKi 7.1) [2264]	JTE-013 (pIC <sub>50</sub> 7.8) [1960]	TY-52156 (pKi 7) [1831]	CYM-50358 (pIC <sub>50</sub> 7.6) [371, 890]	compound 15 (pIC <sub>50</sub> 10) [1589]

**Comments:** The FDA-approved immunomodulator  **fingolimod** (FTY720) is phosphorylated *in vivo* [37] 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 [282, 1634]. Many of the physiological consequences of  **fingolimod**-

**phosphate** administration, 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> [208, 1958]. 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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## 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 [712]**) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRQCWQV; 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	<b>MCHR1</b> , Q99705	<b>MCHR2</b> , Q969V1
Selective antagonists	GW803430 (pIC <sub>50</sub> 9.3) [1002], SNAP-7941 (pA <sub>2</sub> 9.2) [245], T-226296 (pIC <sub>50</sub> 8.3) [2530], ATC0175 (pIC <sub>50</sub> 7.9–8.1) [377]	–
Labelled ligands	[ <sup>125</sup> I]S36057 (Antagonist) (pK <sub>d</sub> 9.2–9.5) [91], [ <sup>125</sup> I][Phe <sup>13</sup> ,Tyr <sup>19</sup> ]MCH (Agonist) [318], [ <sup>3</sup> H]MCH (human, mouse, rat) (Agonist) [318]	–

**Comments:** The MCH<sub>2</sub> receptor appears to be a non-functional pseudogene in rodents [2536].

#### Further reading on Melanin-concentrating hormone receptors

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## Melanocortin receptors

G protein-coupled receptors → Melanocortin receptors

**Overview:** Melanocortin receptors (**provisional nomenclature as recommended by NC-IUPHAR [712]**) 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. **Setmelanotide** was approved by the US FDA for weight management in patients with POMC, PCSK1 or LEPR deficiency,

**bremelanotide** was approved by the US FDA for generalized hypoactive sexual desire disorder in premenopausal women, and NDP-MSH (**afamelanotide**) was approved by the EMA for the treatment of erythropoietic protoporphyria. Several synthetic melanocortin receptor agonists are under clinical development.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16177/full>

Melanin-concentrating hormone receptors S93

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	MC1R, Q01726	MC2R, Q01718	MC3R, P41968	MC4R, P32245	MC5R, P33032
Potency order of endogenous agonists	α-MSH (POMC, P01189) > β-MSH (POMC, P01189) > ACTH (POMC, P01189), γ-MSH (POMC, P01189)	ACTH (POMC, P01189)	γ-MSH (POMC, P01189), β-MSH (POMC, P01189) > ACTH (POMC, P01189), α-MSH (POMC, P01189)	β-MSH (POMC, P01189) > α-MSH (POMC, P01189), ACTH (POMC, P01189) > γ-MSH (POMC, P01189)	α-MSH (POMC, P01189) > β-MSH (POMC, P01189) > ACTH (POMC, P01189) > γ-MSH (POMC, P01189)
Selective agonists	–	corticotropin zinc hydroxide	[D-Trp <sup>8</sup> ]γ-MSH [874]	THIQ [2328], setmelanotide [468, 1380]	–
Antagonists	–	–	PG-106 (pIC <sub>50</sub> 6.7) [875]	–	–
Selective antagonists	–	–	–	MBP10 (pIC <sub>50</sub> 10) [159], HS014 (pKi 8.5) [2296]	–
Labelled ligands	[ <sup>125</sup> I]NDP-MSH (Agonist) [1338]	[ <sup>125</sup> I]ACTH-(1-24) (Agonist)	[ <sup>125</sup> I]NDP-MSH (Agonist) [1338], [ <sup>125</sup> I]SHU9119 (Antagonist) [1891]	[ <sup>125</sup> I]SHU9119 (Antagonist) (pK <sub>d</sub> 9.2) [1891], [ <sup>125</sup> I]NDP-MSH (Agonist) [1338, 2295]	[ <sup>125</sup> I]NDP-MSH (Agonist) [1338]

**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 [376, 681].

#### Further reading on Melanocortin receptors

Caruso V *et al.* (2014) Synaptic changes induced by melanocortin signalling. *Nat Rev Neurosci* **15**: 98-110 [PMID:24588018]

Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]

Renquist BJ *et al.* (2011) Physiological roles of the melanocortin MC<sub>3</sub> receptor. *Eur J Pharmacol* **660**: 13-20 [PMID:21211527]

## Melatonin receptors

G protein-coupled receptors → Melatonin receptors

**Overview:** Melatonin receptors (nomenclature as agreed by the **NC-IUPHAR Subcommittee on Melatonin Receptors** [618]) are activated by the endogenous ligands melatonin and clinically used drugs like ramelteon, agomelatine and tasimelteon.

Nomenclature	MT <sub>1</sub> receptor	MT <sub>2</sub> receptor
HGNC, UniProt	MTNR1A, P48039	MTNR1B, P49286
Endogenous agonists	melatonin [92, 617, 619]	melatonin [92, 617, 619]
Agonists	ramelteon [1224], agomelatine [92, 181], tasimelteon [2123, 2663]	agomelatine [92, 181], tasimelteon [2123, 2663], ramelteon [1224, 2148]
Selective agonists	–	UCM1014 [2437], IIK7 [682, 2480], 5-methoxy-luzindole (Partial agonist) [619]
Selective antagonists	–	4P-PDOT (pK <sub>i</sub> 8.8–9.4) [92, 619, 620], K185 (pK <sub>i</sub> 9.3) [682, 2480], DH97 (pK <sub>i</sub> 8) [2554]
Labelled ligands	[ <sup>125</sup> I]SD6 (Agonist) [1463], 2-[ <sup>125</sup> I]melatonin (Agonist) [92, 619], [ <sup>3</sup> H]melatonin (Agonist) [300]	[ <sup>125</sup> I]SD6 (Agonist) [1463], 2-[ <sup>125</sup> I]melatonin (Agonist) [92, 619], [ <sup>125</sup> I]DIV880 (Agonist, Partial agonist) [1463], [ <sup>3</sup> H]melatonin (Agonist) [300]



**Comments:** Melatonin, 2-iodo-melatonin, agomelatine, GR 196429, LY 156735 and ramelteon [1224] 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) [2586]. 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 [620]. MT<sub>1</sub>/MT<sub>2</sub> heterodimers present different pharmacological profiles from MT<sub>1</sub> and MT<sub>2</sub> receptors [101]. 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 [1765]. Pharmacological investigations of MT<sub>3</sub> binding sites have primarily been conducted in hamster tissues. At this site, The endogenous ligand N-acetylserotonin [640, 1573, 1765, 2063] and 5MCA-NAT [2063] appear to function as agonists, while prazosin [1573] 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 [1913, 1914]). 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 [1081]. *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 [623] although melatonin does not bind to GPR50 receptors. Several variants of the *MTNR1B* gene have been associated with increased type 2 diabetes risk [1217].

### Further reading on Melatonin receptors

- Boutin JA *et al.* (2020) Melatonin receptor ligands: A pharmaco-chemical perspective. *J Pineal Res* **69**: e12672 [PMID:32531076]  
 Ceccon E *et al.* (2018) Melatonin receptors: molecular pharmacology and signalling in the context of system bias. *Br J Pharmacol* **175**: 3263-3280 [PMID:28707298]  
 Dubocovich ML *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacol Rev* **62**: 343-80 [PMID:20605968]

- Jockers R *et al.* (2016) Update on melatonin receptors: IUPHAR Review 20. *Br J Pharmacol* **173**: 2702-25 [PMID:27314810]  
 Karamitri A *et al.* (2019) Melatonin in type 2 diabetes mellitus and obesity. *Nat Rev Endocrinol* **15**: 105-125 [PMID:30531911]  
 Liu J *et al.* (2016) MT1 and MT2 Melatonin Receptors: A Therapeutic Perspective. *Annu Rev Pharmacol Toxicol* **56**: 361-83 [PMID:26514204]

## 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** [2302]) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate [872]. The mGlu family is composed of eight members (named mGlu<sub>1</sub> to mGlu<sub>8</sub>) 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>2</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. mGlu form constitutive dimers, cross-linked by a disulfide bridge. 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 [1383, 1776, 1838, 2614]. The structure of the 7

transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organisation similar to that of other GPCRs, although the helices appear more compacted [450, 605, 2817]. Recent advances in cryo-electron microscopy have provided structures of full-length mGlu receptor homodimers [1317, 1527] and heterodimers [615]. Studies have revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [609]. First characterised in transfected cells, co-localisation and specific pharmacological properties suggest the existence of such heterodimers in the brain [907, 1528, 1709, 1790, 1907, 2890]. Beyond heteromerisation with other mGlu receptor subtypes, increasing evidence suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs (reviewed in [872]).

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 activated by 3,5-DHPG and (S)-3HPG [261] and antagonised by (S)-hexylhomoiibotic acid [1606]. Group-II mGlu receptors may be activated by LY389795 [1777], LY379268 [1777], eglumegad [2303, 2821], DCG-IV and (2R,3R)-APDC [2304], and antagonised by eGlu [1147] and LY307452 [664, 2768]. Group-III mGlu receptors may be activated by L-AP4 and (R,S)-4-PPG [778]. 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 [1287]. 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	<b>mGlu<sub>1</sub> receptor</b>	<b>mGlu<sub>2</sub> receptor</b>	<b>mGlu<sub>3</sub> receptor</b>	<b>mGlu<sub>4</sub> receptor</b>	<b>mGlu<sub>5</sub> receptor</b>
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 [2049]	L-glutamic acid [2049]	L-glutamic acid [2049], NAAG [2316]	L-serine-O-phosphate [2821], L-glutamic acid [2049]	L-glutamic acid [2049]
Agonists	–	–	–	L-AP4 [2821]	–
Selective agonists	–	–	–	LSP4-2022 [856]	(S)-(+)-CBPG (Partial agonist) [1638] – Rat, CHPG [1837]
Antagonists	LY367385 (pIC <sub>50</sub> 5.1) [467]	–	–	MAP4 (pKi 4.6) [928] – Rat	–
Selective antagonists	3-MATIDA (pIC <sub>50</sub> 5.2) [1808] – Rat, (S)-(+)-CBPG (pIC <sub>50</sub> 4.2) [1638] – Rat, (S)-TBPG (pIC <sub>50</sub> 4.2) [489] – Rat, AIDA (pA <sub>2</sub> 4.2) [1809]	PCCG-4 (pIC <sub>50</sub> 5.1) [2012] – Rat	–	–	ACDPP (pIC <sub>50</sub> 6.9) [240]
Allosteric modulators (Positive)	–	CBiPES (pEC <sub>50</sub> 7) [1180], 4-MPPTS (pIC <sub>50</sub> 5.8) [131, 1179, 1180, 2288]	–	SIB-1893 (obtained in the presence of L-AP4) (pEC <sub>50</sub> 6.3–6.8) [1669], MPEP (obtained in the presence of L-AP4) (pEC <sub>50</sub> 6.3–6.6) [1669], PHCCC (obtained in the presence of L-AP4) (pEC <sub>50</sub> 4.5) [1621]	CDPPB (pEC <sub>50</sub> 7.6–8) [1289, 1532]
Allosteric modulators (Negative)	–	–	MNI-137 (pIC <sub>50</sub> 7.7) [993] – Rat, VU0650786 (pIC <sub>50</sub> 6.4) [654]	–	alloswitch-1 (pIC <sub>50</sub> 8.1) [2057] – Rat, MTEP (pK <sub>i</sub> 7.8) [292], MPEP (pIC <sub>50</sub> 7.4–7.7) [777, 779], fenobam (pIC <sub>50</sub> 7.2) [2069]
Selective allosteric modulators	BAY 367620 (Negative) (pK <sub>i</sub> 9.5) [354] – Rat, JNJ16259685 (Negative) (pIC <sub>50</sub> 8.9) [1422], Ro01-6128 (Positive) (pK <sub>i</sub> 7.5–7.7) [1312] – Rat, LY456236 (Negative) (pIC <sub>50</sub> 6.9) [437], CPCCOEt (Negative) (pIC <sub>50</sub> 5.2–5.8) [1535]	Ro64-5229 (Negative) (pIC <sub>50</sub> 7) [1330] – Rat, biphenylindanone A (Positive) (pEC <sub>50</sub> 7) [241]	ML337 (Negative) (pIC <sub>50</sub> 6.2) [2765] – Rat	VU0361737 (Positive) (pEC <sub>50</sub> 6.6) [653], VU0155041 (Positive) (pEC <sub>50</sub> 6.1) [1906]	VU0409551 (Positive) (pK <sub>B</sub> 7.1) [2205], VU0360172 (Positive) (pK <sub>B</sub> 6.6–7) [873, 2196]

