THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: G protein-coupled receptors

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Abstract

The Concise Guide to PHARMACOLOGY 2021/22 is the fifth in this series of biennial publications. The Concise Guide provides concise overviews, mostly in tabular format, of the key properties of nearly 1900 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 constitutes over 500 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/bph.15538. 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-2021, and supersedes data presented in the 2019/20, 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

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

Overview: G protein-coupled receptors (GPCRs) are the largest class of membrane proteins in the human genome. The term "7TM receptor" is commonly used interchangeably with "GPCR", although there are some receptors with seven transmembrane domains that do not signal through G proteins. GPCRs share a common architecture, each consisting of a single polypeptide with an extracellular N-terminus, an intracellular C-terminus and seven hydrophobic transmembrane domains (TM1-TM7) linked by three extracellular loops (ECL1-ECL3) and three intracellular loops (ICL1-ICL3). About 800 GPCRs have been identified in man, of which about half have sensory functions, mediating olfaction (400), taste (33), light perception (10) and pheromone signalling (5) [1617]. 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 [1797, 1948], although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs [1221] divided them, on the basic of sequence homology, into six classes. These classes and their prototype members were as follows: **Class A** (rhodopsin-like), **Class B** (secretin receptor family), **Class C** (metabotropic glutamate), **Class D** (fungal mating pheromone receptors), **Class E** (cyclic AMP receptors) and **Class F** (frizzled/smoothened). Of these, classes D and E are not found in vertebrates. An alternative classification scheme "GRAFS" [2083] divides vertebrate GPCRs into five classes, overlapping with the A-F nomenclature, *viz*:

Glutamate family (class C), which includes metabotropic glutamate receptors, a calcium-sensing receptor and $GABA_B$ receptors, as well as three taste type 1 receptors and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man [1617].

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 evolutionarily ancient motif also found in polycystic kidney disease 1 (PKD1)-like proteins, which has been suggested to be both required and sufficient for autoproteolysis [1909].

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)) [870].

GPCR families

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

[a]Numbers in brackets refer to orphan receptors for which an endogenous ligand has been proposed in at least one publication, see [485]; [b][1784]; [c][1617]; [d][2329].

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_2 adrenoceptor, the latter culminating in the award of the 2012 Nobel Prize in chemistry to Robert Lefkowitz and Brian Kobilka [1209, 1343].

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 containg 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

S30 Orphan and other 7TM receptors
S32 Class A Orphans
– Class B Orphans
S41 Class C Orphans
S41 Opsin receptors
S42 Taste 1 receptors
S43 Taste 2 receptors
S44 Other 7TM proteins
S45 5-Hydroxytryptamine receptors
S48 Acetylcholine receptors (muscarinic)
S50 Adenosine receptors
S52 Adhesion Class GPCRs
S55 Adrenoceptors
S59 Angiotensin receptors
S60 Apelin receptor
S61 Bile acid receptor
S62 Bombesin receptors
S63 Bradykinin receptors
S64 Calcitonin receptors
S66 Calcium-sensing receptor
S67 Cannabinoid receptors
S68 Chemerin receptors
S69 Chemokine receptors
S73 Cholecystokinin receptors
S74 Class Frizzled GPCRs
S76 Complement peptide receptors
S78 Corticotropin-releasing factor receptors
S79 Dopamine receptors
S81 Endothelin receptors
S82 G protein-coupled estrogen receptor
S83 Formylpeptide receptors
S84 Free fatty acid receptors
S86 $GABA_B$ receptors
S87 Galanin receptors
S89 Ghrelin receptor
S90 Glucagon receptor family
S91 Glycoprotein hormone receptors
S92 Gonadotrophin-releasing hormone receptors
S93 GPR18, GPR55 and GPR119
S94 Histamine receptors
S96 Hydroxycarboxylic acid receptors
S97 Kisspeptin receptor
S98 Leukotriene receptors
S100 Lysophospholipid (LPA) receptors
S101 Lysophospholipid (S1P) receptors
S103 Melanin-concentrating hormone receptors
S104 Melanocortin receptors
S105 Melatonin receptors
S106 Metabotropic glutamate receptors
S108 Motilin receptor
S110 Neuromedin U receptors
S111 Neuropeptide FF/neuropeptide AF receptors
S112 Neuropeptide S receptor
S113 Neuropeptide W/neuropeptide B receptors
S114 Neuropeptide Y receptors
S116 Neurotensin receptors
S117 Opioid receptors
S119 Orexin receptors
S120 Oxoglutarate receptor
S120 P2Y receptors
S123 Parathyroid hormone receptors
S124 Platelet-activating factor receptor
S125 Prokineticin receptors
S126 Prolactin-releasing peptide receptor
S127 Prostanoid receptors
S129 Proteinase-activated receptors
S131 QRFP receptor
S132 Relaxin family peptide receptors
S134 Somatostatin receptors
S135 Succinate receptor
S136 Tachykinin receptors
S137 Thyrotropin-releasing hormone receptors
S138 Trace amine receptor
S139 Urotensin receptor
S140 Vasopressin and oxytocin receptors
S142 VIP and PACAP receptors

Orphan and other 7TM receptors

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

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

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]

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 [652]**, 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 [485]. 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*	*GRP65*	*GPR68*	*GPR75*	*GPR84*	*GPR87*
GPR88	*GPR132*	*GPR149*	*GPR161*	*GPR183*	*LGR4*	*LGR5*
LGR6	*MAS1*	*MRGPRD*	*MRGPRX1*	*MRGPRX2*	*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).

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]

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

Nomenclature	*GPR3*	*GPR4*
HGNC, UniProt	*GPR3*, P46089	*GPR4*, P46093
Endogenous ligands	–	Protons
Agonists	diphenyleneiodonium chloride [2626]	–
Comments	Sphingosine 1-phosphate was reported to be an endogenous agonist [2392], but this finding was not replicated in subsequent studies [2630]. Reported to activate adenylyl cyclase constitutively through G_s [584]. Gene disruption results in premature ovarian ageing [1332], reduced β-amyloid deposition [2333] and hypersensitivity to thermal pain [2026] in mice. First small molecule inverse agonist [1067] and agonists identified [2626].	An initial report suggesting activation by lysophosphatidylcholine and sphingosylphosphorylcholine [2688] has been retracted [1746]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [485, 2129]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [2616]. Negative allosteric modulators of GPR4 have been reported [2358].

Nomenclature	*GPR6*	*GPR12*	*GPR15*
HGNC, UniProt	*GPR6*, P46095	*GPR12*, P47775	*GPR15*, P49685
Comments	An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC_{50} value of 39nM) [1012, 2392] was not repeated in arrestin-based assays [2218, 2630]. Reported to activate adenylyl cyclase constitutively through G_s and to be located intracellularly [1801]. GPR6-deficient mice showed reduced striatal cyclic AMP production *in vitro* and selected alterations in instrumental conditioning *in vivo*. [1425].	Reports that sphingosine 1-phosphate is a ligand of GPR12 [1011, 2392] have not been replicated in arrestin-based assays [2218, 2630]. Gene disruption results in dyslipidemia and obesity [183].	Reported to act as a co-receptor for HIV [580]. In an infection-induced colitis model, *Gpr15* knockout mice were more prone to tissue damage and inflammatory cytokine expression [1174].

Nomenclature	*GPR17*	*GPR19*	*GPR20*	*GPR21*
HGNC, UniProt	*GPR17*, Q13304	*GPR19*, Q15760	*GPR20*, Q99678	*GPR21*, Q99679
Endogenous agonists	UDP-glucose [155, 419], LTC_4 [419], UDP-galactose [155, 419], uridine diphosphate [155, 419], LTD_4 [419]	–	–	–
Agonists	–	adropin (*ENHO*, Q6UWT2) [1946]	–	–
Comments	Reported to be a dual leukotriene and uridine diphosphate receptor [419]. Another group instead proposed that GPR17 functions as a negative regulator of the $CysLT_1$ receptor response to leukotriene D_4 (LTD_4). For further discussion, see [485]. Reported to antagonize $CysLT_1$ receptor signalling *in vivo* and *in vitro* [1473]. See reviews [100] and [485].	–	Reported to inhibit adenylyl cyclase constitutively through $G_{i/o}$ [876]. GPR20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [247].	*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 [1793].

Nomenclature	*GPR22*	*GPR25*	*GPR26*	*GPR27*	*GPR31*	*GPR32*	*GPR33*
HGNC, UniProt	*GPR22*, Q99680	*GPR25*, O00155	*GPR26*, Q8NDV2	*GPR27*, Q9NS67	*GPR31*, O00270	*GPR32*, O75388	*GPR33*, Q49SQ1
Potency order of endogenous ligands	–	–	–	–	–	resolvin D1 > LXA_4	–
Endogenous agonists	–	–	–	–	12S-HETE [825] – Mouse	resolvin D1 [1248], LXA_4 [1248]	–
Labelled ligands	–	–	–	–	–	[^{3}H]resolvin D1 (Agonist) [1248]	–
Comments	Gene disruption results in increased severity of functional decompensation following aortic banding [13]. Identified as a susceptibility locus for osteoarthritis [613, 1153, 2410].	–	Has been reported to activate adenylyl cyclase constitutively through G_s [1091]. *Gpr26* knockout mice show increased levels of anxiety and depression-like behaviours [2663].	Knockdown of Gpr27 reduces endogenous mouse insulin promotor activity and glucose-stimulated insulin secretion [1255].	See [485] for discussion of pairing.	Resolvin D1 has been demonstrated to activate GPR32 in two publications [386, 1248]. The pairing was not replicated in a recent study based on arrestin recruitment [2218]. *GPR32* is a pseudogene in mice and rats. See reviews [100] and [485].	*GPR33* is a pseudogene in most individuals, containing a premature stop codon within the second intracellular loop [2004].

Nomenclature	*GPR34*	*GPR35*
HGNC, UniProt	*GPR34*, Q9UPC5	*GPR35*, Q9HC97
Endogenous agonists	lysophosphatidylserine [1193, 2261]	2-oleoyl-LPA [1776], kynurenic acid [2218, 2483]
Comments	Lysophosphatidylserine has been reported to be a ligand of GPR34 in several publications, but the pairing was not replicated in a recent study based on arrestin recruitment [2218]. Fails to respond to a variety of lipid-derived agents [2630]. Gene disruption results in an enhanced immune response [1387]. Characterization of agonists at this receptor is discussed in [1017] and [485].	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 [1256]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [1776] but these results were not replicated in an arrestin assay [2218]. The phosphodiesterase inhibitor zaprinast [2323] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signalling [2323]. GPR35 is also activated by the pharmaceutical adjunct pamoic acid [2677]. See reviews [485] and [539].

Nomenclature	*GPR37*	*GPR37L1*	*GPR39*
HGNC, UniProt	*GPR37*, O15354	*GPR37L1*, O60883	*GPR39*, O43194
Endogenous agonists	–	–	Zn^{2+} [963]
Agonists	neuropeptide head activator [1976]	–	–
Comments	Reported to associate and regulate the dopamine transporter [1506] and to be a substrate for parkin [1504]. Gene disruption results in altered striatal signalling [1505]. The peptides prosaptide and prosaposin are proposed as endogenous ligands for GPR37 and GPR37L1 [1568].	The peptides prosaptide and prosaposin are proposed as endogenous ligands for GPR37 and GPR37L1 [1568].	Zn^{2+} has been reported to be a potent and efficacious agonist of human, mouse and rat GPR39 [2623]. 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 [326]. Gene disruption results in obesity and altered adipocyte metabolism [1860]. Reviewed in [485].

Nomenclature	*GPR45*	*GPR50*	*GPR52*	*GPR61*	*GPR62*	*GPR63*
HGNC, UniProt	*GPR45*, Q9Y5Y3	*GPR50*, Q13585	*GPR52*, Q9Y2T5	*GPR61*, Q9BZJ8	*GPR62*, Q9BZJ7	*GPR63*, Q9BZJ6
Comments	–	GPR50 is structurally related to MT_1 and MT_2 melatonin receptors, with which it heterodimerises constitutively and specifically [1366]. *Gpr50* knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [137].	First small molecule agonist reported [2128].	GPR61 deficient mice exhibit obesity associated with hyperphagia [1692]. Although no endogenous ligands have been identified, 5-(nonyloxy)tryptamine has been reported to be a low affinity inverse agonist [2307].	–	Sphingosine 1-phosphate and dioleoylphosphatidic acid have been reported to be low affinity agonists for GPR63 [1731] but this finding was not replicated in an arrestin-based assay [2630].

Nomenclature	*GPR65*	*GPR68*	*GPR75*	*GPR78*	*GPR79*
HGNC, UniProt	*GPR65*, Q8IYL9	*GPR68*, Q15743	*GPR75*, O95800	*GPR78*, Q96P69	*GPR79*, –
Endogenous ligands	Protons	Protons	–	–	–
Allosteric modulators	–	ogerin (Positive) (pK_B 5) [995], lorazepam (Positive) [995]	–	–	–
Comments	GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [485, 2129]. Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease [1237].	GPR68 was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [2594], but the original publication has been retracted [1]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [485, 2129]. A family of 3,5-disubstituted isoxazoles were identified as agonists of GPR68 [2028].	CCL5 (*CCL5*, P13501) was reported to be an agonist of GPR75 [1013], but the pairing could not be repeated in an arrestin assay [2218].	GPR78 has been reported to be constitutively active, coupled to elevated cAMP production [1091].	–

Nomenclature	*GPR82*	*GPR83*	*GPR84*	*GPR85*	*GPR87*
HGNC, UniProt	*GPR82*, Q96P67	*GPR83*, Q9NYM4	*GPR84*, Q9NQS5	*GPR85*, P60893	*GPR87*, Q9BY21
Endogenous agonists	–	–	–	–	LPA [1673, 2287]
Agonists	–	PEN {Mouse} [771] – Mouse, Zn^{2+} [1664] – Mouse	decanoic acid [2218, 2484], undecanoic acid [2484], lauric acid [2484], 6-nonylpyridine-2,4-diol (orthosteric) [1512], DL-175 (orthosteric) [1512], Embelin (orthosteric) [1512], PSB-16434 (orthosteric) [1512], ZQ-16 (orthosteric) [1512]	–	–
Allosteric modulators	–	–	DIM (Agonist) [1512]	–	–
Comments	Mice with *Gpr82* knockout have a lower body weight and body fat content associated with reduced food intake, decreased serum triglyceride levels, as well as higher insulin sensitivity and glucose tolerance [597].	One isoform has been implicated in the induction of CD4(+) CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [861]. The extracellular N-terminal domain is reported as an intramolecular inverse agonist [1665].	Medium chain free fatty acids with carbon chain lengths of 9-14 activate GPR84 [2275, 2484]. A surrogate ligand for GPR84, 6-n-octylaminouracil has also been proposed [2275]. See review [485] for discussion of classification. Mutational analysis and molecular modelling of GPR84 has been reported [1735].	Proposed to regulate hippocampal neurogenesis in the adult, as well as neurogenesis-dependent learning and memory [368].	–

Nomenclature	*GPR88*	*GPR101*	*GPR132*	*GPR135*	*GPR139*	*GPR141*	*GPR142*
HGNC, UniProt	*GPR88*, Q9GZN0	*GPR101*, Q96P66	*GPR132*, Q9UNW8	*GPR135*, Q8IZ08	*GPR139*, Q6DWJ6	*GPR141*, Q7Z602	*GPR142*, Q7Z601
Endogenous ligands	–	–	Protons	–	–	–	–
Comments	Gene disruption results in altered striatal signalling [1428]. Small molecule agonists have been reported [176].	Mutations in GPR101 have been linked to gigantism and acromegaly [2377].	GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [485, 2129]. Reported to respond to lysophosphatidylcholine [1102], but later retracted [2556].	–	Peptide agonists have been reported [1026].	–	Small molecule agonists have been reported [2359, 2647].

Nomenclature	*GPR146*	*GPR148*	*GPR149*	*GPR150*	*GPR151*	*GPR152*	*GPR153*
HGNC, UniProt	*GPR146*, Q96CH1	*GPR148*, Q8TDV2	*GPR149*, Q86SP6	*GPR150*, Q8NGU9	*GPR151*, Q8TDV0	*GPR152*, Q8TDT2	*GPR153*, Q6NV75
Comments	Yosten *et al.* demonstrated inhibition of proinsulin C-peptide (*INS*, P01308)-induced stimulation of cFos expression folllowing knockdown of GPR146 in KATO III cells, suggesting proinsulin C-peptide as an endogenous ligand of the receptor [2644]. Reviewed in [1403].	–	*Gpr149* knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [581].	–	GPR151 responded to galanin with an EC_{50} value of 2 μM, suggesting that the endogenous ligand shares structural features with galanin (*GAL*, P22466) [1010].	–	–

Nomenclature	*GPR160*	*GPR161*	*GPR162*	*GPR171*	*GPR173*	*GPR174*
HGNC, UniProt	*GPR160*, Q9UJ42	*GPR161*, Q8N6U8	*GPR162*, Q16538	*GPR171*, O14626	*GPR173*, Q9NS66	*GPR174*, Q9BXC1
Endogenous agonists	–	–	–	–	–	lysophosphatidylserine [1021]
Comments	–	A C-terminal truncation (deletion) mutation in Gpr161 causes congenital cataracts and neural tube defects in the vacuolated lens (vl) mouse mutant [1532]. The mutated receptor is associated with cataract, spina bifida and white belly spot phenotypes in mice [1232]. Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish [1362].	–	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 [770].	–	See [1017] which discusses characterization of agonists at this receptor.

Nomenclature	*GPR176*	*GPR182*	*GPR183*
HGNC, UniProt	*GPR176*, Q14439	*GPR182*, O15218	*GPR183*, P32249
Endogenous agonists	–	–	7α,25-dihydroxycholesterol [857, 1415], 7α,27-dihydroxycholesterol [1415], 7β, 25-dihydroxycholesterol [1415], 7β, 27-dihydroxycholesterol [1415]
Comments	–	Rat GPR182 was first proposed as the adrenomedullin receptor [1119]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [1149] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [894].	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 [857, 1415]. 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 [1141, 1848].

Nomenclature	*LGR4*	*LGR5*	*LGR6*
HGNC, UniProt	*LGR4*, Q9BXB1	*LGR5*, O75473	*LGR6*, Q9HBX8
Endogenous agonists	R-spondin-2 (*RSPO2*, Q6UXX9) [315], R-spondin-1 (*RSPO1*, Q2MKA7) [315], R-spondin-3 (*RSPO3*, Q9BXY4) [315], R-spondin-4 (*RSPO4*, Q2I0M5) [315]	R-spondin-2 (*RSPO2*, Q6UXX9) [315], R-spondin-1 (*RSPO1*, Q2MKA7) [315], R-spondin-3 (*RSPO3*, Q9BXY4) [315], R-spondin-4 (*RSPO4*, Q2I0M5) [315]	R-spondin-1 (*RSPO1*, Q2MKA7) [315, 499], R-spondin-2 (*RSPO2*, Q6UXX9) [315, 499], R-spondin-3 (*RSPO3*, Q9BXY4) [315, 499], R-spondin-4 (*RSPO4*, Q2I0M5) [315, 499]
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 [315, 499, 2022]. Gene disruption leads to multiple developmental disorders [1077, 1447, 2214, 2518].	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 [315, 499].	–

Nomenclature	*MAS1*	*MAS1L*	*MRGPRD*	*MRGPRE*	*MRGPRF*
HGNC, UniProt	*MAS1*, P04201	*MAS1L*, P35410	*MRGPRD*, Q8TDS7	*MRGPRE*, Q86SM8	*MRGPRF*, Q96AM1
Endogenous agonists	–	–	β-alanine [2158, 2218]	–	–
Agonists	angiotensin-(1-7) (*AGT*, P01019) [758] – Mouse	–	–	–	–
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 to was shown to be blocked by D-Pro^{7}-angiotensin-(1-7), β-alanine and PD123319 [1303]. Genetic ablation of MRGPRD+ neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [334]. See reviews [485] and [2212].	See reviews [485] and [2212].	MRGPRF has been reported to respond to stimulation by angiotensin metabolites [726]. See reviews [485] and [2212].

Nomenclature	*MRGPRG*	*MRGPRX1*	*MRGPRX2*	*MRGPRX3*	*MRGPRX4*	*P2RY8*	*P2RY10*
HGNC, UniProt	*MRGPRG*, Q86SM5	*MRGPRX1*, Q96LB2	*MRGPRX2*, Q96LB1	*MRGPRX3*, Q96LB0	*MRGPRX4*, Q96LA9	*P2RY8*, Q86VZ1	*P2RY10*, O00398
Endogenous agonists	–	bovine adrenal medulla peptide 8-22 (*PENK*, P01210) [363, 1353, 2218]	PAMP-20 (*ADM*, P35318) [1112]	–	–	–	sphingosine 1-phosphate [1673], LPA [1673]
Agonists	–	–	cortistatin-14 {Mouse, Rat} [1112, 1296, 1998, 2218]	–	–	–	–
Selective agonists	–	–	PAMP-12 (human) [1112]	–	–	–	–
Comments	See reviews [485] and [2212].	Reported to mediate the sensation of itch [1419, 2169]. Reports that bovine adrenal medulla peptide 8-22 (*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 [1353] were replicated in an independent study using an arrestin recruitment assay [2218]. See reviews [485] and [2212].	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 [1998], also confirmed in an independent study using an arrestin recruitment assay [2218]. See reviews [485] and [2212].	–	See reviews [485] and [2212].	–	–

Nomenclature	*TAAR2*	*TAAR3*	*TAAR4P*	*TAAR5*	*TAAR6*	*TAAR8*	*TAAR9*
HGNC, UniProt	*TAAR2*, Q9P1P5	*TAAR3P*, Q9P1P4	*TAAR4P*, –	*TAAR5*, O14804	*TAAR6*, Q96RI8	*TAAR8*, Q969N4	*TAAR9*, Q96RI9
Potency order of endogenous ligands	β-phenylethylamine > tryptamine [219]	–	–	–	–	–	–
Comments	Probable pseudogene in 10-15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [485].	*TAAR3* is thought to be a pseudogene in man though functional in rodents [485].	Pseudogene in man but functional in rodents [485].	Trimethylamine is reported as an agonist [2471] and 3-iodothyronamine an inverse agonist [536].	–	–	*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 [2428].

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.

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]

Nomenclature	*GPR156*	*GPR158*	*GPR179*	*GPRC5A*	*GPRC5B*	*GPRC5C*	*GPRC5D*	GPRC6 receptor
HGNC, UniProt	*GPR156*, Q8NFN8	*GPR158*, Q5T848	*GPR179*, Q6PRD1	*GPRC5A*, Q8NFJ5	*GPRC5B*, Q9NZH0	*GPRC5C*, Q9NQ84	*GPRC5D*, Q9NZD1	*GPRC6A*, Q5T6X5
Comments	–	–	–	–	–	–	–	GPRC6 is a G_q-coupled receptor which responds to basic amino acids [2515].

Opsin receptors

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

Nomenclature	*OPN3*	*OPN4*	*OPN5*
HGNC, UniProt	*OPN3*, Q9H1Y3	*OPN4*, Q9UHM6	*OPN5*, Q6U736
Comments	–	–	Evidence indicates that UV light triggers OPN5 to activate G_i-mediated signalling in mammalian tissues [1219].

Taste 1 receptors

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

Overview: Whilst the taste of acid and salty foods appear to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin- (Gαt3) and Gα14-mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involvement of PLCβ2 [2673], TRPM5 [2673] and IP3 [948] receptors in post-receptor signalling of taste receptors. Although predominantly associated with the oral cavity, taste receptors are also located elsewhere, including further down the gastrointestinal system, in the lungs and in the brain.

Sweet/Umami: T1R3 acts as an obligate partner in T1R1/T1R3 and T1R2/T1R3 heterodimers, which sense umami or sweet, respectively. T1R1/T1R3 heterodimers respond to L-glutamic acid and may be positively allosterically modulated by 5′-nucleoside monophosphates, such as 5′-GMP [1377]. T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin [1711].

Further reading on Taste 1 receptors

Behrens M and Ziegler F (2020) Structure-Function Analyses of Human Bitter Taste Receptors-Where Do We Stand? *Molecules* **25**: [PMID:32993119]

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

Nomenclature	*TAS1R1*	*TAS1R2*	*TAS1R3*
HGNC, UniProt	*TAS1R1*, Q7RTX1	*TAS1R2*, Q8TE23	*TAS1R3*, Q7RTX0

Comments: Positive allosteric modulators of T1R2/T1R3 have been reported [2597]. Such compounds enhance the sweet taste of sucrose mediated by these receptors, but are tasteless on their own.

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 [347], while T2R14 responded to at least eight different bitter tastants, including (-)-α-thujone and picrotoxinin [145].

Specialist database BitterDB contains additional information on bitter compounds and receptors [2541].

Further reading on Taste 2 receptors

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

Nomenclature	*TAS2R1*	*TAS2R3*	*TAS2R4*	*TAS2R5*	*TAS2R7*	*TAS2R8*	*TAS2R9*
HGNC, UniProt	*TAS2R1*, Q9NYW7	*TAS2R3*, Q9NYW6	*TAS2R4*, Q9NYW5	*TAS2R5*, Q9NYW4	*TAS2R7*, Q9NYW3	*TAS2R8*, Q9NYW2	*TAS2R9*, Q9NYW1
Agonists	–	–	–	T5-8 [1166]	–	–	–

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) [1184], GIV3727 (pIC_{50} 5.1–5.2) [2185]	–	–	–
Comments	–	Individuals who are homozygous for the PAV variant of TAS2R38 (so-called 'super-tasters') are hyper-sensitive to the bitter tastes of certain chemicals that are present in some green vegetables (broccoli, sprouts), beer, coffee and dark chocolate. This makes eating these foods exceptionally unpleasant for carriers of this genetic variant.	–	–

Nomenclature	*TAS2R41*	*TAS2R42*	*TAS2R43*	*TAS2R45*	*TAS2R46*	*TAS2R50*	*TAS2R60*
HGNC, UniProt	*TAS2R41*, P59536	*TAS2R42*, Q7RTR8	*TAS2R43*, P59537	*TAS2R45*, P59539	*TAS2R46*, P59540	*TAS2R50*, P59544	*TAS2R60*, P59551

Other 7TM proteins

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

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

Nomenclature	*GPR107*	*GPR137*	*TPRA1*	*GPR143*	*GPR157*
HGNC, UniProt	*GPR107*, Q5VW38	*GPR137*, Q96N19	*TPRA1*, Q86W33	*GPR143*, P51810	*GPR157*, Q5UAW9
Endogenous agonists	–	–	–	levodopa [1433]	–
Comments	GPR107 is a member of the LUSTR family of proteins found in both plants and animals, having similar topology to G protein-coupled receptors [579]	–	TPRA1 shows no homology to known G protein-coupled receptors.	Loss-of-function mutations underlie ocular albinism type 1 [128].	GPR157 has ambiguous sequence similarities to several different GPCR families (class A, class B and the slime mould cyclic AMP receptor). Because of its distant relationship to other GPCRs, it cannot be readily classified.

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 [982] and subsequently revised [875]**) are, with the exception of the ionotropic 5-HT_3 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-HT_{2A} (non-functional), 5-HT_{2C} (non-functional), 5-HT_4, 5-HT_6 (non-functional) and 5-HT_7 receptors. Unique amongst the GPCRs, RNA editing produces 5-HT_{2C} receptor isoforms that differ in function, such as efficiency and specificity of coupling to $G_{q/11}$ and also pharmacology [195, 2525]. Most 5-HT receptors (except 5-ht_{1e} and 5-ht_{5b}) play specific roles mediating functional responses in different tissues (reviewed by [1940, 2445]).

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]

Nomenclature	5-HT_{1A} receptor	5-HT_{1B} receptor	5-HT_{1D} receptor	5-ht_{1e} receptor	5-HT_{1F} receptor
HGNC, UniProt	*HTR1A*, P08908	*HTR1B*, P28222	*HTR1D*, P28221	*HTR1E*, P28566	*HTR1F*, P30939
Agonists	U92016A [1545], vilazodone (Partial agonist) [494], vortioxetine (Partial agonist) [114]	L-694,247 [791], naratriptan (Partial agonist) [1695], eletriptan [1695], frovatriptan [2595], zolmitriptan (Partial agonist) [1695], vortioxetine (Partial agonist) [114], rizatriptan (Partial agonist) [1695]	dihydroergotamine [847, 1361, 1368], ergotamine [762], L-694,247 [2577], naratriptan [544, 1695, 1975], zolmitriptan [1695], frovatriptan [2595], rizatriptan [1695]	BRL-54443 [267]	BRL-54443 [267], eletriptan [1695], sumatriptan [15, 16, 1695, 2464]
Selective agonists	8-OH-DPAT [505, 848, 1109, 1351, 1585, 1722, 1724, 1725], NLX-101 [1723]	CP94253 [1210]	PNU109291 [603] – Gorilla, eletriptan [1695]	–	lasmiditan [1710], LY334370 [2464], 5-BODMT [1200], LY344864 [1867]
Antagonists	(S)-UH 301 (pK_i 7.9) [1722]	–	–	–	–
Selective antagonists	WAY-100635 (pK_i 7.9–9.2) [1722, 1724], robalzotan (pK_i 9.2) [1082]	SB 224289 (Inverse agonist) (pK_i 8.2–8.6) [717, 1720, 2121], SB236057 (Inverse agonist) (pK_i 8.2) [1578], GR-55562 (pK_B 7.4) [983]	SB 714786 (pK_i 9.1) [2495]	–	–
Labelled ligands	[^{3}H]robalzotan (Antagonist) (pK_d 9.8) [1069], [^{3}H]WAY100635 (Antagonist) (pK_d 9.5) [1156], [^{3}H]8-OH-DPAT (Agonist) [188, 1109, 1721, 1724], [^{3}H]NLX-112 (Agonist) [928], [^{11}C]WAY100635 (Antagonist) [2384], p-[^{18}F]MPPF (Antagonist) [445]	[^{3}H]N-methyl-AZ10419369 (Agonist, Partial agonist) [1478], [^{3}H]GR 125,743 (Selective Antagonist) (pK_d 8.6–9.2) [791, 2587], [^{3}H]alniditan (Agonist) [1361], [^{125}I]GTI (Agonist) [228, 273] – Rat, [^{3}H]eletriptan (Agonist, Partial agonist) [1695], [^{3}H]sumatriptan (Agonist, Partial agonist) [1695], [^{11}C]AZ10419369 (Agonist, Partial agonist) [2433]	[^{3}H]eletriptan (Agonist) [1695], [^{3}H]alniditan (Agonist) [1361], [^{125}I]GTI (Selective Agonist) [228, 273] – Rat, [^{3}H]GR 125,743 (Selective Antagonist) (pK_d 8.6) [2587], [^{3}H]sumatriptan (Agonist) [1695]	[^{3}H]5-HT (Agonist) [1541, 1816]	[^{3}H]LY334370 (Agonist) [2464], [^{125}I]LSD (Agonist) [51] – Mouse

Nomenclature	5-HT_{2A} receptor	5-HT_{2B} receptor	5-HT_{2C} receptor
HGNC, UniProt	*HTR2A*, P28223	*HTR2B*, P41595	*HTR2C*, P28335
Agonists	DOI [242, 1709, 2187]	methysergide (Partial agonist) [1205, 2014, 2465], DOI [1274, 1709, 2076]	DOI [583, 1709, 2076], Ro 60-0175 [1183, 1205]
Selective agonists	–	BW723C86 [135, 1205, 2076], Ro 60-0175 [1205]	WAY-163909 [574], lorcaserin [2346]
Antagonists	risperidone (Inverse agonist) (pK_i 9.3–10) [1223, 1251, 2096], mianserin (pK_i 7.7–9.6) [1205, 1238, 1585], ziprasidone (pK_i 8.8–9.5) [1223, 1251, 2096, 2136], volinanserin (pIC_{50} 6.5–9.3) [1205, 1434, 1961], blonanserin (pK_i 9.1) [1761], clozapine (Inverse agonist) (pK_i 7.6–9) [1205, 1251, 1582, 2096, 2427], H05 (pIC_{50} 7.2) [2593]	mianserin (pK_i 7.9–8.8) [214, 1205, 2465]	mianserin (Inverse agonist) (pK_i 8.3–9.2) [648, 1205, 1585], methysergide (pK_i 8.6–9.1) [583, 1205], ziprasidone (Inverse agonist) (pK_i 7.9–9) [921, 1251, 2136], olanzapine (Inverse agonist) (pK_i 8.1–8.4) [921, 1251, 2136], loxapine (Inverse agonist) (pK_i 7.8–8) [921, 1251]
Selective antagonists	compound 3b (pK_i 10.6) [644], ketanserin (pK_i 8.1–9.7) [278, 1205, 1947], pimavanserin (Inverse agonist) (pK_i 9.3) [706, 2427]	BF-1 (pK_i 10.1) [2089], RS-127445 (pK_i 9–9.5) [214, 1205], EGIS-7625 (pK_i 9) [1238]	FR260010 (pK_i 9) [865], SB 242084 (pK_i 8.2–9) [1150, 1205], RS-102221 (pK_i 8.3–8.4) [215, 1205]
Labelled ligands	[^{3}H]fananserin (Antagonist) (pK_d 9.9) [1485] – Rat, [^{3}H]ketanserin (Antagonist) (pK_d 8.6–9.7) [1205, 1947], [^{11}C]volinanserin (Antagonist) [841], [^{18}F]altanserin (Antagonist) [2010]	[^{3}H]LSD (Agonist) [1947], [^{3}H]5-HT (Agonist) [2463] – Rat, [^{3}H]mesulergine (Antagonist, Inverse agonist) (pK_d 7.9) [1205], [^{125}I]DOI (Agonist)	[^{3}H]mesulergine (Antagonist, Inverse agonist) (pK_d 8.7–9.3) [648, 1947], [^{125}I]DOI (Agonist) [648], [^{3}H]LSD (Agonist)

Nomenclature	5-HT_4 receptor	5-HT_{5A} receptor	5-ht_{5b} receptor
HGNC, UniProt	*HTR4*, Q13639	*HTR5A*, P47898	*HTR5BP*, –
Agonists	cisapride (Partial agonist) [96, 153, 738, 1571, 1572, 2415]	–	–
Selective agonists	TD-8954 [1554], ML 10302 (Partial agonist) [165, 192, 1571, 1572, 1573], RS67506 [905] – Rat, relenopride (Partial agonist) [751], velusetrag [1430, 2197], BIMU 8 [423]	–	–
Selective antagonists	RS 100235 (pK_i 8.7–12.2) [423, 1992], SB 204070 (pK_i 9.8–10.4) [153, 1571, 1572, 2415], GR 113808 (pK_i 9.3–10.3) [96, 153, 192, 423, 1572, 1992, 2415]	SB 699551 (pK_i 8.2) [443]	–
Labelled ligands	[^{3}H]GR 113808 (Antagonist) (pK_d 9.7–10.3) [96, 153, 1573, 2415], [^{123}I]SB 207710 (Antagonist) (pK_d 10.1) [268] – Pig, [^{3}H]RS 57639 (Selective Antagonist) (pK_d 9.7) [213] – Guinea pig, [^{11}C]SB207145 (Antagonist) (pK_d 8.6) [1465]	[^{125}I]LSD (Agonist) [790], [^{3}H]5-CT (Agonist) [790]	[^{125}I]LSD (Agonist) [1533] – Mouse, [^{3}H]5-CT (Agonist) [2462] – Mouse

Nomenclature	5-HT_6 receptor	5-HT_7 receptor
HGNC, UniProt	*HTR6*, P50406	*HTR7*, P34969
Selective agonists	WAY-181187 [2080], E6801 (Partial agonist) [958], WAY-208466 [164], EMD-386088 [1534]	LP-12 [1357], LP-44 [1357], LP-211 [1358] – Rat, AS-19 [1176], E55888 [245]
Antagonists	–	lurasidone (pK_i 9.3) [1027], pimozide (pK_i 9.3) [2013] – Rat, vortioxetine (pK_i 6.3) [114]
Selective antagonists	SB399885 (pK_i 9) [947], SB 271046 (pK_i 8.9) [264], cerlapirdine (pK_i 8.9) [433], SB357134 (pK_i 8.5) [265], Ro 63-0563 (pK_i 7.9–8.4) [198, 2186]	SB269970 (pK_i 8.6–8.9) [2340], SB656104 (pK_i 8.7) [653], DR-4004 (pK_i 8.7) [761, 1163], JNJ-18038683 (pK_i 8.2) [211], SB 258719 (Inverse agonist) (pK_i 7.5) [2341]
Labelled ligands	[^{11}C]GSK215083 (Antagonist) (pK_i 9.8) [1815], [^{125}I]SB258585 (Selective Antagonist) (pK_d 9) [947], [^{3}H]LSD (Agonist) [197], [^{3}H]Ro 63-0563 (Antagonist) (pK_d 8.3) [198], [^{3}H]5-CT (Agonist)	[^{3}H]5-CT (Agonist) [2340], [^{3}H]5-HT (Agonist) [117, 2231], [^{3}H]SB269970 (Selective Antagonist) (pK_d 8.9) [2340], [^{3}H]LSD (Agonist) [2231]

Comments: Tabulated pK_i and K_D values refer to binding to human 5-HT receptors unless indicated otherwise. The nomenclature of 5-HT_{1B}/5-HT_{1D} receptors has been revised [875]. Only the non-rodent form of the receptor was previously called 5-HT_{1D}: the human 5-HT_{1B} receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors [858]. Wang *et al.* (2013) report X-ray structures which reveal the binding modality of ergotamine and dihydroergotamine (DHE) to the 5-HT_{1B} receptor in comparison with the structure of the 5-HT_{2B} receptor [2479]; some of these drugs adopt rather different conformations depending on the target receptor [1843]. Various 5-HT receptors have multiple partners in addition to G proteins, which may affect function and pharmacology [1509]. NAS181 is a selective antagonist of the rodent 5-HT_{1B} receptor. Fananserin (LSD) and ketanserin bind with high affinity to dopamine D4 and histamine H_1 receptors respectively, and ketanserin is a potent α1 adrenoceptor antagonist, in addition to blocking 5-HT_{2A} receptors. Lysergic acid (LSD) and ergotamine show a strong preference for arrestin recruitment over G protein coupling at the 5-HT_{2B} receptor, with no such preference evident at 5-HT_{1B} receptors, and they also antagonise 5-HT_{7A} receptors [2460]. DHE (dihydroergocryptine), pergolide and cabergoline also show significant preference for arrestin recruitment over G protein coupling at 5-HT_{2B} receptors [2460]. The 5-HT_{2B} (and other 5-HT) receptors interact with immunocompetent cells [1802]. The serotonin antagonist mesulergine was key to the discovery of the 5-HT_{2C} receptor [1833], initially known as 5-HT_{1C} [90]. The human 5-HT_{5A} receptor may couple to several signal transduction pathways when stably expressed in C6 glioma cells [1748] and rodent prefrontal cortex (layer V pyramidal neurons) [777]. The human orthologue of the mouse 5-ht_{5b} receptor is non-functional (stop codons); the 5-ht_{1e} receptor has not been cloned from mouse, or rat, impeding definition of its function [858]. In addition to accepted receptors, an 'orphan' receptor, unofficially termed 5-HT_{1P}, has been described [743].

