THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: G protein-coupled receptors

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Abstract
The Concise Guide to PHARMACOLOGY 2015/16 provides concise overviews of the key properties of over 1750 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.13348/full. G protein-coupled receptors are one of the eight major pharmacological targets into which the Guide is divided, with the others being: ligand-gated ion channels, voltage-gated ion channels, other 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 Concise Guide is published in landscape format in order to facilitate comparison of related targets.
It is a condensed version of material contemporary to late 2015, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in the previous Guides to Receptors & Channels and the Concise Guide to PHARMACOLOGY 2013/14. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

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

G-Protein-coupled receptors

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) [1309]. The remaining 350 non-sensory GPCRs mediate intercellular signalling by ligands that range in size from small molecules to peptide to large proteins; they are the targets for the majority of drugs in clinical usage [1451, 1560], although only a minority of these receptors are exploited therapeutically.
The first classification scheme to be proposed for GPCRs [984] 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’ [1666] 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 [class C list] and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man [1309].

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) [Class A list].

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 [1538], [Adhesion family list].

Frizzled family (class F) consists of 10 Frizzled proteins (FZD(1-10)) and Smoothened (SMO) [Frizzled family list]. 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 (class B), 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) [703].

GPCR families

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

<sup>a</sup>Numbers in brackets refer to orphan receptors for which an endogenous ligand has been proposed in at least one publication, see [396]<sup>b</sup>, [1443]<sup>c</sup>, [1309]<sup>d</sup>, [1866]<sup>e</sup>.

Much of our current understanding of the structure and function of GPCRs is the result of pioneering work on the visual pigment rhodopsin and on the β<sub>2</sub> adrenoceptor, the latter culminating in the award of the 2012 Nobel Prize in chemistry to Robert Lefkowitz and Brian Kobilka [975, 1073].

Family structure

5746 Orphan and other 7TM receptors
5746 Class A Orphans
5756 Class C Orphans
5756 Taste 1 receptors
5737 Taste 2 receptors
5758 Other 7TM proteins
5759 5-Hydroxytryptamine receptors
5764 Acetylcholine receptors (muscarinic)
5766 Adenosine receptors
5768 Adhesion Class GPCRs
5770 Adrenoceptors
5774 Angiotensin receptors
5775 Apelin receptor
5777 Bile acid receptor
5778 Bombesin receptors
5780 Bradykinin receptors
5781 Calcinotor receptors
5783 Calcium-sensing receptors
5784 Cannabinoid receptors
5785 Chemerin receptor
5785 Chemokine receptors
5791 Cholecystokinin receptors
5792 Class Frizzled GPCRs
5793 Complement peptide receptors
5795 Corticotropin-releasing factor receptors
5796 Dopamine receptors
5798 Endothelin receptors
5799 G protein-coupled estrogen receptor
5800 Formylpeptide receptors
5801 Free fatty acid receptors
5803 GABA<sub>B</sub> receptors
5805 Galanin receptors
5806 Ghrelin receptor
5807 Glucagon receptor family
5809 Glycoprotein hormone receptors
5810 Gonadotrophin-releasing hormone receptors
5811 GPR18, GPR55 and GPR119
5812 Histamine receptors
5814 Hydroxyacylglutaric acid receptors
5815 Kisspeptin receptor
5816 Leukotriene receptors
5818 Lysocephospholipid (LPA) receptors
5819 Lysocephospholipid (S1P) receptors
5820 Melanin-concentrating hormone receptors
5821 Melanocortin receptors

Searchable database: http://www.guidetopharmacology.org/index.jsp
### Orphan and other 7TM receptors

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

**Overview:** Table 1 lists a number of putative GPCRs identified by NC-IUPHAR [530], 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 [396]. The GPCRs in Table 1 are all Class A, rhodopsin-like GPCRs. Class A orphan GPCRs not listed in Table 1 are putative GPCRs with as-yet unidentified endogenous ligands.

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

<table>
<thead>
<tr>
<th>GPR1</th>
<th>GPR3</th>
<th>GPR4</th>
<th>GPR6</th>
<th>GPR12</th>
<th>GPR15</th>
<th>GPR17</th>
<th>GPR20</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPR22</td>
<td>GPR26</td>
<td>GPR31</td>
<td>GPR34</td>
<td>GPR35</td>
<td>GPR37</td>
<td>GPR39</td>
<td>GPR50</td>
</tr>
<tr>
<td>GPR63</td>
<td>GPR65</td>
<td>GPR68</td>
<td>GPR75</td>
<td>GPR84</td>
<td>GPR87</td>
<td>GPR88</td>
<td>GPR132</td>
</tr>
<tr>
<td>GPR149</td>
<td>GPR161</td>
<td>GPR183</td>
<td>LGR4</td>
<td>LGR5</td>
<td>LGR6</td>
<td>MAS1</td>
<td>MRGPRD</td>
</tr>
<tr>
<td>MRGPRX1</td>
<td>MRGPRX2</td>
<td>P2RY10</td>
<td>TAAR2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR1</th>
<th>GPR3</th>
<th>GPR4</th>
<th>GPR6</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GPR1, P46091</td>
<td>GPR3, P46089</td>
<td>GPR4, P46093</td>
<td>GPR6, P46095</td>
</tr>
<tr>
<td>Endogenous ligand</td>
<td>–</td>
<td>–</td>
<td>Protons</td>
<td>–</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>chemerin (RARRES2, Q99969) (pK\textsubscript{d} 8.3) [95]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>–</td>
<td>diphenyleiodonium chloride (pEC\textsubscript{50} 6) [2091]</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

### Nomenclature

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR1</th>
<th>GPR3</th>
<th>GPR4</th>
<th>GPR6</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GPR12, P47775</td>
<td>GPR15, P49685</td>
<td>GPR17, Q13304</td>
<td>GPR19, Q15760</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
<td>UDP-glucose (pEC$<em>{50}$ 5.9–9.5) [130, 344], LTC$<em>4$ (pEC$</em>{50}$ 7.8–9.5) [344], UDP-galactose (pEC$</em>{50}$ 6–8.9) [130, 344], uridine diphosphate (pEC$_{50}$ 6–8.8) [130, 344], LTD$<em>4$ (pEC$</em>{50}$ 8.1–8.4) [344]</td>
<td>–</td>
</tr>
</tbody>
</table>

### Comments

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR1</th>
<th>GPR3</th>
<th>GPR4</th>
<th>GPR6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Reported to act as a co-receptor for HIV [1724]. See review [396] for discussion of pairing with chemerin.</td>
<td>sphingosine 1-phosphate was reported to be an endogenous agonist [1921], but this finding was not replicated in subsequent studies [2093]. Reported to activate adenylyl cyclase constitutively through Gs [466]. Gene disruption results in premature ovarian ageing [1063], reduced β-amyloid deposition [1868] and hypersensitivity to thermal pain [1615] in mice. First small molecule inverse agonist [860] and agonists identified [2091].</td>
<td>An initial report suggesting activation by lysocephatidylcholine and sphingosylphosphorylcholine [2131] has been retracted [2148]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [396, 1704]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [2085]. Negative allosteric modulators of GPR4 have been reported [1889].</td>
<td>An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC$_{50}$ value of 39nM) [815, 1921] was not repeated by arrestin PathHunter™ assays [1785, 2093]. Reported to activate adenylyl cyclase constitutively through Gs and to be located intracellularly [1453]. GPR6-deficient mice showed reduced striatal cyclic AMP production in vitro and selected alterations in instrumental conditioning in vivo. [1134].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR12</th>
<th>GPR15</th>
<th>GPR17</th>
<th>GPR19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

| Comments | Reports that sphingosine 1-phosphate is a ligand of GPR12 [814, 1921] have not been replicated in arrestin-based assays [1785, 2093]. Gene disruption results in dyslipidaemia and obesity [154]. | Reports to act as a co-receptor for HIV [462]. In an infection-induced colitis model, Gpr15 knockout mice were more prone to tissue damage and inflammatory cytokine expression [945]. | Reported to be a dual leukotriene and uridine diphosphate receptor [344]. Another group instead proposed that GPR17 functions as a negative regulator of the CysLT$_1$ receptor response to leukotriene D$_4$ (LTD$_4$). For further discussion, see [396]. Reported to antagonize CysLT$_1$ receptor signalling in vivo and in vitro [1175]. See reviews [250] and [396]. | – |
### Nomenclature

<table>
<thead>
<tr>
<th>GPR20</th>
<th>GPR21</th>
<th>GPR22</th>
<th>GPR25</th>
<th>GPR26</th>
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<tr>
<td>GPR20, Q99678</td>
<td>GPR21, Q99679</td>
<td>GPR22, Q99680</td>
<td>GPR25, Q00155</td>
<td>GPR26, Q8NDV2</td>
</tr>
</tbody>
</table>

### Comments

**GPR20**: Reported to inhibit adenylyl cyclase constitutively through $G_{i/o}$ [708]. GPR20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [207].

**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 [1448].

**GPR22**: Gene disruption results in increased severity of functional decompensation following aortic banding [10]. Identified as a susceptibility locus for osteoarthritis [494, 929, 1935].

**GPR25**: –

**GPR26**: Has been reported to activate adenylyl cyclase constitutively through $G_s$ [880]. Gpr26 knockout mice show increased levels of anxiety and depression-like behaviours [2117].

### Nomenclature

<table>
<thead>
<tr>
<th>GPR27</th>
<th>GPR31</th>
<th>GPR32</th>
<th>GPR33</th>
<th>GPR34</th>
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<tbody>
<tr>
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<td>HGNC, UniProt</td>
<td>HGNC, UniProt</td>
<td>HGNC, UniProt</td>
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</tr>
<tr>
<td>GPR27, Q9NS67</td>
<td>GPR31, Q00270</td>
<td>GPR32, Q75388</td>
<td>GPR33, Q495Q1</td>
<td>GPR34, Q9UPC5</td>
</tr>
</tbody>
</table>

### Rank order of potency

- –

### Endogenous agonists

- – 12S-HETE (Selective) (pEC$_{50}$ 9.6) [665] – Mouse
- – resolvin D1 > LXA$_4$
- – resolvin D1 (pEC$_{50}$ 11.1) [1006], LXA$_4$ (pEC$_{50}$ 9.7) [1006]
- – lyosphosphatidylserine (Selective) (pEC$_{50}$ 6.6–6.9) [960, 1817]
- –

### Labelled ligands

- –
- –
- – 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 [1785]. Fails to respond to a variety of lipid-derived agents [2093]. Gene disruption results in an enhanced immune response [1102]. Characterization of agonists at this receptor is discussed in [819] and [396].

### Comments

**GPR27**: Knockdown of Gpr27 reduces endogenous mouse insulin promotor activity and glucose-stimulated insulin secretion [1012].

**GPR31**: See [396] for discussion of pairing.

**GPR32**: Resolvin D1 has been demonstrated to activate GPR32 in two publications [316, 1006]. The pairing was not replicated in a recent study based on arrestin recruitment [1785]. GPR32 is a pseudogene in mice and rats. See reviews [250] and [396].

**GPR33**: GPR33 is a pseudogene in most individuals, containing a premature stop codon within the coding sequence of the second intracellular loop [1621].

**GPR34**: Lyosphosphatidylserine 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 [1785]. Fails to respond to a variety of lipid-derived agents [2093]. Gene disruption results in an enhanced immune response [1102]. Characterization of agonists at this receptor is discussed in [819] and [396].
Nomenclature  | GPR35 |
HGNC, UniProt | GPR35, Q9HC97 |
Endogenous agonists | 2-oleoyl-LPA (pEC<sub>50</sub> 7.3–7.5) [1436], kynurenic acid (pEC<sub>50</sub> 3.9–4.4) [1785, 1980] |
Agonists | – |
Comments | 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 [1015]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [1436] but these results were not replicated in an arrestin assay [1785]. The phosphodiesterase inhibitor zaprinast [1863] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signalling [1863]. GPR35 is also activated by the pharmaceutical adjunct pamoic acid [2124]. See reviews [396] and [429]. |

Nomenclature  | GPR37 |
HGNC, UniProt | GPR37, O15354 |
Endogenous agonists | – |
Agonists | neuropeptide head activator (pEC<sub>50</sub> 8–8.5) [1578] |
Comments | Reported to associate and regulate the dopamine transporter [1207] and to be a substrate for parkin [1205]. Gene disruption results in altered striatal signalling [1206]. The peptides prosaptide and prosaposin are proposed as endogenous ligands for GPR37 and GPR37L1 [1264]. |

Nomenclature  | GPR39 |
HGNC, UniProt | GPR39, O43194 |
Endogenous agonists | – |
Agonists | compound 1 [PMID: 24900608] (pEC<sub>50</sub> 4.9–7.2) [166] |
Comments | Zn<sup>2+</sup> has been reported to be a potent and efficacious agonist of human, mouse and rat GPR39 [2089]. Obestatin (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 [273]. Gene disruption results in obesity and altered adipocyte metabolism [1497]. Reviewed in [396]. |

Nomenclature  | GPR42 |
HGNC, UniProt | GPR42, O15529 |
Comments | – |

Nomenclature  | GPR45 |
HGNC, UniProt | GPR45, Q9YSY3 |
Comments | – |

Nomenclature  | GPR50 |
HGNC, UniProt | GPR50, Q13585 |
Comments | GPR50 is structurally related to MT<sub>1</sub> and MT<sub>2</sub> melatonin receptors, with which it heterodimerises constitutively and specifically [1089]. Gpr50 knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [111]. |

Nomenclature  | GPR52 |
HGNC, UniProt | GPR52, Q9Y2TS |
Comments | First small molecule agonist reported [1703]. |

Nomenclature  | GPR61 |
HGNC, UniProt | GPR61, Q9BZJ8 |
Comments | GPR61 deficient mice exhibit obesity associated with hyperphagia [1363]. Although no endogenous ligands have been identified, 5-(nonyloxy)tryptamine has been reported to be a low affinity inverse agonist [1852]. |
### GPR62

**HGNC, UniProt**
- GPR62, Q9BZJ7

**Endogenous ligand**
- sphingosine 1-phosphate and dioleoylphosphatidic acid have been reported to be low affinity agonists for GPR63 [1394] but this finding was not replicated in an arrestin-based assay [2093].

**Comments**
- GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [396, 1704].
- GPR68 was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [2068], but the original publication has been retracted [2067].
- A family of 3,5-disubstituted isoxazoles were identified as agonists of GPR68 [1617].

### GPR63

**HGNC, UniProt**
- GPR63, Q9BZJ6

**Endogenous ligand**
- Protons

**Comments**
- GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [396, 1704].
- Reports to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease [1000].

### GPR65

**HGNC, UniProt**
- GPR65, Q8Y1L9

**Endogenous ligand**
- Protons

**Comments**
- CCL5 (CCLS, P13501) was reported to be an agonist of GPR75 [816], but the pairing could not be repeated in an arrestin assay [1785].

### GPR68

**HGNC, UniProt**
- GPR68, Q15743

**Endogenous ligand**
- Protons

**Comments**
- GPR68 was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [2068], but the original publication has been retracted [2067].
- GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [396, 1704].
- A family of 3,5-disubstituted isoxazoles were identified as agonists of GPR68 [1617].

### GPR75

**HGNC, UniProt**
- GPR75, O95800

**Endogenous ligand**
- –

**Comments**
- CCL5 (CCLS, P13501) was reported to be an agonist of GPR75 [816], but the pairing could not be repeated in an arrestin assay [1785].
<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR85</th>
<th>GPR87</th>
<th>GPR88</th>
<th>GPR101</th>
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<tbody>
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<td>GPR85, P60893</td>
<td>GPR87, Q9BY21</td>
<td>GPR88, Q9GZN0</td>
<td>GPR101, Q96P66</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>LPA (pEC₅₀ 7.4) [1344, 1836]</td>
<td>–</td>
<td>compound 2 [PMID: 24793972] (pEC₅₀ 6.2) [868]</td>
</tr>
<tr>
<td>Agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>Proposed to regulate hippocampal neurogenesis in the adult, as well as neurogenesis-dependent learning and memory [303].</td>
<td>–</td>
<td>Gene disruption results in altered striatal signalling [1137]. Small molecule agonists have been reported [147].</td>
<td>Mutations in GPR101 have been linked to gigantism and acromegaly [1906].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR132</th>
<th>GPR135</th>
<th>GPR139</th>
<th>GPR141</th>
<th>GPR142</th>
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<td>HGNC, UniProt</td>
<td>GPR132, Q9UNW8</td>
<td>GPR135, Q8IZ08</td>
<td>GPR139, Q6DWJ6</td>
<td>GPR141, Q7Z602</td>
<td>GPR142, Q7Z601</td>
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<tr>
<td>Endogenous ligand</td>
<td>Protons</td>
<td>–</td>
<td>–</td>
<td>compound 1a [PMID: 24900311] (pEC₅₀ 7.4) [1721]</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>–</td>
<td>–</td>
<td>Peptide agonists have been reported [828].</td>
<td>–</td>
<td>Small molecule agonists have been reported [1890, 2106].</td>
</tr>
<tr>
<td>Comments</td>
<td>GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [396, 1704]. Reported to respond to lysophosphatidylcholine [891], but later retracted [2038].</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Nomenclature</td>
<td>Comments</td>
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<td>--------------</td>
<td>----------</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GPR146, GPR146, Q96CH1</td>
<td>Yosten et al. 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 [2103].</td>
<td></td>
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<tr>
<td>GPR148, GPR148, Q8TDV2</td>
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<td></td>
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<tr>
<td>GPR149, Q86SP6</td>
<td>Gpr149 knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [463].</td>
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<tr>
<td>GPR150, Q8NGU9</td>
<td></td>
<td></td>
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<tr>
<td>GPR151, GPR151, Q8TDV0</td>
<td>GPR151 responded to galanin with an EC50 value of 2 μM, suggesting that the endogenous ligand shares structural features with galanin (GAL, P22466) [813].</td>
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<tr>
<td>GPR152, GPR152, Q8TDT2</td>
<td>A C-terminal truncation (deletion) mutation in Gpr161 causes congenital cataracts and neural tube defects in the vacuolated lens (vl) mouse mutant [1226]. The mutated receptor is associated with cataract, spina bifida and white belly spot phenotypes in mice [994]. Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish [1085].</td>
<td></td>
<td></td>
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<tr>
<td>GPR153, GPR153, Q6NV75</td>
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<td>GPR160, GPR160, Q9UJ42</td>
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<tr>
<td>GPR161, Q8NU68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPR162, GPR162, Q16538</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GPR171, O14626</td>
<td>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 [621].</td>
<td></td>
<td></td>
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<tr>
<td>GPR173, Q9NS66</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GPR174, Q98XC1</td>
<td>lysophosphatidylserine (pEC50 7.1) [825] See [819] which discusses characterization of agonists at this receptor.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GPR176, Q14439</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GPR182, O15218</td>
<td>Rat GPR182 was first proposed as the adrenomedullin receptor [904]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [927] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [722].</td>
<td></td>
<td></td>
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Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)  
### Nomenclature

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<th>LGR5</th>
<th>LGR6</th>
<th>MAST</th>
</tr>
</thead>
<tbody>
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<td>PR183, P32249</td>
<td>LGR4, Q9BXB1</td>
<td>LGR5, Q75473</td>
<td>LGR6, Q9HBX8</td>
<td>MAST, P04201</td>
</tr>
</tbody>
</table>

### Endogenous agonists

- **7α,25-dihydroxycholesterol** (Selective) (pEC$_{50}$ 8.1–9.8) [694, 1125], 7α,27-dihydroxycholesterol (Selective) (pEC$_{50}$ 8.9) [1125], 7β, 25-dihydroxycholesterol (Selective) (pEC$_{50}$ 8.7) [1125], 7β, 27-dihydroxycholesterol (Selective) (pEC$_{50}$ 7.3) [1125]

### Agonists

- angiotensin-(1-7) (AGT, P01019) (pK$_i$ 7.3) [612]

### Comments

- Two independent publications have shown that 7α,25-dihydroxycholesterol is an agonist of GPR183 and have demonstrated by mass spectrometry that this oxysterol is present endogenously in tissues [694, 1125]. 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 [923, 1488].

- 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 [266, 1612, 2140]. Gene disruption leads to multiple developmental disorders [869, 1154, 1781, 2005].

- 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 [266, 2140].
<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>HGNC, UniProt</th>
<th>Endogenous agonists</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS1L</td>
<td>MAS1L, P35410</td>
<td>–</td>
<td>An endogenous peptide with a high degree of sequence similarity to angiotensin-(1-7) (AGT, P01019), alamandine (AGT), was shown to promote NO release in MRGPRD-transfected cells. The binding of alamandine to MRGPRD was shown to be blocked by D-Pro&lt;sup&gt;7&lt;/sup&gt;-angiotensin-(1-7), β-alanine and PD123319 [1045]. Genetic ablation of MRGPRD&lt;sup&gt;+&lt;/sup&gt; neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [278]. See reviews [396] and [1779].</td>
</tr>
<tr>
<td>MRGPRD</td>
<td>MRGPRD, Q8TDS7</td>
<td>β-alanine (pEC&lt;sub&gt;50&lt;/sub&gt; 4.8) [1729, 1785]</td>
<td>See reviews [396] and [1779].</td>
</tr>
<tr>
<td>MRGPRE</td>
<td>MRGPRE, Q86SM8</td>
<td>–</td>
<td>MRGPRF has been reported to respond to stimulation by angiotensin metabolites [589]. See reviews [396] and [1779].</td>
</tr>
<tr>
<td>MRGPRF</td>
<td>MRGPRF, Q96AM1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MRGPRG</td>
<td>MRGPRG, Q86SM5</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>HGNC, UniProt</th>
<th>Endogenous agonists</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRGPRX1</td>
<td>MRGPRX1, Q96LB2</td>
<td>bovine adrenal medulla peptide 8-22 (PENK, P01210) (Selective) (pEC&lt;sub&gt;50&lt;/sub&gt; 5.3–7.8) [299, 1080, 1785]</td>
<td>Reported to mediate the sensation of itch [1131, 1739]. Reports that bovine adrenal medulla peptide 8-22 (PENK, P01210) was the most potent of a series of proenkephalin &lt;sup&gt;A&lt;/sup&gt;-derived peptides as an agonist of MRGPRX1 in assays of calcium mobilisation and radioligand binding [1080] were replicated in an independent study using an arrestin recruitment assay [1785]. See reviews [396] and [1779].</td>
</tr>
<tr>
<td>MRGPRX2</td>
<td>MRGPRX2, Q96LB1</td>
<td>PAMP-20 (ADM, P35318) (Selective) [899]</td>
<td>–</td>
</tr>
<tr>
<td>MRGPRX3</td>
<td>MRGPRX3, Q96LB0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MRGPRX4</td>
<td>MRGPRX4, Q96LA9</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Agonists

Selective agonists

Comments

See reviews [396] and [1779].

A diverse range of substances has been reported to be agonists of MRGPRX2, with cortistatin 14 the highest potency agonist in assays of calcium mobilisation [1594], also confirmed in an independent study using an arrestin recruitment assay [1785]. See reviews [396] and [1779].
### Nomenclature

<table>
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<tr>
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<th>OPN3</th>
<th>OPN4</th>
<th>OPNS</th>
<th>PSRY8</th>
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</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>OPN3, Q9H1Y3</td>
<td>OPN4, Q9UHM6</td>
<td>OPNS, Q6U736</td>
<td>PSRY8, Q86VZ1</td>
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<tr>
<td>Comments</td>
<td>–</td>
<td>–</td>
<td>Evidence indicates OPNS triggers a UV-sensitive G_i-mediated signalling pathway in mammalian tissues [982].</td>
<td>–</td>
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</table>

### Nomenclature

<table>
<thead>
<tr>
<th></th>
<th>P2RY10</th>
<th>TAAR2</th>
<th>TAAR3</th>
<th>TAAR4P</th>
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<tr>
<td>HGNC, UniProt</td>
<td>P2RY10, O00398</td>
<td>TAAR2, Q9P1PS</td>
<td>TAAR3, Q9P1P4</td>
<td>TAAR4P, –</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>–</td>
<td>β-phenylethylamine – tryptamine [185]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>sphingosine 1-phosphate (Selective) (pEC_50 7.3) [1344], LPA (Selective) (pEC_50 6.9) [1344]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>–</td>
<td>Probable pseudogene in 10-15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [396].</td>
<td>TAAR3 is thought to be a pseudogene in man though functional in rodents [396].</td>
<td>Pseudogene in man but functional in rodents [396].</td>
</tr>
</tbody>
</table>

### Nomenclature

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<th>TAAR5</th>
<th>TAAR6</th>
<th>TAAR8</th>
<th>TAAR9</th>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>TAAR5, Q14804</td>
<td>TAAR6, Q96R18</td>
<td>TAAR8, Q969N4</td>
<td>TAAR9, Q96R19</td>
</tr>
<tr>
<td>Comments</td>
<td>Trimethylamine is reported as an agonist [1974] and 3-iodothyronamine an inverse agonist [426].</td>
<td>–</td>
<td>–</td>
<td>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 [1944].</td>
</tr>
</tbody>
</table>

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**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Class C Orphans

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

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR156</th>
<th>GPR158</th>
<th>GPR179</th>
<th>GPRCSA</th>
<th>GPRCS8</th>
<th>GPRCSC</th>
<th>GPRCSD</th>
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<tbody>
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<td>GPR156, Q8NFN8</td>
<td>GPR158, Q8ST48</td>
<td>GPR179, Q6PRD1</td>
<td>GPRCSA, Q8NFJ5</td>
<td>GPRCS8, Q9NZH0</td>
<td>GPRCSC, Q9NQ84</td>
<td>GPRCSD, Q9NZD1</td>
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</tbody>
</table>

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 [2122], TRPM5 [2122] and IP3 [764] 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 [1096]. T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin [1376].

<table>
<thead>
<tr>
<th>Nomenclature</th>
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<th>TAS1R2</th>
<th>TAS1R3</th>
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<td>HGNC, UniProt</td>
<td>TAS1R1, Q7RTX1</td>
<td>TAS1R2, Q8TE23</td>
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Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

### Taste 2 receptors

G protein-coupled receptors → Orphan and other 7TM receptors → Taste 2 receptors

#### Bitter

The composition and stoichiometry of bitter taste receptors is not yet established. Bitter receptors appear to separate into two groups, with very restricted ligand specificity or much broader responsiveness. For example, T2R5 responded to cycloheximide, but not 10 other bitter compounds [287], while T2R14 responded to at least eight different bitter tastants, including (-)-α-thujone and picrotoxinin [119]. Specialist database BitterDB contains additional information on bitter compounds and receptors [2023].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>TAS2R1</th>
<th>TAS2R3</th>
<th>TAS2R4</th>
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<td>TAS2R3, Q9NYW6</td>
<td>TAS2R4, Q9NYW5</td>
<td>TAS2R5, Q9NYW4</td>
<td>TAS2R7, Q9NYW3</td>
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<tr>
<td>HGNC, UniProt</td>
<td>TAS2R9, Q9NYW1</td>
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<td>TAS2R14, Q9NYV8</td>
<td>TAS2R16, Q9NYV7</td>
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<td>TAS2R42, Q7RTR8</td>
<td>TAS2R43, PS9537</td>
<td>TAS2R45, PS9539</td>
<td>TAS2R46, PS9540</td>
<td>TAS2R50, PS9544</td>
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Other 7TM proteins

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

<table>
<thead>
<tr>
<th>Nomenclature</th>
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<th>GPR137</th>
<th>OR51E1</th>
<th>TPRA1</th>
<th>GPR143</th>
<th>GPR157</th>
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<td>GPR107, QSVW38</td>
<td>GPR137, Q96N19</td>
<td>OR51E1, Q8TCB6</td>
<td>TPRA1, Q86W33</td>
<td>GPR143, P51810</td>
<td>GPR157, QSUAW9</td>
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<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>levodopa [1141]</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>GPR107 is a member of the LUSTR family of proteins found in both plants and animals, having similar topology to G protein-coupled receptors [461]</td>
<td>–</td>
<td>OR51E1 is a putative olfactory receptor.</td>
<td>TPRA1 shows no homology to known G protein-coupled receptors.</td>
<td>Loss-of-function mutations underlie ocular albinism type 1 [103].</td>
<td>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.</td>
</tr>
</tbody>
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Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

5-Hydroxytryptamine receptors

**Overview:** 5-HT receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-HT receptors [789] and subsequently revised [707]) are, with the exception of the ionotropic 5-HT2 class, GPCR receptors where the endogenous agonist is 5-hydroxytryptamine. The diversity of metabotropic 5-HT receptors is increased by alternative splicing that produces isoforms of the 5-HT2A (non-functional), 5-HT2C (non-functional), 5-HT4, 5-HT6 (non-functional) and 5-HT7 receptors. Unique amongst the GPCRs, RNA editing produces 5-HT2C receptor isoforms that differ in function, such as efficiency and specificity of coupling to Gq/11 and also pharmacology [164, 2011]. Most 5-HT receptors (except 5-HT1e and 5-HT 5a/5b) play specific roles mediating functional responses in different tissues (reviewed by [1554, 1957]).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>S-HT1A receptor</th>
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<th>S-HT1D receptor</th>
<th>S-HT1E receptor</th>
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<td>HTR1B, P28222</td>
<td>HTR1D, P28221</td>
<td>HTR1E, P28566</td>
<td>HTR1F, P30939</td>
</tr>
</tbody>
</table>

### Agonists
- **U92016A** (pKᵢ 9.7) [1240], vilazodone (Partial agonist) (pKᵢ 9.7) [402], vortioxetine (Partial agonist) (pKᵢ 7.8) [90]
- **L-694,247** (pKᵢ 9.2) [637], naratriptan (Partial agonist) (pKᵢ 8.1) [1365], eletriptan (pKᵢ 8) [2069], zolmitriptan (Partial agonist) (pKᵢ 7.7) [1365], vortioxetine (Partial agonist) (pKᵢ 7.5) [90], rizatriptan (Partial agonist) (pKᵢ 7.9) [1365]
- **CP94253** (pKᵢ 8.7) [976]
- **PNU109291** (pKᵢ 9.1) [483], Gorilla, eletriptan (pKᵢ 8.9) [1365]
- **SB 224289** (Inverse agonist) (pKᵢ 8.2-8.6) [583, 1384, 1696], SB236057 (Inverse agonist) (pKᵢ 8.2) [1272], GR-55562 (pKᵢ 7.4) [791]
- **SB 714786** (pKᵢ 9.1) [1987]

### Selective agonists
- **8-OH-DPAT** (pKᵢ 8.4-9.4) [406, 685, 896, 1079, 1280, 1386, 1388, 1389], NLX-101 (pKᵢ 8.6) [1387]
- **CB 94253** (pKᵢ 8.7) [976]
- **PNU109291** (pKᵢ 9.1) [483], Gorilla, eletriptan (pKᵢ 8.9) [1365]
- **SB 224289** (Inverse agonist) (pKᵢ 8.2-8.6) [583, 1384, 1696], SB236057 (Inverse agonist) (pKᵢ 8.2) [1272], GR-55562 (pKᵢ 7.4) [791]

### Antagonists
- **(S)-UH 301** (pKᵢ 7.9) [1386]
- **WAY-100635** (pKᵢ 7.9-9.2) [1386, 1388], robustan (pKᵢ 9.2) [872]
- **SB 224289** (Inverse agonist) (pKᵢ 8.2-8.6) [583, 1384, 1696], SB236057 (Inverse agonist) (pKᵢ 8.2) [1272], GR-55562 (pKᵢ 7.4) [791]
- **SB 714786** (pKᵢ 9.1) [1987]

### Selective antagonists
- **(S)-UH 301** (pKᵢ 7.9) [1386]
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- **SB 224289** (Inverse agonist) (pKᵢ 8.2-8.6) [583, 1384, 1696], SB236057 (Inverse agonist) (pKᵢ 8.2) [1272], GR-55562 (pKᵢ 7.4) [791]
- **SB 714786** (pKᵢ 9.1) [1987]

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Nomenclature

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<th>pKd/Structure</th>
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<td>[3H]N-conjugated AZ10419369 (Agonist)</td>
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<td>5-HT&lt;sub&gt;1F&lt;/sub&gt; receptor</td>
<td>[3H]GR 125,743 (Selective Antagonist)</td>
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Labelled ligands

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<td>[3H]LY334370</td>
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<td>[125I]LSD</td>
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Comments

Wang et al. (2013) report X-ray structures which reveal the binding modality of ergotamine and dihydroergotamine to the 5-HT<sub>1B</sub> receptor in comparison with the structure of the 5-HT<sub>2B</sub> receptor [1978].
<table>
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<th>Nomenclature</th>
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<th>5-HT&lt;sub&gt;2C&lt;/sub&gt; receptor</th>
<th>5-HT&lt;sub&gt;4&lt;/sub&gt; receptor</th>
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<td>HGNC, UniProt</td>
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<td>HTR2B, P41595</td>
<td>HTR2C, P28335</td>
<td>HTR4, Q13639</td>
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<td>DOI (pK&lt;sub&gt;I&lt;/sub&gt; 7.4–9.2) [204, 1374, 1755]</td>
<td>methysergide (Partial agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 8.4) [970, 1605, 1969], DOI (pK&lt;sub&gt;I&lt;/sub&gt; 7.6–7.7) [1025, 1374, 1659]</td>
<td>DOI (pK&lt;sub&gt;I&lt;/sub&gt; 7.2–8.6) [465, 1374, 1659], Ro 60-0175 (pK&lt;sub&gt;I&lt;/sub&gt; 7.7–8.2) [953, 970]</td>
<td>cisapride (Partial agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 6.4–7.4) [77, 128, 597, 1266, 1267, 1941]</td>
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<td>BW723C86 (pK&lt;sub&gt;I&lt;/sub&gt; 7.3–8.6) [108, 970, 1659], Ro 60-0175 (pK&lt;sub&gt;I&lt;/sub&gt; 8.3) [970]</td>
<td>WAY-163909 (pK&lt;sub&gt;I&lt;/sub&gt; 6.7–8) [454], lorcaserin (pK&lt;sub&gt;I&lt;/sub&gt; 7.8) [1878]</td>
<td>TD-8954 (pK&lt;sub&gt;I&lt;/sub&gt; 9.4) [1250], ML 10302 (Partial agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 7.9–9) [136, 160, 1266, 1267, 1268], R67506 (pEC&lt;sub&gt;50&lt;/sub&gt; 8.8) [731] – Rat, relenopride (Partial agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 8.3) [607], velusetrag (pK&lt;sub&gt;I&lt;/sub&gt; 7.7) [1139, 1763], BIMU 8 (pK&lt;sub&gt;I&lt;/sub&gt; 7.3) [347]</td>
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<td>Antagonists</td>
<td>risperidone (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 9.3–10) [986, 1008, 1675], mianserin (pK&lt;sub&gt;I&lt;/sub&gt; 7.7–9.6) [970, 1001, 1280], ziprasidone (pK&lt;sub&gt;I&lt;/sub&gt; 8.8–9.5) [986, 1008, 1675, 1711], volinanserin (pEC&lt;sub&gt;50&lt;/sub&gt; 6.5–9.3) [970, 1142, 1568], blonanserin (pK&lt;sub&gt;I&lt;/sub&gt; 9.1) [1421], clozapine (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 7.6–9) [970, 1008, 1277, 1675, 1943], olanzapine (pK&lt;sub&gt;I&lt;/sub&gt; 8.6–8.9) [986, 1008, 1675, 1711], nefazodone (pK&lt;sub&gt;I&lt;/sub&gt; 8.2) [1698], chlorpromazine (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 8.1) [1008], loxapine (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 8.1) [1008], trifluoperazine (pK&lt;sub&gt;I&lt;/sub&gt; 7.9) [1008], pimozide (pK&lt;sub&gt;I&lt;/sub&gt; 7.1–7.7) [986, 1008], trazodone (pK&lt;sub&gt;I&lt;/sub&gt; 7.4) [970], haloperidol (pK&lt;sub&gt;I&lt;/sub&gt; 6.7–7.3) [1008, 1277, 1675, 1711, 1943], mesoridazine (pK&lt;sub&gt;I&lt;/sub&gt; 7.3) [326], mirtazapine (pK&lt;sub&gt;I&lt;/sub&gt; 7.2) [513], mirtazapine (pK&lt;sub&gt;I&lt;/sub&gt; 7.2) [513], quetiapine (pK&lt;sub&gt;I&lt;/sub&gt; 6.4–7) [986, 1008], molindone (pK&lt;sub&gt;I&lt;/sub&gt; 6.5) [1008]</td>
<td>mianserin (pK&lt;sub&gt;I&lt;/sub&gt; 7.9–8.8) [180, 970, 1969]</td>
<td>mianserin (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 8.3–9.2) [524, 970, 1280], methysergide (pK&lt;sub&gt;I&lt;/sub&gt; 8.6–9.1) [465, 970], ziprasidone (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 7.9–9) [743, 1008, 1711], olanzapine (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 8.1–8.4) [743, 1008, 1711], loxapine (Inverse agonist) (pK&lt;sub&gt;I&lt;/sub&gt; 7.8–8) [743, 1008], mirtazapine (pK&lt;sub&gt;I&lt;/sub&gt; 7.4) [513], mirtazapine (pK&lt;sub&gt;I&lt;/sub&gt; 7.4) [513], trazodone (pK&lt;sub&gt;I&lt;/sub&gt; 6.6) [970], trifluoperazine (pK&lt;sub&gt;I&lt;/sub&gt; 6.4) [1008], agomelatine (pK&lt;sub&gt;I&lt;/sub&gt; 6.2) [1276]</td>
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<td>Selective antagonists</td>
<td>ketanserin (p&lt;sub&gt;K&lt;/sub&gt;, 8.1–9.7) [234, 970, 1559], pimavanserin (Inverse agonist) (p&lt;sub&gt;K&lt;/sub&gt;, 9.3) [572, 1943]</td>
<td>BF-1 (p&lt;sub&gt;K&lt;/sub&gt;, 10.1) [1671], RS-127445 (p&lt;sub&gt;K&lt;/sub&gt;, 9–9.5) [180, 970], EGIS-7625 (p&lt;sub&gt;K&lt;/sub&gt;, 9) [1001]</td>
<td>FR260010 (p&lt;sub&gt;K&lt;/sub&gt;, 9) [700], SB 242084 (p&lt;sub&gt;K&lt;/sub&gt;, 8.2–9) [928, 970], RS-102221 (p&lt;sub&gt;K&lt;/sub&gt;, 8.3–8.4) [181, 970]</td>
<td>RS 100235 (p&lt;sub&gt;K&lt;/sub&gt;, 8.7–12.2) [347, 1589], SB 204070 (p&lt;sub&gt;K&lt;/sub&gt;, 9.8–10.4) [128, 1266, 1267, 1941], GR 113808 (p&lt;sub&gt;K&lt;/sub&gt;, 9.3–10.3) [77, 128, 160, 347, 1267, 1589, 1941]</td>
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<td>Labelled ligands</td>
<td>[3&lt;sup&gt;H&lt;/sup&gt;]fananserin (Antagonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 9.9) [1188] – Rat, [3&lt;sup&gt;H&lt;/sup&gt;]ketanserin (Antagonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 8.6–9.7) [970, 1559], [11&lt;sup&gt;C&lt;/sup&gt;]volanserin (Antagonist) [676], [18&lt;sup&gt;F&lt;/sup&gt;]altanserin (Antagonist) [1601]</td>
<td>[3&lt;sup&gt;H&lt;/sup&gt;]&lt;sup&gt;LSD&lt;/sup&gt; (Agonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 8.7) [1559], [3&lt;sup&gt;H&lt;/sup&gt;]&lt;sup&gt;S-HT&lt;/sup&gt; (Agonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 8.1) [1967] – Rat, [3&lt;sup&gt;H&lt;/sup&gt;]&lt;sup&gt;mesulergine&lt;/sup&gt; (Antagonist, Inverse agonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 7.9) [970], [1&lt;sup&gt;25&lt;/sup&gt;I]&lt;sup&gt;DOI&lt;/sup&gt; (Agonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 7.7–7.6)</td>
<td>[1&lt;sup&gt;25&lt;/sup&gt;I]&lt;sup&gt;DOI&lt;/sup&gt; (Agonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 8.7–9)</td>
<td>[1&lt;sup&gt;23&lt;/sup&gt;II]SB 207710 (Antagonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 10.1) [228] – Pig, [3&lt;sup&gt;H&lt;/sup&gt;]&lt;sup&gt;GR&lt;/sup&gt; 113808 (Antagonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 10.3–9.7) [77, 128, 1268, 1941], [3&lt;sup&gt;H&lt;/sup&gt;]&lt;sup&gt;RS&lt;/sup&gt; 57639 (Selective Antagonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 9.7) [179] – Guinea pig, [1&lt;sup&gt;11&lt;/sup&gt;C]SB207145 (Antagonist) (p&lt;sub&gt;K&lt;/sub&gt;&lt;sub&gt;d&lt;/sub&gt;, 8.6) [1169]</td>
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Comments