Nomenclature	<b>mGlu<sub>6</sub> receptor</b>	<b>mGlu<sub>7</sub> receptor</b>	<b>mGlu<sub>8</sub> receptor</b>
HGNC, UniProt	<i>GRM6</i> , O15303	<i>GRM7</i> , Q14831	<i>GRM8</i> , O00222
Endogenous agonists	L-glutamic acid [2049]	L-glutamic acid [2049]	L-serine-O-phosphate [1626, 2821], L-glutamic acid [2049]
Agonists	–	LSP4-2022 [856], L-serine-O-phosphate [2821], L-AP4 [2821]	(S)-3,4-DCPG [2572], L-AP4 [1626]
Selective agonists	1-benzyl-APDC [2617] – Rat, homo-AMPA [270]	–	–
Antagonists	MAP4 (pIC <sub>50</sub> 3.5) [2046] – Rat, THPG [2577]	–	MPPG (pIC <sub>50</sub> 4.3) [2821]
Allosteric modulators (Positive)	–	AMN082 (pEC <sub>50</sub> 6.5–6.8) [1752]	VU0422288 (pK <sub>B</sub> 6.7) [1146], VU0155094 (pK <sub>B</sub> 5) [1146]
Allosteric modulators (Negative)	–	MMPIP (pIC <sub>50</sub> 6.1–7.6) [1905, 2497] – Rat, ADX71743 (pIC <sub>50</sub> 7.2) [1203], XAP044 (pIC <sub>50</sub> 5.6) [789]	–

**Comments:** The activity of NAAG as an agonist at mGlu<sub>3</sub> receptors was questioned on the basis of contamination with glutamate [441, 736], but this has been refuted [1864]. Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [<sup>3</sup>H]R214127 [1421] and [<sup>3</sup>H]YM298198 [1322] at mGlu<sub>1</sub> receptors and [<sup>3</sup>H]M-MPEP [777] and [<sup>3</sup>H]methoxymethyl-MTEP [60] 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 [1178, 2316]). 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

#### Further reading on Metabotropic glutamate receptors

Ferraguti F *et al.* (2006) Metabotropic glutamate receptors. *Cell Tissue Res* **326**: 483-504 [PMID:16847639]

Gregory KJ *et al.* (2021) International Union of Basic and Clinical Pharmacology. CXI. Pharmacology, Signaling, and Physiology of Metabotropic Glutamate Receptors. *Pharmacol Rev* **73**: 521-569 [PMID:33361406]

Nicoletti F *et al.* (2011) Metabotropic glutamate receptors: from the workbench to the bedside. *Neuropharmacology* **60**: 1017-41 [PMID:21036182]

receptors and may have unappreciated biased or neutral activity at other subtypes [992]. 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 [2644], 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

phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomobotenic acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but is resistant to LY341495 [458]. 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 [1305, 2010]

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.

Niswender CM *et al.* (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* **50**: 295-322 [PMID:20055706]

Pin JP *et al.* (2016) Organization and functions of mGlu and GABAB receptor complexes. *Nature* **540**: 60-68 [PMID:27905440]

Rondard P *et al.* (2011) The complexity of their activation mechanism opens new possibilities for the modulation of mGlu and GABAB class C G protein-coupled receptors. *Neuropharmacology* **60**: 82-92 [PMID:20713070]

## 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). There are significant species differences in the structure of motilin and its receptor, and in the functions of motilin. In humans and large mammals such as dog, activation of these receptors by motilin

released from endocrine cells in the duodenal mucosa during fasting, induces propulsive phase III movements. This activity is associated with promoting hunger in humans. In humans and other mammals drugs and other non-peptide compounds which activate the motilin receptor may generate a more long-lasting ability to increase cholinergic activity within the upper gut, to promote upper gastrointestinal motility; this activity is suggest-

ed to be responsible for the gastrointestinal prokinetic effects of certain macrolide antibacterials (often called motilides; *e.g.* erythromycin, azithromycin), although for many of these molecules the evidence is sparse. Relatively high doses may induce vomiting and in humans, nausea.

Nomenclature	motilin receptor
HGNC, UniProt	<i>MLNR</i> , O43193
Endogenous agonists	motilin ( <i>MLN</i> , P12872) [494, 1674, 1675, 1676]
Agonists	alemcinal [2566], erythromycin [683, 2566], azithromycin [286]
Selective agonists	camicinal [139, 2262], mitemcinal [1319, 2519] – Rabbit
Selective antagonists	MA-2029 (pA <sub>2</sub> 9.2) [2476], GM-109 (pIC <sub>50</sub> 8) [945] – Rabbit
Labelled ligands	[ <sup>125</sup> I]motilin (human) (Agonist) [683]

**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 human ghrelin receptor and 86% in the transmembrane regions [975, 2519, 2566]. However, differences between the N-terminus regions of these receptors means that their cognate peptide ligands do not readily activate each other [525, 2262]. Where studied the motilin receptor does not appear to have constitutive activity [1042]. Although not proven, the existence of biased agonism at the receptor has been suggested [1676, 1750, 2259]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [5]. Receptor dimerisation has not been reported. It must be noted that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other actions are possible (*e.g.* P2X inhibition by erythromycin; [2940]). Small molecule and selective motilin receptor agonists are now described [1495, 2262, 2773]. Significant species-dependent variations exist. Among mammals, the gene encoding the moti-

lin precursor is absent in laboratory rodents, while the receptor appears to be a pseudogene [975, 2260]. Functions of motilin are not usually detected in rodents, although brain and other responses to motilin and macrolides continue to be reported and the mechanism of these actions is obscure. In some non-laboratory rodents (*e.g.* North American kangaroo rat (*Dipodomys*) and mouse (*Microdipodops*) a functional form of motilin may exist but the motilin receptor is non-functional [1495]. Marked differences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [2261]. Among birds, chicken (*Gallus gallus domesticus*) motilin differs from human motilin at positions 4, 7-10, and 12, and contracts avian upper gastrointestinal tissues more potently than human motilin; in rabbit duodenum, the reverse is apparent [1299]. Chicken motilin receptor has 59% sequence homology with the human motilin receptor [2850]. In chicken, motilin does not mediate phase III activity of the gastric MMC but initiates rhythmic oscillating complexes in the small intestine [2197]. Responsiveness to motilin in the ileum is highest

in avian gastrointestinal tract. Among reptiles, caiman/alligator motilin is similar to avian motilin, but markedly different forms of motilin exist in turtles, anole/lizard and snake. Their activities have not been examined in reptiles. Among amphibians, a motilin-like peptide has been identified in newts but not in frogs, with a structure differing from mammalian motilin. There may be some diversity among the anuran, urodelal and gymno-phional species. Although endogenous motilin is not present in frogs, human motilin caused contraction of the upper gastrointestinal tract [2932]. However, newt but not human motilin caused strong contraction of the stomach of Japanese fire belly newts [2931]. Among teleost fish, sequences for motilin peptide and motilin receptor have been identified (zebrafish, ballan wrasse, spotted sea bass) but the motilin peptides are short and the structure of motilin receptor differs from that of mammals. Zebrafish motilin activates its cognate motilin receptor but fails to cause contraction of gastrointestinal strips *in vitro*, perhaps because of low expression of the motilin receptor [1300].

#### Further reading on Motilin receptor

Kitazawa T *et al.* (2021) Motilin Comparative Study: Structure, Distribution, Receptors, and Gastrointestinal Motility. *Front Endocrinol (Lausanne)* **12**: 700884 [PMID:34497583]  
Sanger GJ *et al.* (2016) Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* **13**: 38-48 [PMID:26392067]

Singaram K *et al.* (2020) Motilin: a panoply of communications between the gut, brain, and pancreas. *Expert Rev Gastroenterol Hepatol* **14**: 103-111 [PMID:31996050]

## Neuromedin U receptors

G protein-coupled receptors → Neuromedin U receptors

**Overview:** Neuromedin U receptors (**provisional nomenclature as recommended by NC-IUPHAR** [712]) 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 [1745]. In humans, NmU-25 appears to be the sole product of a precursor gene (**NMU, P48645**) showing a broad tissue distribution, but which is ex-

pressed at highest levels in the upper gastrointestinal tract, CNS, bone marrow and fetal liver. Much shorter versions of NmU are found in some species, but not in human, and are derived at least in some instances from the proteolytic cleavage of the longer NmU. Despite species differences in NmU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity. Neuromedin

S (**neuromedin S-33 (NMS, Q5H8A3)**) has also been identified as an endogenous agonist [1797]. 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
Agonists	CPN-223 (Partial agonist) [2524]	–
Selective agonists	–	CPN-219 [2526], CPN-116 [2525]

Antagonists	–	R-PSOP (pK <sub>B</sub> 7) [1548]
Comments	CPN-267 is a selective hexapeptidic NMU1 agonist, but the sequence is obscure.	–

**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> [280, 1058, 1069]. NMU1 and NMU2 can be labelled with [<sup>125</sup>I]-NmU and [<sup>125</sup>I]-NmS (of various species, *e.g.* [1710]), BODIPY® TMR-NMU or Cy3B-NMU-8 [280]. 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]  
 Budhiraja S *et al.* (2009) Neuromedin U: physiology, pharmacology and therapeutic potential. *Fundam Clin Pharmacol* **23**: 149-57 [PMID:19645813]

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 [712]**), 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	<i>NPFFR1, Q9GZQ6</i>	<i>NPFFR2, Q9Y5X5</i>
Potency order of endogenous ligands	RFRP-1 ( <i>NPVF, Q9HCQ7</i> ) > RFRP-3 ( <i>NPVF, Q9HCQ7</i> ) > <i>FMRF</i> neuropeptide FF ( <i>NPFF, O15130</i> ) > neuropeptide AF ( <i>NPFF, O15130</i> ) > neuropeptide SF ( <i>NPFF, O15130, QRFP43 (43RFa) (QRFP, P83859), PrRP-31 (PRLH, P81277) [853]</i> )	neuropeptide AF ( <i>NPFF, O15130</i> ), neuropeptide FF ( <i>NPFF, O15130</i> ) > PrRP-31 ( <i>PRLH, P81277</i> ) > <i>FMRF, QRFP43 (43RFa) (QRFP, P83859)</i> > neuropeptide SF ( <i>NPFF, O15130</i> ) [853]
Endogenous agonists	neuropeptide FF ( <i>NPFF, O15130</i> ) [853, 854, 1768], RFRP-3 ( <i>NPVF, Q9HCQ7</i> ) [854, 855, 1768]	neuropeptide FF ( <i>NPFF, O15130</i> ) [854, 1767]
Selective agonists	–	dNPA [2217], AC263093 [1402]
Antagonists	RF9 (pK <sub>i</sub> 7.2) [2390]	–
Selective antagonists	AC262620 (pK <sub>i</sub> 7.7–8.1) [1402], AC262970 (pK <sub>i</sub> 7.4–8.1) [1402]	–
Labelled ligands	[ <sup>125</sup> I]Y-RFRP-3 (Agonist) [854], [ <sup>3</sup> H]NPVF (Agonist) [2532], [ <sup>125</sup> I]NPFF (Agonist) [853]	[ <sup>125</sup> I]EYF (Agonist) [1768], [ <sup>3</sup> H]EYF (Agonist) [2532], [ <sup>125</sup> I]NPFF (Agonist) [853]

**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, [537, 2390]).

**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]  
 Nguyen T *et al.* (2020) Neuropeptide FF and Its Receptors: Therapeutic Applications and Ligand Development. *J Med Chem* **63**: 12387-12402 [PMID:32673481]

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 receptor) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (NPS, POCOP6). NPS activates its receptor at low nanomolar concentrations elevating intracellular cAMP and calcium levels [2161]. Currently, some peptidic and small molecule NPS receptor antagonists are available as research tools [339, 894, 1944, 2233]. No NPS receptor ligands are currently used clinically.

Nomenclature	NPS receptor
HGNC, UniProt	NPSR1, Q6W5P4
Endogenous agonists	neuropeptide S (NPS, POCOP6) [2846]
Selective agonists	PWT1-NPS [2234] – Mouse
Selective antagonists	SHA 68 (pA <sub>2</sub> 8.1) [2235] – Mouse, [ <sup>3</sup> H]-Bu-D-Gly <sup>5</sup> ]NPS (pA <sub>2</sub> 7.1) [894] – Mouse
Labelled ligands	[ <sup>125</sup> I]Tyr <sup>10</sup> NPS (human) (Agonist) [2846]

**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 (Ile107Asn, rs324981). The human NPS receptor Ile107Asn displayed similar binding affinity but higher NPS potency (by approx. 10-fold) than human NPS

receptor Asn107 [2161]. Several epidemiological studies reported an association between the Ile107Asn receptor variant and susceptibility to panic disorders [596, 600, 1945, 2120]. The SNP Ile107Asn (rs324981) has also been linked to sleep behavior [852], inflammatory bowel disease [514], schizophrenia [1473], increased impulsivity and ADHD symptoms [1392]. Interest-

ingly, a carboxy-terminal splice variant of human NPS receptor was found to be overexpressed in asthmatic patients [1400]. Additionally, the gain-of-function variant Tyr206His has been described in a single family where it appears to dramatically reduce total sleep time [2836].

