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

Stephen PH Alexander, Arthur Christopoulos, Anthony P Davenport, Eamonn Kelly, Alistair Mathie, John A Peters, Emma L Veale, Jane F Armstrong, Elena Faccenda, Simon D Harding, Adam JPawson, Joanna L Sharman, Christopher Southan, Jamie A Davies, Simon DHarding, Elena Faccenda, Christopher Southan, Jamie A Davies, S.P.H. Alexander, John A Peters, Stephen PH Alexander, Arthur Christopoulos, Anthony P Davenport, Eamonn Kelly, Alistair Mathie, John A Peters, Emma L Veale, Jane F Armstrong, Elena Faccenda, Simon D Harding, Adam JPawson, Joanna L Sharman, Christopher Southan, Jamie A Davies, Simon DHarding

Abstract

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

Conflict of interest

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

© 2019 The Authors. British Journal of Pharmacology published by John Wiley & Sons Ltd on behalf of The British Pharmacological Society.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

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 (c.400), taste (33), light perception (10) and pheromone signalling (5) [1479]. The remaining 350 non-sensory GPCRs mediate signalling by ligands that range in size from small molecules to peptides to large proteins; they are the targets for the majority of drugs in clinical usage [1642, 1772], although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs [1129] divided them, on the basis of sequence homology, into six classes. These

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
classes and their prototype members were as follows: **Class A** (rhodopsin-like), **Class B** (secretin receptor family), **Class C** (metabotropic glutamate), **Class D** (fungal mating pheromone receptors), **Class E** (cyclic AMP receptors) and **Class F** (frizzled/smoothened). Of these, classes D and E are not found in vertebrates. An alternative classification scheme "GRAFS" [1890] divides vertebrate GPCRs into five classes, overlapping with the A-F nomenclature, viz:

**Glutamate family (class C)**, which includes metabotropic glutamate receptors, a calcium-sensing receptor and GABA<sub>B</sub> receptors, as well as three taste type 1 receptors and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man [1479].

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

**Adhesion family** GPCRs are phylogenetically related to class B receptors, from which they differ by possessing large extracellular N-termini that are autoproteolytically cleaved from their 7TM domains at a conserved "GPCR proteolysis site" (GPS) which lies within a much larger (320 residue) "GPCR autoproteolysis-inducing" (GAIN) domain, an evolutionary ancient motif also found in polycystic kidney disease 1 (PKD1)-like proteins, which has been suggested to be both required and sufficient for autoproteolysis [1743].

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

**Secretin family**, encoded by 15 genes in humans. The ligands for receptors in this family are polypeptide hormones of 27-141 amino acid residues; nine of the mammalian receptors respond to ligands that are structurally related to one another (glucagon, glucagon-like peptides (GLP-1, GLP-2), glucose-dependent insulinotropic polypeptide (GIP), secretin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and growth-hormone-releasing hormone (GHRH)) [811].

**GPCR families**

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

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

Much of our current understanding of the structure and function of GPCRs is the result of pioneering work on the visual pigment rhodopsin and on the β<sub>2</sub> adrenoceptor, the latter culminating in the award of the 2012 Nobel Prize in chemistry to Robert Lefkowitz and Brian Koblika [1121, 1244].

**Pseudogenes**

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

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

**Olfactory receptors**

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

Kenakin T. (2018) Is the Quest for Signaling Bias Worth the Effort? Mol. Pharmacol. 93: 266-269 [PMID:29348268]

Michel MC et al. (2018) Biased Agonism in Drug Discovery—Is It Too Soon to Choose a Path? Mol. Pharmacol. 93: 259-265 [PMID:29326242]

Roth BL et al. (2017) Discovery of new GPCR ligands to illuminate new biology. Nat. Chem. Biol. 13: 1143-1151 [PMID:29045379]

Sriram K et al. (2018) G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs? Mol. Pharmacol. 93: 251-258 [PMID:29298813]

Family structure

Orphan and other 7TM receptors

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

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

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
Class A Orphans

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

Overview: Table 1 lists a number of putative GPCRs identified by NC-IUPHAR [612], for which preliminary evidence for an endogenous ligand has been published, or for which there exists a potential link to a disease, or disorder. These GPCRs have recently been reviewed in detail [455]. The GPCRs in Table 1 are all Class A, rhodopsin-like GPCRs. Class A orphan GPCRs not listed in Table 1 are putative GPCRs with as-yet unidentified endogenous ligands.

Table 1: Class A orphan GPCRs with putative endogenous ligands

| GPR3 | GPR4 | GPR6 | GPR12 | GPR15 | GPR17 | GPR20 |
|------|------|------|-------|-------|-------|-------|
| GPR22 | GPR26 | GPR31 | GPR34 | GPR35 | GPR37 | GPR39 |
| GPR50 | GPR63 | GPR65 | GPR68 | GPR75 | GPR84 | GPR87 |
| GPR88 | GPR132 | GPR149 | GPR161 | GPR183 | LGR4 | LGR5 |
| LGR6 | MAS1 | MGRPRD | MGRPRX1 | MGRPRX2 | P2RY10 | TAAR2 |

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

Nomenclature
HGNC, UniProt
GPR3
GPR3, P46089
Agonists
diphenyleneiodonium chloride [2388]
GPR4
GPR4, P46093
–
–
GPR6
GPR6, P46095
–
–
Endogenous ligands
–
–
–
Comments
Sphingosine 1-phosphate was reported to be an endogenous agonist [2168], but this finding was not replicated in subsequent studies [2389]. Reported to activate adenylyl cyclase constitutively through Gαs [545]. Gene disruption results in premature ovarian ageing [1234], reduced β-amyloid deposition [2112] and hypersensitivity to thermal pain [1837] in mice. First small molecule inverse agonist [993] and agonists identified [2386]
An initial report suggesting activation by lysophosphatidylcholine and sphingosylphosphorylcholine [2440] has been retracted [1597]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [455, 1932]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [2377]. Negative allosteric modulators of GPR4 have been reported [2137].
An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC50 value of 39nM) [941, 2168] was not repeated in arrestin-based assays [2015, 2389]. Reported to activate adenylyl cyclase constitutively through Gαs and to be located intracellularly [1644]. GPR6-deficient mice showed reduced striatal cyclic AMP production in vitro and selected alterations in instrumental conditioning in vivo. [1309].
### GPR12
- HGNC: GPR12
- UniProt: P47775

**Endogenous agonists**
- UDP-glucose [143, 395], LTC₄ [395], UDP-galactose [143, 395], uridine diphosphate [143, 395], LTD₄ [395]

**Comments**
- Reports that sphingosine 1-phosphate is a ligand of GPR12 [940, 2168], have not been replicated in arrestin-based assays [2015, 2389]. Gene disruption results in dyslipidemia and obesity [170].
- Reported to act as a co-receptor for HIV [541]. In an infection-induced colitis model, Gpr17 knockout mice were more prone to tissue damage and inflammatory cytokine expression [1089].

### GPR15
- HGNC: GPR15
- UniProt: P49685

**Endogenous agonists**
- –

**Comments**
- Reported to act as a co-receptor for HIV [541].

### GPR17
- HGNC: GPR17
- UniProt: Q13304

**Endogenous agonists**
- UDP-glucose [143, 395], LTC₄ [395], UDP-galactose [143, 395], uridine diphosphate [143, 395], LTD₄ [395]

**Comments**
- Reported to be a dual leukotriene and uridine diphosphate receptor [395]. Another group instead proposed that GPR17 functions as a negative regulator of the CysLT₁ receptor response to leukotriene D₄ (LTD₄). For further discussion, see [455]. Reported to antagonize CysLT₁ receptor signalling in vivo and in vitro [1350]. See reviews [280] and [455].

### GPR19
- HGNC: GPR19
- UniProt: Q15760

### GPR20
- HGNC: GPR20
- UniProt: Q99678

**Agonists**
- adropin (ENHO, Q6UWT2) [1770]

**Comments**
- Reported to inhibit adenylyl cyclase constitutively through Gᵢ/o [817]. Gpr20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [230].

### GPR21
- HGNC: GPR21
- UniProt: Q99679

**Agonists**
- –

**Comments**
- 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 [1639].

### GPR22
- HGNC: GPR22
- UniProt: Q99680

**Agonists**
- –

**Comments**
- Gene disruption results in increased severity of functional decompensation following aortic banding [10]. Identified as a susceptibility locus for osteoarthritis [574, 1072, 2187].

### GPR25
- HGNC: GPR25
- UniProt: O00155

**Agonists**
- –

**Comments**
- Has been reported to activate adenylyl cyclase constitutively through Gₛ [1016]. Gpr26 knockout mice show increased levels of anxiety and depression-like behaviours [2421].

### GPR26
- HGNC: GPR26
- UniProt: Q8NDV2

**Agonists**
- –

**Comments**
- Knockdown of Gpr27 reduces endogenous mouse insulin promoter activity and glucose-stimulated insulin secretion [1160].

### GPR27
- HGNC: GPR27
- UniProt: Q9NS67

**Agonists**
- –

**Comments**
- –

---

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

**Full Contents of ConciseGuide**: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
| Nomenclature | GPR31 | GPR32 | GPR33 | GPR34 |
|--------------|-------|-------|-------|-------|
| HGNC, UniProt| GPR31, O00270 | GPR32, Q75388 | GPR33, Q49SQ1 | GPR34, Q9UPCS |
| Potency order of endogenous ligands | – | resolvin D1 > LXA₄ | – | – |
| Endogenous agonists | 12S-HETE [769] – Mouse | resolvin D1 [1153], LXA₄ [1153] | – | lysophosphatidylserine [1107, 2054] |
| Labelled ligands | – | [³H]resolvin D1 (Agonist) [1153] | – | – |
| Comments | See [455] for discussion of pairing. | Resolvin D1 has been demonstrated to activate GPR32 in two publications [366, 1153]. The pairing was not replicated in a recent study based on arrestin recruitment [2015]. GPR32 is a pseudogene in mice and rats. See reviews [280] and [455]. | GPR33 is a pseudogene in most individuals, containing a premature stop codon within the coding sequence of the second intracellular loop [1845]. | 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 [2015]. Fails to respond to a variety of lipid-derived agents [2389]. Gene disruption results in an enhanced immune response [1277]. Characterization of agonists at this receptor is discussed in [945] and [455]. |

| Nomenclature | GPR35 | GPR37 |
|--------------|-------|-------|
| HGNC, UniProt| GPR35, Q9HC97 | GPR37, O15354 |
| Endogenous agonists | 2-oleoyl-LPA [1626], kynurenic acid [2015, 2253] | – |
| Agonists | – | neuropeptide head activator [1795] |
| 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 [1162]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [1626] but these results were not replicated in an arrestin assay [2015]. The phosphodiesterase inhibitor zaprinast [2105] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signalling [2105]. GPR35 is also activated by the pharmaceutical adjunct pamoic acid [2432]. See reviews [455] and [502]. | Reported to associate and regulate the dopamine transporter [1382] and to be a substrate for parkin [1380]. Gene disruption results in altered striatal signalling [1381]. The peptides prosaptide and prosaposin are proposed as endogenous ligands for GPR37 and GPR37L1 [1438]. |
### GPR37L1, GPR39, GPR45, GPR50

**Endogenous agonists**
- Zn\(^{2+}\) has been reported to be a potent and efficacious agonist of human, mouse and rat GPR39 [2383].
- 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 [315]. Gene disruption results in obesity and altered adipocyte metabolism [1696]. Reviewed in [455].

GPR50 is structurally related to MT\(_1\) and MT\(_2\) melatonin receptors, with which it heterodimerises constitutively and specifically [1265]. Gpr50 knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [126].

### GPR52, GPR61, GPR62, GPR63

**Endogenous ligands**
- Protons

**Allosteric modulators**
- ogerin (Positive) (pK\(_B\) 5) [925], lorazepam (Positive) [925]

**Comments**
- First small molecule agonist reported [1931].
- Sphingosine 1-phosphate and dioleoylphosphatidic acid have been reported to be low affinity agonists for GPR63 [1584] but this finding was not replicated in an arrestin-based assay [2389].
- GPR68 was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [2358], but the original publication has been retracted [2357]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [455, 1932]. A family of 3,5-disubstituted isoxazoles were identified as agonists of GPR68 [1839].
### Nomenclature

| GPR75 | GPR78 | GPR79 | GPR82 |
|-------|-------|-------|-------|
| HGNC, UniProt | HGNC, UniProt | HGNC, UniProt | HGNC, UniProt |
| GPR75, Q95800 | GPR78, Q96P69 | GPR79, – | GPR82, Q96P67 |

### Comments

- **CCL5 (CCL5, P13501)** was reported to be an agonist of GPR75 [942], but the pairing could not be repeated in an arrestin assay [2015].
- GPR78 has been reported to be constitutively active, coupled to elevated cAMP production [1016].
- Mice with Gpr82 knockout have a lower body weight and body fat content associated with reduced food intake, decreased serum triglyceride levels, as well as higher insulin sensitivity and glucose tolerance [558].

### Nomenclature

| GPR83 | GPR84 | GPR85 | GPR87 | GPR88 | GPR101 |
|-------|-------|-------|-------|-------|-------|
| HGNC, UniProt | HGNC, UniProt | HGNC, UniProt | HGNC, UniProt | HGNC, UniProt | HGNC, UniProt |
| GPR83, Q9NYM4 | GPR84, Q9NQ5S | GPR85, P60893 | GPR87, Q9BY21 | GPR88, Q9GZN0 | GPR101, Q96P66 |

### Endogenous agonists

- **Endogenous agonists**
  - GPR83
  - GPR84
  - GPR85
  - GPR87
  - GPR88
  - GPR101

### Agonists

- **Agonists**
  - PEN {Mouse} [719]
  -Mouse, Zn\(^{2+}\) [1531]
  - Medium chain free fatty acids with carbon chain lengths of 9-14 activate GPR84 [2064, 2254]. A surrogate ligand for GPR84, 6-n-octylaminouracil has also been proposed [2064]. See review [455] for discussion of classification. Mutational analysis and molecular modelling of GPR84 has been reported [1588].

### Comments

- One isoform has been implicated in the induction of CD4(+) CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [803]. The extracellular N-terminal domain is reported as an intramolecular inverse agonist [1532].
- Proposed to regulate hippocampal neurogenesis in the adult, as well as neurogenesis-dependent learning and memory [352].
- Gene disruption results in altered striatal signalling [1312]. Small molecule agonists have been reported [163].
- Mutations in GPR101 have been linked to gigantism and acromegaly [2154].
### Nomenclature

|                   | GPR132 | GPR135 | GPR139 | GPR141 | GPR142 | GPR146 |
|-------------------|--------|--------|--------|--------|--------|--------|
| HGNC, UniProt     | GPR132, Q9UNW8 | GPR135, Q8IZ08 | GPR139, Q6DWJ6 | GPR141, Q7Z602 | GPR142, Q7Z601 | GPR146, Q96CH1 |

### Endogenous ligands

- Protons

### Comments

- GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [455, 1932]. Reported to respond to lysophosphatidylcholine [1027], but later retracted [2321].
- Peptide agonists have been reported [953].
- Small molecule agonists have been reported [2138, 2407].
- 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 [2404].

### Nomenclature

|                   | GPR148 | GPR149 | GPR150 | GPR151 | GPR152 | GPR153 |
|-------------------|--------|--------|--------|--------|--------|--------|
| HGNC, UniProt     | GPR148, Q8TDV2 | GPR149, Q86SP6 | GPR150, Q8NGU9 | GPR151, Q8TDV0 | GPR152, Q8TDT2 | GPR153, Q6NV75 |

### Comments

- Gpr149 knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [542].
- GPR151 responded to galanin with an EC$_{50}$ value of 2 μM, suggesting that the endogenous ligand shares structural features with galanin (GAL, P22460) [939].

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

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
### Nomenclature

| Gene   | HGNC, UniProt                  | Comments |
|--------|-------------------------------|----------|
| GPR161 | GPR161, Q8N6U8                | A C-terminal truncation (deletion) mutation in Gpr161 causes congenital cataracts and neural tube defects in the vacuolated lens (vl) mouse mutant [1403]. The mutated receptor is associated with cataract, spina bifida and white belly spot phenotypes in mice [1140]. Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish [1261]. |
| GPR162 | GPR162, Q16538                |          |
| GPR171 | GPR171, O14626                | 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 [718]. |
| GPR173 | GPR173, Q9NS66                |          |

### Nomenclature

| Gene   | HGNC, UniProt                  | Comments |
|--------|-------------------------------|----------|
| GPR174 | GPR174, Q9BXC1                |          |
| GPR176 | GPR176, Q14439                |          |
| GPR182 | GPR182, O15218                | Rat GPR182 was first proposed as the adrenomedullin receptor [1041]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [1070] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [831]. |
| GPR183 | GPR183, P32249                | 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 [799, 1301]. Gpr183-deficient mice show a reduction in the early antibody response to a T-dependent antigen. GPR183-deficient B cells fail to migrate to the outer follicle and instead stay in the follicle centre [1062, 1685]. |

### Endogenous agonists

- lysophosphatidylserine [949]
- 7α,25-dihydroxycholesterol [799, 1301], 7α,27-dihydroxycholesterol [1301], 7β, 25-dihydroxycholesterol [1301], 7β, 27-dihydroxycholesterol [1301]

### Searchable database:

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

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

S.P.H. Alexander et al. The Concise Guide to PHARMACOLOGY 2019/20: G protein-coupled receptors. *British Journal of Pharmacology* (2019) 176, S21–S141
### Nomenclature

| LGR4 | HGNC, UniProt | LGR5 | HGNC, UniProt | LGR6 | HGNC, UniProt |
|------|--------------|------|--------------|------|--------------|
|     | LGR4, Q9BX81 |     | LGR5, Q75473 |     | LGR6, Q9HBX8 |

### Endogenous agonists

| R-spondin-2 (RSPO2, Q6UXX9) | [305], R-spondin-1 (RSPO1, Q2MKA7) | [305], R-spondin-3 (RSPO3, Q9BXY4) | [305], R-spondin-4 (RSPO4, Q2I0MS) | [305] |

### Comments

LGR4 does not couple to heterotrimeric G proteins or recruit arrestins when stimulated by the R-spondins, indicating a unique mechanism of action. R-spondins bind to LGR4, which specifically associates with Frizzled and LDL receptor-related proteins (LRPs) that are activated by the extracellular Wnt molecules and then trigger canonical Wnt signalling to increase gene expression [305, 467, 1834]. Gene disruption leads to multiple developmental disorders [1002, 1329, 2011, 2284].

The four R-spondins can bind to LGR4, LGR5, and LGR6, which specifically associate with Frizzled and LDL receptor-related proteins (LRPs), proteins that are activated by extracellular Wnt molecules and which then trigger canonical Wnt signalling to increase gene expression [305, 467].

---

### Nomenclature

| MAS1 | HGNC, UniProt | MAS1L | HGNC, UniProt |
|------|--------------|-------|--------------|
|     | MAS1, P04201 |     | MAS1L, P35410 |

### Agonists

angiotensin-(1-7) (AGT, P01019) [707] – Mouse

---

### Nomenclature

| MRGPRD | HGNC, UniProt | MRGPRE | HGNC, UniProt | MRGPRF | HGNC, UniProt | MRGPRG | HGNC, UniProt |
|--------|--------------|--------|--------------|--------|--------------|--------|--------------|
| MRGPRD, Q8TDS7 | | MRGPRE, Q86SM8 | | MRGPRF, Q96AM1 | | MRGPRG, Q86SMS | |

### Endogenous agonists

β-alanine [1958, 2015]

### Comments

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\(^7\)-angiotensin-(1-7), β-alanine and PD123319 [1208]. Genetic ablation of MRGPRD- neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [322]. See reviews [455] and [2009].

MRGPRF has been reported to respond to stimulation by angiotensin metabolites [678]. See reviews [455] and [2009].

See reviews [455] and [2009].
### MRGPRX1, MRGPRX2, MRGPRX3, MRGPRX4, P2RY8, P2RY10

| Nomenclature | HGNC, UniProt |
|--------------|--------------|
| MRGPRX1 | MRGPRX1, Q96LB2 |
| MRGPRX2 | MRGPRX2, Q96LB1 |
| MRGPRX3 | MRGPRX3, Q96LB0 |
| MRGPRX4 | MRGPRX4, Q96LA9 |
| P2RY8 | P2RY8, Q86VZ1 |
| P2RY10 | P2RY10, Q00398 |

**Endogenous agonists**
- bovine adrenal medulla peptide 8-22 \((\text{PENK, P01210})\) [347, 1253, 2015]
- PAMP-20 \((\text{ADM, P35318})\) [1035]

**Agonists**
- cortistatin-14 \((\text{Mouse, Rat})\) [1035, 1202, 1815, 2015]
- PAMP-12 (human) [1035]

**Selective agonists**
- PAMP-12 (human) [1035]

**Comments**
- Reported to mediate the sensation of itch [1305, 1969]. Reports that bovine adrenal medulla peptide 8-22 \((\text{PENK, P01210})\) was the most potent of a series of proenkephalin A-derived peptides as an agonist of MRGPRX1 in assays of calcium mobilisation and radioligand binding [1253] were replicated in an independent study using an arrestin recruitment assay [2015]. See reviews [455] and [2009].
- 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 [1815], also confirmed in an independent study using an arrestin recruitment assay [2015]. See reviews [455] and [2009].

### TAAR2, TAAR3, TAAR4P, TAAR5, TAAR6, TAAR8, TAAR9

| Nomenclature | HGNC, UniProt |
|--------------|--------------|
| TAAR2 | TAAR2, Q9P1P5 |
| TAAR3 | TAAR3P, Q9P1P4 |
| TAAR4P | TAAR4P, – |
| TAAR5 | TAAR5, O14804 |
| TAAR6 | TAAR6, Q96R18 |
| TAAR8 | TAAR8, Q96N4 |
| TAAR9 | TAAR9, Q96R19 |

**Potency order of endogenous ligands**
- β-phenylethylamine > tryptamine [205]

**Comments**
- Probable pseudogene in 10–15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [455].
- TAAR3 is thought to be a pseudogene in man though functional in rodents [455].
- Pseudogene in man but functional in rodents [455].
- Trimethylamine is reported as an agonist [2242] and 3-iodothyronamine an inverse agonist [499].
- Trimethylamine is reported as an agonist [2242] and 3-iodothyronamine an inverse agonist [499].
- 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 [2205].

**Further reading on Class A Orphans**

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

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

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
Class C Orphans

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

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

| Nomenclature | GPR156 | GPR158 | GPR179 | GPRCSA | GPRCSB | GPRSCC | GPRCSD | GPRC6 receptor |
|--------------|--------|--------|--------|--------|--------|--------|--------|---------------|
| HGNC, UniProt| GPR156, Q9NQN8 | GPR158, Q9NQ9A | GPR179, Q6PRD1 | GPRCSA, Q8NFW5 | GPRCSB, Q9NZH0 | GPRSCC, Q9NQ84 | GPRCSD, Q9NZD1 | GPRC6A, QST6X5 |

Comments: GPRC6 is a $G_q$-coupled receptor which responds to basic amino acids [2282].

**Further reading on Class C Orphans**

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

Taste 1 receptors

G protein-coupled receptors → Orphan and other 7TM receptors → Taste 1 receptors

**Overview:** Whilst the taste of acid and salty foods appear to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin- (Gα3) and Gα14-mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involvement of PLCβ2 [2429], TRPM5 [2429] and IP3 [883] receptors in post-receptor signalling of taste receptors. Although predominantly associated with the oral cavity, taste receptors are also located elsewhere, including further down the gastrointestinal system, in the lungs and in the brain.

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

| Nomenclature | T1R1 | T1R2 | T1R3 |
|--------------|------|------|------|
| HGNC, UniProt| TAS1R1, Q7RTX1 | TAS1R2, Q8TE23 | TAS1R3, Q7RTX0 |

Comments: Positive allosteric modulators of T1R2/T1R3 have been reported [2363]. Such compounds enhance the sweet taste of sucrose mediated by these receptors, but are tasteless on their own.
Further reading on Taste 1 receptors

Palmer RK. (2019) A Pharmacological Perspective on the Study of Taste. *Pharmacol. Rev.* **71**: 20-48

[PMID:30559245]

**Taste 2 receptors**

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

**Overview:** The composition and stoichiometry of bitter taste receptors is not yet established. Bitter receptors appear to separate into two groups, with very restricted ligand specificity or much broader responsiveness. For example, T2R5 responded to cycloheximide, but not 10 other bitter compounds [334], while T2R14 responded to at least eight different bitter tastants, including \((-\alpha\)-thujone and picrotoxinin [133].

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

| Nomenclature | TAS2R1 | TAS2R3 | TAS2R4 | TAS2R5 | TAS2R7 | TAS2R8 | TAS2R9 |
|--------------|-------|-------|-------|-------|-------|-------|-------|
| HGNC, UniProt| TAS2R1, Q9NYW7 | TAS2R3, Q9NYW6 | TAS2R4, Q9NYW5 | TAS2R5, Q9NYW4 | TAS2R7, Q9NYW3 | TAS2R8, Q9NYW2 | TAS2R9, Q9NYW1 |

| Nomenclature | TAS2R10 | TAS2R13 | TAS2R14 | TAS2R16 | TAS2R19 | TAS2R20 | TAS2R30 |
|--------------|--------|--------|--------|--------|--------|--------|--------|
| HGNC, UniProt| TAS2R10, Q9NYW0 | TAS2R13, Q9NYV9 | TAS2R14, Q9NYV8 | TAS2R16, Q9NYV7 | TAS2R19, P59542 | TAS2R20, P59543 | TAS2R30, P59541 |

| Nomenclature | TAS2R31 | TAS2R38 | TAS2R39 | TAS2R40 |
|--------------|--------|--------|--------|--------|
| HGNC, UniProt| TAS2R31, P59538 | TAS2R38, P59533 | TAS2R39, P59534 | TAS2R40, P59535 |
| Antagonists   | 6-methoxysakuranetin (pIC\(_{50}\) 5.6) [1098], GIV3727 (pIC\(_{50}\) 5.1–5.2) [1984] | – | – | – |
Further reading on Taste 2 receptors

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

Other 7TM proteins

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

Further reading on Orphan and other 7TM receptors

Davenport AP et al. (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. Pharmacol. Rev. 65: 967-86 [PMID:23686350]

Gilissen J et al. (2016) Insight into SUCNR1 (GPR91) structure and function. Pharmacol. Ther. 159: 56-65 [PMID:26808164]

Insel PA et al. (2015) G Protein-Coupled Receptor (GPCR) Expression in Native Cells: "Novel" endoGPCRs as Physiologic Regulators and Therapeutic Targets. Mol. Pharmacol. 88: 181-7 [PMID:25737495]

Khan MZ et al. (2017) Neuro-psychopharmacological perspective of Orphan receptors of Rhodopsin (class A) family of G protein-coupled receptors. Psychopharmacology (Berl.) 234: 1181-1207 [PMID:28289782]

Mackenzie AE et al. (2017) The emerging pharmacology and function of GPR35 in the nervous system. Neuropharmacology 113: 661-671 [PMID:26232640]

Ngo T et al. (2016) Identifying ligands at orphan GPCRs: current status using structure-based approaches. Br. J. Pharmacol. 173: 2934-51 [PMID:26837045]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
5-Hydroxytryptamine receptors

G protein-coupled receptors → 5-Hydroxytryptamine receptors

Overview: 5-HT receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-HT receptors [914] and subsequently revised [816]) are, with the exception of the ionotropic 5-HT3 class, GPCRs 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 [181, 2291]. Most 5-HT receptors (except 5-HT1A and 5-HT2B) play specific roles mediating functional responses in different tissues (reviewed by [1765, 2219]).

Nomenclature

5-HT1A receptor
HTR1A, P08908

5-HT1B receptor
HTR1B, P28222

Agonists

U92016A [1416], vilazodone (Partial agonist) [463], vortioxetine (Partial agonist) [105], L-694,247 [738], naratriptan (Partial agonist) [1548], eletriptan [1548], frovatriptan [2359], zolmitriptan (Partial agonist) [1548], vortioxetine (Partial agonist) [105], rizatriptan (Partial agonist) [1548]

Selective agonists

8-OH-DPAT [473, 791, 1032, 1251, 1452, 1575, 1577, 1578], NLX-101 [1576], 8-OH-DPAT [473, 791, 1032, 1251, 1452, 1575, 1577, 1578], NLX-101 [1576]

Selective antagonists

(5)-UH 301 (pKᵢ 7.9) [1575], WAY-100635 (pKᵢ 7.9–9.2) [1575, 1577], robalzotan (pKᵢ 9.2) [1007], WAY-100635 (pKᵢ 7.9–9.2) [1575, 1577], robalzotan (pKᵢ 9.2) [1007]

Antagonists

SB 224289 (Inverse agonist) (pKᵢ 8.2–8.6) [670, 1573, 1924], SB236057 (Inverse agonist) (pKᵢ 8.2) [1445], GR-55562 (pKᵢ 7.4) [915], WAY-100635 (pKᵢ 8.2) [1445], GR-55562 (pKᵢ 7.4) [915]

Labelled ligands

[3H]robalzotan (Antagonist) (pKᵢ 9.8) [994], [3H]WAY100635 (Antagonist) (pKᵢ 9.5) [1075], [3H]8-OH-DPAT (Agonist) (pKᵢ 174, 1032, 1574, 1577), [3H]NLX-112 (Agonist) [864], [3H]WAY100635 (Antagonist) [2161], p-[18F]MPPF (Antagonist) [418], [3H]N-methyl-AZ10419369 (Agonist, Partial agonist) [1356], [3H]GR 125,743 (Selective Agonist) (pKᵢ 8.6–9.2) [738, 2350], [3H]alniditan (Agonist) [1260], [125]GTI (Agonist) [213, 256] – Rat, [3H]letriptan (Agonist, Partial agonist) [1548], [3H]sumatriptan (Agonist, Partial agonist) [1548], [11C]AZ10419369 (Agonist, Partial agonist) [2207]
| Nomenclature | S-HT1D receptor | S-HT1E receptor | S-HT1F receptor |
|--------------|----------------|----------------|----------------|
| HGNC, UniProt | HTR1D, P28221 | HTR1F, P28566 | HTR1F, P30939 |
| Agonists     | dihydrexergotamine [790, 1260, 1267], ergotamine [711], L-694,247 [2340], naratriptan [506, 1548, 1794], zolmitriptan [1548], frovatriptan [2359], rizatriptan [1548] | BRL-54443 [250] | BRL-54443 [250], eletriptan [1548], sumatriptan [12, 15, 1488, 2236] |
| Selective agonists | PNU109291 [564] – Gorilla, eletriptan [1548] | – | lasmiditan [1563], LY334370 [2236], S-BODMT [1113], LY344864 [1702] |
| Selective antagonists | SB 714786 (pKᵢ 9.1) [2264] | [3H]5-HT (Agonist) [1413, 1657] | [3H]LY334370 (Agonist) [2236], [125]LSD (Agonist) [48] – Mouse |
| Labelled ligands | [3H]eletriptan (Agonist) [1548], [3H]alnindit (Agonist) [1260], [125]LGD (Selective Agonist) [213, 256] – Rat, [3H]CR 125,743 (Selective Antagonist) (pKi 8.6) [2350], [3H]sumatriptan (Agonist) [1548] | [3H]5-HT (Agonist) [1413, 1657] | [3H]LY334370 (Agonist) [2236], [125]LSD (Agonist) [48] – Mouse |
| Nomenclature | S-HT2A receptor | S-HT2B receptor | S-HT2C receptor |
| HGNC, UniProt | HTR2A, P28223 | HTR2B, P41595 | HTR2C, P28335 |
| Agonists     | DOI [227, 1562, 1986] | methysergide (Partial agonist) [1117, 1827, 2237], DOI [1179, 1562, 1883] | DOI [544, 1562, 1883], Ro 60-0175 [1097, 1117] |
| Selective agonists | – | mianserin (pKi 7.9–8.8) [200, 1117, 2237] | WAY-163909 [533], lorcazerin [2125] |
| Antagonists  | risperidone (Inverse agonist) (pKi 9.3–10) [1131, 1156, 1901], mianserin (pKi 7.7–9.6) [1117, 1146, 1452], ziprasidone (pKi 8.8–9.5) [1131, 1156, 1901, 1939], volinanserin (pIC50 6.5–9.3) [1117, 1317, 1782], blonanserin (pKi 9.1) [1611], clozapine (Inverse agonist) (pKi 7.6–9) [1117, 1156, 1449, 1901, 2201], H05 (pIC50 7.2) [2356] | mianserin (pKi 7.9–8.8) [200, 1117, 2237] | mianserin (Inverse agonist) (pKi 8.3–9.2) [607, 1117, 1452], methysergide (pKi 8.6–9.1) [544, 1117], ziprasidone (Inverse agonist) (pKi 7.9–9) [858, 1156, 1939], olanzapine (Inverse agonist) (pKi 8.1–8.4) [858, 1156, 1939], loxapine (Inverse agonist) (pKi 7.8–8) [858, 1156] |
| Selective antagonists | compound 3b (pKi 10.6) [603], ketanserin (pKi 8.1–9.7) [261, 1117, 1771], pimavanserin (Inverse agonist) (pKi 9.3) [659, 2201] | BF-1 (pKi 10.1) [1895], RS-127445 (pKi 9–9.5) [200, 1117], EGLS-7625 (pKi 9) [1146] | FR260010 (pKi 9) [807], SB 242084 (pKi 8.2–9) [1071, 1117], RS-102221 (pKi 8.3–8.4) [201, 1117] |
| Labelled ligands | [3H]Ilananserin (Antagonist) (pKi 9.9) [1362] – Rat, [3H]ketanserin (Antagonist) (pKi 8.6–9.7) [1117, 1771], [11C]volinanserin (Antagonist) [784], [125]Ialtanserin (Antagonist) [1823] | [3H]LSD (Agonist) [1771], [3H]S-HT (Agonist) [2235] – Rat, [3H]mesulergine (Antagonist, Inverse agonist) (pKi 7.9) [1117], [125]IDOI (Agonist) | [3H]mesulergine (Antagonist, Inverse agonist) (pKi 7.8–9.3) [607, 1771], [125]IDOI (Agonist) [607], [3H]LSD (Agonist) [48] – Mouse |
5-HT receptors have multiple partners in addition to G proteins, which may affect function and pharmacology [1384]. NAS181 is a selective antagonist of the rodent 5-HT1B receptor. Fananserin (LSD) and ketanserin bind with high affinity to dopamine D4 and histamine H1 receptors respectively, and ketanserin is a potent α1-adrenoceptor antagonist, in addition to blocking 5-HT2A receptors. Lysergic acid (LSD) and ergotamine show a strong preference for arrestin recruitment over G protein coupling at the 5-HT2B receptor, with no such preference evident at 5-HT1B receptors, and they also antagonise 5-HT7A receptors [2231]. DHE (dihydroergocryptine), pergolide and cabergoline also show significant preference for arrestin recruitment over G protein coupling at 5-HT2B receptors [2231]. The 5-HT2B (and other 5-HT) receptors interact with immunocompetent cells [1645]. The serotonin antagonist mesulergine was key to the discovery of the 5-HT2C receptor [1672], initially known as 5-HT1C [83]. The human 5-HT7A receptor may couple to several signal transduction pathways when stably expressed in C6 glioma cells [1599] and rodent prefrontal cortex (layer V pyramidal neurons) [724]. The human orthologue of the mouse 5-HT3B receptor is non-functional (stop codons); the 5-HT5B receptor has not been cloned from mouse, or rat, impeding definition of its function [800]. In addition to accepted receptors, an ‘orphan’ receptor, unofficially termed 5-HT1F, has been described [693].
Further reading on 5-Hydroxytryptamine receptors

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

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

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

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

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

Roberts AJ et al. (2012) The 5-HT(7) receptor in learning and memory. *Hippocampus* **22**: 762-71 [PMID:21484935]

Acetylcholine receptors (muscarinic)

G protein-coupled receptors → Acetylcholine receptors (muscarinic)

**Overview:** Muscarinic acetylcholine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Muscarinic Acetylcholine Receptors [318]) are GPCRs of the Class A, rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42, its structural analogues AC-260584 and 77-LH-28-1, N-desmethylclozapine, TBPP and LuAE51090 have been described as functionally selective agonists of the M1 receptor subtype via binding in a mode distinct from that utilized by non-selective agonists [82, 1014, 1198, 1199, 1336, 1561, 1683, 2018, 2019, 2061]. There are two pharmacologically characterised allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine, and the other defined by the binding of KT 5720, WIN 62,577, WIN 51,708 and stauroporine [1215, 1216].

| Nomenclature | M1 receptor | M2 receptor | M3 receptor |
|--------------|-------------|-------------|-------------|
| HGNC, UniProt| CHRM1, P11229 | CHRM2, P08172 | CHRM3, P89485 |
| Agonists     | carbachol [385, 976, 2326], pilocarpine (Partial agonist) [976], bethanechol [976] | carbachol [358, 976, 1147], bethanechol [976] | carbachol [385, 976, 977] |
| Selective agonists | glycopyrrolate (pIC50 9.9) [2037], AE9C90CB (pK1 9.7) [1979], atropine (pK1 8.5–9.6) [385, 636, 878, 923, 1683, 1993], tiotropium (pK1 9.6) [501], 4-DAMP (pK1 9.2) [537] | tiotropium (pK1 9.9) [501], glycopyrrolate (pIC50 9.3) [2037], atropine (pK1 7.8–9.2) [265, 358, 878, 923, 1147, 1561, 1683], AE9C90CB (pK1 8.6) [1979], tolterodine (Inverse agonist) (pK1 8.4–8.6) [704, 1561, 1979] | tiotropium (pK1 9.6) [1351] |
| Selective antagonists | biperiden (pKd 9.3) [190], VU0255035 (pK7 7.8) [1943], guanilylpirenzepine (pK7 7.3–7.6) [25, 2234] – Rat | – | tripitramine (pK7 9.6) [1351] |
| Allosteric modulators | muscarinic toxin 7 (Negative) (pK1 11–11.1) [1606], benzoquinazolinone 12 (Positive) (pK8 6.6) [4], KT 5720 (Positive) (pKd 6.4) [1215], brucine (Positive) (pKd 4.5–5.8) [976, 1214], BQCA (Positive) (pKd 4–4.8) [4, 5, 296, 1336], VU0029767 (Positive) [1385], VU0090157 (Positive) [1385] | W-84 (Negative) (pKd 6–7.5) [1470, 2155], C2/3-phth (Negative) (pKd 7.1) [386], alcuronium (Negative) (pKd 6.1–6.9) [976, 2155], gallamine (Negative) (pKd 5.9–6.3) [399, 1212], LY2119662 (Positive) (pKd 5.7) [437, 1158], LY2033298 (Positive) (pKd 4.4) [2185] | – |
| Labelled ligands | [3H]QNB (Antagonist) (pKd 10.6–10.8) [387, 1683], Cy3B-telenzepine (Antagonist) (pKd 10.5) [856], [3H]N-methyl scopolamine (Antagonist) (pKd 9.4–10.3) [324, 385, 387, 878, 976, 977, 1011, 1074, 1212], [3H](-)telenzepine (Antagonist) (pK1 9.4) [580] – Rat, Alexa-488-telenzepine (Antagonist) (pKd 9.3) [856], [3H]pirenzepine (Antagonist) (pKd 7.9) [2273] | [3H]QNB (Antagonist) (pKd 10.1–10.6) [1683], Cy3B-telenzepine (Antagonist) (pK1 10.4) [1568], [3H]tropolonium (Antagonist) (pK1 10.3) [1856], [3H]N-methyl scopolamine (Antagonist) (pKd 9.3–9.9) [324, 385, 387, 976, 977, 1011, 1074, 1212, 2261], Alexa-488-telenzepine (Antagonist) (pK1 8.8) [1568], [3H]acetylcholine (Agonist) [1213], [3H]oxotrenorine-M (Agonist) [153], [3H]dimethyl-BW4 (Allosteric modulator, Positive) (pKd 8.5) [2154], [1H]F-P-TZTP (Agonist) [975] – Mouse |

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

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

| M3 receptor | CHRM3, P20309 |
|-------------|---------------|
| HGCN, UniProt |

**Agonists**

- pilocarpine (Partial agonist) [976], carbachol [358, 976, 2326], bethanechol [976]

**Antagonists**

- tiotropium (pKd 9.5–11.1) [501, 519], AE9C90CB (pKd 9.9) [1979], atropine (pKd 8.9–9.8) [265, 519, 878, 923, 1683, 1993], ipratropium (pKd 9.3–9.8) [519, 878], acridinium (pIC50 9.8) [1733]

**Selective antagonists**

- –

**Allosteric modulators**

- WIN 62,577 (Positive) (pKd 5.1) [1216], N-chloromethyl-brucine (Positive) (pKd 3.3) [1214]

**Selective allosteric modulators**

- –

**Labelled ligands**

- [3H]tiotropium (Antagonist) (pKd 10.7) [1856], [3H]QNB (Antagonist) (pKd 10.4) [1683], [3H]N-methyl scopolamine (Antagonist) (pKd 9.7–10.2) [324, 358, 878, 923, 976, 1011, 1074, 1212], [3H]difenacin (Antagonist) (pKd 9.5) [1993]

**Comments:** The crystal structures of the M1-M4 receptor subtypes have been reported [777, 2111, 2382]. Direct activation via an allosteric site has been reported for M1 receptors (BQCA, PF-06767832) and M4 receptors (LY2033298) [462, 1225, 1227, 1336, 1550, 1551]. The allosteric site for gallamine and strychnine on M2 receptors can be labelled by [3H]dimethyl-W4 [2155]. McN-A-434 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 [2186]. THRX160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M4 receptors by binding both to the orthosteric and a nearby allosteric site [59, 2028].