- LSD (lysergic acid) 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 S-HT<sub>7A</sub> receptors [1963]. DHE (dihydroergocryptine), pergolide and cabergoline also show significant preference for arrestin recruitment over G protein coupling at 5-HT<sub>2B</sub> receptors [1963].
- The serotonin antagonist mesulergine was key to the discovery of the 5-HT<sub>2C</sub> receptor [1479].
(continued)

<table>
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<th>Nomenclature</th>
<th>S-ht5A receptor</th>
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<td>–</td>
<td>–</td>
<td>lurasidone (pKᵢ 9.3) [829]</td>
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<tr>
<td><strong>Selective antagonists</strong></td>
<td>SB 699551 (pKᵢ 8.2) [366]</td>
<td>–</td>
<td>SB399885 (pKᵢ 9) [763], SB 271046 (pKᵢ 8.9) [224], cerlapirdine (pKᵢ 8.9) [358], SB357134 (pKᵢ 8.5) [225], Ro 63-0563 (pKᵢ 7.9–8.4) [168, 1754]</td>
<td>SB269970 (pKᵢ 8.6–8.9) [1874], SB656104 (pKᵢ 8.7) [531], DR-4004 (pKᵢ 8.7) [615, 938], JS-18038683 (pKᵢ 8.2) [177], SB 258719 (Inverse agonist) (pKᵢ 7.5) [1875]</td>
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<td><strong>Labelled ligands</strong></td>
<td>[¹²⁵I]LSD (Agonist) (pKᵢ 9.7) [636], [³H]5-CT (Agonist) (pKᵢ 8.6) [636]</td>
<td>[¹²⁵I]LSD (Agonist) (pKᵢ 9.3) [1227] – Mouse, [³H]5-CT (Agonist) [1965] – Mouse</td>
<td>[¹¹C]GSK215083 (Agonist) (pKᵢ 9.8) [1462], [¹²⁵I]SB258585 (Selective Antagonist) (pKᵢ 9) [763], [³H]LSD (Agonist) (pKᵢ 8.7) [167], [³H]Ro 63-0563 (Agonist) (pKᵢ 8.3) [168], [³H]5-CT (Agonist)</td>
<td>[³H]JLS-C (Agonist) (pKᵢ 9.4) [1874], [²H]JLS-HT (Agonist) (pKᵢ 8.1–9) [93, 1793], [³H]SB269970 (Selective Antagonist) (pKᵢ 8.9) [1874], [³H]LS (Agonist) (pKᵢ 8.5–8.6) [1793]</td>
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**Comments:** Tabulated pKᵢ and Kᵢ values refer to binding to human S-HT receptors unless indicated otherwise. The nomenclature of S-HT₁B/S-HT₁D receptors has been revised [707]. Only the non-rodent form of the receptor was previously called S-HT₁D: the human S-HT₁B receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS181 is a selective antagonist of the rodent S-HT₁B receptor. Fananserin and ketanserin bind with high affinity to dopamine D₄ and histamine H₁ receptors respectively, and ketanserin is a potent α₁ adrenoceptor antagonist, in addition to blocking S-HT₂A receptors. The human S-HT₅A receptor has been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells [1404]. The human orthologue of the mouse S-HT₅A receptor is non-functional due to interruption of the gene by stop codons. The S-HT₁P receptor appears not to have been cloned from mouse, or rat, impeding definition of its function. In addition to the receptors listed in the table, an ‘orphan’ receptor, unofficially termed S-HT₁P, has been described [600].

**Further Reading**


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Acetylcholine receptors (muscarinic)

G protein-coupled receptors → Acetylcholine receptors (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Muscarinic Acetylcholine Receptors [275]) are GPCRs of the Class A, rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42, its structural analogues AC-260584 and 77-LH-28-1, N-desmethyloxazoline, TBPB and LuAE31090 have been described as functionally selective agonists of the M1 receptor subtype via binding in a mode distinct from that utilized by non-selective agonists [71, 878, 1040, 1041, 1233, 1635, 1786, 1787, 1825]. There are two pharmacologically characterised allosteric sites on muscarinic receptors, one defined by binding gallamine, strychnine and brucine, and the other defined by the binding of KT 5720, WIN 62,577, WIN 51,708 and staurosporine [1052, 1053].

Nomenclature

M1 receptor

M2 receptor

HGN, UniProt

CHRM1, P11229

bethanechol (pK_i 4) [846]

HGN, UniProt

Agonists
carbachol (pK_i 3.2–5.3) [334, 846, 2040], pilocarpine (Partial agonist) (pK_i 5.1) [846],
bethanechol (pK_i 4) [846]

tiotropium (pK_i 6.0) [428], 4-DAMP (pK_i 9.2) [452], dicyclomine (pK_i 9.1) [68],
scopolamine (pK_i 7.9) [797], trihexyphenidyl (pK_i 8.9) [68], tripitramine (pK_i 8.8)

[beta]-telenzepine (pK_i 7.1) [875], otenzepad (pK_d 6.2) [493]

Antagonists
glycopyrrolate (pIC_50 9.2) [1801], ucmelcukim (pK_i 9.8) [1035, 1632], AE9C90CB (pK_i 9.7) [1749],
propantheline (pK_i 9.7) [797], atropine (pK_i 8.5–9.6) [334, 552, 759, 797, 1486, 1762],
tritium (pK_i 9.6) [428], 4-DAMP (pK_i 9.2) [452], dicyclomine (pK_i 9.1) [68],
scopolamine (pK_i 9) [797], trihexyphenidyl (pK_i 8.9) [68], tripitramine (pK_i 8.8)

[11C]telenzepine (pK_i 7.1) [875], otenzepad (pK_d 6.2) [493]

Select拮agonists

biperiden (pK_d 9.3) [173], VU0255035 (pK_i 7.8) [1717], guanypirenepine (pK_i 7.3–7.6) [23, 1966] – Rat

Allosteric modulators

muscarinic toxin 7 (Negative) (pK_i 11–11.1) [1414], benzoquinazoline 12 (Positive)

[pK_d 6.6] [4], KT 5720 (Positive) (pK_d 6.4) [1052], brucine (Positive) (pK_d 4.5–5.8)

[846, 1051], BQCA (Positive) (pK_d 4–4.8) [4, 5, 261, 1161], VU0029767 (Positive)

[1208], VU0090157 (Positive) [1208]

[1H]QNB (Antagonist) (pK_d 10.6–10.8) [336, 1486], Cy3B-teenzenepine (Antagonist)

(pK_d 10.5) [742], [3H]Methyl-scopolamine (Antagonist) (pK_d 9.4–10.3) [280, 334, 336, 759, 846, 847, 875, 932, 1049], [3H] Mecamylacine (Antagonist) (pK_i 9.4) [500] – Rat,
Al-688-teenzenepine (Antagonist) (pK_d 9.3) [742], [3H]pirenzepine (Antagonist)

(pK_d 7.9) [1995], BODIPY-pirenzepine (Antagonist) (pK_i 7) [820], [11C] butylothio-TZTP

(Agonist) [504], [11C]xanomeline (Agonist) [504],

[18F](R,R)-quinuclidinyl-4-fluoromethylbenzilate (Antagonist) [935] – Rat

[3H]QNB (Antagonist) (pK_d 10.1–10.6) [1486], Cy3B-teenzenepine (Antagonist)

(pK_d 10.4) [1380], [3H]tropium (Antagonist) (pK_d 10.3) [1632],
[3H]Methyl-scopolamine (Antagonist) (pK_d 9.3–9.9) [280, 310, 759, 846, 847, 875, 932, 1049, 1985], Alexa-688-teenzenepine (Antagonist) (pK_d 8.8) [1380],
[3H]acetylcholine (Agonist) (pK_d 8.8) [1050], [H]oxotremorex-M (Agonist) (pK_d 8.7)

[137], [3H]dimethyl-V84 (Allosteric modulator, Positive) (pK_d 8.5) [1908], [18F]FP-TZTP

(Agonist) [845] – Mouse

W-84 (Negative) (pK_d 6–7.5) [1299, 1908], C2/3-phth (Negative) (pK_d 7.1) [335],
acuranium (Negative) (pK_d 6.1–6.9) [846, 1908], gallamine (Negative) (pK_d 5.9–6.3)

[348, 1049], LY2119620 (Positive) (pK_d 5.7) [383, 1010], LY2033298 (Positive) (pK_d 4.4) [1933]

[1H]QNB (Antagonist) (pK_d 10.1–10.6) [1486], Cy3B-teenzenepine (Antagonist) (pK_d 10.4) [1380], [3H]tropium (Antagonist) (pK_d 10.3) [1632],
[3H]Methyl-scopolamine (Antagonist) (pK_d 9.3–9.9) [280, 310, 759, 846, 847, 875, 932, 1049, 1985], Alexa-688-teenzenepine (Antagonist) (pK_d 8.8) [1380],
[3H]acetylcholine (Agonist) (pK_d 8.8) [1050], [H]oxotremorex-M (Agonist) (pK_d 8.7)

[137], [3H]dimethyl-V84 (Allosteric modulator, Positive) (pK_d 8.5) [1908], [18F]FP-TZTP

(Agonist) [845] – Mouse

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Acetylcholine receptors (muscarinic) 5764
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<td>CHRM4, P08173</td>
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<td>pilocarpine (Partial agonist) (pKᵢ 5.2) [846], carbachol (pKᵢ 4.3–4.9) [846], bethanechol (pKᵢ 4) [846]</td>
<td>pilocarpine (Partial agonist) (pKᵢ 5) [639], carbachol (pKᵢ 4.9) [2040]</td>
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<td>Antagonists</td>
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<td>ucmeclidinium (pKᵢ 9.2–9.3) [428, 442], glycopyrrolate (pIC₅₀ 9.8) [1801], AE9C90CB (pKᵢ 9.5) [1749], 4-DAMP (pKᵢ 8.9) [458], oxybutynin (pKᵢ 8.7) [1749], biperiden (pKᵢ 8.6) [173], UH-AH 37 (pKᵢ 8.3–8.4) [609, 2012], tolterodine (pKᵢ 8.3–8.4) [609, 1749], AQ-RA 741 (pKᵢ 7.8–8.2) [458, 609], UH-AH 37 (pKᵢ 7.9–8.2) [458, 875, 1286], darifenacin (pKᵢ 7.3–8.1) [609, 730, 759, 1749], AFDX384 (pKᵢ 8) [458], triptiramine (pKᵢ 7.9) [1288], pirenzepine (pKᵢ 7–7.6) [458, 730, 797, 875, 2012], methochromine (pKᵢ 6.6–7.5) [238, 458, 493, 730, 1762], solifenacin (pKᵢ 6.8) [1749], guanaprinpirenzepine (pKᵢ 6.2) [1966] – Rat, VU0255035 (pKᵢ 5.9) [1717], muscarinic toxin 7 (pKᵢ &lt;5) [1414]</td>
<td>ucmeclidinium (pKᵢ 9.2–9.3) [428, 442], glycopyrrolate (pIC₅₀ 9.7) [1801], AE9C90CB (pKᵢ 9.5) [1749], 4-DAMP (pKᵢ 9) [458], tolterodine (pKᵢ 8.5–8.8) [609, 1749], darifenacin (pKᵢ 7.9–8.6) [609, 730, 759, 1749], UH-AH 37 (pKᵢ 8.3) [609, 2012], biperiden (pKᵢ 8.2) [173], oxybutynin (pKᵢ 7.9) [1749], AQ-RA 741 (pKᵢ 6.1–7.8) [458, 609], triptiramine (pKᵢ 7.5) [1176], methochromine (pKᵢ 6.3–7.2) [238, 458, 493, 730, 1749], solifenacin (pKᵢ 7.2) [1749], pirenzepine (pKᵢ 6.8–7.1) [730, 875, 2012], guanaprinpirenzepine (pKᵢ 6.8) [514] – Unknown, hibencine (pKᵢ 5.4–6.5) [458, 875, 1286], AFDX384 (pKᵢ 6.3) [458], muscarinic toxin 3 (pKᵢ &lt;6) [875], otenzepaz (pKᵢ 5.6) [238], muscarinic toxin 7 (pKᵢ &lt;5) [1414]</td>
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<td>Selective antagonists</td>
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<td>ML381 (pKᵢ 6.3) [593]</td>
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<td>Allosteric modulators</td>
<td>WIN 62,577 (Positive) (pKᵦ 5.1) [1053], N-chloromethyl-brucine (Positive) (pKᵦ 3.3) [1051]</td>
<td>muscarinic toxin 3 (Negative) (pKᵦ 8.7) [875, 1444], LY2191620 (Positive) (pKᵦ 5.7) [383], thiochrome (Positive) (pKᵦ 4) [1050], LY2033298 (Positive) [286], VU0152099 (Positive) [201], VU0152100 (Positive) [201]</td>
<td>ML380 (Positive) (pEC₅₀ 6.7) [595]</td>
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<tr>
<td>Selective allosteric modulators</td>
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<td>–</td>
<td>ML375 (Negative) (pIC₅₀ 6.5) [594]</td>
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<td>Labelled ligands</td>
<td>[³H]tiotropium (Antagonist) (pKᵦ 10.7) [1632], [³H]QNB (Antagonist) (pKᵦ 10.4) [1486], [³H]N-methyl scopolamine (Antagonist) (pKᵦ 9.7–10.2) [280, 310, 759, 797, 846, 875, 932, 1049], [³H]darifenacin (Antagonist) (pKᵦ 9.5) [1762]</td>
<td>[³H]QNB (Antagonist) (pKᵦ 9.7–10.5) [336, 1486], [³H]N-methyl scopolamine (Antagonist) (pKᵦ 9.9–10.2) [280, 310, 336, 759, 846, 875, 932, 1049, 1444, 1985], [³H]Acetycholine (Agonist) (pKᵦ 8.2) [1050]</td>
<td>[³H]QNB (Antagonist) (pKᵦ 10.2–10.7), [³H]N-methyl scopolamine (Antagonist) (pKᵦ 9.3–9.7) [280, 310, 759, 875, 932, 1985]</td>
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Acetylcholine receptors (muscarinic) 5765
Comments: LY2033298 and BQCA have also been shown to directly activate the M₄ and M₁ receptors, respectively, via an allosteric site [1059, 1060, 1366, 1367]. The allosteric site for gallamine and strychnine on M₂ receptors can be labelled by [³H]dimethyl-W84 [1908]. McN-A-343 is a functionally selective partial agonist that appears to interact in a bitopic mode with both the orthosteric and an allosteric site on the M₂ muscarinic receptor [1934]. THRX160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M₂ receptors by binding both to the orthosteric and a nearby allosteric site [52, 1796]. Although numerous ligands for muscarinic acetylcholine receptors have been described, relatively few selective antagonists have been described, so it is common to assess the rank order of affinity of a number of antagonists of limited selectivity (e.g. 4-DAMP, darifenacin, pirenzepine) in order to identify the involvement of particular subtypes. It should be noted that the measured affinities of antagonists (and agonists) in radioligand binding studies are sensitive to ionic strength and can increase over 10-fold at low ionic strength compared to its value at physiological ionic strengths [151].

Further Reading


Adenosine receptors

G protein-coupled receptors → Adenosine receptors

Overview: Adenosine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adenosine Receptors [541]) are activated by the endogenous ligand adenosine (potentially inosine also at A₃ receptors). Crystal structures for the antagonist-bound and agonist-bound A₂A adenosine receptors have been described [835, 2065].

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Adenosine receptors 5766
Adenosine receptors

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<tr>
<th>Nomenclature</th>
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<th>A₂A receptor</th>
<th>A₂B receptor</th>
<th>A₃ receptor</th>
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<td>ADORA2B, P29275</td>
<td>ADORA3, P0DMS8</td>
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<td>Agonists</td>
<td>cyclopentyladenosine (pKᵢ 6.5–9.4) [388, 570, 736, 839, 870, 1592, 2141]</td>
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<td>–</td>
<td>–</td>
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<td></td>
<td>NECA (pKᵢ 5.3–8.2) [570, 870, 1592, 1903, 2077]</td>
<td>NECA (pKᵢ 6.9–8.7) [189, 427, 570, 943, 1021, 2077]</td>
<td>NECA (pKᵢ 5.7–6.9) [146, 189, 862, 1113, 1798, 1945, 2077]</td>
<td>NECA (pKᵢ 7.5–8.4) [189, 570, 840, 1634, 1946, 2077]</td>
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<tr>
<td>(Sub)family-selective agonists</td>
<td>5-Cl-5-deoxy-(+)EN-NA (pKᵢ 9.3) [536], CGR2936 (pKᵢ 8.5) [839] – Rat, CCPA (pKᵢ 7.7–8.1) [839, 1419]</td>
<td>apadenosine (pKᵢ 9.3) [1481], UK-432,097 (pKᵢ 8.3) [2065], CGS 21680 (pKᵢ 6.7–8.1) [189, 427, 570, 839, 943, 968, 1021, 1419], regadenoson (pKᵢ 6.5) [839]</td>
<td>BAY 60-6583 (pKᵢ 8–8.5) [460]</td>
<td>IB-MECA (pKᵢ 8.7–9.2) [511, 561, 968, 1946], CI-MECA (pKᵢ 8–8.9) [202, 840, 941], MR5698 (pKᵢ 8.5) [1898]</td>
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<td>Selective agonists</td>
<td>caffeine (pKᵢ 4.3–5) [6, 409, 838]</td>
<td>SCH 58261 (pKᵢ 8.3–9.2) [427, 1021, 1445], theophylline (pKᵢ 5.2–5.8) [427, 838, 968, 1945], caffeine (pKᵢ 4.6–5.6) [6, 838, 1021]</td>
<td>theophylline (pKᵢ 4.1–5) [141, 511, 944, 1419], caffeine (pKᵢ 4.5–5) [141, 188, 944]</td>
<td>caffeine (pKᵢ 4.9) [838]</td>
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<tr>
<td>Antagonists</td>
<td>CGS 15943 (pKᵢ 8.5) [1445], xanthine amine congener (pKᵢ 7.5) [536]</td>
<td>CGS 15943 (pKᵢ 7.7–9.4) [427, 493, 968, 1445], xanthine amine congener (pKᵢ 8.4–9) [427, 968]</td>
<td>xanthine amine congener (pKᵢ 6.9–8.8) [146, 862, 968, 1113, 1798], CGS 15943 (pKᵢ 6–8.1) [65, 862, 968, 1445, 1798]</td>
<td>CGS 15943 (pKᵢ 7–7.9) [949, 968, 1445, 1946], xanthine amine congener (pKᵢ 7–7.4) [968, 1634, 1946]</td>
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<tr>
<td>(Sub)family-selective antagonists</td>
<td>PSB36 (pKᵢ 9.9) [6] – Rat, DPCPX (pKᵢ 7.4–9.2) [826, 1419, 1592, 2015, 2141], denerofylline (pKᵢ 9) [897], WRC-0571 (pKᵢ 8.8) [1210]</td>
<td>SCH442416 (pKᵢ 8.4–10.3) [1728, 1891], ZM-241385 (pKᵢ 8.8–9.1) [1445], PSB-0788 (pKᵢ 9.4) [188], PSB603 (pKᵢ 9.3) [188], MR51754 (pKᵢ 8.8) [862, 948], PSB1115 (pKᵢ 7.3) [723]</td>
<td>PSB-0788 (pKᵢ 9.4) [188], PSB603 (pKᵢ 9.3) [188], MR51754 (pKᵢ 8.8) [862, 948]</td>
<td>MR51220 (pKᵢ 8.2–9.2) [840, 949, 1818, 2090], VUF3574 (pKᵢ 8.4) [2143], MR51523 (pKᵢ 7.7) [1092], MR51191 (pKᵢ 7.5) [840, 866, 1097]</td>
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<tr>
<td>Selective antagonists</td>
<td>PSB36 (pKᵢ 9.9) [6] – Rat, DPCPX (pKᵢ 7.4–9.2) [826, 1419, 1592, 2015, 2141], denerofylline (pKᵢ 9) [897], WRC-0571 (pKᵢ 8.8) [1210]</td>
<td>SCH442416 (pKᵢ 8.4–10.3) [1728, 1891], ZM-241385 (pKᵢ 8.8–9.1) [1445], PSB-0788 (pKᵢ 9.4) [188], PSB603 (pKᵢ 9.3) [188], MR51754 (pKᵢ 8.8) [862, 948], PSB1115 (pKᵢ 7.3) [723]</td>
<td>PSB-0788 (pKᵢ 9.4) [188], PSB603 (pKᵢ 9.3) [188], MR51754 (pKᵢ 8.8) [862, 948]</td>
<td>MR51220 (pKᵢ 8.2–9.2) [840, 949, 1818, 2090], VUF3574 (pKᵢ 8.4) [2143], MR51523 (pKᵢ 7.7) [1092], MR51191 (pKᵢ 7.5) [840, 866, 1097]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]CCPA (Agonist) (pKᵢ 9.2) [968, 1592], [³H]DPCPX (Antagonist) (pKᵢ 8.4–9.2) [388, 511, 968, 1445, 1592, 1903]</td>
<td>[³H]JZM 241385 (Antagonist) (pKᵢ 8.7–9.1) [36, 569], [³H]CGS 21680 (Agonist) (pKᵢ 7.7–7.8) [852, 1976]</td>
<td>[³H]MR51754 (Antagonist) (pKᵢ 8.8) [862]</td>
<td>[¹²5I]AB-MECA (Agonist) (pKᵢ 9–9.1) [1445, 1946]</td>
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</table>

Comments: Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A₂B adenosine receptor (ADORA2BP) with 79% identity to the A₂B adenosine receptor coding sequence, but which is unable to encode a functional receptor [841]. DPCPX also exhibits antagonism at A₂B receptors (pKᵢ ca. 7, 34, 968). Antagonists at A₃ receptors exhibit marked species differences, such that only MR51523 and MR51191 are selective at the rat A₃ receptor. In the absence of other adenosine receptors, [³H]DPCPX and [³H]JZM 241385 can also be used to label A₂B receptors (Kᵢ ca. 30 and 60 nM respectively). [¹²5I]AB-MECA also binds to A₁ receptors [968]. [³H]CGS 21680 is relatively selective for A₂A receptors, but may also bind to other sites in cerebral cortex [384, 871]. [³H]NECA binds to other non-receptor elements, which also recognise adenosine [1143]. XAC-BY630 has been described as a fluorescent antagonist for labelling A₂ adenosine receptors in living cells, although activity at other adenosine receptors was not evaluated [212].
Further Reading


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 "stalk" motif containing a GPCR proteolytic site. The N-terminus often shares structural homology with proteins such as lectins and immunoglobulins, leading to the term adhesion GPCR [543, 2097]. The nomenclature of these receptors was revised in 2015 as recommended by NC-IUPHAR and the Adhesion GPCR Consortium [683].

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<td>ADGRB1 is reported to respond to phosphatidylserine [1461]</td>
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<td>Reported to bind tissue transglutaminase 2 [2066] and collagen, which activates the G12/13 pathway [1155].</td>
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<td>ADGRL3, Q9HAR2</td>
<td>ADGRL4, Q9HBW9</td>
<td>ADGRV1, Q8WXG9</td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
<td>Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [843].</td>
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</table>
Adrenoceptors

G protein-coupled receptors → Adrenoceptors

Overview:

Adrenoceptors, α₁

α₁-Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [248], see also [752]) are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline with equal potency. Phenylephrine, methoxamine and cirazoline are agonists selective for α₁-adrenoceptors relative to α₂-adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are antagonists considered selective for α₁-adrenoceptors relative to α₂-adrenoceptors. [3H]prazosin (0.25 nM) and [125I]HEAT (0.1 nM; also known as B2254) are relatively selective radioligands. The α₁A-adrenoceptor antagonist S(+)-niguldipine also has high affinity for L-type Ca²⁺ channels. The conotoxin rho-TIA acts as a negative allosteric modulator at the α₁B-adrenoceptor [1716], while the snake toxin μ-Dala acts as a selective non-competitive antagonist at the α₁A-adrenoceptor [1236, 1548]. Fluorescent derivatives of prazosin (Bodipy PL-prazosin-QAPB) are increasingly used to examine cellular localisation of α₁-adrenoceptors. The vasoconstrictor effects of selective α₁-adrenoceptor agonists have led to their use as nasal decongestants; antagonists are used to treat hypertension (doxazosin, prazosin) and benign prostatic hyperplasia ( alfuzosin, tamsulosin). The combined α₁– and β₂-adrenoceptor antagonist carvedilol is widely used to treat congestive heart failure, although the contribution of α₁-adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs possess α₁-adrenoceptor blocking properties that are believed to contribute to side effects such as orthostatic hypotension and extrapyramidal effects.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>α₁A-adrenoceptor</th>
<th>α₁B-adrenoceptor</th>
<th>α₁D-adrenoceptor</th>
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<tr>
<td>HGNC, UniProt</td>
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<td>ADRA1B, P35368</td>
<td>ADRA1D, P25100</td>
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<td>Endogenous agonists</td>
<td>–</td>
<td>phenylephrine (pIC₅₀ 6.3–7.5)</td>
<td>(−)-adrenaline (pKᵢ 7.2)</td>
</tr>
<tr>
<td>Agonists</td>
<td>oxymetazoline (pKᵢ 8.8–2.2)</td>
<td>–</td>
<td>[1722]</td>
</tr>
<tr>
<td></td>
<td>[780, 1420, 1722, 1822, 1626]</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>phenylephrine (pKᵢ 5.2–5.4)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1862]</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>methoxamine (pKᵢ 5–5.2)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1722, 1862]</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Selective agonists</td>
<td>A61603 (pIC₅₀ 7.8–8.4)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[532, 969]</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dabuzalgron (pKᵢ 7.4)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[162]</td>
<td>–</td>
<td></td>
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<tr>
<td>Antagonists</td>
<td>prazosin (Inverse agonist) (pKᵢ 9–9.9) [289, 389, 532, 1722, 2029], doxazosin (pKᵢ 9.3) [689], terazosin (pKᵢ 8.7) [1263], phenolamine (pKᵢ 8.6) [1722], alfuzosin (pKᵢ 8.1) [750]</td>
<td>prazosin (Inverse agonist) (pKᵢ 9.6–9.9) [532, 1722, 2029],</td>
<td>prazosin (Inverse agonist) (pKᵢ 9.5–10.2) [532, 1722, 2029], tamsulosin (pKᵢ 9.8–10.2) [532, 1722, 2029], doxazosin (pKᵢ 9.1) [689], terazosin (pKᵢ 9.1) [1263], alfuzosin (pKᵢ 8.4) [750], dapiprazole (pKᵢ 8.4) [68], phenolamine (Inverse agonist) (pKᵢ 8.2) [1722], RS-100329 (pKᵢ 7.9) [2029], labetalol (pKᵢ 6.6) [68]</td>
</tr>
<tr>
<td></td>
<td>[289, 389, 532, 1722, 2029]</td>
<td>doxazosin (pKᵢ 9.1) [689],</td>
<td>tamsulosin (pKᵢ 9.5–9.7) [532, 1722, 2029],</td>
</tr>
<tr>
<td></td>
<td>[1722, 2029]</td>
<td>alfuzosin (pKᵢ 8.6) [751],</td>
<td>doxazosin (pKᵢ 9.1) [689],</td>
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<td></td>
<td>[532, 1722, 2029]</td>
<td>terazosin (pKᵢ 8.6) [1263],</td>
<td>terazosin (pKᵢ 9.1) [1263],</td>
</tr>
<tr>
<td></td>
<td>[1722]</td>
<td>phenolamine (pKᵢ 7.5) [1722]</td>
<td>alfuzosin (pKᵢ 8.4) [750],</td>
</tr>
<tr>
<td></td>
<td>[289, 389, 532, 1722, 2029]</td>
<td></td>
<td>dapiprazole (pKᵢ 8.4) [68],</td>
</tr>
<tr>
<td></td>
<td>[289, 389, 532, 1722, 2029]</td>
<td></td>
<td>phenolamine (Inverse agonist) (pKᵢ 8.2) [1722],</td>
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<td></td>
<td>[1722]</td>
<td></td>
<td>RS-100329 (pKᵢ 7.9) [2029],</td>
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<td></td>
<td>[532, 1722, 2029]</td>
<td></td>
<td>labetalol (pKᵢ 6.6) [68]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>tamsulosin (pKᵢ 10–10.7) [289, 389, 532, 1722, 2029], silodosin (pKᵢ 10.4) [1722], S(+)-niguldipine (pKᵢ 9.3–10) [532, 1722], RS-100329 (pKᵢ 9.6) [2029], SNAP5099 (pKᵢ 8.8–9.4) [750, 1081, 2014], μ-Dala (pKᵢ 9.2–9.3) [1236, 1548], RS-17053 (pKᵢ 9.2–9.3) [289, 389, 529, 532]</td>
<td>Rec 15/2615 (pKᵢ 9.5) [1867], L-765314 (pKᵢ 7.7) [1470], AH 11110 (pKᵢ 7.5) [1652]</td>
<td>BMY-7378 (pKᵢ 8.7–9.1) [268, 2102]</td>
</tr>
</tbody>
</table>

Adrenoceptors, α₂

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

α₂-Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; [248]) are activated by endogenous agonists with a relative potency of (-)-adrenaline – (-)-noradrenaline. Brimonidine and tolazoline are agonists selective for α₂-adrenoceptors relative to α₁-adrenoceptors. Rauwolscine and yohimbine are antagonists selective for α₂-adrenoceptors relative to α₁-adrenoceptors. [3H]Brimonidine (1 nM), [3H]BRL 37344 (0.5 nM and 0.1 nM at α₂C) are relatively selective radioligands. There is species variation in the pharmacology of the α₂A-adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have a 20-fold higher affinity for the human α₂A-adrenoceptor compared to the rat, mouse and bovine receptor. These α₂A orthologues are sometimes referred to as α₂D-adrenoceptors. Multiple mutations of α₂-adrenoceptors have been described, some of which are associated with alterations in function. Presynaptic α₂-adrenoceptors are widespread in the nervous system and regulate many functions, hence the multiplicity of actions. The effects of classical (not subtype selective) α₂-adrenoceptor agonists such as clonidine, guanabenz and brimonidine on central baroreflex control (hypotension and bradycardia), as well as their ability to induce hypnic effects and analgesia, and their ability to modulate seizure activity and platelet aggregation are mediated by α₂A-adrenoceptors. Clonidine has been used as an anti-hypertensive and also to counteract opioid withdrawal. Actions on imidazoline recognition sites may contribute to the pharmacological effects of clonidine. α₂-Adrenoceptor agonists such as dexmedetomidine have been widely used as sedatives and analgesics in veterinary medicine (also xylazine) and are now used frequently in humans. Dexmedetomidine also has analgesic, sympatholytic and anxiolytic properties but is notable for the production of sedation without respiratory depression. α₂-Adrenoceptor antagonists are relatively little used therapeutically although yohimbine has been used to treat erectile dysfunction and several anti-depressants (e.g. Mirtazapine) that block α₂-adrenoceptors may work through this mechanism. The roles of α₂B and α₂C-adrenoceptors are less clear but the α₂B subtype appears to be involved in neurotransmission in the spinal cord and α₂C in regulating catecholamine release from adrenal chromaffin cells.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>α₂A-adrenoceptor</th>
<th>α₂B-adrenoceptor</th>
<th>α₂C-adrenoceptor</th>
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<td>ADRA2C, P18825</td>
</tr>
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<td>Endogenous agonists</td>
<td>(-)-adrenaline (pK₈ 5.6–8.3) [854, 1503]</td>
<td>(-)-noradrenaline (Partial agonist) (pK₈ 5.6–9.1) [854, 1484, 1503]</td>
<td>(-)-noradrenaline (Partial agonist) (pK₈ 5.9–8.7) [854, 1484, 1503]</td>
</tr>
<tr>
<td>Agonists</td>
<td>dexmedetomidine (Partial agonist) (pK₈ 7.6–9.6) [854, 1163, 1484, 1503], clonidine (Partial agonist) (pK₈ 7.2–9.2) [854, 1484, 1503], brimonidine (pKᵢ 6.7–8.7) [854, 1163, 1484, 1503], apraclonidine (pKᵢ 6.5) [1543], guanabenz (pKᵢ 6.8) [68], guanfacine (Partial agonist) (pKᵢ 7.1–7.3) [854, 1165]</td>
<td>dexmedetomidine (pKᵢ 7.5–9.7) [854, 1163, 1484, 1503], clonidine (Partial agonist) (pKᵢ 6.7–9.5) [854, 1484, 1503], brimonidine (Partial agonist) (pKᵢ 6–8.3) [854, 1484, 1503], guanabenz (pIC₅₀ 6.8) [68], guanfacine (pKᵢ 5.8–6.5) [854]</td>
<td>dexmedetomidine (pKᵢ 7–9.3) [854, 1484, 1503], brimonidine (Partial agonist) (pKᵢ 5.7–7.6) [854, 1163, 1484, 1503], apraclonidine (pKᵢ 7.5) [1343], guanfacine (Partial agonist) (pKᵢ 5.4–6.2) [854], guanabenz (pIC₅₀ 6) [68]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>oxymetazoline (Partial agonist) (pKᵢ 8–8.6) [854, 1163, 1922]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>yohimbine (pKᵢ 8.5–9.5) [247, 416, 1922], WB 4101 (pKᵢ 8.4–9.4) [247, 416, 1922], spiroxatrine (pKᵢ 8.9) [1922], mirtazapine (pKᵢ 7.7) [513], tolazoline (pKᵢ 5.4) [854]</td>
<td>yohimbine (pKᵢ 8.4–9.2) [247, 416, 1922], phenoxymazine (pKᵢ 8.5) [2002], tolazoline (pKᵢ 5.5) [854]</td>
<td>yohimbine (pKᵢ 7.9–8.9) [247, 416, 1922], phenoxymazine (pKᵢ 8.5) [2002], tolazoline (pKᵢ 5.5) [854]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>BRL 44408 (pKᵢ 8.2–8.8) [1922, 2104]</td>
<td>imiloxan (pKᵢ 7.3) [1269] – Rat</td>
<td>JP1302 (pKᵢ 7.8) [1631]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>–</td>
<td>–</td>
<td>[3H]MK-912 (Antagonist) (pKᵢ 10.1) [1922]</td>
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</table>

β-Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, [248]) are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Isoproterenol is a synthetic agonist selective for β-adrenoceptors relative to α₁- and α₂-adrenoceptors, while β₁ and β₂ adrenoceptors, propranolol (pKᵢ 8.2–9.2) and cyanopindolol (pKᵢ 10.0–11.0) are relatively selective antagonists. (-)-noradrenaline, xamoterol and (-)-Ro 363 are agonists that show selectivity for β₁-receptor to β₂-adrenoceptors. Pharmacological differences exist between human and mouse β₂-adrenoceptors, and the ‘rodent selective’ agonists BRL 37344 and CL316243 have low efficacy at the human β₂-adrenoceptor whereas CGP 12177 and L 75507 activate human β₂-adrenoceptors [1649]. β₂-Adrenoceptors are relatively resistant to blockade by propranolol (pKᵢ 5.8–7.0), but can be blocked by high concentrations of bupranolol (pKᵢ 6.5) [1650]. SR59230A has reasonably high affinity at β₂-adrenoceptors [1197]. But does not discriminate well between the three β-adrenoceptor subtypes [262] and has been reported to have lower affinity for the β₂-adrenoceptor in some circumstances [913]. L-748337 is the most selective antagonist for β₂ adrenoceptors. [125I]-cyamopindolol, [125I]-hydroxybenzylpindolol and [3H]-alprenolol are high affinity radioligands widely used to label β₁- and β₂-adrenoceptors and β₂-adrenoceptors can be labelled with higher concentrations (nM)
of [125I]-cyanopindolol in the presence of appropriate concentrations of β₁- and β₂- adrenoceptor antagonists. [3H]L-748337 is a β3-selective radioligand. Fluorescent ligands such as BODIPY-TMR-CGP12177 are also increasingly being used to track β-adrenoceptors at the cellular level [86]. Somewhat selective β₁- adrenoceptor selective agonists (denopamine, dobutamine) are used short-term to treat cardiogenic shock but, in the longer term, reduce survival. β₁-Adrenoceptor-prefering antagonists are used to treat hypertension (atenolol, bisoprolol, bisoprolol fumarate and nebivolol), cardiac arrhythmias (atenolol, bisoprolol, esmolol) and cardiac failure (metoprolol, nebivolol). Cardiac failure is also successfully treated with carvedilol which blocks both β₁- and β₂- adrenoceptors, as well as α₁-adrenoceptors. β₂-Adrenoceptor-selective agonists are powerful bronchodilators widely used to treat respiratory disorders. There are both short (salbutamol, terbutaline) and long acting drugs (formoterol, salmeterol). Although many first generation β-adrenoceptor antagonists (propranolol) block both β₁- and β₂- adrenoceptors there are no β₂-adrenoceptor-selective antagonists used therapeutically. The β₃-adrenoceptor agonist mirabegron is used to control overactive bladder syndrome.