**Further reading on Neuropeptide S receptor**

Guerrini R *et al.* (2010) Neurobiology, pharmacology, and medicinal chemistry of neuropeptide S and its receptor. *Med Res Rev* **30**: 751-77 [PMID:19824051]  
 Reinscheid RK *et al.* (2021) Pharmacology, Physiology and Genetics of the Neuropeptide S System. *Pharmaceuticals (Basel)* **14**: [PMID:33922620]  
 Reinscheid RK *et al.* (2005) Pharmacological characterization of human and murine neuropeptide S receptor variants. *J Pharmacol Exp Ther* **315**: 1338-45 [PMID:16144971]

Ruzza C *et al.* (2015) Neuropeptide S reduces mouse aggressiveness in the resident/intruder test through selective activation of the neuropeptide S receptor. *Neuropharmacology* **97**: 1-6 [PMID:25979487]  
 Ruzza C *et al.* (2017) Neuropeptide S receptor ligands: a patent review (2005-2016). *Expert Opin Ther Pat* **27**: 347-362 [PMID:27788040]  
 Xu YL *et al.* (2004) Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. *Neuron* **43**: 487-97 [PMID:15312648]

## Neuropeptide W/neuropeptide B receptors

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

**Overview:** The neuropeptide BW receptor 1 (NPBW1, **provisional nomenclature [712]**) is activated by two 23-amino-acid peptides, neuropeptide W (**neuropeptide W-23 (NPW, Q8N729)**) and neuropeptide B (**neuropeptide B-23 (NPB, Q8NG41)**) [744, 2367]. C-terminally extended forms of the peptides (**neuropeptide W-30 (NPW, Q8N729)** and **neuropeptide**

**B-29 (NPB, Q8NG41)**) also activate NPBW1 [277]. 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 without 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 [277].

Nomenclature	NPBW1 receptor	NPBW2 receptor
HGNC, UniProt	NPBWR1, P48145	NPBWR2, P48146
Potency order of endogenous ligands	neuropeptide B-29 (NPB, Q8NG41) > neuropeptide B-23 (NPB, Q8NG41) > neuropeptide W-23 (NPW, Q8N729) > neuropeptide W-30 (NPW, Q8N729) [277]	neuropeptide W-23 (NPW, Q8N729) > neuropeptide W-30 (NPW, Q8N729) > neuropeptide B-29 (NPB, Q8NG41) > neuropeptide B-23 (NPB, Q8NG41) [277]
Selective agonists	Ava3 [1210], Ava5 [1210]	–
Labelled ligands	[ <sup>125</sup> I]NPW-23 (human) (Agonist) [2392]	[ <sup>125</sup> I]NPW-23 (human) (Agonist) [2367]

**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 [1843]. For a review of the contribution of neuropeptide B/W to social dominance, see Watanabe and Yamamoto, 2015 [2748]. 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 [1815]. Two antagonists

have been discovered and reported to have affinity for NPBW1, ML181 and ML250, the latter exhibiting improved selectivity (~100 fold) for NPBW1 compared to MCH1 receptors [891, 892]. Computational insights into the binding of antagonists to this receptor have also been described [2000, 2004].

### 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 as agreed by the NC-IUPHAR Subcommittee on Neuropeptide Y Receptors [1725]**) 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, [1558]). 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 [870]. Three-dimensional structures have been determined for subtype active receptors Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>4</sub> [1211, 2544] and inactive antagonist bound Y<sub>1</sub> and Y<sub>2</sub> receptors [2543, 2874]. 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 [660]. 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).

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	<a href="#">NPY1R, P25929</a>	<a href="#">NPY2R, P49146</a>	<a href="#">NPY4R, P50391</a>	<a href="#">NPY5R, Q15761</a>	<a href="#">NPY6R, Q99463</a>
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 ( <a href="#">NPY, P01303</a> ), peptide YY ( <a href="#">PYY, P10082</a> )	<a href="#">PYY(3-36) (PYY, P10082)</a> [790, 805], neuropeptide Y ( <a href="#">NPY, P01303</a> ), neuropeptide Y(3-36) ( <a href="#">NPY, P01303</a> ), peptide YY ( <a href="#">PYY, P10082</a> )	pancreatic polypeptide ( <a href="#">PPY, P01298</a> ) [129, 1578, 2604, 2858]	–	–
Agonists	[Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY [502], [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) [330]	–
Selective antagonists	<a href="#">BIBO3304</a> (pIC <sub>50</sub> 9.5) [2783], <a href="#">BIBP3226</a> (pK <sub>i</sub> 8.1–9.3) [603, 2784]	<a href="#">BIIE0246</a> (pIC <sub>50</sub> 8.5) [601], <a href="#">JNJ-5207787</a> (pIC <sub>50</sub> 6.9–7.1) [235]	–	<a href="#">L-152,804</a> (pK <sub>i</sub> 7.6) [1209]	–
Selective allosteric modulators	–	–	(S)- <a href="#">VU0637120</a> (Negative) (pIC <sub>50</sub> 5.6) [2285], <i>tert</i> -butyl-phenoxycyclohexanol (Positive) [2311]	–	–
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) [626] – 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 [804]. [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 Pro<sup>34</sup>-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**: 143-50 [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 [712]**) 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	<i>NTSR1</i> , P30989	<i>NTSR2</i> , O95665
Potency order of endogenous ligands	neurotensin ( <i>NTS</i> , P30990) > neuromedin N {Mouse, Rat} [997]	neurotensin ( <i>NTS</i> , P30990) = neuromedin N {Mouse, Rat} [1685]
Agonists	ABS-201 [439, 2946] – Mouse, ABS-212 [1084, 1494] – Rat	–
Selective agonists	JMV449 [2400] – Rat	levocabastine [1685, 2177]
Selective antagonists	meclinetant (pIC <sub>50</sub> 7.5–8.2) [897]	–
Labelled ligands	[ <sup>3</sup> H]meclinetant (Antagonist) (pK <sub>d</sub> 8.5) [1394] – Rat	–

**Comments:** Neurotensin (*NTS*, P30990) appears to be a low-efficacy agonist at the NTS<sub>2</sub> receptor [2690], while the NTS<sub>1</sub> receptor antagonist meclinetant is an agonist at NTS<sub>2</sub> receptors [2690]. 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 [1895]. It has been reported to interact with the NTS<sub>1</sub> receptor [1660] and the NTS<sub>2</sub> receptor [180], and has been implicated in hormone trafficking and/or neurotensin uptake. A splice variant of the NTS<sub>2</sub> receptor bearing 5 transmembrane

domains has been identified in mouse [250] and later in rat [2026]. The neurotensinergic system is implicated in various physiological and pathological processes related to neuropsychiatric and metabolic functions, cancer growth, food, and drug intake [1127].

## Further reading on Neurotensin receptors

Boules M *et al.* (2013) Diverse roles of neurotensin agonists in the central nervous system. *Front Endocrinol (Lausanne)* **4**: 36 [PMID:23526754]

Christou N *et al.* (2020) Neurotensin pathway in digestive cancers and clinical applications: an overview. *Cell Death Dis* **11**: 1027 [PMID:33268796]

Mazella J *et al.* (2012) Neurotensin and its receptors in the control of glucose homeostasis. *Front Endocrinol (Lausanne)* **3**: 143 [PMID:23230428]

Myers RM *et al.* (2009) Cancer, chemistry, and the cell: molecules that interact with the neurotensin receptors. *ACS Chem Biol* **4**: 503–25 [PMID:19462983]

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

Schroeder LE *et al.* (2018) Role of central neurotensin in regulating feeding: Implications for the development and treatment of body weight disorders. *Biochim Biophys Acta Mol Basis Dis* **1864**: 900–916 [PMID:29288794]

# 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), β-endorphin (*POMC*, P01189) (β-end), α-neodynorphin (*PDYN*, P01213), dynorphin A (*PDYN*, P01213) (dynA), dynorphin B

(*PDYN*, P01213) (dynB), big dynorphin (*PDYN*, P01213) (Big dyn), nociceptin/orphanin FQ (*PNOC*, Q13519) (N/OFQ); endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter nomenclature for the opioid receptors, μ, δ and κ, 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 [500, 572, 712]. However the acronyms MOR, DOR and KOR are still widely used in the literature. 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 [1770], 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**. The majority of clinically used opiates are relatively selective  $\mu$  agonists or partial agonists, though there are some  $\mu/\kappa$  compounds, such as **butorphanol**, in clinical use.  $\kappa$  opioid agonists, such as the alkaloid

**nalfurafine** and the peripherally acting peptide **difelikefalin**, are in clinical use for itch.

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 [2593], BU08028 (Partial agonist) [1259], etorphine [2593], ethylketocyclazocine [2593], cebranopadol [1534], PN6047 (Biased agonist) [481]	(-)-cyclazocine (Partial agonist) [2593], etorphine [2593], ethylketazocine [2593, 2954], cebranopadol [1534], BU08028 [1259]
Selective agonists	UFP-512 [2682], BW373U86 [1433], ADL5859 [1433], DPDPE [1814, 2593], [D-Ala <sup>2</sup> ]deltorphan II [661], ADL5747 [1434], SNC80 [335, 2118]	difelikefalin [2310], U50488 [394, 2005, 2389, 2593, 2698, 2952, 2954], enadoline [1088, 1881], U69593 [1398, 2593], salvinorin A [160, 2212]
Antagonists	UFP-505 (pK <sub>i</sub> 9.8) [582, 583], naltrexone (pK <sub>i</sub> 8) [2593], AT-076 (pK <sub>i</sub> 7.7) [2593, 2914], naloxone (pK <sub>i</sub> 7.2) [2593]	buprenorphine (pK <sub>i</sub> 9.1–10.2) [2593, 2954], nalmefene (pK <sub>i</sub> 9.5) [2593], naltrexone (pK <sub>i</sub> 8.4–9.4) [2005, 2389, 2593], AT-076 (pK <sub>i</sub> 8.9) [2593, 2915], naloxone (pK <sub>i</sub> 7.6–8.6) [2005, 2389, 2593, 2952, 2954]
Selective antagonists	naltriben (pK <sub>i</sub> 10) [2424, 2593], naltrindole (pK <sub>i</sub> 9.7) [2071, 2593], TIPPY (Inverse agonist) (pK <sub>i</sub> 9) [2293, 2593]	nor-binaltorphimine (pK <sub>i</sub> 8.9–11) [2005, 2070, 2389, 2593, 2952, 2954], 5'-guanidinonaltrindole (pK <sub>i</sub> 9.7–9.9) [1187, 2005, 2456], JDTC (pK <sub>i</sub> 9–9.4) [1829, 2571, 2915]
Labelled ligands	[ <sup>3</sup> H]naltrindole (Antagonist) (pK <sub>d</sub> 10.4) [2853] – Rat, [ <sup>3</sup> H][D-Ala <sup>2</sup> ]deltorphan I (Selective Agonist) [2452], [ <sup>3</sup> H]diprenorphine (Agonist) [65, 2593], [ <sup>3</sup> H]DPDPE (Agonist) [32], [ <sup>3</sup> H]deltorphan II (Agonist) [326], [ <sup>3</sup> H]naltriben (Antagonist) [1488]	[ <sup>3</sup> H]diprenorphine (Antagonist) (pK <sub>d</sub> 9.1) [65, 2389], [ <sup>3</sup> H]U69593 (Agonist) [1398, 2005, 2389], [ <sup>3</sup> H]enadoline (Agonist) [2391]

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)	nociceptin/orphanin FQ ( <i>PNOC</i> , Q13519) [14, 201, 1946]
Endogenous agonists	Several additional extended enkephalin peptides or truncated beta-endorphin peptides. [839]	–
Agonists	levorphanol [933], hydromorphone [2766], etorphine [2593], fentanyl [2593], cebranopadol [1534], morphine [836, 2593], buprenorphine (Partial agonist) [2593], BU08028 (Partial agonist) [1259], methadone [2073], UFP-505 [582, 583], codeine [2593], tapentadol [2622], pethidine [2073]	nociceptin/orphanin FQ ( <i>PNOC</i> , Q13519) [14, 201, 1946], cebranopadol [1534], BU08028 (Partial agonist) [1259]
Selective agonists	sufentanil [2693], DAMGO [932, 2593], loperamide [416], PL017 [385, 2593]	N/OFQ-(1-13)-NH <sub>2</sub> [201, 893, 1693, 1946], MCOPPB [973], Ac-RYYRWK-NH <sub>2</sub> (Partial agonist) [604, 1693], UFP-112 [338, 2192], SCH221510 [2674], Ro64-6198 [1156, 2781], AT-403 [73]
Antagonists	naltrexone (pK <sub>i</sub> 9.1–9.7) [1239, 2593], nalmefene (pK <sub>i</sub> 9.5) [2593], nalorphine (pK <sub>i</sub> 8.9) [2593], naloxone (pK <sub>i</sub> 8.9) [2593], AT-076 (pK <sub>i</sub> 8.8) [2593, 2915], methylnaltrexone (pK <sub>i</sub> 8.7) [2766]	AT-076 (pK <sub>i</sub> 8.8) [2915]

Selective antagonists	CTOP (pK <sub>i</sub> 9.7) [898, 2152], <b>alvimopan</b> (peripheral) (pK <sub>i</sub> 9.3) [1432], CTAP (pK <sub>i</sub> 8.6) [385, 2593]	UFP-101 (pK <sub>i</sub> 10.2) [337], LY2940094 (pK <sub>i</sub> 10) [693, 2591], <b>compound 24</b> (pK <sub>i</sub> 9.6) [705], SB 612111 (pK <sub>i</sub> 9.2–9.5) [2438, 2913], J-113397 (pIC <sub>50</sub> 8.3) [1232]
Allosteric modulators (Positive)	BMS-986121 (pK <sub>B</sub> 5.7) [316], BMS-986122 (pK <sub>B</sub> 5.3) [316]	–
Allosteric modulators (Neutral)	BMS-986123 (pK <sub>B</sub> 6) [316], BMS-986124 (pK <sub>B</sub> 5.7) [316]	–
Labelled ligands	[ <sup>3</sup> H]diprenorphine (Antagonist) (pK <sub>d</sub> 10.1) [2152] – Mouse, [ <sup>3</sup> H]DAMGO (Agonist) [2152] – Rat, [ <sup>3</sup> H]CTOP (Selective Antagonist) [2592]	[ <sup>3</sup> H]N/OFQ (Agonist) [604, 1769]

**Comments:** Three genes for naloxone-sensitive opioid receptors have been identified in humans, and while the  $\mu$  receptor in particular may be subject to extensive alternative splicing [1991], 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 [1189], 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 [1388]. 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 [2910].