Although numerous ligands for muscarinic acetylcholine receptors have been described, relatively few selective antagonists have been described, so it is common to assess the rank order of affinity of a number of antagonists of limited selectivity (e.g., 4-DAMP, difenacin, pirenzepine) in order to identify the involvement of particular subtypes. It should be noted that the measured affinities of antagonists (and agonists) in radioligand binding studies are sensitive to ionic strength and can increase over 10-fold at low ionic strength compared to their values at physiological ionic strengths [167].

**Further reading on Acetylcholine receptors (muscarinic)**

- Burger WAC et al. (2018) Toward an understanding of the structural basis of allostery in muscarinic acetylcholine receptors. J Gen Physiol 150: 1360-1372 [PMID:30190312]
- Caulfield MP et al. (1998) International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 50: 279-290 [PMID:9647869]
- Eglen RM. (2012) Overview of muscarinic receptor subtypes. Handb Exp Pharmacol 3-28 [PMID:2222692]
- Kruse AC et al. (2014) Muscarinic acetylcholine receptors: novel opportunities for drug development. Nat Rev Drug Discov 13: 549-60 [PMID:24903776]
- Leach K et al. (2012) Structure-function studies of muscarinic acetylcholine receptors. Handb Exp Pharmacol 29-48 [PMID:22222693]
- Valant C et al. (2012) The best of both worlds? Bitopic orthosteric/allosteric ligands of g protein-coupled receptors. Anna Rev Pharmacol Toxicol 52: 153-78 [PMID:21910627]
Adenosine receptors

G protein-coupled receptors → Adenosine receptors

Overview: Adenosine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adenosine Receptors [624]) are activated by the endogenous ligand adenosine (potentially inosine also at A3 receptors). Crystal structures for the antagonist-bound [410, 964, 1307, 1922], agonist-bound [1232, 1233, 2354] and G protein-bound A3 adenosine receptors [307] have been described. The structures of an antagonist-bound A1 receptor [712] and an adenosine-bound A1 receptor-Gi complex [521] have been resolved by cryo-electronmicroscopy. Another structure of an antagonist-bound A1 receptor obtained with X-ray crystallography has also been reported [361].

| Nomenclature | A1 receptor | A2A receptor | A2B receptor | A3 receptor |
|--------------|-------------|--------------|--------------|-------------|
| HGNC, UniProt | ADORA1, P30542 | ADORA2A, P29274 | ADORA2B, P29275 | ADORA3, P0DMA5 |
| Endogenous agonists | adenosine [2369] | adenosine [2369] | adenosine [2369] | adenosine [2369] |
| Agonists | NECA [658, 1005, 1813, 2151, 2369] | NECA [209, 500, 658, 1088, 1173, 2369] | NECA [160, 209, 995, 1289, 2033, 2203, 2369] | NECA [209, 658, 971, 1858, 2204, 2369] |
| Selective agonists | cyclopentyladenosine [442, 469, 658, 848, 968, 1005, 1813], S-Cl-S-deoxy(-)-ENBA [620], TCPA [162], CCPA [968, 1609], MRS1523 [2148] | apadenoson [1674], UK-432,097 [768, 2354], AZD4635 [410], CGS 21680 [209, 500, 658, 968, 1088, 1115, 1173, 1609], regadenoson [968] | xanthine amine congener (pKi 6.9–8.8) [160, 995, 996, 1115, 1289, 2033], CGS 15943 (pKi 6–8.1) [76, 995, 996, 1115, 1636, 2033] | piclidenoson [592, 647, 1115, 2204], CI-IB-MECA [225, 971, 1085], MRS5698 [2147] |
| Antagonists | CGS 15943 (pKi 8.5) [1636], xanthine amine congener (pKD 7.5) [620] | CGS 15943 (pKi 7–9.4) [500, 1088, 1115, 1636], xanthine amine congener (pKi 8.4–9) [500, 1115] | xanthine amine congener (pKi 6.9–8.8) [160, 995, 996, 1115, 1289, 2033], CGS 15943 (pKi 6–8.1) [76, 995, 996, 1115, 1636, 2033] | CGS 15943 (pKi 7–7.9) [1093, 1115, 1636, 2204], xanthine amine congener (pKi 7–7.4) [1115, 1858, 2204] |
| Selective antagonists | PSB836 (pKi 9.9) [6] – Rat, DPCPX (pKi 7.4–9.2) [469, 950, 1609, 1813, 2295], derenofylline (pKi 9) [1033], WRC-0571 (pKi 8.8) [1387], DU172 (pKi 7.4) [712] | SCH442416 (pKi 8.4–10.3) [1957, 2139], ZM-241385 (pKi 8.8–9.1) [1636] | PSB-0788 (pKi 9.4) [208], PSB603 (pKi 9.3) [208], MRS1754 (pKi 8.8) [995, 1092], PSB1115 (pKi 7.3) [832] | MRS1220 (pKi 8.2–9.2) [971, 1093, 2055, 2384], VUF5574 (pKi 8.4) [2193], MRS1523 (pKi 7.7) [1268], MRS1191 (pKi 7.5) [971, 998, 1273], MRS1195 (pKi 7.5) [971, 998, 1273] |
| Allosteric modulators | PD81723 (Positive) [258] | – | – | LUF6000 (Positive) [772], LUF6096 (Positive) [847] |
| Labelled ligands | [3H]CCPA (Agonist) [1115, 1813], [3H]DPCPX (Agonist) (pKD 8.4–9.2) [442, 592, 1115, 1636, 1813, 2151] | [3H]ZM 241385 (Agonist) (pKD 8.7–9.1) [39, 656], [3H]CGS 21680 (Agonist) [983, 2246] | [3H]MRS1754 (Agonist) (pKi 9.8) [995] | [125I]JAB-MECA (Agonist) [1636, 2204] |

Comments: Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A2B adenosine receptor (ADORA2BP1) with 79% identity to the A2B adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor [972]. DPCPX also exhibits antagonism at A2B receptors (pKi ca. 7.37, 1115). Antagonists at A2 receptors exhibit marked species differences, such that only MRS5125 and MRS1191 are selective at the A3 receptor. In the absence of other adenosine receptors, [3H]DPCPX and [3H]ZM 241385 can also be used to label A3 receptors (Ki ca. 30 and 60 nM respectively). [125I]JAB-MECA also binds to A1 receptors [1115]. [3H]CGS 21680 is relatively selective for A2A receptors, but may also bind to other sites in cerebral cortex [438, 1006]. [3H]NECA binds to other non-receptor elements, which also recognise adenosine [1318]. XAC-BY630 has been described as a fluorescent antagonist for labelling A1 adenosine receptors in living cells, although activity at other adenosine receptors was not examined [234].
Further reading on Adenosine receptors

Borea PA et al. (2015) The A3 adenosine receptor: history and perspectives. *Pharmacol Rev* **67**: 74-102 [PMID:25387804]
Cronstein BN et al. (2017) Adenosine and adenosine receptors in the pathogenesis and treatment of rheumatic diseases. *Nat Rev Rheumatol* **13**: 41-51 [PMID:27829671]
Fredholm BB et al. (2011) International Union of Basic and Clinical Pharmacology. LXXXI. Nomenclature and classification of adenosine receptors—an update. *Pharmacol Rev* **63**: 1-34 [PMID:21303899]
Guo D et al. (2017) Kinetic Aspects of the Interaction between Ligand and G Protein-Coupled Receptor: The Case of the Adenosine Receptors. *Chem Rev* **117**: 38-66 [PMID:27088232]
Göblyös A et al. (2011) Allosteric modulation of adenosine receptors. *Biochim Biophys Acta* **1808**: 1309-18 [PMID:20599682]
Lasley RD. (2011) Adenosine receptors and membrane microdomains. *Biochim Biophys Acta* **1808**: 1284-9 [PMID:20888790]
Mundell S et al. (2011) Adenosine receptor desensitization and trafficking. *Biochim Biophys Acta* **1808**: 1319-28 [PMID:20550943]
Vecchio EA et al. (2018) New paradigms in adenosine receptor pharmacology: allostery, oligomerization and biased agonism. *Br J Pharmacol* **175**: 4036-4046 [PMID:29679502]
Wei CJ et al. (2011) Normal and abnormal functions of adenosine receptors in the central nervous system revealed by genetic knockout studies. *Biochim Biophys Acta* **1808**: 1358-79 [PMID:21185258]

Overview: Adhesion GPCRs are structurally identified on the basis of a large extracellular region, similar to the Class B GPCR, but which is linked to the 7TM region by a GPCR autoproteolysis-inducing (GAIN) domain [60] containing a GPCR proteolytic site. The N-terminus often shares structural homology with adhesive domains (e.g. cadherins, immunoglobulin, lectins) facilitating inter- and matricellular interactions and leading to the term adhesion GPCR [626, 2397]. Several receptors have been suggested to function as mechanosensors [219, 1697, 1900, 2310]. The nomenclature of these receptors was revised in 2015 as recommended by NC-IUPHAR and the Adhesion GPCR Consortium [788].

| Nomenclature | ADGRA1 | ADGRA2 | ADGRA3 | ADGRB1 | ADGRB2 | ADGRB3 |
|--------------|--------|--------|--------|--------|--------|--------|
| HGNC, UniProt | ADGRA1, Q865Q6 | ADGRA2, Q96PE1 | ADGRA3, Q8IWK6 | ADGRB1, O14514 | ADGRB2, O60241 | ADGRB3, O60242 |
| Endogenous agonists | – | – | – | phosphatidylserine [1655] | – | – |
| Comments | Required to assemble higher-order Reck/Gpr124/Frizzled/Lrp5/6 complexes [573, 1726, 2188, 2200, 2436]. | – | – | Reported to mediate phagocytosis through binding of phosphatidylserine [1655] and lipopolysaccharide [447]. | – | Reported to bind C1q-like molecules [194]. |

Adhesion Class GPCRs

G protein-coupled receptors → Adhesion Class GPCRs

Nomenclature

| Nucleotide位 | ADGRA1 | ADGRA2 | ADGRA3 | ADGRB1 | ADGRB2 | ADGRB3 |
|--------------|--------|--------|--------|--------|--------|--------|
| HGNC, UniProt | ADGRA1, Q865Q6 | ADGRA2, Q96PE1 | ADGRA3, Q8IWK6 | ADGRB1, O14514 | ADGRB2, O60241 | ADGRB3, O60242 |
| Endogenous agonists | – | – | – | phosphatidylserine [1655] | – | – |
| Comments | Required to assemble higher-order Reck/Gpr124/Frizzled/Lrp5/6 complexes [573, 1726, 2188, 2200, 2436]. | – | – | Reported to mediate phagocytosis through binding of phosphatidylserine [1655] and lipopolysaccharide [447]. | – | Reported to bind C1q-like molecules [194]. |

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
| Nomenclature | CELSR1 | CELSR2 | CELSR3 | ADGRD1 | ADGRD2 |
|--------------|--------|--------|--------|--------|--------|
| HGNC, UniProt | CELSR1, Q9NYQ6 | CELSR2, Q9HC4 | CELSR3, Q9NYQ7 | ADGRD1, Q6QNK2 | ADGRD2, Q7Z7M1 |
| Comments | Mutated in Joubert syndrome patients [2218]. | High-confidence risk gene for Tourette syndrome [2260]. | | Is a Gs protein-coupled receptor [186, 1278] and highly expressed in glioblastoma [122]. | |

| Nomenclature | ADGRE1 | ADGRE2 | ADGRE3 | ADGRE4P | ADGRE5 |
|--------------|--------|--------|--------|---------|--------|
| HGNC, UniProt | ADGRE1, Q14264 | ADGRE2, Q9UHX3 | ADGRE3, Q9BY15 | ADGRE4P, Q86SQ3 | ADGRE5, P48960 |
| Comments | A mutation destabilizing the GAIN domain sensitizes mast cells to IgE-independent vibration-induced degranulation [219]. Reported to bind chondroitin sulfate B [2024]. | | | Reported to bind CD55 [789], chondroitin sulfate B [2024], α5β1 and α2β3 integrins [2262], and CD90 [2248]. | |

| Nomenclature | ADGRF1 | ADGRF2 | ADGRF3 | ADGRF4 | ADGRF5 |
|--------------|--------|--------|--------|--------|--------|
| HGNC, UniProt | ADGRF1, Q3T601 | ADGRF2, Q8IZF7 | ADGRF3, Q8IZF5 | ADGRF4, Q8IZF3 | ADGRF5, Q8IZF2 |
| Comments | Synaptamide is an agonist at ADGRF1 supporting neurogenesis [1240] and couples to Gs and Gq pathways [482, 2041]. | ADGRF2 is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [1744]. | ADGRF3 is highly expressed in gastrointestinal neuroendocrine tumors [308, 308]. | ADGRF4 couples to Cq/11 Proteins [482], is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [1744]. | ADGRF5 controls alveolar surfactant secretion via Cq/11 Pathway [253]. |

| Nomenclature | ADGRG1 | ADGRG2 | ADGRG3 | ADGRG4 | ADGRG5 | ADGRG6 | ADGRG7 |
|--------------|--------|--------|--------|--------|--------|--------|--------|
| HGNC, UniProt | ADGRG1, Q9Y653 | ADGRG2, Q8IZP9 | ADGRG3, Q8Y634 | ADGRG4, Q8IZF6 | ADGRG5, Q8IZF4 | ADGRG6, Q86SQ4 | ADGRG7, Q96K78 |
| Comments | Reported to bind tissue transglutaminase 2 [2355] and collagen, which activates the G12/13 pathway [1330]. | ADGRG2 is coupled to Gq and Gs pathways [481] and gene deficiency causes congenital obstructive azoospermia [1663]. | ADGRG3 is expressed in immune cells [1947, 2255] and couples to Gq proteins [770]. | ADGRG4 is highly expressed in enterochromaffin cells and gastrointestinal neuroendocrine tumors [1250]. | ADGRG5 is a constitutively active Gs protein-coupled receptor [770, 2310], highly expressed in eosinophils and NK cells [1682]. | ADGRG6 is a key regulator of Schwann cell-mediated myelination [1481], and couples to Gs and Gi/o pathways [1468]. | ADGRG7 is expressed in interstine and involved in interstine contractility regulation [1580]. |
### Nomenclature

| Protein | HGNC, UniProt |
|---------|--------------|
| ADGRL1  | ADGRL1, O94910 |
| ADGRL2  | ADGRL2, O95490 |
| ADGRL3  | ADGRL3, Q9HAR2 |
| ADGRL4  | ADGRL4, Q9HBW9 |
| ADGRV1  | ADGRV1, Q8WXG9 |

### Comments

- Couples to Gₛ and Gₒ pathways [1252, 1533].
- A LPHN3 gene variant in humans is associated with attention-deficit-hyperactivity disorder [62, 2313].
- Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [973].

### Further reading on Adhesion Class GPCRs

- Hamann J *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors. *Pharmacol Rev* 67: 338-67 [PMID:25713288]
- Langenhan T *et al.* (2013) Sticky signaling–adhesion class G protein-coupled receptors take the stage. *Sci Signal* 6: re3 [PMID:23695165]
- Liebscher I *et al.* (2016) Tethered Agonism: A Common Activation Mechanism of Adhesion GPCRs. *Handb Exp Pharmacol* 234: 111-125 [PMID:27832486]
- Monk KR *et al.* (2015) Adhesion G Protein-Coupled Receptors: From In Vitro Pharmacology to In Vivo Mechanisms. *Mol Pharmacol* 88: 617-23 [PMID:25956432]
- Purcell RH *et al.* (2018) Adhesion G Protein-Coupled Receptors as Drug Targets. *Annu Rev Pharmacol Toxicol* 58: 429-449 [PMID:28968187]

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

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
Adrenoceptors, $\alpha_1$

$\alpha_1$-Adrenoceptors are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Phenylephrine, methoxamine and cirazoline are agonists and prazosin and cirazoline antagonists considered selective for $\alpha_1$- relative to $\alpha_2$-adrenoceptors. [$^3$H]prazosin and [$^{125}$I]HEAT (BE2254) are relatively selective radioligands. Si+ niguldipine also has high affinity for L-type Ca$^{2+}$ channels. Fluorescent derivatives of prazosin (Bodipy PLprazosin QAPB) are used to examine cellular localisation of $\alpha_1$-adrenoceptors. Selective $\alpha_1$-adrenoceptor agonists are used as nasal decongestants; antagonists to treat hypertension (doxazosin, prazosin) and benign prostatic hyperplasia (alfuzosin, tamsulosin). The $\alpha_1$- and $\beta_2$-adrenoceptor antagonist carvedilol is used to treat congestive heart failure, although the contribution of $\alpha_1$-adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs are $\alpha_1$-adrenoceptor antagonists contributing to side effects such as orthostatic hypotension and extrapyramidal effects.

### Nomenclature

| Nomenclature | $\alpha_{1A}$-adrenoceptor | $\alpha_{1B}$-adrenoceptor | $\alpha_{1D}$-adrenoceptor |
|--------------|-----------------------------|-----------------------------|-----------------------------|
| HGNC, Uniprot | ADRA1A, P35348              | ADRA1B, P35368              | ADRA1D, P25100              |
| Endogenous agonists | (-)-adrenaline [904, 1948], (-)-noradrenaline [904, 1948, 2104] | – | – |
| Selective agonists | oxytmethylxazine [904, 1610, 1948, 2104], phenylephrine [2104], methoxamine [1948, 2104] | phenylephrine [614, 1459] | – |
| Antagonists | prazosin (Inverse agonist) (pK$_i$ 9–9.9) [335, 443, 614, 1948, 2312], doxazosin (pK$_i$ 9.3) [795], terazosin (pK$_i$ 8.7) [1436], phentolamine (pK$_i$ 8.6) [1948], alfuzosin (pK$_i$ 8.1) [867] | prazosin (Inverse agonist) (pK$_i$ 9.6–9.9) [614, 1948, 2312], tamsulosin (Inverse agonist) (pK$_i$ 9.5–9.7) [614, 1948, 2312], doxazosin (pK$_i$ 9.1) [795], alfuzosin (pK$_i$ 8.6) [868], terazosin (pK$_i$ 8.6) [1436], phentolamine (pK$_i$ 7.5) [1948] | prazosin (Inverse agonist) (pK$_i$ 9.5–10.2) [614, 1948, 2312], tamsulosin (pK$_i$ 9.8–10.2) [614, 1948, 2312], doxazosin (pK$_i$ 9.1) [795], terazosin (pK$_i$ 9.1) [1436], alfuzosin (pK$_i$ 8.4) [867], dapiprazole (pK$_i$ 8.4) [79], phentolamine (Inverse agonist) (pK$_i$ 8.2) [1948], RS-100329 (pK$_i$ 7.9) [2312], labetalol (pK$_i$ 6.6) [79] |
| Selective antagonists | tamsulosin (pK$_i$ 10–10.7) [335, 443, 614, 1948, 2312], silodosin (pK$_i$ 10.4) [1948], Si+ niguldipine (pK$_i$ 9.1–10) [614, 1948], RS-100329 (pK$_i$ 9.6) [2312], SNAP089 (pK$_i$ 8.8–9.4) [867, 1256, 2294], n-Dala (pK$_i$ 9.2–9.3) [1412, 1755], RS-17053 (pK$_i$ 9.2–9.3) [335, 443, 614, 1948] | Rec 15/2615 (pK$_i$ 9.5) [2110], L-765314 (pK$_i$ 7.7) [1662], AH 11110 (pK$_i$ 7.5) [1875] | BMY-7378 (pK$_i$ 8.7–9.1) [310, 2403] |

**Comments**: The $\alpha_{1C}$-adrenoceptor corresponds to the pharmacologically defined $\alpha_{1A}$-adrenoceptor [869]. Some tissues possess $\alpha_{1A}$-adrenoceptors ($\alpha_{1A}$-adrenoceptors [614, 1501]) that display relatively low affinity in functional and binding assays for prazosin indicative of different receptor states or locations. $\alpha_{1A}$-adrenoceptor C-terminal splice variants form homo- and heterodimers, but fail to generate a functional $\alpha_{11}$-adrenoceptor [1768]. $\alpha_{11}$-Adrenoceptors form heterodimers with $\alpha_{1B}$- or $\beta_2$-adrenoceptors that show increased cell-surface expression [2164]. Recombinant $\alpha_{1D}$-adrenoceptors have been shown in some homologous systems to be mainly located intracellularly but cell-surface localization is encouraged by truncation of the N-terminus, or by co-expression of $\alpha_{1B}$- or $\beta_2$-adrenoceptors [779, 2164]. In blood vessels all three $\alpha_{1}$-adrenoceptor subtypes are located on the surface and intracellularly [1433, 1434]. Signalling is predominantly via G$_{i/o}$ but $\alpha_1$-adrenoceptors also couple to G$_{i/o}$, G$_s$ and G$_{12/13}$. Several $\alpha_{1A}$-adrenoceptor agonists display ligand directed signalling bias relative to noradrenaline [575]. There are also differences between subtypes in coupling efficiency to different pathways. In vascular smooth muscle, the potency of agonists is related to the predominant subtype, $\alpha_{1D}$- conveying greater agonist sensitivity than $\alpha_{1A}$-adrenoceptors [609].
Adrenoceptors, α<sub>2</sub>

α<sub>2</sub>-Adrenoceptors are activated by (-)-adrenaline and with lower potency by (-)-noradrenaline. Brimodidine and talipexole are antagonists and rauwolscine and yohimbine antagonists selective for α<sub>2</sub> relative to α<sub>1</sub>-adrenoceptors. [3H]rauwolscine, [3H]brimodidine and [3H]RX821002 are relatively selective radioligands. There is species variation in the pharmacology of the α<sub>2A</sub>-adrenoceptor. Multiple mutations of α<sub>2A</sub>-adrenoceptors have been described, some associated with alterations in function. Presynaptic α<sub>2A</sub>-adrenoceptors regulate many functions in the nervous system. The α<sub>2A</sub>-adrenoceptor agonists clonidine, guanabenz and brimodidine affect central baroreflex control (hypotension and bradycardia), induce hypnotic effects and analgesia, and modulate seizure activity and platelet aggregation. Clonidine is an anti-hypertensive and counteracts opioid withdrawal. Dexmedetomidine (also xylazine) is used as a sedative and analgesic in human and veterinary medicine with sympathetic and anxiolytic properties. The α<sub>2C</sub>-adrenoceptor antagonist yohimbine has been used to treat erectile dysfunction and mirtazapine as an anti-depressant. The α<sub>2C</sub> subtype appears to be involved in neurotransmission in the spinal cord and α<sub>2C</sub> in regulating catecholamine release from adrenalin chromaffin cells.

Nomenclature  
**α<sub>2A</sub>**-adrenoceptor  
**α<sub>2B</sub>**-adrenoceptor  
**α<sub>2C</sub>**-adrenoceptor

HGNC, UniProt  
**α<sub>2A</sub>**-adrenoceptor  
ADRA2A, P08913

Endogenous agonists  
(-)-adrenaline [985, 1704], (-)-noradrenaline [985, 1704]

Agonists  
- dexmedetomidine (Partial agonist) [985, 1339, 1678, 1704], clonidine (Partial agonist) [985, 1678, 1704], brimodidine [985, 1339, 1678, 1704], apraclonidine [1519], guanabenz [79], guanfacine (Partial agonist) [985, 1342]

Selective agonists  
oxymetazoline (Partial agonist) [985, 1339, 2169]

Antagonists  
yohimbine (pK<sub>i</sub> 7.9–8.9) [276, 487, 2169], phenoxybenzamine (pK<sub>i</sub> 8.5) [2280], tolazoline (pK<sub>i</sub> 5.5) [985]

Selective antagonists  
BRL 44408 (pK<sub>i</sub> 8.2–8.8) [2169, 2405], imiloxan (pK<sub>i</sub> 7.3) [1443] – Rat

Labelled ligands  
- [3H]RX821002 [2169]

**Comments:** ARC-239 and prazosin show selectivity for α<sub>2B</sub>- and α<sub>2C</sub>-adrenoceptors over α<sub>2A</sub>-adrenoceptors. Oxymetazoline is a reduced efficacy imidazoline agonist but also binds to non-GPCR binding sites for imidazolines, classified as I<sub>1</sub>, I<sub>2</sub> and I<sub>3</sub> sites [444]; catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands evoking hypotensive effects in vivo. α<sub>1</sub>-imidazoline receptors cause central inhibition of sympathetic tone, I<sub>2</sub>-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I<sub>3</sub>-imidazoline receptors regulate insulin secretion from pancreatic β-cells. The α<sub>2A</sub>-adrenoceptor stimulation reduces insulin secretion from β-islets [2375], with a polymorphism in the 5′-UTR of the ADRA2A gene being associated with increased receptor expression in β-islets and heightened susceptibility to diabetes [1821]. α<sub>2A</sub>- and α<sub>2C</sub>-adrenoceptors form homodimers [1990]. Heterodimers between α<sub>2A</sub>- and either the α<sub>2C</sub>-adrenoceptor or μ opioid peptide receptor exhibit altered signalling and trafficking properties compared to the individual receptors [1990, 2099, 2217]. Signalling by α<sub>2</sub>-adrenoceptors is primarily via G<sub>11</sub> and although the α<sub>2A</sub>-adrenoceptor also couples to G<sub>3</sub> [538]. Imidazoline compounds display bias relative to each other at the α<sub>2A</sub>-adrenoceptor [1670]. The noradrenaline reuptake inhibitor desipramine acts directly on the α<sub>2A</sub>-adrenoceptor to promote internalisation via recruitment of arrestin [421].

Adrenoceptors, β

β-Adrenoceptors are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Isoprenaline is selective for β- adrenoceptors relative to α- and α<sub>2</sub>-adrenoceptors, while propranolol (pK<sub>i</sub> 8.2-9.2) and cyanopindolol (pK<sub>i</sub> 10.0-11.0) are relatively β<sub>1</sub> and β<sub>2</sub> adrenoceptor-selective antagonists. (-)-noradrenaline, xamoterol and (-)-Ro 363 show selectivity for β<sub>1</sub> relative to β<sub>2</sub>-adrenoceptors. Pharmacological differences exist between human and mouse β<sub>1</sub>-adrenoceptors, and the ‘rodent selective’ agonists BRL 37344 and CL316243 have low efficacy at the human β<sub>2</sub>-adrenoceptor whereas CGP 12177 and L 755507 activate human β<sub>2</sub>-adrenoceptors [88]. β<sub>1</sub>-Adrenoceptors are resistant to blockade by propranolol, but can be blocked by high concentrations of butapranolol. SR59230A has reasonably high affinity at β<sub>1</sub>-adrenoceptors, but does not discriminate well between the three β- subtypes whereas L 755507 is more selective. [125I]-cyanoapindolol, [125I]-hydroxy benzylpindolol and [3H]-alprenolol are high affinity radioligands that label β<sub>1</sub> and β<sub>2</sub>-adrenoceptors and β<sub>1</sub>-adrenoceptors can be labelled with higher concentrations (nM) of [125I]-cyanoapindolol together with β<sub>1</sub> and β<sub>2</sub>-adrenoceptor antagonists. [3H]-L-748337 is a β<sub>3</sub>-selective radioligand [2197]. Fluorescent ligands such as BODIPY-TMR-CGP12177 can be used to track β-adrenoceptors at the cellular level [8]. Somewhat selective β<sub>2</sub>-...
adrenoceptor agonists (denopamine, dobutamine) are used short term to treat cardiogenic shock but, chronically, reduce survival. β1-Adrenoceptor-prefering antagonists are used to treat hypertension (atenolol, betaxolol, bisoprolol, metoprolol and nebivolol), cardiac arrhythmias (atenolol, bisoprolol, esmolol) and cardiac failure (metoprolol, nebivolol). Cardiac failure is also treated with carvedilol that blocks β1- and β2-adrenoceptors, as well as α1-adrenoceptors. Short (salbutamol, terbutaline) and long (formoterol, salmeterol) acting β2-adrenoceptor-selective agonists are powerful bronchodilators used to treat respiratory disorders. Many first generation β-adrenoceptor antagonists (propranolol) block both β1- and β2-adrenoceptors and there are no β2-adrenoceptor-selective antagonists used therapeutically. The β3-adrenoceptor agonist mirabegron is used to control overactive bladder syndrome.

| Nomenclature | β1-adrenoceptor | β2-adrenoceptor | β3-adrenoceptor |
|--------------|-----------------|-----------------|-----------------|
| HCNC, UniProt | ADRB1, P08588   | ADRB2, P07550   | ADRB3, P13945   |

Potency order of endogenous ligands

- (-)-noradrenaline > (-)-adrenaline
- (-)-adrenaline [633, 891], (-)-noradrenaline [633]
- (-)-adrenaline [633, 891], (-)-noradrenaline [633]
- (-)-adrenaline [633, 891], (-)-noradrenaline [633, 891]

Agonists

- pindolol (Partial agonist) [1159], isoprenaline [633, 1874], dobutamine (Partial agonist) [956]
- pindolol (Partial agonist) [1159], arformoterol [40], isoprenaline [1874], ephedrine (Partial agonist) [982]
- carazolol [1431]

Selective agonists

- (-)-Ro 363 [1472], xamoterol (Partial agonist) [956], denopamine (Partial agonist) [956, 2066]
- formoterol [94], salmeterol [94], zinterol [94], vilanterol [1737], procaterol [94], indacaterol [123], fenoterol [65], salbutamol (Partial agonist) [96, 956], terbutaline (Partial agonist) [96], orciprenaline [2066]
- L 755507 [94], L742791 [2277], mirabegron [2089], CGB 12177 (Partial agonist) [177, 1319, 1431, 1472], SB251023 [936] – Mouse, BRL 37344 [177, 505, 891, 1431], CLS16243 [2372]

Antagonists

- carvedilol (pKi 9.5) [297], bupranolol (pKi 7.3–9) [297, 1319], SR59230A (pKi 8.6) [297], levobunolol (pKi 8.4) [79], labetalol (pKi 8.2) [79], metoprolol (pKi 7–7.6) [96, 297, 891, 1319], esmolol (pKi 6.9) [79], nadolol (pKi 6.9) [297], practolol (pKi 6.1–6.8) [96, 1319], propafenone (pKi 6.7) [79], sotalol (pKi 6.1) [79]
- carvedilol (pKi 9.4–9.9) [96, 297], timolol (pKi 9.7) [96], propranolol (pKi 9.1–9.5) [96, 99, 956, 1319], SR59230A (pKi 9.3) [297], levobunolol (pKi 9.3) [79], bupropranol (pKi 8.3–9.1) [297, 1319], alprenolol (pKi 9) [96], nadolol (pKi 7–8.6) [96, 297], labetalol (pKi 8) [79], propafenone (pKi 7.4) [79], sotalol (pKi 6.5) [79]
- CGP 20712A (pKi 8.5–9.2) [96, 297, 1319], levobetaxolol (pKi 9.1) [1942], betaxolol (pKi 9.1) [1319], nebivolol (pCo 8.1–8.7) [1669] – Rabbit: atenolol, pKi 6.7–6.7 [96, 1021, 1319], acebutolol, pKi 6.4) [79]

Selective antagonists

- CCG 11855 (Invert agonist) (pKi 9.2–9.5) [96, 99, 1319]
- ICI 118551 (pKi 8.4) [297, 1319, 1431], L748337 (pKi 8.4) [297, 1319, 1431], L748328 (pKi 8.4) [297]

Labelling ligands

- [125I]JCYP (Antagonist) (pKd 10.4–11.3) [956, 1319, 1874]
- [125I]JCYP (Antagonist) (pKd 11.1) [1319, 1874]

Comments

The agonists indicated have less than two orders of magnitude selectivity [94].

Adrenoceptors

- Many ‘antagonists’ of cAMP accumulation, for example carvedilol and bupranolol, weakly activate MAP kinase pathways [98, 577, 644, 645, 1872, 1873] and thus display ‘protean agonism’. Bupranolol acts as a neutral agonist in most systems so far examined. Agonists also display biased signalling at the β2-adrenoceptor via Gs or arrestins [520]. X-ray crystal structures have been described of the agonist bound [2265] and antagonist bound forms of the β1- [2266], agonist-bound [363] and antagonist-bound forms of the β3-adrenoceptors (CL316243, CGB 12177 and carazolol). Many ‘antagonists’ of cAMP accumulation, for example carvedilol and bupranolol, weakly activate MAP kinase pathways [98, 577, 644, 645, 1872, 1873] and thus display ‘protean agonism’. Bupranolol acts as a neutral agonist in most systems so far examined. Agonists also display biased signalling at the β2-adrenoceptor via Gs or arrestins [520]. X-ray crystal structures have been described of the agonist bound [2265] and antagonist bound forms of the β1- [2266], agonist-bound [363] and antagonist-bound forms of the β3-adrenoceptors. Adrenoceptors S47

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
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 [465, 1045]), which have around 30% sequence similarity. The decapetide angiotensin I (AGT, P01019), the octapeptide angiotensin II (AGT, P01019) and the heptapeptide angiotensin III (AGT, P01019) are endogenous ligands. Losartan, candesartan, telmisartan, etc. are clinically used AT1 receptor blockers.

| Nomenclature | AT1 receptor | AT2 receptor |
|--------------|--------------|--------------|
| HGNC, UniProt | AGTR1, P30556 | AGTR2, P50052 |

Endogenous agonists
- angiotensin II (AGT, P01019) [466, 2199], angiotensin III (AGT, P01019) [466], angiotensin IV (AGT, P01019) (Partial agonist) [1222]

Agonists
- [Sar1,Cha4]Ang-II [896, 1464] – Rat

Selective agonists
- L-162,313 [1687], L-163,101 [2175]

Antagonists
- saprisartan (pK<sub>I</sub> 9.1) [870] – Rat, 5-oxo-1,2,4-oxadiazol biphenyl (pIC<sub>50</sub> 8.8) [1583] – Rat, 5-butyl-methyl imidazole carboxylate 30 (pIC<sub>50</sub> 8.5) [161], LY303336 (pIC<sub>50</sub> 8.3) [2198], TRV120027 (pK<sub>Q</sub> 7.7) [2220]

Selective antagonists
- candesartan (pIC<sub>50</sub> 9.5–9.7) [2199], eprosartan (pIC<sub>50</sub> 8.4–8.8) [543], losartan (pIC<sub>50</sub> 7.4–8.7) [466, 2135], telmisartan (pIC<sub>50</sub> 8.4) [1417], olmesartan (pIC<sub>50</sub> 8.1) [1127]

Labelled ligands
- [125I]Candesartan (Antagonist) (pK<sub>D</sub> 10.3) [594], [123I][Sar<sup>1</sup>][Ang-II] (Agonist) (pIC<sub>50</sub> 591) – Rat, [125I][Sar<sup>1</sup>,Ile<sup>8</sup>][Ang-II] (Agonist) (pIC<sub>50</sub> 591) – Rat, [125I]Eprosartan (Antagonist) (pK<sub>I</sub> 9.1) [24] – Rat, [125I]Losartan (Antagonist) (pIC<sub>50</sub> 8.2) [341] – Rat

Comments
- Telmisartan and candesartan are also reported to be agonists of PPARγ [2040].
Comments: AT₁ receptors are predominantly coupled to Gq/11, however they are also linked to arrestin recruitment and stimulate G protein-independent arrestin signalling [1332]. Most species express a single AGTR1 gene, but two related atr1a and atr1b receptor genes are expressed in rodents. The AT₂ receptor counteracts several of the growth responses initiated by the AT₁ receptors. The AT₂ receptor is much less abundant than the AT₁ receptor in adult tissues and is upregulated in pathological conditions. AT₁ receptor antagonists bearing substituted 4-phenylquinoline moieties have been synthesized, which bind to AT₁ receptors with nanomolar affinity and are slightly more potent than losartan in functional studies [300]. The antagonist activity of CGP42112 at the AT₂ receptor has also been reported [1596]. The AT₁ and bradykinin B₂ receptors have been proposed to form a heterodimeric complex [3]. β-Arrestin1 prevents AT₁-B₂ receptor heteromerization[1756]. There is also evidence for an AT₄ receptor that specifically binds angiotensin IV (AGT, P01019) and is located in the brain and kidney. An additional putative endogenous ligand for the AT₄ receptor has been described (LVV-hemorphin (HBB, P68871), a globin decapeptide) [1467].