<table>
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<th>Nomenclature</th>
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<td>ADRB2, P07530</td>
<td>ADRB3, P13945</td>
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<td>Rank order of potency</td>
<td>(-)-noradrenaline &gt; (-)-adrenaline</td>
<td>(-)-adrenaline &gt; (-)-noradrenaline</td>
<td>(-)-noradrenaline = (-)-adrenaline</td>
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<tr>
<td>Endogenous agonists</td>
<td>noradrenaline (pKᵢ 6) [549]</td>
<td>noradrenaline (pKᵢ 6) [549]</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>pindolol (Partial agonist) (pKᵢ 9.3) [1011], isoprenaline (pKᵢ 6.6–7) [549, 1651], dobutamine (Partial agonist) (pKᵢ 5.5) [831]</td>
<td>pindolol (Partial agonist) (pKᵢ 9.4) [1011], arformoterol (pKᵢ 8.6) [57], isoprenaline (pKᵢ 6.4) [1651], dobutamine (Partial agonist) (pKᵢ 6.2) [1100], ephedrine (Partial agonist) (pKᵢ 5.6) [851]</td>
<td>carazolol (pKᵢ 8.7) [1256]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>(-)-Ro 363 (pKᵢ 8) [1301], xamoterol (Partial agonist) (pKᵢ 7) [831], denopamine (Partial agonist) (pKᵢ 5.8) [831, 1830]</td>
<td>formoterol (pEC₅₀ 10.1) [81], salmeterol (pEC₅₀ 9.9) [81], zinteflor (pEC₅₀ 9.5) [81], vilanterol (pEC₅₀ 9.4) [1534], procaterol (pEC₅₀ 8.4) [81], indicaterol (pKᵢ 7.8) [107], fenoterol (pKᵢ 6.9) [55], salbutamol (Partial agonist) (pKᵢ 5.8–6.1) [83, 831], terbutaline (Partial agonist) (pKᵢ 5.6) [83], orciprenaline (pKᵢ 5.3) [784]</td>
<td>L 755507 (pEC₅₀ 10.1) [81], L742791 (pEC₅₀ 8.8) [2000], mirabegron (pEC₅₀ 7.7) [1849], CCP 12177 (Partial agonist) (pKᵢ 6.1–7.3) [159, 1144, 1256, 1301], SBZ 251023 (pEC₅₀ 7.1) [810] – Mouse, BRL 37344 (pKᵢ 6.4–7) [159, 431, 768, 1256], CL 1316243 (pKᵢ 5.2) [2080]</td>
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<tr>
<td>Antagonists</td>
<td>carvedilol (pKᵢ 9.5) [262], bupranolol (pKᵢ 7.3–9) [262, 1144], levolubanolol (pKᵢ 8.4) [68], labetalol (pKᵢ 8.2) [68], metoprolol (pKᵢ 7–7.6) [83, 262, 768, 1144], esmolol (pKᵢ 6.9) [68], nadolol (pKᵢ 6.9) [262], practolol (pKᵢ 6.1–6.8) [83, 1144], propafenone (pKᵢ 6.7) [68], sotalol (pKᵢ 6.1) [68]</td>
<td>carvedilol (pKᵢ 9.4–9.9) [83, 262], timolol (pKᵢ 9.7) [83], propranolol (pKᵢ 9.1–9.5) [83, 86, 831, 1144], levolubanolol (pKᵢ 9.3) [68], bupranolol (pKᵢ 8.3–9.1) [262, 1144], alpenrolol (pKᵢ 9) [83], nadolol (pKᵢ 7–8.6) [83, 262], labetalol (pKᵢ 8) [68], propafenone (pKᵢ 7.4) [68], sotalol (pKᵢ 6.5) [68]</td>
<td>carvedilol (pKᵢ 9.4) [262], bupranolol (pKᵢ 6.8–7.3) [159, 262, 1144, 1256], propranolol (pKᵢ 6.3–7.2) [1144, 1517], levolubanolol (pKᵢ 6.8) [1517]</td>
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<tr>
<td>Selective antagonists</td>
<td>CCP 20712A (pKᵢ 8.5–9.2) [83, 262, 1144], levolubaxatol (pKᵢ 9.1) [1715], betaxalol (pKᵢ 8.8) [1144], nebivolol (pEC₅₀ 8.1–8.7) [1476] – Rabbit, atenolol (pKᵢ 6.7–7.6) [83, 86, 1144], acebutolol (pKᵢ 6.4) [68]</td>
<td>ICI 118551 (Inverse agonist) (pKᵢ 9.2–9.5) [83, 86, 1144]</td>
<td>L-748337 (pKᵢ 8.4) [262], SR59230A (pKᵢ 6.9–8.4) [262, 405, 768], L748328 (pKᵢ 8.4) [262]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]JICYP (Selective Antagonist) (pKᵢ 10.4–11.3) [831, 1144, 1651]</td>
<td>[125I]JICYP (Antagonist) (pKᵢ 11) [1144, 1651]</td>
<td>[125I]JICYP (Agonist, Partial agonist) (pKᵢ 9.2–9.8) [1144, 1301, 1517, 1651, 1806]</td>
</tr>
<tr>
<td>Comments</td>
<td>The agonists indicated have less than two orders of magnitude selectivity [81].</td>
<td>–</td>
<td>Agonist SBZ 251023 has a pEC50 of 6.9 for the splice variant of the mouse β3 receptor, β3D [810].</td>
</tr>
</tbody>
</table>

**Comments:**

**Adrenoceptors, α₁**

The clone originally called the α₁C-adrenoceptor corresponds to the pharmacologically defined α₁A-adrenoceptor [752]. Some tissues possess α₁A-adrenoceptors (termed α₁L-adrenoceptors [532, 1329]) that display relatively low affinity in functional and binding assays for prazosin (pKᵢ < 9) indicative of different receptor states or locations. α₁A-adrenoceptor C-terminal splice variants form homo- and heterodimers, but fail to generate a functional α₁L- adrenoceptor [1557]. α₁D-Adrenoceptors form heterodimers with α₁B- or β₂- adrenoceptors that show increased cell-surface expression [1917]. Recombinant α₁G-adrenoceptors have been shown in some heterologous systems to be mainly located intracellularly but cell-surface localization is attained by truncation of the N-terminus.
Signalling is predominantly via $G_{i/o}$ but $\alpha_1$-adrenoceptors also couple to $G_{q/11}$. Several ligands activating $\alpha_1$-adrenoceptors display ligand directed signalling bias relative to noradrenaline. For example, oxymetazoline is a full agonist for extracellular acidification rate (ECAR) and a partial agonist for Ca$^{2+}$ release but does not stimulate CaMP production. Phenylephrine is biased toward ECAR versus Ca$^{2+}$ release or CaMP accumulation but not between Ca$^{2+}$ release and CaMP accumulation [495]. There are also differences between subtypes in coupling efficiency to different pathways e.g. in some systems coupling efficiency to Ca$^{2+}$ release is $\alpha_1A > \alpha_1B > \alpha_1D$, but for MAP kinase signalling is $\alpha_1D > \alpha_1A > \alpha_1B$. In vascular smooth muscle, the potency of agonists is related to the predominant subtype, $\alpha_1D$, conveying greater agonist sensitivity than $\alpha_1A$-adrenoceptors [526].

Adrenoceptors, $\alpha_2$
ARC-239 (pK$_i$ 8.0) and prazosin (pK$_i$ 7.5) show selectivity for $\alpha_2B$- and $\alpha_2C$-adrenoceptors over $\alpha_2A$-adrenoceptors. Oxymetazoline is a reduced efficacy agonist and is one of many $\alpha_2$-adrenoceptor agonists that are imidazolines or closely related compounds. Other binding sites for imidazolines, distinct from $\alpha_2$-adrenoceptors, and structurally distinct from the 7TM adrenoceptors, have been identified and classified as $\alpha_1$, $\alpha_2$, and $\alpha_3$ sites [390]; catecholamines have a low affinity, whereas rilmenidine and moxonidine are selective ligands for these sites, evoking hypertensive effects in vivo. $\alpha_1$-imidazoline receptors are involved in central inhibition of sympathetic tone, $\alpha_2$-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and $\alpha_3$-imidazoline receptors regulate insulin secretion from $\beta$-islets [2083], 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 [1599]. $\alpha_2A$- and $\alpha_2C$-adrenoceptors display homodimers [1758]. Homodimers between $\alpha_2A$- and either the $\alpha_2A$-, $\alpha_2C$- or $\mu$-opioid peptide receptor exhibit altered signalling and trafficking properties compared to the individual receptors [1758, 1858, 1956]. Signalling by $\alpha_2$-adrenoceptors is primarily via $G_{i/o}$, however the $\alpha_2A$-adrenoceptor also couples to $G_{s}$ [459]. Imidazoline compounds display bias relative to each other at the $\alpha_2A$-adrenoceptor when assayed by [35S]GTP$\gamma$S binding compared to inhibition of CaMP accumulation [1477]. The noradrenaline upregulate inhibitor desipramine acts directly on the $\alpha_2A$-adrenoceptor, promoting internalisation via recruitment of arrestin without activating G proteins [371].

Adrenoceptors, $\beta$
Radioligand binding with [125I]JICYP can be used to define $\beta_1$- or $\beta_2$-adrenoceptors when conducted in the presence of a ‘saturating’ concentration of either a $\beta_1$- or $\beta_2$-adrenoceptor-selective antagonist. [3H]CCP12177 or [3H]dihydroalprenolol can be used in place of [125I]JICYP. Binding of a fluorescent analogue of CCP 12177 to $\beta_2$-adrenoceptors in living cells has been described [84]. [125I]JICYP at higher (nM) concentrations can be used to label $\beta_2$-adrenoceptors in systems where there are few if any other $\beta$-adrenoceptor subtypes. Pharmacological differences exist between human and mouse $\beta_2$-adrenoceptors, and the ‘rodent selective’ agonists BRL 37344 and CL316243 are partial agonists at the human $\beta_3$-adrenoceptor whereas CCP 12177 and L 755507 activate human $\beta_3$-adrenoceptors with greater potency [1650]. The $\beta_2$-adrenoceptor has an intron in the coding region, but splice variants have only been described for the mouse [496], where the isoforms display different signalling characteristics [810].

Further Reading
Gilsbach R et al. (2012) Are the pharmacology and physiology of $\alpha_2$-adrenoceptors determined by $\alpha_2$-heteroreceptors and autoreceptors respectively? Br. J. Pharmacol. 165: 90-102 [PMID:21658028]
Angiotensin receptors

G protein-coupled receptors → Angiotensin receptors

**Overview:** The actions of angiotensin II (AGT, P01019) (Ang II) are mediated by AT₁ and AT₂ receptors ([nomenclature as agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors (2137)], which have around 30% sequence similarity. Endogenous ligands are angiotensin II (AGT, P01019) and angiotensin III (AGT, P01019) (Ang III), while angiotensin I (AGT, P01019) is weakly active in some systems.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>AT₁ receptor</th>
<th>AT₂ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>AGTR1, P30556</td>
<td>AGTR2, P50052</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>L-162,313 (pIC₅₀ 7.8–7.9) [1490]</td>
<td>CGP42112 (pIC₅₀ 9.6) [190], [p-aminoPhe₆]ang II (pKᵦ 9.1–9.4) [1789, 2139]</td>
</tr>
<tr>
<td>Antagonists</td>
<td>telmisartan (pIC₅₀ 8.4) [1241], olmesartan (pIC₅₀ 8.1) [981]</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>candesartan (pIC₅₀ 9.5–9.7) [1942], EXP3174 (pIC₅₀ 7.4–9.5) [1887, 1942], eprosartan (pIC₅₀ 8.4–8.8) [464], irbesartan (pIC₅₀ 8.7–8.8) [1942], losartan (pIC₅₀ 7.4–8.7) [1887, 2139], valsartan (pIC₅₀ 8.6) [2138], azilsartan (pIC₅₀ 8.1–8.3) [1551, 1844]</td>
<td>PD123177 (pIC₅₀ 8.5–9.5) [291, 321, 450] – Rat, EMA401 (pIC₅₀ 8.5–9.3) [518, 1582, 1767], PD123319 (pKᵦ 8.7–9.2) [449, 2025, 2139]</td>
</tr>
</tbody>
</table>

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Comments: AT_{1} receptors are predominantly coupled to G_{q/11}, however they are also linked to arrestin recruitment and stimulate G protein-independent arrestin signalling \[1156\]. Most species express a single \textit{AGTR1} gene, but two related \textit{agtr1a} and \textit{agtr1b} receptor genes are expressed in rodents. The AT_{2} receptor counteracts several of the growth responses initiated by the AT_{1} receptors. The AT_{2} receptor is much less abundant than the AT_{1} receptor in adult tissues and is upregulated in pathological conditions. AT_{1} receptor antagonists bearing substituted 4-phenylquinoline moieties have been synthesized, which bind to AT_{1} receptors with nanomolar affinity and are slightly more potent than \textit{losartan} in functional studies \[264\]. The antagonist activity of \textit{CGP42112} at the AT_{2} receptor has also been reported \[2147\].

Further Reading


Apelin receptor

G protein-coupled receptors $\rightarrow$ Apelin receptor

Overview: The apelin receptor \textbf{(nomenclature as agreed by the NC-IUPHAR Subcommittee on the apelin receptor \[1510\])} responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36 (\textit{APLN}, Q9ULZ1), apelin-13 (\textit{APLN}, Q9ULZ1) and [Pyr]apelin-13 (\textit{APLN}, Q9ULZ1) are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (\textit{APLN}, Q9ULZ1) by a so far unidentified enzymatic pathway \[1864\]. A second family of peptides discovered independently and named Elabela \[323\] or Toddler, that has little sequence similarity to apelin, has been proposed as a second endogenous apelin receptor ligand \[1475\].
**Nomenclature**

- HGNC, UniProt: APLNR, P35414

**Rank order of potency**

- $[^{Pyr}]{\text{apelin-13 (APLN, Q9ULZ1)}} \geq \text{apelin-13 (APLN, Q9ULZ1)}} \geq \text{apelin-36 (APLN, Q9ULZ1)}} \geq \text{[503, 1864]}

**Endogenous agonists**

- APLNR, Q9ULZ1) (Selective) (pIC$_{50}$ 8.8–9.5) [503, 785, 1254], APLNR, Q9ULZ1) (Selective) (pIC$_{50}$ 8.7) [2086], APLNR, Q9ULZ1) (Selective) (pIC$_{50}$ 7.9–9) [468, 1254], APLNR, Q9ULZ1) (Selective) (pIC$_{50}$ 7–8.8) [918, 1254], APLNR, Q9ULZ1) (Selective) (pIC$_{50}$ 8.2–8.6) [503, 785, 918, 1254], Elabela/Toddler-21 (APELA, P0DMC3) (pIC$_{50}$ 8.7) [2086], Elabela/Toddler-32 (APELA, P0DMC3) (pIC$_{50}$ 8.7) [2086], Elabela/Toddler-11 (APELA, P0DMC3) (pIC$_{50}$ 7.2) [2086]

**Selective agonists**

- MM07 (Biased agonist) (pEC$_{50}$ 9.5) [203]

**Antagonists**

- MM54 (pIC$_{50}$ 8.2) [1166]

**Labelled ligands**

- [125I][Nle$^{75}$,Tyr$^{77}$]apelin-36 (human) (Agonist) (pIC$_{50}$ 11.2) [918], [125I][Glp$^{65}$Nle$^{75}$,Tyr$^{77}$]apelin-13 (Agonist) (pIC$_{50}$ 10.7) [785], [125I][Pyr$^{1}$]apelin-13 (Agonist) (pIC$_{50}$ 9.5) [911], [125I]apelin-13 (Agonist) (pIC$_{50}$ 9.2) [503], [3H][Pyr$^{1}$][Met(0)11]-apelin-13 (Agonist) (pIC$_{50}$ 8.6) [1254]

**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 [279]. A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat in vivo [1067], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant apelin receptor [503].

**Further Reading**

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

<table>
<thead>
<tr>
<th>Name</th>
<th>HGNC, UniProt</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPBA receptor</td>
<td>GPBAR1, Q8TDU6</td>
</tr>
</tbody>
</table>

Rank order of potency

lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid (Unknown) [917, 1214]

Selective agonists

betulinic acid (pEC<sub>50</sub> 6) [590], oleanolic acid (pEC<sub>50</sub> 5.7) [1648]

Comments: The triterpenoid natural product betulinic acid has also been reported to inhibit inflammatory signalling through the NFκB pathway [1842]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [1951]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [1138].

Further Reading


Pols TW et al. (2011) The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. J. Hepatol. 54: 1263-72 [PMID:21145931]

Bombesin receptors

**G protein-coupled receptors → Bombesin receptors**

**Overview:** Bombesin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, [857]) are activated by the endogenous ligands gastrin-releasing peptide (GRP, P07492) (GRP), neuromedin B (NMB, P08949) (NMB) and GRP-(18-27) (GRP, P07492) (previously named neuromedin C). Bombesin is a tetradecapeptide, originally derived from amphibians, and is an agonist at BB1 and BB2 receptors. These receptors couple primarily to the G_{q/11} family of G proteins (but see also [857]). Each of these receptors is widely distributed in the CNS and peripheral tissues [625, 857, 1556, 1642]. Activation of BB1 and BB2 receptors causes a wide range of physiological actions, including the stimulation of normal and neoplastic tissue growth, smooth-muscle contraction, appetite and feeding behavior, secretion and many central nervous system effects [857, 858, 859, 1185, 1317, 1556]. A physiological role for the BB3 receptor has yet to be fully defined although recently studies using receptor knockout mice and newly described agonists/antagonists suggest an important role in glucose and insulin regulation, metabolic homeostasis, feeding and other CNS behaviors and growth of normal/neoplastic tissues [625, 1186, 1430].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>BB1 receptor</th>
<th>BB2 receptor</th>
<th>BB3 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>NMBR, P28336</td>
<td>GRPR, P30550</td>
<td>BRS3, P32247</td>
</tr>
</tbody>
</table>

**Endogenous agonists**

- neuromedin B (NMB, P08949) (Selective) (pK_{i} 8.1–10.3) [857, 1556, 1919]
- neuromedin C (pIC_{50} 9.9) [1919], gastrin releasing peptide(14-27) (human) (Selective) (pIC_{50} 9.7–9.8) [1919]

**Selective agonists**

- compound 8a [PMID: 24900283] (pIC_{50} 8.9) [1129], compound 9g [PMID: 24412111] (pEC_{50} 8.8) [1220], MK-7725 (pIC_{50} 8.5) [324], MK-5046 (pK_{i} 7.7–8.4) [1321, 1689], [D-Tyr^{6},Apa^{11},Phe^{13},Nle^{14}]bombesin-(6-14) (pK_{i} 8.1) [1202], compound 17c [PMID: 25497965] (pEC_{50} 7.9) [1219], compound 9t [PMID: 24412111] (pEC_{50} 7.8) [1220], bag-1 (pIC_{50} 7.7) [659], compound 22e [PMID: 20167483] (pIC_{50} 7.6) [727], bag-2 (pIC_{50} 7.6) [659],

**Antagonists**

- D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_{2} (pIC_{50} 6.2–6.6) [624]
**Nomenclature**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>BB₁ receptor</th>
<th>BB₂ receptor</th>
<th>BB₃ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective antagonists</strong></td>
<td>PD 176252 (pIC₅₀ 9.3–9.8) [624], PD 168368 (pIC₅₀ 9.3–9.6) [624], dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH₂</td>
<td>[D-Phe⁶, Leu¹³, Cpa¹⁴, ψ¹³-¹⁴]bombesin-(6-14) (pKᵢ 9.8) [624], JM641 (pIC₅₀ 9.3) [1892] – Mouse, [(3-Ph-Py)⁶, His⁷, D-Ala¹¹, D-Pro¹³, ψ¹³-¹⁴,Phe¹⁴] bombesin-(6-14) (pIC₅₀ 9.2) [624, 1062], [D-Tri⁶, Leu¹³, ψ(CH₂NH)-Leu¹⁴] bombesin-(6-14) (pIC₅₀ 8.9) [624], Ac-GRP-(20-26)-methylester (pIC₅₀ 8.7) [624], JMV594 (pIC₅₀ 8.7–8.8) [1133, 1892] – Mouse</td>
<td>bantag-1 (pIC₅₀ 8.6–8.7) [659, 1321], ML-18 (pIC₅₀ 5.3) [1316]</td>
</tr>
<tr>
<td><strong>Labelled ligands</strong></td>
<td>[¹²⁵I]BH-NMB (human, mouse, rat) (Agonist), [¹²⁵I]Tyr⁴]bombesin (Agonist)</td>
<td>[¹²⁵I][D-Tyr⁶]bombesin-(6-13)-methyl ester (Selective Antagonist) (pKᵢ 9.3) [1201] – Mouse, [¹²⁵I][Tyr⁴]bombesin (Agonist) (pKᵢ 8.2) [131], [¹²⁵I]GRP (human) (Agonist)</td>
<td>[³H]bag-2 (Agonist) (pKᵢ 8.6) [659] – Mouse, [¹²⁵I][D-Tyr⁶,Phe¹³,Nle¹⁴] bombesin-(6-14) (Agonist) (pKᵢ 8–8.4) [1203, 1321]</td>
</tr>
</tbody>
</table>

**Comments:** All three subtypes may be activated by [D-Phe⁶, β-Ala¹¹,Phe¹³,Nle¹⁴] bombesin-(6-14) [1203]. [D-Tyr⁶,Apa-4Cl¹¹,Phe¹³,Nle¹⁴] bombesin-(6-14) has more than 200-fold selectivity for BB₃ receptors over BB₁ and BB₂ [1202].

**Further Reading**


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 [1072]) are activated by the endogenous peptides bradykinin (KNG1, P01042) (BK), [des-Arg9]bradykinin (KNG1, P01042), Lys-BK (kallidin (KNG1, P01042)), [des-Arg10]kallidin (KNG1, P01042), T-kinin (KNG1, P01042) (Ile-Ser-BK), [Hyp3]bradykinin (KNG1, P01042) and Lys-[Hyp3]-bradykinin (KNG1, P01042). The variation in affinity or inactivity of B2 receptor antagonists could reflect the existence of species homologues of B2 receptors.

Nomenclature

<table>
<thead>
<tr>
<th>Bradykinin receptors</th>
<th>B1 receptor</th>
<th>B2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>BDKRB1, P46663</td>
<td>BDKRB2, P30411</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>[des-Arg10]kallidin (KNG1, P01042) &gt; [des-Arg9]bradykinin (KNG1, P01042) = kallidin (KNG1, P01042) &gt; bradykinin (KNG1, P01042)</td>
<td>kallidin (KNG1, P01042) &gt; bradykinin (KNG1, P01042) ≫ [des-Arg9]bradykinin (KNG1, P01042), [des-Arg10]kallidin (KNG1, P01042)</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>[des-Arg10]kallidin (KNG1, P01042) (Selective) (pK9.6–10) [69, 104, 876]</td>
<td>–</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>[Sar,D-Phe8,des-Arg9]bradykinin (pK5.7) [876]</td>
<td>[Hyp3,Tyr(Me)8]BK, [Phe8,μ(CH2-NH)Arg9]BK</td>
</tr>
<tr>
<td>Antagonists</td>
<td>[Leu9,des-Arg10]kallidin (pK9.1–9.3) [69, 104]</td>
<td>icatibant (pK10.2) [39], FR173657 (pA2 8.2) [1593], anatibant (pK8.2) [1537]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>8-9958 (pK9.2–10.3) [596, 1570], R-914 (pA2 8.6) [617], R-715 (pA2 8.5) [618]</td>
<td>[3H]BK (human, mouse, rat) (Agonist) (pKd 9.4) [2034] – Mouse, [3H]NPC17731 (Antagonist) (pKd 9.1–9.4) [2119, 2120], [125I]Tyr8bradykinin (Agonist)</td>
</tr>
</tbody>
</table>

Further Reading


Searchable database: http://www.guidetopharmacology.org/index.jsp
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 [721, 1528]) are generated by the genes CALCR (which codes for the CT receptor (CTR)) and CALCRL (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying proteins), which are single TM domain proteins of ca. 130 amino acids, identified as a family of three members; RAMP1, RAMP2 and RAMP3. There are splice variants of CTR; these in turn produce variants of the AMY receptor [1528], some of which can be potently activated by CGRP. The endogenous agonists are the peptides calcitonin (CALCA, P01258), α-CGRP (CALCA, P06881) (formerly known as CGRP-I), β-CGRP (CALCB, P100992) (formerly known as CGRP-II), amylin (IAPP, P100997) (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 [907]. Olcegepant (also known as BIBN4096BS, pKi 10.5) and telcagepant (also known as MK0974, pKi 9) are the most selective antagonists available, having a high selectivity for CGRP receptors, with a particular preference for those of primate origin. CLR by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, adrenomedullin and adrenomedullin 2/intermedin.
### Calcitonin receptor-like receptor

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>CGRP receptor</th>
<th>AM₁ receptor</th>
<th>AM₂ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>calcitonin receptor-like receptor, RAMP1 (Accessory protein)</td>
<td>calcitonin receptor-like receptor, RAMP2 (Accessory protein)</td>
<td>calcitonin receptor-like receptor, RAMP3 (Accessory protein)</td>
</tr>
<tr>
<td>Subunits</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>α-CGRP (CALCA, P06881) &gt; adrenomedullin (ADM, P33518) &gt; adrenomedullin 2/intermedin (ADM2, Q7Z4H4) &gt; amylin (IAPP, P10997) &gt; calcitonin (salmon)</td>
<td>adrenomedullin (ADM, P33518) &gt; adrenomedullin 2/intermedin (ADM2, Q7Z4H4) &gt; α-CGRP (CALCA, P06881), amylin (IAPP, P10997) &gt; calcitonin (salmon)</td>
<td>adrenomedullin (ADM, P33518) &gt; adrenomedullin 2/intermedin (ADM2, Q7Z4H4) &gt; α-CGRP (CALCA, P06881) &gt; amylin (IAPP, P10997) &gt; calcitonin (salmon)</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>[β-CGRP (CALCB, P10092)] (pKi 9.9–11)</td>
<td>[β-CGRP (CALCA, P06881)] (pKi 9.7–10)</td>
<td>[β-CGRP (CALCA, P06881)] (pKi 9.7–10)</td>
</tr>
<tr>
<td>Antagonists</td>
<td>telcagepant (pKi 10.2–10.7)</td>
<td>telcagepant (pKi 9.1)</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]IøCGRP (human) (Agonist) (pKᵢ 10), [125I]IøCGRP (mouse, rat) (Agonist)</td>
<td>[125I]IAM (rat) (Agonist) (pKᵢ 10–9)</td>
<td>[125I]IAM (rat) (Agonist) (pKᵢ 9–10)</td>
</tr>
</tbody>
</table>

### 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 125I-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 [337, 718, 719]. The major human CTR splice variant (hCTₐ), which does not contain an insert) with RAMP1 (i.e. the AMY₁(a) receptor) has a high affinity for CGRP, unlike hCTₐ-RAMP3 (i.e. AMY₃(a) receptor) [337, 718]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [1886]. In particular, CGRP is a more potent agonist than amylin (IAPP, P10997) at increasing cAMP at the delta 47 hCT(a) receptor, when transfected with RAMP1 (to give the corresponding AMY₁(a) receptor) in Cos 7 cells [1543]. The ligands described represent the best available but their selectivity is limited. For example, adrenomedullin has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM₂ receptors. Adrenomedullin 2/intermedin also has high affinity for the AM₂ receptor [779]. CGRP-(8-37) acts as an antagonist of CGRP (pKi 8) and inhibits some AM and AMY responses (pKi 6-7). It is weak at CT receptors. Salmon CT-(8-32) is an antagonist at both AMY and CT receptors. AC187, a salmon CT analogue, is also an antagonist at AMY and CT receptors. Human AM-(22-52) has some selectivity towards AM receptors, but with modest potency (pKi 7), limiting its use [720]. AM-(22-52) is slightly more effective at AM₁ than AM₂ receptors but this difference is not sufficient for this peptide to be a useful discriminator of the AM receptor subtypes. Telcagepant shows the greatest selectivity between receptors but still has significant affinity for AMY₁ receptors [1972]. Ligand responsiveness at CT and AMY receptors can be affected by receptor splice variation and can depend on the pathway being measured. Particularly for AMY receptors, relative potency can vary with the type and level of RAMP present and can be influenced by other factors such as G proteins [1324, 1886].

Gₛ is a prominent route for effector coupling for CLR and CTR but other pathways (e.g. Ca^{2+}, ERK, Akt), and G proteins can be activated [1972]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, ASL (P04424) is important for the coupling of CLR to adenylly cyclase [498].

[125I]-Salmon CT is the most common radioligand for CT receptors but it has high affinity for AMY receptors and is also poorly reversible. [125I]-TyR₀-CGRP is widely used as a radioligand for CGRP receptors. Some early literature distinguished between CGRP₁ and CGRP₂ receptors. It is now clear that the complex of CALCRL and RAMP₁ represents the CGRP₁ subtype and is now known simply as the CGRP receptor [721]. The CGRP₂ receptor is now considered to have arisen from the actions of CGRP at AM₂ and AMY receptors. This term should not be used [721].

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Calcitonin receptors  5782
Calcium-sensing receptors

G protein-coupled receptors → Calcium-sensing receptors

Overview: The calcium-sensing receptor (CaS, provisional nomenclature as recommended by NC-IUPHAR [530]) responds to extracellular calcium and magnesium in the millimolar range and to gadolinium and some polycations in the micromolar range [229]. The sensitivity of CaS to primary agonists can be increased by aromatic L-amino acids [362] and also by elevated extracellular pH [1544] or decreased extracellular ionic strength [1545]. This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

<table>
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<tr>
<th>Nomenclature</th>
<th>CaS receptor</th>
<th>GPRC6 receptor</th>
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<tbody>
<tr>
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<td>CASR, P41180</td>
<td>GPRC6A, QST6X5</td>
</tr>
<tr>
<td>Amino-acid rank order of potency</td>
<td>L-phenylalanine, L-tryptophan, L-histidine &gt; L-alanine &gt; L-serine, L-proline, L-glutamic acid &gt; L-aspartic acid (not L-lysine, L-arginine, L-leucine and L-isoleucine) [362]</td>
<td>–</td>
</tr>
<tr>
<td>Cation rank order of potency</td>
<td>Gd$^{3+}$ &gt; Ca$^{2+}$ &gt; Mg$^{2+}$ [229]</td>
<td>–</td>
</tr>
<tr>
<td>Polyamine rank order of potency</td>
<td>spermine &gt; spermidine &gt; putrescine [1546]</td>
<td>–</td>
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<tr>
<td>Allosteric modulators</td>
<td>AC265347 (Positive) (pEC$<em>{50}$ 7.6–8.1) [1160], NPS 2143 (Negative) (pIC$</em>{50}$ 7.1–7.4) [1377, 2087], cinacalcet (Positive) (pEC$<em>{50}$ 7.3) [1378], calindol (Positive) (pEC$</em>{50}$ 6.5) [1499], calindol (Positive) (pK$<em>{d}$ 6–6.5) [930], tecalcet (Positive) (pK$</em>{d}$ 6.5) [1379], calhex 231 (Negative) (pIC$_{50}$ 6.4) [1500]</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>2-benzylpyrrolidine derivatives of NPS 2143 are also negative allosteric modulators of the calcium sensing receptor [2087]. etelcalcetide is a novel peptide agonist of the receptor [1975].</td>
<td>GPRC6 is a related G$_{q}$-coupled receptor which responds to basic amino acids [2004].</td>
</tr>
</tbody>
</table>

Comments: Positive allosteric modulators of CaS are termed Type II calcimimetics and can suppress parathyroid hormone (PTH (PTH, P01270)) secretion [1379]. Negative allosteric modulators are called calcilytics and can act to increase PTH (PTH, P01270) secretion [1377]. The central role of CaS in the maintenance of extracellular calcium homeostasis is seen most clearly in patients with loss-of-function CaS mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaS null mice [293, 765], which exhibit similar increases in PTH secretion and blood Ca$^{2+}$ levels. A gain-of-function mutation in the CaS gene is associated with autosomal dominant hypocalcaemia.

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Further Reading


Yarova PL et al. (2015) Calcium-sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma. Sci Transl Med 7: 284ra60 [PMID:25904744]

Cannabinoid receptors

G protein-coupled receptors → Cannabinoid receptors

Overview: Cannabinoid receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Cannabinoid Receptors [1494]) are activated by endogenous ligands that include N-arachidonoyl ethanolamine (anandamide), N-homo-γ-linolenoyl ethanolamine, N-docosatetra-7,10,13,16-enoyl ethanolamine 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 [35].