Acetylcholine receptors (muscarinic)

G protein-coupled receptors → Acetylcholine receptors (muscarinic)

Overview: Muscarinic acetylcholine receptors (mAChRs) (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Muscarinic Acetylcholine Receptors [330]**) are activated by the endogenous agonist acetylcholine. All five (M1-M5) mAChRs are ubiquitously expressed in the human body and are therefore attractive targets for many disorders. Functionally, M_1, M_3, and M_5 mAChRs preferentially couple to $G_{q/11}$ proteins, whilst M_2 and M_4 mAChRs predominantly couple to $G_{i/o}$ proteins. Both agonists and antagonists of mAChRs are clinically approved drugs, including pilocarpine for the treatment of elevated intra-ocular pressure and glaucoma, and atropine for the treatment of bradycardia and poisoning by muscarinic agents such as organophosphates.

Further reading on Acetylcholine receptors (muscarinic)

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Eglen RM. (2012) Overview of muscarinic receptor subtypes. *Handb Exp Pharmacol* 3-28 [PMID:22222692]

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Valant C *et al.* (2012) The best of both worlds? Bitopic orthosteric/allosteric ligands of g protein-coupled receptors. *Annu Rev Pharmacol Toxicol* **52**: 153-78 [PMID:21910627]

Nomenclature	M_1 receptor	M_2 receptor
HGNC, UniProt	*CHRM1*, P11229	*CHRM2*, P08172
Endogenous agonists	acetylcholine [1051, 1152]	acetylcholine [378, 1051, 1152]
Agonists	xanomeline (Partial agonist) [409, 2504, 2562], methacholine [1835, 1984] – Rat, arecoline [1051, 1799, 1984], oxotremorine (Partial agonist) [1051, 1984], carbachol [409, 1051, 2562], pilocarpine (Partial agonist) [1051, 1984], bethanechol [1051, 1984], iperoxo [2097]	iperoxo [2097, 2098], xanomeline [2504, 2562], methacholine [1835, 1984] – Rat, oxotremorine [1051, 1984], arecoline [1051, 1799, 1984], pilocarpine (Partial agonist) [1051, 1984], bethanechol [1051, 1984]
Antagonists	tiotropium (pK_i 9.6–10.7) [538, 1902, 2285, 2324], aclidinium (pIC$_{50}$ 10.1–10.2) [1902, 2324], glycopyrrolate (pIC$_{50}$ 9.6–10.1) [2241, 2285], ipratropium (pK_i 9.3–9.8) [943, 1902], atropine (pK_i 8.5–9.6) [409, 679, 943, 993, 1846, 2196], biperiden (pK_d 9.3) [204], 4-DAMP (pK_i 9.3) [555], darifenacin (pK_i 8.9–9.1) [753, 943, 2180], scopolamine (pK_i 9) [464, 993], oxybutynin (pK_i 8.6) [511, 2180], tolterodine (pK_i 8.4–8.5) [753, 2180], droxidopa (pK_i 7.1) [464]	tiotropium (pK_i 9.9–10.7) [538, 1902, 2285, 2324], aclidinium (pIC$_{50}$ 10.1) [1902, 2324], ipratropium (pK_i 9.3–9.8) [943, 1902], glycopyrrolate (pIC$_{50}$ 8.7–9.5) [2241, 2285], atropine (pK_i 7.8–9.2) [464, 943, 993, 1846], scopolamine (pK_i 8.7) [204, 993], tolterodine (Inverse agonist) (pK_i 8.4–8.5) [753, 2180], 4-DAMP (pK_i 8.4) [555], biperiden (pK_d 8.2) [204], oxybutynin (pK_i 7.9–8.1) [511, 2180], darifenacin (Inverse agonist) (pK_i 7.2–7.3) [753, 943, 2180], tropicamide (pK_i 7.2) [464]
Selective antagonists	pirenzepine (pK_i 7.6–8.3) [281, 555, 904, 993, 1086, 2526], VU0255035 (pK_i 7.8) [2142]	AFDX384 (pK_i 8.1–8.2) [464, 555]
Allosteric modulators	muscarinic toxin 7 (Negative) (pK_i 11–11.1) [679, 1696, 1787], benzoquinazolinone 12 (Positive) (pK_B 6.6) [6], KT 5720 (Positive) (pK_d 6.4) [1310], brucine (Positive) (pK_d 4.5–5.8) [180, 1051, 1309], BQCA (Positive) (pK_B 4–4.8) [6, 7, 306, 1455], VU0029767 (Positive) [1511], VU0090157 (Positive) [1511]	gallamine (Negative) (pK_i 5.8–7.6) [1239, 1626, 2375], W-84 (Negative) (pK_d 6–7.5) [1608, 2375], C_7/3-phth (Negative) (pK_d 7.1) [88, 410], alcuronium (Negative) (pK_d 6.1–6.9) [88, 1051, 2375], gallamine (Negative) (pK_d 5.9–6.3) [424, 1307], LY2119620 (Positive) (pK_d 5.5–5.7) [465, 1253], LY2033298 (Positive) (pK_d 4.4) [2408]
Labelled ligands	[^{3}H]QNB (Antagonist) (pK_d 10.6–10.8) [1052, 1846], [^{3}H]N-methyl scopolamine (Antagonist) (pK_d 9.4–10.3) [336, 409, 411, 943, 1051, 1053, 1086, 1155, 1307], [^{3}H]darifenacin (Selective Antagonist) (pK_d 8.8) [2196], [^{3}H]pirenzepine (Selective Antagonist) (pK_d 7.9) [339, 2074, 2413, 2505]	[^{3}H]QNB (Antagonist) (pK_d 10.1–10.6) [1052, 1846], [^{3}H]N-methyl scopolamine (Antagonist) (pK_d 9.3–9.9) [336, 943, 1052, 1053, 1155, 1307, 2492], [^{3}H]AF DX-384 (Selective Antagonist) (pK_d 9) [339, 1591, 2413]
Comments	Atypical agonists: AC-42 [89, 1292, 1293, 2050, 2221, 2222], 77-LH-28-1 [89, 1292], *N*-desmethylclozapine [2050, 2221, 2272], TBPB [1089, 1152, 2050], McN-A-343 [1051, 1984]	Atypical agonists: AC-42 [1292, 1537], 77-LH-28-1 [1292, 1537], *N*-desmethylclozapine [2272], McN-A-343 [1051, 1537, 1984]

Nomenclature	M_3 receptor	M_4 receptor	M_5 receptor
HGNC, UniProt	*CHRM3*, P20309	*CHRM4*, P08173	*CHRM5*, P08912
Endogenous agonists	acetylcholine [378, 1051, 1152]	acetylcholine [1051, 1152]	acetylcholine [378]
Agonists	xanomeline (Partial agonist) [2504, 2562], methacholine [1835, 1984] – Rat, arecoline [1051, 1799, 1984], oxotremorine [1051, 1984], pilocarpine (Partial agonist) [1051, 1984], carbachol [378, 1051, 2562], bethanechol [1051, 1984], iperoxo [2097]	xanomeline (Partial agonist) [2504, 2562], methacholine [1835, 1984] – Rat, arecoline [1051, 1799, 1984], oxotremorine [1051, 1984], pilocarpine (Partial agonist) [1051, 1984], carbachol [1051, 2562], bethanechol [1051, 1984], iperoxo [2097]	xanomeline (Partial agonist) [793, 2504, 2562], pilocarpine (Partial agonist) [162, 548, 793], carbachol [162, 793, 2562], arecoline [1799, 1984], bethanechol [1984], iperoxo [2097], methacholine [1984]
Antagonists	tiotropium (pK_i 9.5–11.1) [538, 558, 1902, 2285, 2324], aclidinium (pK_i 10.1–10.2) [1902, 2324], atropine (pK_i 8.5–9.8) [464, 943, 993, 1846], glycopyrrolate (pIC_{50} 9.6–9.8) [2241, 2285], ipratropium (pK_i 9.3–9.8) [558, 943, 1902], scopolamine (pK_i 9.4) [204, 993], 4-DAMP (pK_i 9.3) [555], darifenacin (pK_i 8.9–9.1) [753, 943, 2180], oxybutynin (pK_i 8.8) [511, 2180], tolterodine (pK_i 8.4–8.5) [753, 2180], biperiden (pK_d 8.4) [204], tropicamide (pK_i 7) [464]	tiotropium (pK_i 10.2–10.6) [2285, 2324], aclidinium (pK_i 10) [2324], glycopyrrolate (pK_i 9.1–10) [2241, 2285], atropine (pK_i 8.7–9.5) [464, 943, 993, 1846], scopolamine (pK_i 9.1–9.5) [204, 993], ipratropium (pK_i 9.2) [943], 4-DAMP (pK_i 8.9) [555], oxybutynin (pK_i 8.4–8.7) [511, 2180], biperiden (pK_d 8.6) [204], tolterodine (pK_i 8.3–8.4) [753, 2180], darifenacin (pK_i 7.3–8.1) [753, 943, 2180], tropicamide (pK_i 6.9) [318]	tiotropium (pK_i 9.8–10.2) [2285, 2324], aclidinium (pK_i 9.9) [2324], glycopyrrolate (pK_i 8.9–9.9) [2241, 2285], atropine (pK_i 8.3–9.3) [464, 943, 1645], 4-DAMP (pK_i 9) [555], ipratropium (pK_i 8.8) [943], tolterodine (pK_i 8.5–8.8) [753, 2180], scopolamine (pK_i 8.7) [204], darifenacin (pK_i 7.9–8.6) [753, 943, 2180], biperiden (pK_d 8.2) [204], oxybutynin (pK_i 7.9) [511, 2180], tropicamide (pK_i 6.4) [464]
Selective antagonists	–	PCS1055 (pK_i 8.2) [464], AFDX384 (pK_i 7.3–8) [464, 555], PD 102807 (pK_i 7.4–7.6) [464, 1788]	ML381 (pK_i 6.3) [732]
Allosteric modulators	WIN 62,577 (Positive) (pK_d 5.1) [1311], N-chloromethyl-brucine (Positive) (pK_d 3.3) [1309]	muscarinic toxin 3 (Negative) (pK_i 8.7) [1086, 1786], VU0152100 (Positive) (pEC_{50} 6.4) [239] – Rat, VU0152099 (Positive) (pEC_{50} 6.4) [239] – Rat, LY2033298 (Positive) (pK_B 4.9–5.5) [346, 2272], LY2119620 (Positive) (pK_d 5.5) [465], thiochrome (Positive) (pK_d 4) [1308]	amiodarone (Positive) (pK_B 7.2) [2229], ML380 (Positive) (pK_B 4.8) [162, 734]
Selective allosteric modulators	–	–	ML375 (Negative) (pK_B 6.2–6.6) [733, 2458]
Labelled ligands	[^{3}H]QNB (Antagonist) (pK_d 10.4) [1052, 1846], [^{3}H]N-methyl scopolamine (Antagonist) (pK_d 9.7–10.2) [336, 943, 1051, 1052, 1155, 1307], [^{3}H]darifenacin (Selective Antagonist) (pK_d 9.5) [2196], [^{3}H]4-DAMP (Selective Antagonist) (pK_i 8.8–9.4) [339, 1068]	[^{3}H]QNB (Antagonist) (pK_d 9.7–10.5) [1052, 1845], [^{3}H]N-methyl scopolamine (Antagonist) (pK_d 9.9–10.2) [336, 1051, 1052, 1155, 1307, 2492], [^{3}H]AF DX-384 (Selective Antagonist) (pK_d 8.7) [339, 1591, 2413]	[^{3}H]QNB (Antagonist) (pK_d 10.2–10.7) [1052], [^{3}H]N-methyl scopolamine (Antagonist) (pK_d 9.3–9.7) [336, 378, 943, 1052, 1155, 2458, 2492]
Comments	Atypical agonists: AC-42 [1292], 77-LH-28-1 [1292], *N*-desmethylclozapine [2272], McN-A-343 [1051, 1984]	Atypical agonists: AC-42 [1292], 77-LH-28-1 [1292], *N*-desmethylclozapine [2272], McN-A-343 [1051, 1984]	Atypical agonists: AC-42 [1292], 77-LH-28-1 [1292], McN-A-343 [1984]

Comments: Atomic structures for all five mAChRs bound to antagonists [833, 2332, 2458, 2622], and structures of agonist-bound M_2 mAChR [1253] and G protein-bound M1 and M_2 mAChRs [1471] have been reported. These structures show that the orthosteric binding site of this family of receptor is absolutely conserved and, as a consequence, explain why highly selective orthosteric ligand binding to any specific mAChR has been notoriously difficult to achieve. As such, it is common to assess the rank order of affinity for a range of antagonists with limited selectivity (*e.g.*, 4-DAMP, darifenacin, pirenzepine, AFDX384) to identify the involvement of particular subtypes. In addition, some ligands may display selectivity at the level of function (*e.g.*, xanomeline) or binding kinetics (*e.g.*, tiotropium) [2137, 2326].

Structures of the M_1 and M_2 mAChRs in complex with allosteric modulators [1253, 1472] have validated numerous pharmacological studies that indicated the presence of a common mAChR allosteric site located at the extracellular entrance to these receptors. Allosteric ligands proposed to bind to this common allosteric site include gallamine, strychnine, C_7/3-phth, brucine and LY2033298. Additionally, a second allosteric site has been proposed on the mAChRs based on pharmacological analyses of the actions of compounds such as KT 5720, WIN 62,577, WIN 51,708, staurosporine and amiodarone [1310, 1311, 2229]. In the presence of the orthosteric ligand, allosteric modulators can exert positive, negative, or neutral cooperativity with that ligand. Direct receptor activation *via* an allosteric site has been reported for a number of allosteric ligands of the mAChRs [493, 1321, 1324, 1455, 1698, 1699]. 'Atypical agonists' are ligands that have been suggested to have bitopic binding modes for at least one subtype whereby the agonist occupies both the orthosteric and allosteric sites [89, 1151, 2409].

Adenosine receptors

G protein-coupled receptors → Adenosine receptors

Overview: Adenosine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Adenosine Receptors [667]**) are activated by the endogenous ligand adenosine (potentially inosine also at A_3 receptors). Crystal structures for the antagonist-bound [436, 1038, 1421, 2119], agonist-bound [1329, 1330, 2591] and G protein-bound A_{2A} adenosine receptors [317] have been described. The structures of an antagonist-bound A_1 receptor [763] and an adenosine-bound A_1 receptor-G_i complex [560] have been resolved by cryo-electronmicroscopy. Another structure of an antagonist-bound A_1 receptor obtained with X-ray crystallography has also been reported [381]. Caffeine is a nonselective antagonist for adenosine receptors, while istradefylline, a selective A_{2A} receptor antagonist, is on the market for the treatment of Parkinson's disease.

Further reading on Adenosine receptors

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Nomenclature	A_1 receptor	A_{2A} receptor	A_{2B} receptor	A_3 receptor
HGNC, UniProt	*ADORA1*, P30542	*ADORA2A*, P29274	*ADORA2B*, P29275	*ADORA3*, P0DMS8
Endogenous agonists	adenosine [2606]	adenosine [665, 666, 2606]	adenosine [665, 666, 2606]	adenosine [665, 666, 2606]
Agonists	NECA [704, 1080, 1996, 2373, 2606]	NECA [223, 537, 704, 1172, 1267, 2606]	NECA [172, 223, 1070, 1401, 2237, 2429, 2606]	NECA [223, 704, 1047, 2049, 2430, 2606]
Selective agonists	cyclopentyladenosine [471, 501, 704, 911, 1044, 1080, 1996], 5-Cl-5-deoxy-(±)-ENBA [661], TCPA [174], CCPA [1044, 1759], MRS7469 [2370]	apadenoson [1836], UK-432,097 [824, 2591], compound 4g [436], CGS 21680 [223, 537, 704, 1044, 1172, 1202, 1267, 1759], regadenoson [1044]	BAY 60-6583 [578]	piclidenoson [632, 693, 1202, 2430], Cl-IB-MECA [240, 1047, 1169], MRS5698 [2369]
Antagonists	CGS 15943 (pK_i 8.5) [1790], xanthine amine congener (pK_d 7.5) [661]	CGS 15943 (pK_i 7.7–9.4) [537, 1172, 1202, 1790], xanthine amine congener (pK_i 8.4–9) [537, 1202]	xanthine amine congener (pK_i 6.9–8.8) [172, 1070, 1071, 1202, 1401, 2237], CGS 15943 (pK_i 6–8.1) [80, 1070, 1071, 1202, 1790, 2237]	CGS 15943 (pK_i 7–7.9) [1178, 1202, 1790, 2430], xanthine amine congener (pK_i 7–7.4) [1202, 2049, 2430]
Selective antagonists	PSB36 (pK_i 9.9) [8] – Rat, DPCPX (pK_i 7.4–9.2) [501, 1022, 1759, 1996, 2530], derenofylline (pK_i 9) [1110], WRC-0571 (pK_i 8.8) [1514], DU172 (pK_i 7.4) [763]	SCH442416 (pK_i 8.4–10.3) [2157, 2360], ZM-241385 (pK_i 8.8–9.1) [1790]	PSB-0788 (pK_i 9.4) [222], PSB603 (pK_i 9.3) [222], MRS1754 (pK_i 8.8) [1070, 1177], PSB1115 (pK_i 7.3) [895]	MRS1220 (pK_i 8.2–9.2) [1047, 1178, 2262, 2624], VUF5574 (pK_i 8.4) [2418], MRS1523 (pK_i 7.7) [1369], MRS1191 (pK_i 7.5) [1047, 1073, 1382]
Allosteric modulators	PD81723 (Positive) [275]	–	–	LUF6000 (Positive) [767], LUF6096 (Positive) [910]
Labelled ligands	[^{3}H]CCPA (Agonist) [1202, 1996], [^{3}H]DPCPX (Antagonist) (pK_d 8.4–9.2) [471, 632, 1202, 1790, 1996, 2373]	[^{3}H]ZM 241385 (Antagonist) (pK_d 8.7–9.1) [42, 702], [^{3}H]CGS 21680 (Agonist) [1059, 2476]	[^{3}H]MRS1754 (Antagonist) (pK_d 9.8) [1070]	[^{125}I]AB-MECA (Agonist) [1790, 2430]

Comments: Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (*ADORA2BP1*) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor [1048]. DPCPX also exhibits antagonism at A_{2B} receptors (pK_i ca. 7,[40, 1202]). Antagonists at A_3 receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A_3 receptor. In the absence of other adenosine receptors, [^{3}H]DPCPX and [^{3}H]ZM 241385 can also be used to label A_{2B} receptors (K_D *ca*. 30 and 60 nM respectively). [^{125}I]AB-MECA also binds to A_1 receptors [1202]. [^{3}H]CGS 21680 is relatively selective for A_{2A} receptors, but may also bind to other sites in cerebral cortex [466, 1081]. [^{3}H]NECA binds to other non-receptor elements, which also recognise adenosine [1435]. XAC-BY630 has been described as a fluorescent antagonist for labelling A_1 adenosine receptors in living cells, although activity at other adenosine receptors was not examined [251].

Adhesion Class GPCRs

G protein-coupled receptors → Adhesion Class GPCRs

Overview: Adhesion GPCRs are structurally identified on the basis of a large extracellular region, similar to the Class B GPCR, but which is linked to the 7TM region by a GPCR autoproteolysis-inducing (GAIN) domain [62] containing a GPCR proteolytic site. The N-terminus often shares structural homology with adhesive domains (e.g. cadherins, immunolobulin, lectins) facilitating inter- and matricellular interactions and leading to the term adhesion GPCR [669, 2638]. Several receptors have been suggested to function as mechanosensors [233, 1861, 2094, 2545]. **The nomenclature of these receptors was revised in 2015 as recommended by NC-IUPHAR and the Adhesion GPCR Consortium** [845].

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]

Nomenclature	ADGRA1	ADGRA2	ADGRA3	ADGRB1	ADGRB2
HGNC, UniProt	*ADGRA1*, Q86SQ6	*ADGRA2*, Q96PE1	*ADGRA3*, Q8IWK6	*ADGRB1*, O14514	*ADGRB2*, O60241
Endogenous agonists	–	–	–	phosphatidylserine [1814]	–
Comments	–	Required to assemble higher-order Reck/Gpr124/Frizzled/ Lrp5/6 complexes [612, 1895, 2412, 2426, 2683]. Interacts with Reck [394, 612, 2426], Syndecan-1, -2 [397], Integrin-αvβ3 [2411] and heparin [2411]. Principal signal transduction involves Dishevelled [612], β-catenin [1895] and Cdc42 [350].	Principal signal transduction involves Dishevelled [1376].	Reported to mediate phagocytosis through binding of phosphatidylserine [1814] and lipopolysaccharide [477]. Suppresses medulloblastoma formation [2684] and is involved in dendrite development [572]. A recent study disputes the previously reported expression of ADGRB1 by macrophages [987].	Principal signal transduction involves $G\alpha_z$ [1915]. A R1465W mutation confers increased coupling to $G\alpha_i$ [1915].

Nomenclature	ADGRB3	*CELSR1*	*CELSR2*	*CELSR3*	ADGRD1	ADGRD2
Systematic nomenclature	–	ADGRC1	ADGRC2	ADGRC3	–	–
HGNC, UniProt	*ADGRB3*, O60242	*CELSR1*, Q9NYQ6	*CELSR2*, Q9HCU4	*CELSR3*, Q9NYQ7	*ADGRD1*, Q6QNK2	*ADGRD2*, Q7Z7M1
Endogenous agonists	–	–	–	–	Peptides derived from the *Stachel* sequence: THLTNFAILMQVV [1388]	–
Comments	Reported to bind C1q-like molecules [208]. Promotes myoblast fusion in vertebrates [849].	Principal signal transduction involves Rho kinase [1741]. Interacts with Vangl-2 [522, 1348], Frizzled-6 [522] and LRRK2 [2046].	Mutated in Joubert syndrome patients [2444]. Signal transduction is potentially mediated through $G\alpha_{q/11}$ [2151]. Interacts homomerically with CELSR2/ADGRC2 [2151].	High-confidence risk gene for Tourette syndrome [2491]. Signal transduction is potentially mediated through $G\alpha_{q/11}$ [2151]. Interacts with Frizzled-3 [2331], Dystroglycan [1402] and homomerically with CELSR3/ADGRC3 [2151].	Is a G_s protein-coupled receptor [200, 1388] and highly expressed in glioblastoma [133]. Couples also to G_i proteins [1389]. Strong association with body height [1173, 1180, 2365]. Associated with bone mineral density [2038].	–

Nomenclature	ADGRE1	ADGRE2	ADGRE3	ADGRE4P	ADGRE5	ADGRF1	ADGRF2
HGNC, UniProt	*ADGRE1*, Q14246	*ADGRE2*, Q9UHX3	*ADGRE3*, Q9BY15	*ADGRE4P*, Q86SQ3	*ADGRE5*, P48960	*ADGRF1*, Q5T601	*ADGRF2*, Q8IZF7
Endogenous agonists	–	–	–	–	–	Peptides derived from the *Stachel* sequence TSFSILMSPFVPSTIFPVVKWIT [515, 2246]	–
Comments	–	A mutation destabilizing the GAIN domain sensitizes mast cells to IgE-independent vibration-induced degranulation [233]. Reported to bind chondroitin sulfate B [2228].Principal signal transduction involves G protein-coupling [175] and the phospholipase C pathway [1023]. Interacts with FHR1 [1023].	–	–	Reported to bind CD55 [846], chondroitin sulfate B [2228], $\alpha_5\beta_1$ and $\alpha_V\beta_3$ integrins [2493], and CD90 [2478].	*N*-Docosahexaenoylethanolamine is an agonist at ADGRF1 supporting neurogenesis [1338] and couples to G_s and G_q pathways [515, 2246].	ADGRF2 is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [1910].

Nomenclature	ADGRF3	ADGRF4	ADGRF5	ADGRG1
HGNC, UniProt	*ADGRF3*, Q8IZF5	*ADGRF4*, Q8IZF3	*ADGRF5*, Q8IZF2	*ADGRG1*, Q9Y653
Endogenous agonists	–	Peptides derived from the ADGRF5 (GPR116) *Stachel* sequence: TSFSILMSPDSPD [515]	Peptides derived from the *Stachel* sequence: TSFSILMSPDSPD [515]	Peptides derived from the *Stachel* sequence: TYFAVLM [2246]
Comments	ADGRF3 is highly expressed in gastrointestinal neuroendocrine tumors [319, 319].	ADGRF4 couples to $G_{q/11}$ proteins [515], is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [1910].	ADGRF5 controls alveolar surfactant secretion *via* $G_{q/11}$ pathway [270, 515, 1204, 2320]. ADGRF5 deficiency leads to dysregulation of lung surfactant homeostasis [252, 686, 2617].	Reported to bind tissue transglutaminase 2 [2592] and collagen, which activates the $G_{12/13}$ pathway [1448]. Interacts with heparin [387]. Couples to G13 proteins [2246]. 3-α-acetoxydihydrodeoxygedunin is a partial agonist [2247], Dihydromunduletone, a rotenoid derivative, is an antagonist [2245]. Negatively regulates immediate effector functions in human NK cells [349]. Deficiency leads to dysregulation of central and peripheral myelination [11, 749].

Nomenclature	ADGRG2	ADGRG3	ADGRG4	ADGRG5
HGNC, UniProt	*ADGRG2*, Q8IZP9	*ADGRG3*, Q86Y34	*ADGRG4*, Q8IZF6	*ADGRG5*, Q8IZF4
Endogenous agonists	Peptides derived from the *Stachel* sequence: TSFGVLLDLSRTSLPP [514]	–	–	Peptides derived from the *Stachel* sequence: TYFAVLMQLSGDPVPAEL [2245, 2545]
Comments	ADGRG2 is coupled to G_q and G_s pathways [514, 2659] and gene deficiency causes congenital obstructive azoospermia [1822].	ADGRG3 is expressed in immune cells [2146, 2486] and couples to G_o proteins [826], $G\alpha_s$ and $G\alpha_{o/i}$ signaling [986] and G_s proteins [986]. Binds to exogenous ligands beclomethasone dipropionate and cortisol [826, 1877].	ADGRG4 is highly expressed in enterochromaffin cells and gastrointestinal neuroendocrine tumors [1350].	ADGRG5 is a constitutively active G_s protein-coupled receptor [826, 2245, 2545], highly expressed in eosinophils and NK cells [1844]. Dihydromunduletone is an antagonist [2245].

Nomenclature	ADGRG6	ADGRG7
HGNC, UniProt	*ADGRG6*, Q86SQ4	*ADGRG7*, Q96K78
Endogenous agonists	Peptides derived from the *Stachel* sequence: THFGVLMDLPRSASQL [1388]	–
Comments	ADGRG6 is a key regulator of Schwann cell-mediated myelination [1619], and couples to G_s and $G_{i/o}$ pathways [1388, 1606, 1861]. Apomorphine hydrochloride is an exogenous agonist [237]. Binds to Laminin-211 [1861]. ADGRG6 is essential for normal differentiation of promyelinating Schwann cells and for normal myelination of axons [1606, 1619, 1620, 1861] and for proper heart development [1826, 2470]. Further, conditional deletion of Adgrg6 revealed that this adhesion GPCR is involved in regulation of body length and bone mass [2264] and intervertebral disc function [1423]. Involved in arthrogryposis multiplex congenita (lethal congenital contracture syndrome-9) [1954].	ADGRG7 is expressed in intestine and involved in regulation of intestinal contractility [1727].

Nomenclature	ADGRL1	ADGRL2	ADGRL3	ADGRL4	ADGRV1
HGNC, UniProt	*ADGRL1*, O94910	*ADGRL2*, O95490	*ADGRL3*, Q9HAR2	*ADGRL4*, Q9HBW9	*ADGRV1*, Q8WXG9
Comments	Couples to G_s and G_q pathways [1352, 1666]. Principal signal transduction involves $G\alpha_s$ [1666], $G\alpha_o$ [1352, 1933] and $G\alpha_q$ [1933]. Interacts with Teneurin-2 [2171], FLRT-1, -3 [1757], Neurexin-1α, -1β, -2β, -3β [226], Contactin-6 [2694], Shank [1246] and TRIP8b [1887, 1888].	–	A LPHN3 gene variant in humans is associated with attention-deficit-hyperactivity disorder [65, 2548]. Principal signal transduction involves $G\alpha_{12/13}$ [1522] and $G\alpha_q$ [1522]. Interacts with Teneurin-3 [1757], FLRT-1, -3 [1757] and UNC5A [1040].	–	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [1049]. Interacts with Harmonin [1966] and Whirlin [2422].

Adrenoceptors

G protein-coupled receptors → Adrenoceptors

Overview: **The nomenclature of the Adrenoceptors has been agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [295, 933].**

Further reading on Adrenoceptors

Baker JG *et al*. (2011) Evolution of β-blockers: from anti-anginal drugs to ligand-directed signalling. *Trends Pharmacol Sci* **32**: 227-34 [PMID:21429598]

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Jensen BC *et al*. (2011) Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. *J Mol Cell Cardiol* **51**: 518-28 [PMID:21118696]

Kobilka BK. (2011) Structural insights into adrenergic receptor function and pharmacology. *Trends Pharmacol Sci* **32**: 213-8 [PMID:21414670]

Langer SZ. (2015) α2-Adrenoceptors in the treatment of major neuropsychiatric disorders. *Trends Pharmacol Sci* **36**: 196-202 [PMID:25771972]

Michel MC *et al*. (2015) Selectivity of pharmacological tools: implications for use in cell physiology. A review in the theme: Cell signaling: proteins, pathways and mechanisms. *Am J Physiol, Cell Physiol* **308**: C505-20 [PMID:25631871]

Adrenoceptors, α_1

G protein-coupled receptors → Adrenoceptors → Adrenoceptors, α_1

Overview: The three α_1-adrenoceptor subtypes α_{1A}, α_{1B} and α_{1D} are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. -(-)phenylephrine, methoxamine and cirazoline are agonists and prazosin and doxazosin antagonists considered selective for α_1- relative to α_2-adrenoceptors. [^{3}H]prazosin and [^{125}I]HEAT (BE2254) are relatively selective radioligands. S(+)-niguldipine also has high affinity for L-type Ca^{2+} channels. Fluorescent derivatives of prazosin (Bodipy FLprazosin- QAPB) are used to examine cellular localisation of α_1-adrenoceptors. α_1-Adrenoceptor agonists are used as nasal decongestants; antagonists to treat symptoms of benign prostatic hyperplasia (alfuzosin, doxazosin, terazosin, tamsulosin and silodosin, with the last two compounds being $\alpha 1_A$-adrenoceptor selective and claiming to relax bladder neck tone with less hypotension); and to a lesser extent hypertension (doxazosin, terazosin). The α_1- and β_2-adrenoceptor antagonist carvedilol is used to treat congestive heart failure, although the contribution of α_1-adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs are α_1-adrenoceptor antagonists contributing to side effects such as orthostatic hypotension.

Nomenclature	α_{1A}-adrenoceptor	α_{1B}-adrenoceptor	α_{1D}-adrenoceptor
HGNC, UniProt	*ADRA1A*, P35348	*ADRA1B*, P35368	*ADRA1D*, P25100
Endogenous agonists	(-)-adrenaline [971, 2147], (-)-noradrenaline [971, 2147, 2322]	–	(-)-noradrenaline [971, 2147], (-)-adrenaline [971, 2147]
Agonists	oxymetazoline [971, 1760, 2147, 2322], phenylephrine [2322], methoxamine [2147, 2322]	phenylephrine [655, 1594]	–
Selective agonists	A61603 [655, 1203], dabuzalgron [193]	–	–
Antagonists	prazosin (Inverse agonist) (pK_i 9–9.9) [348, 472, 655, 2147, 2547], doxazosin (pK_i 9.3) [853], terazosin (pK_i 8.7) [1566], phentolamine (pK_i 8.6) [2147], alfuzosin (pK_i 8.1) [931]	prazosin (Inverse agonist) (pK_i 9.6–9.9) [655, 2147, 2547], tamsulosin (Inverse agonist) (pK_i 9.5–9.7) [655, 2147, 2547], doxazosin (pK_i 9.1) [853], alfuzosin (pK_i 8.6) [932], terazosin (pK_i 8.6) [1566], phentolamine (pK_i 7.5) [2147]	prazosin (Inverse agonist) (pK_i 9.5–10.2) [655, 2147, 2547], tamsulosin (pK_i 9.8–10.2) [655, 2147, 2547], doxazosin (pK_i 9.1) [853], terazosin (pK_i 9.1) [1566], alfuzosin (pK_i 8.4) [931], dapiprazole (pK_i 8.4) [84], phentolamine (Inverse agonist) (pK_i 8.2) [2147], RS-100329 (pK_i 7.9) [2547], labetalol (pK_i 6.6) [84]
Selective antagonists	tamsulosin (pK_i 10–10.7) [348, 472, 655, 2147, 2547], silodosin (pK_i 10.4) [2147], S(+)-niguldipine (pK_i 9.1–10) [655, 2147], RS-100329 (pK_i 9.6) [2547], SNAP5089 (pK_i 8.8–9.4) [931, 1356, 2529], ρ-Da1a (pK_i 9.2–9.3) [1479, 1928], RS-17053 (pK_i 9.2–9.3) [348, 472, 654, 655]	Rec 15/2615 (pK_i 9.5) [2330], L-765314 (pK_i 7.7) [1821], AH 11110 (pK_i 7.5) [2067]	BMY-7378 (pK_i 8.7–9.1) [321, 2643]

Comments: The three α1-adrenoceptor subtypes are α_{1A}, α_{1B} and α_{1D}. The previously described α_{1C}-adrenoceptor is a species homologue that corresponds to the pharmacologically defined α_{1A}-adrenoceptor [933]. Some tissues possess α_{1A}-adrenoceptors (termed α_{1L}-adrenoceptors [655, 1644]) that display relatively low affinity in functional and binding assays for prazosin indicative of different receptor states or locations. α_{1A}-Adrenoceptor C-terminal splice variants form homo- and heterodimers, and do not generate a functional α_{1L}-adrenoceptor [1944]. Recombinant α_{1D}-adrenoceptors have been shown in some heterologous systems to be mainly located intracellularly but cell-surface localization is encouraged by truncation of the N-terminus, or by co-expression and formation of heterodimers with α_{1B}-α_{1B}- or β_2–β_2-adrenoceptors [835, 2387]. In blood vessels all three α_1-adrenoceptor subtypes are located both at the cell surface and intracellularly [1564, 1565]. Signalling is predominantly via $G_{q/11}$ but α_1-adrenoceptors also couple to $G_{i/o}$, G_s and $G_{12/13}$. Several α_{1A}-adrenoceptor agonists display ligand directed signalling bias relative to noradrenaline [614] although some bias appears to relate to off-target activity [469] . 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, α_{1D}-conveying greater agonist sensitivity compared to α_{1A}-adrenoceptors [650].

Adrenoceptors, α_2

G protein-coupled receptors → Adrenoceptors → Adrenoceptors, α_2

Overview: The three α_2-adrenoceptor subtypes α_{2A}, α_{2B} and α_{2C} are activated by (-)-adrenaline and with lower potency by (-)-noradrenaline. Brimonidine and talipexole are agonists and rauwolscine and yohimbine antagonists selective for α_2- relative to α_1-adrenoceptors. [^{3}H]rauwolscine, [^{3}H]brimonidine and [^{3}H]RX821002 are relatively selective radioligands. There are species variations in the pharmacology of the α_{2A}-adrenoceptor. Multiple mutations of α_2-adrenoceptors have been described, some associated with alterations in function. Presynaptic α_2-adrenoceptors regulate many functions in the nervous system. The α_2-adrenoceptor agonists clonidine, guanabenz and brimonidine affect central baroreflex control (hypotension and bradycardia), induce hypnotic effects and analgesia, and modulate seizure activity and platelet aggregation. Clonidine is an anti-hypertensive (relatively little used) and counteracts opioid withdrawal. Dexmedetomidine (also xylazine) is increasingly used as a sedative and analgesic in human [119] and veterinary medicine and has sympatholytic and anxiolytic properties. The α_2-adrenoceptor antagonist mirtazapine is used as an anti-depressant. The α_{2B} subtype appears to be involved in neurotransmission in the spinal cord and α_{2C} in regulating catecholamine release from adrenal chromaffin cells. Although subtype-selective antagonists have been developed, none are used clinically and they remain experimental tools.