### Further reading on Opioid receptors

Butelman ER *et al.* (2012)  $\kappa$ -opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. *Trends Neurosci* **35**: 587-96 [PMID:22709632]  
 Cox BM *et al.* (2015) Challenges for opioid receptor nomenclature: IUPHAR Review 9. *Br J Pharmacol* **172**: 317-23 [PMID:24528283]  
 Gillis A *et al.* (2020) Intrinsic Efficacy of Opioid Ligands and Its Importance for Apparent Bias, Operational Analysis, and Therapeutic Window. *Mol Pharmacol* **98**: 410-424 [PMID:32665252]

**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 [1927] and the identification of biased signalling by opioid receptor ligands, both agonists and antagonists [301, 1238]. Despite the identification of biased ligands for the  $\mu$  receptor, the relevance with respect to physiological and behavioral actions *in vivo* is not clear [820]. 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 [316, 317]. Negative allosteric modulation of opioid receptors has been previously suggested [1223], whether all compounds are acting at a similar site remains to be established. In the last decade, several opioid receptors structures have been solved in their inactive and active forms:  $\delta$  receptor [688, 689, 864, 2740];  $\kappa$  receptor [395, 396, 2740, 2816];  $\mu$  receptor [679, 1077, 1318, 1636, 2109, 2195, 2723, 2740, 2959]; NOP [1743, 2574, 2740]. This effort is of great importance for novel structure-based drug design studies.

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]  
 Valentino RJ *et al.* (2020) Opioid Research: Past and Future. *Mol Pharmacol* **98**: 389-391 [PMID:32660966]  
 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** [712]) 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 [2248]. Orexin signaling has been associated with regulation of sleep and wakefulness, reward and addiction, appetite and feeding, pain gating, stress response, anxiety and depression. Currently the orexin receptor ligands in clinical use are the dual orexin receptor antagonists **suvorexant** and **lemborexant** and **daridorexant**, which are used

as hypnotics, and several dual and OX<sub>2</sub>-selective antagonists are under development. Multiple orexin agonists are in development for the treatment of narcolepsy and other sleep disorders. Orexin receptor 3D structures have been solved [84, 991, 1048, 2139, 2493, 2886, 2888, 2889].

Nomenclature	$OX_1$ receptor	$OX_2$ receptor
HGNC, UniProt	<i>HCRTR1</i> , O43613	<i>HCRTR2</i> , O43614
Potency order of endogenous ligands	orexin-A ( <i>HCRT</i> , O43612) > orexin-B ( <i>HCRT</i> , O43612) (for $Ca^{2+}$ elevation, unclear/variable for other responses)	orexin-A ( <i>HCRT</i> , O43612) = orexin-B ( <i>HCRT</i> , O43612)
Agonists	RTOXA-43 [2921]	RTOXA-43
Selective agonists	–	[Ala <sup>11</sup> , D-Leu <sup>15</sup> ]orexin-B [85, 2102], danavorexton (TAK-925) [2908], Nag 26 [1113, 1841, 2184], YNT-185 [1113, 1841]
Antagonists	SB-649868 ( $pK_i$ 9.1–9.6) [336, 501, 573], daridorexant ( $pK_B$ 8.8–9.3) [2612], suvorexant ( $pK_i$ 8.7–9.3) [336, 501, 1816, 2139], filorexant ( $pK_i$ 9.2) [2139], filorexant ( $pK_i$ 8.4–9.1) [336, 501, 2798], TCS 1102 ( $pK_B$ 8–8.5) [183, 2184], almorexant ( $pK_i$ 8.3–8.5) [1625, 1628, 2612]	SB-649868 ( $pK_i$ 8.9–9.8) [336, 501], TCS 1102 ( $pK_B$ 8.8–9.7) [183, 2184], filorexant ( $pK_i$ 9.7) [2139], suvorexant ( $pK_i$ 8.9–9.5) [336, 501, 1816, 2139], almorexant ( $pK_i$ 8.6–9.4) [1624, 1625, 1628, 2612], daridorexant ( $pK_B$ 8.9–9.1) [2139, 2612], filorexant ( $pK_i$ 8.9–9.1) [336, 501, 2798]
Selective antagonists	SB-674042 (70–120-fold selective pro- $OX_1$ ) ( $pK_i$ 8.7–9.3) [1411, 1625], SB-334867 (40–150-fold selective pro- $OX_1$ ) ( $pK_i$ 7.2–7.9) [236, 1411, 1625, 2068, 2139], SB-408124 (32–65-fold selective pro- $OX_1$ ) ( $pK_i$ 7.5) [1625]	EMPA (790–3500-fold selective pro- $OX_2$ ) ( $pK_i$ 8.4–9.2) [1624, 1625, 2139], JNJ-10397049 (500–630-fold selective pro- $OX_2$ ) ( $pK_i$ 7.7–8.4) [1687]
Labelled ligands	[ <sup>3</sup> H]SB-674042 (Antagonist) ( $pK_d$ 8.3–9.1) [1411, 1625, 1628], [ <sup>3</sup> H]-almorexant (Antagonist) ( $pK_d$ 8.6–8.9) [1625, 1628], [ <sup>125</sup> I]orexin A (human, mouse, rat) (Useful working concentration sub nM–low nM.) [1371, 2101, 2248]	[ <sup>3</sup> H]-almorexant (Selective Antagonist) ( $pK_d$ 8.9–9.8) [1625, 1628], [ <sup>3</sup> H]Cp-1 (Selective Antagonist) ( $pK_d$ 9.2–9.4) [1625], [ <sup>3</sup> H]EMPA (Selective Antagonist) ( $pK_d$ 8.6–9) [1624, 1628, 1751], [ <sup>125</sup> I]orexin A (human, mouse, rat) (Useful working concentration sub nM–low nM.) [1371, 2101, 2248]

**Comments:** The primary coupling of orexin receptors to  $G_{q/11}$  proteins is rather speculative and based on the strong activation of phospholipase C, though recent studies in recombinant cells also stress the importance of  $G_{q/11}$  [1372]. Coupling of both receptors to  $G_{i/o}$ ,  $G_s$  and  $G_{12/13}$  has also been reported [1109, 1221, 1375, 1474, 2136]. 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 [1373]. Similarly, [Ala<sup>11</sup>, D-Leu<sup>15</sup>]

orexin-B, Nag 26 and YNT-185 may show variable selectivity for  $OX_2$  receptors and may also activate  $OX_1$  receptors [2102, 2184, 2849]. Thorough characterization of many antagonists and radioligands has not been published, but the situation has recently improved for many commercially available ones. Among radioligands, [<sup>3</sup>H]SB-674042, [<sup>3</sup>H]EMPA, [<sup>3</sup>H]-almorexant, [<sup>125</sup>I]orexin A (human, mouse, rat), [<sup>125</sup>I]-orexin-B and [<sup>125</sup>I][Ala<sup>11</sup>, D-Leu<sup>15</sup>] orexin-B are commercially available. [<sup>3</sup>H]-TCS 1102, [<sup>3</sup>H]Cp-1 and Rhodamine Green-orexin-A [522] are also useful labelled

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 [1374, 1860]. Antagonists of the orexin receptors are the focus of major drug discovery efforts for their potential to treat insomnia and other disorders of wakefulness [2198], while agonists would likely be useful in human narcolepsy [674, 2849].

### Further reading on Orexin receptors

Burdakov D. (2019) Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons. *Neuropharmacology* **154**: 61–67 [PMID:30347195]

Jacobson LH *et al.* (2022) Hypocretins (orexins): The ultimate translational neuropeptides. *J Intern Med* **291**: 533–556 [PMID:35043499]

James MH *et al.* (2022) Orexin Reserve: A Mechanistic Framework for the Role of Orexins (Hypocretins) in Addiction. *Biol Psychiatry* **92**: 836–844 [PMID:36328706]

Kukkonen JP *et al.* (2021) Cellular Signaling Mechanisms of Hypocretin/Orexin. *Front Neurol Neurosci* **45**: 91–102 [PMID:34052812]

Sakurai T *et al.* (2021) Interaction between Orexin Neurons and Monoaminergic Systems. *Front Neurol Neurosci* **45**: 11–21 [PMID:34052806]

# Oxoglutarate receptor

G protein-coupled receptors → Oxoglutarate receptor

**Overview: Nomenclature as recommended by NC-IUPHAR [532].**

Nomenclature	oxoglutarate receptor
HGNC, UniProt	<i>OXGR1</i> , Q96P68
Endogenous agonists	$\alpha$ -ketoglutaric acid [979, 2436]

## 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]

# P2Y receptors

G protein-coupled receptors → P2Y receptors

**Overview:** P2Y receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on P2Y Receptors [3, 4, 1133]**) are activated by the endogenous ligands **ATP**, **ADP**, **UTP**, **UDP**, **UDP-glucose** and **adenosine**. The eight mammalian P2Y receptors are activated by distinct nucleotides: P2Y<sub>1</sub>, P2Y<sub>11</sub>, P2Y<sub>12</sub> and P2Y<sub>13</sub> are activated by adenosine-nucleotides; P2Y<sub>2</sub>, P2Y<sub>4</sub> can be activated by both adenosine and uridine nucleotides, with some species-specific differences; P2Y<sub>6</sub> is mainly activated by UDP; P2Y<sub>14</sub> is preferentially activated by sugar-uracil nucleotides. The missing numbers in the receptor nomenclature refer

either to non-mammalian orthologs or receptors having some sequence homology to P2Y receptors but for which there is no functional evidence of responsiveness to nucleotides [2696]. Based on their G protein coupling P2Y receptors can be divided into two subfamilies: P2Y<sub>1</sub>, P2Y<sub>2</sub>, P2Y<sub>4</sub>, P2Y<sub>6</sub> and P2Y<sub>11</sub> receptors couple *via* Gq proteins to stimulate phospholipase C followed by increases in inositol phosphates and mobilization of Ca<sup>2+</sup> from intracellular stores. P2Y<sub>11</sub> receptors couple in addition to Gs proteins followed by increased adenylate cyclase activity. In contrast, P2Y<sub>12</sub>, P2Y<sub>13</sub>, and P2Y<sub>14</sub> receptors signal primarily through

activation of Gi proteins and inhibition of adenylate cyclase activity or control of ion channel activity [2696]. Clinically used drugs acting on these receptors include the dinucleoside polyphosphate **diquafosol**, agonist of the P2Y<sub>2</sub> receptor subtype, approved in Japan and South Korea for the management of dry eye disease [1419], and the P2Y<sub>12</sub> receptor antagonists **prasugrel**, **ticagrelor** and **cangrelor**, all approved as antiplatelet drugs [343, 2081].

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	UTP > ATP	UTP>ATP (at rat recombinant receptors), UTP = ATP)	UDP >> UTP > ADP
Endogenous agonists	ATP (Partial agonist) [2286, 2707], ADP [2286, 2707]	UTP [1273, 1429]	UTP [1246], ATP [2]	UDP [477]
Agonists	ADP $\beta$ S [2522], 2MeSADP [2286, 2707]	–	–	–
Sub/family-selective agonists	–	diquafosol [2015], denufosol [1430, 2015, 2883], UTP $\gamma$ S [1429]	diquafosol [306], denufosol [2883], UTP $\gamma$ S [1430]	–

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Oxoglutarate receptor S107

Selective agonists	MRS2365 [425], 2-Cl-ADP( $\alpha$ -BH <sub>3</sub> ) [102]	MRS2698 [1123], 2-thioUTP [643], PSB1114 (EC <sub>50</sub> value determined using an IP <sub>3</sub> functional assay) [643, 644, 1122]	MRS4062 [1662], MRS2927 [1662], (N) methanocarpa-UTP [1273]	Rp-5-OMe-UDP $\alpha$ B [824, 905], MRS2957 [1661], MRS2693 [192]
Antagonists	suramin (pK <sub>i</sub> 5.3) [2707], PPADS (pK <sub>i</sub> 5.2) [2707]	–	–	–
Sub/family-selective antagonists	–	reactive blue-2 (pIC <sub>50</sub> 6) [1149], suramin (pIC <sub>50</sub> 4.3) [1149, 2286]	PPADS (pEC <sub>50</sub> 2–5) [1135], reactive blue-2 (pIC <sub>50</sub> 4.7) [222] – Rat	reactive blue-2 (pK <sub>B</sub> 6) [2696], PPADS (pK <sub>B</sub> 4) [2696], suramin (pK <sub>B</sub> 4) [2696]
Selective antagonists	MRS2500 (pK <sub>i</sub> 8.8–9.1) [362, 1272], MRS2279 (pK <sub>i</sub> 7.9) [2707], MRS2179 (pK <sub>i</sub> 7–7.1) [260, 2707]	AR-C118925XX (pIC <sub>50</sub> ~6) [1242], AR-C126313 (pEC <sub>50</sub> 6) [1123], PSB-416 (pIC <sub>50</sub> 4.7) [1017]	PSB-16133 (pIC <sub>50</sub> 6.6) [2121], ATP (pK <sub>d</sub> 6.2) [1246]	MRS2578 (pIC <sub>50</sub> 7.4) [1631], MRS2567 (pIC <sub>50</sub> 6.9) [1631], TIM-38 (pIC <sub>50</sub> 5.4) [1119]
Selective allosteric modulators	BMS compound 16 (Negative) (pK <sub>i</sub> 6.9) [2920], 2,2'-pyridylisatogen tosylate (Negative) (pIC <sub>50</sub> 6.8) [766]	–	–	–
Labelled ligands	[ <sup>3</sup> H]MRS2279 (Antagonist) (pK <sub>d</sub> 8.1) [2707], [ <sup>3</sup> H]2MeSADP (Agonist) [2522], [ <sup>35</sup> S]ADPbetaS (Agonist)	–	–	MRS4162-BODIPY conjugate (Selective Agonist) [1155]