Further reading on Angiotensin receptors

Asada H et al. (2018) Crystal structure of the human angiotensin II type 2 receptor bound to an angiotensin II analog. Nat. Struct. Mol. Biol. 25: 570-576 [PMID:29967536]
Karnik SS et al. (2015) International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin Receptors: Interpreters of Pathophysiological Angiotensinergic Stimuli [corrected]. Pharmacol. Rev. 67: 754-819 [PMID:26315714]
Singh KD et al. (2019) Mechanism of Hormone Peptide Activation of a GPCR: Angiotensin II Activated State of AT₁R Initiated by van der Waals Attraction. J Chem Inf Model 59: 373-385 [PMID:30608150]

Wingler LM et al. (2019) Angiotensin Analogs with Divergent Bias Stabilize Distinct Receptor Conformations. Cell 176: 468-478.e11 [PMID:30639099]
Wingler LM et al. (2019) Distinctive Activation Mechanism for Angiotensin Receptor Revealed by a Synthetic Nanobody. Cell 176: 479-490.e12 [PMID:30639100]
Zhang H et al. (2015) Structure of the Angiotensin receptor revealed by serial femtosecond crystallography. Cell 161: 833-44 [PMID:25913193]
Apelin receptor

G protein-coupled receptors → Apelin receptor

**Overview:** The apelin receptor (nomencature as agreed by the NC-IUPHAR Subcommittee on the apelin receptor [1713]) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36 (APLN, Q9ULZ1), apelin-13 (APLN, Q9ULZ1) and [Pyr1]apelin-13 (APLN, Q9ULZ1) are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (APLN, Q9ULZ1) by a so far unidentified enzymatic pathway [2106]. A second family of peptides discovered independently and named Elabela [372] or Toddler, that has little sequence similarity to apelin, is present, and functional at the apelin receptor in the adult cardiovascular system [1668, 2379]. Structure-activity relationship Elabela analogues have been described [1528].

| Nomenclature | apelin receptor |
|--------------|-----------------|
| HGNC, UniProt | APLNR, P35414 |

**Potency order of endogenous ligands**

- [Pyr1]apelin-13 (APLN, Q9ULZ1) \(\geq\) apelin-13 (APLN, Q9ULZ1) \(>\) apelin-36 (APLN, Q9ULZ1) [584, 2106]
- apelin-13 (APLN, Q9ULZ1) [584, 909, 1428], apelin receptor early endogenous ligand (APELA, P0DMC3) [483], apelin-17 (APLN, Q9ULZ1) [547, 1428], [Pyr1]apelin-13 (APLN, Q9ULZ1) [1056, 1428], Elabela/Toddler-21 (APELA, P0DMC3) [2378], Elabela/Toddler-32 (APELA, P0DMC3) [2378], apelin-36 (APLN, Q9ULZ1) [584, 909, 1056, 1428], Elabela/Toddler-11 (APELA, P0DMC3) [2378]

**Endogenous agonists**

- CMF-019 (Biased agonist) [1781], MM07 (Biased agonist) [226]
- MM54 (pKₐ 8.2) [1338]

**Selective agonists**

- \([^{125}]\text{I}[^{Nle75} \text{Tyr77}]\text{apelin-36 (human) (Agonist)} \text{[1056]}, \text{[1}^{25}\text{I}]\text{[Glp65}^{Nle75} \text{Tyr77}]\text{apelin-13 (Agonist)} \text{[909]}, \text{[1}^{25}\text{I}]\text{[Pyr1]}\text{apelin-13 (Agonist)} \text{[1050]}, \text{[1}^{25}\text{I}]\text{apelin-13 (Agonist)} \text{[584]}, \text{[3}^{H}]\text{[Pyr1]}\text{[Met(0)11]}\text{apelin-13 (Agonist)} \text{[1428]}

**Comments:** Potency order determined for heterologously expressed human apelin receptor (pD₂ values range from 9.5 to 8.6). The apelin receptor may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function [323]. A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* [1238], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant apelin receptor [584]. The apelin receptor antagonist, MM54, was reported to suppress tumour growth and increase survival in an intracranial xenograft mouse model of glioblastoma [809].

**Further reading on Apelin receptor**

- Cheng B et al. (2012) Neuroprotection of apelin and its signaling pathway. *Peptides* 37: 171-3 [PMID:22820556]
- Langelaan DN et al. (2009) Structural insight into G-protein coupled receptor binding by apelin. *Biochemistry* 48: 537-48 [PMID:19123778]
- Mughal A et al. (2018) Vascular effects of apelin: Mechanisms and therapeutic potential. *Pharmacol. Ther.* 190: 139-147 [PMID:29807055]
- O’Carroll AM et al. (2013) The apelin receptor APJ: journey from an orphan to a multifaceted regulator of homeostasis. *J. Endocrinol.* 219: R13-35 [PMID:23943882]
- Pitkin SL et al. (2010) International Union of Basic and Clinical Pharmacology. LXXIV. Apelin receptor nomenclature, distribution, pharmacology, and function. *Pharmacol. Rev.* 62: 331-42 [PMID:20605969]
- Yang P et al. (2015) Apelin, Elabela/Toddler, and biased agonists as novel therapeutic agents in the cardiovascular system. *Trends Pharmacol. Sci.* 36: S60-7 [PMID:26143239]
Bile acid receptor

G protein-coupled receptors → Bile acid receptor

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

| Nomenclature | Potency order of endogenous ligands | Selective agonists |
|--------------|----------------------------------|-------------------|
| HGNC, UniProt | lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid [1055, 1392] | S-EMCA [1676] – Mouse, betulinic acid [680], oleanolic acid [1871] |

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

Further reading on Bile acid receptor

Duboc H et al. (2014) The bile acid TGR5 membrane receptor: from basic research to clinical application. *Dig Liver Dis* 46: 302-12 [PMID:24411485]
Lefebvre P et al. (2009) Role of bile acids and bile acid receptors in metabolic regulation. *Physiol. Rev.* 89: 147-91 [PMID:19126757]
van Nierop FS et al. (2017) Clinical relevance of the bile acid receptor TGR5 in metabolism. *Lancet Diabetes Endocrinol* 5: 224-233 [PMID:27639537]

Bombesin receptors

G protein-coupled receptors → Bombesin receptors

Overview: Mammalian bombesin (Bn) receptors comprise 3 subtypes: BB1, BB2, BB3 (nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, [990]). BB1 and BB2 are activated by the endogenous ligands gastrin-releasing peptide (GRP, P07492) (GRP), neumedin B (NMB, P08949) (NMB) and GRP-(18-27) (GRP, P07492). Bombesin is a tetradecapeptide, originally derived from amphibians. The three Bn receptor subtypes couple primarily to the Gq/11 and G12/13 family of G proteins [990]. Each of these receptors is widely distributed in the CNS and peripheral tissues [723, 990, 1721, 1766, 1866, 2420]. Activation of BB1 and BB2 receptors causes a wide range of physiological/pathophysiological actions, including the stimulation of normal and neoplastic tissue growth, smooth-muscle contraction, feeding behavior, secretion and many central nervous system effects including regulation of circadian rhythm and mediation of pruritus [990, 991, 992, 1359, 1489, 1766]. A physiological role for the BB3 receptor has yet to be fully defined although recently studies suggest an important role in glucose and insulin regulation, metabolic homeostasis, feeding, regulation of body temperature, obesity, diabetes mellitus and growth of normal/neoplastic tissues [723, 1360, 1619, 2345].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
### Peptides

| Nomenclature | BB<sub>1</sub> receptor | BB<sub>2</sub> receptor | BB<sub>3</sub> receptor |
|--------------|------------------------|------------------------|------------------------|
| HGNC, UniProt | NMBR, P28336 | GRPR, P30550 | BRS3, P32247 |

**Endogenous agonists**
- neuromedin B (NMB, P08949) [990, 1766, 2166]
- neuromedin C [2166], gastrin releasing peptide [14-27] (human) [2166]

**Selective agonists**
- –
- –
- compound 9g [1398], MK-7725 [373], MK-5046 [1494, 1915], [D-Tyr<sup>6</sup>, Apa-4Cl<sup>11</sup>, Phe<sup>13</sup>, Nle<sup>14</sup>]bombesin-(6-14) [1376], compound 17c [1397], bag-1 [759], compound 22e [836]

**Antagonists**
- D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH<sub>2</sub> (pIC<sub>50</sub> 6.2–6.6) [722]
- –
- bantag-1 (pIC<sub>50</sub> 8.6–8.7) [759, 1494], ML-18 (pIC<sub>50</sub> 5.3) [1488]

**Selective antagonists**
- PD 176252 (pIC<sub>50</sub> 9.3–9.8) [722], PD 168368 (pIC<sub>50</sub> 9.3–9.6) [722], dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH<sub>2</sub>
- [D-Phe<sup>6</sup>, Leu<sup>13</sup>, Cpa<sup>14</sup>, ψ<sup>13-14</sup>]bombesin-(6-14) (pK<sub>i</sub> 9.8) [722], JMV641 (pIC<sub>50</sub> 9.3) [2140] – Mouse,
- [(3-Ph-Pr<sup>6</sup>, His<sup>7</sup>, D-Ala<sup>11</sup>, D-Pro<sup>13</sup>, ψ<sup>13-14</sup>, Phe<sup>14</sup>]bombesin-(6-14) (pIC<sub>50</sub> 9.2) [722, 1231], JMV594 (pIC<sub>50</sub> 8.9) [1308, 2140] – Mouse,
- [D-Tpy<sup>6</sup>, Leu<sup>13</sup>, ψ(CH<sub>2</sub>NH)-Leu<sup>14</sup>]bombesin-(6-14) (pIC<sub>50</sub> 8.9) [722]

**Labelled ligands**
- [I<sup>251</sup>]<sub>H</sub>bag-2 (Agonist) [759] – Mouse,
- [I<sup>125</sup>][D-Tyr<sup>6</sup>, β-Ala<sup>11</sup>, Phe<sup>13</sup>, Nle<sup>14</sup>]bombesin-(6-14) [1377], [D-Tyr<sup>6</sup>, Apa-4Cl<sup>11</sup>, Phe<sup>13</sup>, Nle<sup>14</sup>]bombesin-(6-14) has more than 200-fold selectivity for BB<sub>3</sub> receptors over BB<sub>1</sub> and BB<sub>2</sub> [1376, 1377, 1766, 1767].

**Further reading on Bombesin receptors**

- González N et al. (2015) Bombesin receptor subtype 3 as a potential target for obesity and diabetes. *Expert Opin. Ther. Targets* 19: 1153-70 [PMID:26066663]
- Jensen RT et al. (2008) International Union of Pharmacology. LXVIII. Mammalian bombesin receptors: nomenclature, distribution, pharmacology, signaling, and functions in normal and disease states. *Pharmacol. Rev.* 60: 1-42 [PMID:18055507]
- Maina T et al. (2017) Theranostic Prospects of Gastrin-Releasing Peptide Receptor-Radioantagonists in Oncology. *PET Clin* 12: 297-309 [PMID:28576168]
- Moreno P et al. (2016) Bombesin related peptides/receptors and their promising therapeutic roles in cancer imaging, targeting and treatment. *Expert Opin. Ther. Targets* 20: 1055-73 [PMID:26981612]
- Qu X et al. (2018) Recent insights into biological functions of mammalian bombesin-like peptides and their receptors. *Curr Opin Endocrinol Diabetes Obes* 25: 36-41 [PMID:29120926]
- Ramos-Álvarez I et al. (2015) Insights into bombesin receptors and ligands: Highlighting recent advances. *Peptides* 72: 128-44 [PMID:25976083]
Bradykinin receptors

G protein-coupled receptors → Bradykinin receptors

**Overview:** Bradykinin (or kinin) receptors (nomenclature as agreed by the NC-IUPHAR subcommittee on Bradykinin (kinin) Receptors [1243]) are activated by the endogenous peptides bradykinin (KNG1, P01042) (BK), [des-Arg⁹]bradykinin (KNG1, P01042), Lys-BK (kallidin (KNG1, P01042)), [des-Arg¹⁰]kallidin (KNG1, P01042), [Phospho-Ser⁶]-Bradykinin, T-kinin (KNG1, P01042) (Ile-Ser-BK), [Hyp³]bradykinin (KNG1, P01042) and Lys-[Hyp³]-bradykinin (KNG1, P01042). Variation in pharmacology and activity of B₁ and B₂ receptor antagonists at species orthologs has been documented. Icatibant (Hoe140, Firazir) is approved in North America and Europe for the treatment of acute attacks of hereditary angioedema.

| Nomenclature          | B₁ receptor                  | B₂ receptor                  |
|-----------------------|------------------------------|------------------------------|
| HGNC, UniProt         | BDKRB1, P46663               | BDKRB2, P30411               |
| Potency order of endogenous ligands | [des-Arg¹⁰]kallidin (KNG1, P01042) > [des-Arg⁹]bradykinin (KNG1, P01042) = kallidin (KNG1, P01042) > bradykinin (KNG1, P01042) | kallidin (KNG1, P01042) > bradykinin (KNG1, P01042) ≫ [des-Arg⁹]bradykinin (KNG1, P01042), [des-Arg¹⁰]kallidin (KNG1, P01042) |
| Endogenous agonists   | [des-Arg¹⁰]kallidin (KNG1, P01042) [80, 118, 714, 1012] | bradykinin (KNG1, P01042) |
| Selective agonists    | NG29 [1879], [Sar,D-Phe⁸,des-Arg⁹]bradykinin [1012] | NG29 [282, 1880], [Hyp³,Tyr(Me)⁸]BK, [Phe⁸, ψ(CH₂-NH)Arg⁹]BK, labradimil [282, 1880] |
| Selective antagonists | B-9958 (pKᵢ 9.2-10.3) [689, 1784], [Leu⁹,des-Arg¹⁰]kallidin (pKᵢ 9.1-9.3) [80, 118], SSR240612 (pKᵢ 9.1-9.2) [732], R-954 (pKᵢ 8.6) [715], R-715 (pKᵢ 8.5) [713] | icatibant (pKᵢ 10.2) [43], FR173657 (pKᵢ 8.2) [1814], anatibant (pKᵢ 8.2) [1742] |
| Labelled ligands      | [¹²⁵I]Hpp-desArg⁹HOE140 (pKᵢ 10), [¹³]Hlys-[des-Arg⁹]BK (Agonist), [¹³]Hlys-[Leu⁸]des-Arg⁹]BK (Antagonist) | [¹³]HBK (human, mouse, rat) (Agonist) [2318] – Mouse, [¹³]HNPC17731 (Agonist) (pKᵢ 9.1-9.4) [2423, 2424], [¹²⁵I]Tyr⁸]bradykinin (Agonist) |

**Further reading on Bradykinin receptors**

Campos MM et al. (2006) Non-peptide antagonists for kinin B₁ receptors: new insights into their therapeutic potential for the management of inflammation and pain. Trends Pharmacol. Sci. 27: 646-51 [PMID:17056130]

Duchene J et al. (2009) The kinin B(1) receptor and inflammation: new therapeutic target for cardiovascular disease. Curr Opin Pharmacol 9: 125-31 [PMID:19124274]

Marceau F et al. (2004) Bradykinin receptor ligands: therapeutic perspectives. Nat Rev Drug Discov 3: 845-52 [PMID:15459675]

Paquet JL et al. (1999) Pharmacological characterization of the bradykinin B₂ receptor: inter-species variability and dissociation between binding and functional responses. Br. J. Pharmacol. 126: 1083-90 [PMID:10204994]

Thornton E et al. (2010) Kinin receptor antagonists as potential neuroprotective agents in central nervous system injury. Molecules 15: 6598-618 [PMID:20877247]

Whalley ET et al. (2012) Discovery and therapeutic potential of kinin receptor antagonists. Expert Opin Drug Discov 7: 1129-48 [PMID:23095011]
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, calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors [830, 1732]) are generated by the genes *CALCRL* (which codes for the CT receptor) and *CALCR* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying proteins), which are single TM domain proteins of ca. 130 amino acids, identified as a family of three members; RAMP1, RAMP2 and RAMP3. There are splice variants of the CT receptor; these in turn produce variants of the AMY receptor [1732], some of which can be 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, P10092) (formerly known as CGRP-II), amylin (IAPP, P10097) (occasionally called islet-amyloid polypeptide), adrenomedullin (ADM, P35318) and adrenomedullin 2/intermedin (ADM2, Q7Z4H4). There are species differences in peptide sequences, particularly for the CTs. CTR-stimulating peptide (P1g) (CRSP) is another member of the family with selectivity for the CT receptor but it is not expressed in humans [1047]. Olcegepant (also known as BIBN4096BS, pKi10.5) and telcagepant (also known as MK0974, pKi9) are the most selective antagonists available, showing selectivity for CGRP receptors, with a particular preference for those of primate origin. CLR (calcitonin receptor-like receptor) by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, adrenomedullin and adrenomedullin 2/intermedin.

| Nomenclature | CT receptor | AMY₁ receptor | AMY₂ receptor | AMY₃ receptor |
|--------------|-------------|---------------|---------------|---------------|
| HGNC, UniProt | CALCRL, P30988 | – | – | – |
| Subunits | calcitonin (salmon) > calcitonin (CALCA, P01258) > amylin (IAPP, P10097), α-CGRP (CALCA, P06881), β-CGRP (CALCB, P10092) > adrenomedullin (ADM, P35318), adrenomedullin 2/intermedin (ADM2, Q7Z4H4) | calcitonin (salmon) > amylin (IAPP, P10097) > α-CGRP (CALCA, P06881), β-CGRP (CALCB, P10092) > adrenomedullin (ADM2, Q7Z4H4) > calcitonin (CALCA, P01258) > adrenomedullin (ADM, P35318) | poorly defined | calcitonin (salmon) > amylin (IAPP, P10097) > α-CGRP (CALCA, P06881), β-CGRP (CALCB, P10092) > adrenomedullin 2/intermedin (ADM2, Q7Z4H4) > calcitonin (CALCA, P01258) > adrenomedullin (ADM, P35318) |
| Potency order of endogenous ligands | – | CT receptor, RAMP1 (Accessory protein), CT receptor | CT receptor, RAMP2 (Accessory protein) | CT receptor, RAMP3 (Accessory protein) |
| Endogenous agonists | calcitonin (CALCA, P01258) [35, 68, 827, 1183, 1263, 1517] | α-CGRP (CALCA, P06881) [827, 1182, 1183, 1263, 2241], amylin (IAPP, P10097) [705], β-CGRP (CALCB, P10092) | amylin (IAPP, P10097) [705] | amylin (IAPP, P10097) [705] |
| Sub/family-selective agonists | pramlintide [705] | pramlintide [705] | – | pramlintide [705] |
| Sub/family-selective antagonists | CT-(8-32) (salmon) (pKi 9) [874], AC187 (pKi 7.2) [827] | AC187 (pKi 8) [827], CT-(8-32) (salmon) (pKi 7.8) [827], olcegepant (pKi 7.2) [2241] | CT-(8-32) (salmon) (pKi 7.9) [827], AC187 (pKi 7.7) [827] | – |
| Labelled ligands | [125I]CT (human) (Agonist), [125I]CT (salmon) (Agonist) | [125I]αCGRP (human) (Agonist), [125I]BH-AMY (rat, mouse) (Agonist) | [125I]βCGRP (human) (Agonist), [125I]BH-AMY (rat, mouse) (Agonist) | [125I]BH-AMY (rat, mouse) (Agonist) |
calcitonin receptor-like receptor  CGRP receptor  AM₁ receptor  AM₂ receptor
HGNC, UniProt  CALCR, Q16602  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Subunits  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Potency order of endogenous ligands  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Endogenous agonists  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Antagonists  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Selective antagonists  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Labelled ligands  –  calcitonin receptor-like receptor, RAMP1 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP2 (Accessory protein)  –  calcitonin receptor-like receptor, RAMP3 (Accessory protein)

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 [388, 827, 828]. The major human CTR splice variant (hCT3a), which does not contain an insert) with RAMP1 (i.e. the AMY3a) receptor) has a high affinity for CGRP [2241], unlike hCT3a-RAMP3 (i.e. AMY3a) receptor) [388, 827]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [1495, 1750, 2134]. Emerging data suggests that AMY₁ could be a second CGRP receptor [826].

The ligands described have limited selectivity. Adrenomedullin has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM receptors. Adrenomedullin 2/intermedin also has high affinity for the AM₁ receptor [903]. CGRP-(8-37) acts as an antagonist of CGRP (pKᵦ 8) and inhibits some AM and AMY responses (pKᵦ 6-7). It is weak at CT receptors. Human AM-(22-52) has some selectivity towards AM receptors, but with modest potency (pKᵦ 7), limiting its use [829]. Olcegepant shows the greatest selectivity between receptors but still has significant affinity for AMY₁ receptors [2241].

Gₛ is a prominent route for effector coupling for CLR and CTR but other pathways (e.g. Ca²⁺, ERK, Akt), and G proteins can be activated [2240]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, ASL (P04424) is important for the coupling of CLR to adenylyl cyclase [578].

125I-Salmon CT is the most common radioligand for CT receptors but it has high affinity for AMY receptors and is also poorly reversible.

Further reading on Calcitonin receptors

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

**G protein-coupled receptors → Calcium-sensing receptor**

**Overview:** The calcium-sensing receptor (CaS, provisional nomenclature as recommended by NC-IUPHAR [612]) responds to multiple endogenous ligands, including extracellular calcium and other divalent/trivalent cations, polyamines and polycationic peptides, L-amino acids (particularly L-Trp and L-Phe), glutathione and various peptidic analogues, ionic strength and extracellular pH (reviewed in [1228]). While divalent/trivalent cations, polyamines and polycations are CaS receptor agonists [252, 1754], L-amino acids, glutamyl peptides, ionic strength and pH are allosteric modulators of agonist function [411, 612, 885, 1752, 1753]. Indeed, L-amino acids have been identified as ‘co-agonists’, with both concomitant calcium and L-amino acid binding required for full receptor activation [682, 2416]. The sensitivity of the CaS receptor to primary agonists is increased by elevated extracellular pH [295] or decreased extracellular ionic strength [1753]. This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

| Nomenclature | CaS receptor |
|--------------|--------------|
| HGNC, UniProt | CASR, P41180 |
| Amino-acid rank order of potency | L-phenylalanine, L-tryptophan, L-histidine > L-alanine > L-serine, L-proline, L-glutamic acid > L-aspartic acid (not L-lysine, L-arginine, L-leucine and L-isoleucine) [411] |
| Cation rank order of potency | Gd³⁺ > Ca²⁺ > Mg²⁺ [252] |
| Glutamyl peptide rank order of potency | S-methylglutathione ≈ γGlu-Val-Gly > glutathione > γGlu-Cys [243, 1621, 2256] |
| Polyamine rank order of potency | spermine > spermidine > putrescine [1754] |
| Allosteric modulators | ATF 936 (Negative) (pIC₅₀ 8.9) [2302], encaleret (Negative) (pIC₅₀ 7.9) [1956], SB-423562 (Negative) (pIC₅₀ 7.1) [1176], ronacaleret (Negative) (pIC₅₀ 6.5–6.8) [101], NPS 2143 (Negative) (pKᵢ 6.2–6.7) [459, 1226, 1229], cinacalcet (Positive) (pKᵢ 5.9–6.6) [414, 459, 1226, 1229], tecalcet (Positive) (pKᵢ 6.2–6.6) [414, 459], AC265347 (Positive) (pKᵢ 6.3–6.4) [414, 1226], calhex 231 (Negative) (pIC₅₀ 6.4) [1699], calindol (Positive) (pKᵢ 6.3) [414] |

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

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

Multiple other small molecule chemotypes are positive and negative allosteric modulators of the CaS receptor [1078, 1565]. Further, etelcalcetide is a novel peptide positive allosteric modulator of the receptor [2243]. Agonists and positive allosteric modulators of the CaS receptor are termed Type I and II calcimimetics, respectively, and can suppress parathyroid hormone (PTH (PTH, P01270)) secretion [1567]. Negative allosteric modulators are called calcilytics and can act to increase PTH (PTH, P01270) secretion [1566].

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

**Further reading on Calcium-sensing receptor**

Brown EM. (2013) Role of the calcium-sensing receptor in extracellular calcium homeostasis. Best Pract. Res. Clin. Endocrinol. Metab. 27: 333-43 [PMID:23856263]

Conigrave AD et al. (2013) Calcium-sensing receptor (CaSR): pharmacological properties and signalling pathways. Best Pract. Res. Clin. Endocrinol. Metab. 27: 315-31 [PMID:23856262]

Hannan FM et al. (2018) The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat Rev Endocrinol 15: 33-51 [PMID:30443043]

Nemeth EF et al. (2018) Discovery and Development of Calcimimetic and Calcilytic Compounds. Prog Med Chem 57: 1-86 [PMID:29680147]
Cannabinoid receptors

**G protein-coupled receptors → Cannabinoid receptors**

**Overview:** Cannabinoid receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Cannabinoid Receptors [1692]) are activated by endogenous ligands that include N-arachidonoylethanolamine (anandamide), N-homo-γ-linolenoylthanolamine, N-docosatetra-7,10,13,16-enoylthanolamine and 2-arachidonoylglycerol. Potency determinations of endogenous agonists at these receptors are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion [38].

There are currently three licenced cannabinoid medicines each of which contains a compound that can activate CB₁ and CB₂ receptors [1690]. Two of these medicines were developed to suppress nausea and vomiting produced by chemotherapy. These are nabilone (Cesamet®), a synthetic CB₁/CB₂ receptor agonist, and synthetic Δ⁹-tetrahydrocannabinol (Marinol®; dronabinol), which can also be used as an appetite stimulant. The third medicine, Sativex®, contains mainly Δ⁹-tetrahydrocannabinol and cannabidiol, both extracted from cannabis, and is used to treat multiple sclerosis and cancer pain.

### Nomenclature

| Nomenclature | CB₁ receptor | CB₂ receptor |
|--------------|--------------|--------------|
| HGNC, UniProt | CNR1, P21554 | CNR2, P34972 |

### Agonists

| Agonists | HU-210 [590, 1960], CP55940 [590, 1824, 1960], WIN55212-2 [590, 1959, 1960], Δ⁹-tetrahydrocannabinol (Partial agonist) [590, 1960], cannabidiol (Partial agonist) [590, 1960] | HU-210 [590, 1976, 1960], WIN55212-2 [590, 1959, 1960], CP55940 [590, 1824, 1960], Δ⁹-tetrahydrocannabinol (Partial agonist) [121, 590, 1796, 1960] |

### Selective agonists

- arachidonyl-2-chloroethylamide [872] – Rat, arachidonylcyclopropylamide [872] – Rat, O-1812 [489] – Rat, R(−)-methanandamide [1073] – Rat

### Selective antagonists

- rimonabant (pKᵢ 7.9–8.7) [589, 590, 1804, 1835, 1960], AM6545 (pKᵢ 8.5) [217], AM251 (pKᵢ 8.1) [1196] – Rat, AM281 (pKᵢ 7.9) [1195] – Rat, LY320135 (pKᵢ 6.9) [589]

### Allosteric modulators

- GAT100 (Negative) (pEC₅₀ 7.7) [1172], ZCZ011 (Positive) (pEC₅₀ 6.3) [943] – Mouse, CAT211 (Positive) [1205], cannabidiol (Negative) [1204]

### Labelled ligands

- [³H]rimonabant (Antagonist) (pKᵢ 8.9–10) [228, 880, 1025, 1698, 1806, 1972, 2118] – Rat

### Comments:

Both CB₁ and CB₂ receptors may be labelled with [³H]CP55940 (0.5 nM; [1960]) and [³H]WIN55212-2 (2–2.4 nM; [1987, 2013]). Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [1608, 2444]. There is evidence for an allosteric site on the CB₁ receptor [1735]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [1692]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have been identified [1692]. Moreover, GPR18, GPR55 and GPR119, although showing little structural similarity to CB₁ and CB₂ receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands [1692].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Further reading on Cannabinoid receptors

Howlett AC et al. (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev. 54: 161-202 [PMID:12037135]
Pertwee RG. (2010) Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. Curr. Med. Chem. 17: 1360-81 [PMID:20166927]
Pertwee RG et al. (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. Pharmacol. Rev. 62: 588-631 [PMID:21079038]

Chemerin receptors

G protein-coupled receptors → Chemerin receptors

Overview: Nomenclature for the chemerin receptors is presented as recommended by NC-IUPHAR [455, 1065]. The chemoattractant protein and adipokine, chemerin (RARRES2, Q99969), has been shown to be the endogenous ligand for both chemerin family receptors. Chemerin_1 was the founding family member, and when GPR1 was de-orphanised it was re-named Chemerin_2 [1065]. Chemerin_1 is also activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is formed via the sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase [66, 67]. In addition, two GPCRs for resolvin D1 (RvD1) have been identified: FPR2/ALX, the lipoxin A_4 receptor, and GPR32, an orphan receptor [1153].

| Nomenclature | chemerin receptor 1 | chemerin receptor 2 |
|--------------|---------------------|---------------------|
| Common abbreviation | Chemerin_1 | Chemerin_2 |
| HGNC, UniProt | CMKLR1, Q99788 | GPR1, P46091 |
| Potency order of endogenous ligands | resolvin E1 > chemerin C-terminal peptide > 18R-HEPE > EPA [66] | – |
| Endogenous agonists | – | chemerin (RARRES2, Q99969) [109] |
| Selective agonists | resolvin E1 | – |
| Labelled ligands | [³H]resolvin E1 (Agonist) [66, 67] | – |
| Comments | CCX832 (structure not disclosed) is a selective antagonist, pK<sub>i</sub>=9.2 [1066]. | Reported to act as a co-receptor for HIV [1952]. See review [455] for discussion of pairing with chemerin. |

Further reading on Chemerin receptors

Kennedy AJ et al. (2018) International Union of Basic and Clinical Pharmacology CIII: Chemerin Receptors CMKLR1 (Chemerin1) and GPR1 (Chemerin2) Nomenclature, Pharmacology, and Function. Pharmacol. Rev. 70: 174-196 [PMID:29279346]

Shin WJ et al. (2018) Mechanisms and Functions of Chemerin in Cancer: Potential Roles in Therapeutic Intervention. Front Immunol 9: 2772 [PMID:30555465]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Chemokine receptors

Overview: Chemokine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Chemokine Receptors [90, 1524, 1525]) comprise a large subfamily of 7TM proteins that bind one or more chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes. Additional hematopoietic and non-hematopoietic roles have been identified for many chemokines in the areas of embryonic development, immune cell proliferation, activation and death, viral infection, and as antibiotics, among others. Chemokine receptors can be divided by function into two main groups: G protein-coupled chemokine receptors, which mediate leukocyte trafficking, and ‘Atypical chemokine receptors’, which may signal through non-G protein-coupled mechanisms and act as chemokine scavengers to downregulate inflammation or shape chemokine gradients [90].

Chemokines in turn can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as β-chemokines; n=28), CXC (also known as α-chemokines; n=17) and CX3C (n=1) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines respectively. C chemokines (n=2) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high-affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. G protein-coupled chemokine receptors are named according to the class of chemokines bound, whereas ACKR is the root acronym for atypical chemokine receptors [91]. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and microbial non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, but CCR5 is the only one demonstrated to play an essential role in HIV/AIDS pathogenesis. The tables include both standard chemokine receptor names [2401] and aliases.

---

| Nomenclature | CCR1 | CCR2 | CCR3 |
|--------------|------|------|------|
| HGNC, UniProt | CCR1, P32246 | CCR2, P41597 | CCR3, P51677 |
| Endogenous agonists | CCL3 (CCL3, P10147) [375, 406, 862, 2443], CCL23 (CCL23, P55773) [375], CCL5 (CCL5, P13501) [406, 862], CCL7 (CCL7, P80098) [375, 775], CCL15 (CCL15, Q16663) [423], CCL14 (CCL14, Q16627) [375], CCL13 (CCL13, Q9616) [423], CCL8 (CCL8, P80075) | CCL2 (CCL2, P13500) [423, 1335, 1461, 1658, 2167], CCL13 (CCL13, Q9616) [1335, 2167], CCL7 (CCL7, P80098) [423, 1335, 2167], CCL11 (CCL11, P1671) (Partial agonist) [1335, 1658], CCL16 (CCL16, O15467) | CCL13 (CCL13, Q9616) [1505, 2167], CCL24 (CCL24, O00175) [1505, 1658], CCL5 (CCL5, P13501) [449], CCL7 (CCL7, P80098) [449], CCL11 (CCL11, P1671) [531, 1108, 1505, 1649, 2167], CCL26 (CCL26, Q9Y258) [1108, 1505, 1658], CCL15 (CCL15, Q16663) [423], CCL28 (CCL28, Q9NR15), CCL8 (CCL8, P80075) |
| Agonists | – | – | CCL11 (Mouse) [449] |
| Endogenous agonists | CCL4 (CCL4, P13236) (pIC50 7.1–7.8) [375, 406] | CCL26 (CCL26, Q9Y258) (pIC50 8.5) [1658] | CXCL10 (CXCL10, P02778), CXCL11 (CXCL11, O14625), CXCL9 (CXCL9, Q07325) |
| Selective antagonists | BX 471 (pK1 8.2–9) [1274], compound 2b-1 (pIC50 8.7) [1552], UCB35625 (pIC50 8) [1849], CP-481,715 (pK1 8) [708] | GSK Compound 34 (pK1 7.6) | banyu () (Inverse agonist) (pK1 8.5) [2247], SB328437 (pK1 8.4), BMS compound 87b (pK1 8.1) [2232] |
| Labelled ligands | [125I]CCL7 (human) (Agonist) [140], [125I]CCL3 (human) (Agonist) [180, 720, 1870], [125I]CCL5 (human) (Agonist) [1870] | [125I]CCL2 (human) (Agonist), [125I]CCL7 (human) (Agonist) | [125I]CCL11 (human) (Antagonist) (pK1 8.3) [2247], [125I]CCL5 (human) (Agonist), [125I]CCL7 (human) (Agonist) |
| Nomenclature | Agonists | Endogenous agonists | Antagonists | Selective antagonists | Selective allosteric modulators | Antibodies | Labelled ligands |
|--------------|----------|---------------------|-------------|----------------------|-------------------------------|------------|-----------------|
| CCR4 CCR5 CCR6 CCR7 CCR8 CCR9 CCR10 | vMIP-III | CCL22 (CCL22, [947], CCL17 (CCL17, Q92583) [947]) | vicriviroc (pKi 9.1) [2043], ancriviroc (pKi 7.8–8.7) [1348, 1647, 2043] | compound Bic (pIC50 7.7) [2396] | – | mogamulizumab (Inhibition) [58, 1962] | [125I]CCL17 (human) (Agonist), [125I]CCL27 (human) (Agonist) |
| HGNCS, UniProt | – | – | – | – | – | – | [125I]CCL17 (human) (Agonist), [125I]CCL27 (human) (Agonist) |
| CCR4, P51679 | – | CCL2 (CCL2, P13501) [87, 1547, 1832], CCL4 (CCL4, P13236) [1547, 1833], CCL8 (CCL8, P80075) [1833], CCL3 (CCL3, P10147) [1547, 1833, 2443], CCL11 (CCL11, P51671) [175], CCL2 (CCL2, P13500) [1547], CCL14 (CCL14, Q16627) [1547], CCL16 (CCL16, O15467) | – | – | – | – | – |
| CCR5, P51681 | – | CCL5 (CCL5, P13501) [87, 1547, 1832], CCL4 (CCL4, P13236) [1547, 1833], CCL8 (CCL8, P80075) [1833], CCL3 (CCL3, P10147) [1547, 1833, 2443], CCL11 (CCL11, P51671) [175], CCL2 (CCL2, P13500) [1547], CCL14 (CCL14, Q16627) [1547], CCL16 (CCL16, O15467) | – | – | – | – | – |
| CCR6, P51684 | – | CCL20 (CCL20, P78556) [22, 86, 1730], beta-defensin 4A (DEFB4A DEF84B) (O15263) [2373] | – | – | – | – | – |
| CCR7, P32248 | – | CCL21 (CCL21, O00585) [2399], CCL19 (CCL19, Q99731) [1640, 2398, 2399] | – | – | – | – | – |
| CCR8, P51685 | – | CCL1 (CCL1, P22362) [441, 819, 948], CCL8 (Mouse) | – | – | – | – | – |
| CCR9, P51686 | – | CCL25 (CCL25, O15444) | – | – | – | – | – |
| CCR10, P46092 | – | CCL27 (CCL27, Q9Y4X3) [901], CCL28 (CCL28, Q9NRJ3) | – | – | – | – | – |
| Nomenclature | CXCR1 | CXCR2 | CXCR3 | CXCR4 | CXCR5 | CXCR6 | CX3CR1 |
|--------------|-------|-------|-------|-------|-------|-------|--------|
| HGNC, UniProt| CXCR1, P25024 | CXCR2, P25025 | CXCR3, P49682 | CXCR4, P61073 | CXCR5, P32302 | CXCR6, O00574 | CX3CR1, P49238 |
| Endogenous agonists | CXCL8 (CXCL8, P10145) [157, 783, 1239, 2316, 2336], CXCL6 (CXCL6, P80162) [2341] | CXCL11 (CXCL11, P09341) [157, 783, 1239, 2316, 2336], CXCL7 (PPBP, P02775) [20], CXCL3 (CXCL3, P19876) [20], CXCL2 (CXCL2, P19875) [20], CXCL5 (CXCL5, P42830) [20], CXCL6 (CXCL6, P80162) [2341] | vCXCL1 [1334], HIV-1 matrix protein p17 [698] | – | – | – | – |
| Agonists | vCXCL1 [1334], HIV-1 matrix protein p17 [698] | vCXCL1 [1334], HIV-1 matrix protein p17 [698] | – | – | – | – | – |
| Selective agonists | – | – | – | – | – | – | – |
| Endogenous antagonists | – | – | – | CCL11 (CCL11, P51671) (pKᵢ 7.2) [2285], CCL7 (CCL7, P80098) (pKᵢ 6.6) [2285] | – | – | – | – |
| Antagonists | – | – | – | – | – | – | – |
| Selective antagonists | – | – | – | navarixin (pIC₅₀ 10.3) [90, 535], danirixin (pIC₅₀ 7.9) [1457], SB 225002 (pIC₅₀ 7.7) [2296], elubixin (pIC₅₀ 7.7) [90], SX-S17 (pIC₅₀ 7.2) [1347] | – | – | T134 (pIC₅₀ 8.4) [2096], mavorixafor (pIC₅₀ 7.9) [1980], HIV-Tat | – | – | – |
| Allosteric modulators | reparixin (Negative) (pIC₅₀ 9) [157] | reparixin (Negative) (pIC₅₀ 6.4) [157] | – | – | – | – | – |
| Labelled ligands | [¹²⁵I]CXCL8 (human) (Agonist) [783, 1802] | [¹²⁵I]CXCL8 (human) (Agonist) [783, 1802], [¹²⁵I]CXCL1 (human) (Agonist), [¹²⁵I]CXCL5 (human) (Agonist), [¹²⁵I]CXCL7 (human) (Agonist) | [¹²⁵I]CXCL10 (human) (Agonist) | [¹²⁵I]CXCL12α (human) (Agonist) [491, 861] | [¹²⁵I]CXCL13 (mouse) (Agonist) [245] – Mouse | [¹²⁵I]CXCL16 (human) (Agonist) | [¹²⁵I]CX3CL1 (human) (Agonist) |
**Nomenclature**

| Protein | HGNC, UniProt | Endogenous ligands | Endogenous agonists | Comments |
|---------|--------------|-------------------|-------------------|----------|
| XCR1 | XCR1, P46094 | – | XCL1 (XCL1, P47992) [619], XCL2 (XCL2, Q9UBD3) [619] | XCL1 cannot be iodinated, but a secreted alkaline phophatase (SEAP)-XCL1 fusion peptide can be used as a probe at XCR1. ACKR1 is used by *Plasmodium vivax* and *Plasmodium knowlesi* for entering erythrocytes. |
| ACKR1 | ACKR1, Q16570 | CXCL5 (CXCL5, P42830), CXCL6 (CXCL6, P80162), CXCL8 (CXCL8, P10145), CXCL11 (CXCL11, O14625), CCL2 (CCL2, P13500), CCL5 (CCL5, P13501), CCL7 (CCL7, P80098), CCL13 (CCL13, P51671), CCL14 (CCL14, Q16627), CCL17 (CCL17, Q92583) | CCL2 (CCL2, P13500), CCL3 (CCL3, P10147), CCL4 (CCL4, P13236), CCL5 (CCL5, P13501), CCL7 (CCL7, P80098), CCL8 (CCL8, P80075), CCL11 (CCL11, P51671), CCL13 (CCL13, Q99616), CCL14 (CCL14, Q16627), CCL17 (CCL17, Q92583), CCL22 (CCL22, O00626) | Several lines of evidence have suggested that CGRP and adrenomedullin could be ligands for ACKR3; however, classical direct binding to the receptor has not yet been convincingly demonstrated [2074]. |
| ACKR2 | ACKR2, Q00590 | – | CXCL12α (CXCL12, P48061) [741, 2015], CXCL11 (CXCL11, O14625) | – |
| ACKR3 | ACKR3, P25106 | – | CCL19 (CCL19, Q99731) [2276], CCL25 (CCL25, O15444) [2276], CCL21 (CCL21, O00585) [2276] | – |
| ACKR4 | ACKR4, Q9NPB9 | – | – | – |
| CCRL2 | CCRL2, O00421 | – | – | – |