<table>
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<tr>
<th>Nomenclature</th>
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<th>CB₂ receptor</th>
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<tr>
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<td>CB₁ receptor</td>
<td>CB₂ receptor</td>
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<tr>
<td>(Sub)family-selective agonists</td>
<td>HU-210 (pKᵢ 9.1–10.2) [509, 1733], CP55940 (pKᵢ 8.3–9.2) [509, 1602, 1733], WIN55212-2 (pKᵢ 6.9–8.7) [509, 1733], Δ⁹-tetrahydrocannabinol (Partial agonist) (pKᵢ 7.3–7.4) [509, 1733]</td>
<td>HU-210 (pKᵢ 9.3–9.8) [509, 1579, 1733], WIN55212-2 (pKᵢ 8.4–9.6) [509, 1730, 1733], CP55940 (pKᵢ 8.6–9.2) [509, 1602, 1733], Δ⁹-tetrahydrocannabinol (Partial agonist) (pKᵢ 7.1–7.5) [509, 1579, 1733]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>arachidonoyl-2-chloroethanolamide (pKᵢ 8.9) [755] – Rat, arachidonoylcyclopropylamide (pKᵢ 8.7) [755] – Rat, O-A1812 (pKᵢ 8.5) [420] – Rat, R-(+)-methanandamide (pKᵢ 7.7) [931] – Rat</td>
<td>[WH]-133 (pKᵢ 8.5) [804, 1493], L-759,633 (pKᵢ 7.7–8.2) [576, 1602], AM1241 (pKᵢ 8.1) [2088], L-759,656 (pKᵢ 7–7.9) [576, 1602], HU-308 (pKᵢ 7.6) [699]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>rimonabant (pKᵢ 7.9–8.7) [508, 509, 1586, 1613, 1733], AM251 (pKᵢ 8.1) [1038] – Rat, AM281 (pKᵢ 7.9) [1037] – Rat, LY320135 (pKᵢ 6.9) [508]</td>
<td>SR144528 (pKᵢ 8.3–9.2) [1587, 1602], AM-630 (pKᵢ 7.5) [1602]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]rimonabant (Antagonist) (pKᵢ 8.9–10) [205, 761, 889, 1498, 1588, 1742, 1873] – Rat</td>
<td>–</td>
</tr>
</tbody>
</table>

Comments: Both CB₁ and CB₂ receptors may be labelled with [³H]CP55940 (0.5 nM; [1733]) and [³H]WIN55212-2 (2.2-4 nM; [1756, 1783]). Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [1418, 2135]. There is evidence for an allosteric site on the CB₁ receptor [1532]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [1494]. Moreover, GPR18, GPR55 and GPR119, although showing little structural similarity to CB₁ and CB₂ receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands [1494].
Further Reading


Chemokine receptors

G protein-coupled receptors → Chemokine receptors

Overview: Chemokine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Chemokine Receptors [78, 1346, 1347]) comprise a large subfamily of 7TM proteins that bind one or more chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes. Chemokine receptors can be divided by function into two main groups: G protein-coupled chemokine receptors, which mediate leukocyte trafficking, and “Atypical chemokine receptors”, which may signal through non-G protein-coupled mechanisms and act as chemokine scavengers to downregulate inflammation or shape chemokine gradients [78]. 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

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<th>Nomenclature</th>
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<td>Rank order of potency</td>
<td>resolvin E1 &gt; chemerin C-terminal peptide &gt; 18R-HEPE &gt; EPA [56]</td>
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<td>Selective agonists</td>
<td>resolvin E1</td>
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<tr>
<td>Labelled ligands</td>
<td>[3H]resolvin E1 (Agonist) (pK$_D$ 8) [56, 57]</td>
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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 [79]. Listed are those human agonists with EC<sub>50</sub> values ≤ 50 nM in either Ca<sup>2+</sup> flux or chemotaxis assays at human recombinant G protein-coupled chemokine receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and microbial non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, but CCR5 is the only one demonstrated to play an essential role in HIV/AIDS pathogenesis. The tables include both standard chemokine receptor names [2010] and the most commonly used aliases. Numerical data quoted are typically pK<sub>i</sub> or pIC<sub>50</sub> values from radioligand binding to heterologously expressed receptors.

<table>
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<th>Nomenclature</th>
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<th>CCR3</th>
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<td>CCR2, P41597</td>
<td>CCR3, P51677</td>
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<td>Endogenous agonists</td>
<td>CCL3 (CCL3, P10147) (pK&lt;sub&gt;i&lt;/sub&gt; 7.8–10.2) [328, 357, 747, 2134], CCL23 (CCL23, P35773) (Selective) (pK&lt;sub&gt;i&lt;/sub&gt; 8.9) [328], CCL5 (CCL5, P13501) (pK&lt;sub&gt;i&lt;/sub&gt; 6.8–8.2) [357, 747], CCL7 (CCL7, P80098) (pK&lt;sub&gt;i&lt;/sub&gt; 8.1) [328, 667], CCL15 (CCL15, Q16663) (Selective) (pIC&lt;sub&gt;50&lt;/sub&gt; 7.9) [373], CCL14 (CCL14, Q16662) (pK&lt;sub&gt;i&lt;/sub&gt; 7.4) [328], CCL13 (CCL13, Q99616), CCL8 (CCL8, P80075)</td>
<td>CCL2 (CCL2, P13500) (pIC&lt;sub&gt;50&lt;/sub&gt; 9.3–10.2) [373, 1159, 1291, 1465, 1920], CCL13 (CCL13, Q99616) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.6–8.7) [1159, 1920], CCL7 (CCL7, P80098) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.4–8.7) [373, 1159, 1920], CCL11 (CCL11, P51671) (Partial agonist) (pIC&lt;sub&gt;50&lt;/sub&gt; 7.1–7.7) [1159, 1465], CCL16 (CCL16, Q15467)</td>
<td>CCL13 (CCL13, Q99616) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.7–10.3) [1332, 1920], CCL24 (CCL24, O00175) (Selective) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.9–9.4) [1332, 1465], CCL5 (CCL5, P13501) (pK&lt;sub&gt;i&lt;/sub&gt; 8.5–9.3) [391], CCL7 (CCL7, P80098) (pK&lt;sub&gt;i&lt;/sub&gt; 8.6–9.2) [391], CCL11 (CCL11, P51671) (Selective) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.7–9) [452, 961, 1332, 1625, 1920], CCL26 (CCL26, Q9Y25B) (Selective) (pIC&lt;sub&gt;50&lt;/sub&gt; 7.9–8.9) [961, 1332, 1465], CCL15 (CCL15, Q16663) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.6) [373], CCL28 (CCL28, Q9NR3), CCL8 (CCL8, P80075)</td>
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<tr>
<td>Agonists</td>
<td>–</td>
<td>–</td>
<td>CCL11 (Mouse) (pK&lt;sub&gt;i&lt;/sub&gt; 9.5–10) [391]</td>
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<tr>
<td>Endogenous antagonists</td>
<td>CCL4 (CCL4, P13236) (Selective) (pK&lt;sub&gt;i&lt;/sub&gt; 7.1–7.8) [328, 357]</td>
<td>CCL26 (CCL26, Q9Y258) (Selective) (pIC&lt;sub&gt;50&lt;/sub&gt; 8.5) [1465]</td>
<td>CXCL10 (CXCL10, P02778) (Selective), CXCL11 (CXCL11, Q14625) (Selective), CXCL9 (CXCL9, Q07325) (Selective)</td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
<td>–</td>
<td>banyu () (Inverse agonist) (pK&lt;sub&gt;i&lt;/sub&gt; 8.5) [1977], SB328437 (pK&lt;sub&gt;i&lt;/sub&gt; 8.4), BMS compound 87b (pK&lt;sub&gt;i&lt;/sub&gt; 8.1) [1964]</td>
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<tr>
<td>Selective antagonists</td>
<td>BX 471 (pK&lt;sub&gt;i&lt;/sub&gt; 8.2–9) [1098], compound 2b-1 [PMID: 12614873] (pIC&lt;sub&gt;50&lt;/sub&gt; 8.7) [1368], CP-481,715 (pK&lt;sub&gt;IC&lt;sub&gt;50&lt;/sub&gt;&lt;/sub&gt; 8) [614], UCB35625 (pIC&lt;sub&gt;50&lt;/sub&gt; 8) [1625]</td>
<td>GSK Compound 34 (pK&lt;sub&gt;i&lt;/sub&gt; 7.6)</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>[125]I]CCL11 (human) (Antagonist) (pK&lt;sub&gt;i&lt;/sub&gt; 8.3) [127], [125]I]CCL12 (human) (Agonist), [125]I]CCL7 (human) (Agonist)</td>
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<tr>
<td>Labelled ligands</td>
<td>[125]I]CCL7 (human) (Agonist) (pK&lt;sub&gt;i&lt;/sub&gt; 9.2) [127], [125]I]CCL3 (human) (Agonist) (pK&lt;sub&gt;i&lt;/sub&gt; 8–8.8) [127, 623, 1646], [125]I]CCL5 (human) (Agonist) (pK&lt;sub&gt;i&lt;/sub&gt; 8.2) [1646]</td>
<td>[125]I]CCL2 (human) (Agonist), [125]I]CCL7 (human) (Agonist)</td>
<td>[125]I]CCL11 (human) (Antagonist) (pK&lt;sub&gt;i&lt;/sub&gt; 8.3) [127], [125]I]CCLS (human) (Agonist), [125]I]CCL7 (human) (Agonist)</td>
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<td>CCR5, P51681</td>
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<td>CCL22 (CCL22, O00626) (Selective) (pIC50 9.2) [822], CCL17 (CCL17, Q92583) (Selective) (pIC50 8.7) [822]</td>
<td>CCL5 (CCL5, P13501) (pKᵦ 9.2–9.7) [75, 1364, 1611], CCL4 (CCL4, P13236) (Selective) (pKᵠ 9.4–9.6) [1364, 1611], CCL8 (CCL8, P80075) (pKᵠ 9.3) [1361], CCL3 (CCL3, P10147) (pKᵠ 8–8.9) [1364, 1611, 2134], CCL11 (CCL11, P51671) (pIC50 7.7) [157], CCL2 (CCL2, P13500) (pIC50 7.5) [1364], CCL14 (CCL14, Q16627) (pKᵠ 7.2) [1364], CCL16 (CCL16, O15467)</td>
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<td>Agonists</td>
<td>vMIP-III</td>
<td>RS-HIV-1 gp120</td>
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<td>Endogenous antagonists</td>
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<td>CCL7 (CCL7, P80098) (Selective) (pKᵠ 7.5) [1364]</td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
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</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>E913 (pIC50 8.7) [1174], aplaviroc (pKᵠ 8.5) [1173], maraviroc (pIC50 8.1) [1364], TAK-779 (pKᵠ 7.5) [1173], MRK-1 [1135] – Rat</td>
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<tr>
<td>Antibodies</td>
<td>mogamulizumab (Inhibition) [51, 1731]</td>
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<thead>
<tr>
<th>Nomenclature</th>
<th>CCR6</th>
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<td>CCR8, P51685</td>
<td>CCR9, P51686</td>
<td>CCR10, P46092</td>
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<tr>
<td>Endogenous agonists</td>
<td>CCL20 (CCL20, P78556) (pIC50 7.9–8.5) [18, 74, 1526], beta-defensin 4A (DEFB4A DEFB4B, O15263) (Selective) [2081]</td>
<td>CCL21 (CCL21, O00585) (Selective) (pIC50 9.3) [2099], CCL19 (CCL19, Q99731) (Selective) (pIC50 7.7–9, median 8.6) [1449, 2098, 2099]</td>
<td>CCL1 (CCL1, P23262) (Selective) (pIC50 8.5–9.8) [387, 710, 824], CCL8 (Mouse) – Mouse</td>
<td>CCL25 (CCL25, O15444) (Selective)</td>
<td>CCL27 (CCL27, Q9Y4X3) (Selective), CCL28 (CCL28, Q9H361) (Selective)</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>vMIP-1 (pIC50 8.9–9.9) [387, 824]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>–</td>
<td>vMCC-1 (pIC50 9.4) [387]</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Labelled ligands</td>
<td>[125I]CCL20 (human) (Agonist) (pKᵦ 10) [641]</td>
<td>[125I]CCL19 (human) (Agonist), [125I]CCL21 (human) (Agonist) [856]</td>
<td>[125I]CCL1 (human) (Agonist) (pKᵦ 8.9–9.7) [824, 1597]</td>
<td>[125I]CCL25 (human) (Agonist)</td>
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Chemokine receptors 5787
### Nomenclature

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### Endogenous agonists

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<td>CXCL8</td>
<td>P10145</td>
<td>8.8–9.5</td>
<td>[142, 675, 1068, 2032, 2049]</td>
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<td>CXCL6</td>
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<td>7</td>
<td>[2053]</td>
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<td>6.9–9</td>
<td>[16]</td>
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### Agonists

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### Antagonists

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### Allosteric modulators

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### Labelled ligands

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<td>[125I]CXCL8 (human)</td>
<td>8.9–9.6</td>
<td>[675, 1584]</td>
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<td>[125I]CXCL10 (human)</td>
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<td>[675, 1584]</td>
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<td>9–9.4</td>
<td>[675, 1584]</td>
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<tr>
<td>[125I]CXCL11 (human)</td>
<td>7.3–8.3</td>
<td>[734, 2006]</td>
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</table>

### Comments

Reports on the expression of native CXCR1 by mouse leukocytes are not conclusive. There are reports on the existence of mouse Cxcr1 and on Cxcr1 knockout mice, but the distinct function of the gene and of its knockout phenotype are unclear [118, 351, 1297, 1628, 1794].
### Nomenclature

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>CXCR4</th>
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<td>CXCR6, O00574</td>
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### Endogenous agonists

| CXCL12α (CXCL12, P48061) (Selective) (pKd 7.7–8.2) [746, 1136], CXCL12β (CXCL12, P48061) (Selective) (pKd 7.9) [746] | CXCL13 (CXCL13, O43927) (Selective) (pKd 7.3) [97] | CXCL16 (CXCL16, Q9H2A7) (Selective) (pKd 9) [2026] |

### Agonists

- Selective agonists
  - ALX40-4C (Partial agonist) (pIC$_{50}$ 6.1) [2121], X4-HIV-1 gp120

### Endogenous antagonists

- Selective antagonists
  - plerixafor (pK$_{i}$ 7) [2121]

### Antagonists

- Selective antagonists
  - T134 (pIC$_{50}$ 8.4) [1856], AMD070 (pIC$_{50}$ 7.9) [1750], HIV-Tat

### Allosteric modulators

- Labelled ligands
  - [125I]CXCL12α (human) (Agonist) (pKd 8.1–8.4) [421, 746], [125I]CXCL13 (mouse) (Agonist) [222] – Mouse
  - [125I]CXCL16 (human) (Agonist)

### Comments

- When fused with secreted alkaline phosphatase (SEAP), XCL1 functions as a probe at XCR1
  - ACKR1 is used by *Plasmodium vivax* and *Plasmodium knowlesi* for entering erythrocytes.
Specific chemokine receptors facilitate cell entry by microbes, such as ACKR1 for *Plasmodium vivax* as ACKR1 for human cytomegalovirus and ORF74, which encodes a homologue of CXCR2 in *Herpesvirus saimiri*.

Endogenous chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ORF74, which encodes a homolog of CXC-R2 in *Herpesvirus saimiri* and Herpesvirus-68), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers.

The CC chemokine family (CCL1-28) includes I309 (CCL1 (CCLI, P22362)), MCP-1 (CCL2 (CCLI, P13501)), MCP-3 (CCL7 (CCLI, P80098)), MCP-2 (CCL8 (CCLI, P80075)), eotaxin (CCL11 (CCLI, P15671)), MCP-4 (CCLI13 (CCLI, 99616)), HCC-1 (CCL14 (CCLI, Q16627)), Lkn-1/HCC-2 (CCL15 (CCLI, Q16663)), TARC (CCLI7 (CCLI, Q9283)), ELR (CCLI9 (CCLI, Q99731)), LARC (CCLI20 (CCLI, 78556)), SLC (CCLI21 (CCLI, 000585)), MDC (CCLI22 (P02775)), EMP (CCLI23 (CCLI, P57772)), eosin-2 (CCLI24 (P02775), 00175), TECK (CCLI25 (CCLI, O13444)), eotaxin (CCLI26 (CCLI, Q91528)), eske/C-TACK (CCLI27 (CCLI, Q94X3)) and MEC (CCLI28 (CCLI, Q9NR3)). The CXC chemokine family (CXC1-17) includes GROs (CCLI1 (CCLI, P09341)), GROβ (CCLI2 (CCLI, P19875)), GROγ (CCLI3 (CCLI, P19876)), platelet factor 4 (CCLI4 (PFG, P02776)), ENA78 (CCLI5 (CCLI, P42830)), CCP-2 (CCLI6 (CCLI, P02162)), NAP-2 (CCLI7 (P09344), CCLI8 (P02776)), 8-IL (CCLI8 (CCLI, P10145)), MIG (CCLI9 (CCLI, Q07325)), IP-10 (CCLI10 (P02778)), J-2 (CCLI11 (CCLI, Q14625)), SDF-1 (CCLI12 (CCLI, P13501)), BLC (CCLI13 (CCLI, P43620)), BRAK (CCLI14 (CCLI, P95715)), mouse lungkine (CCLI15 (Mouse)) and CCLI17 (CCLI7, Q6UXB2). The CX3-C chemokine (CX3CL1 (CCLI, P78423)) is also known as fractalkine (neurotactin in the mouse). Like CCLI16 (CCLI, Q9H2A7), and unlike other chemokines, CX3CL1 (CCLI, P78423) is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (CCLI1 (CCLI, P47992)) is also known as lymphotactin.

Two chemokine receptor antagonists have now been approved by the FDA: the CCR5 antagonist maraviroc (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and the CCRX4 antagonist plerixafor (Sanofi) for hematopoietic stem cell mobilization with G-CSF (CSF3, P09919) in patients undergoing transplantation in the context of chemotherapy for lymphoma and multiple myeloma.

Further Reading


Cholecystokinin receptors

Overview: Cholecystokinin receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on CCK receptors [1403]) 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, CCK1 and CCK2 receptors [992, 1986], with some alternatively spliced forms most often identified in neoplastic cells. The CCK receptor subtypes are distinguished by their peptide selectivity, with the CCK1 receptor requiring the carboxyl-terminal heptapeptide-amide that includes a sulfated tyrosine for high affinity and potency, while the CCK2 receptor requires only the carboxyl-terminal tetrapeptide shared by both CCK and gastrin peptides. These receptors have characteristic and distinct distributions, with both present in both the central nervous system and peripheral tissues.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>CCK1 receptor</th>
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<tbody>
<tr>
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<td>CCKAR, P32238</td>
<td>CCKBR, P32239</td>
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<tr>
<td>Rank order of potency</td>
<td>CCK-8 (CCK, P06307) &gt; gastrin-17 (GAST, P01350), desulfated cholecystokinin-8 &gt; CCK-4 (CCK, P06307)</td>
<td>CCK-8 (CCK, P06307) &gt; gastrin-17 (GAST, P01350), desulfated cholecystokinin-8, CCK-4 (CCK, P06307)</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>(Selective) (pIC50 8.3) [805] – Mouse, CCK-4 (CCK, P06307) (pIC50 7.5) [832], desulfated gastrin-14 (GAST, P01350), desulfated gastrin-34 (GAST, P01350), desulfated gastrin-71 (GAST, P01350), gastrin-14 (GAST, P01350), gastrin-34 (GAST, P01350), gastrin-71 (GAST, P01350)</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>A-71623 (pIC50 8.4) [63] – Rat, JMV180 (pIC50 8.3) [926], GW-5823 (pIC50 7.6) [737]</td>
<td>R8-400 (pKi 9.1) [123] – Rat, PBC-264 (pIC50 9.1) [844] – Rat</td>
</tr>
<tr>
<td>Antagonists</td>
<td>lintitript (pIC50 8.3) [632]</td>
<td>–</td>
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<tr>
<td>Selective antagonists</td>
<td>devazepide (pIC50 9.7) [805] – Rat, T-0632 (pIC50 9.6) [1861] – Rat, PD-140548 (pIC50 8.6) [1748] – Rat, lorglumide (pIC50 6.7–8.2) [805, 834] – Rat</td>
<td>YF-476 (pIC50 9.7) [196, 1854], GV150013 (pIC50 9.4) [1930], L-740093 (pIC50 9.2) [1398], YM-022 (pIC50 9.2) [1398], JNJ-26070109 (pIC50 8.5) [1336], L-365260 (pIC50 8.4) [1071], RP73870 (pIC50 8) [1115] – Rat, LY262691 (pIC50 7.5) [1561] – Rat</td>
</tr>
</tbody>
</table>

Comments: While a cancer-specific CCK receptor has been postulated to exist, which also might be responsive to incompletely processed forms of CCK (Gly-extended forms), this has never been isolated. An alternatively spliced form of the CCK2 receptor in which intron 4 is retained, adding 69 amino acids to the intracellular loop 3 (ICL3) region, has been described to be present particularly in certain neoplasms where mRNA mis-splicing has been commonly observed [1764], but it is not clear that this receptor splice form plays a special role in carcinogenesis. Another alternative splicing event for the CCK2 receptor was reported [1782], 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.

Searchable database: http://www.guidetopharmacology.org/index.jsp
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 [1676]), are GPCRs originally identified in Drosophila [285], which are highly conserved across species. FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription regulator β-catenin (CTNNB1, P35222) or being β-catenin-independent (often referred to as canonical vs. non-canonical WNT/FZD signalling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors LRPS (O75197) and LRP6 (O75581), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β-catenin and subsequently its translocation to the nucleus. β-Catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors. β-Catenin-independent FZD signalling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of pertussis toxin-sensitive heterotrimeric G proteins [939], the elevation of intracellular calcium [1757], activation of cGMP-specific PDE6 [17] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [695]. Furthermore, the phosphoprotein Disheveled constitutes a key player in WNT/FZD signalling. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [306], as well as for β-catenin-dependent [235] and -independent [236, 940] 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

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**Comments:** There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. Understanding of the coupling to G proteins is incomplete (see [423]). There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships [937].

**Ligands associated with FZD signalling**

**WNTs:** Wnt-1 (WNT1, P04628), Wnt-2 (WNT2, P09544) (also known as Int-1-related protein), Wnt-2b (WNT2B, Q93097) (also known as WNT-13), Wnt-3 (WNT3, P56703), Wnt-3a (WNT3A, P56704), Wnt-4 (WNT4, P56705), Wnt-5a (WNT5A, P41221), Wnt-5b (WNT5B, Q9H1J7), Wnt-6 (WNT6, Q9Y6F9), Wnt-7a (WNT7A, O00755), Wnt-7b (WNT7B, P56706), Wnt-8a (WNT8A, Q9H1J5), Wnt-8b (WNT8B, Q93098), Wnt-9a (WNT9A, O14904) (also known as WNT-14), Wnt-9b (WNT9B, O14905) (also known as WNT-15 or WNT-14b), Wnt-10a (WNT10A, Q9GZT5), Wnt-10b (WNT10B, O00744) (also known as WNT-12), Wnt-11 (WNT11, Q96014) and Wnt-16 (WNT16, Q9UBV4).

**Extracellular proteins that interact with FZDs:** nomin (NDP, Q00604), R-spondin-1 (RSPO1, Q2MKA7), R-spondin-2 (RSPO2, Q6UX9), R-spondin-3 (RSPO3, Q9BX4), R-spondin-4 (RSPO4, Q210MS), SFRP-1 (SFRP1, Q8N474), SFRP-2 (SFRP2, Q96HF1), SFRP-3 (FRZB, Q92765), SFRP-4 (SFRP4, Q6FH7), SFRP-5 (SFRPS, Q6FH7).

**Extracellular proteins that interact with WNTs or LRPs:** Dickkopf 1 (DKK1, Q94907), WIF1 (Q9YSW5), sclerostin (SOST, Q9BQ84), kremen 1 (KREMEN1, Q96MUB) and kremen 2 (KREMEN2, Q8NCW0).

**Small exogenous ligands:** Foxy-5 [1835], Box-5, UM206 [1031], and XWnt8 (P28026) also known as mini-Wnt8.

**Further Reading**


Koval A et al. (2011) Yellow submarine of the Wnt/Frizzled signaling: submerging from the G protein harbor to the targets. Biochem. Pharmacol. 82: 1311-9 [PMID:21689640]


**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 [967]) are activated by the endogenous 75 amino-acid anaphylatoxin polypeptides C3a (C3, P01024), C4a (C4A, P04628) and C5a (C5, P01031), generated upon stimulation of the complement cascade.
Nomenclature

<table>
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<th>C3a receptor</th>
<th>C5a1 receptor</th>
<th>C5a2 receptor</th>
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<tbody>
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<td>CSAR1, P21730</td>
<td>CSAR2, Q9P296</td>
</tr>
</tbody>
</table>

Rank order of potency

- C3a (C3, P01024) > C5a (CS, P01031) [41]
- C5a (CS, P01031), C5a des-Arg (C5) > C3a (C3, P01024) [41]

Endogenous agonists

- ribosomal protein S19 (RPS19, P39019) [2071]

Agonists

- E7 (pEC50 8.7) [43], compound 21 [PMID: 25259874] (pEC50 7.7) [1571], SQ007-5 (Partial agonist) (pEC50 6.7) [124], Ac-RHYPLWR (pEC50 6) [672]
- N-methyl-Phe-Lys-Pro-D-Cha-D-Arg-CO2H (pIC50 7.6) [916, 989]

Antagonists

- SB290157 (pIC50 7.6) [40], compound 4 [PMID: 25259874] (pIC50 5.9) [1571]
- CHIPs (pKd 9) [1522], W54011 (pKd 8.7) [1819], Ac-Phe-Orn-Pro-D-Cha-Trp-Arg (pIC50 7.9) [2039], N-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO2H (pIC50 7.2) [989]

Labelled ligands

- [125I]C3a (human) (Agonist) (pKd 8.4) [296]
- [125I]C5a (human) (Agonist) (pKd 8.7) [803]
- [125I]C5a (human) (Agonist)

Comments: SB290157 has also been reported to have agonist properties at the C3a receptor [1218]. The putative chemoattractant receptor termed C5a2 (also known as GPR77, C5L2) binds [125I]C5a with no clear signalling function, but has a putative role opposing inflammatory responses [257, 568, 585]. Binding to this site may be displaced with the rank order C5a des-Arg (C5) > C5a (C5, P01031) [257, 1440] while there is controversy over the ability of C3a (C3, P01024) and C3a des Arg (C3, P01024) to compete [778, 894, 895, 1440]. C3a2 appears to lack G protein signalling and has been termed a decoy receptor [1684]. However, C5a2 does recruit arrestin after ligand binding, which might provide a signaling pathway for this receptor [89, 1937], and forms heteromers with C5a1. C5a, but not C5a-des Arg, induces upregulation of heteromer formation between complement C5a receptors C5aR and C5L2 [380]. There are also reports of pro-inflammatory activity of C5a2, mediated by HMGB1, but the signaling pathway that underlies this is currently unclear (reviewed in [1095]).

Further Reading


Corticotropin-releasing factor receptors

Overview: Corticotropin-releasing factor (CRF, nomenclature as agreed by the NC-IUPHAR subcommittee on Corticotropin-releasing Factor Receptors [716]) 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. CRF1 and CRF2 receptors are activated non-selectively by corticotrophin-releasing hormone (CRH, P06850) and urocortin 1 (UCN, P55089). Binding to CRF receptors can be conducted using [125I]Tyr0-CRF or [125I]Tyr0-sauvagine with Kd values of 0.1-0.4 nM. CRF1 and CRF2 receptors are non-selectively antagonized by α-helical CRF, D-Phe-CRF-(12-41) and astressin.

Nomenclature

<table>
<thead>
<tr>
<th>CRF1 receptor</th>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
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</tr>
<tr>
<td></td>
<td>CRHR2, Q13324</td>
</tr>
</tbody>
</table>

Endogenous agonists

- CRHBP (pKd 9.0–9.4) [1153] – Rat, DMP696 (pKd 8.3–9) [726], NBI27914 (pKd 8.3–9) [298], R121919 (pKd 8.3–9) [2133], antalarmin (pKd 8.3–9) [2001], CP376395 (pIC50 6.4–7.1) [284]

Antagonists

- SSR125543A (pKd 8.7) [663]

Selective antagonists

- CP154,526 (pIC50 9.3–10.4) [1153] – Rat, DMP696 (pKd 8.3–9) [726], NBI27914 (pKd 8.3–9) [298], R121919 (pKd 8.3–9) [2133], antalarmin (pKd 8.3–9) [2001], CP376395 (pIC50 6.4–7.1) [284]

Further Reading

Dopamine receptors

G protein-coupled receptors → Dopamine receptors

Overview: Dopamine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Dopamine Receptors [1677]) are commonly divided into D1-like (D1 and D2) and D2-like (D2, D3 and D4) families, where the endogenous agonist is dopamine.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>D1 receptor</th>
<th>D2 receptor</th>
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<tbody>
<tr>
<td>HCNC, UniProt</td>
<td>DRD1, P21728</td>
<td>DRD2, P14416</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>dopamine (pKᵢ 4.3–5.6) [1823, 1884]</td>
<td>dopamine (pKᵢ 4.7–7.2) [245, 545, 1653]</td>
</tr>
<tr>
<td>Agonists</td>
<td>fenoldopam (pKᵢ 6.5–7.9) [1884]</td>
<td>pimozide (pKᵢ 7.8–8.8) [545]</td>
</tr>
<tr>
<td>A68930 (pEC₅₀ 6.8) [1381], SKF-38393 (Partial agonist) (pKᵢ 6.2–6.8) [1823, 1884]</td>
<td>quinpirole (pKᵢ 4.9–7.7) [245, 1273, 1473, 1776, 1778, 1940]</td>
<td></td>
</tr>
<tr>
<td>Selective agonists</td>
<td>SKF-83959 (Biased agonist) (pEC₅₀ 9.7) [364], SKF-81297 (pKᵢ 8.7) [46] – Rat</td>
<td>sumanirole (pKᵢ 8.1) [1239]</td>
</tr>
<tr>
<td>Antagonists</td>
<td>flupenthixol (pKᵢ 7–8.4) [1823, 1884]</td>
<td>blonanserin (pKᵢ 9.9) [1421], pipotiazine (pKᵢ 9.7) [1777], perphenazine (pKᵢ 8.9–9.6) [1008, 1691], risperidone (pKᵢ 9.4) [60], perospirone (pKᵢ 9.2) [1692], trifluoperazine (pKᵢ 8.9–9) [1008, 1693], quinpirole (pKᵢ 8.7) [1777], spiperone (pKᵢ 8.6) [60], prochlorperazine (pKᵢ 8.4) [68], loxapine (pKᵢ 7.9–8.3) [1008, 1693], (c)-sulpiride (pKᵢ 6.3–8) [545]</td>
</tr>
<tr>
<td>SCH-23390 (pKᵢ 7.4–9.5) [1823, 1884], SKF-83556 (pKᵢ 9.5) [1823],</td>
<td>amiluzadine (pKᵢ 9.1) [1211], bromocriptine (pKᵢ 7.3–8.3) [545, 1279, 1653], MSL1547 (Biased agonist) (pKᵢ 8.2) [544], ropinirole (pKᵢ 8.1) [732], apomorphine (Partial agonist) (pKᵢ 5.7–7.5) [245, 545, 1279, 1653, 1776], pramipexole (pKᵢ 5.1–7.4) [1273, 1653], benzquinamide (pKᵢ 5.4) [643]</td>
<td></td>
</tr>
<tr>
<td>ecopipam (pKᵢ 8.3) [1885]</td>
<td>L-741,626 (pKᵢ 7.9–8.5) [655, 1020], domperidone (pKᵢ 7.9–8.4) [545, 1776], raclopride (pKᵢ 8) [1281], ML321 (pKᵢ 7) [2058, 2059]</td>
<td></td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>[3H]flupenthixol (pKᵢ 8.9) [1028] – Rat</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]SCH-23390 (Antagonist) (pKᵢ 9.5) [2127]</td>
<td>[³H]raclopride (Antagonist) (pKᵢ 9.1) [1239], haloperidol (pKᵢ 7.4–8.8) [545, 1164, 1273, 1776, 1885]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]SCH23982 (Antagonist) (pKᵢ 9.5) [408]</td>
<td>[³H]propranolol (Antagonist) (pKᵢ 8.9) [1028] – Rat</td>
</tr>
</tbody>
</table>

Searchable database: http://www.guidetopharmacology.org/index.jsp
### Nomenclature

<table>
<thead>
<tr>
<th>HGNC, UniProt</th>
<th><strong>D₃</strong> receptor</th>
<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRD3</strong>, P35462</td>
<td>dopamine (pKᵢ 6.4–7.3) [245, 545, 1653, 1778]</td>
<td>dopamine (pKᵢ 7.6) [1940]</td>
<td>dopamine (pKᵢ 6.6) [1823]</td>
</tr>
</tbody>
</table>

### Agonists

<table>
<thead>
<tr>
<th><strong>D₃</strong> receptor</th>
<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>pramipexole (pKᵢ 8.4–8.7) [1273, 1653], bromocriptine (Partial agonist) (pKᵢ 7.1–8.2) [545, 1279, 1653], ropinirole (pKᵢ 7.7) [732], apomorphine (Partial agonist) (pKᵢ 6.1–7.6) [245, 545, 1279, 1653, 1776]</td>
<td>apomorphine (Partial agonist) (pKᵢ 8.4) [1279]</td>
<td>–</td>
</tr>
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### Antagonists

<table>
<thead>
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<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinpirole (pKᵢ 6.4–8) [245, 1273, 1281, 1473, 1653, 1776, 1778, 1940]</td>
<td>quinpirole (pKᵢ 7.5) [1279, 1473, 1940]</td>
<td>A68930 (pEC₅₀ 6.6) [1381]</td>
</tr>
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</table>

### Selective agonists

<table>
<thead>
<tr>
<th><strong>D₃</strong> receptor</th>
<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD 128907 (pKᵢ 7.6–7.7) [1539, 1653]</td>
<td>PD168,077 (Partial agonist) (pKᵢ 8.8) [995] – Rat, A412997 (pKᵢ 8.1) [1319] – Rat, A412997 (pKᵢ 8.1) [1319]</td>
<td>–</td>
</tr>
</tbody>
</table>

### Antagonists

<table>
<thead>
<tr>
<th><strong>D₃</strong> receptor</th>
<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>perosprone (pKᵢ 9.6) [1776], sertindole (pKᵢ 8–8.8) [60, 1675, 1691], prochlorperazine (pKᵢ 8.4) [68], (-)-sulpiride (pKᵢ 6.7–7.7) [545, 1776, 1860], loxapine (pKᵢ 7.7) [1691], domperidone (pKᵢ 7.1–7.6) [545, 1776], promazine (pKᵢ 6.8) [246]</td>
<td>perosprone (pKᵢ 10.1) [1694], sertindole (pKᵢ 7.8–9.1) [246, 1691, 1693, 1694], sonepiprazole (pKᵢ 8.9) [1688], loxapine (pKᵢ 8.1) [1693]</td>
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</tr>
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### Selective antagonists

<table>
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<tr>
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<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>haloperidol (pKᵢ 7.5–8.6) [545, 1711, 1776, 1885]</td>
<td>haloperidol (pKᵢ 8.7–8.8) [1033, 1711, 1885]</td>
<td>SCH-23390 (pKᵢ 7.5–9.5) [1823], SKF-83556 (pKᵢ 9.4) [1823], ecopipram (pKᵢ 8.3) [1823]</td>
</tr>
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</table>

### Selective allosteric modulators

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>SB269652 (Negative) (pKᵢ ~ 9) [558]</td>
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### Labelled ligands

<table>
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<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>[³H]Speriprone (Antagonist) (pKᵢ 9.9) [767, 2125] – Rat, [³H]7-OH-DPAT (Agonist) (pKᵢ 9.6) [1581], [³H]PD128907 (Agonist) (pKᵢ 9) [27]</td>
<td>[³H]Speriprone (Antagonist) (pKᵢ 9.5) [749, 1940]</td>
<td>[³H]SCH-23390 (Antagonist) (pKᵢ 9.2) [1580]</td>
</tr>
</tbody>
</table>

### Labelled ligands

<table>
<thead>
<tr>
<th><strong>D₃</strong> receptor</th>
<th><strong>D₄</strong> receptor</th>
<th><strong>D₅</strong> receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>[¹²⁵I]L750667 (Antagonist) (pKᵢ 9.8) [1473], [³H]NGD941 (Antagonist) (pKᵢ 8.3) [1533]</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

### Comments:

The selectivity of many of these agents is less than two orders of magnitude. [³H]raclopride exhibits similar high affinity for D₂ and D₃ receptors (low affinity for D₄), but has been used to label D₂ receptors in the presence of a D₃-selective antagonist. [³H]7-OH-DPAT has similar affinity for D₂ and D₃ receptors, but labels only D₃ receptors in the absence of divalent cations. The pharmacological profile of the D₅ receptor is similar to, yet distinct from, that of the D₁ receptor. The splice variants of the D₂ receptor are commonly termed D₂S and D₂L (short and long). The DRD4 gene encoding the D₄ receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

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Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
G protein-coupled receptors → Endothelin receptors

**Overview:** Endothelin receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Endothelin Receptors [395]) 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)).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>ET&lt;sub&gt;A&lt;/sub&gt; receptor</th>
<th>ET&lt;sub&gt;B&lt;/sub&gt; receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>EDNRA, P25101</td>
<td>EDNRB, P24530</td>
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</tbody>
</table>

**Family selective agonists**

<table>
<thead>
<tr>
<th>Agonist</th>
<th>EDN1</th>
<th>EDN2</th>
<th>EDN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>endothelin-1 (EDN1, P05305) = endothelin-2 (EDN2, P20800) = endothelin-3 (EDN3, P14138)</td>
<td>[1178]</td>
<td></td>
<td></td>
</tr>
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</table>

**Selective agonists**

<table>
<thead>
<tr>
<th>Agonist</th>
<th>EDN1</th>
<th>EDN2</th>
<th>EDN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
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</tr>
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</table>

**(Sub)family-selective antagonists**

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>EDN1</th>
<th>EDN2</th>
<th>EDN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB209670 (pK&lt;sub&gt;A&lt;/sub&gt; 9.4) [474] – Rat, TAK 044 (pA&lt;sub&gt;2&lt;/sub&gt; 8.4) [1993] – Rat, bosentan (pA&lt;sub&gt;2&lt;/sub&gt; 7.2) [354] – Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Selective antagonists**

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>EDN1</th>
<th>EDN2</th>
<th>EDN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>atrasentan (pA&lt;sub&gt;2&lt;/sub&gt; 9.2–10.5) [1446], PD-156707 (pK&lt;sub&gt;D&lt;/sub&gt; 9.9–10.8) [1180], macitentan (pIC&lt;sub&gt;50&lt;/sub&gt; 9.3) [174], sitaxsentan (pA&lt;sub&gt;2&lt;/sub&gt; 8) [2047], PRL139317 (inverse agonist) (pIC&lt;sub&gt;50&lt;/sub&gt; 7.3–7.9) [1178], ambrisentan (pIC&lt;sub&gt;50&lt;/sub&gt; 7.7) [175], BQ231 (pA&lt;sub&gt;2&lt;/sub&gt; 6.9–7.4) [1178], avosentan (pIC&lt;sub&gt;50&lt;/sub&gt; 7.3) [210], ambrisentan (pA&lt;sub&gt;2&lt;/sub&gt; 7.1) [175]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Labeled ligands**

<table>
<thead>
<tr>
<th>Labeled ligand</th>
<th>EDN1</th>
<th>EDN2</th>
<th>EDN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>[125]I-PD164333 (Antagonist) (pK&lt;sub&gt;D&lt;/sub&gt; 9.6–9.8) [398], [H]S0139 (Antagonist) (pK&lt;sub&gt;D&lt;/sub&gt; 9.2), [125]I-PD151242 (Antagonist) (pK&lt;sub&gt;D&lt;/sub&gt; 9.9–1.1) [399], [H]BQ123 (Antagonist) (pK&lt;sub&gt;D&lt;/sub&gt; 8.5) [817]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 [713]. 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 [1295].