Nomenclature	P2Y <sub>11</sub> receptor	P2Y <sub>12</sub> receptor	P2Y <sub>13</sub> receptor	P2Y <sub>14</sub> receptor
HGNC, UniProt	P2RY11, Q96G91	P2RY12, Q9H244	P2RY13, Q9BPV8	P2RY14, Q15391
Potency order of endogenous ligands	ATP>ADP	ADP>ATP	ADP>>ATP	UDP= UDP-glucose
Endogenous agonists	ATP [478, 1136, 2777], UTP [2777], ADP [478]	ADP [1040]	ADP [1657]	UDP [356], UDP-glucose [737], UDP-galactose [379]
Sub/family-selective agonists	ADP $\beta$ S [478]	2MeSADP [1040], ADP $\beta$ S [2522]	2MeSADP [1657], 2MeSATP [1657], ADP $\beta$ S [1657]	–
Selective agonists	AR-C67085 [124, 478], NF546 [1706], ATP $\gamma$ S [478]	–	–	$\alpha$ , $\beta$ -methylene-2-thio-UDP [523], MRS2905 [1132], 2-thio-UDP [523]
Antagonists	–	cangrelor (pIC <sub>50</sub> 9.4) [1136], Ap <sub>4</sub> A (pIC <sub>50</sub> 6) [1657], 2MeSAMP (pIC <sub>50</sub> 5.4) [2522]	cangrelor (pIC <sub>50</sub> 8.3) [1657], Ap <sub>4</sub> A (pIC <sub>50</sub> 6.7) [1657], 2MeSAMP (pIC <sub>50</sub> 5.6) [1657]	–
Sub/family-selective antagonists	suramin (pIC <sub>50</sub> 4.8–6) [478], reactive blue-2 (pIC <sub>50</sub> 5) [478]	–	–	–
Selective antagonists	NF157 (pK <sub>i</sub> 7.3) [2630], NF340 (pIC <sub>50</sub> 6.4–7.1) [1706]	AZD1283 (pK <sub>i</sub> 8) [105, 2925], ARL66096 (pIC <sub>50</sub> 7.9) [1086, 1087], ticagrelor (pK <sub>i</sub> 7.8) [2916]	MRS2603 (pIC <sub>50</sub> 6.2) [1282], MRS2211 (pIC <sub>50</sub> 6) [1282]	PPTN (pK <sub>i</sub> 10.1) [134], MRS4625 (pIC <sub>50</sub> 7.6) [1821]
Labelled ligands	–	[ <sup>3</sup> H]2MeSADP (Agonist) [2522], [ <sup>3</sup> H]PSB-0413 (Antagonist) (pK <sub>d</sub> 8.3–8.5) [642, 1935]	[ <sup>33</sup> P]2MeSADP (Agonist) [1657]	MRS4174 (Selective Antagonist) (pK <sub>i</sub> 10.1) [1294], MRS4183 (Selective Agonist) [1293]

**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 synthesized [1155].

Single nucleotide polymorphisms of the P2Y<sub>1</sub> gene have been associated to different platelet reactivity to ADP [1006]. 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 [322]. ATP acts as partial agonist/antagonist at the human P2Y<sub>4</sub> receptor [2696]. Although UTP was also shown to be a biased agonist at P2Y<sub>11</sub>, this is still

under debate [1811, 2777]. Clinically used drugs acting on these receptors include the dinucleoside polyphosphate **diquafosol**, agonist of the P2Y<sub>2</sub> receptor subtype that is approved in Japan and South Korea for the management of dry eye disease [1419], and the P2Y<sub>12</sub> receptor antagonists **prasugrel**, **ticagrelor** and **cangrelor**, all approved as antiplatelet drugs [14, 65]. 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 [367]. 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 [363]. 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 [54]. The P2Y<sub>14</sub> receptor, previously considered to exclusively bind sugar nucleotides such as UDP-glucose, UDP-galactose, UDP-glucuronic acid and UDP-N-acetyl-glucosamine [379], has been demonstrated to bind also UDP [356]. UDP was also shown to competitively antagonise the UDP-glucose response at the human recombinant P2Y<sub>14</sub> receptor [738].

Further reading on P2Y receptors

Abbraccio MP *et al.* (2006) International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacol Rev* **58**: 281-341 [PMID:16968944]

Jacobson KA *et al.* (2020) Update of P2Y receptor pharmacology: IUPHAR Review 27. *Br J Pharmacol* **177**: 2413-2433 [PMID:32037507]

Jacobson KA *et al.* (2015) Nucleotides Acting at P2Y Receptors: Connecting Structure and Function. *Mol Pharmacol* **88**: 220-30 [PMID:25837834]

von Kügelgen I *et al.* (2016) Pharmacology and structure of P2Y receptors. *Neuropharmacology* **104**: 50-61 [PMID:26519900]

## 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** [772]) are class 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** (**PTHrP**, **P12272**) (141 amino-acids) and related peptides (PTH-(1-34), **PTHrP-(1-36)** (**PTHrP**, **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. The structure of a long-ac-

tive PTH analogue (LA-PTH, an hybrid of PTH-(1-13) and PTHrP-(14-36)) bound to the PTH1 receptor-G<sub>s</sub> complex has been resolved by cryo-electron microscopy [2941]. Another structure of a PTH-(1-34) analog bound to a thermostabilized inactive PTH1 receptor has been obtained with X-ray crystallography [639].

Nomenclature	PTH1 receptor	PTH2 receptor
HGNC, UniProt	<b>PTH1R</b> , Q03431	<b>PTH2R</b> , P49190
Potency order of endogenous ligands	<b>PTH</b> ( <b>PTH</b> , P01270) = <b>PTHrP</b> ( <b>PTHrP</b> , P12272)	<b>TIP39</b> ( <b>PTH2</b> , Q96A98), <b>PTH</b> ( <b>PTH</b> , P01270) ≫ <b>PTHrP</b> ( <b>PTHrP</b> , P12272)
Agonists	teriparatide [770]	<b>TIP39</b> ( <b>PTH2</b> , Q96A98) [846, 1029]
Selective agonists	<b>PTHrP-(1-34)</b> (human) [771] – Rat, <b>abaloparatide</b> [94]	–

**Comments:** The parathyroid hormone type 1 receptor (PTH1R) 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/PTH1R 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 [[1188](#)].

### 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](#)]  
 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](#)]

Sutkeviciute I *et al.* (2020) Structural insights into emergent signaling modes of G protein-coupled receptors. *J Biol Chem* **295**: 11626-11642 [[PMID:32571882](#)]  
 Vilardaga JP *et al.* (2014) Endosomal generation of cAMP in GPCR signaling. *Nat Chem Biol* **10**: 700-6 [[PMID:25271346](#)]

## 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** [[712](#)]) is activated by **PAF** and other suggested endogenous ligands are oxidized phosphatidylcholine [[1645](#)] and **lysophosphatidylcholine** [[1929](#)]. It may also be activated by bacterial lipopolysaccharide [[1847](#)].

Nomenclature	<b>PAF receptor</b>
HGNC, UniProt	<b>PTAFR</b> , P25105
Selective agonists	<b>methylcarbamyl PAF</b>
Selective antagonists	<b>foropafant</b> (pK <sub>i</sub> 10.3) [ <a href="#">996</a> ], <b>ABT-491</b> (pK <sub>i</sub> 9.2) [ <a href="#">36</a> ], <b>CV-6209</b> (pIC <sub>50</sub> 8.1–8.3) [ <a href="#">835</a> , <a href="#">1846</a> ], <b>L659989</b> (pK <sub>i</sub> 7.8) [ <a href="#">1091</a> ], <b>apafant</b> (pK <sub>i</sub> 5.2–7.5) [ <a href="#">1985</a> , <a href="#">2501</a> ]
Labelled ligands	<b>[<sup>3</sup>H]PAF (Agonist)</b> [ <a href="#">746</a> , <a href="#">1846</a> ]

**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**: 279-88 [[PMID:15914470](#)]  
 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](#)]

Prescott SM *et al.* (2000) Platelet-activating factor and related lipid mediators. *Annu Rev Biochem* **69**: 419-45 [[PMID:10966465](#)]

## 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** [[712](#)]) 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 polylepsis*) venom, mamba intestinal toxin 1 (**MIT1**, [[2315](#)]) is a potent, non-selective agonist at prokineticin receptors [[1666](#)], while **Bv8**, an orthologue of PROK2 from amphibians (*Bombina*

*sp.*, [[1766](#)]), is equipotent at recombinant PKR<sub>1</sub> and PKR<sub>2</sub> [[1870](#)], 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	<i>PROKR1</i> , Q8TCW9	<i>PROKR2</i> , Q8NFJ6
Potency order of endogenous ligands	prokineticin-2 ( <i>PROK2</i> , Q9HC23) > prokineticin-1 ( <i>PROK1</i> , Q9HC23) > prokineticin-2β ( <i>PROK2</i> ) [401, 1521, 1666, 2426]	prokineticin-2 ( <i>PROK2</i> , Q9HC23) > prokineticin-1 ( <i>PROK1</i> , Q9HC23) > prokineticin-2β ( <i>PROK2</i> ) [401, 1521, 1666, 2426]
Agonists	MIT1 [1666]	MIT1 [1666]
Selective agonists	IS20 [780], IS1 [780]	–
Labelled ligands	[ <sup>125</sup> I]BH-MIT1 (Agonist) [1666]	[ <sup>125</sup> I]BH-MIT1 (Agonist) [1666]

**Comments:** Genetic mutations in *PROKR1* are associated with Hirschsprung's disease [2228], while genetic mutations in *PROKR2* are associated with hypogonadotropic hypogonadism with anosmia [593], hypopituitarism with pituitary stalk interruption [2167] and Hirschsprung's disease [2228]. PKR<sub>2</sub> has been recently identified as a receptor for *T. cruzi* natural infection [1260]. PROK2 neuropeptide signalling *via* PKR<sub>2</sub> on spinal neurons generates pleasant touch sensation [1537].

#### Further reading on Prokineticin receptors

Boulberda 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]

Negri L *et al.* (2007) Bv8/Prokineticin proteins and their receptors. *Life Sci* **81**: 1103-16 [PMID:17881008]  
 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 (43Rfa) (*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 [1018] derived from a FMRFamide-related peptide precursor (*NPVF*, Q9HCQ7), which is cleaved to generate neuropeptide SF (*NPFF*, 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) [1412]
Endogenous agonists	PrRP-20 ( <i>PRLH</i> , P81277) [655, 1412], PrRP-31 ( <i>PRLH</i> , P81277) [655, 1412]
Endogenous antagonists	neuropeptide Y ( <i>NPY</i> , P01303) (pK <sub>i</sub> 5.4) [1396]
Labelled ligands	[ <sup>125</sup> I]PrRP-20 (human) (Agonist) [1412], [ <sup>125</sup> I]PrRP31 (Agonist) [646]

**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 [2810]**) are activated by the endogenous ligands prostaglandins PGD<sub>2</sub>, PGE<sub>1</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, PGH<sub>2</sub>, prostacyclin [PGI<sub>2</sub>]

and thromboxane A<sub>2</sub>. Differences and similarities between human and rodent prostanoid receptor orthologues, and their specific roles in pathophysiologic conditions are reviewed in [1912]. Measurement of the potency of PGI<sub>2</sub> and thromboxane

A<sub>2</sub> is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

Nomenclature	DP <sub>1</sub> receptor	DP <sub>2</sub> receptor
HGNC, UniProt	<i>PTGDR</i> , Q13258	<i>PTGDR2</i> , Q9Y5Y4
Potency order of endogenous ligands	PGD <sub>2</sub> > PGE <sub>1</sub> ≫ PGE <sub>2</sub> > PGF <sub>2α</sub> > PGI <sub>2</sub> , thromboxane A <sub>2</sub>	PGD <sub>2</sub> ≫ PGF <sub>2α</sub> , PGE <sub>2</sub> > PGI <sub>2</sub> , thromboxane A <sub>2</sub>
Agonists	treprostinil [2505, 2780]	–
Selective agonists	BW 245C [225, 2811, 2812], L-644,698 [2811, 2812]	15(R)-15-methyl-PGD <sub>2</sub> [959, 1778, 2481]
Antagonists	laropiprant (pK <sub>i</sub> 10.1) [1399, 2473]	fevipiprant (pK <sub>d</sub> 9) [2506, 2507], AZD1981 (pIC <sub>50</sub> 8.4) [1576], ramatroban (pK <sub>i</sub> 7.4) [2481]
Selective antagonists	BWA868C (pK <sub>i</sub> 8.6–9.3) [225, 815, 2811], ONO-AE3-237 (pK <sub>i</sub> 7.7) [1020, 2597, 2600]	TM30089 (pIC <sub>50</sub> 8.9) [2222, 2634]
Labelled ligands	[ <sup>3</sup> H]PGD <sub>2</sub> (Agonist) [2793, 2811]	[ <sup>3</sup> H]PGD <sub>2</sub> (Agonist) [1668, 2361]