**Comments:** Specific chemokine receptors facilitate cell entry by microbes, such as ACKR1 for *Plasmodium vivax*, and CCR5 and CXCR4 for HIV-1. Virally encoded chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ORF74, which encodes a homolog of CXCR2 in *Herpesvirus saimiri* and gamma-Herpesvirus-68), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers. Three chemokine receptor antagonists have now been approved by the FDA: 1) the CCR5 antagonist maraviroc (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and 2) the CXCR4 antagonistplerixafor (Sanofi) for hematopoietic stem cell mobilization with G-CSF (CSF3, P09919) in patients undergoing transplantation in the context of chemotherapy for Hodgkin’s Disease and multiple myeloma; and 3) the CCR4 blocking antibody Poteligeo (mogamulizumab-kpc, Kyowa Kirin, Inc.) for mycosis fungoides or Sezary syndrome.
Cholecystokinin receptors

G protein-coupled receptors → Cholecystokinin receptors

Overview: Cholecystokinin receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on CCK receptors [1598]) are activated by the endogenous peptides cholecystokinin-8 (CCK-8 (CCK, P06307)), CCK-33 (CCK, P06307), CCK-S8 (CCK, P06307) and gastrin (gastrin-17 (GAST, P01350)). There are only two distinct subtypes of CCK receptors, CCK1 and CCK2 receptors [1139, 2263], with some alternatively spliced forms most often identified in neoplastic cells. The CCK receptor subtypes are distinguished by their peptide selectivity, with the 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 each CCK and gastrin peptides. These receptors have characteristic and distinct distributions, with both present in both the central nervous system and peripheral tissues.

| Nomenclature   | CCK1 receptor       | CCK2 receptor       |
|----------------|---------------------|---------------------|
| HGNC, UniProt  | CCKAR, P32238       | CCKBR, P32238       |
| Potency order of endogenous ligands | CCK-8 (CCK, P06307), CCK-S8 (CCK, P06307), CCK-33 (CCK, P06307) ≥ gastrin-17 (GAST, P01350), desulfated cholecystokinin-8 ≥ CCK-4 (CCK, P06307) | CCK-8 (CCK, P06307), CCK-33 (CCK, P06307) ≥ gastrin-17 (GAST, P01350), desulfated cholecystokinin-8, CCK-4 (CCK, P06307) |
| Endogenous agonists | CCK-33 (CCK, P06307), CCK-39 (CCK), CCK-S8 (CCK, P06307), CCK-8 (CCK, P06307) | desulfated cholecystokinin-8 [1242], gastrin-17 (GAST, P01350) [931] – Mouse, CCK-4 (CCK, P06307) [957], desulfated gastrin-14 (GAST, P01350) [935], desulfated gastrin-17 (GAST, P01350) [935], desulfated gastrin-34 (GAST, P01350) [935], desulfated gastrin-71 (GAST, P01350), gastrin-14 (GAST, P01350), gastrin-34 (GAST, P01350), gastrin-71 (GAST, P01350) |
| Selective agonists | A-71623 [74] – Rat, JM180 [1068], GW-5823 [851] | RB-400 [138] – Rat, PBC-264 [974] – Rat |
| Antagonists    | Devazepide (pIC<sub>50</sub> 9.7) [931] – Rat, T-0632 (pIC<sub>50</sub> 9.6) [2103] – Rat, PD-140548 (pIC<sub>50</sub> 8.6) [1977] – Rat, Lorglumide (pIC<sub>50</sub> 6.7–8.2) [931, 963] – Rat |
| Selective antagonists | YF-476 (pIC<sub>50</sub> 9.7) [218, 2094], GV150013 (pIC<sub>50</sub> 9.4) [2180], L-740093 (pIC<sub>50</sub> 9.2) [1590], YM-022 (pIC<sub>50</sub> 9.2) [1590], JNJ-26070109 (pIC<sub>50</sub> 8.5) [1510], L-365260 (pIC<sub>50</sub> 8.4) [1242], RP73870 (pIC<sub>50</sub> 8) [1291] – Rat, LY262691 (pIC<sub>50</sub> 7.5) [1773] – Rat |
| Labelled ligands | [3H]Devazepide (Antagonist) (pK<sub>a</sub> 9.7) [338], [125I]D Tyr-Gly-[I(Nle28,31)]CCK-26-33 (Agonist) [1731] | [3H]PD140376 (Antagonist) (pK<sub>a</sub> 9.7–10) [935] – Guinea pig, [125I]PD142308 (Antagonist) (pK<sub>a</sub> 9.6) [905] – Guinea pig, [125I]D Tyr-Gly-[I(Nle28,31)]CCK-26-33 (Agonist) [1731], [125I]gastrin (Agonist), [3H]gastrin (Agonist), [3H]L365260 (Agonist) (pK<sub>a</sub> 8.2–8.5) [1590], [125I]-BDZ2 (Antagonist) (pK<sub>a</sub> 8.4) [27] |

Further reading on Chemokine receptors

Bachelerie F et al. (2015) An atypical addition to the chemokine receptor nomenclature: IUPHAR Review 15. Br. J. Pharmacol. 172: 3945-9 [PMID:25958743]

Coelink P et al. (2012) Targeting chemokine receptors in chronic inflammatory diseases: an extensive review. Pharmacol. Ther. 133: 1-18 [PMID:21839114]

Murphy PM. (2002) International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. Pharmacol. Rev. 54: 227-9 [PMID:12037138]

Murphy PM et al. (2000) International Union of Pharmacology. XXII. Nomenclature for chemokine receptors. Pharmacol. Rev. 52: 145-176 [PMID:10699158]

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

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full

Cholecystokinin receptors
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 [1995], 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 [2012], with alternative donor sites in exon 4 resulting in long (452 amino acids) and short (447 amino acids) forms of the receptor differing by five residues in ICL3, however, no clear functional differences have been observed.

Further reading on Cholecystokinin receptors

Ballaz S. (2017) The unappreciated roles of the cholecystokinin receptor CCK(1) in brain functioning. Rev Neurosci 28: 573-585 [PMID:28343167]

Cawston EE et al. (2010) Therapeutic potential for novel drugs targeting the type 1 cholecystokinin receptor. Br. J. Pharmacol. 159: 1009-21 [PMID:19922535]

Dockray GJ. (2009) Cholecystokinin and gut-brain signalling. Regul. Pept. 155: 6-10 [PMID:19345244]

Dufresne M et al. (2006) Cholecystokinin and gastrin receptors. Physiol. Rev. 86: 805-47 [PMID:16816139]

Class Frizzled GPCRs

G protein-coupled receptors → Class Frizzled GPCRs

Overview: Receptors of the Class Frizzled (FZD, nomenclature as agreed by the NC-IUPHAR subcommittee on the Class Frizzled GPCRs [1902]), are GPCRs originally identified in Drosophila [332], which are highly conserved across species. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it mediates effects in the Hedgehog signalling pathway [1902]. FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription regulator 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 LRPS6 (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 heterotrimeric G proteins [496, 1694, 1903], the elevation of intracellular calcium [1989], activation of cGMP-specific PDE6 [21] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [802]. Novel resonance energy transfer-based tools have allowed the study of the GPCR-like nature of FZDs in greater detail. Upon ligand stimulation, FZDs undergo conformational changes and signal via heterotrimeric G proteins [2332, 2333]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling. Importantly, FZDs exist in at least two distinct conformational states that regulate the pathway selection [2333]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [354], as well as for β-catenin-dependent [262] and -independent [263, 1084] signalling. The pattern of cell signalling is complicated by the presence of additional ligands, which can enhance or inhibit FZD signalling (secreted Frizzled-related proteins (sFRP), Wnt-inhibitory factor (WIF1, Q9Y5W5) (WIF), sclerostin (SOST, Q9QBO4) or Dickkopf (DKK)), as well as modulatory (co-)receptors with Ryk, ROR1, ROR2 and Kremen, which may also function as independent signalling proteins.
| Nomenclature | FZD₁ | FZD₂ | FZD₃ | FZD₄ | FZD₅ |
|--------------|------|------|------|------|------|
| HGNC, UniProt | FZD₁, Q9UP38 | FZD₂, Q14332 | FZD₃, Q9NPG1 | FZD₄, Q9ULV1 | FZD₅, Q13467 |
| Allosteric modulators | – | – | – | Fzm1.8 (Negative) (pIC₅₀: 5.5–7.8) [679], Fzm1.8 (Positive) (pEC₅₀: 6.4) [1799], Fzm1 | – |
| Antibodies | vantictumab (Antagonist) (pIC₅₀: ~9.1) [771] | vantictumab (Antagonist) (pIC₅₀: ~9) [771] | – | vantictumab (Antagonist) (pIC₅₀: ~9) [771] |
| Comments | – | – | – | IgG-2919 and IgG-2921 are FZD₅ antibodies that have exhibited antitumour activities in vitro and in vivo (inhibiting the growth of RNF43-mutant pancreatic ductal adenocarcinoma cells/xenograft tumours), by blocking autocrine Wnt-β-catenin signalling in these mutant, FZD₅-dependent cells [2029]. |

| Nomenclature | FZD₆ | FZD₇ | FZD₈ | FZD₉ | FZD₁₀ |
|--------------|------|------|------|------|-------|
| HGNC, UniProt | FZD₆, O60353 | FZD₇, O75084 | FZD₈, Q9H461 | FZD₉, O00144 | FZD₁₀, Q9ULW2 |
| Selective antagonists | – | Fz7-21 (pIC₅₀: 7) [1589] | – | – | – |
| Antibodies | – | vantictumab (Antagonist) (pIC₅₀: ~9) [771] | vantictumab (Antagonist) (pIC₅₀: ~8) [771] | – | – |
| Comments | – | – | FZD₈-Fc/OMP-54F28 is a FZD₈ antagonist [477] | – | Radio-labelled murine monoclonal antibody MAb 92-13 has been used to demonstrate the therapeutic potential of targeting FZD₁₀-positive tumours [639]. |
### Nomenclature

| Nomenclature     | SMO |
|------------------|-----|
| HGNC, UniProt    | SMO, Q99835 |

### Agonists

**SMO agonist (SAG)** [350] – Mouse, purmorphamine [1978]

### Antagonists

**MRT-92** (pKi 9.5) [890], **SANT-1** (pKi 7.7) [350] – Mouse, cyclopamine-KAAD (pIC50 7.7) [2080] – Mouse, cyclopamine (pIC50 ~7) [2162] – Mouse

### Selective antagonists

**vismodegib** (pKi 7.8) [2252]

### Allosteric modulators

**GSA-10** (Positive) (pEC50 5.9) [726]

### Comments

SANT-3 and SANT-4 are SMO antagonists [350].

### 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) (pEC50 7.7-8.9 [2332]), **Wnt-5b** (WNT5B, Q9H1J7), **Wnt-6** (WNT6, Q9Y6F9), **Wnt-7a** (WNT7A, Q9H1J5), **Wnt-7b** (WNT7B, P56706), **Wnt-8a** (WNT8A, Q9H1J5), **Wnt-8b** (WNT8B, Q9J098), **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

- norrin (NDP, Q00604), R-spondin-4 (RSPO4, Q2105S), sFRP-1 (SFRP1, Q8N474), sFRP-2 (SFRP2, Q9K6H1), sFRP-3 (FRZB, Q92765), sFRP-4 (SFRP4, Q6FHJ7), sFRP-5 (SFRP5, Q6FHJ7).

#### Extracellular proteins that interact with WNTs or LRPs

- Dickkopf 1 (DKKI, Q94907), WIF1 (Q9YSW5), sclerostin (SOST, Q9Q6B4), kremen 1 (KREMEN1, Q96M8U) and kremen 2 (KREMEN2, Q8NCW0)

#### Small exogenous ligands

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

### Ligands associated with SMO signalling

- cholesterol, oxysterols [278, 1325, 1761].

### Further reading on Class Frizzled GPCRs

- Angers S et al. (2009) Proximal events in Wnt signal transduction. *Nat. Rev. Mol. Cell Biol.* **10**: 468-77 [PMID:19536106]
- Schulte G. (2015) Frizzleds and WNT/β-catenin signaling—The black box of ligand-receptor selectivity, complex stoichiometry and activation kinetics. *Eur. J. Pharmacol.* **763**: 191-5 [PMID:26003275]
- Schulte G et al. (2018) Frizzleds as GPCRs - More Conventional Than We Thought! *Trends Pharmacol. Sci.* **39**: 828-842 [PMID:30049420]
- van Amerongen R. (2012) Alternative Wnt pathways and receptors. *Cold Spring Harb Perspect Biol* **4**: [PMID:22935904]
- Wang Y et al. (2016) Frizzled Receptors in Development and Disease. *Curr. Top. Dev. Biol.* **117**: 113-39 [PMID:26969975]
Complement peptide receptors

G protein-coupled receptors → Complement peptide receptors

**Overview:** Complement peptide receptors (nomenclature as agreed by the NC-IUPHAR subcommittee on Complement peptide receptors [1114]) are activated by the endogenous 75 amino-acid anaphylatoxin polypeptides C3a (C3, P01024) and C5a (C5, P01031), generated upon stimulation of the complement cascade. C3a and C5a exert their functions through binding to their receptors (C3AR and C5aR), causing cell activation and triggering cellular degranulation that contributes to the local inflammation.

| Nomenclature | C3a receptor | C5a receptor | C5a2 receptor |
|--------------|--------------|--------------|---------------|
| HGNC, UniProt | C3AR1, Q16581 | C5AR1, P21730 | CSAR2, Q9P296 |
| Potency order of endogenous ligands | C3a (C3, P01024) > C5a (C5, P01031) [45] | C5a (C5, P01031), C5a des-Arg (C5) > C3a (C3, P01024) [45] | – |
| Agonists | compound 17 [1786], compound 21 [1785], casoxin C [2082, 2042], albutensin A [2086, 2042], oryzatensin [1003, 2083, 2042] | NDT9513727 (Inverse agonist) [244], N-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO₂H [1054, 1136], lactomedin 1 [2276, 2042] | – |
| Selective agonists | – | – | PS9 (Biased agonist) [434], P32 (Biased agonist) [434] |
| Antagonists | SB290157 (pIC\textsubscript{50} 7.6) [44], compound 4 (pIC\textsubscript{50} 5.9) [1785] | Avacopan (pIC\textsubscript{50} 9.7) [134], W54011 (pK\textsubscript{i} 8.7) [2056], DF2593A (pIC\textsubscript{50} 8.3) [1499], AcPhe-Orn-Pro-D-Cha-Arg [pIC\textsubscript{50} 7.9] [2323], N-methyl-Phe-Lys-Pro-D-Cha-Trp-Arg-CO₂H (pIC\textsubscript{50} 7.2) [1136] | – |
| Labelled ligands | [\textsuperscript{125}I]C3a (human) (Agonist) [342] | [\textsuperscript{125}I]C5a (human) (Agonist) [929] | [\textsuperscript{125}I]C5a (human) (Agonist) |
| Comments | C3a-C3AR signalling plays a crucial role in inhibiting neural progenitor cell proliferation during neurodevelopment, playing a critical role in the normal development of the mammalian brain [426]. | – | – |

**Comments:** SB290157 has also been reported to have agonist properties at the C3a receptor [1396]. The putative chemoattractant receptor termed C5a\textsubscript{2} (also known as GPR77, C5L2) binds \textsuperscript{125}I-C5a with no clear signalling function, but has a putative role opposing inflammatory responses [291, 655, 673]. Binding to this site may be displaced with the rank order C5a des-Arg (C5) > C5a (C5, P01031) [291, 1631] while there is controversy over the ability of C3a (C3, P01024) and C3a des Arg (C3, P01024) to compete [902, 1029, 1030, 1631]. C5a\textsubscript{2} appears to lack G protein signalling and has been termed a decoy receptor [1910]. However, C5a\textsubscript{2} does recruit arrestin after ligand binding, which might provide a signalling pathway for this receptor [103, 2192], and forms heteromers with C5a\textsubscript{1}. C5a, but not C5a-des Arg, induces upregulation of heteromer formation between complement C5a receptors C5a\textsubscript{1} and C5a\textsubscript{2} [433]. There are also reports of pro-inflammatory activity of C5a\textsubscript{2}, mediated by HMGB1, but the signaling pathway that underlies this is currently unclear (reviewed in [1271]). More recently, work in T cells has shown that C5a\textsubscript{1} and C5a\textsubscript{2} act in opposition to each other and that altering the equilibrium between the two receptors, by differential expression or production of C5a-des Arg (which favours C5a\textsubscript{2}), can affect the final cellular response [61].
Corticotropin-releasing factor receptors

G protein-coupled receptors → Corticotropin-releasing factor receptors

Overview: Corticotropin-releasing factor receptors are non-selectively activated by CRF and UCNs. CRF receptors can be conducted using radioligands labeled with [125I]Tyr3-CRF or [125I]Tyr3-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. CRF1 receptors are selectively antagonized by small molecules NBI27914, R121919, antalarmin, CP 154,526, CP 376,395. CRF2 receptors are selectively antagonized by antisauvagine and astressin 2B.

Nomenclature

CRF1 receptor: CRH1, P34998
CRF2 receptor: CRH2, Q13324

HGNC, UniProt

CRF1 receptor: CRH1
CRF2 receptor: CRH2

Endogenous agonists

urocortin 1 (UCN, P55089) [451, 453, 508], corticotropin-releasing hormone (CRH, P06850) [353, 450, 453, 508, 1648, 2212]

Antagonists

SSR125543A (pKᵢ 8.7) [766], astressin (pKᵢ 8.7) [1812]

Selective antagonists

CP 154,526 (pIC₅₀ 9.3-10.4) [1328] – Rat, DMP696 (pKᵢ 8.3-9) [835], NBI27914 (pKᵢ 8.3-9) [346], R121919 (pKᵢ 8.3-9) [2442], antalarmin (pKᵢ 8.3-9) [2278], CP 376,395 (pIC₅₀ 8.3) [355] – Rat, CRA1000 (pIC₅₀ 6.4-7.1) [330]

NBI27914 (pKᵢ 8.3) [1211], K31440 (pKᵢ 8.7-8.8) [1846]

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

Further reading on Corticotropin-releasing factor receptors

Deussing JM et al. (2018) The Corticotropin-Releasing Factor Family: Physiology of the Stress Response. Physiol. Rev. 98: 2225-2286 [PMID:30109816]

Grammatopoulos DK. (2012) Insights into mechanisms of corticotropin-releasing hormone receptor signal transduction. Br. J. Pharmacol. 166: 85-97 [PMID:21883143]

Li R et al. (2013) CSL2: a controversial receptor of complement anaphylatoxin, C5a. FASEB J. 27: 855-64 [PMID:23239822]

Hauger RL et al. (2003) International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. Pharmacol Rev. 55: 21-26 [PMID:12615952]

Liapakis G et al. (2011) Members of CRF family and their receptors: from past to future. Curr. Med. Chem. 18: 2583-600 [PMID:21568890]

S.P.H. Alexander et al. The Concise Guide to PHARMACOLOGY 2019/20: G protein-coupled receptors. British Journal of Pharmacology (2019) 176, S21–S141

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Dopamine receptors

G protein-coupled receptors → Dopamine receptors

Overview: Dopamine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Dopamine Receptors [1906]) are commonly divided into D₁-like (D₁ and D₅) and D₂-like (D₂, D₃ and D₄) families, where the endogenous agonist is dopamine.

| Nomenclature                  | D₁ receptor | D₂ receptor |
|-------------------------------|-------------|-------------|
| HGNC, UniProt                 | DRD1, P21728| DRD2, P14416|
| Sub/family-selective labelled ligands | [125I]SCH23982 (Antagonist) (pKᵦ 9.5) [478], [3H]SCH-23390 (Antagonist) (pKᵦ 9.5) [2435] | [3H]Spirine (Antagonist) (pKᵦ 10.2) [266, 888, 2433] – Rat |
| Endogenous agonists           | dopamine [2060, 2132] | dopamine [272, 628, 1876] |
| Agonists                      | fenoldopam [2132] | rotigotine [1451], aripiprazole (Partial agonist) [2410], bromocriptine [628, 1451, 1876], ML51547 (Biased agonist) [627], ropinirole [843], apomorphine (Partial agonist) [272, 628, 1451, 1876, 2006], pramipexole [1446, 1876], benzquinamide [744] |
| Sub/family-selective agonists | A68930 [1569], SKF-38393 (Partial agonist) [2060, 2132] | quinpirole [272, 1446, 1665, 2006, 2008, 2196] |
| Selective agonists            | SKF-83959 (Biased agonist) [413], A77636 [1844], SKF-81297 [50] – Rat | sumanirole [1415] |
| Antagonists                   | flupentixol (pKᵦ 7–8.4) [2060, 2132] | bionanserin (pKᵦ 9.9) [1611], pipotizine (pKᵦ 9.7) [2007], perphenazine (pKᵦ 8.9–9.6) [1156, 1920], risperidone (pKᵦ 9.4) [70], perospirone (pKᵦ 9.2) [1919], trifluoperazine (pKᵦ 8.9–9) [1156, 1920], quetiapine (pKᵦ 7.2) [70] |
| Sub/family-selective antagonists | SCH-23390 (pKᵦ 7.4–9.5) [2060, 2132], SKF-83566 (pKᵦ 9.5) [2060], ecopipam (pKᵦ 8.3) [2133] | haloperidol (pKᵦ 7.4–8.8) [628, 1341, 1446, 2006, 2133] |
| Selective antagonists          | – | L-741,626 (pKᵦ 7.9–8.5) [755, 1171], domperidone (pKᵦ 7.9–8.4) [628, 2006], raclopride (pKᵦ 8) [1453], ML321 (pKᵦ 7) [2347, 2348], [3H]Raclopride (Antagonist) (pKᵦ 8.9) [1184] – Rat |
| Labelled ligands               | – | – |
Dopamine receptors (D1–5) are a family of G-protein-coupled receptors (GPCRs) that play a crucial role in mediating various physiological and behavioral functions. The D1 receptor family includes subtypes D1, D2, D3, D4, and D5, each with distinct pharmacological profiles and functional implications.

**Nomenclature**
- **D1 receptor**
- **D2 receptor**
- **D3 receptor**
- **D4 receptor**
- **D5 receptor**

**HGNC, UniProt**
- DRD3, P35462
- DRD4, P21917
- DRD5, P21918

**Sub/family-selective labelled ligands**
- **Dopamine** [272, 628, 1876, 2008]
- [3H]Spiperone (Antagonist) (pKᵦ 9.5) [866, 2196]
- [3H]SCH-23390 (Antagonist) (pKᵦ 9.2) [1797]

**Endogenous agonists**
- Pramipexole [1446, 1876], bromocriptine (Partial agonist) [628, 1451, 1876], ropinirole [843], apomorphine (Partial agonist) [272, 628, 1451, 1876]

**Agonists**
- Quinpirole [272, 1446, 1453, 1665, 1876, 2006, 2196]
- Apomorphine (Partial agonist) [1451]

**Sub/family-selective agonists**
- Quinpirole [272, 1446, 1453, 1665, 1876, 2006, 2196]

**Selective agonists**
- PD 128907 [1745, 1876]
- PD 168,077 (Partial agonist) [1141] – Rat, A412997 [1491] – Rat, A412997 [1491]

**Antagonists**
- Perospirone (pKᵦ 9.6) [2006], sertindole (pKᵦ 8.8) [70, 1901, 1920], prochlorperazine (pKᵦ 8.4) [79], (-)-sulpiride (pKᵦ 6.7–7.7) [628, 2006, 2102], clozapine (pKᵦ 7.7) [1920], dopaminede (pKᵦ 7.1–7.6) [628, 2006], promazine (pKᵦ 6.8) [273]

**Sub/family-selective antagonists**
- Haloperidol (pKᵦ 7.5–8.6) [628, 1939, 2006, 2133]
- L745870 (pKᵦ 9.4) [2006], SKF-83566 (pKᵦ 9.4) [2006], ecopipam (pKᵦ 8.3) [2006]

**Selective antagonists**
- S33084 (pKᵦ 9.6) [1450], nafadotride (pKᵦ 9.5) [1877], PG01037 (pKᵦ 9.2) [756], NCB 2904 (pKᵦ 8.8) [2343], SB 277011-A (pKᵦ 8) [1783], (-)-5-14297 (pKᵦ 6.9–7.9) [1448, 1451]

**Selective allosteric modulators**
- SB269652 (Negative) (pKᵦ ~9) [642]

**Labelled ligands**
- [3H]Spiperone (Antagonist) (pKᵦ 9.9) [888, 2433]
- [3H]7-OH-DPAT (Agonist) [1798], [3H]PD128907 (Agonist) [29]

**Notes:** 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 D1), 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 D3 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.
Further reading on Dopamine receptors

Beaulieu JM et al. (2015) Dopamine receptors - IUPHAR Review 13. Br. J. Pharmacol. 172: 1-23 [PMID:25671228]

Beaulieu JM et al. (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol. Rev. 63: 182-217 [PMID:21303898]

Cumming R. (2011) Absolute abundances and affinity states of dopamine receptors in mammalian brain: A review. Synapse 65: 892-909 [PMID:21308799]

Maggio R. et al. (2010) Dopamine D2-D3 receptor heteromers: pharmacological properties and therapeutic significance. Curr Opin Pharmacol 10: 100-7 [PMID:19896900]

Ptácek R et al. (2011) Dopamine D4 receptor gene DRD4 and its association with psychiatric disorders. Med. Sci. Monit. 17: RA215-20 [PMID:21873960]

Schwartz J-C et al. (1998) Dopamine Receptors. In The IUPHAR Compendium of Receptor Characterization and Classification Edited by Girdlestone D: IUPHAR Media: 141-151

Undieh AS. (2010) Pharmacology of signaling induced by dopamine D(1)-like receptor activation. Pharmacol. Ther. 128: 37-60 [PMID:20547182]

Endothelin receptors

G protein-coupled receptors → Endothelin receptors

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

| Nomenclature | ET<sub>A</sub> receptor | ET<sub>B</sub> receptor |
|--------------|---------------------------|------------------------|
| HGNC, UniProt| EDNRA, P25101             | EDNRB, P24530          |
| Potency order of endogenous ligands | endothelin-1 (EDN1, P05305) = endothelin-2 (EDN2, P20800) > endothelin-3 (EDN3, P14138) [1353] | endothelin-1 (EDN1, P05305) = endothelin-2 (EDN2, P20800), endothelin-3 (EDN3, P14138) [1854] |
| Selective agonists | – | sarafotoxin S6c [1163, 1838], BQ 3020 [1793], [Ala<sup>1,3,11,15</sup>]ET-1 [1471], IRL 1620 [2268] |
| Antagonists | SB209670 (p<sub>Ki</sub> 9.4) [553] – Rat, TAK 044 (p<sub>A2</sub> 8.4) [2271] – Rat, bosentan (p<sub>A2</sub> 7.2) [403] – Rat | SB209670 (p<sub>Ki</sub> 9.4) [553] – Rat, TAK 044 (p<sub>A2</sub> 8.4) [2271] – Rat, bosentan (p<sub>Ki</sub> 7.1) [1527] |
| Selective antagonists | macitentan (pIC<sub>50</sub> 9.3) [192], sitaxsentan (pIC<sub>50</sub> 8) [2334], FR139317 (Inverse agonist) (pIC<sub>50</sub> 7.3–7.9) [1353], BQ123 (p<sub>A2</sub> 6.9–7.4) [1353], ambrisentan (pIC<sub>50</sub> 7.1) [193] | K-8794 (pIC<sub>50</sub> 8.2) [1951], A192621 (p<sub>Kd</sub> 8.1) [2226], BQ788 (p<sub>Kd</sub> 7.9–8) [1838], IRL 2500 (p<sub>Kd</sub> 7.2) [1838], Ro 46-8443 (pIC<sub>50</sub> 7.2) [232] |
| Labelled ligands | [<sup>125</sup>I]PD164333 (Antagonist) (p<sub>Kd</sub> 9.6–9.8) [457], [<sup>3</sup>H]S0139 (Antagonist) (p<sub>Kd</sub> 9.2), [<sup>125</sup>I]PD151242 (Antagonist) (p<sub>Kd</sub> 9.1) [458], [<sup>3</sup>H]BQ123 (Antagonist) (p<sub>Kd</sub> 8.5) [944] | [<sup>125</sup>I]IRL1620 (Agonist) [1544], [<sup>125</sup>I]BQ3020 (Agonist) [810, 1471, 1693], [<sup>125</sup>I]Ala<sup>1,3,11,15</sup>ET-1 (Agonist) [1471] |

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

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Endothelin receptors S71
Further reading on Endothelin receptors

Clozel M et al. (2013) Endothelin receptor antagonists. Handb Exp Pharmacol 218: 199-227 [PMID:24092342]
Davenport AP. (2002) International Union of Pharmacology. XXIX. Update on endothelin receptor nomenclature. Pharmacol. Rev. 54: 219-26 [PMID:12037137]
Davenport AP et al. (2016) Endothelin. Pharmacol. Rev. 68: 357-418 [PMID:26956245]
Maguire JJ et al. (2014) Endothelin@25 - new agonists, antagonists, inhibitors and emerging research frontiers: IUPHAR Review 12. Br. J. Pharmacol. 171: 5555-72 [PMID:25131455]

G protein-coupled estrogen receptor

**Overview:** The G protein-coupled estrogen receptor (GPER, nomenclature as agreed by the NC-IUPHAR Subcommittee on the G protein-coupled estrogen receptor [1740]) was identified following observations of estrogen-evoked cyclic AMP signalling in breast cancer cells [71], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [304]. There are observations of both cell-surface and intracellular expression of the GPER receptor [1789, 2123]. Selective agonist/antagonists for GPER have been characterized [1740]. Antagonists of the nuclear estrogen receptor, such as fulvestrant [596], tamoxifen [1789, 2123] and raloxifene [1700], as well as the flavonoid ‘phytoestrogens’ genistein and quercetin [1352], are agonists of GPER. A complete review of GPER pharmacology has been recently published [1740]. The roles of GPER in physiological systems throughout the body (cardiovascular, metabolic, endocrine, immune, reproductive) and in cancer have also been reviewed [595, 1203, 1437, 1740, 1741].

| Nomenclature | GPER  |
|--------------|-------|
| HGNC, UniProt | GPER1, Q99527 |
| Agonists | fulvestrant [2123], raloxifene [1700], 4-hydroxytamoxifen [1789] |
| Selective agonists | G-1 [195] |
| Selective antagonists | G36 (pIC50 6.8–6.9) [485], G15 (pIC50 6.7) [484] |
| Labelled ligands | [3H]17β-estradiol (Agonist) [2123] |

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

Further reading on G protein-coupled estrogen receptor

Barton M et al. (2018) Twenty years of the G protein-coupled estrogen receptor GPER: Historical and personal perspectives. J. Steroid Biochem. Mol. Biol. 176: 4-15 [PMID:28347854]
Gaudet HM et al. (2015) The G-protein coupled estrogen receptor, GPER: The inside and inside-out story. Mol. Cell. Endocrinol. 418 Pt 3: 207-19 [PMID:26190834]
Prossnitz ER et al. (2015) International Union of Basic and Clinical Pharmacology. XCVII. G Protein-Coupled Estrogen Receptor and Its Pharmacologic Modulators. Pharmacol. Rev. 67: 505-40 [PMID:26023144]
Prossnitz ER et al. (2015) What have we learned about GPER function in physiology and disease from knockout mice? J. Steroid Biochem. Mol. Biol. 153: 114-26 [PMID:26189910]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Formylpeptide receptors

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

**Overview:** The formylpeptide receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on the formylpeptide receptor family [2387]) respond to exogenous ligands such as the bacterial product fMet-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ANXA1, P04083), cathepsin G (CTSG, P08311), amyloid |β42, serum amyloid A and spinorphin, derived from β-haemoglobin (HBB, P68871).

| Nomenclature | FPR1 | FPR2/ALX | FPR3 |
|--------------|------|----------|------|
| HGNC, UniProt | FPR1, P21462 | FPR2, P25090 | FPR3, P25089 |
| Potency order of endogenous ligands | fMet-Leu-Phe > cathepsin G (CTSG, P08311) > annexin I (ANXA1, P04083) [1224, 2058] | LXA₄ = aspirin triggered lipoxin A₄ = ATLa₂ = resolvin D₁ > LTC₄ = 15-deoxy-LXA₄ ≥ fMet-Leu-Phe [401, 600, 602, 750, 2086] | – |
| Endogenous agonists | – | LXA₄ [1153], resolvin D₁ [1153], aspirin-triggered resolvin D₁ [1152], aspirin triggered lipoxin A₄ | F₂L (HEBP₁, Q9NRV9) [1447] |
| Agonists | fMet-Leu-Phe [630, 1963] | – | – |
| Selective agonists | – | ATLa₂ [765] | – |
| Endogenous antagonists | spinorphin (pIC₅₀ 4.3) [1275, 1526] | – | – |
| Antagonists | t-Boc-FLFLF (pKᵢ 6–6.5) [2288] | – | – |
| Selective antagonists | cyclosporin H (pKᵢ 6.1–7.1) [2288, 2370] | WRWWWWW (pIC₅₀ 6.6) [92], t-Boc-FLFLF (pIC₅₀ 4.3–6) [629, 2030, 2245] | – |
| Labellled ligands | [³H]fMet-Leu-Phe (Agonist) [1137] | [³H]LXA₄ (Agonist) [600, 601] | – |
| Comments | A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [833]. | – | – |

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

**Further reading on Formylpeptide receptors**

Dorward DA *et al.* (2015) The Role of Formylated Peptides and Formyl Peptide Receptor 1 in Governing Neutrophil Function during Acute Inflammation. *Am. J. Pathol.* 185: 1172-1184 [PMID:25791526]

Dufton N *et al.* (2010) Therapeutic anti-inflammatory potential of formyl-peptide receptor agonists. *Pharmacol. Ther.* 127: 175-88 [PMID:20546777]

Liu M *et al.* (2012) G protein-coupled receptor FPR1 as a pharmacologic target in inflammation and human glioblastoma. *Int. Immunopharmacol.* 14: 283-8 [PMID:22863814]

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]

Yazid S *et al.* (2012) Anti-inflammatory drugs, eicosanoids and the annexin A1/FPR2 anti-inflammatory system. *Prostaglandins Other Lipid Mediat.* 98: 94-100 [PMID:22123264]

Ye RD *et al.* (2009) International Union of Basic and Clinical Pharmacology. LXXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol. Rev.* 61: 119-61 [PMID:19498085]

---

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

**Full Contents of ConciseGuide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
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 [485, 2039]) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (including C14:0 (myristic acid), C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (linoleic acid), C18:3 (α-linolenic acid), C20:4 (arachidonic acid), C20:5, n-3 (EPA) and C22:6, n-3 (docosahexaenoic acid)) activate FFA1 [239, 958, 1144] and FFA4 receptors [876, 938, 1617], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA2 [249, 1223, 1591] and FFA3 [249, 1223] receptors. The crystal structure for agonist bound FFA1 has been described [2023].

| Nomenclature  | FFA1 receptor | FFA2 receptor |
|---------------|---------------|---------------|
| HGNC, UniProt | FFAR1, O14842 | FFAR2, O15552 |

Endogenous agonists
docosahexaenoic acid [239, 958], α-linolenic acid [239, 958, 1144], oleic acid [239, 958, 1144], myristic acid [239, 958, 1144]

Selective agonists
AMG-837 [1286], compound 4 [381], TUG-770 [380], TUG-905 [379], GW9508 (Partial agonist) [238], fasilglim [1028, 1558, 2023, 2157]

Selective antagonists
GW1100 (pIC50 6) [238, 2038]

GLPG0974 (pIC50 8.1) [1546, 1715], CATPB (pIC50 6.5) [927]

Comments
A wide range of both saturated and unsaturated fatty acids containing from 6 to 22 carbons have been shown to act as agonists at FFA1 [239, 958, 1144]. Antagonist GW1100 is also an oxytocin receptor antagonist [238]. Fasilglim, TUG-770 and GW9508 are approximately 100 fold selective for FFA1 over FFA4 [238, 380, 1558]. AMG-837 and the related analogue AM6331 have been suggested to have an allosteric mechanism of action at FFA1, with respect to the orthosteric fatty acid binding site [1286, 2353].
| Nomenclature | FFA3 receptor | FFA4 receptor | GPR42 |
|--------------|---------------|---------------|-------|
| HGNC, UniProt| FFAR3, O14843 | FFAR4, Q5NUL3 | GPR42, O15529 |

**Endogenous agonists**
- propanoic acid [249, 1223, 1894, 2352], butyric acid [249, 1223, 1894, 2352], 1-methylcyclopropanecarboxylic acid [1894]
- α-linolenic acid [1955], myristic acid [2275], α-linolenic acid [2100] – Rat, oleic acid [2275]
- 1-methylcyclopropanecarboxylic acid [1894]
- α-linolenic acid [2100] – Rat, oleic acid [2275]
- acetic acid [249, 1223, 1894, 2352]
- –

**Selective agonists**
- compound A [1616], TUG-891 [1955], NCG21 [2065]
- –

**Comments**
Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [1095]. A range of FFA3 selective molecules with agonist and antagonist properties, but which bind at sites distinct from the short chain fatty acid binding site (i.e. allosteric modulators), have been described [196, 926, 1337].

A wide range of both saturated and unsaturated fatty acids containing from 6 to 22 carbons have been shown to act as agonists at FFA4 [382] with a small subset listed above. Compound A [PMID 24997608] exhibits more than 1000 fold selectivity [1616], and TUG-891 50-1000 fold selectivity for FFA4 over FFA1 [1955], dependent on the assay. NCG21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [2057].

Comments: Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [1490], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [2275]. The long FFA4 splice variant has not been identified in other primates or rodents to date [876, 1490].