*Searchable database: http://www.guidetopharmacology.org/index.jsp
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 [1536]) was identified following observations of estrogen-evoked cyclic AMP signalling in breast cancer cells [61], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [263]. There are observations of both cell-surface and intracellular expression of the GPER receptor [1573, 1877].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GPER1, Q99527</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>G1 (pKᵢ 8)   [176]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>G36 (pIC₅₀ 6.8–6.9) [414], G15 (pIC₅₀ 6.7) [413]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]17β-estradiol (Agonist) (pKᵢ 8.5–8.6) [1877]</td>
</tr>
</tbody>
</table>

**Comments:** Antagonists at the nuclear estrogen receptor, such as fulvestrant and tamoxifen [515], as well as the flavonoid ‘phytoestrogens’ genistein and quercetin [1177], are agonists at GPER receptors.

**Further Reading**


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Further Reading


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Searching database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Formylpeptide receptors

G protein-coupled receptors → Formylpeptide receptors

Overview: The formylpeptide receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on the formyl peptide receptor family [2092]) respond to exogenous ligands such as the bacterial product fMet-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ANXA1, P04083), cathepsin G (CTSG, P08311), amyloid β(Aβ), serum amyloid A and spinorphin, derived from β-haemoglobin (HBB, P68871).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>FPR1</th>
<th>FPR2/ALX</th>
<th>FPR3</th>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>FPR1, P21462</td>
<td>FPR2, P25090</td>
<td>FPR3, P25089</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>fMet-Leu-Phe &gt; cathepsin G (CTSG, P08311) &gt; annexin I (ANXA1, P04083) [1058, 1821]</td>
<td>LXA₄=aspirin triggered lipoxin A₄=ATLa₂=LTC₄=LTD₄=15-deoxy-LXA₄=fMet-Leu-Phe [352, 519, 521, 651, 1846]</td>
<td>–</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>LXA₄ (Selective) (pEC₅₀ ~12) [1006], resolvin D1 (Selective) (pEC₅₀ ~11.9) [1006], aspirin triggered lipoxin A₄ (Selective)</td>
<td>F2L (HEBP1, Q9NRV9) (Selective) (pEC₅₀ 8–8.2) [1274]</td>
</tr>
<tr>
<td>Agonists</td>
<td>fMet-Leu-Phe (pEC₅₀ 10.1–10.2) [546, 1734]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>ATLa₂ [662]</td>
<td>–</td>
</tr>
<tr>
<td>Endogenous antagonists</td>
<td>spinorphin (Selective) (pIC₅₀ 4.3) [1099, 1348]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antagonists</td>
<td>t-Boc-FLFLF (pKᵢ 6–6.5) [2008]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>cyclosporin H (pKᵢ 6.1–7.1) [2008, 2078]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[³H]fMet-Leu-Phe (Agonist) (pKᵢ 7.6–9.3) [990]</td>
<td>[³H]LXA₄ (Agonist) (pKᵢ 9.2–9.3) [519, 520]</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [724].</td>
<td>The agonist activity of the lipid mediators described has been questioned [697, 1513], which may derive from batch-to-batch differences, partial agonism or biased agonism. Recent results from Cooray et al. (2013) [365] have addressed this issue and the role of homodimers and heterodimers in the intracellular signaling.</td>
<td>–</td>
</tr>
</tbody>
</table>

Comments: Note that the data for FPR2/ALX are also reproduced on the leukotriene receptor page.

Further Reading


Rabiet MJ et al. (2011) N-formyl peptide receptor 3 (FPR3) departs from the homologous FPR2/ALX receptor with regard to the major processes governing chemoattractant receptor regulation, expression at the cell surface, and phosphorylation. J. Biol. Chem. 286: 26718-31 [PMID:21543323]


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


Formylpeptide receptors 5800
**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 [396, 1803]) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (C14:0 (myristic acid), C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (linoleic acid), C18:3, (α-linolenic acid), C20:4 (arachidonic acid), C20:5, n-3 (EPA), C22:6, n-3 (docosahexaenoic acid)) activate FFA1 [218, 833, 998] and FFA4 receptors [757, 812, 1427], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA2 [226, 1057, 1399] and FFA3 [226, 1057] receptors. In addition, thiazolidinedione PPARγ agonists such as rosiglitazone activate FFA1 (pEC50 5.2; [999, 1768, 1802]) and small molecule allosteric modulators, such as 4-CMTB, have recently been characterised for FFA2 [801, 1070, 1769].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>FFA1 receptor</th>
<th>FFA2 receptor</th>
<th>FFA3 receptor</th>
<th>FFA4 receptor</th>
<th>GPR42</th>
</tr>
</thead>
<tbody>
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<td>HGNC, UniProt</td>
<td>FFA1, O14842</td>
<td>FFA2, O15552</td>
<td>FFA3, O14843</td>
<td>FFA4, Q5NUL3</td>
<td>GPR42, O15529</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>docosahexaenoic acid (pEC50 5.4–6) [218, 833]</td>
<td>–</td>
<td>–</td>
<td>α-linolenic acid (pEC50 5.5) [1727]</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>fasiglifam (pEC50 7.1) [893, 1791, 1909]</td>
<td>propanoic acid (pEC50 3–4.9) [226, 1057, 1399, 1670], acetic acid (pEC50 3.1–4.6) [226, 1057, 1399, 1670], butyric acid (pEC50 2.9–4.6) [226, 1057, 1399, 1670], trans-2-methylcrotonic acid (pEC50 3.8) [1670], 1-methylcyclopropanecarboxylic acid (pEC50 2.6) [1670]</td>
<td>propanoic acid (pEC50 3.9–5.7) [226, 1057, 1670, 2063], butyric acid (pEC50 3.8–4.9) [226, 1057, 1670, 2063], 1-methylcyclopropanecarboxylic acid (pEC50 3.9) [1670], acetic acid (pEC50 2.8–3.9) [226, 1057, 1670, 2063]</td>
<td>myristic acid (pEC50 5.2) [1996], oleic acid (pEC50 4.7) [1996]</td>
<td>–</td>
</tr>
<tr>
<td>(Sub)family-selective agonists</td>
<td>α-linolenic acid (pEC50 4.6–5.7) [218, 833, 998], oleic acid (pEC50 3.9–5.7) [218, 833, 998], myristic acid (pEC50 4.5–5.1) [218, 833, 998]</td>
<td>AMG-837 (pEC50 8.5) [1110], TUG-770 (pEC50 8.2) [332], GW9508 (pEC50 7.3) [217], linoleic acid (pEC50 4.4–5.7) [218, 833, 998]</td>
<td>compound 1 [PMID: 23589301 (pEC50 7.1) [800] – Rat, (S)-4-CMTB (pEC50 6.4) [801, 1070]</td>
<td>compound A [PMID 24997608] (pEC50 7.6) [1428], TUG-891 (pEC50 7) [1727] – Unknown, NCG21 (pEC50 5.9) [1829]</td>
<td>–</td>
</tr>
</tbody>
</table>

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
**Nomenclature**

- **FFA1 receptor**
  - GW1100 (pIC\textsubscript{50} 6) [217]

- **FFA2 receptor**
  - GLPC0974 (pIC\textsubscript{50} 8.1) [1512]
  - CATPB (pIC\textsubscript{50} 6.5) [801]

- **FFA3 receptor**
  - Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [951]. 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, have recently been described [799].

- **FFA4 receptor**
  - TUG-770 and GW9508 are both approximately 100 fold selective for FFA1 over FFA4 [217, 332]. 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 [1110, 2064].

- **GPR42**
  - compound A [PMID 24997608] exhibits more than 1000 fold selectivity [1428], and TUG-891 50-1000 fold selectivity for FFA4 over FFA1 [1727], dependent on the assay. NGC21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [1820].

**Selective antagonists**

- Antagonist GW1100 has been shown to reduce [\textsuperscript{35}S]GTP\gamma S binding in FFA1-expressing cells [1802]. GW1100 is also an oxytocin receptor antagonist [217]. TUG-770 and GW9508 are both approximately 100 fold selective for FFA1 over FFA4 [217, 332]. AMC-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 [1110, 2064].

**Comments**

- Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [1318], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [1996]. The long FFA4 splice variant has not been identified in other primates or rodents to date [757, 1318].

**Further Reading**


Watterson KR et al. (2014) Treatment of type 2 diabetes by free Fatty Acid receptor agonists. Front Endocrinol (Lausanne) 5: 137 [PMID:25221541]

**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

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 [194, 1507]) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub> [194, 478, 1506, 1507, 1926]. 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. The GABA<sub>B1</sub> subunit when expressed alone is not transported to the cell membrane and is non-functional. However, Richer et al. (2008) report that GABA<sub>B1</sub> alone can control ERK/MAPK pathway activity [1585]. 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, Cav2.2), or inwardly rectifying potassium channels (Kir3) [144, 194, 195]. The GABA<sub>B2</sub> subunit also determines the rate of internalisation of the dimeric GABA<sub>B</sub> receptor [693]. 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 [194, 591, 592, 1506]. The two subunits interact by direct allosteric coupling [1313], such that GABA<sub>B2</sub> increases the affinity of GABA<sub>B1</sub> for agonists and reciprocally GABA<sub>B1</sub> facilitates the coupling of GABA<sub>B2</sub> to G proteins [591, 1013, 1506]. GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α-helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the GABA<sub>B1</sub> subunit but other domains of the proteins also contribute to their heteromeronisation [144, 243, 1506]. 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 [361, 1505]. 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 [102, 1680, 1914] and reviewed by [1508]. Four isoforms of the human GABA<sub>B1</sub> subunit have been cloned. The predominant GABA<sub>B1(a)</sub> and GABA<sub>B1(b)</sub> isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA<sub>B1(a)</sub>-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA<sub>B1(b)</sub>-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [1541, 1955]. Isoforms generated by alternative splicing are GABA<sub>B1(c)</sub> that differs in the ECD, and GABA<sub>B1(e)</sub>, which is a truncated protein that can heterodimerize with the GABA<sub>B2</sub> subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors [194]. Additional GABA<sub>B1</sub> subunit isoforms have been described in rodents and humans [1065] and reviewed by [144].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GABA&lt;sub&gt;B&lt;/sub&gt; receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subunits</td>
<td>kcdt12b (Accessory protein), KCTD16 (Accessory protein), KCTD12 (Accessory protein), GABA&lt;sub&gt;B2&lt;/sub&gt;, GABA&lt;sub&gt;B1&lt;/sub&gt;, KCTD8 (Accessory protein)</td>
</tr>
<tr>
<td>Agonists</td>
<td>CGP 44532 (pIC&lt;sub&gt;50&lt;/sub&gt; 8.6) [551] – Rat, (R)-baclofen (pIC&lt;sub&gt;50&lt;/sub&gt; 8.5) [551] – Rat, 3-APPA (pK&lt;sub&gt;I&lt;/sub&gt; 5.2–7.2) [762], baclofen (pK&lt;sub&gt;I&lt;/sub&gt; 4.3–6.2) [762, 2041], 3-APMPA (pK&lt;sub&gt;I&lt;/sub&gt; 5.1) [2041]</td>
</tr>
<tr>
<td>Antagonists</td>
<td>CGP 62349 (pK&lt;sub&gt;I&lt;/sub&gt; 8.5–8.9) [762, 2041], CGP 55845 (pK&lt;sub&gt;I&lt;/sub&gt; 7.8) [2041], SCH 50911 (pK&lt;sub&gt;I&lt;/sub&gt; 5.5–6) [762, 2041], CGP 35348 (pK&lt;sub&gt;I&lt;/sub&gt; 4.4) [2041], 2-hydroxy-saclofen (pIC&lt;sub&gt;50&lt;/sub&gt; 4.1) [914] – Rat</td>
</tr>
</tbody>
</table>
Subunits

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GABAB₁</th>
<th>GABAB₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GABBR₁, Q9UBSS</td>
<td>GABBR₂, O75899</td>
</tr>
</tbody>
</table>

**Comments:** Potencies of agonists and antagonists listed in the table, quantified as IC₅₀ values for the inhibition of [³H]CGP27492 binding to rat cerebral cortex membranes, are from [194, 550, 551]. Radioligand KD values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the GABAB₁ subunit [122]. CGP27492 (3-APPA), CGP35024 (3-APMPA) and CGP 44532 act as antagonists at human GABA_A receptors, with potencies in the low micromolar range [550]. In addition to the ligands listed in the table, Ca²⁺ binds to the VTM of the GABAB₁ subunit to act as a positive allosteric modulator of GABA [563]. In cerebellar Purkinje neurones, the interaction of Ca²⁺ with the GABAB receptor enhances the activity of mGlu₁, through functional cross-talk involving G-protein Gβγ subunits [1590, 1837]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 and (+)-BHFF [9, 144, 150, 550]. The site of action of CGP7930 and GS39783 appears to be on the heptahelial domain of the GABAB₂ subunit [455, 1506]. In the presence of CGP7930 or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [550]. A negative allosteric modulator of GABAB activity has been reported [302]. Knock-out of the GABAB₁ subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABAB₁/⁻/⁻ 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 [482, 1932]. A similar phenotype has been found for GABAB₂/⁻/⁻ BALB/c mice [582].

**Further Reading**


Galanin receptors

G protein-coupled receptors → Galanin receptors

**Overview:** Galanin receptors (provisional nomenclature as recommended by NC-IUPHAR [530]) 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 [499]; in other species, it is 29 amino acids long and C-terminally amidated. Amino acids 1-14 of galanin are highly conserved in mammals, birds, reptiles, amphibia and fish. Shorter peptide species (e.g., human galanin-1-19 [139] and porcine galanin-5-29 [1740]) and N-terminally extended forms (e.g., N-terminally seven and nine residue elongated forms of porcine galanin [140, 1740]) have been reported.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GAL1 receptor</th>
<th>GAL2 receptor</th>
<th>GAL3 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GALR1, P47211</td>
<td>GALR2, O43603</td>
<td>GALR3, O60755</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>galanin (GAL, P22466) &gt; galanin-like peptide (GALP, Q9UBC7) [1433]</td>
<td>galanin (GAL, P22466) &gt; galanin-like peptide (GALP, Q9UBC7) ≥ galanin (GAL, P22466) [1433]</td>
<td>galanin-like peptide (GALP, Q9UBC7) ≥ galanin (GAL, P22466) [1039]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>[D-Trp2]-galanin-(1-29) (pKd 8.1) [1765] – Rat</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC50 5.6) [1688]</td>
<td>M871 (pKd 7.9) [1780]</td>
<td>SNAP 398299 (pKd 8.3) [987, 988, 1833], SNAP 37889 (pKd 7.8–7.8) [987, 988, 1833]</td>
</tr>
<tr>
<td>Selective allosteric modulators</td>
<td>–</td>
<td>CYM2503 (Positive) (pEC50 9.2) [1147] – Rat</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>–</td>
<td>The CYM2503 PAM potentiates the anticonvulsant activity of endogenous galanin in mouse seizure models [1147].</td>
<td>–</td>
</tr>
</tbody>
</table>

**Comments:** galanin-(11) is a high-affinity agonist at GAL1/GAL2 (pKd 9), and galanin(2-11) is selective for GAL2 and GAL3 compared with GAL1 [1146]. [125]I-[Tyr26]galanin binds to all three subtypes with Kd values generally reported to range from 0.05 to 1 nM, depending on the assay conditions used [525, 1752, 1765, 1766, 1983]. Porcine galanin-(3-29) does not bind to cloned GAL1, GAL2 or GAL3 receptors, but a receptor that is functionally activated by porcine galanin-(3-29) has been reported in pituitary and gastric smooth muscle cells [658, 2054]. Additional galanin receptor subtypes are also suggested from studies with chimeric peptides (e.g., M15, M35 and M40), which act as agonists in functional assays in the cardiovascular system [1924], spinal cord [2024], locus coeruleus, hippocampus [100] and hypothalamus [101, 1078], but exhibit agonist activity at some peripheral sites [101, 658]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL1 receptors expressed endogenously in Bowes human melanoma cells [1433], and at heterologously expressed recombinant GAL1, GAL2 and GAL3 receptors [525, 1765, 1766]. Recent studies have described the synthesis of a series of novel, systemically-active, galanin analogues, with modest preferential binding at the GAL3 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 [1623].
Ghrelin receptor
G protein-coupled receptors → Ghrelin receptor

Overview: The ghrelin receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [397]) 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 [1222]. Alternative splicing results in the formation of a second peptide, [des-Gln14]ghrelin (GHRL, Q9UBU3) with equipotent biological activity [783]. A unique post-translational modification (octanoylation of Ser3, catalysed by ghrelin O-acyltransferase (MBOAT4, Q96T53) [2082] 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 [983]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [116], 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 [776]. In cell systems, the ghrelin receptor is constitutively active [777], 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 [1458].

Nomenclature
ghrelin receptor
HGNC, UniProt
GHSR, Q92847

Rank order of potency
ghrelin (GHRL, Q9UBU3) = [des-Gln14]ghrelin (GHRL, Q9UBU3) [115, 1222]

Selective antagonists
GSK1614343 (pIC50 8.4) [1624], GSK1614343 (pK8) [1487] – Rat

Labelled ligands
[125][His9]ghrelin (human) (Agonist) (pKd 9.4) [912], [125][Tyr4]ghrelin (human) (Agonist) (pKd 9.4) [1339]

Comments: [des-octanoyl]ghrelin (GHRL, Q9UBU3) has been shown to bind (as [125][Tyr4]des-octanoyl-ghrelin) and have effects in the cardiovascular system [115], which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified ([D-Arg1, D-Phe5, D-Trp7,9, Leu11]substance P, pD2 8.3; [774]). Ulimorelin, described as a ghrelin receptor agonist (pK8 7.8 and pD2 7.5 at human recombinant ghrelin receptors), has been shown to stimulate ghrelin receptor mediated food intake and gastric emptying but not elicit release of growth hormone, or modify ghrelin stimulated growth hormone release, thus pharmacologically discriminating the orexigenic and gastrointestinal actions of ghrelin (GHRL, Q9UBU3) from the release of growth hormone [538]. A number of selective antagonists have been reported, including peptidomimetic [1338] and non-peptide small molecules including GSK1614343 [1487, 1624].
Further Reading


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 [1234]) are activated by the endogenous peptide (27-44 aa) hormones glucagon (GCC, P01275), glucagon-like peptide 1 (GCG, P01275), glucagon-like peptide 2 (GCC, P01275), glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide (GIP, P09681)), GHRH (GHRH, P012786) and secretin (SCT, P09683). One common precursor (GCC) generates glucagon (GCC, P01275), glucagon-like peptide 1 (GCC, P01275) and glucagon-like peptide 2 (GCC, P01275) peptides [827].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GHRH receptor</th>
<th>GIP receptor</th>
<th>GLP-1 receptor</th>
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<tr>
<td>HGNC, UniProt</td>
<td>GHRHR, Q02643</td>
<td>GIPR, P48546</td>
<td>GLP1R, P43220</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>gastric inhibitory polypeptide (GIP, P09681) (Selective) (pKd 8.7) [1961]</td>
<td>glucagon-like peptide 1-(7-36) amide (GCC, P01275) (Selective) (pKd 9.2) [885], glucagon-like peptide 1-(7-37) (GCC, P01275) (Selective) [425]</td>
</tr>
<tr>
<td>Agonists</td>
<td>JJ-38 [255], sermorelin</td>
<td>–</td>
<td>liraquitide (pEC50 10.2) [972], lixisenatide (pKd 8.9) [2010], WB4-24 (pA2 4.9) [502]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>BIM28011 [379], tesamorelin</td>
<td>–</td>
<td>exendin-4 (pIC50 9.2) [1290], exendin-4 (pKd 8.7-9) [885], exendin-3 (P20394) [1564]</td>
</tr>
</tbody>
</table>

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Nomenclature

<table>
<thead>
<tr>
<th>GLP-2 receptor</th>
<th>glucagon receptor</th>
<th>secretin receptor</th>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GLP2R, O95838</td>
<td>GCGR, P47871</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>glucagon-like peptide 2 (GCG, P01275) (Selective) (pIC50 8.5) [1880]</td>
<td>glucagon (GCG, P01275) (Selective) (pEC50 9) [1515]</td>
</tr>
<tr>
<td>Agonists</td>
<td>teduglutide [1248]</td>
<td></td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>L-168,049 (pIC50 8.4) [269], des-His1-[Glu9]glucagon-NH2 (pA2 7.2) [1928, 1929] – Rat, NNC 92-1687 (pKi 5) [1170], BAY27-9955 [1496]</td>
<td>[(CH2NH)4,5]secretin (pKi 5.3) [668]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]glucagon (human, mouse, rat) (Agonist)</td>
<td><a href="Tyr10">125I</a>secretin-27 (rat) (Agonist) [1925] – Rat</td>
</tr>
</tbody>
</table>

Comments: The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems [333], although the physiological significance of this has yet to be established.

Further Reading

Corazzini V et al. (2013) Molecular and clinical aspects of GHRH receptor mutations. Endocr Dev 24: 106-17 [PMID:23392099]

Trujillo JM et al. (2014) GLP-1 receptor agonists for type 2 diabetes mellitus: recent developments and emerging agents. Pharmacotherapy 34: 1174-86 [PMID:25382096]
**Glycoprotein hormone receptors**

G protein-coupled receptors → Glycoprotein hormone receptors

**Overview:** Glycoprotein hormone receptors (provisional nomenclature [530]) are activated by a non-covalent heterodimeric glycoprotein made up of a common α chain (glycoprotein hormone common alpha subunit (CGA, P01215) CGA, P01215), with a unique β chain that confers the biological specificity to FSH (CGA FSHB, P01215 P01225), LH (CGA LHβ, P01215 P01229), hCG (CGA CGB, 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 [1626].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>FSH receptor</th>
<th>LH receptor</th>
<th>TSH receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>FSHR, P23945</td>
<td>LHCGR, P22888</td>
<td>TSHR, P16473</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>hCG (CGA CGB, P01215 P01233) (Selective) (pK&lt;sub&gt;d&lt;/sub&gt; 9.9–11.8) [864, 1353], LH (CGA LHβ, P01215 P01229) (Selective) (pIC&lt;sub&gt;50&lt;/sub&gt; 9.9–10.9) [864, 1353]</td>
<td>–</td>
</tr>
<tr>
<td>Antagonists</td>
<td>FSH deglycosylated α/β (pK&lt;sub&gt;d&lt;/sub&gt; 10) [527, 921]</td>
<td>–</td>
<td>[&lt;sup&gt;125&lt;/sup&gt;I]TSH (human) (Agonist)</td>
</tr>
<tr>
<td>Labelling ligands</td>
<td>[&lt;sup&gt;125&lt;/sup&gt;I]FSH (human) (Agonist)</td>
<td>[&lt;sup&gt;125&lt;/sup&gt;I]LH (Agonist), [&lt;sup&gt;125&lt;/sup&gt;I]chorionic gonadotropin (human) (Agonist)</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders [19, 109, 650, 1900]. The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein [1547].</td>
<td>Loss-of-function mutations of the LH receptor are associated with Leydig cell hypoplasia and gain-of-function mutations are associated with male-limited gonadotropin-independent precocious puberty (e.g. [1044, 1720]) and Leydig cell tumours [1126].</td>
<td>Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Graves’ disease (e.g. [1558]). Mutants of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas [1464] and congenital hyperthyroidism [993]. TSH receptor loss-of-function mutations are associated with TSH resistance [1824].</td>
</tr>
</tbody>
</table>

**Further Reading**


Gonadotrophin-releasing hormone receptors

Overview: GnRH1 and GnRH2 receptors (provisional nomenclature [S30]), also called Type I and Type II GnRH receptor, respectively [1284]), have been cloned from numerous species, most of which express two or three types of GnRH receptor [1283, 1284, 1741]. GnRH I (GNRH1, P01148) (p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2) is a hypothalamic decapeptide also known as luteinizing hormone-releasing hormone, gonadoliberin, liliberin, gonadorelin or simply as GnRH. It is a member of a family of similar peptides found in many species [1283, 1284, 1741] including GnRH II (GNRH2, O43555) (p-Glu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH2) (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 [1283, 1284, 1741]. GnRH2 receptors are expressed primarily by pituitary gonadotrophs, and mediate central control of mammalian reproduction. They are selectively activated by GnRH I and all lack the COOH-terminal tails found in other GPCRs. GnRH2 receptors do have COOH-terminal tails and (where tested) are selective for GnRH II over GnRH I. GnRH II receptors are expressed by some primates but are thought not to be expressed by humans because the human GNRHR2 gene contains a frame shift and an internal stop codon [1325]. An alternative phylogenetic classification divides GnRH receptors into three classes and includes both GnRH I-selective mammalian and GnRH II-selective non-mammalian GnRH receptors as GnRH1 receptors [1284]. A more recent phylogenetic classification groups vertebrate GnRH receptors into five subfamilies [2028] and highlights examples of gene loss through evolution, with humans notably retaining only one ancient gene. Although thousands of peptide analogues of GnRH I have been synthesized and several (agonists and antagonists) are used therapeutically [934], the potency of most of these peptides at GnRH2 receptors is unknown.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GnRH1 receptor</th>
<th>GnRH2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GNRH1, P30968</td>
<td>GNRH2, Q96P88</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>GnRH I (GNRH1, P01148) &gt; GnRH II (GNRH2, O43555) [1284]</td>
<td></td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>triptorelin (pKᵢ 9.3–9.5) [112], leuprolide (pKᵢ 8.5–9.1) [1807], buserelin, gosereulin, histrelin, nafarelin</td>
<td>–</td>
</tr>
<tr>
<td>Antagonists</td>
<td>iturelix (pKᵢ 9.5) [1591]</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>cetrorelix (pKᵢ 9.3–10) [113, 114, 1807], abarelix (pKᵢ 9.1–9.5) [1807], degarelix (pKᵢ 8.8) [1938], ganirelix</td>
<td>trptorelix-1 [1183] – Monkey</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125]buserelin (Agonist) (pKᵢ 7.4) [1024] – Rat, [125]GnRH I (human, mouse, rat) (Agonist)</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>–</td>
<td>Probable transcribed pseudogene in man [1284].</td>
</tr>
</tbody>
</table>

Comments: GnRH1 and GnRH2 receptors couple primarily to Gₒ/q11 [653] but coupling to Gₛ and Gᵢ is evident in some systems [1009, 1024]. GnRH2 receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [276]. 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 [309, 706, 1108, 1661]. In some human cancer cell models GnRH II (GNRH2, O43555) is more potent than GnRH I (GNRH1, P01148), implying mediation by GnRH2 receptors [657]. However, GnRH2 receptors that are expressed by some primates are probably not expressed in humans because the human GNRHR2 gene contains a frame shift and internal stop codon [1325]. The possibility remains that this gene generates GnRH2 receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (GNRH2, O43555) (see [1372]). Alternatively, there is evidence for multiple active GnRH receptor conformations [276, 277, 516, 1231, 1284] raising the possibility that GnRH1 receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand

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Gonadotrophin-releasing hormone receptors 5810
specificity and ligand biased signalling) than effects on Gq/11 in pituitary cells [277, 1231]. Loss-of-function mutations in the GnRH1 receptor and deficiency of GnRH1 (GNRH1, P01148) are associated with hypogonadotropic hypogonadism although some ‘loss of function’ mutations may actually prevent trafficking of ‘functional’ GnRH1 receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists [1061]. Human GnRH1 receptors appear to be poorly expressed at the cell surface because of failure to meet structural quality control criteria for endoplasmic reticulum exit [517, 1061]. This may increase susceptibility to point mutations that further impair trafficking and also increase effects of nonpeptide antagonists on GnRH1 receptor trafficking to the plasma membrane [517, 1061]. GnRH receptor signalling may be dependent upon receptor oligomerisation [363, 1007].

Further Reading


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 CB1 and CB2 cannabinoid receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands [1494]. Although there are multiple reports to indicate that GPR18, GPR55 and GPR119 can be activated in vitro by N-arachidonoylglycine, lysophosphatidylinositol and N-oleoylthanolamide, respectively, there is a lack of evidence for activation by these lipid messengers in vivo. As such, these receptors retain their orphan status.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GPR18</th>
<th>GPR55</th>
<th>GPR119</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GPR18, Q14330</td>
<td>GPR55, Q9Y2T6</td>
<td>GPR119, Q8TDVS</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>–</td>
<td>–</td>
<td>N-oleoylthanolamide, N-palmitoylthanolamine</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>N-arachidonoylglycine [980]</td>
<td>lysophosphatidylinositol (pEC50 5.5–7.3) [738, 1435, 1785], 2-arachidonoylglycerolphosphoinositol (Selective) [1437]</td>
<td>N-oleoylthanolamide (pEC50 5.4–6.3) [338, 1452, 1785], N-palmitoylthanolamine, SEA</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>AM251 (pEC50 5–7.4) [738, 905, 1620]</td>
<td>AS1269574 (pEC50 5.6) [2100], PSN632408 (pEC50 5.3) [1452], PSN375963 (pEC50 5.1) [1452]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>CID16020046 (apparent pA2) (pA2 7.3) [906]</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on arrestin assays [1785, 2093]. See [396] for discussion.</td>
<td>See reviews [396] and [1732].</td>
<td>In addition to those shown above, further small molecule agonists have been reported [687].</td>
</tr>
</tbody>
</table>
**Comments:** GPR18 failed to respond to a variety of lipid-derived agents in an *in vitro* screen [2093], but has been reported to be activated by Δ⁹-tetrahydrocannabinol [1246]. GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB₁ receptor antagonists/inverse agonists [1494]. It has been reported that lysophosphatidylinositol acts at other sites in addition to GPR55 [2075]. N-Arachidonoylserine has been suggested to act as a low efficacy agonist/antagonist at GPR18 *in vitro* [1244]. It has also been suggested oleoyl-lysophosphatidylcholine acts, at least in part, through GPR119 [1400]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleylethanolamide-mediated responses suggests additional mechanisms of action [1400].

**Further Reading**


**Histamine receptors**

G protein-coupled receptors → Histamine receptors

**Overview:** Histamine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors [754, 1459]) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues [754].

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<table>
<thead>
<tr>
<th>Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 receptor</td>
</tr>
<tr>
<td>H2 receptor</td>
</tr>
<tr>
<td>H3 receptor</td>
</tr>
<tr>
<td>H4 receptor</td>
</tr>
<tr>
<td>HGNC, UniProt</td>
</tr>
<tr>
<td>HRH1, P35367</td>
</tr>
<tr>
<td>HRH2, P25021</td>
</tr>
<tr>
<td>HRH3, Q9YSN1</td>
</tr>
<tr>
<td>HRH4, Q9H3N8</td>
</tr>
<tr>
<td>Selective agonists</td>
</tr>
<tr>
<td>methylhistaprodifen (pKᵢ 6.4) [1695], histaprodifen (pKᵢ 5.7) [1107]</td>
</tr>
<tr>
<td>amthamine (pEC₅₀ 6.4) [1003]</td>
</tr>
<tr>
<td>immethidine (pKᵢ 9.1) [963], methimepip (pKᵢ 9) [962], MK-0249 (Inverse agonist) (pKᵢ 8.8) [1354]</td>
</tr>
<tr>
<td>clobenpropit (Partial agonist) (pKᵢ 7.4–8.3) [490, 1107, 1122, 1123, 1335], 4-methylhistamine (pKᵢ 7.3–8.2) [586, 1107], VUF 8430 (pKᵢ 7.5) [1106]</td>
</tr>
<tr>
<td>Antagonists</td>
</tr>
<tr>
<td>cyproheptadine (pKᵢ 10.2) [1298], promethazine (pKᵢ 9.6) [601], pyrilamine (Inverse agonist) (pKᵢ 8.7–9) [184, 1563], hydroxyzine (pKᵢ 8.7) [608], ketotifen (pKᵢ 8.6) [1014], cetirizine (Inverse agonist) (pKᵢ 8.2) [1297], diphenhydramine (pKᵢ 7.9) [184]</td>
</tr>
<tr>
<td>–</td>
</tr>
<tr>
<td>iodophenpropit (pKᵢ 8.2–8.7) [2022, 2051], thioperamide (pKᵢ 7.1–7.7) [355, 489, 490, 1104, 1145, 2022, 2051]</td>
</tr>
<tr>
<td>Selective antagonists</td>
</tr>
<tr>
<td>clemastine (pKᵢ 10.3) [68], desloratadine (pKᵢ 9) [1090], triprolidine (pKᵢ 8.5–9) [184, 1298], azelastine (pKᵢ 8.9) [1535], astemizole (pKᵢ 8.5) [1480], cyclizine (pKᵢ 8.4) [68], chlorpheniramine (pKᵢ 8.1) [1535], fexofenadine (pKᵢ 7.6) [64], loratadine (pKᵢ 7.4) [850], terfenadine (pKᵢ 7.4) [64], triprolidine (pKᵢ 7.4) [635]</td>
</tr>
<tr>
<td>tiotidine (pKᵢ 7.5) [145] – Rat, ranitidine (pKᵢ 7.1) [1086], cimetidine (pKᵢ 6.8) [263]</td>
</tr>
<tr>
<td>clobenpropit (pKᵢ 8.4–9.4) [355, 490, 1104, 1122, 1145, 2022, 2051], A331440 (pKᵢ 8.5) [688]</td>
</tr>
<tr>
<td>Labelled ligands</td>
</tr>
<tr>
<td>[³H]pyrilamine (Antagonist, Inverse agonist) (pKᵢ 8.4–9.1) [403, 1298, 1675, 1695], [¹¹C]doxepin (Antagonist) (pKᵢ 9) [830], [¹¹C]pyrilamine (Antagonist, Inverse agonist)</td>
</tr>
<tr>
<td>[¹²⁵I]iodoaminopotentidine (Antagonist) (pKᵢ 8.7) [1029] – Rat, [³H]tiotidine (Antagonist) (pKᵢ 7.7–8.7) [1310]</td>
</tr>
<tr>
<td>[¹²⁵I]iodoambenpropit (Antagonist) (pKᵢ 10.2) [1104], [¹²⁵I]iodophenpropit (Antagonist) (pKᵢ 9.2) [849] – Rat, <a href="-">³H</a>-α-methylhistamine (Agnost) (pKᵢ 9.2) [1122], N<a href="-">³H</a>-α-methylhistamine (Agnost) (pKᵢ 9) [301] – Mouse</td>
</tr>
<tr>
<td>[³H]histamine has been used to label the H4 receptor in heterologous expression systems.</td>
</tr>
</tbody>
</table>

**Comments:** histaprodifen and methylhistaprodifen are reduced efficacy agonists. The H4 receptor appears to exhibit broadly similar pharmacology to the H3 receptor for imidazole-containing ligands, although (R)-α-methylhistamine and N-α-methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist at the H4 receptor and an antagonist at the H3 receptor [1122, 1360, 1390, 1422, 2132]. Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H4 receptor [1107].
Further Reading


Hydroxycarboxylic acid receptors

G protein-coupled receptors \(\rightarrow\) Hydroxycarboxylic acid receptors

**Overview:** The hydroxycarboxylic acid family of receptors (ENSFM00500000271913, nomenclature as agreed by the NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors [396, 1424]) respond to organic acids, including the endogenous hydroxycarboxylic acids 3-hydroxy butyric acid and L-lactic acid, as well as the lipid lowering agents nicotinic acid (niacin), acipimox and acifran [1774, 1913, 2036]. These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA2 receptors only and is unlikely to be the natural ligand [1913, 2036].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>HCA1 receptor</th>
<th>HCA2 receptor</th>
<th>HCA3 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>HCAR1, Q9BXC0</td>
<td>HCAR2, Q8TDS4</td>
<td>HCAR3, P49019</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>L-lactic acid (Selective) (pEC50 1.3–2.9) [14, 256, 1124, 1785]</td>
<td>(\beta)-D-hydroxybutyric acid (pEC50 3.1) [1838]</td>
<td>3-hydroxyoctanoic acid (pEC50 5.1) [13]</td>
</tr>
<tr>
<td>Agonists</td>
<td>compound 2 [PMID: 24486398] (pEC50 7.2) [1630], 3,5-dihydroxybenzoic acid (pEC50 3.7) [1121]</td>
<td>SCH 900271 (pEC50 8.7) [1454], GSK256073 (pEC50 7.5) [1790]</td>
<td>–</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>MK 6892 (pEC50 7.8) [1719], MK 1903 (pEC50 7.6) [163], nicotinic acid (pEC50 6–7.2) [1774, 1913, 2036], acipimox (pEC50 5.2–5.6) [1774, 2036], monomethylfumarate (pEC50 5) [1859]</td>
<td>compound 6o [PMID: 19524438] (pEC50 8.5) [1751], IBC 293 (pEC50 6.4) [1697]</td>
<td>–</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>–</td>
<td>[^{3}\text{H}]\text{nicotinic acid (Agonist) (pKd 7–7.3) [1774, 1913, 2036]</td>
<td>–</td>
</tr>
</tbody>
</table>

**Comments:** Further closely-related GPCRs include the 5-oxoicosanoid receptor (OXER1, Q8TDS5) and GPR31 (Q00270).

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Further Reading


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


Kisspeptin receptor

G protein-coupled receptors → Kisspeptin receptor

Overview: The kisspeptin receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee on the kisspeptin receptor [958]), like neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) responds to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. Kisspeptin-54 (KISS1, Q15726) (KP54, originally named metastin), kisspeptin-13 (KISS1, Q15726) (KP13) and kisspeptin-10 (KISS1) (KP10) are biologically-active peptides cleaved from the KISS1 (Q15726) gene product.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>kisspeptin receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>KISS1R, Q969F8</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>kisspeptin-10 (KISS1) (Selective) (pKᵢ 8.6–10.4) [996, 1434], kisspeptin-54 (KISS1, Q15726) (Selective) (pKᵢ 8.8–9.5) [996, 1434], kisspeptin-14 (KISS1, Q15726) (pKᵢ 8.8) [996], kisspeptin-13 (KISS1, Q15726) (Selective) (pKᵢ 8.4) [996]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>4-fluorobenzoyl-FGLRW-NH₂ (pEC₅₀ 9.2) [1894], [dY]¹ KP-10 (pIC₅₀ 8.4) [385] – Mouse</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>peptide 234 [1600]</td>
</tr>
</tbody>
</table>

Further Reading


Leukotriene receptors

G protein-coupled receptors → Leukotriene receptors

Overview: Leukotriene receptors (nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene Receptors [249, 250]) is activated by the endogenous ligands leukotrienes (LT), synthesized from lipoxygenase metabolism of arachidonic acid.