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	PGE <sub>2</sub> > PGE <sub>1</sub> > PGF <sub>2α</sub> , PGI <sub>2</sub> > PGD <sub>2</sub> , thromboxane A <sub>2</sub>	PGE <sub>2</sub> = PGE <sub>1</sub> > PGF <sub>2α</sub> , PGI <sub>2</sub> > PGD <sub>2</sub> , thromboxane A <sub>2</sub>	PGE <sub>2</sub> , PGE <sub>1</sub> > PGF <sub>2α</sub> , PGI <sub>2</sub> > PGD <sub>2</sub> , thromboxane A <sub>2</sub>	PGE <sub>2</sub> = PGE <sub>1</sub> > PGF <sub>2α</sub> , PGI <sub>2</sub> > PGD <sub>2</sub> , thromboxane A <sub>2</sub>
Endogenous agonists	–	PGE <sub>2</sub> [9, 2459, 2793]	PGE <sub>2</sub> (EP <sub>3</sub> -III isoform) [9]	–
Agonists	17-phenyl-ω-trinor-PGE <sub>2</sub> [2352]	treprostinil [2505, 2780], PGE <sub>1</sub> [145]	misoprostol (methyl ester) (EP <sub>3</sub> -III isoform) [9]	L-161,982 (EP <sub>4</sub> A) [1599, 2902], 17-phenyl-ω-trinor-PGE <sub>2</sub> [2562]
Selective agonists	ONO-DI-004 [2496] – Mouse	ONO-AE1-259 [2496] – Mouse, omide-nepag [1292], butaprost (free acid form) [9, 2459]	sulprostone (EP <sub>3</sub> -III isoform) [9], ONO-AE-248 [719, 1563]	L902688 [720, 1450], KMN-159 [135], ONO-AE1-329 [719, 720]

Selective antagonists	ONO-8711 (pK <sub>i</sub> 9.2) [2747], SC-51322 (pK <sub>i</sub> 7.9) [9]	PF-04418948 (PF-04418948 has weaker affinity at the EP <sub>2</sub> -receptor in guinea-pigs) (pK <sub>B</sub> 8.3) [17, 205], TG6-129 (pK <sub>B</sub> 8.1) [763], TG8-260 (pK <sub>B</sub> 7.9) [48, 2149]	L-826266 (EP <sub>3</sub> -III isoform (pK <sub>i</sub> =8.04 in the presence of HSA)) (pK <sub>i</sub> 9.1) [1196], ONO-AE3-240 (pIC <sub>50</sub> 8.8) [47] – Mouse, DG-041 (pK <sub>i</sub> 8.4) [1194]	ONO-AE3-208 (pK <sub>i</sub> 8.5), GW 627368 (pK <sub>i</sub> 7–7.1) [2793, 2794]
Labelled ligands	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [9, 2352, 2793]	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [9, 2793]	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [9, 2793]	[ <sup>3</sup> H]PGE <sub>2</sub> (Agonist) [9, 539, 2780, 2793]

Nomenclature	FP receptor	IP receptor	TP receptor
HGNC, UniProt	PTGFR, P43088	PTGIR, P43119	TBXA2R, 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> [2380], PGE <sub>1</sub> [1663, 2461]	–
Agonists	ONO-9054 [2855]	iloprost [9, 2793], treprostinil [2780]	–
Selective agonists	fluprostenol [9], latanoprost (free acid form) [9]	cicaprost [9], MRE-269 [179, 1389]	U46619 [9]
Antagonists	–	–	ramatroban (pK <sub>i</sub> 8) [2563], laropiprant (pK <sub>i</sub> 6.1) [1399]
Selective antagonists	AS604872 (pK <sub>i</sub> 7.5) [463]	CAY10441 (pK <sub>i</sub> 8.7) [213], RO3244794 (pA2 8.5) [213]	vapiprost (pK <sub>i</sub> 8.3–9.4) [79, 1577], SQ-29548 (pK <sub>i</sub> 8.1–9.1) [9, 2504, 2793]
Labelled ligands	[ <sup>3</sup> H]PGF <sub>2α</sub> (Agonist) [9, 10, 2793], [ <sup>3</sup> H](+)-fluprostenol (Agonist)	[ <sup>3</sup> H]iloprost (Agonist) [9, 224, 2780, 2793]	[ <sup>125</sup> I]SAP (Antagonist) (pK <sub>d</sub> 7.7–9.3) [1845], [ <sup>125</sup> I]BOP (Agonist) [1800], [ <sup>3</sup> H]SQ-29548 (Antagonist) (pK <sub>d</sub> 7.4–8.2) [9, 2793]

**Comments:** Whilst **cicaprost** is selective for IP receptors, it does exhibit moderate agonist potency at EP<sub>4</sub> receptors [9]. 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 [719, 2562]. **Butaprost** and **SC46275** may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1517] and TP receptors [1356, 2151]. mRNA for the EP<sub>3</sub> receptor undergoes alternative splicing to produce variants which can interfere with signalling [1948] 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.* [1343, 1868]). The number of EP<sub>3</sub> receptor (protein) variants are vari-

able depending on species. For the human prostaglandin EP<sub>3</sub> receptor, there exist five different EP<sub>3</sub> isoform proteins (EP<sub>3</sub>-I, EP<sub>3</sub>-II, EP<sub>3</sub>-III, EP<sub>3</sub>-IV and EP<sub>3</sub>-e). Three isoforms exist in rat and 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**) [2809].

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 [2353].

References given alongside the TP receptor agonists **I-BOP** [1683] and **STA<sub>2</sub>** [79] 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 [2528, 2750] and in the BEAS-2B human airway epithelial cell line [2796] 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

Norel X *et al.* (2020) International Union of Basic and Clinical Pharmacology. CIX. Differences and Similarities between Human and Rodent Prostaglandin E<sub>2</sub> Receptors (EP<sub>1</sub>-4) and Prostacyclin Receptor (IP): Specific Roles in Pathophysiological Conditions. *Pharmacol Rev* **72**: 910-968 [PMID:32962984]

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 [1037]**) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmasks 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>**, **TRFGAP-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 Gαq-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 [2128]. PAR2 activation by NE regulates inflammation and pain responses [1822, 2942] and triggers mucin secretion from airway epithelial cells [2948].

Nomenclature	PAR1	PAR2	PAR3	PAR4
HGNC, UniProt	<i>F2R</i> , P25116	<i>F2RL1</i> , P55085	<i>F2RL2</i> , O00254	<i>F2RL3</i> , Q96R10
Agonist proteases	thrombin ( <i>F2</i> , P00734), activated protein C ( <i>PROC</i> , P04070), matrix metalloproteinase 1 ( <i>MMP1</i> , P45452), matrix metalloproteinase 13 ( <i>MMP13</i> , P45452) [96]	Trypsin, tryptase, TF/VIIa, Xa; elastase, neutrophil expressed; cathepsin S [1171, 2126]	thrombin ( <i>F2</i> , P00734)	thrombin ( <i>F2</i> , P00734), trypsin, cathepsin G ( <i>CTSG</i> , P08311)
Agonists	F16357	–	–	–
Selective agonists	TFLLR-NH <sub>2</sub> [1039]	Isox-Cha-Chg-Ala-Arg-Dpr(4FB)-NH <sub>2</sub> [1484], AY77 [2879], AZ2429 [1244], GB110 [138], 2-furoyl-LIGRLO-amide [1695], SLIGKV-NH <sub>2</sub> [1457], SLIGRL-NH <sub>2</sub> [1457]	–	AYPGKF-NH <sub>2</sub> , GYPGKF-NH <sub>2</sub> , GYPGQV-NH <sub>2</sub>
Selective antagonists	vorapaxar (pK <sub>i</sub> 8.1) [375], atopaxar (pIC <sub>50</sub> 7.7) [1321], SCH-79797 (pIC <sub>50</sub> 7.2) [23], RWJ-56110 (pIC <sub>50</sub> 6.4) [61]	I-191 (pIC <sub>50</sub> 7.1) [1170], AZ8838 (pK <sub>d</sub> 6.5) [421], GB88 (pIC <sub>50</sub> 5.7) [2478], P2pal18S (pIC <sub>50</sub> 5.4)	–	BMS-986120 (pIC <sub>50</sub> 9.3) [2083, 2805], BMS-986141 (pIC <sub>50</sub> 9.3) [2083], YD-3 (pIC <sub>50</sub> 6.9) [2761], ML354 (pIC <sub>50</sub> 6.8) [2761], P4pal-10 [499], RAG8 [2127]
Allosteric modulators (Negative)	–	AZ3451 (pIC <sub>50</sub> 7.6) [421], I-287 (functionally selective) (pIC <sub>50</sub> 7.1) [97], I-287 (functionally selective) (pIC <sub>50</sub> 6.4) [97]	–	–
Labelled ligands	[ <sup>3</sup> H]haTRAP (Agonist) [22]	Isox-Cha-Chg-ARK(Sulfo-Cy5)-NH <sub>2</sub> (Selective Agonist) [1483], 2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH <sub>2</sub> (Agonist) [1038], 2-furoyl-LIGRL[N- <sup>3</sup> H]propionyl]-O-NH <sub>2</sub> (Agonist) [1038], [ <sup>3</sup> H]2-furoyl-LIGRL-NH <sub>2</sub> (Selective Agonist) [1214], trans-cinnamoyl-LIGRLO [N- <sup>3</sup> H]propionyl]-NH <sub>2</sub> (Agonist) [34]	–	–

Comments	TFLLR-NH <sub>2</sub> is selective relative to the PAR <sub>2</sub> receptor [207, 1228].	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> .	–	–
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**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 (*TPRSS15*, 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).

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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** [1478]; 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 [1452]. 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. QRFP receptor was identified as a Gs-coupled GPCR [392, 1169] that's activated by

the endogenous peptides QRFP43 (43RFa) and QRFP26 (26RFa) [392, 748, 1169]. However, Gq- and Gi/o-mediated signaling was also reported [748, 2130]. Two naturally occurring mutations in the human QRFP receptor lead to distinct and opposite 26RFa-evoked signaling bias [1592].

Nomenclature	QRFP receptor
HGNC, UniProt	QRFP, Q96P65
Endogenous agonists	QRFP43 (43RFa) ( <i>QRFP</i> , P83859) [747, 2436], QRFP26 (26RFa) ( <i>QRFP</i> ) [392, 1169]
Agonists	LV-2186 [46], LV-2172 [1882], LV-2211 [1462]
Selective antagonists	compound 25e (pIC <sub>50</sub> 7.3) [800, 801]
Labelled ligands	[ <sup>125</sup> I]QRFP43 (human) (Agonist) [748, 2527], [ <sup>125</sup> I]26RFa (human) (Agonist) [307]

**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 [146, 919]**) 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 [2322]. 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 [2321]. *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 [2342] and RXFP2 [1028] which direct the N-terminal LDLa modules of the receptors together with a linker domain to act as a tethered ligand to direct receptor signaling [2323]. *INSL5* (*INSL5*, Q9Y5Q6) and relaxin-3 (*RLN3*, Q8WXF3) interact with their receptors using distinct residues in their B-chains for binding, and activation, respectively [1073, 2804].