**Further reading on Free fatty acid receptors**

Bolognini D et al. (2016) The Pharmacology and Function of Receptors for Short-Chain Fatty Acids. *Mol. Pharmacol.* 89: 388-98 [PMID:26719580]

Mancini AD et al. (2013) The fatty acid receptor FFA1/GPR40 a decade later: how much do we know? *Trends Endocrinol. Metab.* 24: 398-407 [PMID:23631851]

Milligan G et al. (2017) Complex Pharmacology of Free Fatty Acid Receptors. *Chem. Rev.* 117: 67-110 [PMID:27299848]

Moniri NH. (2016) Free-fatty acid receptor-4 (GPR120): Cellular and molecular function and its role in metabolic disorders. *Biochem. Pharmacol.* 110-111: 1-15 [PMID:26827942]

Stoddart LA et al. (2008) International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, -2, and -3: pharmacology and pathophysiological functions. *Pharmacol. Rev.* 60: 405-17 [PMID:19047536]

Watterson KR et al. (2014) Treatment of type 2 diabetes by free Fatty Acid receptor agonists. *Front Endocrinol (Lausanne)* 5: 137 [PMID:25221541]
Overview: Functional GABA<sub>B</sub> receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on GABA receptors [215, 1710]) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub> [215, 557, 1709, 1710, 2173]. GABA<sub>B</sub> receptors are widespread in the CNS and regulate both pre- and postsynaptic activity. The GABA<sub>B1</sub> subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10-100-fold less than for the native receptor. Co-expression of GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits allows transport of GABA<sub>B1</sub> to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca<sup>2+</sup> channels (Ca<sub>v</sub>2.1, Ca<sub>v</sub>2.2), or inwardly rectifying potassium channels (Kir3) [159, 215, 216]. The GABA<sub>B1</sub> subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA<sub>B2</sub> subunit mediates G protein-coupled signalling [215, 681, 683, 1709]. The two subunits interact by direct allosteric coupling [1485], such that GABA<sub>B2</sub> increases the affinity of GABA<sub>B1</sub> for agonists and reciprocally GABA<sub>B1</sub> facilitates the coupling of GABA<sub>B2</sub> to G proteins [681, 1161, 1709]. GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α-helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the GABA<sub>B1</sub> subunit but other domains of the proteins also contribute to their heteromerization [159, 270, 1709]. Recent evidence indicates that higher order assemblies of GABA<sub>B</sub> receptor comprising dimers of heterodimers occur in recombinant expression systems and in vivo and that such complexes exhibit negative functional cooperativity between heterodimers [409, 1708]. Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA<sub>B2</sub> subunit to impart altered signalling kinetics and agonist potency to the receptor complex [116, 1907, 2160] and are reviewed by [1711]. The molecular complexity of GABAB receptors is further increased through association with trafficking and effector proteins [Schwenk et al., 2016, Nature Neuroscience 19(2): 233-42] and reviewed by [1707]. Four isoforms of the human GABA<sub>B1</sub> subunit have been cloned. The predominant GABA<sub>B1a</sub> and GABA<sub>B1b</sub> isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA<sub>B1a</sub>-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA<sub>B1b</sub>-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [1749, 2216]. Only the 1a and 1b variants are identified as components of native receptors [215]. Additional GABA<sub>B1</sub> subunit isoforms have been described in rodents and humans [1236] and reviewed by [159].
**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 [215, 634, 635]. Radioligand Kᵦ values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the GABA_B1 subunit [137]. CGP27492 (3-APPA), CGP35024 (3-APMPA) and CGP 44532 act as antagonists at human GABA_A₁ receptors, with potencies in the low micromolar range [634]. In addition to the ligands listed in the table, Ca²⁺ binds to the VTM of the GABA_B1 subunit to act as a positive allosteric modulator of GABA [650]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 [2223] and (+)-BHFF [9, 159, 166, 634]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA_B2 subunit [534, 1709]. In the presence of CGP7930 or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [634]. A negative allosteric modulator of GABA_B activity has been reported [351]. Knock-out of the GABA_B1 subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA_B1⁻/⁻ BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but not familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety [563, 2184]. A similar phenotype has been found for GABA_B2⁻/⁻ BALB/c mice [669].

**Further reading on GABA_B receptors**

Bowery NG et al. (2002) International Union of Pharmacology. XXXIII. Mammalian gamma-aminobutyric acid(B) receptors: structure and function. *Pharmacol Rev.* **54**: 247-264 [PMID:12037141]

Froestl W. (2011) An historical perspective on GABAergic drugs. *Future Med Chem* **3**: 163-75 [PMID:21428811]

Gassmann M et al. (2012) Regulation of neuronal GABA(B) receptor functions by subunit composition. *Nat. Rev. Neurosci.* **13**: 380-94 [PMID:22595784]

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

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

**Overview:** Galanin receptors (provisional nomenclature as recommended by NC-IUPHAR [612]) are activated by the endogenous peptides galanin (GAL, P22466) and galanin-like peptide (GALP, Q9UBC7). Human galanin (GAL, P22466) is a 30 amino-acid non-amidated peptide [579]; in other species, it is 29 amino acids long and C-terminally amidated. Amino acids 1–14 of galanin are highly conserved in mammals, birds, reptiles, amphibia and fish. Shorter peptide species (e.g. human galanin-1–19 [155] and porcine galanin-5–29 [1970]) and N-terminally extended forms (e.g. N-terminally seven and nine residue elongated forms of porcine galanin [156, 1970]) have been reported.

| Nomenclature | GAL\(_1\) receptor | GAL\(_2\) receptor | GAL\(_3\) receptor |
|--------------|---------------------|---------------------|---------------------|
| HGNC, UniProt | GALR\(_1\), P47211 | GALR\(_2\), O43603 | GALR\(_3\), O60755 |
| Potency order of endogenous ligands | galanin (GAL, P22466) > galanin-like peptide (GALP, Q9UBC7) [1623] | galanin-like peptide (GALP, Q9UBC7) > galanin (GAL, P22466) [1623] | galanin-like peptide (GALP, Q9UBC7) > galanin (GAL, P22466) [1197] |
| Agonists | – | galanin(2-29) (rat/mouse) [1651, 22257, 2258, 2259] – Rat | – |
| Selective agonists | – | [D-Trp\(^2\)]galanin-(1-29) [1996] – Rat | – |
| Selective antagonists | 2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC\(_50\) 5.6 [1914]) | M871 (pK\(_i\) 7.9) [2010] | SNAP 398299 (pK\(_i\) 8.3) [1132, 1133, 2069], SNAP 37889 (pK\(_i\) 7.8–7.8) [1132, 1133, 2069] |
| Selective allosteric modulators | – | CYM2503 (Positive) (pEC\(_{50}\) 9.2) [1322] – Rat | – |
| Labelled ligands | \([\^\text{125}}\text{I}\text{[Tyr}^{26}]\text{galanin (human)}\) (Agonist) [608], \([\^\text{125}}\text{I}\text{[Tyr}^{26}]\text{galanin (human)}\) (Agonist) [608] | \([\^\text{125}}\text{I}\text{[Tyr}^{26}]\text{galanin (human)}\) (Agonist) [2258] – Rat | \([\^\text{125}}\text{I}\text{[Tyr}^{26}]\text{galanin (pig)}\) (Agonist) [207, 1997] |
| Comments | – | The CYM2503 PAM potentiates the anticonvulsant activity of endogenous galanin in mouse seizure models [1322]. | – |

**Comments:** Galanin-(1-11) is a high-affinity agonist at GAL\(_1\)/GAL\(_2\) (pK\(_{i}\) 9), and galanin(2-11) is selective for GAL\(_2\) and GAL\(_3\) compared with GAL\(_1\) [1321]. \([\^\text{125}}\text{I}\text{[Tyr}^{26}]\)galanin binds to all three subtypes with K\(_{i}\) values generally reported to range from 0.05 to 1 nM, depending on the assay conditions used [608, 1992, 1996, 1997, 2258]. Porcine galanin-(3-29) does not bind to cloned GAL\(_1\), GAL\(_2\) or GAL\(_3\) receptors, but a receptor that is functionally activated by porcine galanin-(3-29) has been reported in pituitary and gastric smooth muscle cells [758, 2342]. Additional galanin receptor subtypes are also suggested from studies with chimeric peptides (e.g. M15, M35 and M40), which act as antagonists in functional assays in the cardiovascular system [2171], spinal cord [2307], locus coeruleus, hippocampus [114] and hypothalamus [115, 1249], but exhibit agonist activity at some peripheral sites [115, 758]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL\(_1\) receptors expressed endogenously in Bowes human melanoma cells [1623], and at heterologously expressed recombinant GAL\(_1\), GAL\(_2\) and GAL\(_3\) receptors [608, 1996, 1997]. Recent studies have described the synthesis of a series of novel, systemically-active, galanin analogues, with modest preferential binding at the GAL\(_1\) receptor. Specific chemical modifications to the galanin backbone increased brain levels of these peptides after i.v. injection and several of these peptides exerted a potent antidepressant-like effect in mouse models of depression [1847].

**Further reading on Galanin receptors**

Food SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. Pharmacol Rev 57: 279-288 [PMID:15914470]

Lang R et al. (2015) Physiology, signaling, and pharmacology of galanin peptides and receptors: three decades of emerging diversity. Pharmacol. Rev. 67: 118-75 [PMID:25428932]

Lang R et al. (2011) The galanin peptide family in inflammation. Neuropeptides 45: 1-8 [PMID:21087790]

Lawrence C et al. (2011) Galanin-like peptide (GALP) is a hypothalamic regulator of energy homeostasis and reproduction. Front Neuroendocrinol 32: 1-9 [PMID:20558195]

Webling KE et al. (2012) Galanin receptors and ligands. Front Endocrinol (Lausanne) 3: 146 [PMID:23233848]

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

Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
**Ghrelin receptor**

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

**Overview:** The ghrelin receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [456]) is activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (GHRL, Q9UBU3). The human gene encoding the precursor peptide has 83% sequence homology to rat proghrelin, although the mature peptides from rat and human differ by only two amino acids [1399]. Alternative splicing results in the formation of a second peptide, [des-Gln14]ghrelin (GHRL, Q9UBU3) with equipotent biological activity [907]. A unique post-translational modification (octanoylation of Ser3, catalysed by ghrelin O-acyltransferase (MBOAT4, Q969E1) [2374] occurs in both peptides, essential for full activity in binding to ghrelin receptors in the hypothalamus and pituitary, and for the release of growth hormone from the pituitary [1128]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [131], and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin (GHRL, Q9UBU3) function [899]. In cell systems, the ghrelin receptor is constitutively active [900], but this is abolished by a naturally occurring mutation (A204E) that results in decreased cell surface receptor expression and is associated with familial short stature [1652].

| Nomenclature | ghrelin receptor |
|--------------|-----------------|
| HGNC, UniProt| GHSR, Q92847    |
| Potency order of endogenous ligands | ghrelin (GHRL, Q9UBU3) = [des-Gln14]ghrelin (GHRL, Q9UBU3) [130, 1399] |
| Antagonists | liver enriched antimicrobial peptide 2 (LEAP2, Q969E1) (pIC50 8.2) [675] |
| Selective antagonists | GSK1614343 (pIC50 8.4) [1848], GSK1614343 (pKb 8) [1684] – Rat |
| Labelled ligands | [125][His5][ghrelin (human) (Agonist) [1051], [125][Tyr4][ghrelin (human) (Agonist) [1515] |

**Comments:** [des-octanoyl]ghrelin (GHRL, Q9UBU3) has been shown to bind (as [125][Tyr4]-des-octanoyl-ghrelin) and have effects in the cardiovascular system [130], which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified (D-Arg1,D-Phe5,D-Trp7,9,Leu11)substance P, pD2 8.3; [897]). Ulimorelin, described as a ghrelin receptor agonist (pKb 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 [622]. A number of selective antagonists have been reported, including peptidomimetic [1514] and non-peptide small molecules including GSK1614343 [1684, 1848].

**Further reading on Ghrelin receptor**

Andrews ZR. (2011) The extra-hypothalamic actions of ghrelin on neuronal function. Trends Neurosci. 34: 31-40 [PMID:21035199]
Angelidis G et al. (2010) Current and potential roles of ghrelin in clinical practice. J. Endocrinol. Invest. 33: 823-38 [PMID:21293171]
Briggs DI et al. (2011) Metabolic status regulates ghrelin function on energy homeostasis. Neuroendocrinology 93: 48-57 [PMID:21124019]

Callaghan B et al. (2014) Novel and conventional receptors for ghrelin, desacyl-ghrelin, and pharmacologically related compounds. Pharmacol. Rev. 66: 984-1001 [PMID:25107984]
Davenport AP et al. (2005) International Union of Pharmacology. LVI. Ghrelin receptor nomenclature, distribution, and function. Pharmacol. Rev. 57: 541-6 [PMID:16382107]
Glucagon receptor family

G protein-coupled receptors → Glucagon receptor family

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

| Nomenclature | GHRH receptor | GIP receptor | GLP-1 receptor |
|--------------|---------------|--------------|---------------|
| HGNC, UniProt | GHRHR, Q02643 | GIPR, P48546 | GLP1R, P43220 |
| Endogenous agonists | GHRH (GHRH, P01286) | gastric inhibitory polypeptide (GIP, P09681) [2225] | glucagon-like peptide 1-(7-36) amide (GCG, P01275) [1020], glucagon-like peptide 1-(7-37) (GCG, P01275) [498] |
| Agonists | JI-38 [289], sermorelin | – | liraglutide [11199], lixisenatide [2290], WB4-24 [583] |
| Selective agonists | BIM28011 [431], tesamorelin | – | semaglutide [1206], exendin-4 [1460], exendin-4 [1020], exendin-3 (P20394) [1776] |
| Selective antagonists | JV-1-38 (pKₐ 10.1–10.4) [1886, 2205, 206] – Rat, JV-1-38 (pKₐ 10.1) [1886, 2205, 206] – Rat | [Pro³]GIP [672] – Mouse | exendin-(9-39) (pKₐ 8.1) [1020], GLP-1-(9-36) (pIC₅₀ 6.9) [1486] – Rat, T-0632 (pIC₅₀ 4.7) [2131] |
| Labelled ligands | [¹²⁵]GHRH (human) (Agonist) [212] – Rat | [¹²⁵]GIP (human) (Agonist) [648] – Rat | [¹²⁵]GLP-1-(7-36)-amide (Agonist) [1020], [¹²⁵]exendin-(9-39) (Agonist) [8.3] [1020], [¹²⁵]GLP-1-(7-37) (human) (Agonist) |

| Nomenclature | GLP-2 receptor | glucagon receptor | secretin receptor |
|--------------|---------------|------------------|------------------|
| HGNC, UniProt | GLP2R, O95838 | GCGR, P47871 | SCTR, P47872 |
| Endogenous agonists | glucagon-like peptide 2 (GCG, P01275) [2128] | glucagon (GCG, P01275) [1718] | secretin (SCT, P09683) [376] |
| Agonists | teduglutide [1423] | – | – |
| Selective antagonists | – | L-168,049 (pIC₅₀ 8.4) [312], adomeglinavit (pKₐ 8.2) [1059, 1063], des-His¹-[Glu³]glucagon-NH₂ (pAₐ 7.2) [2176, 2177] – Rat, NNC 92-1687 (pKₐ 5) [1345], BAY27-9955 [1695] | [CH₂NH]₄⁺secretin (pKₐ 5.3) [776] |
| Labelled ligands | – | [¹²⁵]glucagon (human, mouse, rat) (Agonist) | [¹²⁵]Tyr¹⁰]secretin-27 (rat) (Agonist) [2172] – Rat |

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

Ahrens B. (2019) Glucagon-like peptide-1 receptor agonists for type 2 diabetes: A rational drug development. *J Diabetes Investig* **10**: 196-201 [PMID:30099845]

Andersen A *et al.* (2018) Glucagon-like peptide 1 in health and disease. *Nat Rev Endocrinol* **14**: 390-403 [PMID:29728598]

Gentilella R *et al.* (2019) Glucagon-like peptide-1 receptor agonists in type 2 diabetes treatment: are they all the same? *Diabetes Metab. Res. Rev.* **35**: e3070 [PMID:30156747]

Graaf Cd *et al.* (2016) Glucagon-Like Peptide-1 and Its Class B G Protein-Coupled Receptors: A Long March to Therapeutic Successes. *Pharmacol. Rev.* **68**: 954-1013 [PMID:27630114]

Romera I *et al.* (2019) A Review of Practical Issues on the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes. *Diabetes Ther* **10**: 5-19 [PMID:30506340]

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]

Zhang Y *et al.* (2017) Cryo-EM structure of the activated GLP-1 receptor in complex with a G protein. *Nature* **546**: 248-253 [PMID:28538729]

---

### Glycoprotein hormone receptors

**G protein-coupled receptors → Glycoprotein hormone receptors**

**Overview:** Glycoprotein hormone receptors (provisional nomenclature [612]) are activated by a non-covalent heterodimeric glycoprotein made up of a common α chain (glycoprotein hormone common alpha subunit (CGA, P01215) with a unique β chain that confers the biological specificity to FSH (CGA FSHB, P01215 P01225), LH (CGA LHB, P01215 P01229), hCG (CGA CGB3, P01215 P01233) or TSH (CGA TSHB, P01215 P01222). There is binding cross-reactivity across the endogenous agonists for each of the glycoprotein hormone receptors. The deglycosylated hormones appear to exhibit reduced efficacy at these receptors [1850].

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

**Further reading on Glycoprotein hormone receptors**

Jiang X *et al.* (2012) Structure of follicle-stimulating hormone in complex with the entire ectodomain of its receptor. *Proc. Natl. Acad. Sci. U.S.A.* **109**: 12491-6 [PMID:22802634]

Kleinau G *et al.* TSH receptor mutations and disease. *Thyroid Disease Manager.* Accessed on 2017-02-23.

Tao YX *et al.* (2009) Follicle stimulating hormone receptor mutations and reproductive disorders. *Prog Mol Biol Transl Sci* **89**: 115-31 [PMID:20374735]

Troppmann B *et al.* (2013) Structural and functional plasticity of the luteinizing hormone/choriogonadotrophin receptor. *Hum. Reprod. Update* **19**: 583-602 [PMID:23686864]

---

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

Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Gonadotrophin-releasing hormone receptors

Overview: GnRH1 and GnRH2 receptors (provisional nomenclature [612]), also called Type I and Type II GnRH receptor, respectively [1456]) have been cloned from numerous species, most of which express two or three types of GnRH receptor [1455, 1456, 1971]. GnRH I (GnRH1, P01148) (p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2) is a hypothalamic decapetide also known as luteinizing hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin or simply as GnRH. It is a member of a family of similar peptides found in many species [1455, 1456, 1971] including GnRH II (GnRH2, O43555) (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 [1455, 1456, 1971]. GnRH1 receptors are expressed by pituitary gonadotropes, where they mediate the effects of GnRH on gonadotropin hormone synthesis and secretion that underpin central control of mammalian reproduction. GnRH analogues are used in assisted reproduction and to treat steroid hormone-dependent conditions [1079]. Notably, agonists cause desensitization of GnRH-stimulated gonadotropin secretion and the consequent reduction in circulating sex steroids is exploited to treat hormone-dependent cancers of the breast, ovary and prostate [1079]. GnRH1 receptors are selectively activated by GnRH I and all lack the COOH-terminal tails in otherGPCRs. GnRH2 receptors do have COOH-terminal tails and (where tested) are selective for GnRH II over GnRH I. GnRH2 receptors are expressed by some primates but not by humans [1496]. Phylogenetic classifications divide GnRH receptors into three [1456] or five groups [2311] and highlight examples of gene loss through evolution, with humans retaining only one ancient gene.

| Nomenclature                  | GnRH1 receptor         | GnRH2 receptor     |
|-------------------------------|------------------------|--------------------|
| HGNC, UniProt                 | GNRRH1, P30968         | GNRRH2, Q96P88     |
| Potency order of endogenous ligands |                        |                    |
| Endogenous agonists           |                        |                    |
| Selective agonists            | buserelin [1555], buserelin [1554], triptorelin [127], leuprolide [2045], goserelein, histrelin, nafarelin |                    |
| Selective antagonists         | icetrolix (pKᵢ 9.5) [1811] |                    |
| Selective antagonists         | cetrorelix (pKᵢ 9.3–10) [128, 129, 2045], abarelix (pKᵢ 9.1–9.5) [2045], degarelix (pKᵢ 8.8) [2194] | trptorelix-1 [1357] – Monkey |
| Labelled ligands              | [125]cetrorelix (Antagonist) (pKᵢ 9.7) [892], [125]triptorelix (Agonist) [480] – Rat, [125]buserelin (Agonist) [1178] – Rat, [125]GnRH I (human, mouse, rat) (Agonist) |                        |

Comments: GnRH1 and GnRH2 receptors couple primarily to Gₛ/₁₁ [752] but coupling to Gₛ and Gₛ is evident in some systems [1157, 1178]. GnRH2 receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [319]. There is increasing evidence for expression of GnRH receptors on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues [357, 814, 1284, 1885]. In some human cancer cell models GnRH II (GnRH2, O43555) is more potent than GnRH I (GnRH1, P01148), implying mediation by GnRH2 receptors [757], but GnRH2 receptors are not expressed by humans because the human GNRHR2 gene contains a frame shift and internal stop codon [1496]. The possibility remains that this gene generates GnRH2 receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (GnRH2, O43555) (see [1560]). Alternatively, evidence for multiple active GnRH receptor conformations [319, 320, 597, 1407, 1456] raises the possibility that GnRH1 receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon a conformation that couples to Gₛ rather than Gₛ₁₁. proteins as in pituitary cells [320, 1407]. Loss-of-function mutations in the GnRH1 receptor and deficiency of GnRH I (GnRH1, P01148) are associated with hypogonadotropic hypogonadism although some ‘loss of function’ mutations may actually prevent trafficking of functional GnRH1 receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists [1230]. Human GnRH1 receptors are poorly expressed at the cell surface because of failure to meet structural quality control criteria for endoplasmic reticulum exit [598, 1232], and this increases susceptibility to point mutations that further impair trafficking [598, 1230]. GnRH receptor signalling may require receptor oligomerization [412, 1155].
Further reading on Gonadotrophin-releasing hormone receptors

Desaulniers AT et al. (2017) Expression and Role of Gonadotropin-Releasing Hormone 2 and Its Receptor in Mammals. *Front Endocrinol (Lausanne)* 8: 269 [PMID:29312140]

Limonta P et al. (2012) GnRH receptors in cancer: from cell biology to novel targeted therapeutic strategies. *Endocr. Rev.* 33: 784-811 [PMID:22778172]

McArdle CA and Roberson MS.. (2015) Gonadotropes and gonadotropin-releasing hormone signaling. In *Knobil and Neill’s Physiology of Reproduction* (4th edition). Edited by Plant TM and Zeleznik AJ.: Elsevier Inc.: [ISBN: 9780123971753]

Millar RP et al. (2004) Gonadotropin-releasing hormone receptors. *Endocr Rev* 25: 235-275 [PMID:15082521]

Tao YX et al. (2014) Chaperoning G protein-coupled receptors: from cell biology to therapeutics. *Endocr. Rev.* 35: 602-47 [PMID:24661201]

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 [1692]. Although there are multiple reports to indicate that GPR18, GPR55 and GPR119 can be activated in vitro by N-arachidonoylglycine, lysophosphatidylglycerol and N-oleoylthanolamide, respectively, there is a lack of evidence for activation by these lipid messengers in vivo. As such, therefore, these receptors retain their orphan status.

| Nomenclature       | GPR18 | GPR55          | GPR119            |
|--------------------|-------|----------------|-------------------|
| HGNC, UniProt      | GPR18, Q14330 | GPR55, Q9Y2T6  | GPR119, Q8TDVS    |
| Potency order       | –     | –              | N-oleoylthanolamide, N-palmitoylethanolamine > SEA (anandamide is ineffective) [1643] |
| Endogenous agonists | N-arachidonoylglycine [1126] | lysophosphatidylglycerol [852, 1625, 2015], 2-arachidonoylglycerophosphoinositol [1627] | N-oleoylthanolamide [389, 1643, 2015], N-palmitoylethanolamine, SEA |
| Selective agonists  | –     | AM251 [852, 1042, 1843] | AS1269574 [2400], PSN632408 [1643], PSN375963 [1643] |
| Selective antagonists | –     | CID16020046 (apparent pA2) (pA2 7.3) [1044], ML193 (pIC50 6.7) [865] | – |
| Comments            | The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on arrestin assays [2015, 2389]. See [455] for discussion. | See reviews [455] and [1961]. | In addition to those shown above, further small molecule agonists have been reported [793]. |

**Comments:** GPR18 failed to respond to a variety of lipid-derived agents in an in vitro screen [2389], but has been reported to be activated by Δ⁹-tetrahydrocannabinol [1422]. GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB1 receptor antagonists/inverse agonists [1692]. It has been reported that lysophosphatidylglycerol acts at other sites in addition to GPR55 [2367]. N-Arachidonoylspermine has been suggested to act as a low efficacy agonist/antagonist at GPR18 in vitro [1420]. It has also been suggested oleoyl-lysophosphatidylcholine acts, at least in part, through GPR119 [1592]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleoylthanolamide-mediated responses suggests additional mechanisms of action [1592].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Histamine receptors

G protein-coupled receptors → Histamine receptors

Overview: Histamine receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors \[871, 1653\]) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues \[871\]. The human and rat H3 receptor genes are subject to significant splice variance \[1653\]. The potency order of histamine at histamine receptor subtypes is H3 = H4 > H2 > H1 \[1653\]. Some agonists at the human H3 receptor display significant ligand bias \[1803\]. Antagonists of all 4 histamine receptors have clinical uses: H1 antagonists for allergies (e.g. cetirizine), H2 antagonists for acid-reflux diseases (e.g. ranitidine), H3 antagonists for narcolepsy (e.g. pitolisant/WAKIX; Registered) and H4 antagonists for atopic dermatitis (e.g. ZPL-3893787; Phase Ila) and vestibular neuritis (AUV) (SENS-111 (Seliforant, previously UR-63325), entered and completed vestibular neuritis (AUV) Phase Ila efficacy and safety trials, respectively) \[75, 2213\].

| Nomenclature | H1 receptor | Selective agonists | Antagonists | Selective antagonists | Labelling ligands |
|--------------|-------------|--------------------|-------------|----------------------|------------------|
| HGNC, UniProt | H1H1, P35367 | methylhistaprodifen \[1923\], histaprodifen \[1283\] | cyproheptadine (pK\text{a} 10.2) \[1469\], promethazin (pK\text{a} 9.6) \[697\], mepyramin (Inverse agonist) (pK\text{a} 8.7–9) \[204, 1775\], cetrizine (Inverse agonist) (pK\text{a} 8.2) \[1469\], diphendydran (pK\text{a} 7.9) \[204\] | clemastin (pK\text{a} 10.3) \[79\], deoloratadine (pK\text{a} 9) \[1266\], triprolidin (pK\text{a} 8.5–9) \[204, 1469\], azelastin (pK\text{a} 8.9) \[1738\], astemizol (pK\text{a} 8.5) \[1673\] | [3H]pyrilamin (Antagonist, Inverse agonist) (pK\text{d} 8.4–9.1) \[464, 1469, 1901, 1923\], [11C]doxepin (Antagonist) (pK\text{d} 9) \[953\], [11C]pyrilamin (Antagonist, Inverse agonist) |
|              | H2 receptor | methylhistaprodifen \[1923\], histaprodifen \[1283\] | cyproheptadine (pK\text{a} 10.2) \[1469\], promethazin (pK\text{a} 9.6) \[697\], mepyramin (Inverse agonist) (pK\text{a} 8.7–9) \[204, 1775\], cetrizine (Inverse agonist) (pK\text{a} 8.2) \[1469\], diphendydran (pK\text{a} 7.9) \[204\] | clemastin (pK\text{a} 10.3) \[79\], deoloratadine (pK\text{a} 9) \[1266\], triprolidin (pK\text{a} 8.5–9) \[204, 1469\], azelastin (pK\text{a} 8.9) \[1738\], astemizol (pK\text{a} 8.5) \[1673\] | [3H]pyrilamin (Antagonist, Inverse agonist) (pK\text{d} 8.4–9.1) \[464, 1469, 1901, 1923\], [11C]doxepin (Antagonist) (pK\text{d} 9) \[953\], [11C]pyrilamin (Antagonist, Inverse agonist) |

Histamine receptors

Histamine receptors S84

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

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

- **H₃ receptor**
  - HGNC, UniProt: HRH3, Q9YSN1
  - Selective agonists: immethridine [1110], methimepip [1109], MK-0249 (Inverse agonist) [1536]
  - Selective antagonists: iodophenpropit (pKᵢ 8.2–8.7) [2305, 2338]
  - Labelled ligands: [¹²³]iodoproxyfan (Antagonist) (pKᵣ 10.2) [1280], [¹²⁵]iodophenpropit (Antagonist) (pKᵣ 9.2) [980] – Rat, [³⁵]H[α]-methylhistamine (Agonist) [1298], N-[³⁵]H[α]-methylhistamine (Agonist) [349] – Mouse

- **H₄ receptor**
  - HGNC, UniProt: HRH4, Q9H3N8
  - Selective agonists: clobenpropit (Partial agonist) [570, 1283, 1298, 1299, 1509], 4-methylhistamine [674, 1283], ST-1006 [1653], VUF 8430 [1282]
  - Selective antagonists: pitolisant (pKᵢ 8.1–8.6) [1653, 2447], A331440 (pKᵢ 8.5) [794], conessine (pKᵢ 8.3) [1653], MK-0249 (pKᵢ 8.2) [1653], thioperamide (Selective for H₃/H₄ compared to H₁ and H₃) (pKᵢ 7.1–7.7) [404, 569, 570, 1280, 1653, 2338], ciproxifan (pKᵢ 6.7–7.3) [404, 569, 570, 1280, 1653, 2338], ZPL-3893787 (pKᵢ 8.3) [2305, 2338] – Rat, INCB-38579 (pKᵢ 8.3) [1653, 2447], JNJ 7777120 (pKᵢ 7.8–8.3) [2305, 2338], JNJ-39758979 (pKᵢ 7.9) [1653, 1878], thioperamide (Selective for H₃/H₄ compared to H₁ and H₃) (pKᵢ 6.3–7.6) [569, 570, 1298, 1299, 1509, 2441], ZPL-3893787 (pKᵢ 8.3) [1653, 2447], INCB-38579 (pKᵢ 8.3) [1653, 2447]
  - Labelled ligands: [¹²³]iodoproxyfan (Antagonist) (pKᵣ 10.2) [1280], [¹²⁵]iodophenpropit (Antagonist) (pKᵣ 9.2) [980] – Rat, [³⁵]H[α]-methylhistamine (Agonist) [1298], N-[³⁵]H[α]-methylhistamine (Agonist) [349] – Mouse

**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 [1298, 1542, 1579, 1612, 2441]. Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H₄ receptor [1283]. [³⁵]Histamine has been used to label the H₄ receptor in heterologous expression systems.

**Further reading on Histamine receptors**

- Gbahou F et al. (2012) The histamine autoreceptor is a short isoform of the H₃ receptor. Br. J. Pharmacol. **166**: 1860-71 [PMID:22356432]
- Nieto-Alamilla G et al. (2016) The Histamine H₃ Receptor: Structure, Pharmacology, and Function. Mol. Pharmacol. **90**: 649-673 [PMID:27563055]
- Panula P et al. (2015) International Union of Basic and Clinical Pharmacology. XCVIII. Histamine Receptors. Pharmacol. Rev. **67**: 601-55 [PMID:26084539]
- van Rijn RM et al. (2008) Cloning and characterization of dominant negative splice variants of the human histamine H₄ receptor. Biochem. J. **414**: 121-31 [PMID:18452403]
Hydroxycarboxylic acid receptors

G protein-coupled receptors → Hydroxycarboxylic acid receptors

Overview: The hydroxycarboxylic acid family of receptors (ENSFM00500000271913, nomenclature as agreed by the NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors [455, 1614]) respond to organic acids, including the endogenous hydroxy carboxylic acids 3-hydroxy butyric acid and L-lactic acid, as well as the lipid lowering agents nicotinic acid (niacin), acipimox and acifran [2004, 2159, 2320]. These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA2 receptors only and is unlikely to be the natural ligand [2159, 2320].

Nomenclature

| Nomenclature | HCA1 receptor | HCA2 receptor | HCA3 receptor |
|--------------|---------------|---------------|---------------|
| HGNC, UniProt | HCAR1, Q9BXC0 | HCAR2, Q8TDS4 | HCAR3, P49019 |

Potency order of endogenous ligands

- β-D-hydroxybutyric acid > butyric acid

Endogenous agonists

- L-lactic acid [18, 290, 1300, 2015]
- 3-hydroxyoctanoic acid [17]

Agonists

- SCH 900271 [1646], GSK256073 [2022]
- compound 2 [1853], 3,5-dihydroxybenzoic acid [1297]
- compound 6o [1981], IBC 293 [1925]
- MK 6892 [1946], MK 1903 [180], nicotinic acid [2004, 2159, 2320], acipimox [2004, 2320], monomethyl fumarate [2101]

Selective agonists

- MK 6892 [1946], MK 1903 [180], nicotinic acid [2004, 2159, 2320], acipimox [2004, 2320], monomethyl fumarate [2101]

Labelled ligands

- [3H]nicotinic acid (Agonist) [2004, 2159, 2320]

Comments: Further closely-related GPCRs include the 5-oxoeicosanoid receptor (OXER1, Q8TDS5) and GPR31 (O00270). Lactate activates HCA1 on adipocytes in an autocrine manner. It inhibits lipolysis and thereby promotes anabolic effects. HCA2 and HCA3 regulate adipocyte lipolysis and immune functions under conditions of increased FFA formation through lipolysis (e.g., during fasting). HCA2 agonists acting mainly through the receptor on immune cells exert antiatherogenic and anti-inflammatory effects. HCA2 is also a receptor for butyrate and mediates some of the beneficial effects of short-chain fatty acids produced by gut microbiota. HCA3 has been shown to be activated by aromatic D-amino acids.

Further reading on Hydroxycarboxylic acid receptors

- Boatman PD et al. (2008) Nicotinic acid receptor agonists. J. Med. Chem. 51: 7653-62 [PMID:18983141]
- Graff EC et al. (2016) Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. Metab. Clin. Exp. 65: 102-13 [PMID:26773933]
- Kamanna VS et al. (2013) Recent advances in niacin and lipid metabolism. Curr. Opin. Lipidol. 24: 239-45 [PMID:23619367]
- Offermanns S et al. (2011) International Union of Basic and Clinical Pharmacology. LXXII: Nomenclature and Classification of Hydroxy-carboxylic Acid Receptors (GPR81, GPR109A, and GPR109B). Pharmacol. Rev. 63: 269-90 [PMID:21454438]
- Offermanns S et al. (2015) Nutritional or pharmacological activation of HCA(2) ameliorates neuroinflammation. Trends Mol Med 21: 245-55 [PMID:25766751]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Kisspeptin receptor

G protein-coupled receptors → Kisspeptin receptor

**Overview:** The kisspeptin receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee on the kisspeptin receptor [1102]), like neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) responds to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. Kisspeptin-54 (KISS1, Q15726) (KP54, originally named metastin), kisspeptin-13 (KISS1, Q15726) (KP13) and kisspeptin-10 (KISS1) (KP10) are biologically-active peptides cleaved from the KISS1 (Q15726) gene product. Kisspeptins have roles in, for example, cancer metastasis, fertility/puberty regulation and glucose homeostasis.

| Nomenclature | kisspeptin receptor |
|--------------|---------------------|
| HGNC, UniProt | KISS1R, Q969F8 |

**Endogenous agonists**
- kisspeptin-10 (KISS1) [1142, 1624], kisspeptin-54 (KISS1, Q15726) [1142, 1624], kisspeptin-14 (KISS1, Q15726) [1142], kisspeptin-13 (KISS1, Q15726) [1142]

**Selective agonists**
- 4-fluorobenzoyl-FGLRW-NH2 [2143], [dY]1 KP-10 [439] – Mouse, TAK-448 [1593]

**Selective antagonists**
- peptide 234 [1822]

**Labelled ligands**
- [125I]Tyr45-kisspeptin-15 (Agonist) [1624], [125I]kisspeptin-13 (human) (Agonist) [1427], [125I]kisspeptin-10 (human) (Agonist) [1142], [125I]kisspeptin-14 (human) (Agonist) [1427], [d-Tyr-14C]TAK-448 (Agonist) [1502]

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

**Further reading on Kisspeptin receptor**

- Harter CJL et al. (2018) The role of kisspeptin neurons in reproduction and metabolism. J. Endocrinol. 238: R173-R183 [PMID:30042117]
- Kanda S et al. (2013) Structure, synthesis, and phylogeny of kisspeptin and its receptor. Adv. Exp. Med. Biol. 784: 9-26 [PMID:23550000]
- Kirby HR et al. (2010) International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. Pharmacol. Rev. 62: 565-78 [PMID:21079036]
- Oakley AE et al. (2009) Kisspeptin signaling in the brain. Endocr. Rev. 30: 713-43 [PMID:19770291]
- Pasquier J et al. (2014) Molecular evolution of GPCRs: Kisspeptin/kisspeptin receptors. J. Mol. Endocrinol. 52: T101-17 [PMID:24577719]

---

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

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

G protein-coupled receptors → Leukotriene receptors

**Overview:** The leukotriene receptors (nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene Receptors [279, 280]) are activated by the endogenous ligands leukotrienes (LT), synthesized from lipoxygenase metabolism of arachidonic acid. The human 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-HPETE, 15S-HPETE, 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 [1288] and the vanilloid TRPV1 ligand-gated nonselective cation channel [1421]. The receptors for the cysteinyl-leukotrienes (i.e. LTC4, LTD4 and 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 [280]. Cysteinyl-leukotrienes have also been suggested to signal through the P2Y12 receptor [625, 1600, 1659], GPR17 [395] and GPR99 [1036].

| Nomenclature | BLT1 receptor | BLT2 receptor | CysLT1 receptor | CysLT2 receptor | OXE receptor | FPR2/ALX |
|--------------|---------------|---------------|-----------------|-----------------|--------------|----------|
| HGNC, UniProt| LTB4R, Q15722 | LTB4R2, Q9NPC1 | CYSLTR1, Q9Y271 | CYSLTR2, Q9NS75 | OXER1, Q8TDSS | FPR2, P25090 |
| Potency order of endogenous ligands | LTB4 > 20-hydroxy-LTB4 ≫12R-HPETE [2395] | 20-hydroxy-LTB4 ≫12R-HPETE ≫15S-HPETE > 12R-HPETE > 20-hydroxy-LTB4 [1633, 2395] | LTDA > LTC4 > LTE4 [1333, 1867] | LTC4 > LTD4 > LTE4 [844, 1604, 2087] | SX-ETO, S-ETO-C20:3, S-ETO-ODE > S-ETO-15-HPETE > SS-HPETE > SS-HETE [739, 908, 1013, 1607, 1664, 1729, 1908] | SX-ETO, S-ETO-C20:3, S-ETO-ODE > S-ETO-15-HPETE > SS-HPETE > SS-HETE [739, 908, 1013, 1607, 1664, 1729, 1908] |
| Endogenous agonists | – | – | – | – | – | – |
| Selective agonists | – | – | – | – | – | – |
| Endogenous antagonists | – |– |– |– |– |– |
| Antagonists | pranlukast (pKi 7.1–8.8) [301, 1777], pobilukast (pKi 7.1) [303] | pranlukast (pA2 7.1) [302], pobilukast (pA2 6.2) [302] | pranlukast (pKi 7.1) [303] | pranlukast (pA2 7.1) [302], pobilukast (pA2 6.2) [302] | – | – |
| Selective antagonists | BIL19260 (pKi 8.8) [168, 536], CP105696 (pIC50 8.1) [1964], U75302 (pKi 6.4) [189] | LY255283 (pIC50 6–7.1) [859, 2395] | ICI198615 (pKi 9.7) [646] – Guinea pig, zafirlukast (zafirlukast is only about 100-fold selective for CysLT1, pKi 8.9) [301, 1777], montelukast (pKi 8.6) [1777], MK-571 (pIC50 8) [1333] | BayCysLT2 (pA4 8.4) [306], BayCysLT2 (pA4 8.3) [306], HAMI3379 (pIC50 7.4) [2339] | – | WRVWWW (pIC50 6.6) [92], t-Boc-FLFLF (pIC50 4.3–6) [629, 2030, 2245] |
| Labelled ligands | [3H]LTB4 (Agonist) [2394], [3H]LCG23131 (Antagonist) (pKd 7.9) [965] | [3H]LTB4 (pKd 7.6–9.7) | [3H]LTD4 (Agonist), [3H]LJCI-198615 (Antagonist) (pKd 10.6) | [3H]LTD4 (Agonist) [844] | [3H]S-ETO-C20:3 (Agonist) [1607] | [3H]LXA4 (Agonist) [600, 601] |

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Lyosphospholipid (LPA) receptors

G protein-coupled receptors → Lyosphospholipid (LPA) receptors

Overview: Lyosphosphatidic acid (LPA) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Lyosphospholipid Receptors [455, 1080]) are activated by the endogenous phospholipid LPA. The first receptor, LPA₁, was identified as ventricular zone gene-1 (vzg-1) [840], leading to deorphanisation of members of the endothelial differentiation gene (edg) family as other LPA receptors along with sphingosine 1-phosphate (SIP) 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 solved and demonstrates extracellular LPA access to the binding pocket, consistent with proposed delivery via autotaxin [378]. These studies have also implicated cross-talk with endocannabinoids via phosphorylated intermediates that can also activate these receptors. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Binding affinities of unlabeled, natural LPA and AEA to LPA₁ were measured using backscattering interferometry (pKₐ = 9) [1466]. Binding affinities were 77-fold lower than values obtained using radioactivity [2371]. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. Independent validation by multiple groups has been reported in the peer-reviewed literature for all six LPA receptors described in the tables, including further validation using a distinct read-out via a novel TGFlite "shedding" assay [949]. LPA has also been described as an agonist for the transient receptor potential (Trp) ion channel TRPV1 [1856] and TRPA1 [1111]. LPA was originally proposed to be a ligand for GPCR35, but data show that in fact it is a receptor for CXCL17 (CXCL17, Q6UXB2) [1379]. All of these proposed non-GPCR receptor identities require confirmation and are not currently recognized as bona fide LPA receptors.