Nomenclature	α_{2A}-adrenoceptor	α_{2B}-adrenoceptor	α_{2C}-adrenoceptor
HGNC, UniProt	*ADRA2A*, P08913	*ADRA2B*, P18089	*ADRA2C*, P18825
Endogenous agonists	(-)-adrenaline [1061, 1869], (-)-noradrenaline [1061, 1869]	(-)-noradrenaline (Partial agonist) [1061, 1869], (-)-adrenaline [1061]	(-)-noradrenaline [1061, 1869], (-)-adrenaline [1061]
Agonists	dexmedetomidine (Partial agonist) [1061, 1460, 1840, 1869], clonidine (Partial agonist) [1061, 1840, 1869], brimonidine [1061, 1460, 1840, 1869], apraclonidine [1668], guanabenz [84], guanfacine (Partial agonist) [1061, 1463]	dexmedetomidine [1061, 1460, 1840, 1869], clonidine (Partial agonist) [1061, 1840, 1869], brimonidine (Partial agonist) [1061, 1840, 1869], guanabenz [84], guanfacine [1061]	dexmedetomidine [1061, 1840, 1869], brimonidine (Partial agonist) [1061, 1460, 1840, 1869], apraclonidine [1668], guanfacine (Partial agonist) [1061], guanabenz [84]
Selective agonists	oxymetazoline (Partial agonist) [1061, 1460, 2391]	–	–
Antagonists	yohimbine (pK_i 8.4–9.2) [294, 521, 2391]	yohimbine (pK_i 7.9–8.9) [294, 521, 2391], phenoxybenzamine (pK_i 8.5) [2512], tolazoline (pK_i 5.5) [1061]	yohimbine (pK_i 8.5–9.5) [294, 521, 2391], WB 4101 (pK_i 8.4–9.4) [294, 521, 2391], spiroxatrine (pK_i 9) [2391], mirtazapine (pK_i 7.7) [633], tolazoline (pK_i 5.4) [1061]
Selective antagonists	BRL 44408 (pK_i 8.2–8.8) [2391, 2645]	imiloxan (pK_i 7.3) [1575] – Rat	JP1302 (pK_B 7.8) [2047]
Labelled ligands	–	–	[^{3}H]MK-912 (Antagonist) (pK_d 10.1) [2391]

Comments: The three α_2-adrenoceptor subtypes are termed α_{2A}, α_{2B} and α_{2C}. ARC-239 and prazosin show some selectivity for α_{2B}- and α_{2C}-adrenoceptors over α_{2A}-adrenoceptors. Oxymetazoline is an imidazoline partial agonist that also binds to non-GPCR binding sites for imidazolines, classified as I_1, I_2 and I_3 [474] at which catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands with hypotensive effects *in vivo*. I_1-imidazoline recognition sites cause central inhibition of sympathetic tone, I_2-imidazoline sites are an allosteric binding site on monoamine oxidase B, and I_3-imidazoline sites regulate insulin secretion from pancreatic β-cells. α_{2A}-adrenoceptor stimulation reduces insulin secretion from β-islets [2614], 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 [2008]. The α_{2A}- and α_{2C}-adrenoceptors form homodimers [2192]. Heterodimers between α_{2A}- and either the α_{2c}-adrenoceptor or μ opioid peptide receptor exhibit altered signalling and trafficking properties compared to the individual receptors [2192, 2315, 2443]. Signalling by α_2-adrenoceptors is primarily via $G_{i/o}$, although the α_{2A}-adrenoceptor also couples to G_s [577]. Imidazoline compounds display bias relative to each other at the α_{2A}-adrenoceptor [1830]. The noradrenaline reuptake inhibitor desipramine acts directly on α_{2A}-adrenoceptors to promote internalisation *via* recruitment of β-arrestin [448]. The structure of the α_{2B}-adrenoceptor has recently been determined by cryo-EM in complex with dexmedetomidine and $G\alpha_o$ at a resolution of 2.9 Å providing insights into the structural requirements required for interactions with α_2-adrenoceptor agonists [2648].

Adrenoceptors, β

G protein-coupled receptors → Adrenoceptors → Adrenoceptors, β

Overview: The three β-adrenoceptor subtypes β_1, β_2 and β_3 are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Isoprenaline is selective for β-adrenoceptors relative to α_1- and α_2-adrenoceptors, while propranolol (pK_i 8.2-9.2) and cyanopindolol (pK_i 10.0-11.0) are relatively selective antagonists for β_1- and β_2- relative to β_3-adrenoceptors. (-)-noradrenaline, xamoterol and (-)-Ro 363 show selectivity for β_1- relative to β_2-adrenoceptors. Pharmacological differences exist between human and mouse β_3-adrenoceptors, and the 'rodent selective' agonists BRL 37344 and CL316243 have low efficacy at the human β_3-adrenoceptor whereas CGP 12177 (low potency) and L 755507 activate human β_3-adrenoceptors [88]. β_3-Adrenoceptors are resistant to blockade by propranolol, but can be blocked by high concentrations of bupranolol. SR59230A has reasonably high affinity at β_3-adrenoceptors, but does not discriminate between the three β- subtypes [1577] whereas L-748337 is more selective. [^{125}I]-cyanopindolol, [^{125}I]-hydroxy benzylpindolol and [^{3}H]-alprenolol are high affinity radioligands that label β_1- and β_2- adrenoceptors and β_3-adrenoceptors can be labelled with higher concentrations (nM) of [^{125}I]-cyanopindolol together with β_1- and β_2-adrenoceptor antagonists. Fluorescent ligands such as BODIPY-TMR-CGP12177 can be used to track β-adrenoceptors at the cellular level [8]. Somewhat selective β_1-adrenoceptor agonists (denopamine, dobutamine) are used short term to treat cardiogenic shock but, chronically, reduce survival. β_1-Adrenoceptor-preferring antagonists are used to treat cardiac arrhythmias (atenolol, bisoprolol, esmolol) and cardiac failure (metoprolol, nebivolol) but also in combination with other treatments to treat hypertension (atenolol, betaxolol, bisoprolol, metoprolol and nebivolol) [2558]. Cardiac failure is also treated with carvedilol that blocks β_1- and β_2-adrenoceptors, as well as α_1-adrenoceptors. Short (salbutamol, terbutaline) and long (formoterol, salmeterol) acting β_2-adrenoceptor-selective agonists are powerful bronchodilators used to treat respiratory disorders. Many first generation β-adrenoceptor antagonists (propranolol) block both β_1- and β_2-adrenoceptors and there are no β_2-adrenoceptor-selective antagonists used therapeutically. The β_3-adrenoceptor agonist mirabegron is used to control overactive bladder syndrome. There is evidence to suggest that β-adrenoceptor antagonists can reduce metastasis in certain types of cancer [937].

Nomenclature	β_1-adrenoceptor	β_2-adrenoceptor	β_3-adrenoceptor
HGNC, UniProt	*ADRB1*, P08588	*ADRB2*, P07550	*ADRB3*, P13945
Potency order of endogenous ligands	(-)-noradrenaline > (-)-adrenaline	(-)-adrenaline > (-)-noradrenaline	(-)-noradrenaline = (-)-adrenaline
Endogenous agonists	(-)-adrenaline [676, 956], (-)-noradrenaline [676, 956], noradrenaline [676]	(-)-adrenaline [676, 956, 1058], (-)-noradrenaline [676, 956]	(-)-noradrenaline [956, 1889, 2250], (-)-adrenaline [956]
Agonists	pindolol (Partial agonist) [1254], isoprenaline [676, 2066], dobutamine (Partial agonist) [1029]	pindolol (Partial agonist) [1254], arformoterol [43], isoprenaline [2066], ephedrine (Partial agonist) [1058]	carazolol [1561]
Selective agonists	(-)-Ro 363 [1610], xamoterol (Partial agonist) [1029], denopamine (Partial agonist) [1029, 2277]	formoterol [103], salmeterol [103], zinterol [103], vilanterol [1906], procaterol [103], indacaterol [134], fenoterol [68], salbutamol (Partial agonist) [104, 1029], terbutaline (Partial agonist) [104], orciprenaline [2217]	L 755507 [103], L742791 [2509], mirabegron [2301], CGP 12177 (Partial agonist) [191, 1436, 1561, 1610], SB251023 [1007] – Mouse, BRL 37344 [191, 543, 956, 1561], CL316243 [2611]
Antagonists	carvedilol (pK_i 9.5) [307], bupranolol (pK_i 7.3–9) [307, 1436], SR59230A (pK_i 8.6) [307], levobunolol (pK_i 8.4) [84], labetalol (pK_i 8.2) [84], metoprolol (pK_i 7–7.6) [104, 307, 956, 1436], esmolol (pK_i 6.9) [84], nadolol (pK_i 6.9) [307], practolol (pK_i 6.1–6.8) [104, 1436], propafenone (pK_i 6.7) [84], sotalol (pK_i 6.1) [84]	carvedilol (pK_i 9.4–9.9) [104, 307], timolol (pK_i 9.7) [104], propranolol (pK_i 9.1–9.5) [104, 106, 1029, 1436], SR59230A (pK_i 9.3) [307], levobunolol (pK_i 9.3) [84], bupranolol (pK_i 8.3–9.1) [307, 1436], alprenolol (pK_i 9) [104], nadolol (pK_i 7–8.6) [104, 307], labetalol (pK_i 8) [84], propafenone (pK_i 7.4) [84], sotalol (pK_i 6.5) [84]	SR59230A (pK_i 6.9–8.4) [307, 502, 956], bupranolol (pK_i 6.8–7.3) [191, 307, 1436, 1561], propranolol (pK_i 6.3–7.2) [1436, 1889], levobunolol (pK_i 6.8) [1889]
Selective antagonists	CGP 20712A (pK_i 8.5–9.2) [104, 307, 1436], levobetaxolol (pK_i 9.1) [2140], betaxolol (pK_i 8.8) [1436], nebivolol (pIC_{50} 8.1–8.7) [1829] – Rabbit, atenolol (pK_i 6.7–7.6) [104, 1096, 1436], acebutolol (pK_i 6.4) [84]	ICI 118551 (Inverse agonist) (pK_i 9.2–9.5) [104, 106, 1436]	L-748337 (pK_i 8.4) [307], L748328 (pK_i 8.4) [307]
Allosteric modulators	–	AS408 [1422]	–
Labelled ligands	[^{125}I]ICYP (Antagonist) (pK_d 10.4–11.3) [1029, 1436, 2066]	[^{125}I]ICYP (Antagonist) (pK_d 11.1) [1436, 2066]	[^{125}I]ICYP (Agonist, Partial agonist) [1436, 1610, 1889, 2066, 2250]
Comments	The agonists indicated have less than two orders of magnitude selectivity [103].	–	Agonist SB251023 has a pEC_{50} of 6.9 for the splice variant of the mouse β_3 receptor, β_{3b} [1007].

Comments: The three β-adrenoceptors are termed β_1, β_2 and β_3. [^{125}I]ICYP can be used to define either β_1- or β_2-adrenoceptors when conducted in the presence of a β_1- or a β_2-adrenoceptor-selective antagonist. A fluorescent analogue of CGP 12177 is used to study β-adrenoceptors in living cells [107]. [^{125}I]ICYP at higher (nM) concentrations has been used to label β_3-adrenoceptors in systems with few if any other β-adrenoceptor subtypes. The β_3-adrenoceptor has an intron in the coding region, but splice variants have only been described for the mouse [615], where the isoforms display different signalling characteristics [1007]. There are three β-adrenoceptors in turkey (termed the tβ, tβ3c and tβ4c) with pharmacology that differs from the human β-adrenoceptors [105]. Numerous polymorphisms have been described for the β-adrenoceptors; some are associated with altered signalling and trafficking, susceptibility to disease and/or altered responses to pharmacotherapy [1390]. All β-adrenoceptors couple to G_s (activating adenylyl cyclase and elevating cAMP levels), but the β_2- and β_3-adrenoceptors in particular can also activate G_i and the β_2-adrenoceptor activates β-arrestin-mediated signalling. Many β_1- and β_2-adrenoceptor antagonists are agonists at β_3-adrenoceptors (CL316243, CGP 12177 and carazolol). Many 'antagonists' of cAMP accumulation, for example carvedilol and bucindolol, weakly activate MAP kinase pathways [108, 616, 690, 691, 2064, 2065] and thus display biased agonism. Bupranolol acts as a neutral antagonist in most systems so far examined. Agonists also display biased signalling at the β_2-adrenoceptor via G_s or arrestins [559]. X-ray crystal structures have been described of the agonist bound [2496] and antagonist bound forms of the β_1- [2497], agonist-bound [383] and antagonist-bound forms of the β_2-adrenoceptor [1949, 2007], as well as a fully active agonist-bound, G_s protein-coupled β_2-adrenoceptor [1950], as well as providing insights into the structural requirements for agonist, partial agonist, antagonist, G protein and β-arrestin coupling [2513]. Structures have also been described for negative allosteric modulators of the β_2-adrenoceptor [1422]. Cryo-EM studies have also been recently described that provide a structural framework for agonist mediated signal transduction [2253]. The agonists carvedilol and bucindolol bind to a site on the β_1-adrenoceptor involving contacts in TM2, 3, and 7 and extracellular loop 2 that may facilitate coupling to arrestins

[2497]. Compounds displaying β-arrestin-biased signalling at the β_2-adrenoceptor have a greater effect on the conformation of TM7, whereas full agonists for G_s coupling promote movement of TM5 and TM6 [1416]. Recent studies using NMR spectroscopy demonstrate significant conformational flexibility in the β_2-adrenoceptor that is stabilized by both agonist and G proteins highlighting the dynamic nature of interactions with both ligand and downstream signalling partners [1175, 1495, 1755]. Such flexibility likely has consequences for our understanding of allosterism and biased agonism, and for the future therapeutic exploitation of these phenomena.

Angiotensin receptors

G protein-coupled receptors → Angiotensin receptors

Overview: The actions of angiotensin II (*AGT*, P01019) (Ang II) are mediated by AT_1 and AT_2 receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Angiotensin receptors [497, 1123]**), which have around 30% sequence similarity. The decapeptide angiotensin I (*AGT*, P01019), the octapeptide angiotensin II (*AGT*, P01019) and the heptapeptide angiotensin III (*AGT*, P01019) are endogenous ligands. Losartan, candesartan, telmisartan, etc. are clinically used AT_1 receptor blockers.

Further reading on Angiotensin receptors

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Singh KD *et al.* (2019) Mechanism of Hormone Peptide Activation of a GPCR: Angiotensin II Activated State of AT_1R Initiated by van der Waals Attraction. *J Chem Inf Model* **59**: 373-385 [PMID:30608150]

Suomivuori CM *et al.* (2020) Molecular mechanism of biased signaling in a prototypical G protein-coupled receptor. *Science* **367**: 881-887 [PMID:32079767]

Wingler LM *et al.* (2019) Distinctive Activation Mechanism for Angiotensin Receptor Revealed by a Synthetic Nanobody. *Cell* **176**: 479-490.e12 [PMID:30639100]

Wingler LM *et al.* (2020) Angiotensin and biased analogs induce structurally distinct active conformations within a GPCR. *Science* **367**: 888-892 [PMID:32079768]

Nomenclature	AT_1 receptor	AT_2 receptor
HGNC, UniProt	*AGTR1*, P30556	*AGTR2*, P50052
Endogenous agonists	angiotensin II (*AGT*, P01019) [498, 2424], angiotensin III (*AGT*, P01019) [498], angiotensin IV (*AGT*, P01019) (Partial agonist) [1318]	angiotensin III (*AGT*, P01019) [459, 498, 2533], angiotensin II (*AGT*, P01019) [498, 2203, 2533], angiotensin-(1-7) (*AGT*, P01019) [224]
Agonists	[Sar^1,Cha^4]Ang-II [961, 1599] – Rat	–
Selective agonists	L-162,313 [1851], L-163,101 [2398]	CGP42112 [224], [p-aminoPhe6]ang II [498, 2224] – Rat, compound 21 [2440]
Antagonists	saprisartan (pK_i 9.1) [934] – Rat, 5-oxo-1-2-4-oxadiazol biphenyl (pIC$_{50}$ 8.8) [1730] – Rat, 5-butyl-methyl immidazole carboxylate 30 (pIC$_{50}$ 8.5) [19], LY303336 (pIC$_{50}$ 8.3) [2425], TRV027 (pK_d 7.7) [2446]	saralasin (pIC$_{50}$ 9) [392] – Rat
Selective antagonists	candesartan (pIC$_{50}$ 9.5–9.7) [2424], eprosartan (pIC$_{50}$ 8.4–8.8) [582], losartan (pIC$_{50}$ 7.4–8.7) [498, 2356], telmisartan (pIC$_{50}$ 8.4) [1546], olmesartan (pIC$_{50}$ 8.1) [1218]	PD123177 (pIC$_{50}$ 8.5–9.5) [352, 392, 569] – Rat, olodanrigan (pIC$_{50}$ 8.5–9.3) [640, 1981, 2201], PD123319 (pK_d 8.7–9.2) [498, 568, 2543]
Labelled ligands	[^{3}H]candesartan (Antagonist) (pK_d 10.3) [635], [^{125}I][Sar^1]Ang-II (Agonist) [631] – Rat, [^{125}I][Sar^1,Ile^8]Ang-II (Agonist, Partial agonist) [631] – Rat, [^{3}H]eprosartan (Antagonist) (pK_d 9.1) [28] – Rat, [^{3}H]losartan (Antagonist) (pK_d 8.2) [356] – Rat	[^{125}I]CGP42112 (Agonist) [498, 2533, 2534], [^{125}I][Sar^1,Ile^8]Ang-II (Agonist) [2313] – Rat
Comments	Telmisartan and candesartan are also reported to be agonists of PPARγ [2244].	–

Comments: AT_1 receptors are predominantly coupled to $G_{q/11}$, however they are also linked to arrestin recruitment and stimulate G protein-independent arrestin signalling [1452]. Most species express a single *AGTR1* gene, but two related *agtr1a* and a*gtr1b* receptor genes are expressed in rodents. The AT_2 receptor counteracts several of the growth responses initiated by the AT_1 receptors. The AT_2 receptor is much less abundant than the AT_1 receptor in adult tissues and is upregulated in pathological conditions. AT_1 receptor antagonists bearing substituted 4-phenylquinoline moieties have been synthesized, which bind to AT_1 receptors with nanomolar affinity and are slightly more potent than losartan in functional studies [310]. The antagonist activity of CGP42112 at the AT_2 receptor has also been reported [2]. The AT_1 and bradykinin B_2 receptors have been proposed to form a heterodimeric complex [5]. β-Arrestin1 prevents AT_1-B_2 receptor heteromerization[1929]. There is also evidence for an AT_4 receptor that specifically binds angiotensin IV (*AGT*, P01019) and is located in the brain and kidney. An additional putative endogenous ligand for the AT_4 receptor has been described (LVV-hemorphin (*HBB*, P68871), a globin decapeptide) [1605]. The crystal structure coordinates of AngII bound AT_1R (PDB id: 6os0) and AT_2R (PDB id: 6jod) [76] have been recently deposited in the protein structure database.

Apelin receptor

G protein-coupled receptors → Apelin receptor

Overview: The apelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the apelin receptor [1879] and subsequently updated [1960]**) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36 (*APLN*, Q9ULZ1), apelin-13 (*APLN*, Q9ULZ1) and [Pyr[1]]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 [2325]. A second family of peptides discovered independently and named Elabela [393] or Toddler, that has little sequence similarity to apelin, is present, and functional at the apelin receptor in the adult cardiovascular system [1828, 2619]. Structure-activity relationship Elabela analogues have been described [1678].

Further reading on Apelin receptor

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Read C *et al.* (2019) International Union of Basic and Clinical Pharmacology. CVII. Structure and Pharmacology of the Apelin Receptor with a Recommendation that Elabela/Toddler Is a Second Endogenous Peptide Ligand. *Pharmacol Rev* **71**: 467-502 [PMID:31492821]

Yang P *et al.* (2015) Apelin, Elabela/Toddler, and biased agonists as novel therapeutic agents in the cardiovascular system. *Trends Pharmacol Sci* **36**: 560-7 [PMID:26143239]

Nomenclature	apelin receptor
HGNC, UniProt	*APLNR*, P35414
Potency order of endogenous ligands	[Pyr[1]]apelin-13 (*APLN*, Q9ULZ1) ≥ apelin-13 (*APLN*, Q9ULZ1) > apelin-36 (*APLN*, Q9ULZ1) [622, 2325]
Endogenous agonists	apelin-13 (*APLN*, Q9ULZ1) [622, 976, 1558], apelin receptor early endogenous ligand (*APELA*, P0DMC3) [516], apelin-17 (*APLN*, Q9ULZ1) [587, 1558], [Pyr[1]]apelin-13 (*APLN*, Q9ULZ1) [1134, 1558], Elabela/Toddler-21 (*APELA*, P0DMC3) [2618], Elabela/Toddler-32 (*APELA*, P0DMC3) [2618], apelin-36 (*APLN*, Q9ULZ1) [622, 976, 1134, 1558], Elabela/Toddler-11 (*APELA*, P0DMC3) [2618]
Selective agonists	CMF-019 (Biased agonist) [1959], MM07 (Biased agonist) [241]
Antagonists	MM54 (pK_i 8.2) [1459]
Labelled ligands	[^{125}I][Nle^{75},Tyr^{77}]apelin-36 (human) (Agonist) [1134], [^{125}I][Glp^{65}Nle^{75},Tyr^{77}]apelin-13 (Agonist) [976], [^{125}I](Pyr^{1})apelin-13 (Agonist) [1128], [^{125}I]apelin-13 (Agonist) [622], [^{3}H](Pyr^{1})[Met(0)11]-apelin-13 (Agonist) [1558]

Comments: Potency order determined for heterologously expressed human apelin receptor (pD_2 values range from 9.5 to 8.6). The apelin receptor may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function [335]. A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* [1335], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant apelin receptor [622]. The apelin receptor antagonist, MM54, was reported to suppress tumour growth and increase survival in an intracranial xenograft mouse model of glioblastoma [867].

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.

Further reading on Bile acid receptor

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van Nierop FS *et al.* (2017) Clinical relevance of the bile acid receptor TGR5 in metabolism. *Lancet Diabetes Endocrinol* **5**: 224-233 [PMID:27639537]

Nomenclature	GPBA receptor
HGNC, UniProt	*GPBAR1*, Q8TDU6
Potency order of endogenous ligands	lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid [1133, 1519]
Selective agonists	S-EMCA [1838] – Mouse, betulinic acid [728], oleanolic acid [2063]

Comments: The triterpenoid natural product betulinic acid has also been reported to inhibit inflammatory signalling through the NFκB pathway [2293]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [2435]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [1429].

Bombesin receptors

G protein-coupled receptors → Bombesin receptors

Overview: Mammalian bombesin (Bn) receptors comprise 3 subtypes: BB_1, BB_2, BB_3 (**nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, [1066]**). BB_1 and BB_2 are activated by the endogenous ligands neuromedin B (*NMB*, P08949) (NMB), gastrin-releasing peptide (*GRP*, P07492) (GRP), and GRP-(18-27) (*GRP*, P07492). Bombesin is a tetra-decapeptide, originally derived from amphibians. The three Bn receptor subtypes couple primarily to the $G_{q/11}$ and $G_{12/13}$ family of G proteins [1066]. Each of these receptors is widely distributed in the CNS and peripheral tissues [774, 1066, 1890, 1942, 2058, 2662]. Activation of BB_1 and BB_2 receptors causes a wide range of physiological/pathophysiological actions, including the stimulation of normal and neoplastic tissue growth, smooth-muscle contraction, gastrointestinal motility, feeding behavior, secretion and many central nervous system effects including regulation of circadian rhythm, body temperature control, sighing and mediation of pruritus [373, 689, 1066, 1374, 1629, 1637, 1923, 1942, 2268, 2475]. A physiological role for the BB_3 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 [774, 1373, 1483, 1635, 1769, 2582]. Bn receptors are one of the most frequently overexpressed receptors in cancers and are receiving increased attention for their roles in tumor growth, as well as for tumour imaging and for receptor targeted cytotoxicity [115, 1480, 1637, 2051].

Further reading on Bombesin receptors

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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]

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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]

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Nomenclature	BB_1 receptor	BB_2 receptor	BB_3 receptor
HGNC, UniProt	*NMBR*, P28336	*GRPR*, P30550	*BRS3*, P32247
Endogenous agonists	neuromedin B (*NMB*, P08949) [1066, 1942, 2389]	neuromedin C [2389], gastrin releasing peptide(14-27) (human) [2389], gastrin-releasing peptide (*GRP*, P07492) [156, 2032, 2389]	–
Selective agonists	–	[D-Tyr^6,β-Ala^{11},N-Me-Ala^{13},Nle^{14}]bombesin-(6-14) [970]	compound 9g [1527, 1943], MK-7725 [395], MK-5046 [1636, 2112], [D-Tyr^6,Apa-4Cl^{11},Phe^{13},Nle^{14}]bombesin-(6-14) [1500], compound 17c [1526], bag-1 [814], compound 22e [899]
Antagonists	D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_2 (pIC_{50} 6.2–6.6) [773]	BAY86-7548 (pIC_{50} 8.6) [1104, 2389]	–
Selective antagonists	PD 176252 (pIC_{50} 9.3–9.8) [773], PD 168368 (pIC_{50} 9.3–9.6) [773], dNal-*cyc*(Cys-Tyr-dTrp-Orn-Val)-Nal-NH_2	[D-Phe^6, Leu^{13}, Cpa^{14},ψ13-14]bombesin-(6-14) (pK_i 9.8) [773], JMV641 (pIC_{50} 9.3) [2361] – Mouse, [(3-Ph-Pr^6), His^7,D-Ala^{11},D-Pro^{13},ψ13-14),Phe^{14}]bombesin-(6-14) (pIC_{50} 9.2) [773, 1328], JMV594 (pIC_{50} 8.9) [1424, 2361] – Mouse, [D-Tpi^6, Leu^{13} ψ(CH_2NH)-Leu^{14}]bombesin-(6-14) (pIC_{50} 8.9) [773]	bantag-1 (pIC_{50} 8.6–8.7) [814, 1636, 1941], ML-18 (pIC_{50} 5.3) [1628]
Labelled ligands	[^{125}I]BH-NMB (human, mouse, rat) (Agonist), [^{125}I][Tyr^4]bombesin (Agonist)	[^{125}I][D-Tyr^6]bombesin-(6-13)-methyl ester (Selective Antagonist) (pK_d 9.3) [1499] – Mouse, [^{125}I][Tyr^4]bombesin (Agonist) [156], [^{125}I]GRP (human) (Agonist)	[^{125}I]bantag-1 (Selective Antagonist) (pK_i 9.6) [1941], [^{3}H]bag-2 (Agonist) [814] – Mouse, [^{125}I][D-Tyr^6,β-Ala^{11},Phe^{13},Nle^{14}]bombesin-(6-14) (Agonist) [1501, 1636]

Comments: All three human subtypes may be activated by [D-Phe^6,β-Ala^{11},Phe^{13},Nle^{14}]bombesin-(6-14) [1501]. Agonists [D-Tyr^6,Apa-4Cl11,Phe^{13},Nle1^4]bombesin-(6-14) has more than 200-fold selectivity for BB_3 receptors over BB_1 and BB_2 [1500, 1501, 1942, 1942, 1943].

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 [1342]**) are activated by the endogenous peptides bradykinin (*KNG1*, P01042) (BK), [des-Arg[9]]bradykinin (*KNG1*, P01042), Lys-BK (kallidin (*KNG1*, P01042)), [des-Arg[10]]kallidin (*KNG1*, P01042), [Phospho-Ser[6]]-Bradykinin, T-kinin (*KNG1*, P01042) (Ile-Ser-BK), [Hyp[3]]bradykinin (*KNG1*, P01042) and Lys-[Hyp[3]]-bradykinin (*KNG1*, P01042). Variation in pharmacology and activity of B_1 and B_2 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.

Further reading on Bradykinin receptors

Blaes N *et al*. (2013) Targeting the 'Janus face' of the B2-bradykinin receptor. *Expert Opin Ther Targets* **17**: 1145-66 [PMID:23957374]

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]

Couture R *et al*. (2014) Kinin receptors in vascular biology and pathology. *Curr Vasc Pharmacol* **12**: 223-48 [PMID:24568157]

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]

Nomenclature	B_1 receptor	B_2 receptor
HGNC, UniProt	*BDKRB1*, P46663	*BDKRB2*, P30411
Potency order of endogenous ligands	[des-Arg[10]]kallidin (*KNG1*, P01042) > [des-Arg[9]]bradykinin (*KNG1*, P01042) = kallidin (*KNG1*, P01042) > bradykinin (*KNG1*, P01042)	kallidin (*KNG1*, P01042) > bradykinin (*KNG1*, P01042) ≫ [des-Arg[9]]bradykinin (*KNG1*, P01042), [des-Arg[10]]kallidin (*KNG1*, P01042)
Endogenous agonists	[des-Arg[10]]kallidin (*KNG1*, P01042) [86, 129, 765, 1087]	bradykinin (*KNG1*, P01042) [63, 924]
Selective agonists	NG29 [2071], [Sar,D-Phe[8],des-Arg[9]]bradykinin [81, 1087]	NG291 [2072], labradimil [2072], [Hyp[3],Tyr(Me)[8]]BK, [Phe[8],$\psi(CH_2\text{-}NH)$Arg[9]]BK
Selective antagonists	B-9958 (pK_i 9.2–10.3) [737, 1963], [Leu[9],des-Arg[10]]kallidin (pK_i 9.1–9.3) [86, 129], SSR240612 (pK_i 9.1–9.2) [785], R-954 (pA_2 8.6) [766], R-715 (pA_2 8.5) [764]	icatibant (pK_i 10.2) [46], FR173657 (pA_2 8.2) [1997], anatibant (pK_i 8.2) [1913]
Labelled ligands	[^{125}I]Hpp-desArg[10]HOE140 (Antagonist) (pK_d 10), [^{3}H]Lys-[des-Arg[9]]BK (Agonist), [^{3}H]Lys-[Leu[8]][des-Arg[9]]BK (Antagonist)	[^{3}H]BK (human, mouse, rat) (Agonist) [2553] – Mouse, [^{3}H]NPC17731 (Antagonist) (pK_d 9.1–9.4) [2667, 2668], [^{125}I]HPP-HOE140 (Antagonist) [503, 1789], [^{125}I][Tyr[8]]bradykinin (Agonist) [1432]

Calcitonin receptors

G protein-coupled receptors → Calcitonin receptors

Overview: This receptor family comprises a group of receptors for the calcitonin/CGRP family of peptides. The calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors [891, 893, 1901]**) are generated by the genes *CALCR* (which codes for the CT receptor) and *CALCRL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying proteins), which are single TM domain proteins of *ca.* 150 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 [1901], 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*, P10997) (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), adrenomedullin (*ADM*, P35318) and adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4). There are species differences in peptide sequences, particularly for the CTs. CTR-stimulating peptide {Pig} (CRSP) is another member of the family with selectivity for the CT receptor but it is not expressed in humans [1125]. CLR (calcitonin receptor-like receptor) by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, adrenomedullin and adrenomedullin 2/intermedin. There are several approved drugs that target this receptor family, such as pramlintide, erenumab, and the "gepant" class of CGRP receptor antagonists.

Further reading on Calcitonin receptors

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

Nomenclature	CT receptor	AMY_1 receptor	AMY_2 receptor	AMY_3 receptor
HGNC, UniProt	*CALCR*, P30988	–	–	–
Subunits	–	CT receptor, RAMP1 (Accessory protein)	CT receptor, RAMP2 (Accessory protein)	CT receptor, RAMP3 (Accessory protein)
Potency order of endogenous ligands	calcitonin (salmon) ≥ calcitonin (*CALCA*, P01258) ≥ amylin (*IAPP*, P10997), α-CGRP (*CALCA*, P06881), β-CGRP (*CALCB*, P10092) > adrenomedullin (*ADM*, P35318), adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4)	calcitonin (salmon) ≥ amylin (*IAPP*, P10997) ≥ α-CGRP (*CALCA*, P06881), β-CGRP (*CALCB*, P10092) > adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4) ≥ calcitonin (*CALCA*, P01258) > adrenomedullin (*ADM*, P35318)	Poorly defined	calcitonin (salmon) ≥ amylin (*IAPP*, P10997) > α-CGRP (*CALCA*, P06881),β-CGRP (*CALCB*, P10092) ≥ adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4) ≥ calcitonin (*CALCA*, P01258) > adrenomedullin (*ADM*, P35318)
Endogenous agonists	calcitonin (*CALCA*, P01258) [38, 71, 889, 1278, 1364, 1661]	α-CGRP (*CALCA*, P06881) [889, 1277, 1278, 1364, 2469], amylin (*IAPP*, P10997) [756], β-CGRP (*CALCB*, P10092)	amylin (*IAPP*, P10997) [756]	amylin (*IAPP*, P10997) [756]
Agonists	pramlintide [756]	pramlintide [756]	–	pramlintide [756]
Antagonists	CT-(8-32) (salmon) (pK_d 9) [939], AC187 (pK_i 7.2) [889]	AC187 (pK_i 8) [889], CT-(8-32) (salmon) (pK_i 7.8) [889], olcegepant (pK_d 7.2) [2469]	–	CT-(8-32) (salmon) (pK_i 7.9) [889], AC187 (pK_i 7.7) [889]
Labelled ligands	[^{125}I]CT (human) (Agonist), [^{125}I]CT (salmon) (Agonist)	[^{125}I]αCGRP (human) (Agonist), [^{125}I]BH-AMY (rat, mouse) (Agonist)	[^{125}I]BH-AMY (rat, mouse) (Agonist)	[^{125}I]BH-AMY (rat, mouse) (Agonist)

Nomenclature	calcitonin receptor-like receptor	CGRP receptor	AM_1 receptor	AM_2 receptor
HGNC, UniProt	*CALCRL*, Q16602	–	–	–
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	–	α-CGRP (*CALCA*, P06881), β-CGRP (*CALCB*, P10092) > adrenomedullin (*ADM*, P35318) ≥ adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4) > amylin (*IAPP*, P10997) ≥ calcitonin (salmon)	adrenomedullin (*ADM*, P35318) > adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4) > α-CGRP (*CALCA*, P06881), β-CGRP (*CALCB*, P10092), amylin (*IAPP*, P10997) > calcitonin (salmon)	adrenomedullin (*ADM*, P35318) ≥ adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4) ≥ α-CGRP (*CALCA*, P06881), β-CGRP (*CALCB*, P10092) > amylin (*IAPP*, P10997) > calcitonin (salmon)
Endogenous agonists	–	β-CGRP (*CALCB*, P10092) [27, 1555], α-CGRP (*CALCA*, P06881) [27, 1555]	adrenomedullin (*ADM*, P35318) [27, 1555]	adrenomedullin (*ADM*, P35318) [27, 664]
Antagonists	–	olcegepant (pK_i 10.7–11) [551, 890, 892, 1097, 1491], telcagepant (pK_i 9.1) [2048]	AM-(22-52) (human) (pK_i 7–7.8) [892]	AM-(22-52) (human)
Labelled ligands	–	[^{125}I]αCGRP (human) (Agonist), [^{125}I]αCGRP (mouse, rat) (Agonist)	[^{125}I]AM (rat) (Agonist)	[^{125}I]AM (rat) (Agonist)

Comments: It is important to note that a complication with the interpretation of pharmacological studies with AMY receptors in transfected cells is that most of this work has likely used a mixed population of receptors, encompassing RAMP-coupled CTR as well as CTR alone. This means that although in binding assays human calcitonin (*CALCA*, P01258) has low affinity for ^{125}I-AMY binding sites, cells transfected with CTR and RAMPs can display potent CT functional responses. Transfection of human CTR with any RAMP can generate receptors with a high affinity for both salmon CT and AMY and varying affinity for different antagonists [412, 889, 890]. The major human CTR splice variant ($hCT_{(a)}$, which does not contain an insert) with RAMP1 (*i.e.* the $AMY_{1(a)}$ receptor) has a high affinity for CGRP [2469], unlike $hCT_{(a)}$-RAMP3 (*i.e.* $AMY_{3(a)}$ receptor) [412, 889]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [1638, 1919, 2355]. Emerging data suggests that AMY_1 could be a second CGRP receptor [888]. There are also species differences in agonist pharmacology.

The ligands described have limited selectivity. Adrenomedullin has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM_2 receptors. Adrenomedullin 2/intermedin also has high affinity for the AM_2 receptor [969]. CGRP-(8-37) acts as an antagonist of CGRP (*p*K_i 8) and inhibits some AM and AMY responses (*p*K_i 6-7). It is weak at CT receptors. Human AM-(22-52) has some selectivity towards AM receptors, but with modest potency (*p*K_i 7), limiting its use [892]. Olcegepant (also known as BIBN4096BS, pK_i10.5) and telcagepant (also known as MK0974, pK_i9) are examples of the "gepant" class of small molecule antagonists. These are selective for the CGRP receptor over the AM receptors but depending on the compound, have variable affinity for the AMY_1 receptor. These antagonists tend to have higher affinity at primate receptors, compared to rodent receptors [1630, 2469].

G_s is a prominent route for effector coupling for CLR and CTR but other pathways (*e.g.* Ca^{2+}, ERK, Akt), and G proteins can be activated [2468]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, *ASL* (P04424) is important for the coupling of CLR to adenylyl cyclase [617].

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

Calcium-sensing receptor

G protein-coupled receptors → Calcium-sensing receptor

Overview: The calcium-sensing receptor (CaS, **provisional nomenclature as recommended by NC-IUPHAR [652] and subsequently updated [1323]**) responds to multiple endogenous ligands, including extracellular calcium and other divalent/trivalent cations, polyamines and polycationic peptides, L-amino acids (particularly L-Trp and L-Phe), glutathione and various peptide analogues, ionic strength and extracellular pH (reviewed in [1325]). While divalent/trivalent cations, polyamines and polycations are CaS receptor agonists [269, 1927], L-amino acids, glutamyl peptides, ionic strength and pH are allosteric modulators of agonist function [438, 652, 950, 1925, 1926]. Indeed, L-amino acids have been identified as "co-agonists", with both concomitant calcium and L-amino acid binding required for full receptor activation [730, 2657]. The sensitivity of the CaS receptor to primary agonists is increased by elevated extracellular pH [305] or decreased extracellular ionic strength [1926]. This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

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 signaling 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]

Leach K *et al.* (2020) International Union of Basic and Clinical Pharmacology. CVIII. Calcium-Sensing Receptor Nomenclature, Pharmacology, and Function. *Pharmacol Rev* **72**: 558-604 [PMID:32467152]

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

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) [438]
Cation rank order of potency	Gd^{3+} > Ca^{2+} > Mg^{2+} [269]
Glutamyl peptide rank order of potency	S-methylglutathione ≈ γGlu-Val-Gly > glutathione > γGlu-Cys [260, 1771, 2487]
Polyamine rank order of potency	spermine > spermidine > putrescine [1927]
Allosteric modulators	ATF936 (Negative) (pIC_{50} 8.9) [2537], encaleret (Negative) (pIC_{50} 7.9) [2156], SB-423562 (Negative) (pIC_{50} 7.1) [1271], evocalcet (Positive) (pEC_{50} 7) [1601], ronacaleret (Negative) (pIC_{50} 6.5–6.8) [110], NPS 2143 (Negative) (pK_B 6.2–6.7) [489, 1322, 1326], cinacalcet (Positive) (pK_B 5.9–6.6) [441, 489, 1322, 1326], tecalcet (Positive) (pK_B 6.2–6.6) [441, 489], AC265347 (Positive) (pK_B 6.3–6.4) [441, 1322], calhex 231 (Negative) (pIC_{50} 6.4) [1863], calindol (Positive) (pK_B 6.3) [441], etelcalcetide (Positive) (pEC_{50} 4.6) [2472]

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 [856]. This is seen most clearly in patients with loss-of-function CaS receptor mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutations) or neonatal severe hyperparathyroidism (heterozygous, compound heterozygous or homozygous mutations) [856] and in *Casr* null mice [354, 950], 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 [856].