Nomenclature	RXFP1	RXFP2
HGNC, UniProt	<i>RXFP1</i> , Q9HBX9	<i>RXFP2</i> , Q8WXD0
Potency order of endogenous ligands	relaxin ( <i>RLN2</i> , P04090) = relaxin-1 ( <i>RLN1</i> , P04808) > relaxin-3 ( <i>RLN3</i> , Q8WXF3) [2477]	<i>INSL3</i> ( <i>INSL3</i> , P51460) > relaxin ( <i>RLN2</i> , P04090) ≫ relaxin-3 ( <i>RLN3</i> , Q8WXF3) [1379, 2477]
Agonists	LY3540378 [2680], SA10SC-RLX [1103, 1629], (B7-33)H2 [569, 1059]	compound 6641 [666]
Antagonists	B-R13/17K H2 relaxin (pIC <sub>50</sub> 5.7–6.7) [1062, 1880]	–
Selective antagonists	–	A(9-26)INSL3 (pK <sub>i</sub> 9.1) [1061], A(10-24)INSL3 (pK <sub>i</sub> 8.7) [1061], A(C10/15S)INSL3 (pK <sub>i</sub> 8.6) [2930], <i>INSL3</i> B chain dimer analogue 8 (pK <sub>i</sub> 8.5) [2349], A(D10/15C)INSL3 (pK <sub>i</sub> 8.3) [2930], cyclic <i>INSL3</i> B-chain analogue 6 (pK <sub>i</sub> 6.7) [2347], <i>INSL3</i> B-chain analogue (pK <sub>i</sub> 5.1) [560], (des 1-8) A-chain <i>INSL3</i> analogue [314]
Labelled ligands	[ <sup>33</sup> P]relaxin (human) (Agonist) [920, 2477], europium-labelled relaxin (Agonist) [2346], TamRLX (Agonist) [1028], Nanoluciferase-labelled relaxin (Agonist) [2820], [ <sup>125</sup> I]relaxin (human) (Agonist)	[ <sup>125</sup> I]INSL3 (human) (Agonist) [1819], [ <sup>33</sup> P]relaxin (human) (Agonist) [920, 2477], europium-labelled <i>INSL3</i> (Agonist) [2348], TamRLX (Agonist) [1028]

Nomenclature	RXFP3	RXFP4
HGNC, UniProt	<i>RXFP3</i> , Q9NSD7	<i>RXFP4</i> , Q8TDU9
Potency order of endogenous ligands	relaxin-3 ( <i>RLN3</i> , Q8WXF3) > relaxin-3 (B chain) ( <i>RLN3</i> , Q8WXF3) > relaxin ( <i>RLN2</i> , P04090) [1540]	<i>INSL5</i> ( <i>INSL5</i> , Q9Y5Q6) = relaxin-3 ( <i>RLN3</i> , Q8WXF3) > relaxin-3 (B chain) ( <i>RLN3</i> , Q8WXF3) [1538, 1539]
Agonists	compound 4 [558], B1-27 [1454], WNN0109-C011 [1523]	compound 4 [558], hINSL5: A8-21 (T15K) [1998], DC591053 [414], JK1 [1524]

Endogenous antagonists	<a href="#">INSL5 (INSL5, Q9Y5Q6)</a> (pK <sub>i</sub> 7) [2953]	–
Antagonists	<a href="#">R3(BA23-27)R/15 chimeric peptide</a> (pIC <sub>50</sub> 9.2) [1368], <a href="#">R3 B1-22R</a> (pK <sub>i</sub> 7.7) [963]	<a href="#">R3(BA23-27)R/15 chimeric peptide</a> (pIC <sub>50</sub> 8–8.6) [962, 1368], <a href="#">INSL5-A13NR</a> (pIC <sub>50</sub> 7.4) [2100]
Selective antagonists	<a href="#">minimised relaxin-3 analogue 3</a> (pK <sub>i</sub> 7.6) [2345], <a href="#">R3 B1-22R</a> (pK <sub>i</sub> 7.4) [962]	<a href="#">minimised relaxin-3 analogue 3</a> (pIC <sub>50</sub> 6.6) [2345]
Labelled ligands	<a href="#">[<sup>125</sup>I]relaxin-3 (human)</a> (Agonist) [1540], <a href="#">[<sup>125</sup>I]relaxin-3-B/INSL5 A chimera</a> (Agonist) [1538], <a href="#">europium-labelled relaxin-3-B/INSL5 A chimera</a> (Agonist) [962], <a href="#">NanoLuc R3/15 chimera</a> (Agonist) [2728, 2729]	<a href="#">[<sup>125</sup>I]relaxin-3 (human)</a> (Agonist) [1539], <a href="#">[<sup>125</sup>I]relaxin-3-B/INSL5 A chimera</a> (Agonist) [1538], <a href="#">europium-labelled mouse INSL5</a> (Agonist) [169], <a href="#">europium-labelled relaxin-3-B/INSL5 A chimera</a> (Agonist) [962], <a href="#">europium-labelled INSL5</a> (pK <sub>d</sub> 8.3) [962], <a href="#">NanoLuc R3/15 chimera</a> (Agonist) [1072, 2728]

**Comments:** [Relaxin \(RLN2, P04090\)](#) is the cognate peptide ligand for RXFP1 and is a potential treatment for heart failure [614]. Relaxin has vasodilatory, anti-fibrotic, angiogenic, anti-apoptotic and anti-inflammatory effects. A small molecule allosteric agonist [ML290](#) has been developed [2357, 2832], that displays anti-fibrotic properties [1198], and a relaxin B-chain mimetic peptide B7-33 has been developed which has cell specific signaling properties [1060]. The antifibrotic actions of relaxin are dependent on the angiotensin receptor AT<sub>2</sub> [444] and are blocked by either AT<sub>1</sub> or AT<sub>2</sub> receptor antagonists. [INSL3 \(INSL3, P51460\)](#) is the cognate peptide for RXFP2 and is a circulating hormone that in males is essential for testicular descent *in utero* [1867] and in females has important roles in ovarian follicle function [1124]. In adults, INSL3 has potential roles in testicular function [1125] and the musculo-skeletal system [552].

RXFP2 is also present in brain, associated with cortico-thalamic motor circuits [2329]. cAMP elevation is the major signalling pathway for both RXFP1 and RXFP2 [1070, 1071], but RXFP1 also activates MAP kinases, nitric oxide signalling, and tyrosine kinase phosphorylation; and relaxin can interact with glucocorticoid receptors [921]. RXFP1 displays ultra-sensitive responses to sub picomolar levels of relaxin [464]. Receptor expression profiles suggest that RXFP3 is a brain neuropeptide receptor [1593, 1594, 2409] and RXFP4 a gut hormone receptor [762]. The brain relaxin-3/RXFP3 system modulates feeding [761, 762, 962, 2345, 2408] *via* effects in hypothalamus [542, 761, 1212, 1213], anxiety [1665, 2236, 2240, 2917], reward and motivated, goal-directed behaviours [1054, 2236, 2708], and spatial and social memory [38, 913, 914]. 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. Single chain peptide agonists and antagonists have been developed for RXFP3 [961, 1454] and a small molecular weight agonist active at RXFP3 and RXFP4 [558]. [INSL5 \(INSL5, Q9Y5Q6\)](#) is secreted from enteroendocrine L cells and the INSL5/RXFP4 system affects food intake [880], colon motility [591] and glucose homeostasis [1582]. RXFP3 and RXFP4 couple to G<sub>i/o</sub> and inhibit adenylyl cyclase [1540, 2654], and also cause Erk1/2 phosphorylation [2654]. RXFP4 also causes phosphorylation of p38MAPK, Akt and S6RP [64] and GLP-1 secretion *in vitro* [63]. There is evidence that at RXFP3, [relaxin \(RLN2, P04090\)](#) is a biased ligand compared to the cognate ligand [relaxin-3 \(RLN3, Q8WXF3\)](#) [2654].

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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** [899]). 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 [547].

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16177/full>

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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	<i>SSTR1</i> , P30872	<i>SSTR2</i> , P30874	<i>SSTR3</i> , P32745	<i>SSTR4</i> , P31391	<i>SSTR5</i> , P35346
Agonists	pasireotide [2298]	pasireotide [2298], veldoreotide [18]	pasireotide [2298]	NNC269100 [1552], veldoreotide [18]	pasireotide [2298], veldoreotide [18]
Selective agonists	L-797,591 [2199], Des-Ala <sup>1,2,5</sup> -[D-Trp <sup>8</sup> ,I-Amp <sup>9</sup> ]SRIF [659]	L-054,522 [2868], BIM 23027 [359], L-779,976 [2199], octreotide [304, 1997, 2381, 2382, 2383, 2868], lanreotide [304, 1997, 2381, 2382, 2383]	L-796,778 [2199]	L-803,087 [2199], J-2156 [656]	BIM 23052 [1716, 2381, 2382, 2383], L-817,818 [2199]
Selective antagonists	SRA880 (pK <sub>d</sub> 8–8.1) [1065]	DOTA-IR11 [373]	MK-4256 (pIC <sub>50</sub> 9.2) [978], ACQ090 (pK <sub>i</sub> 7.9) [1066]	–	S5A1 (pK <sub>i</sub> 9.3) [680]

**Comments:** [125I]Tyr<sup>11</sup>-SRIF-14, [125I]LTT-SRIF-28, [125I]CGP 23996 and [125I]Tyr<sup>10</sup>-CST14 may be used to label somatostatin receptors nonselectively. A number of nonpeptide subtype-selective agonists have been synthesised [2199]. 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 [2060, 2368].

### Further reading on Somatostatin receptors

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## Succinate receptor

G protein-coupled receptors → Succinate receptor

**Overview: Nomenclature as recommended by NC-IU-PHAR [532].** The succinate receptor (GPR91, *SUCNRI*) is activated by the tricarboxylic acid (or Krebs) cycle intermediate succinate and other dicarboxylic acids with less clear physiological relevance such as maleate [979]. Since its pairing with its endogenous ligand in 2004, intense research has focused on the receptor-ligand pair role in various (patho)physiological processes such as regulation of renin production [979, 2594], ischemia

injury [979], fibrosis [1600], retinal angiogenesis [2266], inflammation [1536, 1600], immune response [2223], obesity [1237, 1692, 2687], diabetes [1499, 2594, 2655], platelet aggregation [2441, 2545] or cancer [2119, 2818]. The succinate receptor is coupled to G<sub>i/o</sub> [817, 979] and G<sub>q/11</sub> protein families [979, 2194, 2610]. Although the receptor is, upon ligand addition, rapidly desensitized [1035, 2194], and in some cells internalized [979], it seems to recruit arrestins weakly [809]. The cellular activation of

the succinate receptor triggers various signalling pathways such as decrease of cAMP levels, [Ca<sup>2+</sup>]<sub>i</sub> mobilization and activation of kinases (ERK, c-Jun, Akt, Src, p38, PI3Kβ, *etc.*) [818]. The receptor is broadly expressed but is notably abundant in immune cells (M2 macrophages [1237, 2610], monocytes [2223], immature dendritic cells [2223], adipocytes [2687], platelets [2441, 2545], *etc.*) and in the kidney [979].



Nomenclature	succinate receptor
HGNC, UniProt	<a href="#">SUCNR1</a> , <a href="#">Q9BXAS</a>
Endogenous agonists	succinic acid [979, 2436], maleic acid [809, 817, 979]
Agonists	compound 31 (Partial agonist) [2165], compound 130 (Partial agonist) [2611], cis-epoxysuccinic acid [809]
Antagonists	NF-56-EJ40 (pK <sub>i</sub> 7.8) [909]

**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.* [2801] 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.

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## Tachykinin receptors

G protein-coupled receptors → Tachykinin receptors

**Overview:** Tachykinin receptors (**provisional nomenclature as recommended by NC-IUPHAR [712]**) 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), **neuro-**

**peptide 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.

Nomenclature	NK <sub>1</sub> receptor	NK <sub>2</sub> receptor	NK <sub>3</sub> receptor
HGNC, UniProt	<a href="#">TACR1</a> , P25103	<a href="#">TACR2</a> , P21452	<a href="#">TACR3</a> , 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) ≫ 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 [2580]	–	–
Selective agonists	[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP [2580], septide [173, 958], [Pro <sup>9</sup> ]SP [2599] – Rat	[Lys <sup>5</sup> ,Me-Leu <sup>9</sup> ,Nle <sup>10</sup> ]NKA-(4-10) [1680] – Rat, GR64349 [555] – Rat, [βAla <sup>8</sup> ]neurokinin A-(4-10) [650]	[Phe(Me) <sup>7</sup> ]neurokinin B [2268, 2269], senktide [2268, 2269, 2580]
Antagonists	L760735 (pIC <sub>50</sub> 9.7) [953]	–	–

Selective antagonists	<a href="#">aprepitant</a> (pK <sub>i</sub> 10.1) [915, 916], <a href="#">CP 99994</a> (pK <sub>i</sub> 9.3–9.7) [66, 2269], <a href="#">RP67580</a> (pIC <sub>50</sub> 7.7) [711]	<a href="#">GR94800</a> (pK <sub>i</sub> 9.8) [264], <a href="#">saredutant</a> (pK <sub>i</sub> 9.4–9.7) [66, 650, 2269], <a href="#">GR 159897</a> (pK <sub>d</sub> 7.8–9.5) [182, 650, 2417], <a href="#">MEN10627</a> (pK <sub>i</sub> 9.2) [812], <a href="#">nepadutant</a> (pK <sub>i</sub> 8.5–8.7) [361, 460]	<a href="#">osanetant</a> (pK <sub>i</sub> 8.4–9.7) [66, 152, 459, 649, 1206, 1965, 2268, 2269, 2580], <a href="#">talnetant</a> (pK <sub>i</sub> 7.4–9) [176, 813, 2268, 2269], <a href="#">PD157672</a> (pIC <sub>50</sub> 7.8–7.9) [219, 2580]
Labelled ligands	[ <sup>125</sup> I]L703,606 (Antagonist) (pK <sub>d</sub> 9.5) [723], [ <sup>125</sup> I]BH-[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP (Agonist) [2606] – Rat, [ <sup>3</sup> H]SP (human, mouse, rat) (Agonist) [112], [ <sup>125</sup> I]SP (human, mouse, rat) (Agonist), [ <sup>18</sup> F]SPA-RQ (Antagonist) [430]	[ <sup>3</sup> H]saredutant (Antagonist) (pK <sub>d</sub> 9.7) [878] – Rat, [ <sup>125</sup> I]NKA (human, mouse, rat) (Agonist) [2745], [ <sup>3</sup> H]GR100679 (Antagonist) (pK <sub>d</sub> 9.2) [911]	[ <sup>3</sup> H]osanetant (Antagonist) (pK <sub>d</sub> 9.9), [ <sup>3</sup> H]senktide (Agonist) [889] – 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> [2216]. The crystal structure of the human NK<sub>1</sub> receptor in complex with antagonists has been determined [2306, 2887]. The hexapeptide agonist septide 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 [598, 1355]. NK<sub>1</sub> receptor

antagonists affect cellular physiology including inflammation, apoptosis and cell trafficking and have a role in therapeutics [1828, 2444].