Comments: The FPR2/ALX receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee on Leukotriene and Lipoxin Receptors [280]) is activated by the endogenous lipiderived, anti-inflammatory ligands lipoxin A₄ (LXA₄) and 15-eicosanoid receptors (OXE, nomenclature agreed by the NC-IUPHAR Subcommittee on Oxoeicosanoid Receptors [236]) are activated by endogenous chemotactc eicosanoid ligands oxidised at the C-5 position, with S-oxo-ETE the most potent agonist identified for this receptor. Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as docosahexaenoic acid and EPA, acted as receptor antagonists [908].

Further reading on Leukotriene receptors

Brink C et al. (2004) International Union of Pharmacology XLIV. Nomenclature for the Oxoeicosanoid Receptor. Pharmacol. Rev. 56: 149-157 [PMID:15001665]

Brink C et al. (2003) International Union of Pharmacology XXXVII. Nomenclature for leukotriene and lipoxin receptors. Pharmacol. Rev. 55: 195-227 [PMID:12615958]

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

Bäck M et al. (2014) Update on leukotriene, lipoxin and oxoeicosanoid receptors: IUPHAR Review 7. Br. J. Pharmacol. 171: 3551-74 [PMID:24588652]

Laidlaw TM et al. (2012) Cysteinyl leukotriene receptors, old and new; implications for asthma. Clin. Exp. Allergy 42: 1313-20 [PMID:22925317]

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

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

HGNC, UniProt

Selective agonists

Antagonists

Sub/family-selective antagonists

Selective antagonists

Comments: Ki16425 [1622], VPC12249 [846] and VPC32179 [839] have dual 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 [2408], fetal hyoxia [857], lung fibrosis [1618], systemic sclerosis [1618] and atherosclerosis progression [1154]. The LPA2 selective agonist, GRI977143, also shows efficacy in an animal model of multiple sclerosis [1896]. The LPA5 selective antagonist, AS2717638, is effective in pain models [1058].

Further reading on Lysophospholipid (LPA) receptors

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

Kihara Y et al. (2014) Lysophospholipid receptor nomenclature review: IUPHAR Review 8. Br. J. Pharmacol. 171: 3575-94 [PMID:24602016]

Lysoosphospholipid (S1P) receptors

Overview: Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors [1080]) are activated by the endogenous lipid sphingosine 1-phosphate (S1P). Originally cloned as orphan members of the endothelial differentiation gene (edg) family, current gene names have been designated as S1P1R through S1P5R [884]. S1PRs, particularly S1P1, are expressed throughout all mammalian organ systems. Ligand delivery occurs via two known carriers (or "chaperones"): albumin and HDL-bound apolipoprotein M (ApoM), the latter of which elicits biased agonist signaling by S1P1 in multiple cell types [173, 649]. The five S1PRs, two chaperones, and active cellular metabolism have complicated analyses of receptor ligand binding in native systems. Signaling pathways and physiological roles have been characterized through radioligand binding in heterologous expression sys-

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full

Lysoosphospholipid (S1P) receptors S90
tems, targeted deletion of the different S1PRs, and most recently, mouse models that report in vivo S1PR activation [1134, 1135]. A crystal structure of an S1P1-T4 fusion protein confirmed aspects of ligand binding, specificity, and receptor activation determined previously through biochemical and genetic studies [172, 805]. Fingolimod (FTY720), the first drug to target any of the lysophospholipid receptors, binds to four of the five S1PRs, and was the first oral therapy for multiple sclerosis [390]. The mechanisms of action of fingolimod and other S1PR modulating drugs in development include binding S1PRs in multiple organ systems, e.g., immune and nervous systems, although the precise nature of their receptor interactions requires clarification [405, 753, 754, 1739].

| Nomenclature | S1P₁ receptor | S1P₂ receptor | S1P₃ receptor | S1P₄ receptor | S1P₅ receptor |
|--------------|---------------|---------------|---------------|---------------|---------------|
| HGNC, UniProt | S1PR1, P21453 | S1PR2, O95136 | S1PR3, Q99500 | S1PR4, O95977 | S1PR5, Q9H228 |
| Potency order of endogenous ligands | sphingosine 1-phosphate > dihydrosphingosine 1-phosphate (p49, 1628) | sphingosine 1-phosphate > dihydrosphingosine 1-phosphate (p49, 1628) | sphingosine 1-phosphate > dihydrosphingosine 1-phosphate (p1628) | sphingosine 1-phosphate > dihydrosphingosine 1-phosphate (p2189) | sphingosine 1-phosphate > dihydrosphingosine 1-phosphate (p946) |
| Agonists | fingolimod-phosphate [237, 615], siponimod [709, 1649], etrasimod [275] | – | fingolimod-phosphate [237, 615], fingolimod-phosphate [237, 615] | fingolimod-phosphate [237, 615, 1650, 1864, 2362], etrasimod [274, 275] | fingolimod-phosphate [237, 615, 1650], siponimod [671, 694, 2178], etrasimod [275] |
| Selective agonists | RP-001 [288], ponoseimod [191], cenerimod [1703], CYM4542 [721], SEW2871 [1864] – Mouse | – | CYM-5541 [1004] | CYM-50308 [2179] | A-971432 [490, 889] |
| Antagonists | VPC23019 (pKᵢ 7.9) [460], VPC03090-P (pKᵢ 7.6–7.7) [1069], VPC44116 (pIC₅₀ 7.6) [616] | – | VPC44116 (pKᵢ 6.5) [616], VPC23019 (pKᵢ 5.9) [460] | – | – |
| Selective antagonists | NIBR-0213 (pIC₅₀ 8.6) [1751], WT146 (pKᵢ 7.1) [1865] | JTE-013 (pIC₅₀ 7.8) [1638] | TY-52156 (pKᵢ 7) [1522] | CYM-50358 (pIC₅₀ 7.6) [325, 761] | – |

**Comments:** The FDA-approved immunomodulator fingolimod (FTY720) is phosphorylated in vivo [33] to generate an agonist with activity at S1P₁, S1P₃, S1P₄ and S1P₅ receptors [237, 1371]. Many of the physiological consequences of fingolimod-phosphate administration, as well as those of other currently described S1P₁ agonists, may involve functional antagonism via ubiquitination and subsequent degradation of S1P₁ [1637]. Additionally, receptor specificities of the different compounds may depend on the functional assay system utilized and from which species the receptor sequence originated.

**Further reading on Lysophospholipid (S1P) receptors**

Chew WS et al. (2016) To fingolimod and beyond: The rich pipeline of drug candidates that target S1P signaling. Pharmacol. Res. 113: 521-532 [PMID:27663260]

Chun J et al. (2010) International Union of Basic and Clinical Pharmacology. LXXXVIII. Lysosphospholipid receptor nomenclature. Pharmacol. Rev. 62: 579-87 [PMID:21079037]

Cyster JG et al. (2012) Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. Annu. Rev. Immunol. 30: 69-94 [PMID:22149932]

Pyne NJ et al. (2017) Sphingosine 1-Phosphate Receptor 1 Signaling in Mammalian Cells. Molecules 22: [PMID:28241498]

Rosen H et al. (2013) Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. Annu. Rev. Biochem. 82: 637-62 [PMID:23527695]

Yanagida K et al. (2017) Vascular and Immunobiology of the Circulatory Sphingosine 1-Phosphate Gradient. Annu. Rev. Physiol. 79: 67-91 [PMID:27813829]
Melanin-concentrating hormone receptors

G protein-coupled receptors → Melanin-concentrating hormone receptors

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

| Nomenclature | MCH₁ receptor | MCH₂ receptor |
|--------------|---------------|---------------|
| HGNC, UniProt | MCHR₁, Q99705 | MCHR₂, Q969V1 |
| Selective antagonists | GW803430 (pIC₅₀ 9.3) [860], SNAP-7941 (pA₂ 9.2) [206], T-226296 (pIC₅₀ 8.3) [2093], ATC0175 (pIC₅₀ 7.9–8.1) [329] | – |
| Labelled ligands | [¹²⁵I]S36057 (Antagonist) (pKᵦ 9.2–9.5) [77], [¹²⁵I][Phe¹³,Tyr¹⁹]MCH (Agonist) [269], [³H]MCH (human, mouse, rat) (Agonist) [269] | – |

**Comments:** The MCH₂ receptor appears to be a non-functional pseudogene in rodents [2098].

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

Chung S et al. (2011) Recent updates on the melanin-concentrating hormone (MCH) and its receptor system: lessons from MCH1R antagonists. *J. Mol. Neurosci.* 43: 115-21 [PMID:20582487]
Eberle AN et al. (2010) Cellular models for the study of the pharmacology and signaling of melanin-concentrating hormone receptors. *J. Recept. Signal Transduct. Res.* 30: 385-402 [PMID:21083507]

Foord SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279-288 [PMID:15914470]
Takase K et al. (2014) Meta-analysis of melanin-concentrating hormone signaling-deficient mice on behavioral and metabolic phenotypes. *PLoS ONE* 9: e99961 [PMID:24924345]
Melanocortin receptors

G protein-coupled receptors → Melanocortin receptors

Overview: Melanocortin receptors (provisional nomenclature as recommended by NC-IUPHAR [612]) are activated by members of the melanocortin family (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). ACTH(1-24) was approved by the US FDA as a diagnostic agent for adrenal function test, whilst NDP-MSH was approved by EMA for the treatment of erythropoietic protoporphyria. Several synthetic melanocortin receptor agonists are under clinical development.

| Nomenclature | MC1 receptor | MC2 receptor | MC3 receptor | MC4 receptor | MC5 receptor |
|--------------|--------------|--------------|--------------|--------------|--------------|
| HGNC, UniProt | MC1R, Q01726 | MC2R, Q01718 | MC3R, P41968 | MC4R, P32245 | MC5R, P33032 |
| Potency order of endogenous agonists | α-MSH (POMC, P01189) > β-MSH (POMC, P01189) > ACTH (POMC, P01189) | γ-MSH (POMC, P01189), β-MSH (POMC, P01189) > ACTH (POMC, P01189), α-MSH (POMC, P01189) | β-MSH (POMC, P01189) > ACTH (POMC, P01189), α-MSH (POMC, P01189), γ-MSH (POMC, P01189) | α-MSH (POMC, P01189) > β-MSH (POMC, P01189) > ACTH (POMC, P01189) |
| Selective agonists | – | corticotropin zinc hydroxide | [D-Trp⁸]-γ-MSH [745] | THIQ [1916] | – |
| Antagonists | – | – | PG-106 (pIC₅₀ 6.7) [746] | – | – |
| Selective antagonists | – | – | – | MBP10 (pIC₅₀ 10) [132], HS014 (pKᵢ 8.5) [1891] | – |
| Labelled ligands | [¹²⁵I]NDP-MSH (Agonist) [1138] | [¹²⁵I]ACTH-(1-24) (Agonist) | [¹²⁵I]NDP-MSH (Agonist) [1138], [¹²⁵I]SHU9119 (Antagonist) [1581] | [¹²⁵I]SHU9119 (Antagonist) (pKᵢ 9.2) [1581], [¹²⁵I]NDP-MSH (Agonist) [1138, 1889] | – |

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 [328, 586].

Further reading on Melanocortin receptors

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

Foord SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. Pharmacol Rev 57: 279-288 [PMID:15914470]

Renquist BJ et al. (2011) Physiological roles of the melanocortin MC3 receptor. Eur. J. Pharmacol. 660: 13-20 [PMID:21211527]
Melatonin receptors

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

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

| Nomenclature   | MT₁ receptor |               | MT₂ receptor |               |
|----------------|--------------|---------------|--------------|---------------|
| HGNC, UniProt  | MTNR1A, P48039 |               | MTNR1B, P49286 |               |
| Endogenous agonists | melatonin [78, 524, 526] |               | melanolin [78, 524, 526] |               |
| Agonists       | ramelteon [1049], agomelatine [78, 146], tasimelteon [1759] |               | agomelatine [78, 146], ramelteon [1049, 1778], tasimelteon [1759] |               |
| Selective agonists | – |               | UCM1014 [2016], IIK7 [587, 2051], 5-methoxy-luzindole (Partial agonist) [526] |               |
| Selective antagonists | – |               | 4P-PDOT (pKᵢ 8.8–9.4) [78, 526, 527], K185 (pKᵢ 9.3) [587, 2051], DH97 (pKᵢ 8) [2107] |               |
| Labelled ligands | [125]SD6 (Agonist) [1245], 2-[125]I-melatonin (Agonist) [78, 526], [3]H-melatonin (Agonist) [254] |               | [125]SD6 (Agonist) [1245], 2-[125]I-melatonin (Agonist) [78, 526], [125]IDV880 (Agonist, Partial agonist) [1245], [3]H-melatonin (Agonist) [254] |

**Comments:** Melatonin, 2-iodo-melatonin, agomelatine, GR 196429, LY 156735 and ramelteon [1049] are nonselective agonists for MT₁ and MT₂ receptors. (-)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC for rat MT₁ receptors (see AMMTC for structure) [2136]. Luzindole is an MT₁/MT₂ non-selective competitive melatonin receptor antagonist with about 15-25 fold selectivity for the MT₂ receptor [527]. MT₁/MT₂ heterodimers present different pharmacological profiles from MT₁ and MT₂ receptors [84]. The MT₂ binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML₂ receptor, binds selectively 2-iodo-[125]I-SMCA-NAT [1473]. Pharmacological investigations of MT₃ binding sites have primarily been conducted in hamster tissues. At this site, The endogenous ligand N-acetylserotonin [546, 1324, 1473, 1719] and SMCA-NAT [1719] are specific as agonists, while prazosin [1324] functions as an antagonist. The MT₃ binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (NQO2, P16083 [1601, 1602]). The MT₂ binding site activated by 5MCA-NAT in eye ciliary body is positively coupled to adenyl cyclase and regulates chloride secretion [928]. Xenopus melanophores and chick brain express a distinct receptor (x420, P49219; c346, P49288, initially termed Mel₁c) coupled to the Gₛₒ family of G proteins, for which GPR50 has recently been suggested to be a mammalian counterpart [530] although melatonin does not bind to GPR50 receptors. Several variants of the MTNR1B gene have been associated with increased type 2 diabetes risk [1043].

**Further reading on Melatonin receptors**

Cecon E et al. (2018) Melatonin receptors: molecular pharmacology and signalling in the context of system bias. Br J Pharmacol. 175: 3263-3280 [PMID:28707298]

Dubocovich ML et al. (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. Pharmacol Rev. 62: 343-80 [PMID:20605968]

Jockers R et al. (2016) Update on melatonin receptors: IUPHAR Review 20. Br J Pharmacol. 173: 2702-25 [PMID:27314810]

Karamitri A et al. (2019) Melatonin in type 2 diabetes mellitus and obesity. Nat Rev Endocrinol 15: 105-125 [PMID:30531911]

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

Zlotos DP et al. (2014) MT1 and MT2 melatonin receptors: ligands, models, oligomers, and therapeutic potential. J Med Chem. 57: 3161-85 [PMID:24228714]
Metabotropic glutamate receptors

G protein-coupled receptors → Metabotropic glutamate receptors

**Overview:** Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [1899]) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate. The mGlu family is composed of eight members (named mGlu1 to mGlu8) which are divided into three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I (mGlu1 and mGlu5), Group-II (mGlu2 and mGlu3) and Group-III (mGlu4, mGlu6, mGlu7 and mGlu8) (see Further reading).

Structurally, mGlu are composed of three juxtaposed domains: a core G protein-activating seven-transmembrane domain (TM), common to all GPCRs, is linked via a rigid cysteine-rich domain to the intracellular domain where glutamate binds. The structures of the VFTD of mGlu1, mGlu2, mGlu3, mGlu5 and mGlu7 have been solved [1177, 1482, 1530, 2156]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organization similar to that of other GPCRs, although the helices appear more compacted [383, 515, 2335]. mGlu form constitutive dimers crosslinked by a disulfide bridge. Recent studies revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [518]. Although well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [1493, 2393].

The endogenous ligands of mGlu are L-glutamic acid, L-serine-O-phosphate, N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Group-I mGlu receptors may be activated by 3,5-DHPG and (S)-3HPG [221] and antagonized by (S)-hexylhomolbotenic acid [1346]. Group-II mGlu receptors may be activated by LY389795 [1483], LY379268 [1483], eglumegad [1898 2337], DCG-IV and (2R,3R)-APDC [1899], and antagonised by eGlut [979] and LY307452 [571, 2289]. Group-III mGlu receptors may be activated by L-AP4 and (R,S)-4-PGG [606]. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu2 and mGlu3 at low nanomolar concentrations, mGlu8 at high nanomolar concentrations, and mGlu4, mGlu5, and mGlu7 in the micromolar range [1099]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that bind within the TM domain have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as ‘potentiators’ of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

| Nomenclature | mGlu1 receptor | mGlu2 receptor | mGlu3 receptor | mGlu4 receptor | mGlu5 receptor |
|--------------|----------------|----------------|----------------|----------------|----------------|
| HGNC, UniProt| GRM1, Q13255  | GRM2, Q14416   | GRM3, Q14832   | GRM4, Q14833   | GRM5, P41594   |
| Endogenous agonists | L-glutamic acid [1705] | L-glutamic acid [1705] | L-glutamic acid [1705], NAAG [1906] | L-glutamic acid [1705] | L-glutamic acid [1705] |
| Agonists | – | – | – | – | – |
| Selective agonists | – | – | – | L-AP4 [2337], L-serine-O-phosphate [2337] | – |
| Antagonists | LY367385 (pEC50, 5.1) [400] | – | – | MAP4 (pKi, 4.6) [792] – Rat | ACDDP (pEC50, 6.9) [202] |
| Selective antagonists | 3-MATIDA (pIC50, 5.2) [1506] – Rat, (S)-(+) -CBPG (pIC50, 4.2) [1373] – Rat, (S)-TPBG (pIC50, 4.2) [417] – Rat, AIDA (pA2 4.2) [1507] | – | – | – | – |
| Allosteric modulators | – | – | CBIPES (Positive) (pEC50, 7) [1010], 4-MPPTS (Positive) (pIC50, 5.8) [108, 1009, 1010, 1884] | – | – |
| Selective allosteric modulators | BAY 367620 (Negative) (pKi, 9.5) [309] – Rat, JNJ16259685 (Negative) (pIC50, 8.9) [1210], R001-6128 (Positive) (pKi, 7.5–7.7) [1118] – Rat, LY456236 (Negative) (pIC50, 6.9) [1270], CPCCOEt (Negative) (pIC50, 5.2–5.8) [1293] | Ro64-5229 (Negative) (pIC50, 7) [1130] – Rat, bipyridyllanone A (Positive) (pEC50, 7) [203] | ML337 (Negative) (pIC50, 6.2) [2286] – Rat | VU0361737 (Positive) (pEC50, 6.6) [559], VU0155041 (Positive) (pEC50, 6.1) [1595] | – |

The endogenous ligands of mGlu are L-glutamic acid, L-serine-O-phosphate, N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Group-I mGlu receptors may be activated by 3,5-DHPG and (S)-3HPG [221] and antagonized by (S)-hexylhomolbotenic acid [1346]. Group-II mGlu receptors may be activated by LY389795 [1483], LY379268 [1483], eglumegad [1898 2337], DCG-IV and (2R,3R)-APDC [1899], and antagonised by eGlut [979] and LY307452 [571, 2289]. Group-III mGlu receptors may be activated by L-AP4 and (R,S)-4-PGG [606]. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu2 and mGlu3 at low nanomolar concentrations, mGlu8 at high nanomolar concentrations, and mGlu4, mGlu5, and mGlu7 in the micromolar range [1099]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that bind within the TM domain have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as ‘potentiators’ of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.
mGlu receptor

| Nomenclature | mGlu receptor | mGlu receptor | mGlu receptor |
|--------------|--------------|--------------|--------------|
| mGlu | mGlu2 | mGlu4 |
| HGNCl, UniProt | GRM6, Q14831 | GRM8, O00222 | L-glutamic acid [1705] |
| Endogenous agonists | L-glutamic acid [1705] | L-serine-O-phosphate [1365], L-glutamic acid [1705] |
| Agonists | – | – | (S)-3,4-DCPG [2122], L-AP4 [1365] |
| Selective agonists | 1-benzyl-APDC [2158] – Rat, homo-AMPA [264] | – | – |
| Antagonists | MAP4 (pIC50 3.5) [1706] – Rat, THPG [2126] | – | MMPG (pIC50 4.3) [2337] |
| Allosteric modulators | – | – | VU0422288 (Positive) (pKb 6.7) [978], VU0155094 (Positive) (pKb 5) [978] |

**Comments**: The activity of NAAG as an agonist at mGlu1 receptors was questioned on the basis of contamination with glutamate [374, 631], but this has been refuted [1553].

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [3H]R214127 [1209] and [3H]YM298198 [1125] at mGlu1 receptors and [3H]M-MPEP [665] and [3H]methoxymethyl-MTEP [51] at mGlu5 receptors; [3H]LY341495 and [3H]4-methylhomoibotenic acid for mGlu2 and mGlu3 receptors [1008, 1906]). Although a number of radioligands have been used to examine binding in native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors and may have unappreciated biased or neutral activity at other subtypes [849]. Potential differences linked to the species (e.g. human versus rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(S)-(−)-CBPG is an antagonist at mGlu1, but is an agonist (albeit of reduced efficacy) at mGlu5 receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors [2183], and is an antagonist at all Group-III mGluRs with an IC50 of 30 μM. A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomolobtenic acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but is resistant to LY341495 [392]. There are also reports of a distinct metabotropic glutamate receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification [1112, 1675].

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

All selective antagonists at metabotropic glutamate receptors are competitive.

**Further reading on Metabotropic glutamate receptors**

Conn PJ et al. (1997) Pharmacology and functions of metabotropic glutamate receptors. *Annu. Rev. Pharmacol. Toxicol.* 37: 205-237 [PMID:9131252]

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

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

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

Rondard P et al. (2011) The complexity of their activation mechanism opens new possibilities for the modulation of mGlu and GABAB class C G protein-coupled receptors. *Neuropsychopharmacology* 46: 82-92 [PMID:20713070]
Motilin receptor

G protein-coupled receptors \(\rightarrow\) Motilin receptor

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

### Nomenclature

HGNC, UniProt: MLNR, O43193

### Endogenous agonists

Motilin (MLN, P12872) [422, 1400, 1401, 1402]

### Agonists

Alemcinal [2117], erythromycin [588, 2117], azithromycin [241]

### Selective agonists

Camicinal [113, 1863], mitemcinal [1123, 2085] – Rabbit

### Selective antagonists

MA-2029 (pA2 9.2) [2048], GM-109 (pIC50 8) [808] – Rabbit

### Labelled ligands

[^125I] motilin (human) (Agonist) [588]

### Comments

In terms of structure, the motilin receptor has closest homology with the ghrelin receptor. Thus, the human motilin receptor shares 52% overall amino acid identity with the ghrelin receptor and 86% in the transmembrane regions [834, 2085, 2117]. However, differences between the N-terminus regions of these receptors means that their cognate peptide ligands do not readily activate each other [448, 1863]. In laboratory rodents, the gene encoding the motilin precursor appears to be absent, while the receptor appears to be a pseudogene [834, 1861]. Functions of motilin (MLN, P12872) are not usually detected in rodents, although brain and other responses to motilin and the macrolide alemcinal have been reported and the mechanism of these actions is obscure [1424, 1587]. Notably, in some non-laboratory rodents (e.g. the North American kangaroo rat (Dipodomys) and mouse (Microdipodops) a functional form of motilin may exist but the motilin receptor is non-functional [1269]. Marked differences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [1862]. Note that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other actions are possible (e.g. P2X inhibition by erythromycin; [2430]). Small molecule motilin receptor agonists are now described [1269, 1863, 2293]. The motilin receptor does not appear to have constitutive activity [897]. Although not proven, the existence of biased agonism at the receptor has been suggested [1402, 1462, 1860]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [588]. Receptor dimerisation has not been reported.

### Further reading on Motilin receptor

De Smet B et al. (2009) Motilin and ghrelin as prokinetic drug targets. *Pharmacol. Ther.* **123**: 207-23 [PMID:19427331]

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

Sanger GJ et al. (2016) Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* **13**: 38-48 [PMID:26392067]

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

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
Neuromedin U receptors

G protein-coupled receptors → Neuromedin U receptors

Overview: Neuromedin U receptors (provisional nomenclature as recommended by NC-IUPHAR [612]) are activated by the endogenous 25 amino acid peptide neuromedin U (neuromedin U-25 (NMU, P48645), NmU-25), a peptide originally isolated from pig spinal cord [1458]. In humans, NmU-25 appears to be the sole product of a precursor gene (NMU, P48645) showing a broad tissue distribution, but which is expressed at highest 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 [1497]. NmS-33 is, as its name suggests, a 33 amino-acid product of a precursor protein derived from a single gene and contains an amidated C-terminal heptapeptide identical to NmU. NmS-33 appears to activate NMU receptors with equivalent potency to NmU-25.

| Nomenclature | NMU1 receptor | NMU2 receptor |
|--------------|---------------|---------------|
| HGNC, UniProt | NMUR1, Q9HB89 | NMUR2, Q9GZQ4 |
| Antagonists  | –             | R-PSOP (pKg 7) [1303] |

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

Further reading on Neuromedin U receptors

Brighton PJ et al. (2004) Neuromedin U and its receptors: structure, function, and physiological roles. Pharmacol. Rev. 56: 231-48 [PMID:15169928]

Budhiraja S et al. (2009) Neuromedin U: physiology, pharmacology and therapeutic potential. Fundam Clin Pharmacol 23: 149-57 [PMID:19645813]

Mitchell JD et al. (2009) Emerging pharmacology and physiology of neuromedin U and the structurally related peptide neuromedin S. Br. J. Pharmacol. 158: 87-103 [PMID:19519756]

Novak CM. (2009) Neuromedin S and U. Endocrinology 150: 2985-7 [PMID:19549882]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Neuropeptide FF/neuropeptide AF receptors

**Overview:** The Neuropeptide FF receptor family contains two subtypes, NPFF1 and NPFF2 (provisional nomenclature [612]), which exhibit high affinities for neuropeptide FF (NPFF, O15130) and RFamide related peptides (RFRP: precursor gene symbol NPVF, Q9HCQ7). NPFF1 is broadly distributed in the central nervous system with the highest levels found in the limbic system and the hypothalamus. NPFE2 is present in high density in the superficial layers of the mammalian spinal cord where it is involved in nociception and modulation of opioid functions.

| Nomenclature | NPFF1 receptor | NPFF2 receptor |
|--------------|----------------|---------------|
| HGNC, UniProt | NPFFR1, Q9GZQ6 | NPFFR2, Q9Y5XS |

**Potency order of endogenous ligands**

| RFRP-1 (NPVF, Q9HCQ7) > RFRP-3 (NPVF, Q9HCQ7) > FMRFamide (NPFF, O15130) | neuropeptide AF (NPFF, O15130), neuropeptide FF (NPFF, O15130) > PrRP-31 (PRLH, P81277) > FMRF, QRFP43 (QRFP, P83859) > neuropeptide SF (NPFF, O15130) |

**Endogenous agonists**

| neuropeptide FF (NPFF, O15130) [728, 729, 1476], RFRP-3 (NPVF, Q9HCQ7) [729, 730, 1476] | neuropeptide FF (NPFF, O15130) [729, 1475] |

**Selective agonists**

| – | – |

**Antagonists**

| RF9 (pK_i 7.2) [1974] | dNPA [1829], AC263093 [1194] |

**Selective antagonists**

| AC262620 (pK_i 7.4–8.1) [1194], AC262970 (pK_i 7.4–8.1) [1194] | – |

**Labelled ligands**

| [125]I-RFRP-3 (Agonist) [729], [3H]NPVF (Agonist) [2095], [125]I-NPFF (Agonist) [728] | [125]I-EYF (Agonist) [1476], [3H]EYF (Agonist) [2095], [125]I-NPFF (Agonist) [728] |

**Comments:** An orphan receptor GPR83 (Q9NYM4) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors. The antagonist RF9 is selective for NPFF receptors, but does not distinguish between the NPFF1 and NPFF2 subtypes (pK_i 7.1 and 7.2, respectively, [1974]).

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

Moulédous L et al. (2010) Opioid-modulating properties of the neuropeptide FF system. Biofactors 36: 423–9 [PMID:20803521]

Vyas N et al. (2006) Structure-activity relationships of neuropeptide FF and related peptidic and non-peptidic derivatives. Peptides 27: 990-6 [PMID:16490282]

Yang HY et al. (2008) Modulatory role of neuropeptide FF system in nociception and opiate analgesia. Neuropeptides 42: 1-18 [PMID:17854890]
Neuropeptide S receptor

G protein-coupled receptors → Neuropeptide S receptor

**Overview**: The neuropeptide S receptor (NPS, provisional nomenclature [612]) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (NPS, P0C0P6).

**Nomenclature**
- NPS receptor
- HGNC, UniProt: NPSR1, Q6W5P4
- Endogenous agonists: neuropeptide S (NPS, P0C0P6) [2360]
- Selective agonists: PWT1-NPS [1840] – Mouse
- Selective antagonists: NCGC 84 (pA2 9) [2127], SHA 68 (pA2 8.1) [1841] – Mouse, RTI-118 [2428]
- Labelled ligands: [125I]Tyr10NPS (human) (Agonist) [2360]

**Comments**: Multiple single-nucleotide polymorphisms (SNP) and several splice variants have been identified in the human NPS receptor. The most interesting of these is an Asn-Ile exchange at position 107 (Asn107Ile). The human NPS receptor Asn107Ile displayed similar binding affinity but higher NPS potency (by approx. 10-fold) than human NPS receptor Asn107 [1787]. Several epidemiological studies reported an association between Asn107Ile receptor variant and susceptibility to panic disorders [507, 510, 1629, 1758]. The SNP Asn107Ile has also been linked to sleep behavior [727], inflammatory bowel disease [440], schizophrenia [1254], increased impulsivity and ADHD symptoms [1186]. Interestingly, a carboxy-terminal splice variant of human NPS receptor was found to be overexpressed in asthmatic patients [1193].

**Further reading on Neuropeptide S receptor**

Grund T et al. (2019) Brain neuropeptide S: via GPCR activation to a powerful neuromodulator of socio-emotional behaviors. Cell Tissue Res. **375**: 123-132 [PMID:30112573]

Guerrini R et al. (2010) Neurobiology, pharmacology, and medicinal chemistry of neuropeptide S and its receptor. Med Res Rev **30**: 751-77 [PMID:19824051]

Ruzza C et al. (2017) Neuropeptide S receptor ligands: a patent review (2005-2016). Expert Opin Ther Pat **27**: 347-362 [PMID:27788040]

Xu YL et al. (2004) Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. Neuron **43**: 487-497 [PMID:15312648]
Neuropeptide W/neuropeptide B receptors

**Overview:** The neuropeptide BW receptor 1 (NPBW1, provisional nomenclature [612]) is activated by two 23-amino-acid peptides, neuropeptide W (neuropeptide W-23 (NPW, Q8N729)) and neuropeptide B (neuropeptide B-23 (NPB, Q8NG41)) [638, 1953]. C-terminally extended forms of the peptides (neuropeptide W-30 (NPW, Q8N729) and neuropeptide B-29 (NPB, Q8NG41)) also activate NPBW1 [233]. Unique to both forms of neuropeptide B is the N-terminal bromination of the first tryptophan residue, and it is from this post-translational modification that the nomenclature NPB is derived. These peptides were first identified from bovine hypothalamus and therefore are classed as neuropeptides. Endogenous variants of the peptides 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 [233].

| Nomenclature | NPBW1 receptor | NPBW2 receptor |
|--------------|----------------|----------------|
| HGNC, UniProt | NPBW1R, P48145 | NPBW2R2, P48146 |

**Potency order of endogenous ligands**
- neuropeptide B-29 (NPB, Q8NG41) > neuropeptide B-23 (NPB, Q8NG41) > neuropeptide W-30 (NPW, Q8N729) [233]
- neuropeptide W-23 (NPW, Q8N729) > neuropeptide W-30 (NPW, Q8N729) > neuropeptide B-29 (NPB, Q8NG41) > neuropeptide W-23 (NPW, Q8N729) [233]

**Selective agonists**
- Ava3 [1038], Ava5 [1038]
- [125I]NPW-23 (human) (Agonist) [1976]

**Labelled ligands**
- [125I]NPW-23 (human) (Agonist) [1953]

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

NPBW1−/− mice show changes in social behavior, suggesting that the NPBW1 pathway may have an important role in the emotional responses of social interaction [1537]. For a review of the contribution of neuropeptide B/W to social dominance, see Watanabe and Yamamoto, 2015 [2270]. It has been reported that neuropeptide W may have a key role in the gating of stressful stimuli when mice are exposed to novel environments [1512]. Two antagonists have been discovered and reported to have affinity for NPBW1, ML181 and ML250, the latter exhibiting improved selectivity (100 fold) for NPBW1 compared to MCH1 receptors [762, 763]. Computational insights into the binding of antagonists to this receptor have also been described [1667].

**Further reading on Neuropeptide W/neuropeptide B receptors**
- Sakurai T. (2013) NPBW1R and NPBW2R: Implications in Energy Homeostasis, Pain, and Emotion. *Front Endocrinol (Lausanne)* 4: 23 [PMID:23515889]
- Singh G et al. (2006) Neuropeptide B and W: neurotransmitters in an emerging G-protein-coupled receptor system. *Br. J. Pharmacol.* 148: 1033-41 [PMID:16847439]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Neuropeptide Y receptors

**Overview:** Neuropeptide Y (NPY) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Neuropeptide Y Receptors [1444]) are activated by the endogenous peptides neuropeptide Y (NPY, P01303), neuropeptide Y-(3-36), peptide YY (PYY, P10082), PYY-(3-36) and pancreatic polypeptide (PP, P01298) (PP). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine receptor (originally named LESTR, [1310]). The y6 receptor is a functional gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated non-functional gene [743]. Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the potency of PP is greater at the rat Y4 receptor than at the human receptor [566]. In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [125]I-PYY or [125]I-NPY can be used to label Y1, Y2, Y5 and Y6 subtypes non-selectively, while [125]I[cPP(1-7), NPY(19-23), Ala31, Aib32, Gln34]hPP may be used to label Y5 receptors preferentially (note that cPP denotes chicken peptide sequence and hPP is the human sequence).

| Nomenclature | Y₁ receptor | Y₂ receptor | Y₄ receptor | Y₅ receptor | Y₆ receptor |
|--------------|-------------|-------------|-------------|-------------|-------------|
| HGNC, UniProt | NPY1R, P25929 | NPY2R, P49146 | NPY4R, P50391 | NPY5R, Q15761 | NPY6R, Q99463 |
| Potency order of endogenous ligands | neuropeptide Y = peptide YY ≫ pancreatic polypeptide | peptide YY = peptide YY(3-36) = neuropeptide Y = peptide YY(3-36) ≫ pancreatic polypeptide | pancreatic polypeptide ≫ neuropeptide Y = peptide YY | – | – |
| Endogenous agonists | neuropeptide Y (NPY, P01303), peptide YY (PYY, P10082) | PYY-(3-36) (PYY, P10082) [677, 692], neuropeptide Y (NPY, P01303), peptide YY (PYY, P10082) | pancreatic polypeptide | – | – |
| Agonists | [Leu31].Pro34].NPY [430], [Leu31].Pro34].PYY (human), [Pro34].NPY, [Pro34].PYY (human) | – | – | – | – |
| Selective agonists | – | – | – | [Ala31, Aib32].NPY (pig) [287] | – |
| Selective antagonists | BIBO3304 (pIC50 9.5) [2303], BIBP3226 (pKᵢ 8.1-9.3) [513, 2304] | BIIE0246 (pIC50 8.5) [511], JNP-520778 (pIC50 6.9-7.1) [198] | – | L-152,804 (pKᵢ 7.6) [1037] | – |
| Selective allosteric modulators | [3H]BIBP3226 (Antagonist) (pKᵢ 8.7), [125]I[Leu31].Pro34].NPY (Agonist) | [125]I[PYY-(3-36) (human) (Agonist) | nicosamide (Positive) [1988] | – | – |
| Labelled ligands | – | – | [125]I[P (human) (Agonist) | [125]I[cPP(1-7), NPY(19-23), Ala31, Aib32, Gln34]hPP (Agonist) [532] – Rat |
| Comments | Note that Pro34-containing NPY and PYY can also bind Y4 and Y5 receptors, so strictly speaking are not selective, but are the ‘preferred’ agonists. | – | – | – | – |

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

Searchable database: http://www.guidetopharmaco.org/index.jsp
Comments: The Y1 agonists indicated are selective relative to Y2 receptors. BIBP3226 is selective relative to Y2, Y4 and Y5 receptors [691]. NPY-(13-36) is Y2 selective relative to Y1 and Y5 receptors. PYY-(3-36) is Y2 selective relative to Y1 receptors. Note that Pro34-containing NPY and PYY can also bind Y4 and Y5, thus they are selective only relative to Y2. The Y6 receptor is a pseudogene in humans, but is functional in mouse, rabbit and some other mammals.