The CaS receptor primarily couples to $G_{q/11}$, $G_{12/13}$ and $G_{i/o}$ [489, 741, 992, 2345], but in some cell types can couple to G_s [1493]. However, the CaS receptor can form heteromers with Class C $GABA_B$ [355, 382] and mGlu1/5 receptors [697], which may introduce further complexity in its signalling capabilities.

Multiple other small molecule chemotypes are positive and negative allosteric modulators of the CaS receptor [1159, 1713]. Further, etelcalcetide is a novel peptide positive allosteric modulator of the receptor, that also displays weak agonist activity [2472]. 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 [1715]. Negative allosteric modulators are called calcilytics and can act to increase PTH (*PTH*, P01270) secretion [1714].

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

Cannabinoid receptors

G protein-coupled receptors → Cannabinoid receptors

Overview: Cannabinoid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Cannabinoid Receptors [1856]**) are activated by endogenous ligands that include N-arachidonoylethanolamine (anandamide), N-homo-γ-linolenoylethanolamine, N-docosatetra-7,10,13,16-enoylethanolamine 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 [41].

There are currently three licenced cannabinoid medicines each of which contains a compound that can activate CB_1 and CB_2 receptors [1854]. Two of these medicines were developed to suppress nausea and vomiting produced by chemotherapy. These are nabilone (Cesamet®), a synthetic CB_1/CB_2 receptor agonist, and synthetic Δ^9-tetrahydrocannabinol (Marinol®; dronabinol), which can also be used as an appetite stimulant. The third medicine, Sativex®, contains mainly Δ^9-tetrahydrocannabinol and cannabidiol, both extracted from cannabis, and is used to treat multiple sclerosis and cancer pain.

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]

Nomenclature	CB_1 receptor	CB_2 receptor
HGNC, UniProt	*CNR1*, P21554	*CNR2*, P34972
Agonists	HU-210 [628, 2162], CP55940 [628, 2011, 2162], WIN55212-2 [628, 2159, 2162], Δ^9-tetrahydrocannabinol (Partial agonist) [628, 2162], cannabinol (Partial agonist) [628, 2162]	HU-210 [628, 1977, 2162], WIN55212-2 [628, 2159, 2162], CP55940 [628, 2011, 2162], Δ^9-tetrahydrocannabinol (Partial agonist) [132, 628, 1977, 2162]
Selective agonists	arachidonyl-2-chloroethylamide [936] – Rat, arachidonylcyclopropylamide [936] – Rat, O-1812 [525] – Rat, *R*-(+)-methanandamide [1154] – Rat	JWH-133 [1000, 1855], L-759,633 [710, 2011], AM1241 [2621], L-759,656 [710, 2011], HU-308 [864], GW405833 (Partial agonist) [1510]
Selective antagonists	JD5037 (pK_i 9.5) [2311], rimonabant (pK_i 7.9–8.7) [627, 628, 1987, 2024, 2162], AM6545 (pK_i 8.5) [231], AM251 (pK_i 8.1) [1290] – Rat, AM281 (pK_i 7.9) [1289] – Rat, LY320135 (pK_i 6.9) [627]	SR144528 (pK_i 8.3–9.2) [1988, 2011], AM-630 (pK_i 7.5) [2011]
Allosteric modulators	GAT100 (Negative) (pEC_{50} 7.7) [1266], ZCZ011 (Positive) (pEC_{50} 6.3) [1014] – Mouse, GAT211 (Positive) [1300], cannabidiol (Negative) [1299]	pepcan-12 (Positive) (pK_i ~7.3) [1866], compound C2 (Positive) [688]
Labelled ligands	[^{3}H]rimonabant (Antagonist) (pK_d 8.9–10) [244, 945, 1100, 1862, 1989, 2173, 2339] – Rat	–

Comments: Both CB_1 and CB_2 receptors may be labelled with [^{3}H]CP55940 (0.5 nM; [2162]) and [^{3}H]WIN55212-2 (2-2.4 nM; [2189, 2216]). Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [1758, 2695]. There is evidence for an allosteric site on the CB_1 receptor [1904]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [1856]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have been identified [1856]. Moreover, GPR18, GPR55 and GPR119, although showing little structural similarity to CB_1 and CB_2 receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands [1856].

Chemerin receptors

G protein-coupled receptors → Chemerin receptors

Overview: Nomenclature for the chemerin receptors is presented as **recommended by NC-IUPHAR [485, 1144]**). 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 Chermerin$_2$ [1144]. 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 [69, 70]. In addition, two GPCRs for resolvin D1 (RvD1) have been identified: FPR2/ALX, the lipoxin A$_4$ receptor, and GPR32, an orphan receptor [1248].

Further reading on Chemerin receptors

Kennedy AJ *et al.* (2018) International Union of Basic and Clinical Pharmacology CIII: Chemerin Receptors CMKLR1 (Chemerin1) and GPR1 (Chemerin2) Nomenclature, Pharmacology, and Function. *Pharmacol Rev* **70**: 174-196 [PMID:29279348]

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

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 [69]	–
Endogenous agonists	–	chemerin (*RARRES2*, Q99969) [120]
Selective agonists	resolvin E1	–
Labelled ligands	[^{3}H]resolvin E1 (Agonist) [69, 70]	–
Comments	–	Reported to act as a co-receptor for HIV [2152]. See review [485] for discussion of pairing with chemerin.

Comments: CCX832 (structure not disclosed) is a selective antagonist, pK_i=9.2 [1145].

Chemokine receptors

G protein-coupled receptors → Chemokine receptors

Overview: Chemokine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Chemokine Receptors [97, 1674, 1675]**) 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 [97].

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 acccording to the class of chemokines bound, whereas ACKR is the root acronym for atypical chemokine receptors [98]. 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 [2691] and aliases.

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]

Koelink PJ *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**: 145-76 [PMID:10699158]

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

Nomenclature	CCR1	CCR2	CCR3
HGNC, UniProt	*CCR1*, P32246	*CCR2*, P41597	*CCR3*, P51677
Endogenous agonists	CCL3 (*CCL3*, P10147) [399, 432, 926, 2693], CCL23 (*CCL23*, P55773) [399], CCL5 (*CCL5*, P13501) [432, 926], CCL7 (*CCL7*, P80098) [399, 829], CCL15 (*CCL15*, Q16663) [450], CCL14 (*CCL14*, Q16627) [399], CCL13 (*CCL13*, Q99616), CCL8 (*CCL8*, P80075)	CCL2 (*CCL2*, P13500) [450, 1451, 1596, 1817, 2390], CCL13 (*CCL13*, Q99616) [1451, 2390], CCL7 (*CCL7*, P80098) [450, 1451, 2390], CCL11 (*CCL11*, P51671) (Partial agonist) [1451, 1817], CCL16 (*CCL16*, O15467)	CCL13 (*CCL13*, Q99616) [1649, 2390], CCL24 (*CCL24*, O00175) [1649, 1817], CCL5 (*CCL5*, P13501) [479], CCL7 (*CCL7*, P80098) [479], CCL11 (*CCL11*, P51671) [571, 1194, 1649, 2039, 2390], CCL26 (*CCL26*, Q9Y258) [1194, 1649, 1817], CCL15 (*CCL15*, Q16663) [450], CCL28 (*CCL28*, Q9NRJ3), CCL8 (*CCL8*, P80075)
Agonists	–	–	CCL11 {Mouse} [479]
Endogenous antagonists	CCL4 (*CCL4*, P13236) (pK_i 7.1–7.8) [399, 432]	CCL26 (*CCL26*, Q9Y258) (pIC$_{50}$ 8.5) [1817]	CXCL10 (*CXCL10*, P02778), CXCL11 (*CXCL11*, O14625), CXCL9 (*CXCL9*, Q07325)
Selective antagonists	BX 471 (pK_i 8.2–9) [1383], compound 2b-1 (pIC$_{50}$ 8.7) [1700], UCB35625 (pIC$_{50}$ 8) [2039], CP-481,715 (pK_d 8) [759]	GSK Compound 34 (pK_i 7.6)	banyu (I) (Inverse agonist) (pK_i 8.5) [2477], SB328437 (pK_i 8.4), BMS compound 87b (pK_i 8.1) [2461]
Labelled ligands	[^{125}I]CCL7 (human) (Agonist) [152], [^{125}I]CCL3 (human) (Agonist) [152, 772, 2062], [^{125}I]CCL5 (human) (Agonist) [2062]	[^{125}I]CCL2 (human) (Agonist), [^{125}I]CCL7 (human) (Agonist)	[^{125}I]CCL11 (human) (Antagonist) (pK_d 8.3) [2477], [^{125}I]CCL5 (human) (Agonist), [^{125}I]CCL7 (human) (Agonist)

Nomenclature	CCR4	CCR5	CCR6	CCR7	CCR8	CCR9	CCR10
HGNC, UniProt	*CCR4*, P51679	*CCR5*, P51681	*CCR6*, P51684	*CCR7*, P32248	*CCR8*, P51685	*CCR9*, P51686	*CCR10*, P46092
Endogenous agonists	CCL22 (*CCL22*, O00626) [1019], CCL17 (*CCL17*, Q92583) [1019]	CCL5 (*CCL5*, P13501) [94, 1694, 2021], CCL4 (*CCL4*, P13236) [1694, 2021], CCL8 (*CCL8*, P80075) [2021], CCL3 (*CCL3*, P10147) [1694, 2021, 2693], CCL11 (*CCL11*, P51671) [189], CCL2 (*CCL2*, P13500) [1694], CCL14 (*CCL14*, Q16627) [1694], CCL16 (*CCL16*, O15467)	CCL20 (*CCL20*, P78556) [26, 93, 1899], beta-defensin 4A (*DEFB4A DEFB4B*, O15263) [2612]	CCL21 (*CCL21*, O00585) [2640], CCL19 (*CCL19*, Q99731) [1795, 2639, 2640]	CCL1 (*CCL1*, P22362) [470, 878, 1020], CCL8 {Mouse}	CCL25 (*CCL25*, O15444)	CCL27 (*CCL27*, Q9Y4X3) [966], CCL28 (*CCL28*, Q9NRJ3)
Agonists	vMIP-III	R5-HIV-1 gp120	–	–	vMIP-I [470, 1020]	–	–
Endogenous antagonists	–	CCL7 (*CCL7*, P80098) (pK_i 7.5) [1694]	–	–	–	–	–
Antagonists	–	vicriviroc (pK_i 9.1) [2249], ancriviroc (pK_i 7.8–8.7) [1469, 1804, 2249]	–	–	–	–	–
Selective antagonists	compound 8ic (pIC$_{50}$ 7.7) [2637]	E913 (pIC$_{50}$ 8.7) [1470], aplaviroc (pK_i 8.5) [1469], maraviroc (pIC$_{50}$ 8.1) [1694], TAK-779 (pK_i 7.5) [1469], MRK-1 [1270] – Rat	–	–	vMCC-I (pIC$_{50}$ 9.4) [470]	–	–
Selective allosteric modulators	–	–	–	–	–	vercirnon (Antagonist) (pIC$_{50}$ 8.2) [2473]	–
Antibodies	mogamulizumab (Inhibition) [61, 2160]	–	–	–	–	–	–
Labelled ligands	[^{125}I]CCL17 (human) (Agonist), [^{125}I]CCL27 (human) (Agonist)	[^{125}I]CCL4 (human) (Agonist) [1694], [^{125}I]CCL3 (human) (Agonist), [^{125}I]CCL5 (human) (Agonist), [^{125}I]CCL8 (human) (Agonist)	[^{125}I]CCL20 (human) (Agonist) [795]	[^{125}I]CCL19 (human) (Agonist), [^{125}I]CCL21 (human) (Agonist) [1065]	[^{125}I]CCL1 (human) (Agonist) [1020, 2006]	[^{125}I]CCL25 (human) (Agonist)	–

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6	CX_3CR1
HGNC, UniProt	*CXCR1*, P25024	*CXCR2*, P25025	*CXCR3*, P49682	*CXCR4*, P61073	*CXCR5*, P32302	*CXCR6*, O00574	*CX3CR1*, P49238
Endogenous agonists	CXCL8 (*CXCL8*, P10145) [169, 840, 1337, 2551, 2572], CXCL6 (*CXCL6*, P80162) [2578]	CXCL1 (*CXCL1*, P09341) [840, 1337, 2572], CXCL8 (*CXCL8*, P10145) [169, 840, 1337, 2551, 2572], CXCL7 (*PPBP*, P02775) [24], CXCL3 (*CXCL3*, P19876) [24], CXCL2 (*CXCL2*, P19875) [24], CXCL5 (*CXCL5*, P42830) [24], CXCL6 (*CXCL6*, P80162) [2578]	CXCL11 (*CXCL11*, O14625) [908], CXCL10 (*CXCL10*, P02778) [908, 2519], CXCL9 (*CXCL9*, Q07325) [908, 2519]	CXCL12α (*CXCL12*, P48061) [925, 1427], CXCL12β (*CXCL12*, P48061) [925]	CXCL13 (*CXCL13*, O43927) [122]	CXCL16 (*CXCL16*, Q9H2A7) [2544]	CX_3CL1 (*CX3CL1*, P78423) [711]
Agonists	vCXCL1 [1450], HIV-1 matrix protein p17 [746]	vCXCL1 [1450], HIV-1 matrix protein p17 [746]	–	–	–	–	–
Selective agonists	–	–	–	ALX40-4C (Partial agonist) [2670], X4-HIV-1 gp120	–	–	–
Endogenous antagonists	–	–	CCL11 (*CCL11*, P51671) (pK_i 7.2) [2519], CCL7 (*CCL7*, P80098) (pK_i 6.6) [2519]	–	–	–	–
Antagonists	–	–	–	plerixafor (pK_i 7) [2670]	–	–	–
Selective antagonists	–	navarixin (pIC_{50} 10.3) [97, 576], danirixin (pIC_{50} 7.9) [1590], SB 225002 (pIC_{50} 7.7) [2531], elubirixin (pIC_{50} 7.7) [97], SX-517 (pIC_{50} 7.2) [1468]	–	T134 (pIC_{50} 8.4) [2312], mavorixafor (pIC_{50} 7.9) [2181], HIV-Tat	–	–	–
Allosteric modulators	–	reparixin (Negative) (pIC_{50} 6.4) [169]	–	–	–	–	–
Labelled ligands	[^{125}I]CXCL8 (human) (Agonist) [840, 1985]	[^{125}I]CXCL8 (human) (Agonist) [840, 1985], [^{125}I]CXCL1 (human) (Agonist), [^{125}I]CXCL5 (human) (Agonist), [^{125}I]CXCL7 (human) (Agonist)	[^{125}I]CXCL10 (human) (Agonist), [^{125}I]CXCL11 (human) (Agonist)	[^{125}I]CXCL12α (human) (Agonist) [527, 925]	[^{125}I]CXCL13 (mouse) (Agonist) [262] – Mouse	[^{125}I]CXCL16 (human) (Agonist)	[^{125}I]CX_3CL1 (human) (Agonist)

Nomenclature	XCR1	ACKR1	ACKR2	ACKR3	ACKR4	CCRL2
HGNC, UniProt	*XCR1*, P46094	*ACKR1*, Q16570	*ACKR2*, O00590	*ACKR3*, P25106	*ACKR4*, Q9NPB9	*CCRL2*, O00421
Endogenous ligands	–	CXCL5 (*CXCL5*, P42830), CXCL6 (*CXCL6*, P80162), CXCL8 (*CXCL8*, P10145), CXCL11 (*CXCL11*, O14625), CCL2 (*CCL2*, P13500), CCL5 (*CCL5*, P13501), CCL7 (*CCL7*, P80098), CCL11 (*CCL11*, P51671), CCL14 (*CCL14*, Q16627), CCL17 (*CCL17*, Q92583)	–	–	–	chemerin C-terminal peptide, CCL19 (*CCL19*, Q99731) [120]
Endogenous agonists	XCL1 (*XCL1*, P47992) [660], XCL2 (*XCL2*, Q9UBD3) [660]	–	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)	CXCL12α (*CXCL12*, P48061) [794, 2218], CXCL11 (*CXCL11*, O14625)	CCL19 (*CCL19*, Q99731) [2508], CCL25 (*CCL25*, O15444) [2508], CCL21 (*CCL21*, O00585) [2508]	–
Selective antagonists	–	–	–	LIH383 (pEC_{50} 9.2) [1570]	–	–
Comments	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 knowlsei* for entering erythrocytes.	–	Several lines of evidence have suggested that CGRP and adrenomedullin could be ligands for ACKR3; however, classical direct binding to the receptor has not yet been convincingly demonstrated [2286].	–	–

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

Cholecystokinin receptors

G protein-coupled receptors → Cholecystokinin receptors

Overview: Cholecystokinin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CCK receptors [1747]**) are activated by the endogenous peptides cholecystokinin-8 (CCK-8 (*CCK*, P06307)), CCK-33 (*CCK*, P06307), CCK-58 (*CCK*, P06307) and gastrin (gastrin-17 (*GAST*, P01350)). There are only two distinct subtypes of CCK receptors, CCK_1 and CCK_2 receptors [1231, 2494], with some alternatively spliced forms most often identified in neoplastic cells. The CCK receptor subtypes are distinguished by their peptide selectivity, with the CCK_1 receptor requiring the carboxyl-terminal heptapeptide-amide that includes a sulfated tyrosine for high affinity and potency, while the CCK_2 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.

Further reading on Cholecystokinin receptors

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Rehfeld JF. (2017) Cholecystokinin-From Local Gut Hormone to Ubiquitous Messenger. *Front Endocrinol (Lausanne)* **8**: 47 [PMID:28450850]

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Nomenclature	CCK_1 receptor	CCK_2 receptor
HGNC, UniProt	*CCKAR*, P32238	*CCKBR*, P32239
Potency order of endogenous ligands	CCK-8 (*CCK*, P06307), CCK-58 (*CCK*, P06307), CCK-39 (*CCK*), CCK-33 (*CCK*, P06307) ≫ gastrin-17 (*GAST*, P01350), desulfated cholecystokinin-8 > CCK-4 (*CCK*, P06307)	CCK-8 (*CCK*, P06307), CCK-39 (*CCK*), CCK-33 (*CCK*, P06307), CCK-58 (*CCK*, P06307) ≥ gastrin-17 (*GAST*, P01350), desulfated cholecystokinin-8, CCK-4 (*CCK*, P06307)
Endogenous agonists	CCK-33 (*CCK*, P06307), CCK-39 (*CCK*), CCK-58 (*CCK*, P06307), CCK-8 (*CCK*, P06307)	desulfated cholecystokinin-8 [1340], gastrin-17 (*GAST*, P01350) [1002] – Mouse, CCK-4 (*CCK*, P06307) [1031], desulfated gastrin-14 (*GAST*, P01350), desulfated gastrin-17 (*GAST*, P01350), desulfated gastrin-34 (*GAST*, P01350), desulfated gastrin-71 (*GAST*, P01350), gastrin-14 (*GAST*, P01350), gastrin-34 (*GAST*, P01350), gastrin-71 (*GAST*, P01350)
Selective agonists	A-71623 [78] – Rat, JMV180 [1147], GW-5823 [915]	RB-400 [150] – Rat, PBC-264 [1050] – Rat
Antagonists	lintitript (pIC_{50} 8.3) [786]	–
Selective antagonists	devazepide (pIC_{50} 9.7) [1002] – Rat, T-0632 (pIC_{50} 9.6) [2321] – Rat, PD-140548 (pIC_{50} 8.6) [2178] – Rat, lorglumide (pIC_{50} 6.7–8.2) [1002, 1037] – Rat	YF-476 (pIC_{50} 9.7) [232, 2309], GV150013 (pIC_{50} 9.4) [2403], L-740093 (pIC_{50} 9.2) [1737], YM-022 (pIC_{50} 9.2) [1737], JNJ-26070109 (pIC_{50} 8.5) [1654], L-365260 (pIC_{50} 8.4) [1340], RP73870 (pIC_{50} 8) [1405] – Rat, LY262691 (pIC_{50} 7.5) [1949] – Rat
Labelled ligands	[^{3}H]devazepide (Antagonist) (pK_d 9.7) [353], [^{125}I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [1900]	[^{3}H]PD140376 (Antagonist) (pK_i 9.7–10) [1006] – Guinea pig, [^{125}I]PD142308 (Antagonist) (pK_d 9.6) [972] – Guinea pig, [^{125}I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [1900], [^{125}I]gastrin (Agonist), [^{3}H]gastrin (Agonist), [^{3}H]L365260 (Antagonist) (pK_d 8.2–8.5) [1737], [^{125}I]-BDZ_2 (Antagonist) (pK_i 8.4) [30]

Comments: While a cancer-specific CCK receptor has been postulated to exist, which also might be responsive to incompletely processed forms of CCK (Gly-extended forms), this has never been isolated. An alternatively spliced form of the CCK_2 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 [2198], but it is not clear that this receptor splice form plays a special role in carcinogenesis. Another alternative splicing event for the CCK_2 receptor was reported [2215], 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.

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 [2099]**), are GPCRs originally identified in *Drosophila* [345], which are highly conserved across species. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it mediates effects in the Hedgehog signaling pathway [2099]. FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription regulator β-catenin (*CTNNB1*, P35222) or being β-catenin-independent (often referred to as canonical *vs.* non-canonical WNT/FZD signalling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors *LRP5* (O75197) and *LRP6* (O75581), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β-catenin and subsequently its translocation to the nucleus. β-catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors. WNT/β-catenin-independent signalling can also be activated by FZD subtype-specific WNT surrogates [1574]. 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 [533, 1858, 2100], the elevation of intracellular calcium [2191], activation of cGMP-specific PDE6 [25] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [860]. 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 [1242, 2081, 2568, 2569]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling towards planar-cell-polarity-like pathways. Importantly, FZDs exist in at least two distinct conformational states that regulate pathway selection [2569]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [372], as well as for β-catenin-dependent [279] and -independent [280, 1168] signalling. The pattern of cell signalling is complicated by the presence of additional ligands, which can enhance or inhibit FZD signalling (secreted Frizzled-related proteins (sFRP), Wnt-inhibitory factor (*WIF1*, Q9Y5W5) (WIF), sclerostin (*SOST*, Q9BQB4) or Dickkopf (DKK)), as well as modulatory (co)-receptors with Ryk, ROR1, ROR2 and Kremen, which may also function as independent signalling proteins.

Further reading on Class Frizzled GPCRs

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Nomenclature	FZD_1	FZD_2	FZD_3	FZD_4	FZD_5
HGNC, UniProt	*FZD1*, Q9UP38	*FZD2*, Q14332	*FZD3*, Q9NPG1	*FZD4*, Q9ULV1	*FZD5*, Q13467
Allosteric modulators	–	–	–	FzM1.8 (Negative) (pIC_{50} 5.5–7.8) [727], FzM1.8 (Positive) (pEC_{50} 6.4) [1980], FzM1 (Negative) (pIC_{50} 6.2) [727, 1980]	–
Antibodies	vantictumab (Antagonist) (pIC_{50} ~9.1) [827]	vantictumab (Antagonist) (pIC_{50} ~9) [827]	–	–	vantictumab (Antagonist) (pIC_{50} ~9) [827]
Comments	–	–	–	–	IgG-2919 and IgG-2921 are FZD_5 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, FZD_5-dependent cells [2233].

Nomenclature	FZD_6	FZD_7	FZD_8	FZD_9	FZD_{10}
HGNC, UniProt	*FZD6*, O60353	*FZD7*, O75084	*FZD8*, Q9H461	*FZD9*, O00144	*FZD10*, Q9ULW2
Selective antagonists	–	Fz7-21 (pIC_{50} 7) [1736]	–	–	–
Allosteric modulators	–	–	carbamazepine (Negative) (pK_d 4.8) [2678]	–	–
Antibodies	–	vantictumab (Antagonist) (pIC_{50} ~9) [827]	vantictumab (Antagonist) (pIC_{50} ~8) [827]	–	–
Comments	SAG1.3 and purmorphamine have been described as weak partial agonists with varying potencies depending on a read-out [1242].	–	FZD8-Fc/OMP-54F28 is a FZD_8 antagonist [508].	–	Radio-labelled murine monoclonal antibody MAb 92-13 has been used to demonstrate the therapeutic potential of targeting FZD_{10}-positive tumours [682].

Nomenclature	SMO
HGNC, UniProt	*SMO*, Q99835
Agonists	SAG1.3 [366] – Mouse, purmorphamine [2179]
Antagonists	MRT-92 (pK_d 9.5) [955], SANT-1 (pK_i 7.7) [366] – Mouse, cyclopamine-KAAD (pIC_{50} 7.7) [2291] – Mouse, cyclopamine (pIC_{50} ~7) [2385] – Mouse
Selective antagonists	vismodegib (pK_i 7.8) [2482]
Allosteric modulators	GSA-10 (Positive) (pEC_{50} 5.9) [779]
Comments	SANT-3 and SANT-4 are SMO antagonists [366]. Cyclopamine-KAAD can act as an inverse agonist [2569].

Comments: There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. Understanding of the FZD and SMO coupling to G proteins is incomplete, but progress have been made [75, 520, 533, 1164, 1498, 1920, 1921, 1991, 2144, 2456, 2568]. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships [1162]. However, progress in understanding WNT-FZD interactions has been initiated with generation of eGFP-tagged WNT-3A [2292, 2527]. Development of pharmacological tools [1241] for SMO has been faciliated by successful determination of several SMO structures [296, 520, 994, 1920, 1921, 2480, 2481, 2511, 2671]. The recently solved FZD4 and FZD5 structures in apo state have provided first insights into FZD transmembrane organization [2380, 2620].

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 [2568]), Wnt-5b (*WNT5B*, Q9H1J7), Wnt-6 (*WNT6*, Q9Y6F9), Wnt-7a (*WNT7A*, O00755), Wnt-7b (*WNT7B*, P56706), Wnt-8a (*WNT8A*, Q9H1J5), Wnt-8b (*WNT8B*, Q93098), Wnt-9a (*WNT9A*, O14904) (also known as WNT-14), Wnt-9b (*WNT9B*, O14905) (also known as WNT-15 or WNT-14b), Wnt-10a (*WNT10A*, Q9GZT5), Wnt-10b (*WNT10B*, O00744) (also known as WNT-12), Wnt-11 (*WNT11*, O96014) and Wnt-16 (*WNT16*, Q9UBV4).

Extracellular proteins that interact with FZDs: norrin (*NDP*, Q00604), R-spondin-4 (*RSPO4*, Q2I0M5), sFRP-1 (*SFRP1*, Q8N474), sFRP-2 (*SFRP2*, Q96HF1), sFRP-3 (*FRZB*, Q92765), sFRP-4 (*SFRP4*, Q6FHJ7), sFRP-5 (*SFRP5*, Q6FHJ7).

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

Small exogenous ligands: Foxy-5 [2040], Box-5 [1064], UM206 [1282], and XWnt8 (P28026) also known as mini-Wnt8.

Ligands associated with SMO signalling: cholesterol, oxysterols [296, 1442, 1936].

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 [1201]**) 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, C5aR1 and C5aR2), causing cell recruitment and triggering cellular degranulation that contributes to local inflammation.

Further reading on Complement peptide receptors

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Coulthard LG *et al.* (2015) Is the complement activation product C3a a proinflammatory molecule? Re-evaluating the evidence and the myth. *J Immunol* **194**: 3542-8 [PMID:25848071]

Laumonnier Y *et al.* (2017) Novel insights into the expression pattern of anaphylatoxin receptors in mice and men. *Mol Immunol* **89**: 44-58 [PMID:28600003]

Li XX *et al.* (2019) The Complement Receptor C5aR2: A Powerful Modulator of Innate and Adaptive Immunity. *J Immunol* **202**: 3339-3348 [PMID:31160390]

Pandey S *et al.* (2020) Emerging Insights into the Structure and Function of Complement C5a Receptors. *Trends Biochem Sci* **45**: 693-705 [PMID:32402749]

Reichhardt MP *et al.* (2018) Intracellular complement activation-An alarm raising mechanism? *Semin Immunol* **38**: 54-62 [PMID:29631809]

Nomenclature	C3a receptor
HGNC, UniProt	*C3AR1*, Q16581
Potency order of endogenous ligands	C3a (*C3*, P01024) > C5a (*C5*, P01031) [48]
Agonists	compound 17 [1965], compound 21 [1964], casoxin C [2294, 2642], albutensin A [2296, 2642], oryzatensin [1078, 2295, 2642]
Antagonists	JR14a (pIC_{50} 8) [2018], SB290157 (SB290157 has also been reported to have agonist properties at the C3a receptor) (pIC_{50} 7.6) [47, 1379]
Labelled ligands	[^{125}I]C3a (human) (Agonist) [357], Eu-DTPA-hC3a (Agonist) [473]
Comments	Dual pro- and anti-inflammatory roles of C3aR have been reported in pathological conditions [453]. In particular, C3 and the C3aR have been identified as being involved in regulating the intestinal immune response during chronic colitis [2270, 2517]. Protective roles of C3aR were reported for traumatic spinal cord injury [246], melanoma [1681] and systemic lupus erythematosus [1165]. C3a-C3aR signalling inhibits neural progenitor cell proliferation during neurodevelopment, playing a critical role in the normal development of the mammalian brain [370].

Nomenclature	$C5a_1$ receptor	$C5a_2$ receptor
HGNC, UniProt	*C5AR1*, P21730	*C5AR2*, Q9P296
Potency order of endogenous ligands	C5a (*C5*, P01031), C5a des-Arg (*C5*) > C3a (*C3*, P01024) [48]	–
Endogenous agonists	ribosomal protein S19 (*RPS19*, P39019) [2600]	C5a (*C5*, P01031) [301]
Agonists	NDT9513727 (Inverse agonist) [261], *N*-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO_2H [1132, 1228], lactomedin 1 [1808, 2506, 2642]	$C5a^{pep}$ (Partial agonist) [1808]
Selective agonists	–	P59 (Biased agonist) [461], P32 (Biased agonist) [461]
Antagonists	avacopan (pIC_{50} 9.7) [146], W54011 (pK_i 8.7) [2263], DF2593A (pIC_{50} 8.3) [1642], AcPhe-Orn-Pro-D-Cha-Trp-Arg (pIC_{50} 7.9) [2559], PMX205 (pIC_{50} 7.5) [1381, 1507], *N*-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO_2H (pIC_{50} 7.2) [1228]	–
Labelled ligands	$[^{125}I]$C5a (human) (Agonist) [999]	$[^{125}I]$C5a (human) (Agonist)
Comments	$C5a_1$ receptor is currently referred to as C5aR1 in the literature. $C5a_1$ has been an attractive target for pharmacological inhibition to treat a myriad of inflammatory and neurodegenerative diseases. Several $C5a_1$ antagonists have been reported that have progressed to various stages of clinical development [887, 1381, 1621], although none are yet approved for use in humans. The non-peptide C5aR1 inhibitor CCX168 (Avacopan®), developed by ChemoCentryx, is currently the most clinically advanced $C5aR_1$ inhibitor [146]. The drug has recently completed a Phase III clinical trial for ANCA-associated vasculitis under a concomitant treatment scheme with rituximab or cyclophosphamide/azathioprine (NCT02994927). Considering the potential benefits of blocking the C5a-C5aR1 axis to limit myeloid infiltration and prevent excessive lung inflammation in Coronavirus disease 2019 (COVID-19) [323], the two anti-C5a/C5aR1 blocking antibodies, avdoralimab (IPH5401) and vilobelimab (IFX-1), are currently being studied in patients with COVID-19 severe pneumonia (NCT04371367 and NCT04333420 for IPH5401 and IFX-1, respectively) [2449].	$C5a_2$ receptor is commonly referred to as C5L2 and C5aR2 in the literature. $C5a_2$ was traditionally recognized as a decoy receptor for C5a, as it has no reported G protein signalling capacity. New research however, shows C5aR2 is capable of mediating its own set of signalling events and immunomodulatory actions, not only towards C5aR1 but also other complement, chemokine and pattern recognition receptors [1378].

Comments: SB290157 has also been reported to have agonist properties at the C3a receptor [1379, 1525]. The chemoattractant receptor $C5a_2$ (also known as GPR77, C5L2) binds C5a and has putative roles in either opposing or promoting inflammatory responses [301, 701, 720, 1380, 1809]. Binding to this site may be displaced with the rank order C5a des-Arg (*C5*)> C5a (*C5*, P01031) [301, 1781] while there is controversy over the ability of C3a (*C3*, P01024) and C3a des Arg (*C3*, P01024) to compete [967, 1106, 1107, 1781]. $C5a_2$ appears to lack G protein signalling and has been termed a decoy receptor [2107]. However, $C5a_2$ does recruit β-arrestin 2 after ligand binding, which might provide a signaling pathway for this receptor [112, 2417], and forms heteromers with $C5a_1$. C5a, but not C5a-des Arg, induces upregulation of heteromer formation between complement C5a receptors $C5a_1$ and $C5a_2$ [460]. There are also reports of pro-inflammatory activity of $C5a_2$, mediated by HMGB1, likely through AKT and MAPK signalling pathways (reviewed in [1375, 2669]). In T cells it has been shown that $C5a_1$ and $C5a_2$ 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 $C5a_2$), can affect the final cellular response [64]. Recently in human macrophages, $C5a_2$ was observed to modulate multiple complement and chemokine receptor-mediated signalling and pattern recognition-induced cytokine responses, independent of $C5a_1$ [1378]. In addition, $C5a_2$ is reported to act as a C5a transporter on endothelial cells, and is required for the transport of C5a into the vessel lumen and the subsequent neutrophil arrest in arthritis [1600].

Corticotropin-releasing factor receptors

Overview: Corticotropin-releasing factor (CRF, **nomenclature as agreed by the NC-IUPHAR subcommittee on Corticotropin-releasing Factor Receptors [885]**) receptors are activated by the endogenous peptides corticotrophin-releasing hormone (*CRH*, P06850), a 41 amino-acid peptide, urocortin 1 (*UCN*, P55089), 40 amino-acids, urocortin 2 (*UCN2*, Q96RP3), 38 amino-acids and urocortin 3 (*UCN3*, Q969E3), 38 amino-acids. CRF_1 and CRF_2 receptors are activated non-selectively by CRH and UCN. CRF_2 receptors are selectively activated by UCN2 and UCN3. Binding to CRF receptors can be conducted using radioligands $[^{125}I]Tyr^0$-CRF or $[^{125}I]Tyr^0$-sauvagine with K_d values of 0.1-0.4 nM. CRF_1 and CRF_2 receptors are non-selectively antagonized by α-helical CRF, D-Phe-CRF-(12-41) and astressin. CRF_1 receptors are selectively antagonized by small molecules NBI27914, R121919, antalarmin, CP 154,526, CP 376,395. CRF_2 receptors are selectively antagonized by antisauvagine and astressin 2B.

Further reading on Corticotropin-releasing factor receptors

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

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**: 21-6 [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]

Slater PG *et al.* (2016) Corticotropin-Releasing Factor Receptors and Their Interacting Proteins: Functional Consequences. *Mol Pharmacol* **90**: 627-632 [PMID:27612874]

Zelenay V *et al.* (2017) Structures of the First Extracellular Domain of CRF Receptors. *Curr Mol Pharmacol* **10**: 318-324 [PMID:28103782]

Nomenclature	CRF_1 receptor	CRF_2 receptor
HGNC, UniProt	*CRHR1*, P34998	*CRHR2*, Q13324
Endogenous agonists	urocortin 1 (*UCN*, P55089) [481, 483, 546], corticotrophin-releasing hormone (*CRH*, P06850) [369, 480, 483, 546, 1805, 2438]	urocortin 2 (*UCN2*, Q96RP3) [481], urocortin 3 (*UCN3*, Q969E3) [481]
Antagonists	SSR125543A (pK_i 8.7) [821], astressin (pK_i 8.7) [1995]	astressin (pIC_{50} 9.2) [1993]
Selective antagonists	CP 154,526 (pIC_{50} 9.3–10.4) [1446] – Rat, DMP696 (pK_i 8.3–9) [898], NBI27914 (pK_i 8.3–9) [361], R121919 (pK_i 8.3–9) [2692], antalarmin (pK_i 8.3–9) [2510], NBI-35965 (pK_i 8.4) [1592] – Rat, CP 376,395 (pIC_{50} 8.3) [375] – Rat, CRA1000 (pIC_{50} 6.4–7.1) [343]	antisauvagine (pK_d 8.8–9.6) [483], K41498 (pK_i 9.2) [1306], astressin 2B (pIC_{50} 8.9) [1993], K31440 (pK_i 8.7–8.8) [2023]

Comments: A CRF binding protein has been identified (*CRHBP*, P24387) to which both corticotrophin-releasing hormone (*CRH*, P06850) and urocortin 1 (*UCN*, P55089) bind with high affinities, which has been suggested to bind and inactivate circulating corticotrophin-releasing hormone (*CRH*, P06850) [490, 1850].