The human BLT1 receptor is the high affinity LTB4 receptor whereas the BLT2 receptor in addition to being a low-affinity LTB4 receptor also binds several other lipoxygenase-products, such as 12S-HETE, 12S-HPETE, 15S-HETE, and the thromboxane synthase product 12-hydroxyheptadecatrienoic acid. The BLT receptors mediate chemotaxis and immunomodulation in several leukocyte populations and are in addition expressed on non-myeloid cells, such as vascular smooth muscle and endothelial cells. In addition to BLT receptors, LTB4 has been reported to bind to the peroxisome proliferator activated receptor (PPAR) α [1112] and the vanilloid TRPV1 ligand-gated nonselective cation channel [1245].

The receptors for the cysteinyl-leukotrienes (i.e. LTC4, LTD4, LTE4) are termed CysLT1 and CysLT2 and exhibit distinct expression patterns in human tissues, mediating for example smooth muscle cell contraction, regulation of vascular permeability, and leukocyte activation. There is also evidence in the literature for additional CysLT receptor subtypes, derived from functional in vitro studies, radioligand binding and in mice lacking both CysLT1 and CysLT2 receptors [250]. Cysteinyl-leukotrienes have also been suggested to signal through the P2Y12 receptor [542, 1407, 1466], GPR17 [344] and GPR99 [900].

Nomenclature

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>BLT1 receptor</th>
<th>BLT2 receptor</th>
<th>CysLT1 receptor</th>
<th>CysLT2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>LTB4R, Q15722</td>
<td>LTB4R2, Q9NPC1</td>
<td>CYSLTR1, Q9Y271</td>
<td>CYSLTR2, Q9NS75</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>12S-HETE (Partial agonist) (pEC50 &lt; 7.5) [2096]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
<td>–</td>
<td>ICI198615 (&lt; 8.4–8.6)</td>
<td>BAYu9773 (against LTC4 and LTD4 induced contraction in smooth muscle preparation) (pA2 6.8–7.7) [1912] – Rat</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>BIIL 260 (pKi 8.8) [152, 457], CP105696 (pIC50 8.1) [1735], U75302 (pKi 6.4) [172]</td>
<td>LY255283 (pIC50 6–7.1) [744, 2096]</td>
<td>zafirlukast (against [3H]LTD4 in COS-7 or Hek-293 cells) (pIC50 8.6–8.7) [1157, 1643], SR2640 (pKi 8.7), montelukast (against [3H]LTD4 in COS-7 or hek-293 cells) (pIC50 8.3–8.6) [1157, 1643], sulukast (pKi 8.3), pobilukast (against [3H]LTD4 in hek-293) (pIC50 7.5) [1643]</td>
<td>BayCysLT2 (against 30-300nM LTD4 [β-arrestin assay in C2C12 myotubroblasts] (pIC50 6.6–7.3) [1391]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[3H]LTB4 (Agonist) (pKd 9.8) [2095], [3H]CGS25313</td>
<td>[3H]LTB4 (pKd 7.6–9.7)</td>
<td>[3H]LTD4 (Agonist) (pKd 8–10.7), [3H]ICI-198615 (Agonist) (pKd 10.6) [1608]</td>
<td>[3H]LTD4 (Agonist) (pKd 7.3–9.4) [733]</td>
</tr>
</tbody>
</table>
### Nomenclature

<table>
<thead>
<tr>
<th>Term</th>
<th>Symbol(s)</th>
<th>HGNC, UniProt</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPR2/ALX</td>
<td>FPR2, P25090</td>
<td></td>
</tr>
<tr>
<td>OXE receptor</td>
<td>OXER1, Q8TDSS</td>
<td></td>
</tr>
</tbody>
</table>

### Endogenous agonists

- LXA₄ (Selective) (pEC₅₀ ~12) [1006], resolvin D1 (Selective) (pEC₅₀ ~11.9) [1006], aspirin triggered lipoxin A₄ (Selective)
- 5-oxo-ETE (Selective) (pEC₅₀ 8.3–8.5) [638, 1417, 1472, 1525, 1681]

### Selective agonists

- ATLa2 [662]

### Endogenous antagonists

- 5-oxo-12-HETE (Selective) (pIC₅₀ 6.3) [1524]

### Antagonists

- –

### Selective antagonists

- –

### Labelled ligands

- [³H]LXA₄ (Agonist) (pKᵩ 9.2–9.3) [519, 520]
- [³H]5-oxo-ETE (Agonist) (pKᵩ 8.4) [1417]

### Comments

The agonist activity of the lipid mediators described has been questioned [697, 1513], which may derive from batch-to-batch differences, partial agonism or biased agonism. Recent results from Cooray et al. (2013) [365] have addressed this issue and the role of homodimers and heterodimers in the intracellular signaling.

Oxoeicosanoid receptors (OXE, nomenclature agreed by the NC-IUPHAR subcommittee on Oxoeicosanoid Receptors [214]) 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 OXER receptor suggested that polyunsaturated fatty acids, such as docosahexaenoic acid and EPA, acted as receptor antagonists [784].

---

**Further Reading**


**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 [396, 936]) are activated by the endogenous phospholipid metabolite LPA. The first receptor, LPA1, was identified as ventricular zone gene-1 (vzg-1), leading to deorphanisation of members of the endothelial differentiation gene (edg) family as other LPA receptors along with sphingosine 1-phosphate (S1P) receptors. Additional LPA receptor GPCRs were later identified. Gene names have been codified as LPAR1, etc. to reflect the receptor function of proteins. The crystal structure of LPA1 was recently solved and demonstrates ligand access characteristics that allows for extracellular LPA binding [331]; these studies have also implicated cross-talk with endocannabinoids via phosphorylated intermediates that can activate this receptor. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Radioligand binding has been conducted in heterologous expression systems using [3H]LPA (e.g. [556]). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding, and therefore the relationship between recombinant and endogenously expressed receptors is unclear. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. Independent validation by multiple groups has been reported in the peer-reviewed literature for all six LPA receptors described in the tables, including further validation using a distinct read-out via a novel TGFα “shedding” assay [825]. LPA has also been described as an agonist at other orphan GPCRs (PSP24, GPR87 and GPR35), as well as at the nuclear hormone PPARγ receptors [1247, 1743], although the physiological significance of these observations remain unclear.

**Nomenclature**

| LPA1 receptor | LPA2 receptor | LPA3 receptor |
| LPAR1, Q92633 | LPAR2, Q9HBW0 | LPAR3, Q9UBYS |

**Selective agonists**

| dodecylphosphate (pEC50 6.2) [1958], decyl dihydrogen phosphate (pEC50 5.4) [1958], GR977143 (pEC50 4.5) [959] |

**Selective antagonists**

| AM966 (pIC50 6.7–7.8) [1832] |

**Comments:**

Virtual screening experiments have shown H2L5186303 to be a potent antagonist of LPA2 [510]. dodecylphosphate is also an antagonist at LPA3 receptors [1958].

**Nomenclature**

| LPA4 receptor | LPA5 receptor | LPA6 receptor |
| LPAR4, Q99677 | LPAR5, Q9H1C0 | LPAR6, P43657 |

**Comments:** Ki16425 [1432], VPC12249 [735] and VPC32179 [729] have antagonist activity at LPA1 and LPA3 receptors. There is growing evidence for in vivo efficacy of these chemical antagonists in several disorders, including fetal hydrocephalus [2107], lung fibrosis [1429], and systemic sclerosis [1429].

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Further Reading

Yung YC et al. (2014) LPA receptor signaling: pharmacology, physiology, and pathophysiology. J. Lipid Res. 55: 1192-1214 [PMID:24643338]

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 [936]) are activated by the endogenous lipid sphingosine 1-phosphate (S1P) and with lower apparent affinity, sphingosylphosphorylcholine (SPC). Originally cloned as orphan members of the endothelial differentiation gene (edg) family, deorphanisation as lysophospholipid receptors for S1P was based on sequence homology to LPA receptors. Current gene names have been codified as S1PR1, etc. to reflect the receptor function of these proteins. Most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms; S1P has also been described to act at intracellular sites [1841], and awaits precise definition. Previously-proposed SPC (or lysophospholipidylcholine) receptors- G2A, TDAG8, OGR1 and GPR4 - continue to lack confirmation of these roles [396]. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [32P]S1P (e.g [1438]). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding. Targeted deletion of several S1P receptors and key enzymes involved in S1P biosynthesis or degradation has clarified signalling pathways and physiological roles. A crystal structure of an S1P1-T4 fusion protein has been described [698].

The S1P receptor modulator, fingolimod (FTY720, Gilenya), has received worldwide approval as the first oral therapy for relapsing forms of multiple sclerosis. This drug has a novel mechanism of action involving modulation of S1P receptors in both the immune and nervous systems [325, 356, 654], although the precise nature of its interaction requires clarification.

Nomenclature
HGNC, UniProt

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Gene Symbol</th>
<th>UniProt Accession</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1P1 receptor</td>
<td>S1PR1, P21453</td>
<td></td>
</tr>
<tr>
<td>S1P2 receptor</td>
<td>S1PR2, Q95136</td>
<td></td>
</tr>
<tr>
<td>S1P3 receptor</td>
<td>S1PR3, Q99500</td>
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</tr>
<tr>
<td>S1P4 receptor</td>
<td>S1PR4, Q95977</td>
<td></td>
</tr>
<tr>
<td>S1P5 receptor</td>
<td>S1PR5, Q9H228</td>
<td></td>
</tr>
</tbody>
</table>

Rank order of potency

- sphingosine 1-phosphate > dihydro sphingosine-1-phosphate > sphingosylphosphorylcholine [45, 1438]

Agonists

- SEW2871 (pK_i 5.5–7.7) [1640]
Nomenclature

MCH1 receptor | MCHR1, Q99705

HGNC, UniProt

Melanin-concentrating hormone receptors

Overview: Melanin-concentrating hormone (MCH) receptors (provisional nomenclature as recommended by NC-IUPHAR [530]) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRPCWQV) generated from a precursor (PMCH, P20382), which also produces neuropeptide EI (PMCH, P20382) and neuropeptide GE (PMCH, P20382).

Nomenclature

HGNC, UniProt

MCH1 receptor | MCHR1, Q99705

MCH2 receptor | MCHR2, Q969V1

Rank order of potency

melanin-concentrating hormone (PMCH, P20382) > MCH (salmon)

melanin-concentrating hormone (PMCH, P20382) = MCH (salmon) [753]

Selective antagonists

GW803430 (pIC50 9.3) [745], SNAP-7941 (pA2 9.2) [186], T-226296 (pIC50 8.3) [1853], ATC0175 (pIC50 7.9–8.1) [283]

Labelling ligands

[125I]S36057 (Antagonist) (pKd 9.2–9.5) [66], [125I][Phe13,Tyr19]MCH (Agonist) (pKd 9.2) [242], [3H]MCH (human, mouse, rat) (Agonist) [242]

Comments: The MCH2 receptor appears to be a non-functional pseudogene in rodents [1857].
Further Reading


Melanocortin receptors

G protein-coupled receptors → Melanocortin receptors

**Overview:** Melanocortin receptors (provisional nomenclature as recommended by NC-IUPHAR [530]) are activated by members of the melanocortin family (α-MSH (POMC, P01189), β-MSH (POMC, P01189) and γ-MSH (POMC, P01189)) forms; -δ form is not found in mammals) and adrenocorticotrophin (ACTH (POMC, P01189)). Endogenous antagonists include agouti (ASIP, P42127) and agouti-related protein (AGRP, O00253).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>MC_1 receptor</th>
<th>MC_2 receptor</th>
<th>MC_3 receptor</th>
<th>MC_4 receptor</th>
<th>MC_5 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>MC1R, Q01726</td>
<td>MC2R, Q01718</td>
<td>MC3R, P41968</td>
<td>MC4R, P32245</td>
<td>MC5R, P33032</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>α-MSH (POMC, P01189) &gt; β-MSH (POMC, P01189) &gt; ACTH (POMC, P01189), γ-MSH (POMC, P01189)</td>
<td>ACTH (POMC, P01189)</td>
<td>γ-MSH (POMC, P01189), β-MSH (POMC, P01189), α-MSH (POMC, P01189)</td>
<td>β-MSH (POMC, P01189) &gt; α-MSH (POMC, P01189) &gt; ACTH (POMC, P01189), γ-MSH (POMC, P01189)</td>
<td>α-MSH (POMC, P01189) &gt; β-MSH (POMC, P01189) &gt; ACTH (POMC, P01189)</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>corticotropin zinc hydroxide</td>
<td>[D-Trp^8]γ-MSH (pIC_{50} 8.2) [645]</td>
<td>THIQ (pIC_{50} 8.9) [1690]</td>
<td>–</td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
<td>–</td>
<td>PG-106 (pIC_{50} 6.7) [646]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MBP10 (pIC_{50} 10) [117], HS014 (pK_i 8.5) [1667]</td>
<td>–</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]NDP-MSH (Agonist) (pK_d 9.5) [991]</td>
<td>[125I]ACTH-(1-24) (Agonist)</td>
<td>[125I]NDP-MSH (Agonist) (pK_d 9.7) [991], [125I]SHU9119 (Antagonist) [1392]</td>
<td>[125I]SHU9119 (Agonist) (pK_d 9.2) [1392], [125I]NDP-MSH (Agonist) (pK_d 8.4–8.9) [991, 1665]</td>
<td>–</td>
</tr>
</tbody>
</table>

**Comments:** Polymorphisms of the MC1 receptor have been linked to variations in skin pigmentation. Defects of the MC2 receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC4 receptor have been linked to obesity [282, 505].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Melatonin receptors

**G protein-coupled receptors → Melatonin receptors**

**Overview:** Melatonin receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Melatonin Receptors [446]) are activated by the endogenous ligands melatonin and N-acetylserotonin.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>MT&lt;sub&gt;1&lt;/sub&gt; receptor</th>
<th>MT&lt;sub&gt;2&lt;/sub&gt; receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>MTNR1A, P48039</td>
<td>MTNR1B, P49286</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>melatonin (pK&lt;sub&gt;i&lt;/sub&gt; 9.1–9.7) [67, 445, 447]</td>
<td>melatonin (pK&lt;sub&gt;i&lt;/sub&gt; 9.4–9.8) [67, 445, 447]</td>
</tr>
<tr>
<td>Agonists</td>
<td>rameleotonin (pK&lt;sub&gt;i&lt;/sub&gt; 10.9) [909], agomelatine (pK&lt;sub&gt;i&lt;/sub&gt; 10–10.4) [67, 132]</td>
<td>agomelatine (pK&lt;sub&gt;i&lt;/sub&gt; 9.9–10.5) [67, 132], rameleotonin (pK&lt;sub&gt;i&lt;/sub&gt; 10) [909, 1565]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>ILK7 (pK&lt;sub&gt;i&lt;/sub&gt; 10.3) [506, 1814], 5-methoxy-luzindole (Partial agonist) (pK&lt;sub&gt;i&lt;/sub&gt; 9.6) [447]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>4P-PDOT (pK&lt;sub&gt;i&lt;/sub&gt; 8.8–9.4) [67, 447, 448], K185 (pK&lt;sub&gt;i&lt;/sub&gt; 9.3) [506, 1814], DH97 (pK&lt;sub&gt;i&lt;/sub&gt; 8) [1865]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]SD6 (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 10.9) [1074], 2-[125I]melatonin (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 9.9–10.7) [67, 447], [3H]melatonin (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 9.4–9.9) [230]</td>
<td>[125I]SD6 (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 10.2) [1074], 2-[125I]melatonin (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 9.7–10) [67, 447], [125I]JDR880 (Agonist, Partial agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 9.7) [1074], [3H]melatonin (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 9.9–9.6) [230]</td>
</tr>
</tbody>
</table>

**Comments:** melatonin, 2-iodo-melatonin, agomelatine, GR 196429, LY 156735 and rameleotonin [909] 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) [1888]. Luzindole is an MT<sub>1</sub>/MT<sub>2</sub> melatonin receptor-selective competitive antagonist with some selectivity for the MT<sub>2</sub> receptor [448]. MT<sub>1</sub>/MT<sub>2</sub> heterodimers present different pharmacological profiles from MT<sub>1</sub> and MT<sub>2</sub> receptors [72]. The MT<sub>2</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-[125I]SMCA-NAT [1302]. Pharmacological investigations of MT<sub>3</sub> binding sites have primarily been conducted in hamster tissues. At this site, N-acetylserotonin [467, 1149, 1302, 1516] and

Further Reading


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 [1672]) are activated by the endogenous ligands L-glutamic acid, L-serine-O-phosphate, N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are (1S,3R)-ACPD and L-CCG-I, which show limited selectivity for Group-II receptors. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu2 and mGlu5 at low nanomolar concentrations, mGlu6 at high nanomolar concentrations, and mGlu4, mGlu6, and mGlu7 in the micromolar range [955]. Three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I (mGlu1 and mGlu3), Group-II (mGlu2 and mGlu3) and Group-III (mGlu4, mGlu5, mGlu7 and mGlu8) (see Further reading). Group-I mGlu receptors may be activated by 3,5-DHPG and (S)-3HPG [198] and antagonized by (S)-hexylhomoibotenic acid [1171]. Group-II mGlu receptors may be activated by LY389795 [1311], LY379268 [1311], eglumegad [1673, 2050], DCG-IV and (2S,3R)-APDC [1674], and antagonised by eGlu (4,3, [848] and LY307452 [491, 2009]. Group-III mGlu receptors may be activated by L-AP4 and (R,S)-4-PPG [579]. In addition to orthosteric ligands that directly interact with the glutamate recognition site directly, allosteric modulators have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as ‘potentiators’ of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Although mGlu receptors have been thought to only form homodimers, recent studies revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [441]. Although well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [2094]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organization similar to that of other GPCRs, although the helices appear more compacted [438, 2048].
<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>mGlu_{1} receptor</th>
<th>mGlu_{2} receptor</th>
<th>mGlu_{3} receptor</th>
<th>mGlu_{4} receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GRM1, Q13255</td>
<td>GRM2, Q14416</td>
<td>GRM3, Q14832</td>
<td>GRM4, Q14833</td>
</tr>
<tr>
<td>Endogenous</td>
<td>–</td>
<td>–</td>
<td>NAAG (Selective)</td>
<td>–</td>
</tr>
<tr>
<td>agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>L-AP4 (pEC_{50} 6.5) [2050]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>L-serine-O-phosphate (pEC_{50} 5.9) [2050]</td>
</tr>
<tr>
<td>Antagonists</td>
<td>LY367385 (pIC_{50} 5.1) [349]</td>
<td>–</td>
<td>–</td>
<td>LSP4-2022 (pEC_{50} 7) [631]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>3-MATIDA (pIC_{50} 5.2) [1333] – Rat, (S)-(−)-CBPG (pIC_{50} 4.2) [1200] – Rat, (S)-TBPG (pIC_{50} 4.2) [367] – Rat, AIDA (pK_{I} 4.2) [1334]</td>
<td>PCCG-4 (pIC_{50} 5.1) [1483] – Rat</td>
<td>–</td>
<td>MAP4 (pK_{I} 4.6) [686] – Rat</td>
</tr>
<tr>
<td>Allosteric</td>
<td>YM298198 (Neg) (pIC_{50} 7.8) [979] – Rat</td>
<td>CBiPES (Pos) (pEC_{50} 7) [874], 4-MPPTS (Pos) (pIC_{50} 5.8) [94, 873, 874, 1660]</td>
<td>–</td>
<td>SIB-1893 (Pos) (pEC_{50} 6.3–6.8) [1217], MPEP (Pos) (pEC_{50} 6.3–6.6) [1217], PHCCC (Pos) (pEC_{50} 4.5) [1184]</td>
</tr>
<tr>
<td>modulators</td>
<td>BAY 367620 (Neg) (pK_{I} 9.5) [267] – Rat, <a href="%E2%88%92">N</a>16259685 (Neg) (pIC_{50} 8.9) [1047], A-841720 (Neg) (pIC_{50} 8) [2126], Ro67-7476 (Pos) (pK_{I} 7.5–7.9) [971] – Rat, 3,5-dimethyl PPP (Neg) (pIC_{50} 7.8) [1271] – Rat, EM-TBPC (Neg) (pK_{I} 7.8) [1191] – Rat, Ro01-6128 (Pos) (pK_{I} 7.5–7.7) [971] – Rat, LY456236 (Neg) (pIC_{50} 6.9) [1094], CPCCCOEt (Neg) (pIC_{50} 5.2–5.8) [1116], Ro67-4853 (Pos) (pK_{I} 5.1) [971] – Rat, PHCCC (Pos)</td>
<td>Ro64-5229 (Neg) (pIC_{50} 7) [985] – Rat, biphenylindanone A (Pos) (pIC_{50} 7) [183]</td>
<td>–</td>
<td>VU0361737 (Pos) (pEC_{50} 6.6) [480], VU0155041 (Pos) (pEC_{50} 6.1) [1402]</td>
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<tr>
<td>Selective allosteric modulators</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>modulators</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

Comments – – – pEC_{50} values for MPEP and SIB-1893 were obtained in the presence of L-AP4 [1217].
<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>mGlu5 receptor</th>
<th>mGlu6 receptor</th>
<th>mGlu7 receptor</th>
<th>mGlu8 receptor</th>
</tr>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>GRMS, P41594</td>
<td>GRM6, O15303</td>
<td>GRM7, Q14831</td>
<td>GRM8, O00222</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>L-serine-O-phosphate (pIC50 6.2–7.2)</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[1192, 2050]</td>
</tr>
<tr>
<td>Agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(S)-3,4-DCPG (pIC50 7.5) [1876], L-AP4 (pIC50 7–7.2) [1192]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>(S)-(+)-CBPG (Partial agonist) (pEC50 4.3) [1200] – Rat, CHPG (pIC50 3.4) [1350]</td>
<td>1-benzyl-APDC (pEC50 4.7) [1911] – Rat, homo-AMPA (pEC50 4.1) [237]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>MAP4 (pIC50 3.5) [1504] – Rat, THPG [1879] – Unknown</td>
<td>–</td>
<td>–</td>
<td>MPPG (pIC50 4.3) [2050]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>ACDPP (pIC50 6.9) [182]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Allosteric modulators</td>
<td>3,3′-difluorobenzaldazine (Positive) (pIC50 5.6–8.5) [1415, 1416], alloswitch-1 (Negative) (pIC50 8.1) [1511] – Rat, CDPPB (Positive) (pEC50 7.6–8) [956, 1114], MTEP (Negative) (pKi 7.8) [223], MPEP (Negative) (pIC50 7.4–7.7) [578, 580], fenobam (Negative) (pIC50 7.2) [1519], SIB-1893 (Negative) (pIC50 5.9–6.5) [578, 1949], SIB-1757 (Negative) (pIC50 6–6.4) [578, 1949], CPPHA (Positive) (pIC50 6.3) [1416]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective allosteric modulators</td>
<td>VU-1545 (Positive) (pEC50 8) [2142]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Comments:** The activity of NAAG as an agonist at mGlu5 receptors was questioned on the basis of contamination with glutamate [327, 347], but this has been refuted [1369]. Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [3H]LY214127 [1046] and [3H]YM298198 [979] at mGlu1 receptors and [3H]M-MPEP [578] and [3H]methoxyethyl-MTEP [47] at mGlu5 receptors. Although a number of radioligands have been used to examine binding in native tissues, correlation with individual subtypes is limited. Many pharmacological agonists have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (e.g. human versus rat or mouse) of the receptor and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling. (S)-(+)-CBPG is an antagonist at mGlu1, but is an agonist (albeit of reduced efficacy) at mGlu5 receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors [1931], and is an antagonist at all group-III mGluRs with an IC50 of 30 μM. A potential novel metabotropic glutamate receptor coupled to phosphoinoside turnover has been observed in rat brain; it is activated by 4-methyl-homocytobotic acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but resistant to LY341495 [341]. 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 [964, 1482]. 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.
Motilin receptor

G protein-coupled receptors → Motilin receptor

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

Nomenclature  
HGNC, UniProt  
motilin receptor  
MLNR, O43193

Endogenous agonists  
motilin (MLN, P12872) (pKᵢ 8.4–8.7) [372, 1223, 1224, 1225]

Agonists  
alemcinal (pIC₅₀ 7.2) [1872], erythromycin-A (pIC₅₀ 5.5–6.5) [507, 1872], azithromycin (pEC₅₀ 5.5) [220]

Selective agonists  
camicinal (pEC₅₀ 7.9) [99, 1639], mitemcinal (pEC₅₀ 7.5–7.8) [977, 1845] – Rabbit

Selective antagonists  
MA-2029 (pA₂ 9.2) [1811], CM-109 (pIC₅₀ 8) [701] – Pig

Labelled ligands  
[¹²⁵I]motilin (human) (Agonist) (pKᵢ 10) [507]  
[¹²⁵I]motilin (human) (Antagonist) (pKᵢ 11) [372, 1223, 1224, 1225]

Comments: In laboratory rodents, the gene encoding the motilin precursor appears to be absent, while the receptor appears to be a pseudogene [725, 1637]. Functions of motilin (MLN, P12872) are not usually detected in rodents, although brain and other responses to motilin and the macrolide alemcinal have been reported and the mechanism of these actions are obscure [1249, 1396]. Marked differences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [1638]. Note 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; [2123]). Small molecule motilin receptor agonists are now described [1093, 1639, 2013]. The motilin receptor does not appear to have constitutive activity [774]. Although not proven, the existence of biased agonism at the receptor has been suggested [1225, 1292, 1636]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [507].
Neuromedin U receptors

G protein-coupled receptors → Neuromedin U receptors

**Overview:** Neuromedin U receptors (provisional nomenclature as recommended by NC-IUPHAR [530]) 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 [1287]. In humans, NmU-25 appears to be the sole product of a precursor gene (NMU, P48645) showing a broad tissue distribution, but which is expressed at highest levels in the upper gastrointestinal tract, CNS, bone marrow and fetal liver. Much shorter versions of NmU are found in some species, but not in human, and are derived at least in some instances from the proteolytic cleavage of the longer NmU. Despite species differences in NmU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity. Neuromedin S (neuromedin S-33 (NMS, Q5H8A3)) has also been identified as an endogenous agonist [1326]. 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

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>NMU1 receptor</th>
<th>NMU2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>NMUR1, Q9HB89</td>
<td>NMUR2, Q9CZQ4</td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
<td>R-PSOP (pK_B 7) [1128]</td>
</tr>
</tbody>
</table>

**Comments:** NMU1 and NMU2 couple predominantly to G_q/11 although there is evidence of good coupling to G_s/o [213, 786, 794]. NMU1 and NMU2 can be labelled with ^125^I-NmU and ^125^I-NmS (of various species, e.g. [1259]), BODIPY® TMR-NMU or Cy3B-NMU-8 [213]. A range of radiolabelled (^125^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, QSHBA3) are now commercially available.

Further Reading

Neuropeptide FF/neuropeptide AF receptors

**Overview:** The Neuropeptide FF receptor family contains two subtypes, NPFF1 and NPFF2 (provisional nomenclature [530]), 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.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>NPFF1 receptor</th>
<th>NPFF2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>NPFFR1, Q9GZQ6</td>
<td>NPFFR2, Q9YSX5</td>
</tr>
</tbody>
</table>

**Rank order of potency**

- RF9 (pK_i 7.2) [1745]
- AC262620 (pK_i 7.7–8.1) [1036], AC262970 (pK_i 7.4–8.1) [1036]

**Endogenous agonists**

- neuropeptide FF (NPFF, O15130) (Selective) (pK_i 8.5–9.9) [628, 629, 1306]
- RFRP-3 (NPVF, Q9HCQ7) (Selective) (pK_i 9.2–9.3) [629, 630, 1306]

**Selective agonists**

- dNPA (pK_i 10.6) [1607], AC263093 (pEC50 5.2–5.9) [1036]

**Antagonists**

- RF9 (pK_i 7.2) [1745]
- AC262620 (pK_i 7.7–8.1) [1036], AC262970 (pK_i 7.4–8.1) [1036]

**Labelled ligands**

- [125I]Y-RFRP-3 (Agonist) (pK_d 9.7) [629], [3H]NPVF (Agonist) (pK_d 8.6) [1855], [125I]NPFF (Agonist) [628]
- [125I]JEYF (Agonist) (pK_d 10.2) [1306], [3H]JEYF (Agonist) (pK_d 9.3) [1855], [125I]NPFF (Agonist) [628]

**Comments:** An orphan receptor GPR83 (Q9NYM4) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors. The antagonist RF9 is selective for NPFF receptors, but does not distinguish between the NPFF1 and NPFF2 subtypes (pK_i 7.1 and 7.2, respectively, [1745]).

**Further Reading**


Neuropeptide S receptor

G protein-coupled receptors → Neuropeptide S receptor

Overview: The neuropeptide S receptor (NPS, provisional nomenclature [530]) responds to the 20 amino-acid peptide neuropeptide S derived from the precursor (NPS, P0C0P6).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Neuropeptide S receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>NPSR1, Q6W5P4</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>neuropeptide S (NPS, POC0P6) (pEC_{50} 8) [2070]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]Tyr10NPS (human) (Agonist) (pK_{d} 9.5) [2070]</td>
</tr>
</tbody>
</table>

Comments: Polymorphisms in the NPS receptor have been suggested to be associated with asthma [1953] and irritable bowel syndrome [386].

Further Reading

Cannella N et al. (2013) The role of the neuropeptide S system in addiction: focus on its interaction with the CRF and hypocretin/orexin neurotransmission. Prog. Neurobiol. 100: 48-59 [PMID:23041581]

Neuropeptide W/neuropeptide B receptors

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

Overview: The neuropeptide BW receptor 1 (NPBW1, provisional nomenclature [530]) is activated by two 23-amino-acid peptides, neuropeptide W (neuropeptide W-23 (NPW, Q8N729)) and neuropeptide B (neuropeptide B-23 (NPB, Q8NG41)) [554, 1725]. C-terminally extended forms of the peptides (neuropeptide W-30 (NPW, Q8N729) and neuropeptide B-29 (NPB, Q8NG41)) also activate NPBW1 [211]. 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 [211].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Nomenclature: NPBW1 receptor (HGNC, UniProt: NPBW1, Accession: P48145) NPBW2 receptor (HGNC, UniProt: NPBW2, Accession: P48146)

Rank order of potency: neuropeptide B-29 (NPB, Q8NG41) > neuropeptide B-23 (NPB, Q8NG41) > neuropeptide W-23 (NPW, Q8N729) > neuropeptide W-30 (NPW, Q8N729) [211] neuropeptide W-29 (NPW, Q8N729) > neuropeptide W-23 (NPW, Q8N729) [211] neuropeptide W-30 (NPW, Q8N729) > neuropeptide W-23 (NPW, Q8N729) [211] neuropeptide W-29 (NPW, Q8N729)

Selective agonists: Ava3 (pKᵢ 9.4–9.4) [902], Ava5 (pKᵢ 8.8–9) [902]

Labelled ligands: [125I]NPW-23 (human) (Agonist) (pKᵢ 9.4) [1747] [125I]NPW-23 (human) (Agonist) (pKᵢ 7.7) [1725]

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

NPBW1/− mice show changes in social behavior, suggesting that the NPBW1 pathway may have an important role in the emotional responses of social interaction [1355].

Further Reading:

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 [1270]), 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, [1135]). 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 [642]. 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 Y₅ receptor than at the human receptor [485]. In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [125I]-PYY or [125I]-NPY can be used to label Y₁, Y₂, Y₅ and Y₆ subtypes non-selectively, while [125I][cPP(1-7), NPY(19-23), Ala³¹, Aib³², Glc³⁴]hPP may be used to label Y₅ receptors preferentially (note that cPP denotes chicken peptide sequence and hPP is the human sequence).
### Nomenclature

<table>
<thead>
<tr>
<th>HGNC, UniProt</th>
<th>Y&lt;sub&gt;1&lt;/sub&gt; receptor</th>
<th>Y&lt;sub&gt;2&lt;/sub&gt; receptor</th>
<th>Y&lt;sub&gt;4&lt;/sub&gt; receptor</th>
<th>Y&lt;sub&gt;5&lt;/sub&gt; receptor</th>
<th>Y&lt;sub&gt;6&lt;/sub&gt; receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPY1R, P25929</td>
<td>NPY2R, P49146</td>
<td>NPY4R, P50391</td>
<td>NPY5R, Q15761</td>
<td>NPY6R, Q99463</td>
</tr>
</tbody>
</table>

### Rank order of potency

- Neuropeptide Y = peptide YY >> Pancreatic polypeptide
- Neuropeptide Y (NPY, P01303), peptide YY (PYY, P01082)
- Pancreatic polypeptide (PPY, P01298) (pK<sub>i</sub> 8.7–10.9) [92, 1152, 1899, 2076]

### Endogenous agonists

- **Neuropeptide Y (NPY, P01303), peptide YY (PYY, P01082)**
- **Pancreatic polypeptide (PPY, P01298)** (pK<sub>i</sub> 8.7–10.9) [92, 1152, 1899, 2076]

### Selective agonists

- [Leu<sup>31</sup>, Pro<sup>34</sup>]<sub>NPY</sub> (pEC<sub>50</sub> 7.1) [378], [Leu<sup>31</sup>, Pro<sup>34</sup>]<sub>PYY</sub> (human), [Pro<sup>34</sup>]<sub>NPY</sub>, [Pro<sup>34</sup>]<sub>PYY</sub> (human)

### Selective antagonists

- BIBO3304 (pIC<sub>50</sub> 9.5) [2020], BIBP3226 (pK<sub>i</sub> 8.1–9.3) [436, 2021]
- BIIE0246 (pIC<sub>50</sub> 8.5) [434], JNJ-5207787 (pIC<sub>50</sub> 6.9–7.1) [178]
- L-152,804 (pK<sub>i</sub> 7.6) [901]

### Labelled ligands

- [<sup>3</sup>H]BIBP3226 (Agonist) (pK<sub>d</sub> 8.7), [125]<sub>I</sub>PYY-(3-36) (human) (Agonist)
- [125]<sub>I</sub>PP (human) (Agonist)
- [125]<sub>I</sub>[cPP(1-7), NPY(19-23), Ala<sup>31</sup>, Aib<sup>32</sup>, Gln<sup>34</sup>]hPP (Agonist) (pK<sub>d</sub> 9.2–9.3) [453] – 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 [598]. 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.

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**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Neurotensin receptors

G protein-coupled receptors $\rightarrow$ Neurotensin receptors

**Overview:** Neurotensin receptors (nomenclature as recommended by NC-IUPHAR [530]) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (NTS, P30990), which also generates neuromedin N, an agonist at the NTS$_2$ receptor. A nonpeptide antagonist, SR142948A, shows high affinity ($pK_i$ = 9) at both NTS$_1$ and NTS$_2$ receptors [664]. $[^3H]$neurotensin (human, mouse, rat) and $[^{125}I]$neurotensin (human, mouse, rat) may be used to label NTS$_1$ and NTS$_2$ receptors at 0.1-0.3 and 3-5 nM concentrations respectively.