Further reading on Neuropeptide Y receptors

Bowers ME et al. (2012) Neuropeptide regulation of fear and anxiety: Implications of cholecystokinin, endogenous opioids, and neuropeptide Y. Physiol. Behav. 107: 699-710 [PMID:22429904]
Michel MC et al. (1998) XVI. International Union of Pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY and pancreatic polypeptide receptors. Pharmacol. Rev. 50: 143-150 [PMID:9549761]
Pedragosa-Badia X et al. (2013) Neuropeptide Y receptors: how to get subtype selectivity. Front Endocrinol (Lausanne) 4: 5 [PMID:23382728]
Zhang L et al. (2011) The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. Pharmacol. Ther. 131: 91-113 [PMID:21439311]

Neurotensin receptors

G protein-coupled receptors → Neurotensin receptors

Overview: Neurotensin receptors (nomenclature as recommended by NC-IUPHAR [612]) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (NTS, 30990), which also generates neuromedin N, an agonist at the NTS2 receptor. [3H]neurotensin (human, mouse, rat) and [125I]neurotensin (human, mouse, rat) may be used to label NTS1 and NTS2 receptors at 0.1-0.3 and 3-5 nM concentrations respectively.

| Nomenclature | NTS1 receptor | NTS2 receptor |
|--------------|---------------|---------------|
| HGNC, UniProt | NTSR1, P30989 | NTSR2, O95665 |
| Potency order of endogenous ligands | neurotensin (NTS, P30990) > neuromedin N (Mouse, Rat) [855] | neurotensin (NTS, P30990) = neuromedin N (Mouse, Rat) [1411] |
| Selective agonists | JMV449 [1983] – Rat | levocabastine [1411, 1801] |
| Selective antagonists | meclinertant (pIC50 7.5–8.2) [767] | – |
| Labelled ligands | [3H]meclinertant (Antagonist) (pKd 8.5) [1188] – Rat | – |

Comments: Neurotensin (NTS, P30990) appears to be a low-efficacy agonist at the NTS2 receptor [2222], while the NTS1 receptor antagonist meclinertant is an agonist at NTS2 receptors [2222]. An additional protein, provisionally termed NTS3 (also known as NTR3, gpr95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation [1585]. It has been reported to interact with the NTS1 receptor [1388] and the NTS2 receptor [283], and has been implicated in hormone trafficking and/or neurotensin uptake. A splice variant of the NTS2 receptor bearing 5 transmembrane domains has been identified in mouse [211] and later in rat [1689].

Further reading on Neurotensin receptors

Boules M et al. (2013) Diverse roles of neurotensin agonists in the central nervous system. Front Endocrinol (Lausanne) 4: 36 [PMID:23526754]
Mazella J et al. (2012) Neurotensin and its receptors in the control of glucose homeostasis. Front Endocrinol (Lausanne) 3: 143 [PMID:23230428]
Myers RM et al. (2009) Cancer, chemistry, and the cell: molecules that interact with the neurotensin receptors. ACS Chem. Biol. 4: 503-25 [PMID:19462983]
Ouyang Q et al. (2017) Oncogenic role of neurotensin and neurotensin receptors in various cancers. Clin. Exp. Pharmacol. Physiol. 44: 841-846 [PMID:28556374]
Opioid receptors

G protein-coupled receptors → Opioid receptors

Overview: Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (PENK, P01210) (met), [Leu]enkephalin (PENK, P01210) (leu), β-endorphin (POMC, P01189) (β-end), α-neoendorphin (PDYN, P01213), dynorphin A (PDYN, P01213) (dynA), dynorphin B (PDYN, P01213) (dynB), big dynorphin (PDYN, P01213) (Big dyn), nociceptin/orphanin FQ (PNC, Q13519) (N/OFQ); endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter nomenclature for the opioid receptors, μ, δ and κ, is well established, and NC-IUPHAR considers this nomenclature appropriate, along with the symbols spelled out (mu, delta, and kappa), and the acronyms, MOP, DOP, and KOP. [428, 488, 612]. The human N/OFQ receptor, NOP, is considered ‘opioid-related’ rather than opioid because, while it exhibits a high degree of structural homology with the conventional opioid receptors [1478], it displays a distinct pharmacology. Currently there are numerous clinically used drugs, such as morphine and many other opioid analgesics, as well as antagonists such as naloxone, however only for the μ receptor.

| Nomenclature          | δ receptor       | κ receptor       |
|-----------------------|------------------|------------------|
| HGNC, UniProt         | OPRD1, P41143    |                 |
| Principal endogenous agonists | β-endorphin (POMC, P01189), [Leu]enkephalin (PENK, P01210), [Met]enkephalin (PENK, P01210) | big dynorphin (PDYN, P01213), dynorphin A (PDYN, P01213) |
| Agonists              | DADLE [2142], etorphine [2142], ethylketocyclazocine [2142] | – |
| Sub/family-selective agonists | BU08028 (Partial agonist) [1076] | US0488 [345, 1671, 1973, 2142, 2230, 2437, 2439], enadoline [934, 1571], U69593 [1192, 2142], salvinorin A [281, 1825] |
| Selective agonists    | UFP-S12 [2215], BW373U86 [1220], ADLS589 [1220], DPDPE [1511, 2142], [D-Ala²]deltorphin II [568], ADLS747 [1221], SNC80 [292, 1757] | buparephine (pKᵢ 9.1–10.2) [2142, 2439], nalbuphine (pKᵢ 9.5) [2142], naltrexone (pKᵢ 8.4–9.4) [1671, 1973, 2142], naloxone (pKᵢ 7.6–8.6) [1671, 1973, 2142, 2437, 2439] |
| Antagonists           | UFP-S09 (pKᵢ 9.8) [494, 495], naltrexone (pKᵢ 8) [2142], naloxone (pKᵢ 7.2) [2142] | – |
| Sub/family-selective antagonists | AT-076 (pKᵢ 7.7) [2142, 2412] | AT-076 (pKᵢ 8.9) [2142, 2413] |
| Selective antagonists  | naltrexone (pKᵢ 10) [2003, 2142], naltrexone (pKᵢ 9.7) [1725, 2142], TIPP (Inverse agonist) (pKᵢ 9) [1888, 2142] | nor-binaltorphimine (pKᵢ 8.9–11) [1671, 1724, 1973, 2142, 2437, 2439], S⁻-quanydionoraltorphimine (pKᵢ 9.7–9.9) [1017, 1671, 2031], JDTic (pKᵢ 9.9–9.4) [1520, 2121, 2413] |
| Labelled ligands      | [³H]Naltrexone (Antagonist) (pKᵢ 10.4) [2364] – Rat, [³H][D-Ala²]deltorphin I (Selective Agonist) [2027], [³H]Diprenorphine (Agonist) [56, 2142], [³H]DPDPE (Agonist) [28], [³H]Deltorphin II (Agonist) [284], [³H]Naltriben (Antagonist) [1264] | [³H]Diprenorphine (Antagonist) (pKᵢ 9.1) [56, 1973], [³H]U69593 (Agonist) [1192, 1671, 1973], [³H]Enadoline (Agonist) [1975] |
Nomenclature | μ receptor | NOP receptor
---|---|---
HGN, Uniprot | OPRM1, P35372 | OPRL1, P41146
Potential endogenous agonists | endomorphin-1, endomorphin-2 | –
Principal endogenous agonists | β-endorphin (POMC, P01189), [Met]enkephalin (PENK, P01210), [Leu]enkephalin (PENK, P01210) | –
Endogenous agonists | – | nociceptin/orphanin FQ (Pnoc, Q13519) [11, 165, 1630]
Agonists | levorphanol [797], hydromorphone [2287], fentanyl [2142], buprenorphine (Partial agonist) [2142], methadone [1727], UFP-505 [494, 495], codeine [2142], tapentadol [2163], pethidine [1727] | –
Sub/family-selective agonists | BU08028 (Partial agonist) [1076] | cebranopadil [1292], BU08028 (Partial agonist) [1076]
Selective agonists | sufentanil [2224], DAMGO [796, 2142], loperamide [356], morphine [717, 2142], PL017 [336, 2142] | N/OFQ-(1-13)-NH2 [165, 764, 1418, 1630], Ac-RYYRWW-K-NH2 (Partial agonist) [514, 1418], SCH221510 [2208], Ro64-6198 [987, 2301], AT-403 [63]
Antagonists | naltrexone (pKi 9.1–9.7) [1061, 2142], nalmefene (pKi 9.5) [2142], nalorphine (pKi 8.9) [2142], naltrexone (pKi 8.9) [2142], methylnaltrexone (pKi 8.7) [2287] | –
Sub/family-selective antagonists | AT-076 (pKi 8.8) [2142, 2413] | AT-076 (pKi 8.8) [2413]
Selective antagonists | alvimopan (pKi 9.3) [1219], levallorphan (pKi 8.8–9.3) [1361], CTAP (pKi 8.6) [336, 2142] | UFP-101 (pKi 10.2) [294], LY2940094 (pKi 10) [2141], compound 24 (pKi 9.6) [605], SB 612111 (pKi 9.2–9.5) [2017, 2411], J-113397 (pIC50 8.3) [1057]
Allosteric modulators | BMS-986123 (Neutral) (pKg 6) [267], BMS-986121 (Positive) (pKg 5.7) [267], BMS-986124 (Neutral) (pKg 5.7) [267], BMS-986122 (Positive) (pKg 5.3) [267] | –
Labelled ligands | [3H]diprenorphine (Antagonist) (pKd 10.1) [1780] – Mouse, [3H]DAMGO (Agonist) [1780] – Rat, [3H]PLO17 (Agonist) [825] – Rat | [3H]N/OFQ (Agonist) [514, 1477]

**Comments:** Three naltrexone-sensitive opioid receptor genes have been identified in humans, and while the μ-receptor in particular may be subject to extensive alternative splicing [1660], these putative isoforms have not been correlated with any of the subtypes of receptor proposed in years past. Opioid receptors may heterodimerize with each other or with other 7TM receptors [1019], and give rise to complexes with a unique pharmacology, however, evidence for such heterodimers in native cells is equivocal and the consequences of this heterodimerization for signalling remains largely unknown. For μ-opioid receptors at least, dimerization does not seem to be required for signalling [1180]. A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (OGPR, 9NZT2) and termed an opioid growth factor receptor [2409].

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

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human μ-receptors [1613] and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists [255]. Pathway bias for agonists makes general rank orders of potency and efficacy somewhat obsolete, so these do not appear in the table. As ever, the mechanisms underlying the acute and long term regulation of opioid receptor function are the subject of intense investigation and debate.

The richness of opioid receptor pharmacology has been enhanced with the recent discovery of allosteric modulators of μ and δ receptors, notably the positive allosteric modulators and silent allosteric ‘antagonists’ outlined [267, 268]. Negative allosteric modulation of opioid receptors has been previously suggested [1048], whether all compounds are acting at a similar site remains to be established.
Further reading on Opioid receptors
Butelman ER et al. (2012) \(\alpha\)-opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. Trends Neurosci. 35: 587-96 [PMID:22709632]
Cox BM et al. (2015) Challenges for opioid receptor nomenclature: IUPHAR Review 9. Br. J. Pharmacol. 172: 317-23 [PMID:24528283]
Pradhan AA et al. (2011) The delta opioid receptor: an evolving target for the treatment of brain disorders. Trends Pharmacol. Sci. 32: 581-90 [PMID:21925742]
Williams JT et al. (2013) Regulation of \(\mu\)-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. Pharmacol. Rev. 65: 223-54 [PMID:23321159]

Orexin receptors

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

Overview: Orexin receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Orexin receptors {612}) are activated by the endogenous polypeptides orexin-A (HCRT, O43612) and orexin-B (HCRT, O43612) (also known as hypocretin-1 and -2; 33 and 28 aa) derived from a common precursor, preproorexin or orexin precursor, by proteolytic cleavage and some typical peptide modifications [1852]. Currently the only orexin receptor ligand in clinical use is suvorexant, which is used as a hypnotic. Orexin receptor crystal structures have been solved [2390, 2392].

| Nomenclature | OX1 receptor |
|--------------|--------------|
| HGNC, UniProt | HCRT1, O43613 |

| Selectivity order of endogenous ligands | orexin-A (HCRT, O43612) > orexin-B (HCRT, O43612) |
|----------------------------------------|--------------------------------------------------|
| Selective agonists | - |
| Antagonists | SB-649868 (pK\(_{i}\) 9.3–9.6) [293, 429], suvorexant (pK\(_{i}\) 8.7–9.3) [293, 429, 1513], florexan (pK\(_{i}\) 8.4–9.1) [293, 429, 2319], TCS 1102 (pK\(_{i}\) 8.5) [148], almorexan (pK\(_{i}\) 7.8–8.5) [293, 581, 1363, 1366, 1367], Cp-1 (pK\(_{i}\) 7.6–8) [1363, 1364] |
| Selective antagonists | SB-674042 (70–300-fold selective) (pK\(_{i}\) 8.7–9.3) [1200, 1363, 1364, 1367], SB-334867 (50–150-fold selective) (pK\(_{i}\) 7.2–7.9) [1200, 1363, 1364, 1722, 1746, 1991], SB-408124 (60–80-fold selective) (pK\(_{i}\) 7.2–7.9) [1200, 1364, 1513] |
| Labelled ligands | \[^{3}H\]SB-674042 (Antagonist) (pK\(_{d}\) 8.3–9.1) [1200, 1364, 1367], \[^{3}H\]Almorexan (Antagonist) (pK\(_{d}\) 8.6–8.9) [1364, 1367], \[^{125}I\]Orexin-A (Agonist) [1168, 1747, 1852] |

Comments: The primary coupling of orexin receptors to G\(_{q/11}\) proteins is rather speculative and based on the strong activation of phospholipase C, though recent studies in recombinant cells also stress the importance of G\(_{q/11}\) [1167]. Coupling of both receptors to G\(_{q/11}\) and G\(_{i}\) has also been reported [1046, 1170, 1255, 1769]. For most native cellular responses observed, the G protein pathway is unknown. The relative potency order of endogenous ligands depends on the cellular signal transduction machinery [1166]. Similarly, [Ala\(^{1}\), D-Leu\(^{15}\)]Orexin-B, Nag 26 and YNT-185 may show variable selectivity for OX\(_{2}\) receptors and are also likely to activate OX\(_{1}\) receptors [1748, 1807]. Many antagonists and radioligands are not well-characterized, and thus the affinities are uncertain. Among radioligands, \[^{3}H\]SB-674042, \[^{3}H\]HEMPA and \[^{3}H\]Almorexan are commercially available. \[^{3}H\]TCS 1102 (pK\(_{d}\)O01 8.2, pK\(_{d}\)O02 9.0) [293] and Rhodamine Green-orexin-A [445] are also useful radioligand tools. Orexin receptors have been reported to be able to form complexes with each other and some other GPCRs as well as \(\alpha\)1 receptors, which might affect the signaling and pharmacology [1169, 1549]. Loss-of-function mutations in the gene encoding the OX\(_{2}\) receptor underlie canine hereditary narcolepsy [1287]. Antagonists of the orexin receptors are the focus of major drug discovery efforts for their potential to treat insomnia and other disorders of wakefulness [1816], while agonists would likely be useful in human narcolepsy.
Further reading on Orexin receptors

Baimel C et al. (2015) Orexin/hypocretin role in reward: implications for opioid and other addictions. Br. J. Pharmacol. 172: 334-48 [PMID:24641197]
Burdakov D. (2018) Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons. Neuroparmacology [PMID:30347195]
Kukkonen JP. (2013) Physiology of the orexinergic/hypocretinergic system: a revisit in 2012. Am. J. Physiol., Cell Physiol. 304: C2-32 [PMID:23034387]

Li SB et al. (2016) Hypocretins, Neural Systems, Physiology, and Psychiatric Disorders. Curr Psychiatry Rep 18: 7 [PMID:26733323]
Mahler SV et al. (2014) Motivational activation: a unifying hypothesis of orexin/hypocretin function. Nat. Neurosci. 17: 1298-303 [PMID:25254979]

Oxoglutarate receptor

G protein-coupled receptors → Oxoglutarate receptor

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

| Nomenclature          | oxoglutarate receptor |
|-----------------------|-----------------------|
| HGNC, UniProt         | OXGR1, Q96P68         |
| Endogenous agonists   | α-ketoglutaric acid [838, 2015] |

Further reading on Oxoglutarate receptor

Davenport AP et al. (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. Pharmacol. Rev. 65: 967-86 [PMID:23686350]
Grimm PR and Welling PA (2017) alpha-Ketoglutarate drives electroneutral NaCl reabsorption in intercalated cells by activating a G-protein coupled receptor. Oxgr1. Curr. Opin. Nephrol. Hypertens. 26: 426-433 [PMID:28771454]
**P2Y receptors**

G protein-coupled receptors → P2Y receptors

**Overview**: P2Y receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on P2Y Receptors [1, 2]) are activated by the endogenous ligands ATP, ADP, uridine triphosphate, uridine diphosphate and UDP-glucose. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established and so it might be appropriate to use wording such as 'uridine triphosphate-prefering (or ATP-, etc.) P2Y receptor' or 'P2Y1-like', etc., until further, as yet undefined, corroborative criteria can be applied [271, 567, 966, 2227, 2281].

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

| Nomenclature | P2Y<sub>1</sub> receptor | P2Y<sub>2</sub> receptor | P2Y<sub>4</sub> receptor | P2Y<sub>6</sub> receptor |
|--------------|-------------------------|-------------------------|-------------------------|-------------------------|
| HGNC, UniProt | P2RY1, P47900            | P2RY2, P41231            | P2RY4, P51582            | P2RY6, Q15077            |
| Potency order of endogenous ligands | ADP ≈ ATP | uridine triphosphate > ATP [1217] | uridine triphosphate > ATP (at rat recombinant receptors, UTP = ATP) | uridine diphosphate ≫ uridine triphosphate > ADP |
| Endogenous agonists | — | uridine triphosphate [1087, 1217] | — | — |
| Agonists | ADPβS [2088], 2MeSADP [1882, 2238] | diquafosol [1680], denufosol [1218, 1680, 2388], UTPβS [1217] | diquafosol [259], denufosol [2388], UTPβS [1218] | — |
| Subfamily-selective agonists | — | MRS2365 [364], 2-Cl-ADP(α-BH<sub>3</sub>) [85] | MRS4062 [1390], MRS2927 [1390], (N)methanocarba-UTP [1087] | Rp-5-O-Me-UDPα8 [706, 774], MRS2957 [1389], MRS2693 [158] |
| Selective agonists | suramin (pK<sub>i</sub> 5.3) [2238], PPADS (pK<sub>i</sub> 5.2) [2238] | reactive blue-2 (pIC<sub>50</sub> 6) [981], suramin (pIC<sub>50</sub> 4.3) [981, 1882] | PPADS (pEC<sub>50</sub> 2–5) [969], reactive blue-2 (pIC<sub>50</sub> 4.7) [185] – Rat ATP (pK<sub>a</sub> 6.2) [1067] | reactive blue-2 (pK<sub>a</sub> 6) [2228], PPADS (pK<sub>a</sub> 4) [2228], suramin (pK<sub>a</sub> 4) [2228] |
| Antagonists | — | — | — | — |
| Endogenous antagonists | — | MRS2500 (pK<sub>i</sub> 8.8–9.1) [316, 1086], MRS2279 (pK<sub>i</sub> 7.9) [2238], MRS2179 (pK<sub>i</sub> 7–7.1) [220, 2238] | AR-C118925XX (pIC<sub>50</sub> 7–6) [1064], AR-C126313 (pIC<sub>50</sub> 6) [960], PSB-416 (pIC<sub>50</sub> 4.7) [873] | MRS2578 (pIC<sub>50</sub> 7.4) [1369], MRS2567 (pIC<sub>50</sub> 6.9) [1369] |
| Selective antagonists | — | — | — | — |
| Selective allosteric modulators | BMS compound 16 (Negative) (pK<sub>i</sub> 6.9) [2417], 2,2′-pyridylisatogen tosylate (Negative) (pIC<sub>50</sub> 6.8) [657] | — | — | — |
| Labelled ligands | [3H]MRS2279 (Antagonist) (pK<sub>a</sub> 8.1) [2238], [3H]2MeSADP (Agonist) [2088], [35S]ADPβS (Agonist) | — | — | MRS4162 (Selective Antagonist) (pEC<sub>50</sub> 7.6) [986] |

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

Full Contents of Concise Guide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
| Nomenclature | P2Y<sub>11</sub> receptor | P2Y<sub>12</sub> receptor | P2Y<sub>13</sub> receptor | P2Y<sub>14</sub> receptor |
|-------------|---------------------------|---------------------------|---------------------------|---------------------------|
| HGNC, UniProt | P2RY11, Q96C91            | P2RY12, Q9H244             | P2RY13, Q9BPV8             | P2RY14, Q15391            |
| Potency order of endogenous ligands | ATP &gt; ADP | ADP &gt; ATP | ADP &gt; ATP | uridine diphosphate= UDP-glucose |
| Endogenous agonists | – | ADP [854] | – | – |
| Sub/family-selective agonists | – | 2MeSADP [854], ADPβS [2088] | 2MeSADP [1386], 2MeSATP [1386], ADPβS [1386] | – |
| Selective agonists | AR-C67085 [102, 408], NF546 [1430], ATPγS [408] | – | – | α,β-methylene-2-thio-UDP [446], MRS2905 [967], 2-thio-UDP [446] |
| Antagonists | – | cangrelor (pIC<sub>50</sub> 9.4) [970], Ap4A (pIC<sub>50</sub> 6) [1386], 2MeSAMP (pIC<sub>50</sub> 5.4) [2088] | cangrelor (pIC<sub>50</sub> 8.3) [1386], Ap4A (pIC<sub>50</sub> 6.7) [1386], 2MeSAMP (pIC<sub>50</sub> 5.6) [1386] | – |
| Sub/family-selective antagonists | suramin (pIC<sub>50</sub> 4.8–6) [408], reactive blue-2 (pIC<sub>50</sub> 5) [408] | – | – | – |
| Selective antagonists | NF157 (pK<sub>i</sub> 7.3) [2170], NF340 (pIC<sub>50</sub> 6.4–7.1) [1430] | AZD1283 (pK<sub>i</sub> 8) [88, 2419], ARL66096 (pIC<sub>50</sub> 7.9) [932, 933], ticagrelor (pK<sub>i</sub> 7.8) [2414] | MRS2603 (pIC<sub>50</sub> 6.2) [1094], MRS2211 | PPTN (pK<sub>i</sub> 10.1) [110] |
| Labelled ligands | – | [<sup>3</sup>H]2MeSADP (Agonist) [2088], [<sup>3</sup>H]PSB-0413 (Antagonist) (pK<sub>d</sub> 8.3–8.5) [548, 1620] | [<sup>3</sup>P]2MeSADP (Agonist) [1386] | MRS4174 (Selective Antagonist) (pK<sub>i</sub> 10.1) [1105], MRS4183 (Selective Agonist) [1104] |

**Comments:** A series of 4-alkyloxyimino derivatives of uridine-5'-triphosphate which could be useful for derivatization as fluorescent P2Y<sub>2</sub>/4/6 receptor probes has been recently synthesized [986]. Single nucleotide polymorphisms of the P2RY<sub>1</sub> gene have been associated to different platelet reactivity to ADP, ADP [863]. Three frequent non synonymous P2Y<sub>2</sub> receptor polymorphisms have been identified, one of which was significantly more common in cystic fibrosis patients. This polymorphism is linked to increases in Ca<sup>2+</sup> influx in transfected cells, and might therefore play a role in disease development [286]. Although uridine triphosphate (UTP) was also shown to be a biased agonist at P2Y<sub>11</sub>, this is still under debate [1508, 2297]. A group of single nucleotide polymorphisms in the P2Y<sub>12</sub> gene, forming the so called P2Y<sub>12</sub> H2 haplotype, has been associated with increased platelet responsiveness to ADP, increased risk of peripheral arterial disease and with coronary artery disease [321]. The platelet-type bleeding disorder due to P2Y<sub>12</sub> receptor defects is an autosomal recessive condition characterized by mild to moderate mucocutaneous bleeding and excessive bleeding after surgery or trauma. The defect is due to the inability of ADP to induce platelet aggregation [317]. The P2Y<sub>13</sub> receptor Met-158-Thr polymorphism, which is in linkage disequilibrium with the P2Y<sub>12</sub> locus, is not associated with acute myocardial infarction, diabetes mellitus or related risk factors [47]. The P2Y<sub>14</sub> receptor was previously considered to exclusively bind sugar nucleotides such as UDP-glucose and UDP-galactose [331]. However, more recent evidence with several cell lines has demonstrated that uridine diphosphate (UDP) is 5-fold more potent than UDP-glucose [311]. UDP was also shown to competitively antagonise the UDP-glucose response at the human recombinant P2Y<sub>14</sub> receptor [632].

**Further reading on P2Y receptors**

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

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

[Searchable database: http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)  
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Parathyroid hormone receptors

G protein-coupled receptors → Parathyroid hormone receptors

**Overview:** The parathyroid hormone receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Parathyroid Hormone Receptors [662]) are family B G protein-coupled receptors. The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor (PTH1 receptor) is activated by precursor-derived peptides: PTH (PTH, P01270) (84 amino acids), and PTHrP (PTHLH, P12272) (141 amino-acids) and related peptides (PTH-(1-34), PTHrP-(1-36) (PTHLH, P12272)). The parathyroid hormone 2 receptor (PTH2 receptor) is activated by the precursor-derived peptide TIP39 (PTH2, Q96A98) (39 amino acids). [\(^{125}\)I]PTH may be used to label both PTH1 and PTH2 receptors.

| Nomenclature | PTH1 receptor | PTH2 receptor |
|--------------|---------------|---------------|
| HGNC, UniProt | PTH1R, Q03431 | PTH2R, P49190 |

**Potency order of endogenous ligands**

PTH (PTH, P01270) = PTHrP (PTHLH, P12272)

**Agonists**

PTHrP-(1-34) (human) [661] – Rat

**Selective agonists**

| Agonists | Selective agonists |
|----------|-------------------|
| teriparatide [660] | TIP39 (PTH2, Q96A98), PTH (PTH, P01270) ≫ PTHrP (PTHLH, P12272) |
| – | – |

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

Although PTH (PTH, P01270) is an agonist at human PTH2 receptors, it fails to activate the rodent orthologues. TIP39 (PTH2, Q96A98) is a weak antagonist at PTH1 receptors [1018].

**Further reading on Parathyroid hormone receptors**

Cheloha RW et al. (2015) PTH receptor-1 signalling-mechanistic insights and therapeutic prospects. *Nat Rev Endocrinol* 11: 712-24 [PMID:26303600]

Gardella TJ et al. (2015) International Union of Basic and Clinical Pharmacology. XCIII. The Parathyroid Hormone Receptors-Family B G Protein-Coupled Receptors. *Pharmacol. Rev.* 67: 310-37 [PMID:25713287]

Vilardaga JP et al. (2014) Endosomal generation of cAMP in GPCR signaling. *Nat. Chem. Biol.* 10: 700-6 [PMID:25271346]
Platelet-activating factor receptor

G protein-coupled receptors → Platelet-activating factor receptor

**Overview:** Platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is an ether phospholipid mediator associated with platelet coagulation, but also subserves inflammatory roles. The PAF receptor (provisional nomenclature recommended by NC-IUPHAR [612]) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1378] and lysophosphatidylcholine [1615]. It may also be activated by bacterial lipopolysaccharide [1540].

| Nomenclature       | PAF receptor                                                                 |
|--------------------|-------------------------------------------------------------------------------|
| HGNC, UniProt      | PTA, P2510S                                                                   |
| Selective agonists | methylcarbamyl PAF                                                            |
| Selective antagonists | foropafant (pK_i 10.3) [853], ABT-491 (pK_i 9.2) [32], CV-6209 (pIC50 8.1–8.3) [716, 1539], L659989 (pK_i 7.8) [937], apafant (pK_i 5.2–7.5) [1654, 2067] |
| Labelled ligands   | [3H]PAF (Agonist) [640, 1539]                                                 |

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

**Further reading on Platelet-activating factor receptor**

Foord SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279-288 [PMID:15914470]

Ishii S et al. (2000) Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice. *Prog. Lipid Res.* 39: 41-82 [PMID:10729607]

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

G protein-coupled receptors → Prokineticin receptors

Overview: Prokineticin receptors, PKR₁ and PKR₂ (provisional nomenclature as recommended by NC-IUPHAR [612]) respond to the cysteine-rich 81-86 amino-acid peptides prokineticin-1 (PROK₁, Q9HC23) (also known as endocrine gland-derived vascular endothelial growth factor, mambakine) and prokineticin-2 (PROK₂, Q9HC23) (protein Bv8 homologue). An orthologue of PROK₁ from black mamba (Dendroaspis polylepis) venom, mamba intestinal toxin 1 (MIT₁, [1905]) is a potent, non-selective agonist at prokineticin receptors [1393], while Bv8, an orthologue of PROK₂ from amphibians (Bombina sp., [1474]), is equipotent at recombinant PKR₁ and PKR₂ [1559], and has high potency in macrophage chemotaxis assays, which are lost in PKR₁-null mice.

Nomenclature

| PKR₁ | PKR₂ |
| --- | --- |
| HGNC, UniProt | PROKR1, Q8TCW9 | PROKR2, Q8NFJ6 |
| Potency order of endogenous ligands | prokineticin-2 (PROK₂, Q9HC23) > prokineticin-1 (PROK₁, Q9HC23) > prokineticin-2β (PROK₂) [348, 1285, 1393, 2005] | prokineticin-2 (PROK₂, Q9HC23) > prokineticin-1 (PROK₁, Q9HC23) > prokineticin-2β (PROK₂) [348, 1285, 1393, 2005] |
| Agonists | MIT₁ [1393] | MIT₁ [1393] |
| Selective agonists | IS₂₀ [668], IS₁ [668] | – |
| Labelled ligands | [²¹⁵]BH-MIT₁ (Agonist) [1393] | [²¹⁵]BH-MIT₁ (Agonist) [1393] |

Comments: Genetic mutations in PROKR₁ are associated with Hirschsprung’s disease [1836], while genetic mutations in PROKR₂ are associated with hypogonadotropic hypogonadism with anosmia [504], hypopituitarism with pituitary stalk interruption [1792] and Hirschsprung’s disease [1836]. PKR₂ has been recently identified as a receptor for T. cruzi natural infection [1077].

Further reading on Prokineticin receptors

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

Negri L et al. (2007) Bv8/Prokineticin proteins and their receptors. Life Sci. 81: 1103-16 [PMID:17881008]
Ngan ES et al. (2008) Prokineticin-signaling pathway. Int. J. Biochem. Cell Biol. 40: 1679-84 [PMID:18440852]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Prolactin-releasing peptide receptor

Overview: The precursor (PRLH, P81277) for PrRP generates 31 and 20-amino-acid versions. QRFP43 (QRFP, P83859) (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from QRFP (P83859) and is also known as P518 or 26RFa. RFRP is an RF amide-related peptide [875] derived from a FMRFamide-related peptide precursor (NPVF, Q9HCQ7), which is cleaved to generate neuropeptide SF (NPFF, O15130), neuropeptide RFRP-1 (NPVF, Q9HCQ7), neuropeptide RFRP-2 (NPVF, Q9HCQ7) and neuropeptide RFRP-3 (NPVF, Q9HCQ7) (neuropeptide NPVF).

Nomenclature
HGNC, UniProt
Prlp receptor

Potency order of endogenous ligands
PrRP-20 (PRLH, P81277) = PrRP-31 (PRLH, P81277) [1201]
PrRP-20 (PRLH, P81277) [561, 1201], PrRP-31 (PRLH, P81277) [561, 1201]

Endogenous agonists

Endogenous antagonists

Labeled ligands

[125I]PrRP-20 (human) (Agonist) [1201], [125I]PrRP31 (Agonist) [552]

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

Further reading on Prolactin-releasing peptide receptor

Samson WK et al. (2006) Prolactin releasing peptide (PrRP): an endogenous regulator of cell growth. Peptides 27: 1099-103 [PMID:16500730]

Takayanagi Y et al. (2010) Roles of prolactin-releasing peptide and RFamide related peptides in the control of stress and food intake. FEBS J. 277: 4998-5005 [PMID:21126313]
Prostanoid receptors

G protein-coupled receptors → Prostanoid receptors

Overview: Prostanoid receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors [2329]) are activated by the endogenous ligands prostaglandins PGD₂, PGE₁, 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.

| Nomenclature | DP₁ receptor | DP₂ receptor |
|--------------|--------------|--------------|
| HGNC, UniProt | PTGDR, Q13258 | PTGDR₂, Q9YSY4 |
| Potency order of endogenous ligands | PGD₂ > PGE₁ > PGE₂ > PGF₂α > PGI₂, thromboxane A₂ | PGD₂ > PGF₂α, PGE₂ > PGI₂, thromboxane A₂ |
| Agonists | treprostinil [2071, 2300] | – |
| Selective agonists | BW 245C [188, 2330, 2331], L-644,698 [2330, 2331] | 15(6)-15-methyl-PGD₂ [821, 1484, 2052] |
| Antagonists | – | fevipiprant (pKi 9) [2072, 2073], ramaroban (pKi 7.4) [2052] |
| Selective antagonists | laropiprant (pKi 10.1) [2046], BWA868C (pKi 8.6–9.3) [188, 701, 2330], ONO-AE3-237 (pKi 7.7) [877, 2144, 2146], CAY 10471 (pIC₅₀ 8.9) [1832, 2174] | |
| Labelled ligands | [³H]PGD₂ (Agonist) [2314, 2330] | [³H]PGD₂ (Agonist) [1394, 1949] |

| Nomenclature | EP₁ receptor | EP₂ receptor | EP₃ receptor | EP₄ receptor |
|--------------|--------------|--------------|--------------|--------------|
| HGNC, UniProt | PTGER₁, P34995 | PTGER₂, P43116 | PTGER₃, P43115 | PTGER₄, P35408 |
| Potency order of endogenous ligands | PGE₂ > PGE₁ > PGF₂α, PGI₂ > PGD₂, thromboxane A₂ | PGE₂ = PGE₁ > PGF₂α, PGI₂ > PGD₂, thromboxane A₂ | PGE₂, PGE₁ > PGF₂α, PGI₂ > PGD₂, thromboxane A₂ | PGE₂ = PGE₁ > PGF₂α, PGI₂ > PGD₂, thromboxane A₂ |
| Endogenous agonists | – | PGE₂ [7, 2034, 2314] | – | – |
| Agonists | 17-phenyl-ω-trinor-PGE₂ [1940] | treprostinil [2071, 2300], PGE₁ [119] | misoprostol (methyl ester) (EP₃-III isofrom) [7] | 17-phenyl-ω-trinor-PGE₂ [2113] |
| Selective agonists | ONO-DI-004 [2062] – Mouse | ONO-AE1-259 [2062] – Mouse, omidenepag [1103], butaprost (free acid form) [7, 2034] | sulprostone (EP₃-III isofrom) [7], ONO-AE-248 [617, 1315] | L902688 [618, 1235], ONO-AE1-329 [617, 618] |
| Antagonists | – | – | – | EP₄A (pKi 7.6–8.5) [1340, 2406] |
| Selective antagonists | ONO-8711 (pKi 9.2) [2269], SC-51322 (pKi 7.9) [7] | PF-04418948 (PF-04418948 has weaker affinity at the EP2-receptor in guinea-pigs) (pKi 8.3) [14, 169], TC6-129 (pKi 8.1) [654] | L-826266 (EP₃-III isofrom (pKi=8.04 in the presence of HSA) (pKi 9.1) [1026], ONO-AE3-240 (pIC₅₀ 8.8) [42] – Mouse, DG-041 (pKi 8.4) [1024] | ONO-AE3-208 (pKi 8.5), GW 627368 (pKi 7–7.1) [2314, 2315] |
| Labelled ligands | [³H]PGE₂ (Agonist) [7, 1940, 2314] | [³H]PGE₂ (Agonist) [7, 2314] | [³H]PGE₂ (Agonist) [7, 2314] | [³H]PGE₂ (Agonist) [7, 461, 2300, 2314] |
Nomenclature
HGNC, UniProt
FP receptor
PTGR, P43088
IP receptor
PTGIR, P43119
TP receptor
78XA28, P21731

Potency order of endogenous ligands
PGF₂α > PGD₂ > PGE₂ > PGI₂, thromboxane A₂

Endogenous agonists
–

Agonists
ONO-9054 [2366]

Selective agonists
fluprostanol [7], latanoprost (free acid form) [7]

Antagonists
–

Selective antagonists
AS604872 (pKᵢ 7.5) [397]

Labelled ligands
[^1]H)PGF₂α (Agonist) [7, 8, 2314], [^3]H)fluprostanol (Agonist)
[^3]H)iloprost (Agonist) [7, 187, 2300, 2314]

Comments: Whilst cicaprost is selective for IP receptors, it does exhibit moderate agonist potency at EP₄ receptors [7]. Apart from IP receptors, iloprost also binds to EP₁ receptors.

The EP₁ agonist 17-phenyl-β-carboxamido-PGE₂ also shows agonist activity at EP₃ and EP₄ receptors [617, 2113]. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1281] and TP receptors [1151, 1779]. mRNA for the EP₁ receptor undergoes alternative splicing to produce variants which can interfere with signalling [1632] or generate complex patterns of G-protein (G₄₁₀, G₄₁₁, G₁ and G₁₂,13) coupling (e.g. [1143, 1557]). The number of EP₃ receptor (protein) variants are variable depending on species, with five in human, three in rat and three in mouse. Putative receptor(s) for prostanamide F (which as yet lack molecular correlates) and which preferentially recognize PGF₂-1-ethanolamide and its analogues (e.g. Bimatoprost) have been identified, together with moderate-potency antagonists (e.g. AGN 211334) [2328].

The free acid form of AL-12182, AL12180, used in in vitro studies, has an EC₅₀ of 15nM which is the concentration of the compound giving half-maximal stimulation of inositol phosphate turnover in HEK-293 cells expressing the human FP receptor [1941].

References given alongside the TP receptor agonists I-BOP [1409] and STA₂ [69] use human platelets as the source of TP receptors for competition radio-ligand binding assays to determine the indicated activity values.

Pharmacological evidence for a second IP receptor, denoted IP₂, in the central nervous system [2091, 2272] and in the BEAS-2B human airway epithelial cell line [2317] is available. This receptor is selectively activated by 15R-17,18,19,20-tetranor-16-m-toly-isocarbacyclin (15R-TIC) and 15R-Deoxy 17,18,19,20-tetranor-16-m-toly-isocarbacyclin (15-deoxy-TIC). However, molecular biological evidence for an IP₂ subtype is currently lacking.