Dopamine receptors

G protein-coupled receptors → Dopamine receptors

Overview: Dopamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Dopamine Receptors [2101]**) are commonly divided into D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) families, where the endogenous agonist is dopamine.

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]

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

Moritz AE *et al.* (2018) Advances and challenges in the search for D_2 and D_3 dopamine receptor-selective compounds. *Cell Signal* **41**: 75-81 [PMID:28716664]

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

Urs NM *et al.* (2017) New Concepts in Dopamine D_2 Receptor Biased Signaling and Implications for Schizophrenia Therapy. *Biol Psychiatry* **81**: 78-85 [PMID:27832841]

Nomenclature	D_1 receptor	D_2 receptor
HGNC, UniProt	*DRD1*, P21728	*DRD2*, P14416
Sub/family-selective labelled ligands	[^{125}I]SCH23982 (Antagonist) (pK_d 9.5) [509], [^{3}H]SCH-23390 (Antagonist) (pK_d 9.5) [2682]	[^{3}H]spiperone (Antagonist) (pK_d 10.2) [283, 953, 2680] – Rat
Endogenous agonists	dopamine [2269, 2353]	dopamine [288, 671, 2068]
Agonists	fenoldopam [2353]	rotigotine [534], cabergoline (Partial agonist) [1584], aripiprazole (Partial agonist) [2651], bromocriptine [671, 1584, 2068], MLS1547 (Biased agonist) [670], ropinirole [906], apomorphine (Partial agonist) [288, 671, 1584, 2068, 2209], pramipexole [1579, 2068], benzquinamide [797]
Sub/family-selective agonists	A68930 [1716], SKF-38393 (Partial agonist) [2269, 2353]	quinpirole [288, 1579, 1824, 2209, 2211, 2421]
Selective agonists	SKF-83959 (Biased agonist) [440], A77636 [2034], SKF-81297 [53] – Rat	sumanirole [1544]
Antagonists	flupentixol (pK_i 7–8.4) [2269, 2353]	blonanserin (pK_i 9.9) [1761], pipotiazine (pK_i 9.7) [2210], perphenazine (pK_i 8.9–9.6) [1251, 2115], risperidone (pK_i 9.4) [73], perospirone (pK_i 9.2) [2116], trifluoperazine (pK_i 8.9–9) [1251, 2117], quetiapine (pK_i 7.2) [73]
Sub/family-selective antagonists	SCH-23390 (pK_i 7.4–9.5) [2269, 2353], SKF-83566 (pK_i 9.5) [2269], ecopipam (pK_i 8.3) [2354]	haloperidol (pK_i 7.4–8.8) [671, 1462, 1579, 2209, 2354]
Selective antagonists	–	L-741,626 (pK_i 7.9–8.5) [811, 1265], domperidone (pK_i 7.9–8.4) [671, 2209], raclopride (pK_i 8) [1586], ML321 (pK_i 7) [2584, 2585]
Labelled ligands	–	[^{3}H]raclopride (Antagonist) (pK_d 8.9) [1216] – Rat

Nomenclature	D_3 receptor	D_4 receptor	D_5 receptor
HGNC, UniProt	*DRD3*, P35462	*DRD4*, P21917	*DRD5*, P21918
Sub/family-selective labelled ligands	–	[^{3}H]spiperone (Antagonist) (pK_d 9.5) [930, 2421]	[^{3}H]SCH-23390 (Antagonist) (pK_d 9.2) [1978]
Endogenous agonists	dopamine [288, 671, 2068, 2211]	dopamine [2421]	dopamine [2269]
Agonists	pramipexole [1579, 2068], bromocriptine (Partial agonist) [671, 1584, 2068], ropinirole [906], apomorphine (Partial agonist) [288, 671, 1584, 2068, 2209]	apomorphine (Partial agonist) [1584]	–
Sub/family-selective agonists	quinpirole [288, 1579, 1586, 1824, 2068, 2209, 2211, 2421]	quinpirole [1584, 1824, 2421]	A68930 [1716]
Selective agonists	PD 128907 [1914, 2068]	PD168,077 (Partial agonist) [1233] – Rat, A412997 [1632] – Rat, A412997 [1632]	–
Antagonists	perospirone (pK_i 9.6) [2209], sertindole (pK_i 8–8.8) [73, 2096, 2115], prochlorperazine (pK_i 8.4) [84], (-)-sulpiride (pK_i 6.7–7.7) [671, 2209, 2319], loxapine (pK_i 7.7) [2115], domperidone (pK_i 7.1–7.6) [671, 2209], promazine (pK_i 6.8) [289]	perospirone (pK_i 10.1) [2118], sertindole (pK_i 7.8–9.1) [289, 2115, 2117, 2118], sonepiprazole (pK_i 8.9) [2086], loxapine (pK_i 8.1) [2117]	–
Sub/family-selective antagonists	haloperidol (pK_i 7.5–8.6) [671, 2136, 2209, 2354]	haloperidol (pK_i 8.7–8.8) [1284, 2136, 2354]	SCH-23390 (pK_i 7.5–9.5) [2269], SKF-83566 (pK_i 9.4) [2269], ecopipam (pK_i 8.3) [2269]
Selective antagonists	S33084 (pK_i 9.6) [1583], nafadotride (pK_i 9.5) [2069], PG01037 (pK_i 9.2) [812], NGB 2904 (pK_i 8.8) [2580], SB 277011-A (pK_i 8) [1962], (+)-S-14297 (pK_i 6.9–7.9) [1581, 1586]	L745870 (pK_i 9.4) [1265], A-381393 (pK_i 8.8) [1690], L741742 (pK_i 8.5) [2019], ML398 (pK_i 7.4) [166]	–
Selective allosteric modulators	SB269652 (Negative) (pK_i ~9) [687]	–	–
Labelled ligands	[^{3}H]spiperone (Antagonist) (pK_d 9.9) [953, 2680] – Rat, [^{3}H]7-OH-DPAT (Agonist) [1979], [^{3}H]PD128907 (Agonist) [32]	[^{125}I]L750667 (Antagonist) (pK_d 9.8) [1824], [^{3}H]NGD941 (Antagonist) (pK_d 8.3) [1905]	[^{125}I]SCH23982 (Antagonist) (pK_d 9.1)

Comments: The selectivity of many of these agents is less than two orders of magnitude. [^{3}H]raclopride exhibits similar high affinity for D_2 and D_3 receptors (low affinity for D_4), but has been used to label D_2 receptors in the presence of a D_3-selective antagonist. [^{3}H]7-OH-DPAT has similar affinity for D_2 and D_3 receptors, but labels only D_3 receptors in the absence of divalent cations. The pharmacological profile of the D_5 receptor is similar to, yet distinct from, that of the D_1 receptor. The splice variants of the D_2 receptor are commonly termed D_{2S} and D_{2L} (short and long). The *DRD4* gene encoding the D_4 receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

Endothelin receptors

G protein-coupled receptors → Endothelin receptors

Overview: Endothelin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Endothelin Receptors [484]**) 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)).

Further reading on Endothelin receptors

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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]
Davenport AP *et al.* (2018) New drugs and emerging therapeutic targets in the endothelin signaling pathway and prospects for personalized precision medicine. *Physiol Res* **67**: S37-S54 [PMID:29947527]
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]

Nomenclature	ET_A receptor	ET_B receptor
HGNC, UniProt	*EDNRA*, P25101	*EDNRB*, P24530
Potency order of endogenous ligands	endothelin-1 (*EDN1*, P05305) = endothelin-2 (*EDN2*, P20800) > endothelin-3 (*EDN3*, P14138) [1475]	endothelin-1 (*EDN1*, P05305) = endothelin-2 (*EDN2*, P20800), endothelin-3 (*EDN3*, P14138) [2045]
Selective agonists	–	sarafotoxin S6c [1257, 2027], BQ 3020 [1974], [Ala^{1,3,11,15}]ET-1 [1609], IRL 1620 [2499]
Antagonists	SB209670 (pK_B 9.4) [593] – Rat, TAK 044 (pA_2 8.4) [2502] – Rat, bosentan (pA_2 7.2) [429] – Rat	SB209670 (pK_B 9.4) [593] – Rat, TAK 044 (pA_2 8.4) [2502] – Rat, bosentan (pK_i 7.1) [1677]
Selective antagonists	macitentan (pIC$_{50}$ 9.3) [206], sitaxsentan (pA_2 8) [2570], FR139317 (Inverse agonist) (pIC$_{50}$ 7.3–7.9) [1475], BQ123 (pA_2 6.9–7.4) [1475], ambrisentan (pA_2 7.1) [207]	K-8794 (pIC$_{50}$ 8.2) [2150], A192621 (pK_d 8.1) [2453], BQ788 (pK_d 7.9–8) [2027], IRL 2500 (pK_d 7.2) [2027], Ro 46-8443 (pIC$_{50}$ 7.2) [249]
Labelled ligands	[^{125}I]PD164333 (Antagonist) (pK_d 9.6–9.8) [487], [^{3}H]S0139 (Antagonist) (pK_d 9.2), [^{125}I]PD151242 (Antagonist) (pK_d 9–9.1) [488], [^{3}H]BQ123 (Antagonist) (pK_d 8.5) [1015]	[^{125}I]IRL1620 (Agonist) [1691], [^{125}I]BQ3020 (Agonist) [869, 1609, 1857], [^{125}I][Ala^{1,3,11,15}]ET-1 (Agonist) [1609]

Comments: Splice variants of the ET_A receptor have been identified in rat pituitary cells; one of these, ET_AR-C13, appeared to show loss of function with comparable plasma membrane expression to wild type receptor [881]. Subtypes of the ET_B receptor have been proposed, although gene disruption studies in mice suggest that only a single gene product exists [1602]. Crystal structures of the ET_B receptor bound to the antagonist bosentan and ET_B selective analogue K-8794 [2150] and selective ET_B agonists endothelin-3 (*EDN3*, P14138) and IRL 1620 [2149] have been reported.

G protein-coupled estrogen receptor

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

Overview: The G protein-coupled estrogen receptor (GPER, **nomenclature as agreed by the NC-IUPHAR Subcommittee on the G protein-coupled estrogen receptor [1911]**) was identified following observations of estrogen-evoked cyclic AMP signalling in breast cancer cells [74], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [314]. There are observations of both cell-surface and intracellular expression of the GPER receptor [1969, 2344]. Selective agonist/ antagonists for GPER have been characterized [1911]. Antagonists of the nuclear estrogen receptor, such as fulvestrant [637], tamoxifen [1969, 2344] and raloxifene [1865], as well as the flavonoid 'phytoestrogens' genistein and quercetin [1474], are agonists of GPER. A complete review of GPER pharmacology has been published [1911]. The roles of GPER in physiological systems throughout the body (cardiovascular, metabolic, endocrine, immune, reproductive) and in cancer have also been reviewed [636, 1298, 1567, 1911, 1912]. The GPER-selective agonist G-1 is currently in Phase I/II clinical trials for cancer (NCT04130516).

Further reading on G protein-coupled estrogen receptor

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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]

Nomenclature	GPER
HGNC, UniProt	*GPER1*, Q99527
Endogenous agonists	17β-estradiol [1969, 2344]
Agonists	fulvestrant [2344], raloxifene [1865], 4-hydroxytamoxifen [1969]
Selective agonists	G-1 [209]
Selective antagonists	G36 (pIC_{50} 6.8–6.9) [518], G15 (pIC_{50} 6.7) [517]
Labelled ligands	[^{3}H]17β-estradiol (Agonist) [2344]

Formylpeptide receptors

G protein-coupled receptors → Formylpeptide receptors

Overview: The formylpeptide receptors (**nomenclature agreed by the NC-IUPHAR Subcommittee on the formylpeptide receptor family [2628]**) respond to exogenous ligands such as the bacterial product fMet-Leu-Phe (fMLP) and endogenous ligands such as lipoxin A_4 (LXA_4), 15-*epi*-lipoxin A_4, annexin I (*ANXA1*, P04083) , cathepsin G (*CTSG*, P08311), amyloid β42, serum amyloid A and spinorphin, derived from β-haemoglobin (*HBB*, P68871). FPR1 also serves as a plague receptor for selective destruction of human immune cells by *Y. pestis* [1794]. The FPR1/2 agonists 'compound 17b' and 'compound 43' have shown cardiac protective functions [705, 1922].

Further reading on Formylpeptide receptors

Dahlgren C *et al.* (2016) Basic characteristics of the neutrophil receptors that recognize formylated peptides, a danger-associated molecular pattern generated by bacteria and mitochondria. *Biochem Pharmacol* **114**: 22-39 [PMID:27131862]

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]

Krepel SA *et al.* (2019) Chemotactic Ligands that Activate G-Protein-Coupled Formylpeptide Receptors. *Int J Mol Sci* **20**: [PMID:31336833]

Perretti M *et al.* (2020) Formyl peptide receptor type 2 agonists to kick-start resolution pharmacology. *Br J Pharmacol* **177**: 4595-4600 [PMID:32954491]

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. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev* **61**: 119-61 [PMID:19498085]

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) [1320, 2266]	LXA_4 = aspirin triggered lipoxin A4 = ATLa2 = resolvin D1 > LTC_4 = LTD_4 ≫ 15-deoxy-LXA4 ≫ fMet-Leu-Phe [427, 641, 643, 805, 2298]	–
Endogenous agonists	–	LXA_4 [1248], resolvin D1 [1248], aspirin-triggered resolvin D1 [1247], aspirin triggered lipoxin A4	F2L (*HEBP1*, Q9NRV9) [1580]
Agonists	fMet-Leu-Phe [673, 2163]	–	–
Selective agonists	–	ATLa2 [820]	–
Endogenous antagonists	spinorphin (pIC_{50} 4.3) [1384, 1676]	–	–
Antagonists	t-Boc-FLFLF (pK_i 6–6.5) [2522]	–	–
Selective antagonists	cyclosporin H (pK_i 6.1–7.1) [2522, 2607]	WRWWWW (pIC_{50} 6.6) [101], t-Boc-FLFLF (pIC_{50} 4.3–6) [672, 2234, 2474]	–
Labelled ligands	$[^3H]$fMet-Leu-Phe (Agonist) [1229]	$[^3H]LXA_4$ (Agonist) [641, 642]	–
Comments	A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [896].	–	–

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

FPR1 has been reported to be the plague receptor on host immune cells [1794]. By interacting with LcrV, the needle cap protein of the type III secretion system of *Y. pestis*, FPR1 serves to promote translocation of virulent factors of the bacteria. The R190W mutation of FPR1 confers resistance to this function of *Y. pestis*. Several FPR1/2 agonists including 'compound 17b' and 'compound 43' have been shown to display cardiac protective functions in mouse models of myocardial ischemia-reperfusion injury [705, 1922]. Studies have been conducted to explore the mechanisms by which FPR2 mediates both inflammatory and anti-inflammatory signaling in a ligand-dependent manner. The status of FPR2 dimerization is a determining factor for ligand-specific conformational changes leading to biased signaling [442]. There is also a report on ligand concentration-dependent dual modulation of FPR2 by lipoxin A_4 for receptor-activation *vs.* anti-inflammatory activities [723]. Some FPR2 ligands may display allosteric modulatory effects that cause changes in FPR2 conformational states and receptor signaling [2664]. The 3-D structure of FPR2 has been solved by the use of cryo-electron microscopy [2690] and receptor protein crystallization [371]. The FPR2 structure reveals a large binding pocket that can accommodate several ligands of different shapes and sizes.

Free fatty acid receptors

Overview: Free fatty acid receptors (FFA, **nomenclature as agreed by the NC-IUPHAR Subcommittee on free fatty acid receptors [485, 2243]**) 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 [257, 1032, 1236] and FFA4 receptors [941, 1009, 1767], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA2 [266, 1319, 1738] and FFA3 [266, 1319] receptors. The crystal structure for agonist bound FFA1 has been described [2227].

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]

Nomenclature	FFA1 receptor	FFA2 receptor
HGNC, UniProt	*FFAR1*, O14842	*FFAR2*, O15552
Endogenous agonists	docosahexaenoic acid [257, 1032], α-linolenic acid [257, 1032, 1236], oleic acid [257, 1032, 1236], myristic acid [257, 1032, 1236]	propanoic acid [266, 1319, 1738, 2088], acetic acid [266, 1319, 1738, 2088], butyric acid [266, 1319, 1738, 2088], *trans*-2-methylcrotonic acid [2088], 1-methylcyclopropanecarboxylic acid [2088]
Agonists	HWL-088 [374]	–
Selective agonists	AMG-837 [1397], compound 4 [405], TUG-770 [404], TUG-905 [403], GW9508 (Partial agonist) [256], fasiglifam [1105, 1706, 2227, 2379]	TUG-1375 [859]
Selective antagonists	GW1100 (pIC_{50} 6) [256, 2242]	GLPG0974 (pIC_{50} 8.1) [1693, 1881], CATPB (pIC_{50} 6.5) [997]
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 [257, 1032, 1236]. Antagonist GW1100 is also an oxytocin receptor antagonist [256]. Fasiglifam, TUG-770 and GW9508 are approximately 100 fold selective for FFA1 over FFA4 [256, 404, 1706]. 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 [1397, 2590].	–

Nomenclature	FFA3 receptor	FFA4 receptor	*GPR42*
HGNC, UniProt	*FFAR3*, O14843	*FFAR4*, Q5NUL3	*GPR42*, O15529
Endogenous agonists	propanoic acid [266, 1319, 2088, 2589], butyric acid [266, 1319, 2088, 2589], 1-methylcyclopropanecarboxylic acid [2088]	α-linolenic acid [2155], myristic acid [2507], α-linolenic acid [2316] – Rat, oleic acid [2507]	–
Agonists	acetic acid [266, 1319, 2088, 2589]	–	–
Selective agonists	–	compound A [1766], TUG-891 [2155], NCG21 [2276]	–
Comments	Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [1181]. 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 [210, 996, 1456].	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 [406] with a small subset listed above. Compound A [PMID 24997608] exhibits more than 1000 fold selectivity [1766], and TUG-891 50-1000 fold selectivity for FFA4 over FFA1 [2155], dependent on the assay. NGC21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [2265].	–

Comments: Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [1631], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [2507]. The long FFA4 splice variant has not been identified in other primates or rodents to date [941, 1631].

GPR42 was originally described as a pseudogene within the family (ENSFM00250000002583), but the discovery of several polymorphisms suggests that some versions of GPR42 may be functional [1385]. *GPR84* is a structurally-unrelated G protein-coupled receptor which has been found to respond to medium chain fatty acids [2484].

$GABA_B$ receptors

G protein-coupled receptors → $GABA_B$ receptors

Overview: Functional $GABA_B$ receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on $GABA_B$ receptors [229, 1875]**) are formed from the heterodimerization of two similar 7TM subunits termed $GABA_{B1}$ and $GABA_{B2}$ [229, 596, 1874, 1875, 2396]. $GABA_B$ receptors are widespread in the CNS and regulate both pre- and postsynaptic activity. The $GABA_{B1}$ subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10-100-fold less than for the native receptor. Co-expression of $GABA_{B1}$ and $GABA_{B2}$ subunits allows transport of $GABA_{B1}$ to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca^{2+} channels (Ca_V2.1, Ca_V2.2), or inwardly rectifying potassium channels (Kir3) [171, 229, 230]. The $GABA_{B1}$ subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the $GABA_{B2}$ subunit mediates G protein-coupled signalling [229, 729, 731, 1874]. The cryo-electron microscopy structures of the human full-length $GABA_{B1}$-$GABA_{B2}$ heterodimer have been solved in the inactive apo state, two intermediate agonist-bound forms and an active state in which the heterodimer is bound to an agonist and a positive allosteric modulator [2141]. The positive allosteric modulator binds to the transmembrane dimerization interface and stabilizes the active state. Recent evidence indicates that higher order assemblies of $GABA_B$ receptor comprising dimers of heterodimers occur in recombinant expression systems and *in vivo* and that such complexes exhibit negative functional cooperativity between heterodimers [435, 1872]. Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the $GABA_{B2}$ subunit to impart altered signalling kinetics and agonist potency to the receptor complex [127, 2104, 2383] and are reviewed by [1876]. The molecular complexity of $GABA_B$ receptors is further increased through association with trafficking and effector proteins [2105] and reviewed by [1871]. The predominant $GABA_{B1a}$ and $GABA_{B1b}$ 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. $GABA_{B1a}$-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 $GABA_{B1b}$-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [1849, 2442]. Amyloid precursor protein (APP) and soluble APP (sAPP) bind to the N- terminal sushi domain of the $GABA_{B1a}$ isoform to regulate axonal trafficking of $GABA_B$ receptors and release of neurotransmitters [1982].

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**: 247-64 [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]

Nomenclature	$GABA_B$ receptor
Subunits	$GABA_{B1}$, $GABA_{B2}$, KCTD8 (Accessory protein), KCTD12 (Accessory protein), kctd12b (Accessory protein), KCTD16 (Accessory protein)
Agonists	CGP 44532 [678] – Rat, (-)-baclofen [678] – Rat, 3-APPA [946], baclofen [946, 2563], 3-APMPA [2563]
Antagonists	CGP 62349 (pK_i 8.5–8.9) [946, 2563], CGP 55845 (pK_i 7.8) [2563], SCH 50911 (pK_i 5.5–6) [946, 2563], CGP 35348 (pK_i 4.4) [2563], 2-hydroxy-saclofen (pIC_{50} 4.1) [1130] – Rat
Allosteric modulators	*rac*-BHFF (Positive) (pEC_{50} 6.6) [1489], GS39783 (Positive) (pK_B 4.7) [913, 2405], compound 14 (Negative) (pIC_{50} 4.4) [367], CGP7930 (Positive) [2404]
Labelled ligands	[^{3}H]CGP 54626 (Antagonist) (pK_i 9.1) [1090] – Rat, [^{3}H]CGP 62349 (Antagonist) (pK_d 9.1) [1139] – Rat, [^{125}I]CGP 64213 (Antagonist) (pK_d 9) [696] – Rat, [^{125}I]CGP 71872 (Antagonist) (pK_d 9) [1130] – Rat, [^{3}H](R)-(-)-baclofen (Agonist)

Subunits

Nomenclature	$GABA_{B1}$	$GABA_{B2}$
HGNC, UniProt	*GABBR1*, Q9UBS5	*GABBR2*, O75899

Comments: Potencies of agonists and antagonists listed in the table, quantified as IC_{50} values for the inhibition of [^{3}H]CGP27492 binding to rat cerebral cortex membranes, are from [229, 677, 678]. Radioligand K_D values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the $GABA_{B1}$ subunit [149]. CGP27492 (3-APPA), CGP35024 (3-APMPA) and CGP 44532 act as antagonists at human $GABA_A$ ρ1 receptors, with potencies in the low micromolar range [677]. In addition to the ligands listed in the table, Ca^{2+} binds to the VTM of the $GABA_{B1}$ subunit to act as a positive allosteric modulator of GABA [696]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 [2450] and (+)-BHFF [12, 171, 179, 677]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the $GABA_{B2}$ subunit [575, 1874]. In the presence of CGP7930 or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [677]. A negative allosteric modulator of $GABA_B$ activity has been reported [367]. 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 [602, 2407]. A similar phenotype has been found for $GABA_{B2}{}^{-/-}$ BALB/c mice [716].

Galanin receptors

G protein-coupled receptors → Galanin receptors

Overview: Galanin receptors (**provisional nomenclature as recommended by NC-IUPHAR [652]**) 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 [618]; 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 [167] and porcine galanin-5-29 [2170]) and N-terminally extended forms (*e.g.* N-terminally seven and nine residue elongated forms of porcine galanin [168, 2170]) have been reported. More recently, the newly-identified peptide, spexin (SPX), has been reported to activate human GAL2 and GAL3 (but not GAL1) receptors in heterologous expression systems; and to alter GAL2/3 receptor-related behaviours in animals [1167].

Further reading on Galanin receptors

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

Nomenclature	GAL_1 receptor	GAL_2 receptor	GAL_3 receptor
HGNC, UniProt	*GALR1*, P47211	*GALR2*, O43603	*GALR3*, O60755
Potency order of endogenous ligands	galanin (*GAL*, P22466) > galanin-like peptide (*GALP*, Q9UBC7) [1773]	galanin-like peptide (*GALP*, Q9UBC7) ≥ galanin (*GAL*, P22466) [1773]	galanin-like peptide (*GALP*, Q9UBC7) > galanin (*GAL*, P22466) [1291]
Endogenous agonists	–	spexin-1 (*SPX*, Q9BT56) [1167]	spexin-1 (*SPX*, Q9BT56) [1167]
Agonists	–	galanin(2-29) (rat/mouse) [1810, 2488, 2489, 2490] – Rat	–
Selective agonists	–	[D-Trp^2]galanin-(1-29) [2199] – Rat, Qu-SPX [1341]	–
Selective antagonists	2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC_{50} 5.6) [2111]	M871 (pK_i 7.9) [2213]	SNAP 398299 (pK_i 8.3) [1224, 1225, 2280], SNAP 37889 (pK_i 7.8–7.8) [1224, 1225, 2280]
Selective allosteric modulators	–	CYM2503 (Positive) (pEC_{50} 9.2) [1439] – Rat	–
Labelled ligands	[^{125}I][Tyr^{26}]galanin (human) (Agonist) [649], [^{125}I][Tyr^{26}]galanin (human) (Agonist) [649]	[^{125}I][Tyr^{26}]galanin (human) (Agonist) [2489] – Rat, [^{125}I]spexin-1 (Agonist) [1167]	[^{125}I][Tyr^{26}]galanin (pig) (Agonist) [221, 2200], [^{125}I]spexin-1 (Agonist) [1167]
Comments	–	The CYM2503 PAM potentiates the anticonvulsant activity of endogenous galanin in mouse seizure models [1439]. Activation and binding potency of spexin at human GAL_2 receptor is less than galanin (GAL) [1167].	Activation and binding potency of spexin at human GAL_3 receptor is higher than galanin (GAL) [1167].

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 [1438]. [^{125}I]-[Tyr^{26}]galanin binds to all three subtypes with K_d values generally reported to range from 0.05 to 1 nM, depending on the assay conditions used [649, 2183, 2199, 2200, 2489]. 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 [813, 2579]. 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 [2394], spinal cord [2542], locus coeruleus, hippocampus [125] and hypothalamus [126, 1349], but exhibit agonist activity at some peripheral sites [126, 813]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL_1 receptors expressed endogenously in Bowes human melanoma cells [1773], and at heterologously expressed recombinant GAL_1, GAL_2 and GAL_3 receptors [649, 2199, 2200]. Further studies described the synthesis of a series of novel, systemically-active, galanin analogues, with modest preferential binding at the GAL_2 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 [2036]. More recent studies have identified synthetic spexin (SPX)-based peptides that are selective GAL_2 receptor agonists [1341, 1972].

Ghrelin receptor

G protein-coupled receptors → Ghrelin receptor

Overview: The ghrelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [486]**) is activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (*GHRL*, Q9UBU3). The human gene encoding the precursor peptide has 83% sequence homology to rat prepro-ghrelin, although the mature peptides from rat and human differ by only two amino acids [1528]. Alternative splicing results in the formation of a second peptide, [des-Gln^{14}]ghrelin (*GHRL*, Q9UBU3) with equipotent biological activity [974]. A unique post-translational modification (octanoylation of Ser^3, catalysed by ghrelin O-acyltransferase (*MBOAT4*, Q96T53) [2613] 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 [1220]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [142], 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 [964]. An endogenous antagonist and inverse agonist called Liver enriched antimicrobial peptide 2 (Leap2), expressed primarily in hepatocytes and in enterocytes of the proximal intestine [722, 1454] inhibits ghrelin receptor-induced GH secretion and food intake [722]. The secretion of Leap2 and ghrelin is inversely regulated under various metabolic conditions [1496]. In cell systems, the ghrelin receptor is constitutively active [965], 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 [1811].

Further reading on Ghrelin receptor

Andrews ZB. (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]

Nomenclature	ghrelin receptor
HGNC, UniProt	*GHSR*, Q92847
Potency order of endogenous ligands	ghrelin (*GHRL*, Q9UBU3) = [des-Gln^{14}]ghrelin (*GHRL*, Q9UBU3) [141, 1528]
Antagonists	liver enriched antimicrobial peptide 2 (*LEAP2*, Q969E1) (pIC$_{50}$ 8.2) [722]
Selective antagonists	GSK1614343 (pIC$_{50}$ 8.4) [2037], GSK1614343 (pK_B 8) [1847] – Rat
Labelled ligands	[^{125}I][His^9]ghrelin (human) (Agonist) [1129], [^{125}I][Tyr^4]ghrelin (human) (Agonist) [1659]

Comments: [des-octanoyl]ghrelin (*GHRL*, Q9UBU3) has been shown to bind (as [^{125}I]Tyr^4-des-octanoyl-ghrelin) and have effects in the cardiovascular system [141], which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified ([D-Arg^1,D-Phe^5,D-Trp^{7,9},Leu^{11}]substance P, pD_2 8.3; [962]). Ulimorelin, described as a ghrelin receptor agonist (pK_i 7.8 and pD_2 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 [663]. Similar discrimination of ghrelin receptor mediated physiological functions can be obtained by activation of distinct signaling pathways [1562]. A number of selective antagonists have been reported, including peptidomimetic [1658] and non-peptide small molecules including GSK1614343 [1831, 1847, 2037].

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 [1539]**) are activated by the endogenous peptide (27-44 aa) hormones glucagon (*GCG*, P01275), glucagon-like peptide 1 (*GCG*, P01275), glucagon-like peptide 2 (*GCG*, P01275), glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide (*GIP*, P09681)), GHRH (*GHRH*, P01286) and secretin (*SCT*, P09683). One common precursor (*GCG*) generates glucagon (*GCG*, P01275), glucagon-like peptide 1 (*GCG*, P01275) and glucagon-like peptide 2 (*GCG*, P01275) peptides [1025]. For a recent review on the current understanding of the structures of GLP-1 and GLP-1R, the molecular basis of their interaction, and the associated signaling events, see de Graaf et al., 2016 [789].

Further reading on Glucagon receptor family

Chang R *et al.* (2020) Cryo-electron microscopy structure of the glucagon receptor with a dual-agonist peptide. *J Biol Chem* **295**: 9313-9325 [PMID:32371397]

Dong M *et al.* (2020) Structure and dynamics of the active Gs-coupled human secretin receptor. *Nat Commun* **11**: 4137 [PMID:32811827]

Drucker DJ. (2019) The Discovery of GLP-2 and Development of Teduglutide for Short Bowel Syndrome. *ACS Pharmacol Transl Sci* **2**: 134-142 [PMID:32219218]

Holst JJ *et al.* (2020) GIP as a Therapeutic Target in Diabetes and Obesity: Insight From Incretin Co-agonists. *J Clin Endocrinol Metab* **105**: [PMID:32459834]

Liang YL *et al.* (2020) Toward a Structural Understanding of Class B GPCR Peptide Binding and Activation. *Mol Cell* **77**: 656-668.e5 [PMID:32004469]

Zhang X *et al.* (2020) Differential GLP-1R Binding and Activation by Peptide and Non-peptide Agonists. *Mol Cell* **80**: 485-500.e7 [PMID:33027691]

Zhou F *et al.* (2020) Structural basis for activation of the growth hormone-releasing hormone receptor. *Nat Commun* **11**: 5205 [PMID:33060564]

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) [2452]	glucagon-like peptide 1-(7-36) amide (*GCG*, P01275) [1095], glucagon-like peptide 1-(7-37) (*GCG*, P01275) [535]
Agonists	JI-38 [299], sermorelin	–	liraglutide [1207], lixisenatide [2524], WB4-24 [621]
Selective agonists	BIM28011 [458], tesamorelin	–	semaglutide [1301], exendin-4 [1595], exendin-4 [1095], exendin-3 (P20394) [1952]
Selective antagonists	JV-1-36 (pK_i 10.1–10.4) [2079, 2431, 2432] – Rat, JV-1-38 (pK_i 10.1) [2079, 2431, 2432] – Rat	[Pro^3]GIP [719] – Mouse	exendin-(9-39) (pK_i 8.1) [1095], GLP-1-(9-36) (pIC$_{50}$ 6.9) [1625] – Rat, T-0632 (pIC$_{50}$ 4.7) [2352]
Labelled ligands	[^{125}I]GHRH (human) (Agonist) [227] – Rat	[^{125}I]GIP (human) (Agonist) [694] – Rat	[^{125}I]GLP-1-(7-36)-amide (Agonist) [1095], [^{125}I]exendin-(9-39) (Antagonist) (pK_d 8.3) [1095], [^{125}I]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) [2349]	glucagon (*GCG*, P01275) [1884]	secretin (*SCT*, P09683) [400]
Agonists	teduglutide [1552]	NNC1702 [2660]	–
Selective agonists	apraglutide [868, 2188]	–	–
Selective antagonists	–	L-168,049 (pIC_{50} 8.4) [324], adomeglivant (pK_i 8.2) [1138, 1142], des-His[1]-[Glu[9]]glucagon-NH_2 (pA_2 7.2) [2399, 2400] – Rat, NNC 92-1687 (pK_i 5) [1466], BAY27-9955 [1859]	[$(CH_2NH)^{4,5}$]secretin (pK_i 5.3) [831]
Labelled ligands	–	[^{125}I]glucagon (human, mouse, rat) (Agonist)	[^{125}I](Tyr[10])secretin-27 (rat) (Agonist) [2395] – Rat

Comments: The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems [408], although the physiological significance of this has yet to be established.

Glycoprotein hormone receptors

G protein-coupled receptors → Glycoprotein hormone receptors

Overview: Glycoprotein hormone receptors (**provisional nomenclature [652]**) are activated by a non-covalent heterodimeric glycoprotein made up of a common α chain (glycoprotein hormone common alpha subunit (*CGA*, P01215) *CGA*, P01215), with a unique β chain that confers the biological specificity to FSH (*CGA FSHB*, P01215 P01225), LH (*CGA 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 [490, 2041].

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 USA* **109**: 12491-6 [PMID:22802634]

Kleinau G *et al.* Thyroid Disease Manager. Accessed on 2017-02-23.

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

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

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) [1072, 1667]	TSH (*CGA TSHB*, P01215 P01222)
Labelled ligands	[^{125}I]FSH (human) (Agonist)	[^{125}I]LH (Agonist), [^{125}I]chorionic gonadotropin (human) (Agonist)	[^{125}I]TSH (human) (Agonist)

Gonadotrophin-releasing hormone receptors

G protein-coupled receptors → Gonadotrophin-releasing hormone receptors

Overview: $GnRH_1$ and $GnRH_2$ receptors (**provisional nomenclature [652]**, also called Type I and Type II GnRH receptor, respectively [1589]) have been cloned from numerous species, most of which express two or three types of GnRH receptor [1588, 1589, 2172]. GnRH I (*GNRH1*, P01148) (p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2) is a hypothalamic decapeptide also known as luteinizing hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin or simply as GnRH. It is a member of a family of similar peptides found in many species [1588, 1589, 2172] including GnRH II (*GNRH2*, O43555) (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH_2 (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 [1588, 1589, 2172]. $GnRH_1$ receptors are expressed by pituitary gonadotrophs, where they mediate the effects of GnRH on gonadotropin hormone synthesis and secretion that underpin central control of mammalian reproduction. GnRH analogues are used in assisted reproduction and to treat steroid hormone-dependent conditions [1160]. 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 [1160]. $GnRH_1$ receptors are selectively activated by GnRH I and all lack the COOH-terminal tails found in other GPCRs. $GnRH_2$ receptors do have COOH-terminal tails and (where tested) are selective for GnRH II over GnRH I. $GnRH_2$ receptors are expressed by some primates but not by humans [1639]. Phylogenetic classifications divide GnRH receptors into three [1589] or five groups [2546] and highlight examples of gene loss through evolution, with humans retaining only one ancient gene. The structure of the $GnRH_1$ receptor in complex with elagolix has been elucidated [2608].

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) *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**: 235-75 [PMID:15082521]

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

Nomenclature	$GnRH_1$ receptor	$GnRH_2$ receptor
HGNC, UniProt	*GNRHR*, P30968	*GNRHR2*, Q96P88
Potency order of endogenous ligands	GnRH I (*GNRH1*, P01148) > GnRH II (*GNRH2*, O43555) [1589]	GnRH II (*GNRH2*, O43555) > GnRH I (*GNRH1*, P01148) (Monkey) [1587]
Endogenous agonists	GnRH I (*GNRH1*, P01148) [1440], GnRH II (*GNRH2*, O43555) [647, 1440, 2236]	GnRH II (*GNRH2*, O43555) [1587] – Monkey, GnRH I (*GNRH1*, P01148) [1587, 1589] – Monkey
Selective agonists	buserelin [1702, 1703], triptorelin [138], leuprolide [2251], goserelin, histrelin, nafarelin	–
Antagonists	iturelix (pK_i 9.5) [1994]	–
Selective antagonists	cetrorelix (pK_i 9.3–10) [139, 140, 2251], abarelix (pK_i 9.1–9.5) [2251], elagolix (pK_i 9.1) [362, 1287], degarelix (pK_i 8.8) [2419], ganirelix	trptorelix-1 [1481] – Monkey
Labelled ligands	[^{125}I]cetrorelix (Antagonist) (pK_d 9.7) [957], [^{125}I]triptorelin (Agonist) [513] – Rat, [^{125}I]buserelin (Agonist) [1273] – Rat, [^{125}I]GnRH I (human, mouse, rat) (Agonist)	–

Comments: $GnRH_1$ and $GnRH_2$ receptors couple primarily to $G_{q/11}$ [807] but coupling to G_s and G_i is evident in some systems [1252, 1273]. $GnRH_2$ receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [331]. 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 [377, 873, 1395, 2078]. In some human cancer cell models GnRH II (*GNRH2*, O43555) is more potent than GnRH I (*GNRH1*, P01148), implying mediation by $GnRH_2$ receptors [810], but $GnRH_2$ receptors are not expressed by humans because the human GNRHR2 gene contains a frame shift and internal stop codon [1639]. The possibility remains that this gene generates $GnRH_2$ receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (*GNRH2*, O43555) (see [1708]). Alternatively, evidence for multiple active GnRH receptor conformations [331, 332, 638, 1536, 1589] raises the possibility that $GnRH_1$ receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon a conformation that couples to G_i rather than $G_{q/11}$ proteins as in pituitary cells [332, 1536]. Loss-of-function mutations in the $GnRH_1$ receptor and deficiency of GnRH I (*GNRH1*, P01148) are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' $GnRH_1$ receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists [1327]. Human $GnRH_1$ receptors are poorly expressed at the cell surface because of failure to meet structural quality control criteria for endoplasmic reticulum exit [639, 1327], and this increases susceptibility to point mutations that further impair trafficking [639, 1327]. GnRH receptor signalling may require receptor oligomerisation [439, 1250].