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** [712]) 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 [2489]. [<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 [1705].

Nomenclature	<a href="#">TRH1 receptor</a>	<a href="#">TRH2 receptor</a>
HGNC, UniProt	<a href="#">TRHR</a> , <a href="#">P34981</a>	–
Antagonists	<a href="#">diazepam</a> (pK <sub>i</sub> 5.2) [613] – Rat	–
Selective antagonists	<a href="#">midazolam</a> (pK <sub>i</sub> 5.5) [613] – Rat, <a href="#">chlordiazepoxide</a> (pK <sub>i</sub> 4.8) [613] – Rat, <a href="#">chlordiazepoxide</a> (pK <sub>i</sub> 4.7) [2469] – Mouse	–
Comments	–	A class A G protein-coupled receptor: not present in man

**Further reading on Thyrotropin-releasing hormone receptors**

Bílek R *et al.* (2011) TRH-like peptides. *Physiol Res* **60**: 207-15 [PMID:21114375]  
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Nilni EA. (2010) Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Front Neuroendocrinol* **31**: 134-56 [PMID:20074584]

## 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 [244], where 15 mammalian orthologues were identified and divided into two families. The TA<sub>1</sub> receptor (**nomenclature as agreed by the NC-IU-PHAR Subcommittee for the Trace amine receptor**

[1616]) has affinity for the endogenous trace amines **tyramine**, **β-phenylethylamine** and **octopamine** in addition to the classical amine **dopamine** [244]. Emerging evidence suggests that TA<sub>1</sub> is a modulator of monoaminergic activity in the brain [2835] with TA<sub>1</sub> and dopamine D<sub>2</sub> receptors shown to form constitutive het-

erodimers when co-expressed [665]. 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, Q96RJ0
Potency order of endogenous ligands	tyramine > β-phenylethylamine > octopamine = dopamine [244]
Agonists	RO5166017 [2164]
Antagonists	EPPTB (Inverse agonist) (pIC <sub>50</sub> 5.1) [262]
Labelled ligands	[ <sup>3</sup> H]tyramine (Agonist) [244]

**Comments:** In addition to TA<sub>1</sub>, in man there are up to 5 functional TAAR genes (TAAR2,5,6,8,9). See [244] 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> [244].

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), TAAR6 (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> [2283]. 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> [2449].

**Further reading on Trace amine receptor**

Maguire JJ *et al.* (2009) International Union of Pharmacology. LXXII. Recommendations for trace amine receptor nomenclature. *Pharmacol Rev* **61**: 1-8 [PMID:19325074]

Pei Y *et al.* (2016) Trace Amines and the Trace Amine-Associated Receptor 1: Pharmacology, Neurochemistry, and Clinical Implications. *Front Neurosci* **10**: 148 [PMID:27092049]

## 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** [608, 712, 2677]) is activated by the endogenous dodecapeptide **urotensin-II** (UTS2, O95399), orig-

inally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [185, 2676]. Several structural forms of U-II exist in fish and amphibians [2677]. The goby orthologue was used to identify U-II as the cognate ligand

for the predicted receptor encoded by the rat gene *gpr14* [52, 497, 1549, 1798, 1915]. Human **urotensin-II** (UTS2, O95399), an 11-amino-acid peptide [497], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand

binding [285, 1290, 1479]. 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 [496]. A second endogenous ligand for the UT has been

discovered in rat [2482]. 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 [616]. UT exhibits relatively high sequence identity with somatostatin, opioid and galanin receptors [2677]. The urotensinergic system displays an unprecedented repertoire of four or five ancient UT in some vertebrate lineages and five U-II family peptides in teleost fish [2603].

Nomenclature	<b>UT receptor</b>
HGNC, UniProt	<i>UTS2R</i> , Q9UKP6
Endogenous agonists	<b>urotensin II-related peptide</b> ( <i>UTS2B</i> , Q76510) [616, 2482], <b>urotensin-II</b> ( <i>UTS2</i> , O95399) [52, 1549, 1798, 1915]
Selective agonists	[Pen <sup>5</sup> ]U-(4-11) (human) [876], U-II-(4-11) (human) [876], [3-iodo-Tyr <sup>6</sup> ]U-II-(4-11) (human) [1393], Urolinin [126], FL104 [1464, 1466], AC-7954 [508, 1465]
Selective antagonists	DS37001789 (pIC <sub>50</sub> 9.1) [1902], RCI-0879 (pIC <sub>50</sub> 9) [2539], urantide (pK <sub>i</sub> 8.3) [1992], SR101099 (pIC <sub>50</sub> 8) [1970], [Orn <sup>5</sup> ]URP (pK <sub>i</sub> 7.2) [579] – Rat, palosuran (pIC <sub>50</sub> 7.1) [470], SB-611812 (pK <sub>i</sub> 6.6) [2124], [Cha <sup>6</sup> ]U-II-(4-11) (pK <sub>i</sub> 6.4) [393] – Rat
Labelled ligands	[ <sup>125</sup> I]U-II (human) (Agonist) [52, 393, 1615], [ <sup>125</sup> I]N-biotin-[Ahx <sup>0</sup> , Bpa <sup>3</sup> ]U-II (human) [592]

**Comments:** In the human vasculature, human **urotensin-II** (*UTS2*, O95399) elicits both vasoconstrictor (pD<sub>2</sub> 9.3-10.1, [1615]) and vasodilator (pIC<sub>50</sub> 10.3-10.4, [2460]) responses.

#### Further reading on Urotensin receptor

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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 [712]**) 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 [554].

Nomenclature	<b>V<sub>1A</sub> receptor</b>	<b>V<sub>1B</sub> receptor</b>
HGNC, UniProt	<i>AVPR1A</i> , P37288	<i>AVPR1B</i> , P47901
Potency order of endogenous ligands	vasopressin ( <i>AVP</i> , P01185) > oxytocin ( <i>OXT</i> , P01178) [30, 420, 491, 1848, 2247, 2512, 2564]	vasopressin ( <i>AVP</i> , P01185) > oxytocin ( <i>OXT</i> , P01178) [30, 420, 567, 877, 1848, 2247, 2512, 2565]
Selective agonists	selepressin [1414], F180 [62, 491]	d[Leu <sup>4</sup> ]LVP [2014], d[Cha <sup>4</sup> ]AVP [567, 877]
Antagonists	conivaptan (pK <sub>i</sub> 8.2–8.4) [2512, 2513]	nelivaptan (pK <sub>i</sub> 8.4–9.3) [877, 2341]
Selective antagonists	relcovaptan (pK <sub>i</sub> 8.1–9.3) [30, 491, 877, 2512, 2564], d(CH2)5[Tyr(Me)2,Arg8]VP (pK <sub>i</sub> 9)	–

Labelled ligands	[ <sup>125</sup> I]OH-LVA (Antagonist) (p <i>K<sub>d</sub></i> 10.3–10.4) [432, 491], [ <sup>3</sup> H]AVP (human, mouse, rat) (Agonist) [275, 432, 2512, 2513, 2564], [ <sup>3</sup> H]d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me) <sub>2</sub> ]AVP (Antagonist) (p <i>K<sub>d</sub></i> 9)	[ <sup>3</sup> H]AVP (human, mouse, rat) (Agonist) [567, 2247, 2512, 2513, 2565]
Nomenclature	V <sub>2</sub> receptor	OT receptor
HGNC, UniProt	AVPR2, P30518	OXTR, P30559
Potency order of endogenous ligands	vasopressin (AVP, P01185) > oxytocin (OXT, P01178) [30, 420, 432, 2014, 2339, 2512, 2854]	oxytocin (OXT, P01178) > vasopressin (AVP, P01185) [30, 432, 433, 462, 877, 1153, 1285]
Selective agonists	VNA932 [675], OPC-51803 [1848], d[Val <sup>4</sup> ,DArg <sup>8</sup> ]VP	[Thr <sup>4</sup> ,Gly <sup>7</sup> ]OT [323, 433, 645, 1153]
Antagonists	–	L-371,257 (p <i>K<sub>i</sub></i> 8.8) [877]
Selective antagonists	conivaptan (p <i>K<sub>i</sub></i> 9.4) [507], tolvaptan (p <i>K<sub>i</sub></i> 9.4) [2854], satavaptan (p <i>K<sub>i</sub></i> 8.4–9.3) [30, 492, 2338, 2339, 2512], lixivaptan (Inverse agonist) (p <i>K<sub>i</sub></i> 8.9–9.2) [40, 2339], d(CH <sub>2</sub> ) <sub>5</sub> [D-Ile <sup>2</sup> ,Ile <sup>4</sup> ]AVP (p <i>K<sub>i</sub></i> 6.9–8.4) [492, 2339], mozavaptan (Inverse agonist) (p <i>K<sub>i</sub></i> 7.4–8.1) [492, 2339, 2512, 2565, 2854]	retosiban (p <i>K<sub>i</sub></i> 9–9.2) [1511, 1688], SSR126768A (p <i>K<sub>i</sub></i> 8.8–9.1) [2340], es-GlyNH <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 (p <i>K<sub>i</sub></i> 8.5), L-372662 (p <i>K<sub>i</sub></i> 8.4) [170]
Labelled ligands	[ <sup>3</sup> H]AVP (human, mouse, rat) (Agonist) [492, 1848, 2512, 2513, 2854], [ <sup>3</sup> H]dDAVP (Agonist) [1651], [ <sup>3</sup> H]desGly-NH <sub>2</sub> [D-Ile <sup>2</sup> ,Ile <sup>4</sup> ]VP (p <i>K<sub>d</sub></i> 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) (p <i>K<sub>d</sub></i> 10), [ <sup>3</sup> H]OT (human, mouse, rat) (Agonist) [432, 743, 1153, 1285], [ <sup>111</sup> In]DOTA-dLVT (p <i>K<sub>d</sub></i> 8.3) [431]

**Comments:** Vasopressin and OT 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 [35]. Similarly, desmopressin

(dDAVP) is more V<sub>2</sub> selective in the rat than in the human [2247]. The gene encoding the V<sub>2</sub> receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [200]. Agonist d[Cha<sup>4</sup>]AVP is selective only for the human and bovine V<sub>1B</sub> receptors [567], while d[Leu<sup>4</sup>]LVP has high affinity for the rat V<sub>1B</sub> receptor [2014]. There are a group of V<sub>1B</sub> receptor antagonists - TASP0233278, TASP0380325 and TASP0434299 that exhibit good selectivity profiles (human, rat) [1101, 1320]. Agonist and

antagonist selectivity for the OT receptor may vary in different species, as shown for Thr<sup>4</sup>Gly<sup>7</sup>OT in mice, rats and humans [323]. Knockouts of vasopressin and OT 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 [950, 951]**) 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 display 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 [529]. **PG 99-465 [1789]** has been used as a selective VPAC<sub>2</sub> receptor antagonist in a number of physiological studies, but has been reported to have

significant activity at VPAC<sub>1</sub> and PAC<sub>1</sub> receptors [581]. 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 [1805]. Two deletion variants of **maxadilan**, **M65 [2624]** and **Max.d.4 [1806]** 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	<b>ADCYAP1R1, P41586</b>	<b>VIPR1, P32241</b>	<b>VIPR2, P41587</b>
Potency order of endogenous ligands	<b>PACAP-27 (ADCYAP1, P18509)</b> , <b>PACAP-38 (ADCYAP1, P18509)</b> ≫ <b>VIP (VIP, P01282)</b>	<b>VIP (VIP, P01282)</b> , <b>PACAP-27 (ADCYAP1, P18509)</b> , <b>PACAP-38 (ADCYAP1, P18509)</b> ≫ <b>GHRH (GHRH, P01286)</b> , <b>PHI {Pig}</b> , <b>secretin (SCT, P09683)</b>	<b>VIP (VIP, P01282)</b> , <b>PACAP-38 (ADCYAP1, P18509)</b> , <b>PACAP-27 (ADCYAP1, P18509)</b> > <b>PHI {Pig}</b> ≫ <b>GHRH (GHRH, P01286)</b> , <b>secretin (SCT, P09683)</b>
Selective agonists	<b>maxadilan [581]</b> , <b>maxadilan [581]</b>	<b>[Lys15,Arg16,Leu27]VIP-(1-7)/GRF-(8-27)-NH<sub>2</sub> [1781]</b> , <b>[Ala11,22,28]VIP [1892]</b>	<b>Ro 25-1553 [860, 1193, 1781]</b> , <b>Ro 25-1392 [2828]</b>
Selective antagonists	–	<b>PG 97-269 (pIC<sub>50</sub> 8.7) [859, 1193]</b>	–
Labelled ligands	<b>[<sup>125</sup>I]PACAP-27 (Agonist) [2055]</b>	<b>[<sup>125</sup>I]VIP (human, mouse, rat) (Agonist) [1892]</b> , <b>[<sup>125</sup>I]PACAP-27 (Agonist)</b>	<b>[<sup>125</sup>I]VIP (human, mouse, rat) (Agonist) [1892]</b> , <b>[<sup>125</sup>I]PACAP-27 (Agonist)</b>

**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 [2659], or from alternative splicing of PAC<sub>1</sub> receptor mRNA [2442].

## Further reading on VIP and PACAP receptors

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