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

G protein-coupled receptors → Proteinase-activated receptors

Overview: Proteinase-activated receptors (PARs, nomenclature as agreed by the NC-IUPHAR Subcommittee on Proteinase-activated Receptors [894]) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis 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 SLILRN-NH2, SLIGKV-NH2, TFRGAP-NH2 and GYPGQV-NH2, respectively. With the exception of PAR3, synthetic peptides with these sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation of Gαq-coupled calcium signalling, thereby preventing activation by activating proteinases but not by agonist peptides. Neutrophil elastase (NE) cleavage of PAR1 and PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [1764]. PAR2 activation by NE regulates inflammation and pain responses [1518, 2431] and triggers mucin secretion from airway epithelial cells [2434].

| Nomenclature | PAR1 | PAR2 | PAR3 | PAR4 |
|-------------|------|------|------|------|
| HGNC, UniProt | F2R, P25116 | F2R1, P55085 | – | F2R2L2, O00254 |
| Agonist proteases | thrombin (F2, P00734), activated protein C (PROC, P04070), matrix metalloproteinase 1 (MMP1, P45452), matrix metalloproteinase 13 (MMP13, P45452) [81] | Trypsin, tryptase, TF/VIIa, Xα; elastase, neutrophil expressed; cathepsin S [1001, 1762] | – | thrombin (F2, P00734) |
| Agonists | F16357 | – | – | – |
| Selective agonists | TFLLR-NH2 [391] | – | – | – |
| Selective antagonists | vorapaxar (pEC50 8.1) [327], atopaxar (pIC50 7.7) [1124], RWJ-56110 (pIC50 6.4) [52] | I-191 (pIC50 7.1) [1000], AZ8838 (pKd 6.5) [360], G888 (pIC50 5.7) [2050], P2pal18s [1933] | – | – |
| Allosteric modulators | – | AZ3451 (Negative) (pIC50 7.6) [360] | – | – |
| Labelled ligands | [3H]haTRAP (Agonist) [19] | 2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH2 (Agonist) [895], 2-furoyl-LIGRL[N-[3H]propionyl]-O-NH2 (Agonist) [895], [3H]2-furoyl-LIGRL-NH2 (Selective Agonist) [1040], trans-cinnamoyl-LIGRL [N-[3H]propionyl]-NH2 (Agonist) [30] | – | – |
| Comments | TFLLR-NH2 is selective relative to the PAR2 receptor [171, 1053]. | 2-Furoyl-LIGRL-NH2 activity was measured via calcium mobilisation in HEK 293 cells which constitutively coexpress human PAR1 and PAR2. | – | – |

**Comments:** Endogenous serine proteinases (EC 3.4.21.) active at the proteinase-activated receptors include: thrombin (F2, P00734), generated by the action of Factor X (F10, P00742) on liver-derived prothrombin (F2, P00734); trypsin, generated by the action of enterokinase (TMPS15, P98073) on pancreatic-derived trypsinogen (PRSS1, P07477); tryptase, a family of enzymes (α/β TPSAB1, Q15661; γ TPSG1, Q9NRR2; δ TPSD1, Q9BFZ3) 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).

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Further reading on Proteinase-activated receptors

Adams MN et al. (2011) Structure, function and pathophysiology of protease activated receptors. Pharmacol. Ther. 130: 248-82 [PMID:21277892]
Canto I et al. (2012) Allosteric modulation of protease-activated receptor signaling. Mini Rev Med Chem 12: 804-11 [PMID:22681248]
Garcia PS et al. (2010) The role of thrombin and protease-activated receptors in pain mechanisms. Thromb. Haemost. 103: 1145-51 [PMID:20431855]
Hollenberg MD et al. (2002) International Union of Pharmacology. XXVIII. Proteinase-activated receptors. Pharmacol. Rev. 54: 203-17 [PMID:12037136]
Ramachandran R et al. (2012) Targeting proteinase-activated receptors: therapeutic potential and challenges. Nat Rev Drug Discov 11: 69-86 [PMID:22212680]
Soh U et al. (2010) Signal transduction by protease-activated receptors. Br. J. Pharmacol. 160: 191-203 [PMID:20423334]

QRFP receptor

G protein-coupled receptors → QRFP receptor

Overview: The human gene encoding the QRFP receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee on the QRFP receptor [1259]; QRFPR, formerly known as the Peptide P518 receptor), previously designated as an orphan GPCR receptor was identified in 2001 by Lee et al. from a hypothalamus cDNA library [1237]. However, the reported cDNA (AF411117) is a chimera with bases 1-127 derived from chromosome 1 and bases 155-1368 derived from chromosome 4. When corrected, QRFPR (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 Gal1 (35%) receptors.

| Nomenclature | QRFP receptor |
| HGNC, UniProt | QRFPR, Q96P65 |
| Endogenous agonists | QRFP26 (QRFP) [343, 999] |
| Agonists | LV-2186 [41], LV-2172 [1572] |
| Selective antagonists | compound 25e (pIC_{50} 7.3) [687, 688] |
| Labelled ligands | [\textsuperscript{125}I]QRFP43 (human) (Agonist) [641, 1164, 2090], [\textsuperscript{125}I]26RFa (human) (Agonist) [260] |

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

Further reading on QRFP receptor

Chartrel N et al. (2011) The RFamide neuropeptide 26RFa and its role in the control of neuroendocrine functions. Front Neuroendocrinol 32: 387-97 [PMID:21530572]
Fukusumi S et al. (2006) Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. Peptides 27: 1073-86 [PMID:16500002]
Relaxin family peptide receptors

G protein-coupled receptors → Relaxin family peptide receptors

**Overview:** Relaxin family peptide receptors (RXFP, nomenclature as agreed by the NC-IUPHAR Subcommittee on Relaxin family peptide receptors [120, 788]) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are heterodimeric peptide hormones structurally related to insulin: relaxin-1 (RLN1, P04808), relaxin (RLN2, P04090), relaxin-3 (RLN3, Q8W XF3) (also known as INSL7), insulin-like peptide 3 (INSL3, INSL3, P51460) and INSL5 (INSL5, Q9Y5Q6). Species homologues of relaxin have distinct pharmacology and relaxin (RLN2, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [1912]. Relaxin-3 (RLN3, QBW XF3) is the ligand for RXFP3 but it also binds to RXFP1 and RXFP4 and has differential affinity for RXFP2 between species [1911]. INSL5 (INSL5, Q9Y5Q6) is the ligand for RXFP4 but is a weak antagonist of RXFP3. Relaxin (RLN2, P04090) and INSL3 (INSL3, P51460) have multiple complex binding interactions with RXFP1 [1930] and RXFP2 [886] which direct the N-terminal LDLa modules of the receptors together with a linker domain to act as a tethered ligand to direct receptor signaling [1913]. INSL5 (INSL5, Q9Y5Q6) and relaxin-3 (RLN3, QBW XF3) interact with their receptors using distinct residues in their B-chains for binding, and activation, respectively [921, 2324].

| Nomenclature | RXFP1 | RXFP2 | RXFP3 | RXFP4 |
|--------------|-------|-------|-------|-------|
| HGNC, UniProt | RXFP1, Q9HBX9 | RXFP2, Q8W XD0 | RXFP3, Q9NSD7 | RXFP4, Q8TDU9 |
| Potency order of endogenous ligands | relaxin (RLN2, P04090) > relaxin-3 (RLN3, Q8W XF3) [2049] | INSL3 (INSL3, P51460) > relaxin (RLN2, P04090) > relaxin-3 (RLN3, Q8W XF3) [1174, 2049] | relaxin-3 (RLN3, QBW XF3) > relaxin-3 (B chain) (RLN3, QBW XF3) > relaxin (RLN2, P04090) [1296] | INSL5 (INSL5, Q9Y5Q6) (pKᵢ, 7) [2438] |
| Endogenous antagonists | – | – | – | – |
| Antagonists | B-R13/17K H2 relaxin (pECₛₒ, 5.7–6.7) [913, 1570] | – | R3(B,Δ23-27)R/I5 chimeric peptide (pICₛₒ, 9.2) [1165] | R3(B,Δ23-27)R/I5 chimeric peptide (pICₛₒ, 8.8–6.6) [823, 1165] |
| Selective antagonists | – | Ar(9-26)INSL3 (pKᵢ, 9.1) [912], A(10-24)INSL3 (pKᵢ, 8.7) [912], A(C10/15S)INSL3 (pKᵢ, 8.6) [2422], INSL3 B chain dimer analogue 8 (pKᵢ, 8.5) [1938], A(10/15C)INSL3 (pKᵢ, 8.3) [2422], cyclic INSL3 B-chain analogue 6 (pKᵢ, 6.7) [1936], INSL3 B-chain analogue (pKᵢ, 5.1) [479], (des 1-8) A-chain INSL3 analogue [285] | minimised relaxin-3 analogue 3 (pKᵢ, 7.6) [1934], R3-B1-22R (pKᵢ, 7.4) [823] | minimised relaxin-3 analogue 3 (pICₛₒ, 6.6) [1934] |
| Allosteric modulators | ML290 (Agonist) (pECₛₒ, 7) [2346, 2349] | – | – | – |
| Labelled ligands | [33]P relaxin (human) (Agonist) [786, 2049], europium-labelled relaxin (Agonist) [1935], [125]I INSL3 (human) (Agonist) [1516], [33]P relaxin (human) (Agonist) [786, 2049], [125]I relaxin-3 (human) (Agonist) [1296], [125]I relaxin-3-B/INSL3 A chimera (Agonist) [1294], europium-labelled relaxin-3-B/INSL3 A chimera (Agonist) [823] | – | – |
| Comments | Europium-labelled INSL3 is a fluorescent ligand for this receptor (Kᵢ, 1nM) [1937]. | – | – | – |

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

**Full Contents of Concise Guide:** http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full
Comments: Relaxin (RLN2, P04090) is the cognate peptide ligand for RXFP1 and is in extended Phase III clinical trials for the treatment of acute heart failure [1435]. Relaxin has vasodilatory, anti-fibrotic, angiogenic, anti-apoptotic and anti-inflammatory effects. A small molecule allosteric agonists ML290 has been developed [1944, 2349], and a relaxin B-chain mimetic peptide B7-33 has been developed which that has cell specific signaling properties [911]. The antifibrotic actions of relaxin are dependent on the angiotensin receptor AT₂ [377]. INSL3 (INSL3, P51460) is the cognate peptide for RXFP2 and is a circulating hormone that in males is essential for testicular descent in utero [1556] and in females has important roles in ovarian follicle function [961]. In adults, INSL3 has potential roles in testicular function [962] and the musculoskeletal system [472]. RXFP2 is also present in brain, associated with cortico-thalamic motor circuits [1917]. cAMP elevation is the major signalling pathway for both RXFP1 and RXFP2 [919, 920], but RXFP1 also activates MAP kinases, nitric oxide signalling, and tyrosine kinase phosphorylation; and relaxin can interact with glucocorticoid receptors [787]. Receptor expression profiles suggest that RXFP3 is a brain neuropeptide receptor and RXFP4 a gut hormone receptor. The brain relaxin-3/RXFP3 system modulates feeding [652, 653, 823, 1934, 1992] via effects in hypothalamus [475, 652, 1039], anxiety [1842, 2415], reward and motivated, goal-directed behaviours [906, 1842, 2239], and spatial and social memory [34, 780]. Of the other relaxin peptides, relaxin-3 (RLN3, Q8WXF3) is an agonist at RXFP3 and RXFP4 whereas INSL5 (INSL5, Q9YSQ6) is an agonist at RXFP4 and a weak antagonist at RXFP3. INSL5 (INSL5, Q9YSQ6) is secreted from enteroendocrine L cells and the INSL5/RXFP4 system affects food intake [751] and glucose homeostasis [1331]. RXFP3 and RXFP4 couple to Gᵢₒ and inhibit adenylyl cyclase [1296, 2191], and also cause Erk1/2 phosphorylation [2191]. RXFP4 also causes phosphorylation of p38MAPK, Akt and S6RP [55] and GLP-1 secretion in vitro [54].

Further reading on Relaxin family peptide receptors

Bathgate RA et al. (2013) Relaxin family peptides and their receptors. Physiol. Rev. 93: 405-80 [PMID:23303914]
Du XJ et al. (2010) Cardiovascular effects of relaxin: from basic science to clinical therapy. Nat Rev Cardiol 7: 48-58 [PMID:19935741]
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]

Ivell R et al. (2011) Relaxin family peptides in the male reproductive system--a critical appraisal. Mol. Hum. Reprod. 17: 71-84 [PMID:20952422]
Somatostatin receptors

G protein-coupled receptors → Somatostatin receptors

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

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

Comments: [125]¹[Tyr<sup>11</sup>-SRIF-14, [125]¹[LTT-SRIF-28, [125]¹CGP 23996 and [125]¹Tyr<sup>10</sup>-CST14 may be used to label somatostatin receptors nonselectively. A number of nonpeptide subtype-selective agonists have been synthesised [1817]. Octreotide and lanreotide are being used in the treatment of SST<sub>2</sub>-expressing neuroendocrine tumors and pasireotide for SST<sub>3</sub>-expressing neuroendocrine tumors. A novel peptide somatostatin analogue, veldoreotide (COR-005), has affinity for SST<sub>2</sub>, SST<sub>4</sub> and SST<sub>5</sub> receptors and is a potent inhibitor of GH secretion [1717, 1954].

Further reading on Somatostatin receptors

Colao A et al. (2011) Resistance to somatostatin analogs in acromegaly. Endocr. Rev. 32: 247-71 [PMID:21123741]

Günther T et al. (2018) International Union of Basic and Clinical Pharmacology. CV. Somatostatin Receptors: Structure, Function, Ligands, and New Nomenclature. Pharmacol. Rev. 70: 763-835 [PMID:30232095]

Hoyer D et al. (2000) Somatostatin receptors. In The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edn. Edited by Watson SP, Girdlestone D: IUPHAR Media: 354-364

Schulz S et al. (2014) Fine-tuning somatostatin receptor signalling by agonist-selective phosphorylation and dephosphorylation: IUPHAR Review 5. Br. J. Pharmacol. 171: 1591-9 [PMID:24328848]

Weckbecker G et al. (2003) Opportunities in somatostatin research: biological, chemical and therapeutic aspects. Nat Rev Drug Discov 2: 999-1017 [PMID:14654798]

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

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

G protein-coupled receptors → Succinate receptor

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

| Nomenclature         | succinate receptor |
|----------------------|--------------------|
| HGNC, UniProt        | SUCNR1, Q9BXA5     |
| Endogenous agonists  | succinic acid [838, 2015], maleic acid [696] |
| Agonists             | compound 31 (Partial agonist) [1791], cis-epoxysuccinic acid [2153], compound 130 (Partial agonist) [2153], cis-epoxysuccinic acid [696], maleic acid [703], maleic acid [838] |

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

**Further reading on Succinate receptor**

Ariza AC et al. (2012) The succinate receptor as a novel therapeutic target for oxidative and metabolic stress-related conditions. *Front Endocrinol (Lausanne)* 3: 22 [PMID:22649411]
de Castro Fonseca M et al. (2016) GPR91: expanding the frontiers of Krebs cycle intermediates. *Cell Commun. Signal* 14: 3 [PMID:26759054]

Gilissen J et al. (2016) Insight into SUCNR1 (GPR91) structure and function. *Pharmacol. Ther.* 159: 56-65 [PMID:26808164]

Grimolizzi F et al. (2018) Multiple faces of succinate beyond metabolism in blood. *Haematologica* 103: 1586-1592 [PMID:29954939]
## Tachykinin receptors

### G protein-coupled receptors → Tachykinin receptors

#### Overview:
Tachykinin receptors (provisional nomenclature as recommended by NC-IUPHAR [612]) are activated by the endogenous peptides 

- **substance P** (TAC1, P20366) (SP),
- **neurokinin A** (TAC1, P20366) (NKA; previously known as substance K, neurokinin 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 neuropeptides (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in in vitro pharmacology exist for all three receptors, in the context of nonpeptide ligands. Antagonists such as aprepitant and fosaprepitant were approved by FDA and EMA, in combination with other antiemetic agents, for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

| Nomenclature | NK1 receptor | NK2 receptor | NK3 receptor |
|--------------|--------------|--------------|--------------|
| HGNC, UniProt | TACR1, P21503 | TACR2, P21452 | TACR3, P29371 |
| Potency order of endogenous ligands | substance P (TAC1, P20366) > neurokinin A (TAC1, P20366) > neurokinin B (TAC3, Q9UHF0) | neurokinin A (TAC1, P20366) > neurokinin B (TAC3, Q9UHF0) > substance P (TAC1, P20366) | neurokinin B (TAC3, Q9UHF0) > neurokinin A (TAC1, P20366) > substance P (TAC1, P20366) |
| Agonists | [Phe]SP (human, mouse, rat) [1868], H[MePhe]NKA (human, mouse, rat) [778] | [Phe]SP (human, mouse, rat) [1868], H[MePhe]NKA (human, mouse, rat) [778] | [Phe]SP (human, mouse, rat) [1868], H[MePhe]NKA (human, mouse, rat) [778] |
| Selective agonists | [Phe]SP (human, mouse, rat) [1868], H[MePhe]NKA (human, mouse, rat) [778] | [Phe]SP (human, mouse, rat) [1868], H[MePhe]NKA (human, mouse, rat) [778] | [Phe]SP (human, mouse, rat) [1868], H[MePhe]NKA (human, mouse, rat) [778] |
| Selective antagonists | aprepitant (pK<sub>i</sub> 10.1) [781, 782], CP 99994 (pK<sub>i</sub> 9.3–9.7) [57, 1869], RP67580 (pIC<sub>50</sub> 7.7) [610] | CR94800 (pK<sub>i</sub> 9.8) [223], saredutant (pK<sub>i</sub> 9.4–9.7) [57, 1869], GR 159897 (pK<sub>d</sub> 7.8–9.5) [147, 556, 1999], MEN10627 (pK<sub>i</sub> 9.2) [699], neepadutant (pK<sub>i</sub> 8.5–8.7) [314, 394] | osanetant (pK<sub>i</sub> 8.4–9.7) [57, 125, 393, 555, 1034, 1641, 1868, 2130], talnetan (pK<sub>i</sub> 7.4–9) [142, 700, 1868, 1869], PD157672 (pIC<sub>50</sub> 7.8–7.9) [182, 2130] |
| Labellised ligands | [125I]JL703,606 (Antagonist) (pK<sub>d</sub> 9.5) [621], [125I]BBH-[Phe]<sub>5</sub>[Met(O)<sub>2</sub>]SP (Agonist) [2150] – Rat, [3H]SP (human, mouse, rat) (Agonist) [93], [125I]SP (human, mouse, rat) (Agonist) | [3H]saredutant (Antagonist) (pK<sub>d</sub> 9.7) [749] – Rat, [125I]NKA (human, mouse, rat) (Agonist) [2267], [3H]GR100679 (Antagonist) (pK<sub>d</sub> 9.2) [778] | [3H]osanetant (Antagonist) (pK<sub>d</sub> 9.9), [3H]senktide (Agonist) [760] – Guinea pig, [125I]MePhe<sub>7</sub>NKB (Agonist) |

#### Comments:
The NK<sub>1</sub> receptor has also been described to couple to G proteins other than G<sub;q/11</sub> [1828]. The crystal structure of the human NK<sub>1</sub> receptor in complex with antagonists has been determined [1909, 2391]. The hexapeptide agonist peptide appears to bind to an overlapping but non-identical site to substance P (TAC1, P20366) on the NK<sub>1</sub> receptor. There are additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK<sub>3</sub> receptor was found to respond to NKB when expressed in Xenopus oocytes or Chinese hamster ovary cells [509, 1150].

---

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

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
Further reading on Tachykinin receptors

Douglas SD et al. (2011) Neurokinin-1 receptor: functional significance in the immune system in reference to selected infections and inflammation. *Ann. N. Y. Acad. Sci.* **1217**: 83-95 [PMID:21091716]

Foord SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-288 [PMID:15914470]

Jones S et al. (2008) The neurokinin 1 receptor: a potential new target for anti-platelet therapy? *Curr Opin Pharmacol* **8**: 114-9 [PMID:18296119]

Steinhoff MS et al. (2014) Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol. Rev.* **94**: 265-301 [PMID:24382888]

Yin J et al. (2018) Crystal structure of the human NK_1 tachykinin receptor. *Proc. Natl. Acad. Sci. U.S.A.* **115**: 13264-13269 [PMID:30538204]

Thyrotropin-releasing hormone receptors

G protein-coupled receptors → Thyrotropin-releasing hormone receptors

**Overview**: Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature as recommended by NC-IUPHAR [612]) are activated by the endogenous tripeptide TRH (TRH, P20396) (pGlu-His-ProNH2). TRH (TRH, P20396) and TRH analogues fail to distinguish TRH$_1$ and TRH$_2$ receptors [2059]. [3H]TRH (human, mouse, rat) is able to label both TRH$_1$ and TRH$_2$ receptors with $K_d$ values of 13 and 9 nM respectively. Synthesis and biology of ring-modified L-Histidine containing TRH analogues has been reported [1429].

| Nomenclature | TRH$_1$ receptor | TRH$_2$ receptor |
|--------------|-----------------|-----------------|
| HGNC, UniProt | TRHR, P34981    | –               |
| Antagonists   | diazepam (pK$_i$ 5.2) [522] – Rat | –               |
| Selective antagonists | midazolam (pK$_i$ 5.5) [522] – Rat, chlordiazepoxide (pK$_i$ 4.8) [522] – Rat, chlordiazepoxide (pK$_i$ 4.7) [2042] – Mouse | –               |
| Comments      | –               | A class A G protein-coupled receptor: not present in man |

Further reading on Thyrotropin-releasing hormone receptors

Bílek R et al. (2011) TRH-like peptides. *Physiol Res* **60**: 207-15 [PMID:2114375]

Foord SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-288 [PMID:15914470]

Nilini EA. (2010) Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Front Neuroendocrinol* **31**: 134-56 [PMID:20074584]
Trace amine receptor

G protein-coupled receptors → Trace amine receptor

**Overview:** Trace amine-associated receptors were discovered from a search for novel 5-HT receptors [205], 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 [1355]) has affinity for the endogenous trace amines tyramine, β-phenylethylamine and octopamine in addition to the classical amine dopamine [205]. Emerging evidence suggests that TA1 is a modulator of monoaminergic activity in the brain [2351] with TA1 and dopamine D2 receptors shown to form constitutive heterodimers when co-expressed [572]. In addition to trace amines, receptors can be activated by amphetamine-like psychostimulants, and endogenous thyronamines.

| Nomenclature | TA1 receptor |
|--------------|-------------|
| HGNC, UniProt | TAAR1, Q96RJ0 |
| Potency order of endogenous ligands | tyramine > β-phenylethylamine > octopamine = dopamine [205] |
| Agonists | RO5166017 [1790] |
| Antagonists | EPPTB (Inverse agonist) (pIC_{50} 5.1) [222] |
| Labelled ligands | [{^3}H]tyramine (Agonist) [205] |

**Comments:** In addition to TA1, in man there are up to 5 functional TAAR genes (TAAR2,5,6,8,9). See [205] for detailed discussion. The product of the gene TAAR2 (also known as GPR58) appears to respond to β-phenylethylamine > tyramine and to couple through G_{1} [205]. 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, 96R18), TAAR8 (Trace amine receptor 8, GPR102: TAAR8, Q969N4) and TAAR9 (trace amine associated receptor 9: TAAR9, 96R19) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have affinity for rodent cloned trace amine receptors, including TA1 [1881]. An antagonist EPPTB has recently been described with a pK_{i} of 9.1 at the mouse TA1 but >5.3 for human TA1 [2025].

**Further reading on Trace amine receptor**

Maguire JJ et al. (2009) International Union of Pharmacology. LXXII. Recommendations for trace amine receptor nomenclature. *Pharmacol. Rev.* 61: 1-8 [PMID:19325074]  
Pei Y et al. (2016) Trace Amines and the Trace Amine-Associated Receptor 1: Pharmacology, Neurochemistry, and Clinical Implications. *Front Neurosci* 10: 148 [PMID:27092049]
Urotensin receptor

G protein-coupled receptors → Urotensin receptor

**Overview:** The urotensin-II (U-II) receptor (UT, nomenclature as agreed by the NC-IUPHAR Subcommittee on the Urotensin receptor [516, 612, 2211]) is activated by the endogenous dodecapeptide urotensin-II (UTS2, O95399), originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [150, 2210]. Several structural forms of U-II exist in fish and amphibians. The goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene gpr14 [425, 1304, 1498, 1603]. Human urotensin-II (UTS2, O95399), an 11-amino-acid peptide [425], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding [240, 1101]. This sequence is also conserved in the deduced amino-acid sequence of rat urotensin-II [Rat] (14 amino-acids) and mouse urotensin-II [Mouse] (14 amino-acids), although the N-terminal is more divergent from the human sequence [424]. A second endogenous ligand for the UT has been discovered in rat [2053]. This is the urotensin II-related peptide (UTS2B, Q765I0), an octapeptide that is derived from a different gene, but shares the C-terminal sequence (CFVKYCV) common to U-II from other species. Identical sequences to rat urotensin II-related peptide (UTS2B, Q765I0) are predicted for the mature mouse and human peptides [523]. UT exhibits relatively high sequence identity with somatostatin, opioid and galanin receptors [2211].

| Nomenclature | UT receptor |
|--------------|-------------|
| HGNC, UniProt | UTS2, Q9UKP6 |
| Endogenous agonists | urotensin II-related peptide (UTS2B, Q765I0) [523, 1354], urotensin-II (UTS2, O95399) [517, 554, 747] |
| Selective agonists | [Pen^5]U-(4-11) (human) [747], U-II-(4-11) (human) [747], [3-iodo-Tyr^6]U-II-(4-11) (human) [1187], Urolinin [104], FL104 [1246, 1248], AC-7954 [436, 1247] |
| Selective antagonists | urantide (pK_i 8.3) [1661], [Orn^5]JURP (pK_i 7.2) [492] – Rat, palosuran (pIC_{50} 7.1) [402], SB-611812 (pK_i 6.6) [1760], [Cha^6]U-II-(4-11) (pK_i 6.4) [344] – Rat |
| Labelled ligands | [^{125}I]U-II (human) (Agonist) [46, 214, 344, 1354], [^{125}I]N-biotin-[Ahx^6, Bpa^8]U-II (human) [503] |

**Comments:** In the human vasculature, human urotensin-II (UTS2, O95399) elicits both vasoconstrictor (pD_{2} 9.3-10.1, [1354]) and vasodilator (pIC_{50} 10.3-10.4, [2035]) responses.

**Further reading on Urotensin receptor**

Foord SM et al. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279-288 [PMID:15914470]

Hunt BD et al. (2010) A rat brain atlas of urotensin-II receptor expression and a review of central urotensin-II effects. *Naunyn Schmiedebergs Arch. Pharmacol.* 382: 1-31 [PMID:20422157]

Maryanoff BE et al. (2010) Urotensin-II receptor modulators as potential drugs. *J. Med. Chem.* 53: 2695-708 [PMID:20043680]

Ross B et al. (2010) Role of urotensin II in health and disease. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 298: R1156-72 [PMID:20421634]

Vaudry H et al. (2015) International Union of Basic and Clinical Pharmacology. XCII. Urotensin II, urotensin II-related peptide, and their receptor: from structure to function. *Pharmacol. Rev.* 67: 214-58 [PMID:25535277]
### Vasopressin and oxytocin receptors

**G protein-coupled receptors → Vasopressin and oxytocin receptors**

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

#### Nomenclature

| Nomenclature | V<sub>1A</sub> receptor | V<sub>1B</sub> receptor |
|--------------|--------------------------|--------------------------|
| HGNC, UniProt | AVPR1A, P37288           | AVPR1B, P47901           |

#### Potency order of endogenous ligands

| Vasopressin (AVP, P01185) > oxytocin (OXT, P01178) | vasopressin (AVP, P01185) > oxytocin (OXT, P01178) |
|---------------------------------------------------|---------------------------------------------------|
| [26, 359, 419, 1541, 1851, 2078, 2115]             | [26, 359, 486, 748, 1541, 1851, 2078, 2116]        |

#### Selective agonists

| F180 [33, 419] | d[Leu<sup>4</sup>][LVP [1679], d[Cha<sup>4</sup>][AVP [486, 748] |
|----------------|----------------------|

#### Antagonists

| conivaptan (p<sub>K<sub>i</sub> 8.2–8.4) [2078, 2079] | nelivaptan (p<sub>K<sub>i</sub> 8.4–9.3) [748, 1929] |
|-------------------------------------------------|--------------------------------------------------|

#### Selective antagonists

| relcovaptan (p<sub>K<sub>i</sub> 8.1–9.3) [26, 419, 748, 2078, 2115], d(CH<sub>2</sub>]<sub>3</sub>[Tyr<sub>(Me)<sub>2</sub>],Arg<sup>8</sup>]<sub>AVP (Antagonist) (p<sub>K<sub>i</sub> 9) | - |
|----------------------------------------------------------|--------------------------------------------------|

#### Labelled ligands

| [<sup>125</sup>I]OH-LVA (Antagonist) (p<sub>K<sub>d</sub> 10.3–10.4) [369, 419], [<sup>3</sup>H]AVP (human, mouse, rat) (Agonist) [231, 369, 2078, 2079, 2115] | [<sup>3</sup>H]AVP (human, mouse, rat) (Agonist) [486, 1851, 2078, 2079, 2116] |
|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|

#### Nomenclature

| Nomenclature | V<sub>2</sub> receptor | OT receptor |
|--------------|------------------------|-------------|
| HGNC, UniProt | AVPR2, P30518          | OXTR, P30559 |

#### Potency order of endogenous ligands

| vasopressin (AVP, P01185) > oxytocin (OXT, P01178) | oxytocin (OXT, P01178) > vasopressin (AVP, P01185) |
|---------------------------------------------------|---------------------------------------------------|
| [26, 359, 369, 1679, 1927, 2078, 2365]            | [26, 369, 370, 396, 748, 984, 1096]               |

#### Selective agonists

| VNA932 [582], OPC-51803 [1541], d[Val<sub>4</sub>,DArg<sup>8</sup>]<sub>AVP | [Thr<sub>4</sub>,Gly<sup>2</sup>]<sub>OYOT [370, 551, 984] |
|------------------------------------------------|--------------------------|

#### Antagonists

| conivaptan (p<sub>K<sub>i</sub> 9.4) [435], tolvaptan (p<sub>K<sub>i</sub> 9.4) [2365], satavaptan (p<sub>K<sub>i</sub> 8.4–9.3) [26, 420, 1926, 1927, 2078], lixivaptan (Inverse agonist) (p<sub>K<sub>i</sub> 8.9–9.2) [36, 1927], d(CH<sub>2</sub>]<sub>3</sub>[D-Ile<sup>8</sup>]<sub>4</sub>VAP (p<sub>K<sub>i</sub> 6.9–8.4) [420, 1927], mozavaptan (Inverse agonist) (p<sub>K<sub>i</sub> 7.4–8.1) [420, 1927, 2078, 2116, 2365] | L-371,257 (p<sub>K</sub> 8.8) [748] |
|------------------------------------------------|-----------------------------------|

#### Selective antagonists

| conivaptan (p<sub>K<sub>i</sub> 9.4) [435], tolvaptan (p<sub>K<sub>i</sub> 9.4) [2365], satavaptan (p<sub>K<sub>i</sub> 8.4–9.3) [26, 420, 1926, 1927, 2078], lixivaptan (Inverse agonist) (p<sub>K<sub>i</sub> 8.9–9.2) [36, 1927], d(CH<sub>2</sub>]<sub>3</sub>[D-Ile<sup>8</sup>]<sub>4</sub>VAP (p<sub>K<sub>i</sub> 6.9–8.4) [420, 1927], mozavaptan (Inverse agonist) (p<sub>K<sub>i</sub> 7.4–8.1) [420, 1927, 2078, 2116, 2365] | L-371,257 (p<sub>K</sub> 8.8) [748] |
|------------------------------------------------|-----------------------------------|

#### Labelled ligands

| [<sup>3</sup>H]AVP (human, mouse, rat) (Agonist) [420, 1541, 2078, 2079, 2365], [<sup>3</sup>H]dDAVP (Agonist) [1383], [<sup>3</sup>H]desGly-NH<sub>2</sub>[D-Ile<sup>8</sup>]<sub>4</sub>VAP (p<sub>K<sub>d</sub> 8.6) | [<sup>125</sup>I]d(CH<sub>2</sub>]<sub>3</sub>[Tyr<sub>(Me)<sub>2</sub>],Thr<sub>4</sub>,Orn<sup>8</sup>,Tyr-NH<sub>2</sub><sup>9</sup>OVT (Antagonist) (p<sub>K<sub>d</sub> 10), [<sup>3</sup>H]OT (human, mouse, rat) (Agonist) [369, 637, 984, 1098], [<sup>111</sup>In]DOTA-dLVT (p<sub>K<sub>d</sub> 8.3) [368] |
|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|

[Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.14748/full)
**Comments**: Vasopressin and oxytocin receptors have a characteristic and sometimes overlapping distribution in a number of tissues including brain. There are phylogenetic, ontogenetic and sex-specific differences in the levels and distribution of these receptors, particularly in the brain. The V_2 receptor exhibits marked species differences, such that many ligands (d(CH2)5[D-Ile4]AVP and [2H]desGly-NH2[D-Ile4]VIP) exhibit low affinity at human V_2 receptors [31]. Similarly, DAVP is more V_2 selective in the rat than in the human [1851]. The gene encoding the V_2 receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [164]. D[Cha4]AVP is selective only for the human and bovine V_1B receptors [486], while d[Leu4]VIP has high affinity for the rat V_1B receptor [1679]. Knockouts of vasopressin and oxytocin receptors have systemspecific defects (e.g., impaired ability to concentrate urine in V_2 receptor knockouts) which include behavioural deficits (principally in V_1A, V_1B and OT receptor knockouts).

**Further reading on Vasopressin and oxytocin receptors**

Knepper MA. (2012) Systems biology in physiology: the vasopressin signaling network in kidney. *Am. J. Physiol., Cell Physiol.* **303**: C1115-24 [PMID:22932685]

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

Manning M et al. (2012) Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics. *J. Neuroendocrinol.* **24**: 609-28 [PMID:22375852]

Meyer-Lindenberg A et al. (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat. Rev. Neurosci.* **12**: 524-38 [PMID:21852800]

Neumann ID et al. (2012) Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci.* **35**: 649-59 [PMID:22974560]

---

**VIP and PACAP receptors**

**G protein-coupled receptors → VIP and PACAP receptors**

**Overview**: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors [812, 813]) are activated by the endogenous peptides VIP (VIP, P01282), PACAP-38 (ADCYAPI, P18509), PACAP-27 (ADCYAPI, P18509), peptide histidine isoleucineamide (PHI [Mouse, Rat]), peptide histidine methionineamide (PHM (VIP, P01282)) and peptide histidine valine (PHV (VIP, P01282)). VPAC_1 and VPAC_2 receptors display comparable affinity for the PACAP peptides, PACAP-27 (ADCYAPI, P18509) and PACAP-38 (ADCYAPI, P18509), and VIP (VIP, P01282), whereas PACAP-27 (ADCYAPI, P18509) and PACAP-38 (ADCYAPI, P18509) are >100 fold more potent than VIP (VIP, P01282) as agonists of most isoforms of the PAC_1 receptor. However, one splice variant of the human PAC_1 receptor has been reported to respond to PACAP-38 (ADCYAPI, P18509), PACAP-27 (ADCYAPI, P18509) and VIP (VIP, P01282) with comparable affinity [452]. PG 99-465 [1492] has been used as a selective VPAC_2 receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC_1 and PAC_1 receptors [493]. The selective PAC_1 receptor agonist maxadilan, was extracted from the salivary glands of sand flies (*Lutzomyia longipalpis*) and has no sequence homology to VIP (VIP, P01282) or the PACAP peptides [1503]. Two deletion variants of maxadilan, M65 [2165] and Max.d.4 [1504] have been reported to be PAC_1 receptor antagonists, but these peptides have not been extensively characterised.
**Nomenclature**

| HGNC, UniProt | PAC₁ receptor | VPAC₁ receptor | VPAC₂ receptor |
|---------------|---------------|---------------|---------------|
| ADCYAP1R1, P41586 | VIPR1, P32241 | VIPR2, P41587 |

**Potency order of endogenous ligands**

| Ligand | PACAP-27 (ADCYAP1, P18509) | PACAP-38 (ADCYAP1, P18509) | VIP (VIP, P01282) | PHI (Pig) | secretin (SCT, P09683) | GHRH (GHRH, P01286) |
|--------|---------------------------|---------------------------|-----------------|----------|------------------------|---------------------|
| [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ | [Ala¹¹,²²,²⁸]VIP | [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ | [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ | [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ | [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ | [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ |

**Selective agonists**

- maxadilan [493], maxadilan [493] [Lys¹⁵, Arg¹⁶, Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ [1487], [Ala¹¹,²²,²⁸]VIP [1582]
- [¹²⁵]VIP (human, mouse, rat) (Agonist) [1582], [¹²⁵]PACAP-27 (Agonist) [1712]

**Selective antagonists**

- PG 97-269 (pIC₅₀ 8.7) [734, 1023]
- [¹²⁵]VIP (human, mouse, rat) (Agonist) [1582], [¹²⁵]PACAP-27 (Agonist) [1712]

**Labelled ligands**

- [¹²⁵]PACAP-27 (Agonist) [1712]
- [¹²⁵]VIP (human, mouse, rat) (Agonist) [1582], [¹²⁵]PACAP-27 (Agonist) [1712]

**Comments:** Subtypes of PAC₁ receptors have been proposed based on tissue differences in the potencies of PACAP-27 (ADCYAP1, P18509) and PACAP-38 (ADCYAP1, P18509); these might result from differences in G protein coupling and second messenger mechanisms [2195], or from alternative splicing of PAC₁ receptor mRNA [2020].

**Further reading on VIP and PACAP receptors**

Harmar AJ et al. (1998) International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. Pharmacol Rev 50: 265-270 [PMID:9647867]

Harmar AJ et al. (2012) Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR review 1. Br J Pharmacol. 166: 4-17 [PMID:22289055]

Reglodi D et al. (2012) Effects of pituitary adenylate cyclase activating polypeptide in the urinary system, with special emphasis on its protective effects in the kidney. Neuropeptides 46: 61-70 [PMID:21621841]

Smith CB et al. (2012) Is PACAP the major neurotransmitter for stress transduction at the adrenomedullary synapse? J. Mol. Neurosci. 48: 403-12 [PMID:22610912]
Searchable database: http://www.guidetopharmacology.org/index.jsp

References S135

Full Contents of Concise Guide: http://onlinelibrary.wiley.com/do/10.1111/bph.14748/full
| Reference | Authors | Year | Title |
|-----------|---------|------|-------|
| [1] | Shepherd, D.A. et al. | 2005 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [2] | Volpe, D.A. et al. | 2006 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [3] | Thomsen, A.R. et al. | 2012 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [4] | Thomsen, A.R. et al. | 2013 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [5] | Thomsen, A.R. et al. | 2014 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [6] | Thomsen, A.R. et al. | 2015 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [7] | Thomsen, A.R. et al. | 2016 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [8] | Thomsen, A.R. et al. | 2017 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [9] | Thomsen, A.R. et al. | 2018 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |
| [10] | Thomsen, A.R. et al. | 2019 | **Nutrients in Dairy and Their Implications for Health** (2019) 176, S21–S141 |

**References**

S140