GPR18, GPR55 and GPR119

G protein-coupled receptors → GPR18, GPR55 and GPR119

Overview: GPR18, GPR55 and GPR119 (**provisional nomenclature**), although showing little structural similarity to CB_1 and CB_2 cannabinoid receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands [1856]. Although there are multiple reports to indicate that GPR18, GPR55 and GPR119 can be activated *in vitro* by N-arachidonoylglycine, lysophosphatidylinositol and N-oleoylethanolamide, respectively, there is a lack of evidence for activation by these lipid messengers *in vivo*. As such, therefore, these receptors retain their orphan status.

Further reading on GPR18, GPR55 and GPR119

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

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

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

Pertwee RG *et al*. (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. *Pharmacol Rev* **62**: 588-631 [PMID:21079038]

Nomenclature	*GPR18*	*GPR55*	*GPR119*
HGNC, UniProt	*GPR18*, Q14330	*GPR55*, Q9Y2T6	*GPR119*, Q8TDV5
Potency order of endogenous ligands	–	–	N-oleoylethanolamide, N-palmitoylethanolamine > SEA (anandamide is ineffective) [1798]
Endogenous agonists	N-arachidonoylglycine [1217]	lysophosphatidylinositol [916, 1775, 2218], 2-arachidonoylglycerolphosphoinositol [1777]	N-oleoylethanolamide [413, 1798, 2218], N-palmitoylethanolamine, SEA
Selective agonists	–	AM251 [916, 1120, 2033]	AS1269574 [2641], PSN632408 [1798], PSN375963 [1798]
Selective antagonists	–	CID16020046 (apparent pA_2) (pA_2 7.3) [1122], ML193 (pIC_{50} 6.7) [929]	–
Comments	The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on arrestin assays [2218, 2630]. See [485] for discussion.	See reviews [485] and [2161].	In addition to those shown above, further small molecule agonists have been reported [851].

Comments: GPR18 failed to respond to a variety of lipid-derived agents in an *in vitro* screen [2630], but has been reported to be activated by Δ^9-tetrahydrocannabinol [1551]. GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB_1 receptor antagonists/inverse agonists [1856]. It has been reported that lysophosphatidylinositol acts at other sites in addition to GPR55 [2604]. N-Arachidonoylserine has been suggested to act as a low efficacy agonist/antagonist at GPR18 *in vitro* [1549]. It has also been suggested oleoyl-lysophosphatidylcholine acts, at least in part, through GPR119 [1739]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleoylethanolamide-mediated responses suggests additional mechanisms of action [1739].

Histamine receptors

G protein-coupled receptors → Histamine receptors

Overview: Histamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors [935, 1812]**) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues [935]. The human and rat H_3 receptor genes are subject to significant splice variance [109]. The potency order of histamine at histamine receptor subtypes is $H_3 = H_4 > H_2 > H_1$ [1812]. Some agonists at the human H_3 receptor display significant ligand bias [1986]. Antagonists of all 4 histamine receptors have clinical uses: H_1 antagonists for allergies (*e.g.* cetirizine), H_2 antagonists for acid-reflux diseases (*e.g.* ranitidine), H_3 antagonists for narcolepsy (*e.g.* pitolisant/WAKIX; Registered) and H_4 antagonists for atopic dermatitis (*e.g.* adriforant; Phase IIa) [1812] and vestibular neuritis (AUV) (SENS-111 (Seliforant, previously UR-63325), entered and completed vestibular neuritis (AUV) Phase IIa efficacy and safety trials, respectively) [79, 2439].

Further reading on Histamine receptors

Gbahou F *et al*. (2012) The histamine autoreceptor is a short isoform of the H_3 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]

Nomenclature	H_1 receptor	H_2 receptor
HGNC, UniProt	*HRH1*, P35367	*HRH2*, P25021
Selective agonists	methylhistaprodifen [2120], histaprodifen [1394]	amthamine [1243]
Antagonists	cyproheptadine (pK_i 10.2) [1607], promethazine (pK_i 9.6) [745], mepyramine (Inverse agonist) (pK_i 8.7–9) [218, 1951], cetirizine (Inverse agonist) (pK_i 8.2) [1607], diphenhydramine (pK_i 7.9) [218]	–
Selective antagonists	clemastine (pK_i 10.3) [84], desloratadine (pK_i 9) [1367], triprolidine (pK_i 8.5–9) [218, 1607], azelastine (pK_i 8.9) [1907], astemizole (pK_i 8.5) [1834]	tiotidine (pK_i 7.5) [173] – Rat, ranitidine (pK_i 7.1) [1363], cimetidine (pK_i 6.8) [309]
Labelled ligands	[^{3}H]pyrilamine (Antagonist, Inverse agonist) (pK_d 8.4–9.1) [496, 1607, 2096, 2120], [^{11}C]doxepin (Antagonist) (pK_d 9) [1028], [^{11}C]pyrilamine (Antagonist, Inverse agonist)	[^{125}I]iodoaminopotentidine (Antagonist) (pK_d 8.7) [1259] – Rat, [^{3}H]tiotidine (Antagonist) (pK_d 7.7–8.7) [1618]

Nomenclature	H_3 receptor	H_4 receptor
HGNC, UniProt	*HRH3*, Q9Y5N1	*HRH4*, Q9H3N8
Selective agonists	GSK-189254 (Inverse agonist) [1557], immethridine [1197], methimepip [1196], MK-0249 (Inverse agonist) [1683]	clobenpropit (Partial agonist) [609, 1394, 1412, 1413, 1653], 4-methylhistamine [721, 1394], ST-1006 [1812], VUF 8430 [1393]
Antagonists	iodophenpropit (pK_i 8.2–8.7) [2540, 2575]	SENS-111 [1864]
Selective antagonists	pitolisant (pK_i 8.1–8.6) [1314, 1812], A331440 (pK_i 8.5) [852], conessine (pK_i 8.3) [1812], MK-0249 (pK_i 8.2) [1812], thioperamide (Selective for H_3/H_4 compared to H_1 and H_3.) (pK_i 7.1–7.7) [430, 608, 609, 1391, 1437, 2540, 2575], ciproxifan (pK_i 6.7–7.3) [430, 608, 609, 1391, 1812, 2575]	adriforant (pK_i 8.3) [1812], INCB-38579 (pK_i 8.3) [1812], JNJ 7777120 (pK_i 7.8–8.3) [1394, 2204, 2350], JNJ-39758979 (pK_i 7.9) [1812, 2070], thioperamide (Selective for H_3/H_4 compared to H_1 and H_3.) (pK_i 6.3–7.6) [608, 609, 1412, 1413, 1653, 2689]
Labelled ligands	[^{123}I]iodoproxyfan (Antagonist) (pK_d 10.2) [1391], [^{125}I]iodophenpropit (Antagonist) (pK_d 9.2) [1056] – Rat, [^{3}H](*R*)-α-methylhistamine (Agonist) [1412], *N*-[^{3}H]α-methylhistamine (Agonist) [365] – Mouse	[^{3}H]JNJ 7777120 (Antagonist) (pK_d 8.4) [2350]

Comments: Histaprodifen and methylhistaprodifen are reduced efficacy agonists. The H_4 receptor appears to exhibit broadly similar pharmacology to the H_3 receptor for imidazole-containing ligands, although (*R*)-α-methylhistamine and *N*-α-methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist at the H_4 receptor and an antagonist at the H_3 receptor [1412, 1689, 1726, 1762, 2689]. Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H_4 receptor [1394]. [^{3}H]histamine has been used to label the H_4 receptor in heterologous expression systems.

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 [485, 1764]**) 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 [2207, 2382, 2555]. These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA_2 receptors only and is unlikely to be the natural ligand [2382, 2555].

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

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

Offermanns S *et al.* (2015) Nutritional or pharmacological activation of HCA(2) ameliorates neuroinflammation. *Trends Mol Med* **21**: 245-55 [PMID:25766751]

Nomenclature	HCA_1 receptor	HCA_2 receptor	HCA_3 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 [21, 300, 1414, 2218]	β-D-hydroxybutyric acid [2288], butyric acid	3-hydroxyoctanoic acid [20]
Agonists	compound 2 [2044], 3,5-dihydroxybenzoic acid [1411]	SCH 900271 [1803], GSK256073 [2226]	–
Selective agonists	–	MK 6892 [2145], MK 1903 [194], nicotinic acid [2207, 2382, 2555], acipimox [2207, 2555], monomethyl fumarate [2318]	compound 6o [2182], IBC 293 [2122]
Labelled ligands	–	$[^3H]$nicotinic acid (Agonist) [2207, 2382, 2555]	–

Comments: Further closely-related GPCRs include the 5-oxoeicosanoid receptor (*OXER1*, Q8TDS5) and *GPR31* (O00270). Lactate activates HCA_1 on adipocytes in an autocrine manner. It inhibits lipolysis and thereby promotes anabolic effects. HCA_2 and HCA_3 regulate adipocyte lipolysis and immune functions under conditions of increased FFA formation through lipolysis (e.g., during fasting). HCA_2 agonists acting mainly through the receptor on immune cells exert antiatherogenic and anti-inflammatory effects. HCA_2 is also a receptor for butyrate and mediates some of the beneficial effects of short-chain fatty acids produced by gut microbiota. HCA_3 has been shown to be activated by aromatic D-amino acids.

Kisspeptin receptor

G protein-coupled receptors → Kisspeptin receptor

Overview: The kisspeptin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the kisspeptin receptor [1188]**), 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.

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]

Nomenclature	kisspeptin receptor
HGNC, UniProt	*KISS1R*, Q969F8
Endogenous agonists	kisspeptin-10 (*KISS1*) [1234, 1774], kisspeptin-54 (*KISS1*, Q15726) [1234, 1774], kisspeptin-14 (*KISS1*, Q15726) [1234], kisspeptin-13 (*KISS1*, Q15726) [1234]
Selective agonists	4-fluorobenzoyl-FGLRW-NH2 [2364], [dY]^{1}KP-10 [467] – Mouse, TAK-448 [1742]
Selective antagonists	peptide 234 [2009]
Labelled ligands	[^{125}I]Tyr^{45}-kisspeptin-15 (Agonist) [1774], [^{125}I]kisspeptin-13 (human) (Agonist) [1556], [^{125}I]kisspeptin-10 (human) (Agonist) [1234], [^{125}I]kisspeptin-14 (human) (Agonist) [1556], [d-Tyr-^{14}C]TAK-448 (Agonist) [1646]

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 [490, 1208].

Leukotriene receptors

Overview: The leukotriene receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene Receptors [99, 100]**) are activated by the endogenous ligands leukotrienes (LT), synthesized from lipoxygenase metabolism of arachidonic acid. The human BLT_1 receptor is the high affinity LTB_4 receptor whereas the BLT_2 receptor in addition to being a low-affinity LTB_4 receptor also binds several other lipoxygenase-products, such as 12S-HETE, 12S-HPETE, 15S-HETE, and the thromboxane synthase product 12-hydroxyheptadecatrienoic acid. The BLT receptors mediate chemotaxis and immunomodulation in several leukocyte populations and are in addition expressed on non-myeloid cells, such as vascular smooth muscle and endothelial cells. In addition to BLT receptors, LTB_4 has been reported to bind to the peroxisome proliferator activated receptor (PPAR) α [1400] and the vanilloid TRPV1 ligand-gated nonselective cation channel [1550]. The receptors for the cysteinyl-leukotrienes (*i.e.* LTC_4, LTD_4 and LTE_4) are termed $CysLT_1$ and $CysLT_2$ 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 $CysLT_1$ and $CysLT_2$ receptors [100]. Cysteinyl-leukotrienes have also been suggested to signal through the $P2Y_{12}$ receptor [668, 1749, 1818], GPR17 [419] and GPR99 [1113].

Further reading on Leukotriene receptors

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

Brink C *et al.* (2004) International Union of Pharmacology XLIV. Nomenclature for the oxoeicosanoid receptor. *Pharmacol Rev* **56**: 149-57 [PMID:15001665]

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]

Nomenclature	BLT_1 receptor	BLT_2 receptor	$CysLT_1$ receptor	$CysLT_2$ receptor	OXE receptor	FPR2/ALX
HGNC, UniProt	*LTB4R*, Q15722	*LTB4R2*, Q9NPC1	*CYSLTR1*, Q9Y271	*CYSLTR2*, Q9NS75	*OXER1*, Q8TDS5	*FPR2*, P25090
Potency order of endogenous ligands	LTB_4 > 20-hydroxy-LTB_4 ≫ 12R-HETE [2636]	12-hydroxyheptadecatrienoic acid > LTB_4 > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE > 20-hydroxy-LTB_4 [1783, 2636]	LTD_4 > LTC_4 > LTE_4 [1453, 2059]	LTC_4 ≥ LTD_4 ≫ LTE_4 [907, 1754, 2299]	5-oxo-ETE, 5-oxo-C20:3, 5-oxo-ODE > 5-oxo-15-HETE > 5S-HPETE > 5S-HETE [792, 975, 1088, 1756, 1823, 1898, 2106]	LXA_4 = aspirin triggered lipoxin A4 = ATLa2 = resolvin D1 > LTC_4 = LTD_4 ≫ 15-deoxy-LXA4 ≫ fMet-Leu-Phe [427, 641, 643, 805, 2298]
Endogenous agonists	–	–	–	–	–	LXA_4 [1248], resolvin D1 [1248], aspirin-triggered resolvin D1 [1247], aspirin triggered lipoxin A4
Selective agonists	–	–	–	–	–	ATLa2 [820]
Endogenous antagonists	–	–	–	–	5-oxo-12-HETE (pIC_{50} 6.3) [1897]	–
Antagonists	–	–	pranlukast (pK_i 7.1–8.8) [311, 1953], pobilukast (pK_i 7.1) [313]	pranlukast (pA_2 7.1) [312], pobilukast (pA_2 6.2) [312]	*S*-Y048 (pIC_{50} 10.7) [2627]	–
Selective antagonists	BIIL 260 (pK_i 8.8) [181, 529], CP105696 (pIC_{50} 8.1) [2164], U75302 (pK_i 6.4) [203]	LY255283 (pIC_{50} 6–7.1) [922, 2636]	ICI198615 (pK_i 9.7) [692] – Guinea pig, zafirlukast (zafirlukast is only about 100-fold selective for $CysLT_1$) (pK_i 8.9) [311, 1953], montelukast (pK_i 8.6) [1953], MK-571 (pIC_{50} 8) [1453]	$BayCysLT_2$ (pA_2 8.4) [316], $BayCysLT_2$ (pA_2 8.3) [316], HAMI3379 (pIC_{50} 7.4) [2576]	–	WRWWWW (pIC_{50} 6.6) [101], t-Boc-FLFLF (pIC_{50} 4.3–6) [672, 2234, 2474]
Labelled ligands	[^{3}H]LTB_4 (Agonist) [2635], [^{3}H]CGS23131 (Antagonist) (pK_d 7.9) [1039]	[^{3}H]LTB_4 (pK_d 7.6–9.7)	[^{3}H]LTD_4 (Agonist), [^{3}H]ICI-198615 (Antagonist) (pK_d 10.6) [2017]	[^{3}H]LTD_4 (Agonist) [907]	[^{3}H]5-oxo-ETE (Agonist) [1756]	[^{3}H]LXA_4 (Agonist) [641, 642]

Comments: The FPR2/ALX receptor (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene and Lipoxin Receptors [100]**) is activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A_4 (LXA_4) and 15-epi-LXA_4 (aspirin triggered lipoxin A4, ATL). The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide [385] as well as annexin I (*ANXA1*, P04083) (ANXA1) and its *N*-terminal peptides [442, 1852]. In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the FPR2/ALX receptor [1968]. Furthermore, FPR2/ALX has been suggested to act as a receptor mediating the proinflammatory actions of the acute-phase reactant, serum amyloid A [2205, 2254]. FPR2/ALX has also been reported to be activated by resolvin D1 [1712]. The agonist activity of the lipid mediators described has been questioned [862, 1882], which may derive from batch-to-batch differences, partial agonism or biased agonism. Results from Cooray *et al.* (2013) [442] have addressed this issue and the role of homodimers and heterodimers in intracellular signaling. A receptor selective for LXB_4 has been suggested from functional studies [67, 1464, 2003]. Note that the data for FPR2/ALX are also reproduced on the Formylpeptide receptor pages.

Oxoeicosanoid receptors (OXE, **nomenclature agreed by the NC-IUPHAR subcommittee on Leukotriene receptors [254]**) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-ETE the most potent agonist identified for this receptor. Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as docosahexaenoic acid and EPA, acted as receptor antagonists [975].

Lysophospholipid (LPA) receptors

G protein-coupled receptors → Lysophospholipid (LPA) receptors

Overview: Lysophosphatidic acid (LPA) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid Receptors [485, 1161, 1603, 2610]**) are activated by the endogenous phospholipid LPA. The first receptor, LPA_1, was identified as *ventricular zone gene-1* (*vzg-1*) [903], This discovery represented the beginning of the de-orphanisation of members of the endothelial differentiation gene (edg) family, as other LPA and sphingosine 1-phosphate (S1P) receptors were found. Five additional LPA receptors ($LPA_{2,3,4,5,6}$) have since been identified [1603] and their gene nomenclature codified for human *LPAR1, LPAR2, etc.* (HUGO Gene Nomenclature Committee, HGNC) and *Lpar1, Lpar2, etc.* for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function of their corresponding proteins. The crystal structure of LPA1 is solved and indicates that LPA accesses the extracellular binding pocket, consistent with its proposed delivery via autotaxin [402]. These studies have also implicated cross-talk with endocannabinoids *via* phosphorylated intermediates that can also activate these receptors. The binding affinities to LPA_1 of unlabeled, natural LPA and anandamide phosphate (AEAp) were measured using backscattering interferometry (pK_d = 9) [1604, 1956]. Utilization of this method indicated affinities that were 77-fold lower than when measured using radioactivity-based protocols [2609]. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. Multiple groups have independently published validation of all six LPA receptors described in these tables, and further validation was achieved using a distinct read-out via a novel TGFα "shedding* assay [1021]. LPA has been proposed to be a ligand for GPR35 [1776], supported by a study revealing that LPA modulates macrophage function through GPR35 [1137]. However chemokine (C-X-C motif) ligand 17 (CXCL17 (*CXCL17*, Q6UXB2)) is reported to be a ligand for GPR35/CXCR8 [1503]. Moreover, LPA has also been described as an agonist for the transient receptor potential (Trp) ion channels TRPV1 [1733] and TRPA1 [1198]. All of these proposed non-GPCR receptor identities require confirmation and are not currently recognized as *bona fide* LPA receptors.

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]

Mizuno H *et al.* (2020) Druggable Lipid GPCRs: Past, Present, and Prospects. *Adv Exp Med Biol* **1274**: 223-258 [PMID:32894513]

Yung YC *et al.* (2015) Lysophosphatidic Acid signaling in the nervous system. *Neuron* **85**: 669-82 [PMID:25695267]

Nomenclature	LPA_1 receptor	LPA_2 receptor	LPA_3 receptor	LPA_4 receptor	LPA_5 receptor	LPA_6 receptor
HGNC, UniProt	*LPAR1*, Q92633	*LPAR2*, Q9HBW0	*LPAR3*, Q9UBY5	*LPAR4*, Q99677	*LPAR5*, Q9H1C0	*LPAR6*, P43657
Agonists	UCM-05194 [776]	–	–	–	–	–
Selective agonists	–	dodecylphosphate [2447], decyl dihydrogen phosphate [2447], GRI977143 [1192]	OMPT [877]	–	–	–
Antagonists	Ki16425 (pIC_{50} 6.6–6.9) [1772] – Mouse, VPC12249 (pK_i 5.2–6.9) [909] – Mouse, VPC32179 [902]	–	VPC12249 (pK_i 6.4) [909], VPC32179 [902]	–	–	–
Sub/family-selective antagonists	–	–	Ki16425 (pK_i 6.4) [1772]	–	–	–
Selective antagonists	BMS-986020 (pIC_{50} 8.9), AM966 (pIC_{50} 6.7–7.8) [2279], ONO-7300243 (pIC_{50} 6.8) [2328], AM095 (pIC_{50} 6–6.1) [2279]	H2L5186303 (pIC_{50} 8.1) [629, 630]	dioctanoylglycerol pyrophosphate (pK_i 5.5–7) [645, 1772]	–	AS2717638 (pIC_{50} 7.4) [1671], TCLPA5 (pIC_{50} 6.1) [1240]	–

Comments: Ki16425 [1772], VPC12249 [909] and VPC32179 [902] have dual antagonist activity at LPA_1 and LPA_3 receptors. There is growing evidence for *in vivo* efficacy of these chemical antagonists in several disorders, including fetal hydrocephalus [2649], fetal hypoxia [920], lung fibrosis [1768], systemic sclerosis [1768] and atherosclerosis progression [1249]. LPA_2 selective antagonist SAR100842 [1331], and LPA_1 selective agonist UCM-05194 [776], are proposed for therapy of systemic sclerosis and neuropathic pain, respectively. The LPA_2 selective agonist, GRI977143, shows efficacy in an animal model of multiple sclerosis [2090]. The LPA_5 selective antagonist, AS2717638, is effective in pain models [1136]. Antidepressants, amitriptyline, clomipramine, and mianserin, are reported to show profibrotic responses *via* LPA_1 [1785].

Lysophospholipid (S1P) receptors

G protein-coupled receptors → Lysophospholipid (S1P) receptors

Overview: Sphingosine 1-phosphate (S1P) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors [1161]**) are activated by the endogenous lipid sphingosine 1-phosphate (S1P). Originally cloned as orphan members of the endothelial differentiation gene (*edg*) family [185, 1603], the receptors are currently designated as $S1P_1R$ through $S1P_5R$ [185, 949, 1603]. Their gene nomenclature has been codified as human *S1PR1, S1PR2, etc.* (HUGO Gene Nomenclature Committee, HGNC) and *S1pr1, S1pr2, etc.* for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function. All S1P receptors have been knocked-out in mice constitutively and in some cases, conditionally. S1PRs, particularly $S1P_1$, are expressed throughout all mammalian organ systems. Ligand delivery occurs *via* two known carriers (or "chaperones"): albumin and HDL-bound apolipoprotein M (ApoM), the latter of which elicits biased agonist signaling by $S1P_1$ in multiple cell types [187, 695]. The five S1PRs, two chaperones, and active cellular metabolism have complicated analyses of receptor ligand binding in native systems.

Signaling pathways and physiological roles have been characterized through radioligand binding in heterologous expression systems, targeted deletion of the different S1PRs, and most recently, mouse models that report *in vivo* $S1P_1R$ activation [1226, 1227]. A crystal structure of an $S1P_1$-T4 fusion protein confirmed aspects of ligand binding, specificity, and receptor activation, determined previously through biochemical and genetic studies [186, 863]. Fingolimod (FTY720), the first FDA-approved drug to target any of the lysophospholipid receptors, binds as a phosphorylated metabolite to four of the five S1PRs, and was the first oral therapy for multiple sclerosis (MS) [414]. Siponimod and ozanimod that target $S1P_1$ and $S1P_5$ are also FDA approved for the treatment of various MS forms [185, 1603]. The mechanisms of action of fingolimod and other S1PR-modulating drugs now in development include binding S1PRs in multiple organ systems, *e.g.*, immune and nervous systems, although the precise nature of their receptor interactions requires clarification [431, 808, 809, 1908].

Further reading on Lysophospholipid (S1P) receptors

Cartier A *et al.* (2019) Sphingosine 1-phosphate: Lipid signaling in pathology and therapy. *Science* **366**: [PMID:31624181]

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. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* **62**: 579-87 [PMID:21079037]

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]

Nomenclature	$S1P_1$ receptor	$S1P_2$ receptor	$S1P_3$ receptor	$S1P_4$ receptor	$S1P_5$ receptor
HGNC, UniProt	*S1PR1*, P21453	*S1PR2*, O95136	*S1PR3*, Q99500	*S1PR4*, O95977	*S1PR5*, Q9H228
Potency order of endogenous ligands	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate [52, 1778]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate [52, 1778]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate [1778]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate [2414]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate [1018]
Agonists	fingolimod-phosphate [255, 656], siponimod [760, 1806], BMS-986166 (Partial agonist) [755], BMS-986104 derivative 12 (Biased agonist) [754], BMS-986104 derivative 24 (Biased agonist) [754], etrasimod [292], SAR247799 (Biased agonist) [1885]	S1P d20:1 (Partial agonist) [2459]	fingolimod-phosphate [255, 656], fingolimod-phosphate [255, 656]	fingolimod-phosphate [255, 656, 1807, 2056, 2599], etrasimod [291, 292]	fingolimod-phosphate [255, 656, 1807], siponimod [718, 742, 2401], etrasimod [292]
Selective agonists	RP-001 [298], cenerimod [1868], CYM5442 [775], ponesimod [205], SEW2871 [2056] – Mouse	–	CYM-5541 [1079]	CYM-50308 [2402]	A-971432 [526, 954]
Antagonists	VPC23019 (pK_i 7.9) [491], VPC03090-P (pK_i 7.6–7.7) [1148], VPC44116 (pIC_{50} 7.6) [657]	–	VPC44116 (pK_i 6.5) [657], VPC23019 (pK_i 5.9) [491]	–	–
Selective antagonists	NIBR-0213 (pIC_{50} 8.6) [1924], W146 (pK_i 7.1) [2057]	JTE-013 (pIC_{50} 7.8) [1792]	TY-52156 (pK_i 7) [1672]	CYM-50358 (pIC_{50} 7.6) [337, 816]	–

Comments: The FDA-approved immunomodulator fingolimod (FTY720) is phosphorylated *in vivo* [36] to generate an agonist with activity at $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$ receptors [255, 1494]. Many of the physiological consequences of fingolimod-phosphate administration, as well as those of other currently described $S1P_1$ agonists, may involve functional antagonism *via* ubiquitination and subsequent degradation of $S1P_1$ [185, 1791]. Additionally, receptor specificities of the different compounds may depend on the functional assay system utilized and from which species the receptor sequence originated.

Melanin-concentrating hormone receptors

Overview: Melanin-concentrating hormone (MCH) receptors (**provisional nomenclature as recommended by NC-IUPHAR [652]**) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRPCWQV; mammalian MCH) generated from a precursor (*PMCH*, P20382), which also produces neuropeptide EI (*PMCH*, P20382) and neuropeptide GE (*PMCH*, P20382).

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**: 279-88 [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]

Nomenclature	MCH_1 receptor	MCH_2 receptor
HGNC, UniProt	*MCHR1*, Q99705	*MCHR2*, Q969V1
Selective antagonists	GW803430 (pIC_{50} 9.3) [923], SNAP-7941 (pA_2 9.2) [220], T-226296 (pIC_{50} 8.3) [2308], ATC0175 (pIC_{50} 7.9–8.1) [342]	–
Labelled ligands	[^{125}I]S36057 (Antagonist) (pK_d 9.2–9.5) [82], [^{125}I][Phe^{13},Tyr^{19}]MCH (Agonist) [286], [^{3}H]MCH (human, mouse, rat) (Agonist) [286]	–

Comments: The MCH_2 receptor appears to be a non-functional pseudogene in rodents [2314].

Melanocortin receptors

G protein-coupled receptors → Melanocortin receptors

Overview: Melanocortin receptors (**provisional nomenclature as recommended by NC-IUPHAR [652]**) 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.

Further reading on Melanocortin receptors

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

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

Renquist BJ *et al.* (2011) Physiological roles of the melanocortin MC_3 receptor. *Eur J Pharmacol* **660**: 13-20 [PMID:21211527]

Nomenclature	MC_1 receptor	MC_2 receptor	MC_3 receptor	MC_4 receptor	MC_5 receptor
HGNC, UniProt	*MC1R*, Q01726	*MC2R*, Q01718	*MC3R*, P41968	*MC4R*, P32245	*MC5R*, P33032
Potency order of endogenous agonists	α-MSH (*POMC*, P01189) > β-MSH (*POMC*, P01189) > ACTH (*POMC*, P01189), γ-MSH (*POMC*, P01189)	ACTH (*POMC*, P01189)	γ-MSH (*POMC*, P01189), β-MSH (*POMC*, P01189) > ACTH (*POMC*, P01189), α-MSH (*POMC*, P01189)	β-MSH (*POMC*, P01189) > α-MSH (*POMC*, P01189), ACTH (*POMC*, P01189) > γ-MSH (*POMC*, P01189)	α-MSH (*POMC*, P01189) > β-MSH (*POMC*, P01189) > ACTH (*POMC*, P01189) > γ-MSH (*POMC*, P01189)
Selective agonists	–	corticotropin zinc hydroxide	[D-Trp[8]]γ-MSH [800]	THIQ [2113], setmelanotide [426, 1269]	–
Antagonists	–	–	PG-106 (pIC_{50} 6.7) [801]	–	–
Selective antagonists	–	–	–	MBP10 (pIC_{50} 10) [143], HS014 (pK_i 8.5) [2085]	–
Labelled ligands	[^{125}I]NDP-MSH (Agonist) [1230]	[^{125}I]ACTH-(1-24) (Agonist)	[^{125}I]NDP-MSH (Agonist) [1230], [^{125}I]SHU9119 (Antagonist) [1728]	[^{125}I]SHU9119 (Antagonist) (pK_d 9.2) [1728], [^{125}I]NDP-MSH (Agonist) [1230, 2084]	[^{125}I]NDP-MSH (Agonist) [1230]

Comments: Polymorphisms of the MC_1 receptor have been linked to variations in skin pigmentation. Defects of the MC_2 receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC_4 receptor have been linked to obesity [341, 624].

Melatonin receptors

G protein-coupled receptors → Melatonin receptors

Overview: Melatonin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Melatonin Receptors [565]**) are activated by the endogenous ligands melatonin and clinically used drugs like ramelteon, agomelatine and tasimelteon.

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]

Nomenclature	MT_1 receptor	MT_2 receptor
HGNC, UniProt	*MTNR1A*, P48039	*MTNR1B*, P49286
Endogenous agonists	melatonin [83, 564, 566]	melatonin [83, 564, 566]
Agonists	ramelteon [1127], agomelatine [83, 159], tasimelteon [1934, 2423]	agomelatine [83, 159], tasimelteon [1934, 2423], ramelteon [1127, 1955]
Selective agonists	–	UCM1014 [2219], IIK7 [625, 2258], 5-methoxy-luzindole (Partial agonist) [566]
Selective antagonists	–	4P-PDOT (pK_i 8.8–9.4) [83, 566, 567], K185 (pK_i 9.3) [625, 2258], DH97 (pK_i 8) [2327]
Labelled ligands	[^{125}I]SD6 (Agonist) [1344], 2-[^{125}I]melatonin (Agonist) [83, 566], [^{3}H]melatonin (Agonist) [271]	[^{125}I]SD6 (Agonist) [1344], 2-[^{125}I]melatonin (Agonist) [83, 566], [^{125}I]DIV880 (Agonist, Partial agonist) [1344], [^{3}H]melatonin (Agonist) [271]

Comments: Melatonin, 2-iodo-melatonin, agomelatine, GR 196429, LY 156735 and ramelteon [1127] are nonselective agonists for MT_1 and MT_2 receptors. (-)-AMMTC displays an 400-fold greater agonist potency than (+)-AMMTC at rat MT_1 receptors (see AMMTC for structure) [2357]. Luzindole is an MT_1/MT_2 non-selective competitive melatonin receptor antagonist with about 15-25 fold selectivity for the MT_2 receptor [567]. MT_1/MT_2 heterodimers present different pharmacological profiles from MT_1 and MT_2 receptors [91].

The MT_3 binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML_2 receptor, binds selectively 2-iodo-[^{125}I]5MCA-NAT [1611]. Pharmacological investigations of MT_3 binding sites have primarily been conducted in hamster tissues. At this site, The endogenous ligand N-acetylserotonin [586, 1441, 1611, 1886] and 5MCA-NAT [1886] appear to function as agonists, while prazosin [1441] functions as an antagonist. The MT_3 binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (*NQO2*, P16083 [1751, 1752]). The MT_3 binding site activated by 5MCA-NAT in eye ciliary body is positively coupled to adenylyl cyclase and regulates chloride secretion [998]. *Xenopus* melanophores and chick brain express a distinct receptor (x420, P49219; c346, P49288, initially termed Mel_{1C}) coupled to the $G_{i/o}$ family of G proteins, for which GPR50 has recently been suggested to be a mammalian counterpart [570] although melatonin does not bind to GPR50 receptors. Several variants of the *MTNR1B* gene have been associated with increased type 2 diabetes risk [1121].

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 [2091]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate. The mGlu family is composed of eight members (named mGlu1 to $mGlu_8$) which are divided in three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I ($mGlu_1$ and $mGlu_5$), Group-II ($mGlu_2$ and $mGlu_3$) and Group-III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) (see Further reading).

Structurally, mGlu are composed of three juxtaposed domains: a core G protein-activating seven-transmembrane domain (TM), common to all GPCRs, is linked *via* a rigid cysteine-rich domain (CRD) to the Venus Flytrap domain (VFTD), a large bi-lobed extracellular domain where glutamate binds. mGlu form constitutive dimers, cross-linked by a disulfide bridge. The structures of the VFTD of $mGlu_1$, $mGlu_2$, $mGlu_3$, $mGlu_5$ and $mGlu_7$ have been solved [1272, 1622, 1680, 2378]. 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 [407, 554, 2571]. Recent advances in cryo-electron microscopy have provided structures of full-length mGlu receptor dimers [1211]. Studies have revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [557]. First well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [1634].[830, 1745, 2634]. Beyond heteromerization with other mGlu receptor subtypes, increasing evidence suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs (reviewed in [798]).

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 [235] and antagonized by (S)-hexylhomoibotenic acid [1467]. Group-II mGlu receptors may be activated by LY389795 [1623], LY379268 [1623], eglumegad [2092, 2574], DCG-IV and (2*R*,3*R*)-APDC [2093], and antagonised by eGlu [1055] and LY307452 [610, 2523]. Group-III mGlu receptors may be activated by L-AP4 and (*R,S*)-4-PPG [713]. An example of an antagonist selective for mGlu receptors is LY341495, which blocks $mGlu_2$ and $mGlu_3$ at low nanomolar concentrations, $mGlu_8$ at high nanomolar concentrations, and $mGlu_4$, $mGlu_5$, and $mGlu_7$ in the micromolar range [1185]. 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.

Further reading on Metabotropic glutamate receptors

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

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

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

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

Nomenclature	mGlu$_1$ receptor	mGlu$_2$ receptor	mGlu$_3$ receptor	mGlu$_4$ receptor	mGlu$_5$ receptor
HGNC, UniProt	*GRM1*, Q13255	*GRM2*, Q14416	*GRM3*, Q14832	*GRM4*, Q14833	*GRM5*, P41594
Endogenous agonists	L-glutamic acid [1873]	L-glutamic acid [1873]	L-glutamic acid [1873], NAAG [2103]	L-serine-O-phosphate [2574], L-glutamic acid [1873]	L-glutamic acid [1873]
Agonists	–	–	–	L-AP4 [2574]	–
Selective agonists	–	–	–	LSP4-2022 [784]	(S)-(+)-CBPG (Partial agonist) [1497] – Rat, CHPG [1679]
Antagonists	LY367385 (pIC$_{50}$ 5.1) [425]	–	–	MAP4 (pK_i 4.6) [850] – Rat	–
Selective antagonists	3-MATIDA (pIC$_{50}$ 5.2) [1650] – Rat, (S)-(+)-CBPG (pIC$_{50}$ 4.2) [1497] – Rat, (*S*)-TBPG (pIC$_{50}$ 4.2) [444] – Rat, AIDA (pA_2 4.2) [1651]	PCCG-4 (pIC$_{50}$ 5.1) [1839] – Rat	–	–	ACDPP (pIC$_{50}$ 6.9) [216]
Allosteric modulators	–	CBiPES (Positive) (pEC$_{50}$ 7) [1085], 4-MPPTS (Positive) (pIC$_{50}$ 5.8) [118, 1084, 1085, 2077]	MNI-137 (Negative) (pIC$_{50}$ 7.7) [914] – Rat, VU0650786 (Negative) (pIC$_{50}$ 6.4) [599]	SIB-1893 (Positive) (pEC$_{50}$ 6.3–6.8) [1524], MPEP (Positive) (pEC$_{50}$ 6.3–6.6) [1524], PHCCC (Positive) (pEC$_{50}$ 4.5) [1482]	alloswitch-1 (Negative) (pIC$_{50}$ 8.1) [1880] – Rat, CDPPB (Positive) (pEC$_{50}$ 7.6–8) [1186, 1404], MTEP (Negative) (pK_i 7.8) [263], MPEP (Negative) (pIC$_{50}$ 7.4–7.7) [712, 714], fenobam (Negative) (pIC$_{50}$ 7.2) [1892]
Selective allosteric modulators	BAY 367620 (Negative) (pK_i 9.5) [320] – Rat, JNJ16259685 (Negative) (pIC$_{50}$ 8.9) [1305], Ro01-6128 (Positive) (pK_i 7.5–7.7) [1206] – Rat, LY456236 (Negative) (pIC$_{50}$ 6.9) [1372], CPCCOEt (Negative) (pIC$_{50}$ 5.2–5.8) [1407]	Ro64-5229 (Negative) (pIC$_{50}$ 7) [1222] – Rat, biphenylindanone A (Positive) (pEC$_{50}$ 7) [217]	ML337 (Negative) (pIC$_{50}$ 6.2) [2520] – Rat	VU0361737 (Positive) (pEC$_{50}$ 6.6) [598], VU0155041 (Positive) (pEC$_{50}$ 6.1) [1744]	VU0409551 (Positive) (pK_B 7.1) [2005], VU0360172 (Positive) (pK_B 6.6–7) [799, 1999]

Nomenclature	mGlu$_6$ receptor	mGlu$_7$ receptor	mGlu$_8$ receptor
HGNC, UniProt	*GRM6*, O15303	*GRM7*, Q14831	*GRM8*, O00222
Endogenous agonists	L-glutamic acid [1873]	L-glutamic acid [1873]	L-serine-O-phosphate [1488, 2574], L-glutamic acid [1873]
Agonists	–	LSP4-2022 [784], L-serine-O-phosphate [2574], L-AP4 [2574]	(*S*)-3,4-DCPG [2343], L-AP4 [1488]
Selective agonists	1-benzyl-APDC [2381] – Rat, homo-AMPA [243]	–	–
Antagonists	MAP4 (pIC$_{50}$ 3.5) [1870] – Rat, THPG [2347]	–	MPPG (pIC$_{50}$ 4.3) [2574]
Allosteric modulators	–	MMPIP (Negative) (pIC$_{50}$ 6.1–7.6) [1743, 2274] – Rat, ADX71743 (Negative) (pIC$_{50}$ 7.2) [1108], AMN082 (Positive) (pEC$_{50}$ 6.5–6.8) [1598], XAP044 (Negative) (pIC$_{50}$ 5.6) [724]	VU0422288 (Positive) (pK_B 6.7) [1054], VU0155094 (Positive) (pK_B 5) [1054]

Comments: The activity of NAAG as an agonist at $mGlu_3$ receptors was questioned on the basis of contamination with glutamate [398, 674], but this has been refuted [1701].