**Nomenclature**
- HGNC, UniProt: NTSR1, P30989
- Rank order of potency: neurotensin (NTS, P30990) > neuromedin N (Mouse, Rat) [741]
- Selective agonists: JMV449 ($pK_i$ 10) [1753] – Rat
- Antagonists: meclinertant ($pIC_{50}$ 7.5–8.2) [664]
- Labelled ligands: $[^3H]$meclinertant (Antagonist) ($pK_{d}$ 8.5) [1030] – Rat
- Comments: –

**NTS$_1$ receptor**
- $[^3H]$meclinertant (Antagonist) ($pK_{d}$ 8.5) [1030] – Rat

**NTS$_2$ receptor**
- $[^3H]$neurotensin (NTS, P30990) = neuromedin N (Mouse, Rat) [1235]
- levocabastine ($pK_i$ 6.8) [1235, 1583]
- meclinertant ($pIC_{50}$ 7.5–8.2) [664]
- $[^3H]$meclinertant (Antagonist) ($pK_{d}$ 8.5) [1030] – Rat
- $[^{125}I]$neurotensin (human, mouse, rat) may be used to label NTS$_1$ and NTS$_2$ receptors at 0.1-0.3 and 3-5 nM concentrations respectively.

**Comments:** neurotensin (NTS, P30990) appears to be a low-efficacy agonist at the NTS$_2$ receptor [1959], while the NTS$_1$ receptor antagonist meclinertant is an agonist at NTS$_2$ receptors [1959]. An additional protein, provisionally termed NTS$_3$ (also known as NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation [1395]. It has been reported to interact with the NTS$_1$ receptor [1211] and has been implicated in hormone trafficking and/or neurotensin uptake.

**Further Reading**
- Boules M et al. (2013) Diverse roles of neurotensin agonists in the central nervous system. *Front Endocrinol (Lausanne)* 4: 36 [PMID:23526754]
- Dupouy S et al. (2011) The potential use of the neurotensin high affinity receptor 1 as a biomarker for cancer progression and as a component of personalized medicine in selective cancers. *Biochimie* 93: 1369-78 [PMID:21605619]
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-neoendorphin (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); endorphin-1 and endorphin-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 most appropriate [376, 417, 530]. The human N/OFQ receptor is considered ‘opioid-related’ rather than opioid because while it exhibits a high degree of structural homology with the conventional opioid receptors [1308], it displays a distinct pharmacology.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>δ receptor</th>
<th>κ receptor</th>
<th>µ receptor</th>
<th>NOP receptor</th>
</tr>
</thead>
<tbody>
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<td>OPRD1, P41143</td>
<td>OPRK1, P41145</td>
<td>OPRM1, P35372</td>
<td>OPR1, P41146</td>
</tr>
<tr>
<td>Principal endogenous</td>
<td>β-endorphin (POMC, P01189),</td>
<td>big dynorphin (PDYN, P01213),</td>
<td>β-endorphin (POMC, P01189),</td>
<td>nociceptin/orphanin FQ (PNOC,</td>
</tr>
<tr>
<td>agonists</td>
<td>[Leu]enkephalin (PENK, P01210),</td>
<td>dynorphin A (PDYN, P01213),</td>
<td>[Leu]enkephalin (PENK, P01210),</td>
<td>Q13519) (Selective) (pKᵦ 9.7–10.4)</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
<td>endorphin-1, endorphin-2</td>
<td>[149, 1242, 1303, 1307, 1439]</td>
</tr>
<tr>
<td>Agonists</td>
<td>–</td>
<td>–</td>
<td>[622, 2109]</td>
<td>–</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>[D-Ala²]deltorphin I (pKᵦ 9.4) [487, 1795], [D-Ala²]deltorphin II (pKᵦ 8.8) [488], SNC80 (pKᵦ 7.2) [258, 1549]</td>
<td>[297, 1478, 1744, 1893, 1962, 2128, 2130], [808, 1383], [1034, 1893], [251, 1603]</td>
<td>sufentanil (pKᵦ 9.9) [1960], DAMGO (pKᵦ 9.3) [691, 1893], loperamide (pKᵦ 9.3) [308], morphine (pKᵦ 9) [620, 1893], PL017 (pKᵦ 8.2) [290, 1893]</td>
<td>N/OFQ-(1-13)-NH₂ (pKᵦ 10.1–10.4) [149, 661, 1242, 1439], Ro64-6198 (pKᵦ 9.6) [855]</td>
</tr>
<tr>
<td>Nomenclature</td>
<td>κ receptor</td>
<td>μ receptor</td>
<td>NOP receptor</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td></td>
</tr>
<tr>
<td>Antagonists</td>
<td>buprenorphine (pKᵢ 9.1–10.2) [1893, 2130], nalmefene (pKᵢ 9.5) [1893],</td>
<td>naltrexone (pKᵢ 9.7) [1893], nalmefene (pKᵢ 9.5) [1893],</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>naltrexone (pKᵢ 8.4–9.4) [1478, 1744, 1893], naloxone (pKᵢ 7.6–8.6) [1478,</td>
<td>naltrexone (pKᵢ 9.5) [1893], nalorphine (pKᵢ 8.9) [1893],</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1744, 1893, 2128, 2130]</td>
<td>methylnaltrexone (pKᵢ 8.7) [2007]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>nor-binaltorphimine (pKᵢ 8.9–11) [1478, 1520, 1744, 1893, 2128, 2130],</td>
<td>alvimopan (pKᵢ 9.3) [1056], levallorphan (pKᵢ 8.8–9.3) [1187], CTAP</td>
<td>UFP-101 (pKᵢ 10.2) [259],</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5′-guanidinonaltrindole (pKᵢ 9.7–9.9) [882, 1478, 1797]</td>
<td>(pKᵢ 8.6) [290, 1893]</td>
<td>Banyu Compound-24 (pKᵢ 9.6)</td>
<td></td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[3H]naltrindole (Antagonist) (pKᵢ 10.4) [2072] – Rat, [3H]DPDPE (Agonist)</td>
<td>[3H]DAMGO (Agonist) (pKᵢ 9.2)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>[26], [3H]deltorphin II (Agonist) [252], [3H]naltriben (Antagonist) [1088]</td>
<td>[3H]enadoline (Agonist) [1746]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:** Three naloxone-sensitive opioid receptor genes have been identified in humans, and while the μ-receptor in particular may be subject to extensive alternative splicing [1468], 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 [884], and give rise to complexes with a unique pharmacology, however, evidence for such heterodimers in native cells is equivocal and the consequences this heterodimerization for signalling remains largely unknown. For μ-opioid receptors at least, dimerization does not seem to be required for signalling [1026]. 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 [2110].

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

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human μ-receptors [1423] and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists [231]. 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 MOP and DOPr, notably the positive allosteric modulators and silent allosteric “agonists” outlined in [240, 241]. Negative allosteric modulation of opioid receptors has been previously suggested [908], whether all compounds are acting at a similar site remains to be established.

**Further Reading**


Orexin receptors

G protein-coupled receptors \(\rightarrow\) Orexin receptors

Overview: Orexin receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Orexin receptors [627]) 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 [1629]. Binding to both receptors may be accomplished with \([125I]\)orexin A (human, mouse, rat) [773].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>OX1 receptor</th>
<th>OX2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>HCRTR1, O43613</td>
<td>HCRTR2, O43614</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>orexin-A (HCRT, O43612) (\rightarrow) orexin-B (HCRT, O43612)</td>
<td>orexin-A (HCRT, O43612) = orexin-B (HCRT, O43612)</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>–</td>
<td>[Ala11, D-Leu15]orexin-B (pEC50 9.9) [62]</td>
</tr>
<tr>
<td>(Sub)family-selective antagonists</td>
<td>suvorexant (pK1 9.3) [377], SB-649686 (pK1 9.1) [419], filorexant (pK1 8.6) [2035], almorexant (pEC50 7.9) [216]</td>
<td>filorexant (pK1 9.5) [2035], suvorexant (pK1 9.5) [377], SB-649686 (pK1 8.9) [419], almorexant (pEC50 8.1) [216]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>SB-408124 (pK1 7.2–7.6) [1042, 1190], SB-334867 (pK1 7.4–7.5) [1190, 1518]</td>
<td>EMPA (pK1 9) [1189], JNJ 10397049 (pK1 7.9–8.6) [1238], TCS-OX2-29 (pK1 7.4) [760]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>([^3H]SB-674042) (Antagonist) (pKD 8.3–9.1) [1042, 1190, 1193]</td>
<td>–</td>
</tr>
</tbody>
</table>

Comments: The primary coupling of orexin receptors to \(G_{q/11}\) proteins is rather speculative and based on the strong activation of phospholipase C. Coupling of both receptors to \(G_{i/o}\) and \(G_{s}\) has also been reported [1019, 1555]; for most cellular responses observed, the \(G\) protein pathway is unknown. The rank order of endogenous agonist potency may depend on the cellular signal transduction machinery. The synthetic [Ala11, D-Leu15]orexin-B may show poor OX2 receptor selectivity [1540]. Loss-of-function mutations in the gene encoding the OX2 receptor underlie canine hereditary narcolepsy [1111].

Further Reading


Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Oxoglutarate receptor

G protein-coupled receptors → Oxoglutarate receptor

Overview: Nomenclature as recommended by NC-IUPHAR [396].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>oxoglutarate receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>OXGR1, Q96P68</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>α-ketoglutaric acid (pEC&lt;sub&gt;50&lt;/sub&gt; 3.3–4.5) [728, 1785]</td>
</tr>
</tbody>
</table>

P2Y receptors

G protein-coupled receptors → P2Y receptors

Overview: P2Y receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on P2Y Receptors [1, 2]) are activated by the endogenous ligands ATP, adenosine diphosphate, uridine triphosphate, uridine diphosphate and UDP-glucose. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established and so it might be appropriate to use wording such as ‘uridine triphosphate-preferring (or ATP-, etc.) P2Y receptor’ or ‘P2Y1-like’, etc., until further, as yet undefined, corroborative criteria can be applied [244, 486, 837, 2003, 2146].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>P2Y&lt;sub&gt;1&lt;/sub&gt; receptor</th>
<th>P2Y&lt;sub&gt;2&lt;/sub&gt; receptor</th>
<th>P2Y&lt;sub&gt;4&lt;/sub&gt; receptor</th>
<th>P2Y&lt;sub&gt;6&lt;/sub&gt; receptor</th>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>P2RY1, P47900</td>
<td>P2RY2, P41231</td>
<td>P2RY4, P51582</td>
<td>P2RY6, Q15077</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>adenosine diphosphate=ATP</td>
<td>uridine triphosphate=ATP</td>
<td>uridine triphosphate=ATP (at rat recombinant receptors, UTP = ATP)</td>
<td>uridine diphosphate=ATP</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>ADPβS (pEC&lt;sub&gt;50&lt;/sub&gt; 7.3) [1848], 2MeSADP (pIC&lt;sub&gt;50&lt;/sub&gt; 5.4–7) [1658, 1970]</td>
<td>–</td>
<td>–</td>
<td>Rp-S-OMe-UDPβB (pEC&lt;sub&gt;50&lt;/sub&gt; 8.1) [611, 666]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>MRS2365 (pEC&lt;sub&gt;50&lt;/sub&gt; 9.4) [314], 2-Cl-ADP(α-BH3) (pEC&lt;sub&gt;50&lt;/sub&gt; 8.1) [73]</td>
<td>2-thiouTP (pEC&lt;sub&gt;50&lt;/sub&gt; 7.3) [470], PSB1114 (EC&lt;sub&gt;50&lt;/sub&gt; value determined using an IP&lt;sub&gt;3&lt;/sub&gt; functional assay) (pEC&lt;sub&gt;50&lt;/sub&gt; 6.9) [471], ApuA (pEC&lt;sub&gt;50&lt;/sub&gt; 6.1) [270, 1471], UTPγS (pEC&lt;sub&gt;50&lt;/sub&gt; 5.8) [1054], MRS2768 (EC&lt;sub&gt;50&lt;/sub&gt; value determined using an IP&lt;sub&gt;3&lt;/sub&gt; functional assay) (pEC&lt;sub&gt;50&lt;/sub&gt; 5.7) [973]</td>
<td>MRS4062 (pEC&lt;sub&gt;50&lt;/sub&gt; 7.6) [1213], UTPγS [1055] – Unknown</td>
<td>MRS2957 (pEC&lt;sub&gt;50&lt;/sub&gt; 7.9) [1212], MRS2693 (pEC&lt;sub&gt;50&lt;/sub&gt; 7.8) [143], 3-phenacyl-UDP (pEC&lt;sub&gt;50&lt;/sub&gt; 7.2) [470]</td>
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Searchable database: http://www.guidetopharmacology.org/index.jsp
### Nomenclature

<table>
<thead>
<tr>
<th>P2Y1 receptor</th>
<th>P2Y2 receptor</th>
<th>P2Y4 receptor</th>
<th>P2Y6 receptor</th>
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</thead>
<tbody>
<tr>
<td>ATP</td>
<td>ATP</td>
<td>ATP</td>
<td>ATP</td>
</tr>
<tr>
<td>MRS2500 (pKᵢ 8.8–9.1) [274, 942], BMS compound 16 [PMID:23368907] (pKᵢ 8.2) [295, 2115], MRS2279 (pKᵢ 7.9) [1970], MRS2179 (pKᵢ 7–7.1) [197, 1970], 2,2′-pyridylisatogen tosylate (pKᵢ 6.8) [570]</td>
<td>AR-C118925XX (pIC₅₀ ~6) [924]</td>
<td>–</td>
<td>MRS2278 (pIC₅₀ 7.4) [1196]</td>
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### Antagonists

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>P2Y1 receptor</th>
<th>P2Y2 receptor</th>
<th>P2Y4 receptor</th>
<th>P2Y6 receptor</th>
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</thead>
<tbody>
<tr>
<td>MRS2500</td>
<td>–</td>
<td>–</td>
<td>ATP (pKᵢ 6.2) [925]</td>
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### Selective antagonists

<table>
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<th>Nomenclature</th>
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<th>P2Y4 receptor</th>
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<tbody>
<tr>
<td>MRS2500</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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### Labelled ligands

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<th>P2Y4 receptor</th>
<th>P2Y6 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>[³H]MRS2279 (Antagonist) (pKᵢ 8.1) [1970], [³H]2MeSADP (Agonist) (pKᵢ 7.3) [1848], [³5S]ADPβS (Agonist) – Unknown</td>
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<td>–</td>
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### Nomenclature

<table>
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<th>P2Y13 receptor</th>
<th>P2Y14 receptor</th>
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</thead>
<tbody>
<tr>
<td>ATP–uridine triphosphate</td>
<td>–</td>
<td>adenosine diphosphate–ATP</td>
<td>uridine diphosphate ≥ UDP-glucose</td>
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### Ranking of potency

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<th>Nomenclature</th>
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### Endogenous agonists

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<th>P2Y12 receptor</th>
<th>P2Y13 receptor</th>
<th>P2Y14 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP–uridine triphosphate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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### Agonists

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<tbody>
<tr>
<td>ATP–uridine triphosphate</td>
<td>–</td>
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### Selective agonists

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<th>P2Y14 receptor</th>
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<td>–</td>
<td>–</td>
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### Antagonists

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<thead>
<tr>
<th>Nomenclature</th>
<th>P2Y11 receptor</th>
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<th>P2Y13 receptor</th>
<th>P2Y14 receptor</th>
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### Selective antagonist

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<th>Nomenclature</th>
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<th>P2Y14 receptor</th>
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<tbody>
<tr>
<td>ATP–uridine triphosphate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
**Comments:** cangrelor shows selectivity for P2Y\textsubscript{12} and P2Y\textsubscript{13} receptors compared with other P2Y receptors [1209, 1848]. NPY157 also has antagonistic activity at P2X\textsubscript{7} receptors [1923]. Uridine diphosphate has been reported to be an antagonist at the P2Y\textsubscript{14} receptor [548]. \cite{35}JATP injection has been used to label P2Y receptors in rat synaptosomal membranes [1682, 1683]. An orphan GPCR suggested to be a ‘P2Y\textsubscript{15}’ receptor [823] appears not to be a genuine nucleotide receptor [2], but rather responds to dicarboxylic acids [728]. Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a p2y\textsubscript{3} receptor (ENSGALG000000017327), couples to the G\textsubscript{q/11} family of G proteins and shows the rank order of potency adenosine diphosphate $\rightarrow$ uridine triphosphate $\rightarrow$ ATP $\rightarrow$ uridine diphosphate [1998]. In addition, human sources have yielded a clone with a preliminary identification of p2y\textsubscript{5} (LPAR\textsubscript{6}, P43657) and contradictory evidence of responses to ATP [954, 1999]. This protein is now classified as LPA\textsubscript{5}, a receptor for lysophosphatidic acid (LPA) [1467, 2079]. The clone termed p2y\textsubscript{9} (LPAR\textsubscript{4}, Q99677) is also a receptor for lysophosphatidic acid, LPA\textsubscript{4} [1406]. The p2y\textsubscript{2} clone (NOPR, Q86U38), originally suggested to be a P2Y receptor [22], has been shown to encode a leukotriene receptor [2095]. A P2Y receptor that was initially termed a p2y\textsubscript{8} receptor (P79928) has been cloned from Xenopus laevis; it shows the rank order of potency ADP\textsubscript{IS} $\rightarrow$ ATP $\rightarrow$ uridine triphosphate $\rightarrow$ guanosine-5’-triphosphate $\rightarrow$ CTP $\rightarrow$ TTP $\rightarrow$ ITP $\rightarrow$ ATP\textsubscript{S} and elicits a Ca\textsuperscript{2+}-dependent Cl\textsuperscript{-} current in Xenopus oocytes [169]. The p2y\textsubscript{10} clone (P2R10, 000398) lacks functional data. Diadenosine polyphosphates also have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap\textsubscript{4}A $\rightarrow$ Ap\textsubscript{3}A $\rightarrow$ Ap\textsubscript{2}A, coupling via G\textsubscript{q/11} [270]. P2Y-like receptors have recently been described on mitochondria [126]. CysLT1 and CysLT2 leukotriene receptors respond to nanomolar concentrations of uridine diphosphate, although they are activated principally by leukotrienes LTC\textsubscript{4} and LTD\textsubscript{4} [1257, 1258]. Human GPR17 (13304) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes [1542] as well as uridine diphosphate and UDP-glucose [344, 540]. Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and cangrelor [344].

**Further Reading**

**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 [575]) are family B G protein-coupled receptors. The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor (PTHR1 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 (PTHR2 receptor) is activated by the precursor-derived peptide TIP39 (PTH2, Q96A98) (39 amino acids). [125]PTH may be used to label both PTHR1 and PTHR2 receptors.
Nomenclature | PTH1 receptor | PTH2 receptor  
HGNC, UniProt | PTH1R, Q03431 | PTH2R, P49190  
Rank order of potency | PTH (PTH, P01270) = PTHrP (PTHLH, P12272) | TIP39 (PTH2, Q96A98), PTH (PTH, P01270) > PTHrP (PTHLH, P12272)  
Endogenous agonists | – | TIP39 (PTH2, Q96A98) (pIC50 7.6–9.2) [626, 766]  
Agonists | teriparatide (pIC50 7.4) [573] | –  
Selective agonists | PTHrP-(1-34) (human) (pIC50 7.8–8.1) [574] – Rat | –  

Comments: Although PTH (PTH, P01270) is an agonist at human PTH2 receptors, it fails to activate the rodent orthologues. TIP39 (PTH2, Q96A98) is a weak antagonist at PTH1 receptors [883].

Further Reading

**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** [530]) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1204] and lysophosphatidylcholine [1425]. It may also be activated by bacterial lipopolysaccharide [1358].

Nomenclature | PAF receptor  
HGNC, UniProt | PTAFR, P25105  
Selective agonists | methylcarbamyl PAF – Unknown  
Selective antagonists | foropafant (pK_i 10.3) [739], ABT-491 (pK_i 9.2) [30], CV-6209 (pIC50 8.1–8.3) [619, 1357], L659989 (pK_i 7.8) [811], apafant (pK_i 5.2–7.5) [1460, 1831]  
Labelled ligands | [3H]PAF (Agonist) (pK_i 8.8–8.9) [555, 1357]  

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)  
Prokineticin receptors

G protein-coupled receptors → Prokineticin receptors

Overview: Prokineticin receptors, PKR₁ and PKR₂ (provisional nomenclature as recommended by NC-IUPHAR [530]) respond to the cysteine-rich 81-86 amino-acid peptides prokineticin-1 (PROK₁, Q9HC23) (also known as endocrine gland-derived vascular endothelial growth factor, mambakine) and prokineticin-2 (PROK₂, Q9HC23) (protein Bv8 homologue). An orthologue of PROK1 from black mamba (Dendroaspis polylepis) venom, mamba intestinal toxin 1 (MIT1, [1679]) is a potent, non-selective agonist at prokineticin receptors [1215], while Bv8, an orthologue of PROK2 from amphibians (Bombina sp., [1304]), is equipotent at recombinant PKR₁ and PKR₂ [1371], and has high potency in macrophage chemotaxis assays, which are lost in PKR₁-null mice.

Nomenclature
- PKR₁: PROK₁, Q8TCW9
- PKR₂: PROK₂, Q8NFJ6

Rank order of potency
- prokineticin-2 (PROK₂, Q9HC23) > prokineticin-1 (PROK₁, Q9HC23) > prokineticin-2β (PROK₂) [1109, 1215, 1775]

Endogenous agonists
- prokineticin-2 (PROK₂, Q9HC23) (pIC₅₀ 8.2–8.4) [300, 1215], prokineticin-1 (PROK₁, Q9HC23) (pIC₅₀ 6.6–7.6) [300, 1215], prokineticin-2β (PROK₂) (pIC₅₀ 7.5) [300]

Agonists
- MIT1 (pIC₅₀ 8.4) [1215]
- IS20 (pEC₅₀ 7.4) [581], IS1 (pIC₅₀ 5.6) [581]

Selective agonists
- triazine compound PC1 (pKᵢ 7.7) [87], triazine compound PC7 (pIC₅₀ 7.5) [842, 1552], triazine compound PC10 (pIC₅₀ 7) [842]

Selective antagonists
- triazine compound PC1 (pKᵢ 7.7) [87], triazine compound PC7 (pIC₅₀ 7.5) [842, 1552], triazine compound PC10 (pIC₅₀ 7) [842]

Labelled ligands
- [125I]BH-MIT1 (Agonist) (pIC₅₀ 8.4) [1215]
Comments: Genetic mutations in PROKR1 are associated with Hirschsprung's disease [1614], while genetic mutations in PROKR2 are associated with hypogonadotropic hypogonadism with anosmia [430], hypopituitarism with pituitary stalk interruption [1575] and Hirschsprung's disease [1614].

Further Reading


### Prolactin-releasing peptide receptor

**G protein-coupled receptors → Prolactin-releasing peptide receptor**

**Overview:** The precursor (PRLH, P81277) for PrRP generates 31 and 20-amino-acid versions. QRFP43 (QRFP, P83859) (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from QRFP (P83859) and is also known as P518 or 26RFa. RFRP is an RF amide-related peptide [756] 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).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>PrRP receptor</th>
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<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>PRLHR, P49683</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>PrRP-20 (PRLH, P81277), PrRP-31 (PRLH, P81277) [1043]</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>PrRP-20 (PRLH, P81277) (Selective) (pKᵦ 9–9.6) [481, 1043], PrRP-31 (PRLH, P81277) (Selective) (pKᵦ 9–9.2) [481, 1043]</td>
</tr>
<tr>
<td>Endogenous antagonists</td>
<td>neuropeptide Y (NPY, P01303) (Selective) (pKᵦ 5.4) [1032]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]PrRP-20 (human) (Agonist) (pKᵦ 9.2–10.6) [1043], [125I]PrRP31 (Agonist) [473]</td>
</tr>
</tbody>
</table>

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

Further Reading


Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Prostanoid receptors

G protein-coupled receptors → Prostanoid receptors

**Overview:** Prostanoid receptors (*nomenclature as agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors [2043]*) are activated by the endogenous ligands prostaglandins PGD₂, PGE₂, PGF₂α, PGH₂, prostacyclin [PGI₂] and thromboxane A₂. Measurement of the potency of PGI₂ and thromboxane A₂ is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

<table>
<thead>
<tr>
<th>Nomenclature</th>
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<th>TP receptor</th>
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<td>PTGDR2, Q9YSY4</td>
<td>PTGIR, P43119</td>
<td>PTGFR, P43088</td>
<td>TBX2AR, P21731</td>
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<td>Rank order of potency</td>
<td>PGD₂ &gt; PGE₂ &gt; PGF₂α &gt; PGI₂, thromboxane A₂</td>
<td>–</td>
<td>PGF₂α &gt; PGD₂ &gt; PGE₂ &gt; PGI₂ &gt; thromboxane A₂</td>
<td>PGF₂α &gt; PGD₂ &gt; PGE₂ &gt; PGI₂, thromboxane A₂</td>
<td>thromboxane A₂ = PGH₂ &gt; PGD₂, PGE₂, PGF₂α, PGI₂</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>–</td>
<td>PGD₂ &gt; PGF₂α, PGE₂ &gt; PGI₂, thromboxane A₂</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Agonists</td>
<td>–</td>
<td>13,14-dihydro-15-keto-PGD₂ (pKᵢ 7.4–8.5) [712, 1656, 1815]</td>
<td>iloprost (pKᵢ 7.5–8) [7, 2030], treprostinil (pKᵢ 7.5) [2019]</td>
<td>bimatoprost (pIC₅₀ 5.3) [2044]</td>
<td>–</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>BW 245C (pKᵢ 8.4–9.4) [171, 2045, 2046], L-644,698 (pKᵢ 8.9–9.3) [2045, 2046], SQ-27986 (pKᵢ 8) [1712], RS 93520 (Partial agonist) (pKᵢ 7.5) [1712], ZK118182 (pKᵢ 7.3) [1712]</td>
<td>15(R)-15-methyl-PGD₂ (pKᵢ 8.9) [712, 1312, 1815]</td>
<td>AFP-07 (pIC₅₀ 8.5) [288], BMY 45778 (pIC₅₀ 8) [881], esuberaprost (pKᵢ 7.9) [892], cicaprost (pKᵢ 7.8) [7]</td>
<td>fluoprostenol (pKᵢ 8.6) [7], latanoprost (free acid form) (pKᵢ 8.6) [7], AL12180 (pEC₅₀ 7.7–7.9) [1714], talifoprost [1845]</td>
<td>I-BOP (pKᵢ 8.9–9.3) [1233], U46619 (pKᵢ 7.5) [7], STA₂ (pIC₅₀ 6.4–7.1) [59]</td>
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<tr>
<td>Antagonists</td>
<td>–</td>
<td>ramatroban (pKᵢ 7.4) [1815]</td>
<td>–</td>
<td>–</td>
<td>ramatroban (pKᵢ 8) [1869]</td>
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<td>Selective antagonists</td>
<td>laropiprant (pKᵢ 10.1) [1808], – Unknown, BW21731 (pKᵢ 8.6–9.3) [171, 606, 2045], S-5751 (pKᵢ 8.8) [54], ONO-AT237-237 (pKᵢ 7.7) [758, 1895, 1897]</td>
<td>ramatroban (pKᵢ 8) [1869], vapiprost (pKᵢ 8.3–9.4) [59, 1151], SQ-29548 (pKᵢ 8.1–9.1) [7, 1834, 2030], ONO-3708 (pKᵢ 7.4–8.9) [910]</td>
<td>–</td>
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<td>Labelled ligands</td>
<td>[³H]PGD₂ (Agonist) (pKᵢ 7.9–9.5) [2030, 2045]</td>
<td>[³H]PGD₂ (Agonist) (pKᵢ 7.8–8.2) [1216, 1723]</td>
<td>[³H]iloprost (Agonist) (pKᵢ 7.7–9) [7, 170, 2030]</td>
<td>[³H]PGF₂α (Agonist) (pKᵢ 8.1–9) [7, 8, 2030], <a href="-">³H</a>-fluprostanol (Agonist) (pKᵢ 7.5) – Unknown</td>
<td>[¹²⁵I]SAP (Antagonist) (pKᵢ 7.7–9.3) [1356], [¹²⁵I]BOP (Agonist) (pKᵢ 8.7) [1328], [³H]SQ-29548 (Antagonist) (pKᵢ 7.4–8.2) [7, 2030]</td>
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<td>Nomenclature</td>
<td>EP&lt;sub&gt;1&lt;/sub&gt; receptor</td>
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<td>EP&lt;sub&gt;3&lt;/sub&gt; receptor</td>
<td>EP&lt;sub&gt;4&lt;/sub&gt; receptor</td>
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<td>PTGER3, P43115</td>
<td>PTGER4, P35408</td>
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<td>Rank order of potency</td>
<td>PG&lt;sub&gt;E2&lt;/sub&gt; &amp; PG&lt;sub&gt;F6&lt;/sub&gt;, PG&lt;sub&gt;I2&lt;/sub&gt; &amp; PG&lt;sub&gt;D2&lt;/sub&gt;, thromboxane A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PG&lt;sub&gt;E2&lt;/sub&gt; &amp; PG&lt;sub&gt;F6&lt;/sub&gt;, PG&lt;sub&gt;I2&lt;/sub&gt; &amp; PG&lt;sub&gt;D2&lt;/sub&gt;, thromboxane A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PG&lt;sub&gt;E2&lt;/sub&gt; &amp; PG&lt;sub&gt;F6&lt;/sub&gt;, PG&lt;sub&gt;I2&lt;/sub&gt; &amp; PG&lt;sub&gt;D2&lt;/sub&gt;, thromboxane A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PG&lt;sub&gt;E2&lt;/sub&gt; &amp; PG&lt;sub&gt;F6&lt;/sub&gt;, PG&lt;sub&gt;I2&lt;/sub&gt; &amp; PG&lt;sub&gt;D2&lt;/sub&gt;, thromboxane A&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>Endogenous agonists</td>
<td>PG&lt;sub&gt;E2&lt;/sub&gt; (pK&lt;sub&gt;i&lt;/sub&gt; 6.8) [1713], PG&lt;sub&gt;I2&lt;/sub&gt; (pK&lt;sub&gt;i&lt;/sub&gt; 4.8) [1713]</td>
<td>PG&lt;sub&gt;E2&lt;/sub&gt; (pK&lt;sub&gt;i&lt;/sub&gt; 7.5–8.3) [7, 1799, 2030]</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>Agonists</td>
<td>17-phenyl-&lt;i&gt;ω&lt;/i&gt;-trinar-PGE&lt;sub&gt;2&lt;/sub&gt; (pK&lt;sub&gt;i&lt;/sub&gt; 8.1) [1713]</td>
<td>evanetapag (pIC&lt;sub&gt;50&lt;/sub&gt; 7.3) [260] – Rat</td>
<td>misoprostol (methyl ester) (EP&lt;sub&gt;3&lt;/sub&gt;-III isom. form) (pK&lt;sub&gt;i&lt;/sub&gt; 6.5) [7]</td>
<td>–</td>
<td></td>
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<tr>
<td>Selective agonists</td>
<td>ONO-DI-004 (pK&lt;sub&gt;i&lt;/sub&gt; 6.8) [1826] – Mouse</td>
<td>ONO-AE1-259 (pK&lt;sub&gt;i&lt;/sub&gt; 8.5) [1826] – Mouse, butaprost (free acid form) (pK&lt;sub&gt;i&lt;/sub&gt; 5.9–7) [7, 1799]</td>
<td>SC46275 (pIC&lt;sub&gt;50&lt;/sub&gt; 10.4) [1655] – Guinea pig, MB-28767 (EP&lt;sub&gt;3&lt;/sub&gt;-III isom.) (pK&lt;sub&gt;i&lt;/sub&gt; 9.9) [7], ONO-AE-248 (pIC&lt;sub&gt;50&lt;/sub&gt; 5.6–6.7) [534, 1140]</td>
<td>L902688 (pEC&lt;sub&gt;50&lt;/sub&gt; 8.1–10.3) [535, 1064], ONO-AE-1437 (pK&lt;sub&gt;i&lt;/sub&gt; 9.1) [1294] – Mouse, CP734432 (pIC&lt;sub&gt;50&lt;/sub&gt; 8.7) [1529], ONO-AE-329 (pIC&lt;sub&gt;50&lt;/sub&gt; 7.7–7.8) [534, 535]</td>
<td></td>
</tr>
<tr>
<td>Antagonists</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>evanetapag (pK&lt;sub&gt;i&lt;/sub&gt; 8.6) [1345],</td>
<td></td>
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<tr>
<td>Selective antagonists</td>
<td>ONO-8711 (pK&lt;sub&gt;i&lt;/sub&gt; 9.2) [1992], GW848687X (pIC&lt;sub&gt;50&lt;/sub&gt; 8.6) [605], SC-51322 (pK&lt;sub&gt;i&lt;/sub&gt; 7.9) [7]</td>
<td>TG4-155 (TG4-155 also has affinity for the human DP1 receptor (pK&lt;sub&gt;i&lt;/sub&gt; 7.8)) (pK&lt;sub&gt;i&lt;/sub&gt; 8.6) [865], TG7-171 (pK&lt;sub&gt;i&lt;/sub&gt; 8.6) [567], PF-04852946 (pK&lt;sub&gt;i&lt;/sub&gt; 8.4–8.5) [920], PF-04418948 (PF-04418948 has weaker affinity at the EP2-receptor in guinea-pigs) (pK&lt;sub&gt;i&lt;/sub&gt; 8.3) [153, 2136]</td>
<td>L-798,106 (EP&lt;sub&gt;3&lt;/sub&gt;-III isom.) (pK&lt;sub&gt;i&lt;/sub&gt; 7.8–9.7) [888, 890, 1810], L-826266 (EP&lt;sub&gt;3&lt;/sub&gt;-III isom. (pK&lt;sub&gt;i&lt;/sub&gt;=8.04 in the presence of HSA)) (pK&lt;sub&gt;i&lt;/sub&gt; 9.1) [890], ONO-AE-240 (pIC&lt;sub&gt;50&lt;/sub&gt; 8.8) [38] – Mouse, DG-041 (pK&lt;sub&gt;i&lt;/sub&gt; 8.4) [888]</td>
<td>MK-2894 (pK&lt;sub&gt;i&lt;/sub&gt; 9.2) [7, 161, 350], ONO-AE3-208 (pK&lt;sub&gt;i&lt;/sub&gt; 8.5), BGC201531 (pK&lt;sub&gt;i&lt;/sub&gt; 7.9) [1230], ER819762 (pIC&lt;sub&gt;50&lt;/sub&gt; 7.2) [304], GW 627368 (pK&lt;sub&gt;i&lt;/sub&gt; 7–7.1) [2030, 2031]</td>
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</tr>
<tr>
<td>Labelled ligands</td>
<td>&lt;sup&gt;3&lt;/sup&gt;HJPG&lt;sub&gt;E2&lt;/sub&gt; (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 7.6–7.9) [7, 1713, 2030]</td>
<td>&lt;sup&gt;3&lt;/sup&gt;HJPG&lt;sub&gt;E2&lt;/sub&gt; (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 7.7–7.9) [7, 2030]</td>
<td>&lt;sup&gt;3&lt;/sup&gt;HJPG&lt;sub&gt;E2&lt;/sub&gt; (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 8.2–9.5) [7, 2030]</td>
<td>&lt;sup&gt;3&lt;/sup&gt;HJPG&lt;sub&gt;E2&lt;/sub&gt; (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 7.6–9.5) [7, 401, 2019, 2030]</td>
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</tbody>
</table>

**Comments:** ramatroban is an antagonist at both DP<sub>2</sub> and TP receptors. Whilst cicaprost is selective for IP receptors, it does exhibit moderate agonist potency at EP<sub>4</sub> receptors [7]. Apart from IP receptors, iloprost also binds to other prostanoid receptors such as EP<sub>1</sub> receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail [1566]. The IP receptor agonist treprostinil binds also to human EP<sub>2</sub> and DP<sub>1</sub> receptors with high affinity (pK<sub>i</sub> 8.4 and 8.36, respectively).

The EP<sub>1</sub> agonist 17-phenyl-<i>ω</i>-trinar-PGE<sub>2</sub> also shows agonist activity at EP<sub>3</sub> receptors. Butaprost and SC46275 may require deesterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1105], IP [1851, 2037] and TP [1005] receptors. mRNA for the EP<sub>1</sub> and EP<sub>3</sub> receptors undergo alternative splicing to produce two [1441] and at least six variants, respectively, which can interfere with signalling [1441] 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. [997, 1370]). The number of EP<sub>3</sub> receptor (protein) variants are variable depending on species, with live in human, three in rat and three in mouse. The possibility of additional receptors for the isoprostanes is possible depending on species, with five in human, three in rat and three in mouse. The possibility of additional receptors for the isoprostanes is possible depending on species, with five in human, three in rat and three in mouse.

The free acid form of AL-12182, AL12180, used in *in vitro* studies, has an EC<sub>50</sub> value 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 [1714].

References given alongside the TP receptor agonists l-BOP [1233] and STAG [59] 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 [1851, 1994] and in the BEAS-2B human airway epithelial cell line [2033] 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 the IP<sub>2</sub> subtype is currently lacking.
Further Reading


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 [770]) 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-NH2, SLIGKV-NH2, TFRGAP-NH2 and GYPGQV-NH2, respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation of Gαq-coupled calcium signalling, thereby preventing activation by activating proteinases but not by agonist peptides. Neutrophil elastase cleavage of PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [1553]. The role of such an action in vivo is unclear.