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [^{3}H]R214127 [1304] and [^{3}H]YM298198 [1215] at $mGlu_1$ receptors and [^{3}H]M-MPEP [712] and [^{3}H]methoxymethyl-MTEP [54] at $mGlu_5$ receptors; [^{3}H]LY341495 and [^{3}H]eglumegad for $mGlu_2$ and $mGlu_3$ receptors [1083, 2103]). 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 [913]. Potential differences linked to the species (*e.g.* human *versus* rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(S)-(+)-CBPG is an antagonist at $mGlu_1$, but is an agonist (albeit of reduced efficacy) at $mGlu_5$ receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors [2406], and is an antagonist at all Group-III mGluRs with an IC_{50} of 30μM. A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomoibotenic acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but is resistant to LY341495 [416]. 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 [1199, 1837]

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

All selective antagonists at metabotropic glutamate receptors are competitive.

Motilin receptor

G protein-coupled receptors → Motilin receptor

Overview: Motilin receptors (**provisional nomenclature**) are activated by motilin (*MLN*, P12872), a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a motilin-associated peptide (*MLN*, P12872). There are significant species differences in the structure of motilin and its receptor. In humans and large mammals such as dog, activation of these receptors by motilin released from endocrine cells in the duodenal mucosa during fasting, induces propulsive phase III movements. This activity is associated with promoting hunger in humans. Drugs and other non-peptide compounds which activate the motilin receptor may generate a more long-lasting ability to increase cholinergic activity within the upper gut, to promote gastrointestinal motility; this activity is suggested to be responsible for the gastrointestinal prokinetic effects of certain macrolide antibiotics (often called motilides; *e.g.* erythromycin, azithromycin), although for many of these molecules the evidence is sparse. Relatively high doses may induce vomiting and in humans, nausea.

Further reading on Motilin receptor

Deloose E *et al.* (2019) Motilin: from gastric motility stimulation to hunger signalling. *Nat Rev Endocrinol* **15**: 238-250 [PMID:30675023]

Kitazawa T *et al.* (2019) Regulation of Gastrointestinal Motility by Motilin and Ghrelin in Vertebrates. *Front Endocrinol (Lausanne)* **10**: 278 [PMID:31156548]

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

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

Nomenclature	motilin receptor
HGNC, UniProt	*MLNR*, O43193
Endogenous agonists	motilin (*MLN*, P12872) [449, 1529, 1530, 1531]
Agonists	alemcinal [2338], erythromycin [626, 2338], azithromycin [259]
Selective agonists	camicinal [124, 2055], mitemcinal [1212, 2297] – Rabbit
Selective antagonists	MA-2029 (pA_2 9.2) [2255], GM-109 (pIC_{50} 8) [866] – Rabbit
Labelled ligands	[^{125}I]motilin (human) (Agonist) [626]

Comments: In terms of structure, the motilin receptor has closest homology with the ghrelin receptor. Thus, the human motilin receptor shares 52% overall amino acid identity with the human ghrelin receptor and 86% in the transmembrane regions [897, 2297, 2338]. However, differences between the N-terminus regions of these receptors means that their cognate peptide ligands do not readily activate each other [478, 2055]. Where studied the motilin receptor does not appear to have constitutive activity [962]. Although not proven, the existence of biased agonism at the receptor has been suggested [1531, 1597, 2052]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [5]. Receptor dimerisation has not been reported. It must be noted that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other actions are possible (*e.g.* P2X inhibition by erythromycin; [2674]). Small molecule and selective motilin receptor agonists are now described [1371, 2055, 2528]. Significant species-dependent variations exist. Among mammals, the gene encoding the motilin percursor is absent in laboratory rodents, while the receptor appears to be a pseudogene [897, 2053]. Functions of motilin 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 [1553, 1734]. In some non-laboratory rodents (*e.g.* North American kangaroo rat (*Dipodomys*) and mouse (*Microdipodops*) a functional form of motilin may exist but the motilin receptor is non-functional [1371]. Marked differences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [2054]. Among birds, chicken (*Gallus gallus domesticus*) motilin differs from human motilin at positions 4, 7-10, and 12, and contracts avian upper gastrointestinal tissues more potently than human motilin; in rabbit duodenum, the reverse is apparent [1195]. Chicken motilin receptor has 59% sequence homology with the human motilin receptor [2598]. In chicken, motilin does not mediate phase III activity of the MMC but initiates rhythmic oscillating complexes in the small intestine [2000]. Among reptiles, caiman/alligator motilin is similar to avian motilin, but markedly different forms of motilin exist in turtles, anole/lizard and snake. Their activities have not been examined in reptiles. Among amphibians, a motilin-like peptide has been identified in newts, with a structure differing from mammalian motilin. There may be some diversity among the anuran, urodelal and gymnophional species. In the upper gastrointestinal tract of frogs, human motilin but not erythromycin caused contraction [2666]. Among teleost fish, sequences for motilin peptide and motilin receptor have been identified (zebrafish, ballan wrasse, spotted sea bass) but the motilin peptides are short and the structure of motilin receptor differs from that of mammals.

Neuromedin U receptors

G protein-coupled receptors → Neuromedin U receptors

Overview: Neuromedin U receptors (**provisional nomenclature as recommended by NC-IUPHAR [652]**) 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 [1593]. 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 [1640]. 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.

Further reading on Neuromedin U receptors

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

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

Nomenclature	NMU1 receptor	NMU2 receptor
HGNC, UniProt	*NMUR1*, Q9HB89	*NMUR2*, Q9GZQ4
Agonists	CPN-223 (Partial agonist) [2302]	–
Selective agonists	–	CPN-219 [2304], CPN-116 [2303]
Antagonists	–	R-PSOP (pK_B 7) [1417]
Comments	CPN-267 is a selective hexapeptidic NMUR1 agonist, but the sequence is obscure.	–

Comments: NMU1 and NMU2 couple predominantly to $G_{q/11}$ although there is evidence of good coupling to $G_{i/o}$ [253, 977, 988]. NMU1 and NMU2 can be labelled with [^{125}I]-NmU and [^{125}I]-NmS (of various species, *e.g.* [1563]), BODIPY® TMR-NMU or Cy3B-NMU-8 [253]. A range of radiolabelled (^{125}I-), fluorescently labelled (*e.g.* Cy3, Cy5, rhodamine and FAM) and biotin labelled versions of neuromedin U-25 (*NMU*, P48645) and neuromedin S-33 (*NMS*, Q5H8A3) are now commercially available.

Neuropeptide FF/neuropeptide AF receptors

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

Overview: The Neuropeptide FF receptor family contains two subtypes, NPFF1 and NPFF2 (**provisional nomenclature [652]**), which exhibit high affinities for neuropeptide FF (*NPFF*, O15130) and RFamide related peptides (RFRP: precursor gene symbol NPVF, Q9HCQ7). NPFF1 is broadly distributed in the central nervous system with the highest levels found in the limbic system and the hypothalamus. NPFF2 is present in high density in the superficial layers of the mammalian spinal cord where it is involved in nociception and modulation of opioid functions.

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]

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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]

Nomenclature	NPFF1 receptor	NPFF2 receptor
HGNC, UniProt	*NPFFR1*, Q9GZQ6	*NPFFR2*, Q9Y5X5
Potency order of endogenous ligands	RFRP-1 (*NPVF*, Q9HCQ7) > RFRP-3 (*NPVF*, Q9HCQ7) > FMRFneuropeptide FF (*NPFF*, O15130) > neuropeptide AF (*NPFF*, O15130) > neuropeptide SF (*NPFF*, O15130), QRFP43 (43RFa) (*QRFP*, P83859), PrRP-31 (*PRLH*, P81277) [781]	neuropeptide AF (*NPFF*, O15130), neuropeptide FF (*NPFF*, O15130) > PrRP-31 (*PRLH*, P81277) > FMRF, QRFP43 (43RFa) (*QRFP*, P83859) > neuropeptide SF (*NPFF*, O15130) [781]
Endogenous agonists	neuropeptide FF (*NPFF*, O15130) [781, 782, 1614], RFRP-3 (*NPVF*, Q9HCQ7) [782, 783, 1614]	neuropeptide FF (*NPFF*, O15130) [782, 1613]
Selective agonists	–	dNPA [2016], AC263093 [1288]
Antagonists	RF9 (pK_i 7.2) [2175]	–
Selective antagonists	AC262620 (pK_i 7.7–8.1) [1288], AC262970 (pK_i 7.4–8.1) [1288]	–
Labelled ligands	[^{125}I]Y-RFRP-3 (Agonist) [782], [^{3}H]NPVF (Agonist) [2310], [^{125}I]NPFF (Agonist) [781]	[^{125}I]EYF (Agonist) [1614], [^{3}H]EYF (Agonist) [2310], [^{125}I]NPFF (Agonist) [781]

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, [490, 2175]).

Neuropeptide S receptor

G protein-coupled receptors → Neuropeptide S receptor

Overview: The neuropeptide S receptor (NPS, **provisional nomenclature [652]**) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (*NPS*, P0C0P6).

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]

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

Xu YL *et al.* (2004) Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. *Neuron* **43**: 487-97 [PMID:15312648]

Nomenclature	NPS receptor
HGNC, UniProt	*NPSR1*, Q6W5P4
Endogenous agonists	neuropeptide S (*NPS*, P0C0P6) [2596]
Selective agonists	PWT1-NPS [2029] – Mouse
Selective antagonists	NCGC 84 (pA_2 9) [2348], SHA 68 (pA_2 8.1) [2030] – Mouse, RTI-118 [2672]
Labelled ligands	[^{125}I]Tyr^{10}NPS (human) (Agonist) [2596]

Comments: Multiple single-nucleotide polymorphisms (SNP) and several splice variants have been identified in the human NPS receptor. The most interesting of these is an Asn-Ile exchange at position 107 (Asn^{107}Ile). The human NPS receptor Asn^{107}Ile displayed similar binding affinity but higher NPS potency (by approx. 10-fold) than human NPS receptor Asn107 [1967]. Several epidemiological studies reported an association between Asn^{107}Ile receptor variant and susceptibility to panic disorders [545, 549, 1779, 1931]. The SNP Asn^{107}Ile has also been linked to sleep behavior [780], inflammatory bowel disease [468], schizophrenia [1354], increased impulsivity and ADHD symptoms [1279]. Interestingly, a carboxy-terminal splice variant of human NPS receptor was found to be overexpressed in asthmatic patients [1286].

Neuropeptide W/neuropeptide B receptors

Overview: The neuropeptide BW receptor 1 (NPBW1, **provisional nomenclature [652]**) is activated by two 23-amino-acid peptides, neuropeptide W (neuropeptide W-23 (*NPW*, Q8N729)) and neuropeptide B (neuropeptide B-23 (*NPB*, Q8NG41)) [681, 2153]. C-terminally extended forms of the peptides (neuropeptide W-30 (*NPW*, Q8N729) and neuropeptide B-29 (*NPB*, Q8NG41)) also activate NPBW1 [250]. 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 [250].

Further reading on Neuropeptide W/neuropeptide B receptors

Sakurai T. (2013) NPBWR1 and NPBWR2: Implications in Energy Homeostasis, Pain, and Emotion. *Front Endocrinol (Lausanne)* **4**: 23 [PMID:23515889]

Singh G *et al.* (2006) Neuropeptide B and W: neurotransmitters in an emerging G-protein-coupled receptor system. *Br J Pharmacol* **148**: 1033-41 [PMID:16847439]

Nomenclature	NPBW1 receptor	NPBW2 receptor
HGNC, UniProt	*NPBWR1*, P48145	*NPBWR2*, P48146
Potency order of endogenous ligands	neuropeptide B-29 (*NPB*, Q8NG41) > neuropeptide B-23 (*NPB*, Q8NG41) > neuropeptide W-23 (*NPW*, Q8N729) > neuropeptide W-30 (*NPW*, Q8N729) [250]	neuropeptide W-23 (*NPW*, Q8N729) > neuropeptide W-30 (*NPW*, Q8N729) > neuropeptide B-29 (*NPB*, Q8NG41) > neuropeptide B-23 (*NPB*, Q8NG41) [250]
Selective agonists	Ava3 [1115], Ava5 [1115]	–
Labelled ligands	[^{125}I]NPW-23 (human) (Agonist) [2177]	[^{125}I]NPW-23 (human) (Agonist) [2153]

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 [1684]. For a review of the contribution of neuropeptide B/W to social dominance, see Watanabe and Yamamoto, 2015 [2501]. 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 [1656]. 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 [817, 818]. Computational insights into the binding of antagonists to this receptor have also been described [1827, 1831].

Neuropeptide Y receptors

Overview: Neuropeptide Y (NPY) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Neuropeptide Y Receptors [1576]**) are activated by the endogenous peptides neuropeptide Y (*NPY*, P01303), neuropeptide Y-(3-36), peptide YY (*PYY*, P10082), PYY-(3-36) and pancreatic polypeptide (*PPY*, P01298) (PP). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine recepter (originally named LESTR, [1426]). 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 [796]. Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the potency of PP is greater at the rat Y_4 receptor than at the human receptor [605]. 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 Y_1, Y_2, Y_5 and y_6 subtypes non-selectively, while [^{125}I][cPP(1-7), NPY(19-23), Ala^{31}, Aib^{32}, Gln^{34}]hPP may be used to label Y_5 receptors preferentially (note that cPP denotes chicken peptide sequence and hPP is the human sequence).

Further reading on Neuropeptide Y receptors

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

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

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

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

Nomenclature	Y_1 receptor	Y_2 receptor	Y_4 receptor	Y_5 receptor	y_6 receptor
HGNC, UniProt	*NPY1R*, P25929	*NPY2R*, P49146	*NPY4R*, P50391	*NPY5R*, Q15761	*NPY6R*, Q99463
Potency order of endogenous ligands	neuropeptide Y = peptide YY ≫ pancreatic polypeptide	peptide YY = peptide YY(3-36) = neuropeptide Y = neuropeptide Y(3-36) ≫ pancreatic polypeptide	pancreatic polypeptide ≫ neuropeptide Y = peptide YY	neuropeptide Y > peptide YY > pancreatic polypeptide	neuropeptide Y = peptide YY > pancreatic polypeptide
Endogenous agonists	neuropeptide Y (*NPY*, P01303), peptide YY (*PYY*, P10082)	PYY-(3-36) (*PYY*, P10082) [725, 740], neuropeptide Y (*NPY*, P01303), neuropeptide Y-(3-36) (*NPY*, P01303), peptide YY (*PYY*, P10082)	pancreatic polypeptide (*PPY*, P01298) [116, 1445, 2371, 2605]	–	–
Agonists	[Leu^{31},Pro^{34}]NPY [457], [Leu^{31},Pro^{34}]PYY (human), [Pro^{34}]NPY, [Pro^{34}]PYY (human)	–	–	–	–
Selective agonists	–	–	–	[Ala^{31},Aib^{32}]NPY (pig) [297]	–
Selective antagonists	BIBO3304 (pIC_{50} 9.5) [2538], BIBP3226 (pK_i 8.1–9.3) [552, 2539]	BIIE0246 (pIC_{50} 8.5) [550], JNJ-5207787 (pIC_{50} 6.9–7.1) [212]	–	L-152,804 (pK_i 7.6) [1114]	–
Selective allosteric modulators	–	–	niclosamide (Positive) [2190]	–	–
Labelled ligands	[^{3}H]BIBP3226 (Antagonist) (pK_d 8.7), [^{125}I][Leu^{31},Pro^{34}]NPY (Agonist)	[^{125}I]PYY-(3-36) (human) (Agonist)	[^{125}I]PP (human) (Agonist)	[^{125}I][cPP(1-7), NPY(19-23), Ala^{31}, Aib^{32}, Gln^{34}]hPP (Agonist) [573] – Rat	–
Comments	Note that Pro^{34}-containing NPY and PYY can also bind Y_4 and Y_5 receptors, so strictly speaking are not selective, but are the 'preferred' agonists.	–	–	–	–

Comments: The Y_1 agonists indicated are selective relative to Y_2 receptors. BIBP3226 is selective relative to Y_2, Y_4 and Y_5 receptors [739]. NPY-(13-36) is Y_2 selective relative to Y_1 and Y_5 receptors. PYY-(3-36) is Y_2 selective relative to Y_1 receptors. Note that Pro34-containing NPY and PYY can also bind Y_4 and Y_5, thus they are selective only relative to Y_2. The y_6 receptor is a pseudogene in humans, but is functional in mouse, rabbit and some other mammals.

Neurotensin receptors

G protein-coupled receptors → Neurotensin receptors

Overview: Neurotensin receptors (**nomenclature as recommended by NC-IUPHAR [652]**) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (*NTS*, 30990), which also generates neuromedin N, an agonist at the NTS_2 receptor. [^{3}H]neurotensin (human, mouse, rat) and [^{125}I]neurotensin (human, mouse, rat) may be used to label NTS_1 and NTS_2 receptors at 0.1-0.3 and 3-5 nM concentrations respectively.

Further reading on Neurotensin receptors

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

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

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

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

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

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

Nomenclature	NTS_1 receptor	NTS_2 receptor
HGNC, UniProt	*NTSR1*, P30989	*NTSR2*, O95665
Potency order of endogenous ligands	neurotensin (*NTS*, P30990) > neuromedin N {Mouse, Rat} [919]	neurotensin (*NTS*, P30990) = neuromedin N {Mouse, Rat} [1540]
Agonists	ABS-201 [396, 2679] – Mouse, ABS-212 [1001, 1370] – Rat	–
Selective agonists	JMV449 [2184] – Rat	levocabastine [1540, 1983]
Selective antagonists	meclinertant (pIC_{50} 7.5–8.2) [822]	–
Labelled ligands	[^{3}H]meclinertant (Antagonist) (pK_d 8.5) [1281] – Rat	–

Comments: Neurotensin (*NTS*, P30990) appears to be a low-efficacy agonist at the NTS_2 receptor [2448], while the NTS_1 receptor antagonist meclinertant is an agonist at NTS_2 receptors [2448]. An additional protein, provisionally termed NTS_3 (also known as NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation [1732]. It has been reported to interact with the NTS_1 receptor [1515] and the NTS_2 receptor [158], and has been implicated in hormone trafficking and/or neurotensin uptake. A splice variant of the NTS_2 receptor bearing 5 transmembrane domains has been identified in mouse [225] and later in rat [1853].

Opioid receptors

G protein-coupled receptors → Opioid receptors

Overview: Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (*PENK*, P01210) (met), [Leu]enkephalin (*PENK*, P01210) (leu), β-endorphin (*POMC*, P01189) (β-end), α-neodynorphin (*PDYN*, P01213), dynorphin A (*PDYN*, P01213) (dynA), dynorphin B (*PDYN*, P01213) (dynB), big dynorphin (*PDYN*, P01213) (Big dyn), nociceptin/orphanin FQ (*PNOC*, Q13519) (N/OFQ); endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter nomenclature for the opioid receptors, μ, δ and κ, is well established, and **NC-IUPHAR** considers this nomenclature appropriate, along with the symbols spelled out (mu, delta, and kappa), and the acronyms, MOP, DOP, and KOP. [455, 523, 652]. 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 [1616], 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.

Further reading on Opioid receptors

Butelman ER *et al.* (2012) κ-opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. *Trends Neurosci* **35**: 587-96 [PMID:22709632]

Cox BM *et al.* (2015) Challenges for opioid receptor nomenclature: IUPHAR Review 9. *Br J Pharmacol* **172**: 317-23 [PMID:24528283]

Gillis A *et al.* (2020) Intrinsic Efficacy of Opioid Ligands and Its Importance for Apparent Bias, Operational Analysis, and Therapeutic Window. *Mol Pharmacol* **98**: 410-424 [PMID:32665252]

Pradhan AA *et al.* (2011) The delta opioid receptor: an evolving target for the treatment of brain disorders. *Trends Pharmacol Sci* **32**: 581-90 [PMID:21925742]

Valentino RJ *et al.* (2020) Opioid Research: Past and Future. *Mol Pharmacol* **98**: 389-391 [PMID:32660966]

Williams JT *et al.* (2013) Regulation of μ-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev* **65**: 223-54 [PMID:23321159]

Nomenclature	δ receptor	κ receptor
HGNC, UniProt	*OPRD1*, P41143	*OPRK1*, P41145
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 [2363], etorphine [2363], ethylketocyclazocine [2363], PN6047 (Biased agonist) [437]	–
Sub/family-selective agonists	BU08028 (Partial agonist) [1157]	BU08028 [1157]
Selective agonists	UFP-512 [2441], BW373U86 [1316], ADL5859 [1316], DPDPE [1655, 2363], [D-Ala²]deltorphin II [607], ADL5747 [1317], SNC80 [302, 1930]	U50488 [360, 1832, 2174, 2363, 2457, 2685, 2687], enadoline [1005, 1718], U69593 [1285, 2363], salvinorin A [144, 2012]
Antagonists	UFP-505 (pK_i 9.8) [531, 532], naltrexone (pK_i 8) [2363], naloxone (pK_i 7.2) [2363]	buprenorphine (pK_i 9.1–10.2) [2363, 2687], nalmefene (pK_i 9.5) [2363], naltrexone (pK_i 8.4–9.4) [1832, 2174, 2363], naloxone (pK_i 7.6–8.6) [1832, 2174, 2363, 2685, 2687]
Sub/family-selective antagonists	AT-076 (pK_i 7.7) [2363, 2653]	AT-076 (pK_i 8.9) [2363, 2654]
Selective antagonists	naltriben (pK_i 10) [2206, 2363], naltrindole (pK_i 9.7) [1894, 2363], TIPPψ (Inverse agonist) (pK_i 9) [2082, 2363]	nor-binaltorphimine (pK_i 8.9–11) [1832, 1893, 2174, 2363, 2685, 2687], 5′-guanidinonaltrindole (pK_i 9.7–9.9) [1092, 1832, 2235], JDTic (pK_i 9–9.4) [1670, 2342, 2654]
Labelled ligands	[³H]naltrindole (Antagonist) (pK_d 10.4) [2601] – Rat, [³H][D-Ala2]deltorphin I (Selective Agonist) [2232], [³H]diprenorphine (Agonist) [59, 2363], [³H]DPDPE (Agonist) [31], [³H]deltorphin II (Agonist) [293], [³H]naltriben (Antagonist) [1365]	[³H]diprenorphine (Antagonist) (pK_d 9.1) [59, 2174], [³H]U69593 (Agonist) [1285, 1832, 2174], [³H]enadoline (Agonist) [2176]

Nomenclature	μ receptor	NOP receptor
HGNC, 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) [14, 178, 1780]
Agonists	levorphanol [855], hydromorphone [2521], fentanyl [2363], buprenorphine (Partial agonist) [2363], methadone [1896], UFP-505 [531, 532], codeine [2363], tapentadol [2386], pethidine [1896]	–
Sub/family-selective agonists	BU08028 (Partial agonist) [1157]	cebranopadol [1406], BU08028 (Partial agonist) [1157]
Selective agonists	sufentanil [2451], DAMGO [854, 2363], loperamide [376], morphine [769, 2363], PL017 [351, 2363]	N/OFQ-(1-13)-NH_2 [178, 819, 1547, 1780], Ac-RYYRWK-NH_2 (Partial agonist) [553, 1547], SCH221510 [2434], Ro64-6198 [1063, 2536], AT-403 [66]
Antagonists	naltrexone (pK_i 9.1–9.7) [1140, 2363], nalmefene (pK_i 9.5) [2363], nalorphine (pK_i 8.9) [2363], naloxone (pK_i 8.9) [2363], methylnaltrexone (pK_i 8.7) [2521]	–
Sub/family-selective antagonists	AT-076 (pK_i 8.8) [2363, 2654]	AT-076 (pK_i 8.8) [2654]
Selective antagonists	alvimopan (pK_i 9.3) [1315], levallorphan (pK_i 8.8–9.3) [1484], CTAP (pK_i 8.6) [351, 2363]	UFP-101 (pK_i 10.2) [304], LY2940094 (pK_i 10) [634, 2362], compound 24 (pK_i 9.6) [646], SB 612111 (pK_i 9.2–9.5) [2220, 2652], J-113397 (pIC_{50} 8.3) [1135]
Allosteric modulators	BMS-986123 (Neutral) (pK_B 6) [284], BMS-986121 (Positive) (pK_B 5.7) [284], BMS-986124 (Neutral) (pK_B 5.7) [284], BMS-986122 (Positive) (pK_B 5.3) [284]	–
Labelled ligands	[^{3}H]diprenorphine (Antagonist) (pK_d 10.1) [1958] – Mouse, [^{3}H]DAMGO (Agonist) [1958] – Rat, [^{3}H]PL017 (Agonist) [886] – Rat	[^{3}H]N/OFQ (Agonist) [553, 1615]

Comments: Three naloxone-sensitive opioid receptor genes have been identified in humans, and while the μ-receptor in particular may be subject to extensive alternative splicing [1819], 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 [1094], 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 [1275]. A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (*OGFR*, 9NZT2) and termed an opioid growth factor receptor [2650].

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 [1763] and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists [272]. 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 in [284, 285]. Negative allosteric modulation of opioid receptors has been previously suggested [1126], whether all compounds are acting at a similar site remains to be established.

Orexin receptors

G protein-coupled receptors → Orexin receptors

Overview: Orexin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Orexin receptors [652]**) 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 [2043]. Currently the only orexin receptor ligands in clinical use are suvorexant and lemborexant, which are used as hypnotics. Orexin receptor crystal structures have been solved [968, 2271, 2631, 2633].

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. (2019) Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons. *Neuropharmacology* **154**: 61-67 [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]

Nomenclature	OX_1 receptor	OX_2 receptor
HGNC, UniProt	*HCRTR1*, O43613	*HCRTR2*, O43614
Potency order of endogenous ligands	orexin-A (*HCRT*, O43612) > orexin-B (*HCRT*, O43612) (for Ca^{2+} elevation, unclear/variable for other responses)	orexin-A (*HCRT*, O43612) = orexin-B (*HCRT*, O43612)
Selective agonists	–	[Ala^{11}, D-Leu^{15}]orexin-B [77, 1918], Nag 26 [1024, 1682, 1990], YNT-185 [1024, 1682, 1990]
Antagonists	SB-649868 (pK_i 9.1–9.6) [303, 456, 524], suvorexant (pK_i 8.7–9.3) [303, 456, 1657], filorexant (pK_i 8.4–9.1) [303, 456, 2554], TCS 1102 (pK_i 8.5) [161], almorexant (pK_i 7.8–8.5) [303, 619, 1486, 1487, 1490], Cp-1 (pK_i 7.6–8) [1486, 1487]	SB-649868 (pK_i 8.9–9.8) [303, 456], TCS 1102 (pK_i 9.7) [161], suvorexant (pK_i 8.9–9.5) [303, 456, 1657], Cp-1 (pK_i 8.5–9.3) [1486, 1487], filorexant (pK_i 8.9–9.1) [303, 456, 2554]
Selective antagonists	SB-674042 (70-300-fold selective) (pK_i 8.7–9.3) [1294, 1486, 1487, 1490], JH112 (pK_i 9.1) [912], SB-334867 (50-150-fold selective) (pK_i 7.2–7.9) [1294, 1486, 1487, 1891, 1916, 2193], SB-408124 (60-80-fold selective) (pK_i 7.2–7.9) [1294, 1487, 1657]	EMPA (300-3000-fold selective) (pK_i 8.4–9.2) [1486, 1487, 1490, 1657, 2374], JNJ-10397049 (200-800-fold selective) (pK_i 7.7–8.4) [456, 1542, 2374], TCS-OX2-29 (pK_i 6.9–7.5) [944, 1657]
Labelled ligands	[^{3}H]SB-674042 (Antagonist) (pK_d 8.3–9.1) [1294, 1487, 1490], [^{3}H]-almorexant (Antagonist) (pK_d 8.6–8.9) [1487, 1490], [^{125}I]-orexin-A (Agonist) [1260, 1917, 2043]	[^{3}H]-almorexant (Selective Antagonist) (pK_d 8.9–9.8) [1487, 1490], [^{3}H]Cp-1 (Selective Antagonist) (pK_d 9.2–9.4) [1487], [^{3}H]EMPA (Selective Antagonist) (pK_d 8.6–9) [1486, 1490], [^{125}I]-orexin-A (Agonist) [1260, 1917, 2043]

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 $G_{q/11}$ [1261]. Coupling of both receptors to $G_{i/o}$ and G_s has also been reported [1124, 1264, 1355, 1945]. 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 [1262]. Similarly, [Ala^{11}, 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 [1918, 1990]. Many antagonists and radioligands are poorly characterized, and thus the affinities are uncertain. Among radioligands, [^{3}H]SB-674042, [^{3}H]EMPA, [^{3}H]-almorexant and [^{125}I]-orexin-A are commercially available. [^{3}H]-TCS 1102, [^{3}H]Cp-1 and Rhodamine Green-orexin-A [475] are also useful labelled tools. Orexin receptors have been reported to be able to form complexes with each other and some other GPCRs as well as σ1-receptors, which might affect the signaling and pharmacology [1263, 1697]. Loss-of-function mutations in the gene encoding the OX_2 receptor underlie canine hereditary narcolepsy [1399]. Antagonists of the orexin receptors are the focus of major drug discovery efforts for their potential to treat insomnia and other disorders of wakefulness [2001], while agonists would likely be useful in human narcolepsy.

Oxoglutarate receptor

G protein-coupled receptors → Oxoglutarate receptor

Overview: **Nomenclature as recommended by NC-IUPHAR [485].**

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]

Nomenclature	oxoglutarate receptor
HGNC, UniProt	*OXGR1*, Q96P68
Endogenous agonists	α-ketoglutaric acid [901, 2218]

P2Y receptors

G protein-coupled receptors → P2Y receptors

Overview: P2Y receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on P2Y Receptors [3, 4, 1043]**) 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-preferring (or ATP-, *etc.*) P2Y receptor' or '$P2Y_1$-like', *etc.*, until further, as yet undefined, corroborative criteria can be applied [287, 606, 1041, 2454, 2514]. Clinically used drugs acting on these receptors include the dinucleoside polyphosphate diquafosol, agonist of the $P2Y_2$ receptor subtype, approved in Japan for the management of dry eye disease [1302], and the $P2Y_{12}$ receptor antagonists prasugrel, ticagrelor and cangrelor, all approved as antiplatelet drugs [308, 1903].

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

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

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

Nomenclature	$P2Y_1$ receptor	$P2Y_2$ receptor	$P2Y_4$ receptor	$P2Y_6$ receptor
HGNC, UniProt	*P2RY1*, P47900	*P2RY2*, P41231	*P2RY4*, P51582	*P2RY6*, Q15077
Potency order of endogenous ligands	ADP>ATP	uridine triphosphate > ATP [1312]	uridine triphosphate>ATP (at rat recombinant receptors, UTP = ATP)	uridine diphosphate ≫ uridine triphosphate > ADP
Endogenous agonists	–	uridine triphosphate [1171, 1312]	–	–
Agonists	ADPβS [2300], 2MeSADP [2075, 2466]	–	–	–
Sub/family-selective agonists	–	diquafosol [1842], denufosol [1313, 1842, 2629], UTPγS [1312]	diquafosol [276], denufosol [2629], UTPγS [1313]	–
Selective agonists	MRS2365 [384], 2-Cl-ADP(α-BH_3) [92]	MRS2698 [1034], 2-thioUTP [589], PSB1114 (EC_{50} value determined using an IP_3 functional assay) [589, 590, 1033]	MRS4062 [1517], MRS2927 [1517], (N)methanocarba-UTP [1171]	Rp-5-OMe-UDPαB [757, 828], MRS2957 [1516], MRS2693 [170]
Antagonists	suramin (pK_i 5.3) [2466], PPADS (pK_i 5.2) [2466]	–	–	–
Sub/family-selective antagonists	–	reactive blue-2 (pIC_{50} 6) [1057], suramin (pIC_{50} 4.3) [1057, 2075]	PPADS (pEC_{50} 2–5) [1045], reactive blue-2 (pIC_{50} 4.7) [199] – Rat	reactive blue-2 (pK_B 6) [2455], PPADS (pK_B 4) [2455], suramin (pK_B 4) [2455]
Selective antagonists	MRS2500 (pK_i 8.8–9.1) [328, 1170], MRS2279 (pK_i 7.9) [2466], MRS2179 (pK_i 7–7.1) [234, 2466]	AR-C118925XX (pIC_{50} ~6) [1143], AR-C126313 (pEC_{50} 6) [1034], PSB-416 (pIC_{50} 4.7) [938]	PSB-16133 (pIC_{50} 6.6) [1932], ATP (pK_d 6.2) [1146]	MRS2578 (pIC_{50} 7.4) [1492], MRS2567 (pIC_{50} 6.9) [1492], TIM-38 (pIC_{50} 5.4) [1030]
Selective allosteric modulators	BMS compound 16 (Negative) (pK_i 6.9) [2658], 2,2'-pyridylisatogen tosylate (Negative) (pIC_{50} 6.8) [703]	–	–	–
Labelled ligands	[^{3}H]MRS2279 (Antagonist) (pK_d 8.1) [2466], [^{3}H]2MeSADP (Agonist) [2300], [^{35}S]ADPβS (Agonist)	–	–	MRS4162 (Selective Agonist) [1062]

Nomenclature	$P2Y_{11}$ receptor	$P2Y_{12}$ receptor	$P2Y_{13}$ receptor	$P2Y_{14}$ receptor
HGNC, UniProt	*P2RY11*, Q96G91	*P2RY12*, Q9H244	*P2RY13*, Q9BPV8	*P2RY14*, Q15391
Potency order of endogenous ligands	ATP>ADP	ADP>ATP	ADP≫ATP	uridine diphosphate= UDP-glucose [322]
Endogenous agonists	–	ADP [918]	–	–
Sub/family-selective agonists	–	2MeSADP [918], ADPβS [2300]	2MeSADP [1513], 2MeSATP [1513], ADPβS [1513]	–
Selective agonists	AR-C67085 [111, 434], NF546 [1560], ATPγS [434]	–	–	α.β-methylene-2-thio-UDP [476], MRS2905 [1042], 2-thio-UDP [476]
Antagonists	–	cangrelor (pIC_{50} 9.4) [1046], Ap_4A (pIC_{50} 6) [1513], 2MeSAMP (pIC_{50} 5.4) [2300]	cangrelor (pIC_{50} 8.3) [1513], Ap_4A (pIC_{50} 6.7) [1513], 2MeSAMP (pIC_{50} 5.6) [1513]	–
Sub/family-selective antagonists	suramin (pIC_{50} 4.8–6) [434], reactive blue-2 (pIC_{50} 5) [434]	–	–	–
Selective antagonists	NF157 (pK_i 7.3) [2393], NF340 (pIC_{50} 6.4–7.1) [1560]	AZD1283 (pK_i 8) [95, 2661], ARL66096 (pIC_{50} 7.9) [1003, 1004], ticagrelor (pK_i 7.8) [2655]	MRS2603 (pIC_{50} 6.2) [1179], MRS2211 (pIC_{50} 6) [1179]	PPTN (pK_i 10.1) [121], MRS4625 (pIC_{50} 7.6) [1662]
Labelled ligands	–	[^{3}H]2MeSADP (Agonist) [2300], [^{3}H]PSB-0413 (Antagonist) (pK_d 8.3–8.5) [588, 1770]	[^{33}P]2MeSADP (Agonist) [1513]	MRS4174 (Selective Antagonist) (pK_i 10.1) [1191], MRS4183 (Selective Agonist) [1190]

Comments: A series of 4-alkyloxyimino derivatives of uridine-5'-triphosphate which could be useful for derivatization as fluorescent $P2Y_{2/4/6}$ receptor probes has been recently synthesized [1062].