<table>
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<tr>
<th>Nomenclature</th>
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<th>PAR3</th>
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<td>F2RL1, P5S085</td>
<td>F2RL2, O00254</td>
<td>F2RL3, Q96R10</td>
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<td>Agonist proteases</td>
<td>thrombin (F2, P00734), activated protein C (PROC, P04070), matrix metalloproteinase 1 (MMP1, P45452), matrix metalloproteinase 13 (MMP13, P45452) [70]</td>
<td>Trypsin, tryptase, TF/VIIa, Xa</td>
<td>thrombin (F2, P00734)</td>
<td>thrombin (F2, P00734), trypsin, cathepsin G (CTSG, P08311)</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>TFLLR-NH2 (pEC50, 5.4) [340]</td>
<td>GB110 (pEC50 6.5) [98], 2-furoyl-LIGRLO-amide (pKᵢ 5.4) [1243], SLIGKV-NH2 [1069], SLIGRL-NH2 [1069]</td>
<td>–</td>
<td>AYPGF-NH2, GYPGF-NH2, GYPGQV-NH2</td>
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Searchable database: http://www.guidetopharmacology.org/index.jsp
(continued)

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<tr>
<td>Selective antagonists</td>
<td>vorapaxar (pK&lt;sub&gt;i&lt;/sub&gt; 8.1) [281], atopaxar (pIC&lt;sub&gt;50&lt;/sub&gt; 7.7) [978], RWJ-56110 (pIC&lt;sub&gt;50&lt;/sub&gt; 6.4) [48]</td>
<td>G888 (pIC&lt;sub&gt;50&lt;/sub&gt; 5.7) [1813], P2pal18s [1705]</td>
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</table>

Comments: TFLLR-NH<sub>2</sub> is selective relative to the PAR<sub>2</sub> receptor [155, 915].

2-Furoyl-LIGRLO-NH<sub>2</sub> activity was measured via calcium mobilisation in HEK 293 cells which constitutively express human PAR<sub>1</sub> and PAR<sub>2</sub>.

Comments: thrombin (F2, P00734) is inactive at the PAR<sub>2</sub> receptor.

Endogenous serine proteases (EC 3.4.21.) active at the protease-activated receptors include: thrombin (F2, P00734), generated by the action of Factor X (F10, P00742) on liver-derived prothrombin (F2, P00734); trypsin, generated by the action of enterokinase (TMPRSS15, P98073) on pancreatic-derived trypsinogen (PRSS1, P07477); trypsinase, a family of enzymes (a/b1 TPSAB1, Q15661; g1 TPSG1, Q9NRR2; â1 TPSD1, Q9BZJ3) secreted from mast cells; cathepsin G (CTSG, P08311) generated from leukocytes; liver-derived protein C (PROC, P04070) generated in plasma by thrombin (F2, P00734) and matrix metalloproteinase 1 (MMP1, P45452).

Further Reading


QRFP receptor

G protein-coupled receptors → QRFP receptor

**Overview:** The human gene encoding the QRFP receptor (QRFP, also 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 [1066]. 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 Y2 (37%) and galanin GalR1 (35%) receptors.

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<td>HGNC, UniProt</td>
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<tr>
<td>Endogenous agonists</td>
<td>QRFP43 (QRFP, P83859) (pIC_{50} 7.8–9.3) [SS7, 1850] – Rat, QRFP26 (QRFP) (pEC_{50} 8.2) [867]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]QRFP43 (human) (Agonist) (pK_{d} 7.8–10.3) [SS7, 1017, 1850]</td>
</tr>
</tbody>
</table>

**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


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 [105, 677]) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: 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, Q9YSQ6). Species homologues of relaxin have distinct pharmacology - relaxin (RLN2, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [1686] and porcine relaxin may have a higher efficacy than human relaxin (RLN2, P04090) [678]. Relaxin-3 (RLN3, Q8WXF3) has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for relaxin-3 (RLN3, Q8WXF3) [1685]. At least two binding sites have been identified on the RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane domain [678, 1812]. The unique N-terminal LDLa module of RXFP1 and RXFP2 is essential for receptor signalling [1687].

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<td>RXFP2, Q8WWX0</td>
<td>RXFP3, Q9N5D7</td>
<td>RXFP4, Q8TDU9</td>
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<td>Rank order of potency</td>
<td>relaxin (RLN2, P04090) &gt; relaxin-1 (RLN1, P04808) &gt; relaxin-3 (RLN3, Q8WWX3) [1812]</td>
<td>INSL3 (INSL3, P51460) &gt; relaxin-3 (RLN3, Q8WWX3) &gt; relaxin-3 (B chain) (RLN3, Q8WWX3) &gt; relaxin (RLN2, P04090) [1119]</td>
<td>relaxin-3 (RLN3, Q8WXF3) &gt; relaxin-3 (B chain) (RLN3, Q8WXF3) &gt; relaxin (RLN2, P04090) [1119]</td>
<td>INSL5 (INSL5, Q9YSQ6) = relaxin-3 (RLN3, Q8WXF3) = relaxin-3 (B chain) (RLN3, Q8WXF3) [1117, 1118]</td>
</tr>
<tr>
<td>Endogenous antagonists</td>
<td>–</td>
<td>–</td>
<td>INSL5 (INSL5, Q9YSQ6) (pKi 7) [2129]</td>
<td>–</td>
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<tr>
<td>Antagonists</td>
<td>B-R13/17K H2 relaxin (pEC50 5.7–6.7) [788, 1382], LGR7-truncate [1687]</td>
<td>–</td>
<td>R3(Bs 23-27)R/IS chimeric peptide (pIC50 9.2) [1018]</td>
<td>R3(Bs 23-27)R/IS chimeric peptide (pIC50 8–8.6) [714, 1018]</td>
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<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>A(9-26)INSL3 (pKi 9.1) [787], A(10-24)INSL3 (pKi 8.7) [787], A(C10/15S)INSL3 (pKi 8.6) [2118], INSL3 B chain dimer analogue 8 (pKi 8.5) [1710], A(Δ10/15C)INSL3 (pKi 8.3) [2118], cyclic INSL3 B chain analogue 6 (pKi 6.7) [1708], INSL3 B chain analogue (pKi 5.1) [411], (des 1-8) A chain INSL3 analogue [253]</td>
<td>minimised relaxin-3 analogue 3 (pKi 7.6) [1706], R3-B1-22R (pIC50 7.4) [714]</td>
<td>minimised relaxin-3 analogue 3 (pIC50 6.6) [1706]</td>
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<td>Selective allosteric modulators</td>
<td>ML290 (A agonist) (pEC50 7) [2057, 2060]</td>
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<td>Labelled ligands</td>
<td>[33P]relaxin (human) (Agonist) (pKd 9.3–9.7) [678, 1812], [125I]relaxin (human) (Agonist) (pKd 10) [1340], [33P]relaxin (human) (Agonist) (pKd 9–9.2) [678, 1812]</td>
<td>[125I]relaxin-3 (human) (Agonist) (pKd 9.5) [1119], [125I]relaxin-3 (human) (Agonist) (pKd 9.3) [1117]</td>
<td>[125I]relaxin-3 (human) (Agonist) (pKd 8.7–9.7) [1118], [125I]relaxin-3 (human) (Agonist) (pKd 8.9) [1117], europium-labelled INSL5 (pKd 8.3) [714]</td>
<td>europium-labelled relaxin-3-B/INSL5 A chimera (Agonist) (pKd 8.9) [1117], europium-labelled relaxin-3-B/INSL5 A chimera is a fluorescent probe at this receptor (Kd=5nM) [714]. europium-labelled mouse INSL5 is a fluorescent ligand at this receptor (Kd=5nM) [120].</td>
</tr>
<tr>
<td>Comments</td>
<td>europium-labelled relaxin is a fluorescent ligand for this receptor (Kd=0.5nM) [1707].</td>
<td>europium-labelled INSL3 is a fluorescent ligand for this receptor (Kd=1nM) [1709].</td>
<td>europium-labelled relaxin-3-B/INSL5 A chimera and R3-B1-22R are fluorescent ligands for this receptor (Kd=5nM and 28nM) [714, 715].</td>
<td>europium-labelled relaxin-3-B/INSL5 A chimera is a fluorescent probe at this receptor (Kd=5nM) [714]. europium-labelled mouse INSL5 is a fluorescent ligand at this receptor (Kd=5nM) [120].</td>
</tr>
</tbody>
</table>

**Comments**: Relaxin has recently successfully completed a Phase III clinical trial for the treatment of acute heart failure. 48 hr infusion of relaxin reduced dyspnoea and 180 day mortality [1262]. Small molecule agonists active at RXFP1 receptors have been developed [1718, 2060], and one of these (ML290) is an allosteric agonist at RXFP1 [2060]. The antifibrotic actions of relaxin are dependent on the angiotensin receptor AT2, are absent in AT2 knockout mice, and are associated with heterodimer formation between RXFP1 and AT2 [330]. Mutations in INSL3 and LGR8 (RXFP2) have been reported in populations of patients with cryptorchidism [512]. Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, most of which do not bind relaxin family peptides [1340]. Splice variants of RXFP1 encoding the N-terminal LDLa module act as antagonists of RXFP1 signalling [1685, 1687]. cAMP elevation appears to be a major signalling pathway for RXFP1 and RXFP2 [795, 796].

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but RXFP1 also activates MAP kinases, nitric oxide signalling, tyrosine kinase phosphorylation and relaxin can interact with glucocorticoid receptors [68]. RXFP1 signalling involves lipid rafts, residues in the C-terminus of the receptor and activation of phosphatidylinositol-3-kinase [682]. More recent studies provide evidence that RXFP1 is pre-assembled in signalosomes with other signalling proteins including Goα, Gβγ and adenylyl cyclase 2 that display constitutive activity and are exquisitely sensitive to sub-picomolar concentrations of relaxin [679]. The cyclic AMP signalling pattern is highly dependent on the cell type in which RXFP1 is expressed [680].

The receptor expression profiles suggested that RXFP3 was a neu-ropetide receptor and RXFP4 a gut hormone receptor. Studies in rats and mice (including wildtype, and relaxin-3 and RXFP3 gene-deletion strains [671, 782, 1759, 1971] have revealed putative roles for the relaxin-3/RXFP3 system in the modulation of feeding [564, 566, 714, 1706, 1760], anxiety [1618, 2114], and reward and motivated, goal-directed behaviours [782, 1619, 1971], particularly in relation to the integration of stress and corticotrophin-releasing factor signalling [1162], with implications for the therapeutic treatment of clinical anxiety, depression, eating disorders and addiction (see [655, 1761] for review). Relaxin-3 (RLN3, Q8WXF3) acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 (Q8YSTQ6) is an agonist at RXFP4 and a weak antagonist at RXFP3. Unlike RXFP1 and RXFP2 both RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino acids at the N-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes [2027]. Recent studies suggest that INSL5 is an incretin secreted from enterodendocrine L cells and that the INLS5/RXFP4 system has roles in controlling food intake and glucose homeostasis [652]. RXFP3 couples to Gi/0 and inhibits adenylyl cyclase [1119, 2144], and also causes Erk1/2 phosphorylation [2144]. Relatively little is known about RXFP4 signalling but like RXFP3 it couples to inhibitory Gi/0 G-proteins [1120]. Recent studies suggest that relaxin (RLN2, P04090) also interacts with RXFP3 to cause a pattern of activation of signalling pathways that are a subset of those activated by relaxin-3 (RLN3, Q8WXF3). The two patterns of signaling observed in several cell types expressing RXFP3 are strong inhibition of forskolin-stimulated cyclic AMP accumulation, ERK1/2 activation and nuclear factor NF-κB reporter gene activation with relaxin-3 (RLN3, Q8WXF3), and weaker activity with relaxin (RLN2, P04090), porcine relaxin, or insulin-like peptide 3 (INLS3 (INLS3, P51460)) and a strong stimulation of activa-tor protein (AP)-1 reporter genes with relaxin (RLN2, P04090), and weaker activation with relaxin-3 (RLN3, Q8WXF3) or porcine relaxin [2144]. Thus at RXFP3, relaxin (RLN2, P04090) is a biased ligand compared to the cognate ligand relaxin-3 (RLN3, Q8WXF3). Two pharmacologically distinct ligand binding sites were also identified on RXFP3-expressing cells using [125I]relaxin-3-B/INSL5 A chimera which binds with high affinity and displays competition by relaxin-3 (RLN3, Q8WXF3) or a relaxin-3 (B chain) (RLN3, Q8WXF3) peptide, and [125I]relaxin (human) which displays competition by relaxin (RLN2, P04090), relaxin-3 (RLN3, Q8WXF3), or INLS3 (INLS3, P51460) and weakly by porcine relaxin.

Further Reading


Halls ML et al. (2015) International Union of Basic and Clinical Pharmacology. XCV. Recent advances in the understanding of the pharmacology and biological roles of relaxin family peptide receptors 1-4, the receptors for relaxin family peptides. Pharmacol Rev. 67: 389-440 [PMID:25761609]


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 (sst1-sst5; nomenclature as agreed by the NC-IUPHAR Subcommittee on Somatostatin Receptors [790]): Activation of these receptors produces a wide range of physiological effects throughout the body including the inhibition of secretion of many hormones. The relationship of the cloned receptors to endogenously expressed receptors is not yet well established in some cases. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14 (SSL, P61278)) and somatostatin-28 (SRIF-28 (SSL, P61278)). Cortistatin-14 (Mouse, Rat) has also been suggested to be an endogenous ligand for somatostatin receptors [404].

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### Nomenclature

<table>
<thead>
<tr>
<th>Receptor</th>
<th>HGNC, UniProt</th>
<th>Agonists</th>
<th>Selective agonists</th>
<th>Selective antagonists</th>
<th>Labelled ligands</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>sst1 receptor</td>
<td>SSTR1, P30872</td>
<td>pasireotide (plC50 8) [1669]</td>
<td>L-797,591 (pK&lt;sub&gt;i&lt;/sub&gt; 8.8) [1595], Des-Ala&lt;sub&gt;1,2,5&lt;/sub&gt;-[D-Trp&lt;sup&gt;8&lt;/sup&gt;, IAmp&lt;sup&gt;9&lt;/sup&gt;]SRIF (plC50 7.5) [484]</td>
<td>SRA880 (pK&lt;sub&gt;d&lt;/sub&gt; 8–8.1) [792]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>sst2 receptor</td>
<td>SSTR2, P30874</td>
<td>vapreotide (pK&lt;sub&gt;i&lt;/sub&gt; 8.3–10.1) [233, 1474], pasireotide (plC50 9) [1669]</td>
<td>L-054,522 (pK&lt;sub&gt;i&lt;/sub&gt; 11) [2084], BIM 23027 (plC50 10.9) [271], seglitide (pK&lt;sub&gt;i&lt;/sub&gt; 8.8–10.3) [233, 1474, 1736, 1737, 2084], octreotide (pK&lt;sub&gt;i&lt;/sub&gt; 8.7–9.9) [233, 1474, 1736, 1737, 2084]</td>
<td>[D-Tyr&lt;sup&gt;8&lt;/sup&gt;]CYN 154806 (pK&lt;sub&gt;d&lt;/sub&gt; 8.1–8.9) [1412]</td>
<td>[125&lt;sup&gt;II&lt;/sup&gt;Tyr&lt;sup&gt;3&lt;/sup&gt; SMS 201-995 (Agonist) (pK&lt;sub&gt;d&lt;/sub&gt; 9.9) [1736, 1737], [125&lt;sup&gt;II&lt;/sup&gt;BIM23027 (Agonist) (plC50 9.7) [772] – Rat</td>
<td>–</td>
</tr>
<tr>
<td>sst3 receptor</td>
<td>SSTR3, P32745</td>
<td>pasireotide (plC50 8.8) [1669], vapreotide (pK&lt;sub&gt;i&lt;/sub&gt; 7.4–7.9) [233, 1474, 1738]</td>
<td>L-796,778 (pK&lt;sub&gt;i&lt;/sub&gt; 7.6) [1595]</td>
<td>–</td>
<td>–</td>
<td>Troxler et al. (2010) describe the identification of non-peptidic, subtype-selective sst3 receptor antagonists [1907].</td>
</tr>
<tr>
<td>sst4 receptor</td>
<td>SSTR4, P31391</td>
<td>pasireotide (pK&lt;sub&gt;i&lt;/sub&gt; 8) [1132]</td>
<td>L-803,087 (pK&lt;sub&gt;i&lt;/sub&gt; 9.2) [1595]</td>
<td>NVP ACQ090 (pK&lt;sub&gt;i&lt;/sub&gt; 7.9) [793]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>sst5 receptor</td>
<td>SSTR5, P35346</td>
<td>vapreotide (pK&lt;sub&gt;i&lt;/sub&gt; 7.3–9.2) [233, 1265, 1474, 1736, 1737, 1738]</td>
<td>BIM 23052 (pK&lt;sub&gt;i&lt;/sub&gt; 7.4–9.6) [1265], L-817,818 (pK&lt;sub&gt;i&lt;/sub&gt; 9.4) [1595], BIM 23268 (pK&lt;sub&gt;i&lt;/sub&gt; 8.7) [1265]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Comments:** [125<sup>II</sup>Tyr<sup>11</sup>-SRIF-14, [125<sup>II</sup>Tyr<sup>11</sup>]-TTT-SRIF-28, [125<sup>II</sup>C]CGP 23996 and [125<sup>II</sup>Tyr<sup>10</sup>]-CST14 may be used to label somatostatin receptors nonselectively. A number of nonpeptide subtype-selective agonists have been synthesised [1595]. A novel peptide somatostatin analogue, somatoprim, 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 [1514, 1726].

**Further Reading**


### Succinate receptor

**G protein-coupled receptors** → Succinate receptor

**Overview:** Nomenclature as recommended by [NC-IUPHAR](#) [396].

<table>
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<tr>
<th>Nomenclature</th>
<th>succinate receptor</th>
</tr>
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<tr>
<td>HGNC, UniProt</td>
<td>SUCNR1, Q8BXA5</td>
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<tr>
<td>Endogenous agonists</td>
<td>succinic acid (pEC$_{50}$ 3.1–4.7) [728, 1785]</td>
</tr>
</tbody>
</table>

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### Tachykinin receptors

**G protein-coupled receptors** → Tachykinin receptors

**Overview:** Tachykinin receptors (provisional nomenclature as recommended by [NC-IUPHAR](#) [530]) are activated by the endogenous peptides substance P (TAC1, P20366) (SP), neurokinin A (TAC1, P20366) (NKA; previously known as substance K, neurokinin α, neuromedin L), neurokinin B (TAC3, Q9UHF0) (NKB; previously known as neurokinin β, neuromedin K), neuropeptide K (TAC1, P20366) and neuropeptide γ (TAC1, P20366) (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in *in vitro* pharmacology exist for all three receptors, in the context of nonpeptide ligands.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>NK$_1$ receptor</th>
<th>NK$_2$ receptor</th>
<th>NK$_3$ receptor</th>
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<tbody>
<tr>
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<td>TACR1, P25103</td>
<td>TACR2, P21452</td>
<td>TACR3, P29371</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>substance P (TAC1, P20366) &gt; neurokinin A (TAC1, P20366) &gt; neurokinin B (TAC3, Q9UHF0)</td>
<td>neurokinin A (TAC1, P20366) &gt; neurokinin B (TAC3, Q9UHF0) &gt; substance P (TAC1, P20366)</td>
<td>neurokinin B (TAC3, Q9UHF0) &gt; neurokinin A (TAC1, P20366) &gt; substance P (TAC1, P20366)</td>
</tr>
<tr>
<td>Agonists</td>
<td>substance P-OMe (pIC$_{50}$ 7.4–7.5) [1882]</td>
<td>[Lys$^5$, Me-Leu$^9$, Nle$^{10}$]NKA-(4-10) (pIC$<em>{50}$ 8.8–9.4) [1229] – Rat, GR64349 (pEC$</em>{50}$ 8.4) [407] – Rat, [βAla$^8$]neurokinin A-(4-10) (pK$_{d}$ 6) [477]</td>
<td>[βAla$^8$]neurokinin B (pK$<em>{d}$ 8.7–9.6) [1644, 1645], senktide (pK$</em>{d}$ 7.1–8.6) [1644, 1645, 1882]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>[Sar$^9$, Met(O$<em>{2}$)$</em>{2}$]$^{11}$SP (pIC$<em>{50}$ 9.7–9.9) [1882], [Pro$^9$]SP (pIC$</em>{50}$ 8.6) [1896] – Rat</td>
<td>[Lys$^5$, Me-Leu$^9$, Nle$^{10}$]NKA-(4-10) (pIC$<em>{50}$ 8.8–9.4) [1229] – Rat, GR64349 (pEC$</em>{50}$ 8.4) [407] – Rat, [βAla$^8$]neurokinin A-(4-10) (pK$_{d}$ 6) [477]</td>
<td>[βAla$^8$]neurokinin B (pK$<em>{d}$ 8.7–9.6) [1644, 1645], senktide (pK$</em>{d}$ 7.1–8.6) [1644, 1645, 1882]</td>
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**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

**Nomenclature**

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<thead>
<tr>
<th>Receptor</th>
<th>Selective Antagonists</th>
<th>Labelled Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK₁</td>
<td>aprepitant (pKᵢ 10.1) [673, 674], laneepitant (pKᵢ 9.8–10) [613], laneepitant (pIC₅₀ 9.8) [798], CP 99994 (pKᵢ 9.3–9.7) [50, 1645], casopitant (pKᵢ 9.4) [798, 1905], vestipitant (pKᵢ 9.4) [221, 418], nolpitantium (pIC₅₀ 8.9–9) [1882], RP67580 (pIC₅₀ 7.7) [528]</td>
<td>[¹²⁵I] L703,606 (Antagonist) (pKD 9.5) [537], [¹²⁵I] BH-[Sar⁹, Met⁰₂] SP (Agonist) (pKᵢ 9) [1901] – Rat, [³⁵S] SP (human, mouse, rat) (Agonist) (pKᵢ 8.6) [80], [¹²⁵I] SP (human, mouse, rat) (Agonist), [¹¹⁴C] SP (human, mouse, rat) (Agonist) [317]</td>
</tr>
<tr>
<td>NK₂</td>
<td>CR948000 (pKᵢ 9.8) [200], saredutant (pKᵢ 9.4–9.7) [50, 477, 1645], GR 159897 (pKD 7.8–9.5) [133, 477, 1770], MEN10627 (pKᵢ 9.2) [603], nepadutant (pKᵢ 8.5–8.7) [272, 343]</td>
<td>[³⁵S] saredutant (Antagonist) (pKᵢ 9.7) [649] – Rat, [¹²⁵I] NKA (human, mouse, rat) (Agonist) (pKᵢ 9.3) [1990], [³⁵S] GR100679 (Antagonist) (pKD 9.2) [669]</td>
</tr>
<tr>
<td>NK₃</td>
<td>osanetant (pKᵢ 8.4–9.7) [50, 110, 342, 476, 898, 1450, 1644, 1645, 1882], talnetant (pKᵢ 7.4–9) [129, 604, 1644, 1645], PD157672 (pIC₅₀ 7.8–7.9) [165, 1882]</td>
<td>[³⁵S] osanetant (Antagonist) (pKᵢ 9.9), [³⁵S] senktide (Agonist) (pKᵢ 8.1–8.7) [660] – Guinea pig, [¹²⁵I] [MePhe⁷]NKB (Agonist)</td>
</tr>
</tbody>
</table>

**Comments:** The NK₁ receptor has also been described to couple to other G proteins [1606]. The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to substance P (TAC1, P20366) on the NK₁ receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK₃ receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells [433, 1004].

**Further Reading**


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 [530]) are activated by the endogenous tripeptide TRH (TRH, P20396) (pGlu-His-ProNH₂). TRH (TRH, P20396) and TRH analogues fail to distinguish TRH₁ and TRH₂ receptors [1822]. [³H]TRH (human, mouse, rat) is able to label both TRH₁ and TRH₂ receptors with Kᵋ values of 13 and 9 nM respectively.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>TRH₁ receptor</th>
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<tbody>
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<td>HGNC, UniProt</td>
<td>TRHR, P34981</td>
<td>–</td>
</tr>
<tr>
<td>Antagonists</td>
<td>diazepam (pKᵋ 5.2) [444] – Rat</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>midazolam (pKᵋ 5.5) [444] – Rat, clordiazepoxide (pKᵋ 4.8) [444] – Rat, clordiazepoxide (pKᵋ 4.7) [1804] – Mouse</td>
<td>–</td>
</tr>
<tr>
<td>Comments</td>
<td>–</td>
<td>A class A G protein-coupled receptor: not present in man</td>
</tr>
</tbody>
</table>

Further Reading


Trace amine receptor

G protein-coupled receptors → Trace amine receptor

**Overview:** Trace amine-associated receptors were initially discovered as a result of a search for novel 5-HT receptors [185], where 15 mammalian orthologues were identified and divided into two families. The TA₁ receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee for the Trace amine receptor [1181]) has been shown to have affinity for the endogenous trace amines tyramine, β-phenylethylamine and octopamine in addition to the classical amine dopamine [185]. Emerging evidence suggests that TA₁ is a modulator of monoaminergic activity in the brain [2062] with TA₁ and dopamine D₂ receptors shown to form constitutive heterodimers when co-expressed [492]. In addition to trace amines, receptors can be activated by amphetamine-like psychostimulants, and endogenous thyronamines such as thyronamine and 3-iodothyronamine.

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Nomenclature | TA₁ receptor  
HGNC, UniProt | TAAR1, Q96RJ0  
Rank order of potency | tyramine > β-phenylethylamine > octopamine = dopamine [185]  
Agonists | ROS166017 (pEC₅₀ 7.3) [1574]  
Antagonists | EPPTB (Inverse agonist) (pIC₅₀ 5.1) [199]  
Labelled ligands | [³H]tyramine (Agonist) (pKₐ 7.7) [185]  

**Comments:** In addition to TA₁, analysis has shown that in man there are up to 5 functional TAAR genes (TAAR2,5,6,8,9). See [185] for detailed discussion. The product of the gene TAAR2 (also known as GPR58) appears to respond to β-phenylethylamine > tyramine and to couple through Gs [185]. TAAR3, in some individuals, and TAAR4 are pseudogenes in man, although functional in rodents. The signalling characteristics and pharmacology of TAAR5 (PNR, Putative Neurotransmitter Receptor: TAAR5, O14804), TAAR6 (Trace amine receptor 4, TaR-4: TAAR6, 96RI8), TAAR8 (Trace amine receptor 5, GPR102: TAAR8, Q969N4) and TAAR9 (trace amine associated receptor 9: TAAR9, 96RI9) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have been shown to have affinity for rodent cloned trace amine receptors, including TA₁ [1657]. An antagonist EPPTB has recently been described that has a pKᵢ of 9.1 at the mouse TA₁ but less than 5.3 for human TA₁ [1792].

**Further Reading**


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 [439, 340, 1952]) is activated by the endogenous dodecapeptide urotensin-II (UTS2, Q95399), originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [134]. Several structural forms of U-II exist in fish and amphibians. The Goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene gpr14 [375, 1130, 1327, 1410]. Human urotensin-II (UTS2, Q95399), an 11-amino-acid peptide [375], retains the cyclo-hexapeptide sequence of goby U-II that is thought to be important in ligand binding [219, 957]. 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 [374]. A second endogenous ligand for UT has been discovered in rat [1816]. 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.

<table>
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</tr>
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<tr>
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<tr>
<td>Endogenous agonists</td>
<td>urotensin II-related peptide (UTS2B, Q76510) (pKᵩ 9.6) [1179], urotensin-II (UTS2, Q95399) (pKᵩ 8.6) [440, 475, 647]</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>[Pen5]-U (4-11) (human) (pKᵩ 9.7) [647], U-II-(4-11) (human) (pKᵩ 9.6) [647], FL104 (pEC5₀ 5.8–7.5) [1075, 1077], AC-7954 (pKᵩ 6.6) [382, 1076]</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>urantide (pKᵩ 8.3) [1469], SB-706375 (pKᵩ 8) [440], palosuran (pIC5₀ 7.1) [353], SB-611812 (pKᵩ 6.6) [1550]</td>
</tr>
<tr>
<td>Labelled ligands</td>
<td>[125I]U-II (human) (Agonist) (pKᵩ 9.4–9.6) [42, 1179]</td>
</tr>
</tbody>
</table>

**Comments:** In human vasculature, human urotensin-II (UTS2, Q95399) elicits both vasoconstrictor (pD₂ 9.3-10.1, [1179]) and vasodilator (pIC₅₀ 10.3-10.4, [1800]) responses.

**Further Reading**


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 [340]) 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).
**Nomenclature**

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<thead>
<tr>
<th>Receptor</th>
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<tbody>
<tr>
<td>V1A receptor</td>
<td>AVPR1A, P37288</td>
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<tr>
<td>V1B receptor</td>
<td>AVPR1B, P47901</td>
</tr>
<tr>
<td>V2 receptor</td>
<td>AVPR2, P30518</td>
</tr>
<tr>
<td>OT receptor</td>
<td>OXTR, P30559</td>
</tr>
</tbody>
</table>

**Endogenous agonists**

- Vasopressin (AVP, P01185) (pKᵦ 8.5–9.3)
- Vasopressin (AVP, P01185) (pKᵦ 9–9.5)
- Vasopressin (AVP, P01185) (pKᵦ 7.9–9.1)

**Selective agonists**

- d[Leu⁴]LVP (pKᵦ 9.8) [1485]
- d[Cha⁴]AVP (pKᵦ 9–9.7) [415, 468]

**Selective antagonists**

- Conivaptan (pKᵦ 8.2–8.4) [1839, 1840]
- Tolvaptan (pKᵦ 9–9.4) [355, 381, 432, 472, 485, 520]
- SSRI26768A (pKᵦ 8.8–9.1) [1701]

**Labelled ligands**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>[¹²⁵]I-OH-LVA (Antagonist) (pKᵦ 10.3–10.4)</td>
<td>[319, 369, 1501]</td>
</tr>
<tr>
<td>[³⁵]SAVP (human, mouse, rat) (Antagonist) (pKᵦ 8.6–9.6)</td>
<td>[208, 319, 369, 370, 1359, 1501, 1627, 1839, 1840, 1870, 1871, 1910, 2073]</td>
</tr>
<tr>
<td>[³⁵]I [d(CH₂)₅[Tyr(Me)²,Arg⁸]AVP (Antagonist) (pKᵦ 9)</td>
<td></td>
</tr>
<tr>
<td>[³⁵]I [d(CH₂)₅[Tyr(Me)²,Arg⁸]AVP (Antagonist) (pKᵦ 9)</td>
<td></td>
</tr>
<tr>
<td>[³⁵]I [d(CH₂)₅[Tyr(Me)²,Arg⁸]AVP (Antagonist) (pKᵦ 9)</td>
<td></td>
</tr>
</tbody>
</table>

**Comments:** The V2 receptor exhibits marked species differences, such that many ligands (d[CH₂]₅[D-ile²,ile⁴]AVP and [³⁵]I [d(Gly-NH₂-NH₂-D-ile²,ile⁴]VP) exhibit low affinity at human V2 receptors [29]. Similarly, [³⁵]I [d(D-Arg⁸]VP is V₂ selective in the rat, not in the human [1627]. The gene encoding the V₂ receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [148]. D[Cha⁴]AVP is selective only for the human and bovine V₁b receptors [415], while d[Leu⁴]LVP has high affinity for the rat V₁b receptor [1485].

**Further Reading**


Koshimizu TA et al. (2012) Vasopressin V1a and V1b receptors: from molecules to physiological systems. Physiol. Rev. 92: 1813–64 [PMID:23073632]


VIP and PACAP receptors

G protein-coupled receptors \(\rightarrow\) 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 \([704, 705]\)) 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)). VPAC1 and VPAC2 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 \(\sim 100\) fold more potent than VIP (VIP, P01282) as agonists of most isoforms of the PAC1 receptor. However, one splice variant of the human PAC1 receptor has been reported to respond to PACAP-38 (ADCYAP1, P18509), PACAP-27 (ADCYAP1, P18509) and VIP (VIP, P01282) with comparable affinity \([393]\). PG 99-465 \([1320]\) has been used as a selective VPAC2 receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC1 and PAC1 receptors \([422]\). The selective PAC1 receptor agonist maxadilan, was extracted from the salivary glands of sand flies \((Lutzomyia longipalpis)\) and has no sequence homology to VIP (VIP, P01282) or the PACAP peptides \([1330]\). Two deletion variants of maxadilan, M65 \([1918]\) and Max.d.4 \([1331]\) have been reported to be PAC1 receptor antagonists, but these peptides have not been extensively characterised.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>PAC1 receptor</th>
<th>VPAC1 receptor</th>
<th>VPAC2 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>ADCYAP1R1, P41586</td>
<td>VIPR1, P32241</td>
<td>VIPR2, P41587</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>PACAP-27 (ADCYAP1, P18509), PACAP-38 (ADCYAP1, P18509) (\gg) VIP (VIP, P01282)</td>
<td>PACAP-27 (ADCYAP1, P18509), PACAP-38 (ADCYAP1, P18509) (\gg) GHRH (GHRH, P01286), PHI (Pig), secretin (SCT, P09683)</td>
<td>PACAP-27 (ADCYAP1, P18509), PACAP-38 (ADCYAP1, P18509) (\gg) PHI (Pig), secretin (SCT, P09683)</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>maxadilan (pEC50 10.3) ([422]), maxadilan (pEC50 6.2) ([422])</td>
<td>[Lys15,Arg16,Leu27-VIP-(1-7)/GRF-(8-27)-NH2 (pEC50 8.3) ([1315]), [Ala11,22,28-VIP (pKd 8.1) ([1393])</td>
<td>Ro 25-1553 (pIC50 7.8–9.5) ([634, 887, 1315]), Ro 25-1392 (pKd 8) ([2056])</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>–</td>
<td>PG 97-269 (pIC50 8.7) ([633, 887])</td>
<td>–</td>
</tr>
</tbody>
</table>

Comments: Subtypes of PAC1 receptors have been proposed based on tissue differences in the potencies of PACAP-27 (ADCYAP1, P18509) and PACAP-38 (ADCYAP1, P18509), or from alternative splicing of PAC1 receptor mRNA \([1788]\).

Further Reading


Searchable database: http://www.guidetopharmacology.org/index.jsp
353. Clozel M et al. (2004) [15146030]
354. Clozel M et al. (1994) [8035319]
355. Clozel M et al. (1997) [11284713]
356. Cohen JA et al. (2001) [21520239]
357. Combadière C et al. (1995) [8530354]
359. Commini D et al. (1996) [8670200]
360. Commini D et al. (1999) [10578132]
361. Comp-Agrar L et al. (2011) [21552208]
362. Conigrove AD et al. (2000) [10781086]
363. Conn PM et al. (1982) [6282571]
364. Conroy JL et al. (2015) [25660762]
365. Cooray SN et al. (2013) [24108853]
366. Corbett DF et al. (2005) [16002289]
367. Costantino G et al. (2001) [11249114]
368. Costes N et al. (2005) [16330560]
369. Cotte N et al. (2000) [10868830]
370. Cotte N et al. (1998) [9792651]
371. Cottingham C et al. (2011) [21859713]
372. Coulie B et al. (2001) [11461914]
373. Coulin F et al. (1997) [9346309]
374. Couluar Y et al. (1999) [10486537]
375. Couluar Y et al. (1998) [9861051]
376. Cox BM et al. (2013) [24528283]
377. Cox CD et al. (2010) [20565975]
378. Cox HM et al. (1995) [8590988]
379. Coy DH et al. (1996) [8993400]
380. Croker DE et al. (2013) [24060963]
381. Crobbe AL et al. (2010) [20471658]
382. Croston GE et al. (2002) [12408704]
383. Croy CH et al. (2014) [24807965]
384. Cunha RA et al. (1999) [8692800]
385. Curtis AE et al. (2010) [19934405]
386. D’Amato M et al. (2007) [17854592]
387. Dairaghi DJ et al. (1999) [10419462]
388. Dalpiaz A et al. (1998) [9827575]
389. Daniels DV et al. (1999) [10334511]
390. Dardonneau C et al. (2004) [15224384]
391. Daugherty BL et al. (1996) [8642344]
392. Dartzenberg FM et al. (2004) [15450949]
393. Dartzenberg FM et al. (1999) [10583729]
394. Dartzenberg FM et al. (2001) [11123370]
et al. (1998) [19154445]
2132. Zhu Y et al. (2001) [11179436]
2133. Zobel AW et al. (2000) [10867111]
2134. Zoffmann S et al. (2001) [11170631]
2135. Zygmunt PM et al. (1999) [10440374]
2136. af Forselles KJ et al. (2011) [21595651]
2137. de Gasparo M et al. (2000) [10977869]
2138. de Gasparo M et al. (1995) [8577935]
2140. de Lau W et al. (2011) [21727895]
2141. de Ligt RA et al. (2005) [15740718]
2142. de Paulis T et al. (2006) [16722652]
2143. van Muilwijk-Koezen JE et al. (2000) [10841801]
2144. van der Westhuisen ET et al. (2010) [20159943]
2145. von Geldern TW et al. (1999) [10479298]
2146. von Kügelgen I et al. (2011) [21586365]
2147. (1988) [3071214]