Single nucleotide polymorphisms of the $P2YR_1$ gene have been associated with different platelet reactivity to ADP [927]. Three frequent nonsynonymous $P2Y_2$ receptor polymorphisms have been identified, one of which was significantly more common in cystic fibrosis patients. This polymorphism is linked to increases in Ca^{2+} influx in transfected cells, and might therefore play a role in disease development [290]. Although uridine triphosphate (UTP) was also shown to be a biased agonist at $P2Y_{11}$, this is still under debate [1652, 2532]. A group of single nucleotide polymorphisms in the $P2Y_{12}$ gene, forming the so called $P2Y_{12}$ H2 haplotype, has been associated with increased platelet responsiveness to ADP, increased risk of peripheral arterial disease and with coronary artery disease [333]. The platelet-type bleeding disorder due to $P2Y_{12}$ 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 [329]. The $P2Y_{13}$ receptor Met-158-Thr polymorphism, which is in linkage disequilibrium with the $P2Y_{12}$ locus, is not associated with acute myocardial infarction, diabetes mellitus or related risk factors [50]. The $P2Y_{14}$ receptor was previously considered to exclusively bind sugar nucleotides such as UDP-glucose and UDP-galactose [344]. However, more recent evidence with several cell lines has demonstrated that uridine diphosphate (UDP) is 5-fold more potent than UDP-glucose [322]. UDP was also shown to competitively antagonise the UDP-glucose response at the human recombinant $P2Y_{14}$ receptor [675].

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 [709]**) are class B G protein-coupled receptors. The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor (PTH1 receptor) is activated by precursor-derived peptides: PTH (*PTH*, P01270) (84 amino acids), and PTHrP (*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. The structure of a long-active PTH analogue (LA-PTH, a hybrid of PTH-(1-13) and PTHrP-(14-36)) bound to the PTH1 receptor-G_s complex has been resolved by cryo-electron microscopy [2675]. Another structure of a PTH-(1-34) analog bound to a thermostabilized inactive PTH1 receptor has been obtained with X-ray crytallography [585].

Further reading on Parathyroid hormone receptors

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

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

Sutkeviciute I *et al.* (2020) Structural insights into emergent signaling modes of G protein-coupled receptors. *J Biol Chem* **295**: 11626-11642 [PMID:32571882]

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

Nomenclature	PTH1 receptor	PTH2 receptor
HGNC, UniProt	*PTH1R*, Q03431	*PTH2R*, P49190
Potency order of endogenous ligands	PTH (*PTH*, P01270) = PTHrP (*PTHLH*, P12272)	TIP39 (*PTH2*, Q96A98), PTH (*PTH*, P01270) ≫ PTHrP (*PTHLH*, P12272)
Agonists	teriparatide [707]	TIP39 (*PTH2*, Q96A98) [778, 952]
Selective agonists	PTHrP-(1-34) (human) [708] – Rat, abaloparatide [85]	–

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 administrated (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 [1093].

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 [652]**) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1502] and lysophosphatidylcholine [1765]. It may also be activated by bacterial lipopolysaccharide [1687].

Further reading on Platelet-activating factor receptor

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

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

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

Nomenclature	PAF receptor
HGNC, UniProt	*PTAFR*, P25105
Selective agonists	methylcarbamyl PAF
Selective antagonists	foropafant (pK_i 10.3) [917], ABT-491 (pK_i 9.2) [35], CV-6209 (pIC_{50} 8.1–8.3) [768, 1686], L659989 (pK_i 7.8) [1008], apafant (pK_i 5.2–7.5) [1813, 2278]
Labelled ligands	[^{3}H]PAF (Agonist) [683, 1686]

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

Prokineticin receptors

G protein-coupled receptors → Prokineticin receptors

Overview: Prokineticin receptors, PKR_1 and PKR_2 (**provisional nomenclature as recommended by NC-IUPHAR [652]**) 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, [2102]) is a potent, non-selective agonist at prokineticin receptors [1521], while Bv8, an orthologue of PROK2 from amphibians (*Bombina sp.*, [1612]), is equipotent at recombinant PKR_1 and PKR_2 [1707], and has high potency in macrophage chemotaxis assays, which are lost in PKR_1-null mice.

Further reading on Prokineticin receptors

Boulberdaa M *et al.* (2011) Prokineticin receptor 1 (PKR1) signalling in cardiovascular and kidney functions. *Cardiovasc Res* **92**: 191-8 [PMID:21856786]

Negri L *et al.* (2018) The Prokineticins: Neuromodulators and Mediators of Inflammation and Myeloid Cell-Dependent Angiogenesis. *Physiol Rev* **98**: 1055-1082 [PMID:29537336]

Negri L *et al.* (2012) Bv8/PK2 and prokineticin receptors: a druggable pronociceptive system. *Curr Opin Pharmacol* **12**: 62-6 [PMID:22136937]

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]

Nomenclature	PKR_1	PKR_2
HGNC, UniProt	*PROKR1*, Q8TCW9	*PROKR2*, Q8NFJ6
Potency order of endogenous ligands	prokineticin-2 (*PROK2*, Q9HC23) > prokineticin-1 (*PROK1*, Q9HC23) > prokineticin-2β (*PROK2*) [364, 1396, 1521, 2208]	prokineticin-2 (*PROK2*, Q9HC23) > prokineticin-1 (*PROK1*, Q9HC23) > prokineticin-2β (*PROK2*) [364, 1396, 1521, 2208]
Agonists	MIT1 [1521]	MIT1 [1521]
Selective agonists	IS20 [715], IS1 [715]	–
Labelled ligands	[^{125}I]BH-MIT1 (Agonist) [1521]	[^{125}I]BH-MIT1 (Agonist) [1521]

Comments: Genetic mutations in *PROKR1* are associated with Hirschsprung's disease [2025], while genetic mutations in *PROKR2* are associated with hypogonadotropic hypogonadism with anosmia [542], hypopituitarism with pituitary stalk interruption [1973] and Hirschsprung's disease [2025]. PKR_2 has been recently identified as a receptor for *T. cruzi* natural infection [1158].

Prolactin-releasing peptide receptor

G protein-coupled receptors → Prolactin-releasing peptide receptor

Overview: The precursor (*PRLH*, P81277) for PrRP generates 31 and 20-amino-acid versions. QRFP43 (43RFa) (*QRFP*, P83859) (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from QRFP (P83859) and is also known as P518 or 26RFa. RFRP is an RF amide-related peptide [940] 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).

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]

Nomenclature	PrRP receptor
HGNC, UniProt	*PRLHR*, P49683
Potency order of endogenous ligands	PrRP-20 (*PRLH*, P81277) = PrRP-31 (*PRLH*, P81277) [1295]
Endogenous agonists	PrRP-20 (*PRLH*, P81277) [600, 1295], PrRP-31 (*PRLH*, P81277) [600, 1295]
Endogenous antagonists	neuropeptide Y (*NPY*, P01303) (pK_i 5.4) [1283]
Labelled ligands	[^{125}I]PrRP-20 (human) (Agonist) [1295], [^{125}I]PrRP31 (Agonist) [592]

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

Prostanoid receptors

G protein-coupled receptors → Prostanoid receptors

Overview: Prostanoid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors [2565]**) are activated by the endogenous ligands prostaglandins PGD_2, PGE_1, PGE_2 , $PGF_{2\alpha}$, PGH_2, prostacyclin [PGI_2] and thromboxane A_2. Differences and similarities between human and rodent prostanoid receptor orthologues, and their specific roles in pathophysiologic conditions are reviewed in [1750]. Measurement of the potency of PGI_2 and thromboxane A_2 is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

Further reading on Prostanoid receptors

Norel X *et al.* (2020) International Union of Basic and Clinical Pharmacology. CIX. Differences and Similarities between Human and Rodent Prostaglandin E_2 Receptors (EP1-4) and Prostacyclin Receptor (IP): Specific Roles in Pathophysiologic Conditions. *Pharmacol Rev* **72**: 910-968 [PMID:32962984]

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

Nomenclature	DP_1 receptor	DP_2 receptor
HGNC, UniProt	*PTGDR*, Q13258	*PTGDR2*, Q9Y5Y4
Potency order of endogenous ligands	PGD_2 > PGE_1 ≫ PGE_2 > $PGF_{2\alpha}$ > PGI_2, thromboxane A_2	PGD_2 ≫ $PGF_{2\alpha}$, PGE_2 > PGI_2, thromboxane A_2
Agonists	treprostinil [2282, 2535]	–
Selective agonists	BW 245C [202, 2566, 2567], L-644,698 [2566, 2567]	15(*R*)-15-methyl-PGD_2 [880, 1624, 2259]
Antagonists	–	fevipiprant (pK_d 9) [2283, 2284], AZD1981 (pIC_{50} 8.4) [1443], ramatroban (pK_i 7.4) [2259]
Selective antagonists	laropiprant (pK_i 10.1) [2252], BWA868C (pK_i 8.6–9.3) [202, 750, 2566], ONO-AE3-237 (pK_i 7.7) [942, 2366, 2368]	CAY 10471 (pIC_{50} 8.9) [2020, 2397]
Labelled ligands	[^{3}H]PGD_2 (Agonist) [2549, 2566]	[^{3}H]PGD_2 (Agonist) [1523, 2148]

Nomenclature	EP_1 receptor	EP_2 receptor	EP_3 receptor	EP_4 receptor
HGNC, UniProt	*PTGER1*, P34995	*PTGER2*, P43116	*PTGER3*, P43115	*PTGER4*, P35408
Potency order of endogenous ligands	PGE_2 > PGE_1 > $PGF_{2\alpha}$, PGI_2 > PGD_2, thromboxane A_2	PGE_2 = PGE_1 > $PGF_{2\alpha}$, PGI_2 > PGD_2, thromboxane A_2	PGE_2, PGE_1 > $PGF_{2\alpha}$, PGI_2 > PGD_2, thromboxane A_2	PGE_2 = PGE_1 > $PGF_{2\alpha}$, PGI_2 > PGD_2, thromboxane A_2
Endogenous agonists	–	PGE_2 [9, 2238, 2549]	PGE_2 (EP_3-III isoform) [9]	–
Agonists	17-phenyl-ω-trinor-PGE_2 [2138]	treprostinil [2282, 2535], PGE_1 [130]	misoprostol (methyl ester) (EP_3-III isoform) [9]	17-phenyl-ω-trinor-PGE_2 [2334]
Selective agonists	ONO-DI-004 [2273] – Mouse	ONO-AE1-259 [2273] – Mouse, omidenepag [1189], butaprost (free acid form) [9, 2238]	sulprostone (EP_3-III isoform) [9], ONO-AE-248 [658, 1431]	L902688 [659, 1333], ONO-AE1-329 [658, 659]
Antagonists	–	–	–	EP_4A (pK_i 7.6–8.5) [1461, 2646]
Selective antagonists	ONO-8711 (pK_i 9.2) [2500], SC-51322 (pK_i 7.9) [9]	PF-04418948 (PF-04418948 has weaker affinity at the EP2-receptor in guinea-pigs) (pK_B 8.3) [17, 182], TG6-129 (pK_B 8.1) [700]	L-826266 (EP_3-III isoform (pK_i=8.04 in the presence of HSA)) (pK_i 9.1) [1101], ONO-AE3-240 (pIC_{50} 8.8) [45] – Mouse, DG-041 (pK_i 8.4) [1099]	ONO-AE3-208 (pK_i 8.5), GW 627368 (pK_i 7–7.1) [2549, 2550]
Labelled ligands	[^{3}H]PGE_2 (Agonist) [9, 2138, 2549]	[^{3}H]PGE_2 (Agonist) [9, 2549]	[^{3}H]PGE_2 (Agonist) [9, 2549]	[^{3}H]PGE_2 (Agonist) [9, 492, 2535, 2549]

Nomenclature	FP receptor	IP receptor	TP receptor
HGNC, UniProt	*PTGFR*, P43088	*PTGIR*, P43119	*TBXA2R*, P21731
Potency order of endogenous ligands	$PGF_{2\alpha}$ > PGD_2 > PGE_2 > PGI_2, thromboxane A_2	PGI_2 ≫ PGE_1 > PGD_2, $PGF_{2\alpha}$ > thromboxane A_2	thromboxane A_2 = PGH_2 ≫ PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2
Endogenous agonists	–	PGI_2 [2165], PGE_1 [1518, 2240]	–
Agonists	ONO-9054 [2603]	iloprost [9, 2549], treprostinil [2535]	–
Selective agonists	fluprostenol [9], latanoprost (free acid form) [9]	cicaprost [9], MRE-269 [157, 1276]	U46619 [9]
Antagonists	–	–	ramatroban (pK_i 8) [2335]
Selective antagonists	AS604872 (pK_i 7.5) [421]	RO1138452 (pK_i 8.7) [190], RO3244794 (pA_2 8.5) [190]	vapiprost (pK_i 8.3–9.4) [72, 1444], SQ-29548 (pK_i 8.1–9.1) [9, 2281, 2549]
Labelled ligands	[^{3}H]$PGF_{2\alpha}$ (Agonist) [9, 10, 2549], [^{3}H](+)-fluprostenol (Agonist)	[^{3}H]iloprost (Agonist) [9, 201, 2535, 2549]	[^{125}I]SAP (Antagonist) (pK_d 7.7–9.3) [1685], [^{125}I]BOP (Agonist) [1643], [^{3}H]SQ-29548 (Antagonist) (pK_d 7.4–8.2) [9, 2549]

Comments: Whilst cicaprost is selective for IP receptors, it does exhibit moderate agonist potency at EP_4 receptors [9]. Apart from IP receptors, iloprost also binds to EP_1 receptors.

The EP_1 agonist 17-phenyl-ω-trinor-PGE_2 also shows agonist activity at EP_3 and EP_4 receptors [658, 2334]. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1392] and TP receptors [1245, 1957]. mRNA for the EP_3 receptor undergoes alternative splicing to produce variants which can interfere with signalling [1782] or generate complex patterns of G-protein ($G_{i/o}$, $G_{q/11}$, G_s and $G_{12,13}$) coupling (*e.g.* [1235, 1705]). The number of EP_3 receptor (protein) variants are variable depending on species, with five in human, three in rat and three in mouse. Putative receptor(s) for prostamide F (which as yet lack molecular correlates) and which preferentially recognize PGF2-1-ethanolamide and its analogues (*e.g.* Bimatoprost) have been identified, together with moderate-potency antagonists (*e.g.* AGN 211334) [2564].

The free acid form of AL-12182, AL12180, used in *in vitro* studies, has a EC_{50} 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 [2139].

References given alongside the TP receptor agonists I-BOP [1538] and STA_2 [72] use human platelets as the source of TP receptors for competition radio-ligand binding assays to determine the indicated activity values.

Pharmacological evidence for a second IP receptor, denoted IP_2, in the central nervous system [2306, 2503] and in the BEAS-2B human airway epithelial cell line [2552] is available. This receptor is selectively activated by 15R-17,18,19,20-tetranor-16-m-tolyl-isocarbacyclin (15R-TIC) and 15R-deoxy 17,18,19,20-tetranor-16-m-tolyl-isocarbacyclin (15-deoxy-TIC). However, molecular biological evidence for an IP_2 subtype is currently lacking.

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 [959]**) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmasks a tethered ligand (TL) at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. TL sequences at human PAR1-4 are SFLLRN-NH_2, SLIGKV-NH_2, TFRGAP-NH_2 and GYPGQV-NH_2, 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 [1939]. PAR2 activation by NE regulates inflammation and pain responses [1663, 2676] and triggers mucin secretion from airway epithelial cells [2681].

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]

García 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 UJ *et al.* (2010) Signal transduction by protease-activated receptors. *Br J Pharmacol* **160**: 191-203 [PMID:20423334]

Nomenclature	PAR1	PAR2	PAR3	PAR4
HGNC, UniProt	*F2R*, P25116	*F2RL1*, P55085	*F2RL2*, O00254	*F2RL3*, Q96RI0
Agonist proteases	thrombin (*F2*, P00734), activated protein C (*PROC*, P04070), matrix metalloproteinase 1 (*MMP1*, P45452), matrix metalloproteinase 13 (*MMP13*, P45452) [87]	Trypsin, tryptase, TF/VIIa, Xa; elastase, neutrophil expressed; cathepsin S [1076, 1937]	thrombin (*F2*, P00734)	thrombin (*F2*, P00734), trypsin, cathepsin G (*CTSG*, P08311)
Agonists	F16357	–	–	–
Selective agonists	TFLLR-NH_2 [415]	AY77 [2625], GB110 [123], 2-furoyl-LIGRLO-amide [1548], SLIGKV-NH_2 [1339], SLIGRL-NH_2 [1339]	–	AYPGKF-NH2, GYPGKF-NH2, GYPGQV-NH_2
Selective antagonists	vorapaxar (pK_i 8.1) [340], atopaxar (pIC_{50} 7.7) [1214], SCH-79797 (pIC_{50} 7.2) [23], RWJ-56110 (pIC_{50} 6.4) [55]	I-191 (pIC_{50} 7.1) [1075], AZ8838 (pK_d 6.5) [380], GB88 (pIC_{50} 5.7) [2257], P2pal18s [2130]	–	BMS-986120 (pK_d 10) [2561], YD-3 (pIC_{50} 6.9) [2516], ML354 (pIC_{50} 6.8) [2516], P4pal-10 [454], RAG8 (Agonist) [1938]
Allosteric modulators	–	AZ3451 (Negative) (pIC_{50} 7.6) [380]	–	–
Labelled ligands	[^{3}H]haTRAP (Agonist) [22]	2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH_2 (Agonist) [960], 2-furoyl-LIGRL[N[^{3}H]propionyl]-O-NH_2 (Agonist) [960], [^{3}H]2-furoyl-LIGRL-NH_2 (Selective Agonist) [1118], trans-cinnamoyl-LIGRLO [N-[^{3}H]propionyl]-NH_2 (Agonist) [33]	–	–
Comments	TFLLR-NH_2 is selective relative to the PAR_2 receptor [184, 1131].	2-Furoyl-LIGRLO-NH_2 activity was measured via calcium mobilisation in HEK 293 cells which constitutively coexpress human PAR_1 and PAR_2.	–	–

Comments: Endogenous serine proteases (EC 3.4.21.) active at the proteinase-activated receptors include: thrombin (*F2*, P00734), generated by the action of Factor X (*F10*, P00742) on liver-derived prothrombin (*F2*, P00734); trypsin, generated by the action of enterokinase (*TMPRSS15*, P98073) on pancreatic-derived trypsinogen (*PRSS1*, P07477); tryptase, a family of enzymes (α/β1 *TPSAB1*, Q15661 ; γ1 *TPSG1*, Q9NRR2; δ1 *TPSD1*, Q9BZJ3) secreted from mast cells; cathepsin G (*CTSG*, P08311) generated from leukocytes; liver-derived protein C (*PROC*, P04070) generated in plasma by thrombin (*F2*, P00734) and matrix metalloproteinase 1 (*MMP1*, P45452).

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 [1359]**; 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 [1334]. 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 Y_2 (37%) and galanin Gal_1 (35%) 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]

Leprince J *et al.* (2017) The Arg-Phe-amide peptide 26RFa/glutamine RF-amide peptide and its receptor: IUPHAR Review 24. *Br J Pharmacol* **174**: 3573-3607 [PMID:28613414]

Prévost G *et al.* (2019) Neuropeptide 26RFa (QRFP) is a key regulator of glucose homeostasis and its activity is markedly altered in obese/hyperglycemic mice. *Am J Physiol Endocrinol Metab* **317**: E147-E157 [PMID:31084498]

Nomenclature	QRFP receptor
HGNC, UniProt	*QRFPR*, Q96P65
Endogenous agonists	QRFP43 (43RFa) (*QRFP*, P83859) [684, 2218], QRFP26 (26RFa) (*QRFP*) [358, 1074]
Agonists	LV-2186 [44], LV-2172 [1719]
Selective antagonists	compound 25e (pIC_{50} 7.3) [735, 736]
Labelled ligands	[^{125}I]QRFP43 (human) (Agonist) [685, 2305], [^{125}I]26RFa (human) (Agonist) [277]

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

Relaxin family peptide receptors

Overview: Relaxin family peptide receptors (RXFP, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Relaxin family peptide receptors [131, 842]**) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are heterodimeric peptide hormones structurally related to insulin: relaxin-1 (*RLN1*, P04808), relaxin (*RLN2*, P04090), relaxin-3 (*RLN3*, Q8WXF3) (also known as INSL7), insulin-like peptide 3 (INSL3 (*INSL3*, P51460)) and INSL5 (*INSL5*, Q9Y5Q6). Species homologues of relaxin have distinct pharmacology and relaxin (*RLN2*, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [2109]. Relaxin-3 (*RLN3*, Q8WXF3) is the ligand for RXFP3 but it also binds to RXFP1 and RXFP4 and has differential affinity for RXFP2 between species [2108]. 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 [2127] and RXFP2 [951] 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 [2110]. INSL5 (*INSL5*, Q9Y5Q6) and relaxin-3 (*RLN3*, Q8WXF3) interact with their receptors using distinct residues in their B-chains for binding, and activation, respectively [991, 2560].

Further reading on Relaxin family peptide receptors

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Bathgate RAD *et al.* (2018) The relaxin receptor as a therapeutic target - perspectives from evolution and drug targeting. *Pharmacol Ther* **187**: 114-132 [PMID:29458108]

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]

Nomenclature	RXFP1	RXFP2
HGNC, UniProt	*RXFP1*, Q9HBX9	*RXFP2*, Q8WXD0
Potency order of endogenous ligands	relaxin (*RLN2*, P04090) = relaxin-1 (*RLN1*, P04808) > relaxin-3 (*RLN3*, Q8WXF3) [2256]	INSL3 (*INSL3*, P51460) > relaxin (*RLN2*, P04090) ≫ relaxin-3 (*RLN3*, Q8WXF3) [1268, 2256]
Agonists	ML290 [2583, 2586], (B7-33)H2 [978]	–
Antagonists	B-R13/17K H2 relaxin (pIC_{50} 5.7–6.7) [981, 1717]	–
Selective antagonists	–	A(9-26)INSL3 (pK_i 9.1) [980], A(10-24)INSL3 (pK_i 8.7) [980], A(C10/15S)INSL3 (pK_i 8.6) [2665], INSL3 B chain dimer analogue 8 (pK_i 8.5) [2135], A(Δ10/15C)INSL3 (pK_i 8.3) [2665], cyclic INSL3 B-chain analogue 6 (pK_i 6.7) [2133], INSL3 B-chain analogue (pK_i 5.1) [512], (des 1-8) A-chain INSL3 analogue [282]
Labelled ligands	[^{33}P]relaxin (human) (Agonist) [843, 2256], europium-labelled relaxin (Agonist) [2132], TamRLX (Agonist) [951], Nanoluciferase-labelled relaxin (Agonist) [2573], [^{125}I]relaxin (human) (Agonist)	[^{125}I]INSL3 (human) (Agonist) [1660], [^{33}P]relaxin (human) (Agonist) [843, 2256], europium-labelled INSL3 (Agonist) [2134], TamRLX (Agonist) [951]

Nomenclature	RXFP3	RXFP4
HGNC, UniProt	*RXFP3*, Q9NSD7	*RXFP4*, Q8TDU9
Potency order of endogenous ligands	relaxin-3 (*RLN3*, Q8WXF3) > relaxin-3 (B chain) (*RLN3*, Q8WXF3) > relaxin (*RLN2*, P04090) [1410]	INSL5 (*INSL5*, Q9Y5Q6) = relaxin-3 (*RLN3*, Q8WXF3) > relaxin-3 (B chain) (*RLN3*, Q8WXF3) [1408, 1409]
Agonists	compound 4 [510], B1-27 [1336]	compound 4 [510], JK1 [1398]
Endogenous antagonists	INSL5 (*INSL5*, Q9Y5Q6) (pK_i 7) [2686]	–
Antagonists	R3(BΔ23-27)R/I5 chimeric peptide (pIC$_{50}$ 9.2) [1258], R3 B1-22R (pK_i 7.7) [884]	R3(BΔ23-27)R/I5 chimeric peptide (pIC$_{50}$ 8–8.6) [883, 1258]
Selective antagonists	minimised relaxin-3 analogue 3 (pK_i 7.6) [2131], R3-B1-22R (pK_i 7.4) [883]	minimised relaxin-3 analogue 3 (pIC$_{50}$ 6.6) [2131]
Labelled ligands	[^{125}I]relaxin-3 (human) (Agonist) [1410], [^{125}I]relaxin-3-B/INSL5 A chimera (Agonist) [1408], europium-labelled relaxin-3-B/INSL5 A chimera (Agonist) [883], NanoLuc R3/I5 chimera (Agonist) [2485]	[^{125}I]relaxin-3 (human) (Agonist) [1409], [^{125}I]relaxin-3-B/INSL5 A chimera (Agonist) [1408], europium-labelled mouse INSL5 (Agonist) [147], europium-labelled relaxin-3-B/INSL5 A chimera (Agonist) [883], europium-labelled INSL5 (pK_d 8.3) [883], NanoLuc R3/I5 chimera (Agonist) [2485]

Comments: Relaxin (*RLN2*, P04090) is the cognate peptide ligand for RXFP1 and is a potential treatment for heart failure [562]. Relaxin has vasodilatory, anti-fibrotic, angiogenic, anti-apoptotic and anti-inflammatory effects. A small molecule allosteric agonist ML290 has been developed [2143, 2586], that displays anti-fibrotic properties [1103], and a relaxin B-chain mimetic peptide B7-33 has been developed which has cell specific signaling properties [979]. The antifibrotic actions of relaxin are dependent on the angiotensin receptor AT_2 [401] and are blocked by either AT_1 or AT_2 receptor antagonists. INSL3 (*INSL3*, P51460) is the cognate peptide for RXFP2 and is a circulating hormone that in males is essential for testicular descent *in utero* [1704] and in females has important roles in ovarian follicle function [1035]. In adults, INSL3 has potential roles in testicular function [1036] and the musculo-skeletal system [504]. RXFP2 is also present in brain, associated with cortico-thalamic motor circuits [2114]. cAMP elevation is the major signalling pathway for both RXFP1 and RXFP2 [989, 990], but RXFP1 also activates MAP kinases, nitric oxide signalling, and tyrosine kinase phosphorylation; and relaxin can interact with glucocorticoid receptors [844]. RXFP1 displays ultra-sensitive responses to sub picomolar levels of relaxin [422]. Receptor expression profiles suggest that RXFP3 is a brain neuropeptide receptor [1457, 1458, 2195] and RXFP4 a gut hormone receptor [699]. The brain relaxin-3/RXFP3 system modulates feeding [698, 699, 883, 2131, 2194] *via* effects in hypothalamus [495, 698, 1116, 1117], anxiety [1520, 2031, 2035, 2656], reward and motivated, goal-directed behaviours [973, 2031, 2467], and spatial and social memory [37, 836, 837]. Of the other relaxin peptides, relaxin-3 (*RLN3*, Q8WXF3) is an agonist at RXFP3 and RXFP4 whereas INSL5 (*INSL5*, Q9Y5Q6) is an agonist at RXFP4 and a weak antagonist at RXFP3. Single chain peptide agonists and antagonists have been developed for RXFP3 [882, 1336] and a small molecular weight agonist active at RXFP3 and RXFP4 [510]. INSL5 (*INSL5*, Q9Y5Q6) is secreted from enteroendocrine L cells and the INSL5/RXFP4 system affects food intake [806], colon motility [540] and glucose homeostasis [1449]. RXFP3 and RXFP4 couple to $G_{i/o}$ and inhibit adenylyl cyclase [1410, 2416], and also cause Erk1/2 phosphorylation [2416]. RXFP4 also causes phosphorylation of p38MAPK, Akt and S6RP [58] and GLP-1 secretion *in vitro* [57]. There is evidence that at RXFP3, relaxin (*RLN2*, P04090) is a biased ligand compared to the cognate ligand relaxin-3 (*RLN3*, Q8WXF3) [2416].

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_1-SST_5; **nomenclature as agreed by the NC-IUPHAR Subcommittee on Somatostatin Receptors [823]**). 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 [500].

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) *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]

Nomenclature	SST_1 receptor	SST_2 receptor	SST_3 receptor	SST_4 receptor	SST_5 receptor
HGNC, UniProt	*SSTR1*, P30872	*SSTR2*, P30874	*SSTR3*, P32745	*SSTR4*, P31391	*SSTR5*, P35346
Agonists	pasireotide [2087]	pasireotide [2087], veldoreotide [18]	pasireotide [2087]	NNC269100 [1420], veldoreotide [18]	pasireotide [2087], veldoreotide [18]
Selective agonists	L-797,591 [2002], Des-Ala^{1,2,5}-[D-Trp^{8}, IAmp^{9}]SRIF [604]	L-054,522 [2615], BIM 23027 [325], L-779,976 [2002], octreotide [274, 1825, 2166, 2167, 2168, 2615], lanreotide [274, 1825, 2166, 2167, 2168]	L-796,778 [2002]	L-803,087 [2002], J-2156 [601]	BIM 23052 [1569, 2166, 2167, 2168], L-817,818 [2002]
Selective antagonists	SRA880 (pK_d 8–8.1) [984]	DOTA-$_{JR11}$ [338]	MK-4256 (pIC_{50} 9.2) [900], ACQ090 (pK_i 7.9) [985]	–	S5A1 (pK_i 9.3) [623]

Comments: [^{125}I]Tyr^{11}-SRIF-14, [^{125}I]LTT-SRIF-28, [^{125}I]CGP 23996 and [^{125}I]Tyr^{10}-CST14 may be used to label somatostatin receptors nonselectively. A number of nonpeptide subtype-selective agonists have been synthesised [2002]. Octreotide and lanreotide are being used in the treatment of SST_2-expressing neuroendocrine tumors and pasireotide for SST_5-expressing neuroendocrine tumors. A novel peptide somatostatin analogue, veldoreotide (COR-005), has affinity for SST_2, SST_4 and SST_5 receptors and is a potent inhibitor of GH secretion [1883, 2154].

Succinate receptor

G protein-coupled receptors → Succinate receptor

Overview: **Nomenclature as recommended by NC-IUPHAR [485]**. The Succinate receptor was 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 the immune response.

Further reading on Succinate receptor

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]

Krzak G *et al.* (2021) Succinate Receptor 1: An Emerging Regulator of Myeloid Cell Function in Inflammation. *Trends Immunol* **42**: 45-58 [PMID:33279412]

Lückmann M *et al.* (2020) Structural basis for GPCR signaling by small polar versus large lipid metabolites-discovery of non-metabolite ligands. *Curr Opin Cell Biol* **63**: 38-48 [PMID:31951921]

Nomenclature	succinate receptor
HGNC, UniProt	*SUCNR1*, Q9BXA5
Endogenous agonists	succinic acid [901, 2218], maleic acid [744, 752, 901]
Agonists	compound 31 (Partial agonist) [1971], *cis*-epoxysuccinic acid [2376], compound 130 (Partial agonist) [2376], *cis*-epoxysuccinic acid [744]
Antagonists	NF-56-EJ40 (pK_i 7.8) [832]

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.* [2557] 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.

Tachykinin receptors

G protein-coupled receptors → Tachykinin receptors

Overview: Tachykinin receptors (**provisional nomenclature as recommended by NC-IUPHAR [652]**) are activated by the endogenous peptides substance P (*TAC1*, P20366) (SP), neurokinin A (*TAC1*, P20366) (NKA; previously known as substance K, neurokinin α, neuromedin L), neurokinin B (*TAC3*, Q9UHF0) (NKB; previously known as neurokinin β, neuromedin K), neuropeptide K (*TAC1*, P20366) and neuropeptide γ (*TAC1*, P20366) (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in *in vitro* pharmacology exist for all three receptors, in the context of nonpeptide ligands. 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.

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**: 279-88 [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 USA* **115**: 13264-13269 [PMID:30538204]

Nomenclature	NK_1 receptor	NK_2 receptor	NK_3 receptor
HGNC, UniProt	*TACR1*, P25103	*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	substance P-OMe [2351]	–	–
Selective agonists	[Sar^9,$Met(O_2)^{11}$]SP [2351], septide [151, 879], [Pro^9]SP [2367] – Rat	[Lys^5,Me-Leu^9,Nle^{10}]NKA-(4-10) [1535] – Rat, GR64349 [507] – Rat, [βAla^8]neurokinin A-(4-10) [595]	[$Phe(Me)^7$]neurokinin B [2060, 2061], senktide [2060, 2061, 2351]
Antagonists	L760735 (pIC_{50} 9.7) [874]	–	–
Selective antagonists	aprepitant (pK_i 10.1) [838, 839], CP 99994 (pK_i 9.3–9.7) [60, 2061], RP67580 (pIC_{50} 7.7) [651]	GR94800 (pK_i 9.8) [238], saredutant (pK_i 9.4–9.7) [60, 595, 2061], GR 159897 (pK_d 7.8–9.5) [160, 595, 2202], MEN10627 (pK_i 9.2) [747], nepadutant (pK_i 8.5–8.7) [327, 418]	osanetant (pK_i 8.4–9.7) [60, 136, 417, 594, 1111, 1796, 2060, 2061, 2351], talnetant (pK_i 7.4–9) [154, 748, 2060, 2061], PD157672 (pIC_{50} 7.8–7.9) [196, 2351]
Labelled ligands	[^{125}I]L703,606 (Antagonist) (pK_d 9.5) [662], [^{125}I]BH-[Sar^9,$Met(O_2)^{11}$]SP (Agonist) [2372] – Rat, [^{3}H]SP (human, mouse, rat) (Agonist) [102], [^{125}I]SP (human, mouse, rat) (Agonist), [^{18}F]SPA-RQ (Antagonist) [388]	[^{3}H]saredutant (Antagonist) (pK_d 9.7) [804] – Rat, [^{125}I]NKA (human, mouse, rat) (Agonist) [2498], [^{3}H]GR100679 (Antagonist) (pK_d 9.2) [834]	[^{3}H]osanetant (Antagonist) (pK_d 9.9), [^{3}H]senktide (Agonist) [815] – Guinea pig, [^{125}I][$MePhe^7$]NKB (Agonist)

Comments: The NK_1 receptor has also been described to couple to G proteins other than $G_{q/11}$ [2015]. The crystal structure of the human NK_1 receptor in complex with antagonists has been determined [2095, 2632]. The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to substance P (*TAC1*, P20366) on the NK_1 receptor. There are additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK_3 receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells [547, 1244]. NK_1 receptor antagonists affect cellular physiology including inflammation, apoptosis and cell trafficking and have a role in therapeutics [1669, 2225].

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 [652]**) 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 [2267]. $[^3H]$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 [1559].

Further reading on Thyrotropin-releasing hormone receptors

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

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

Nomenclature	TRH_1 receptor	TRH_2 receptor
HGNC, UniProt	*TRHR*, P34981	–
Antagonists	diazepam (pK_i 5.2) [561] – Rat	–
Selective antagonists	midazolam (pK_i 5.5) [561] – Rat, chlordiazepoxide (pK_i 4.8) [561] – Rat, chlordiazepoxide (pK_i 4.7) [2248] – Mouse	–
Comments	–	A class A G protein-coupled receptor: not present in man

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 [219], where 15 mammalian orthologues were identified and divided into two families. The TA_1 receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Trace amine receptor [1477]**) has affinity for the endogenous trace amines tyramine, β-phenylethylamine and octopamine in addition to the classical amine dopamine [219]. Emerging evidence suggests that TA_1 is a modulator of monoaminergic activity in the brain [2588] with TA_1 and dopamine D_2 receptors shown to form constitutive heterodimers when co-expressed [611]. In addition to trace amines, receptors can be activated by amphetamine-like psychostimulants, and endogenous thyronamines.

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]

Nomenclature	TA_1 receptor
HGNC, UniProt	*TAAR1*, Q96RJ0
Potency order of endogenous ligands	tyramine > β-phenylethylamine > octopamine = dopamine [219]
Agonists	RO5166017 [1970]
Antagonists	EPPTB (Inverse agonist) (pIC_{50} 5.1) [236]
Labelled ligands	[^{3}H]tyramine (Agonist) [219]

Comments: In addition to TA_1, in man there are up to 5 functional TAAR genes (TAAR2,5,6,8,9). See [219] 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_s [219].

TAAR3, in some individuals, and *TAAR4* are pseudogenes in man, although functional in rodents. The signalling characteristics and pharmacology of $TAAR_5$ (PNR, Putative Neurotransmitter Receptor: *TAAR5*, O14804), $TAAR_6$ (Trace amine receptor 4, TaR-4: *TAAR6*, 96RI8), $TAAR_8$ (Trace amine receptor 5, GPR102: *TAAR8*, Q969N4) and $TAAR_9$ (trace amine associated receptor 9: TAAR9, 96RI9) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have affinity for rodent cloned trace amine receptors, including TA_1 [2073]. An antagonist EPPTB has recently been described with a pK_i of 9.1 at the mouse TA_1 but >5.3 for human TA_1 [2230].

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 [556, 652, 2437]**) 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 [163, 2436]. Several structural forms of U-II exist in fish and amphibians [2437]. The goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* [49, 452, 1418, 1641, 1753]. Human urotensin-II (*UTS2*, O95399), an 11-amino-acid peptide [452], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding [258, 1187, 1360]. 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 [451]. A second endogenous ligand for the UT has been discovered in rat [2260]. This is the urotensin II-related peptide (*UTS2B*, Q765I0), an octapeptide that is derived from a different gene, but shares the C-terminal sequence (CFWKYCV) common to U-II from other species. Identical sequences to rat urotensin II-related peptide (*UTS2B*, Q765I0) are predicted for the mature mouse and human peptides [563]. UT exhibits relatively high sequence identity with somatostatin, opioid and galanin receptors [2437].

Further reading on Urotensin receptor

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

Nomenclature	UT receptor
HGNC, UniProt	*UTS2R*, Q9UKP6
Endogenous agonists	urotensin II-related peptide (*UTS2B*, Q765I0) [563, 2260], urotensin-II (*UTS2*, O95399) [49, 1418, 1641, 1753]
Selective agonists	[Pen^5]U-(4-11) (human) [802], U-II-(4-11) (human) [802], [3-iodo-Tyr^6]U-II-(4-11) (human) [1280], Urolinin [113], FL104 [1345, 1347], AC-7954 [463, 1346]
Selective antagonists	DS37001789 (pIC$_{50}$ 9.1) [1740], RCI-0879 (pIC$_{50}$ 9) [2317], urantide (pK_i 8.3) [1820], SR101099 (pIC$_{50}$ 8) [1800], [Orn^5]URP (pK_i 7.2) [528] – Rat, palosuran (pIC$_{50}$ 7.1) [428], SB-611812 (pK_i 6.6) [1935], [Cha^6]U-II-(4-11) (pK_i 6.4) [359] – Rat
Labelled ligands	[^{125}I]U-II (human) (Agonist) [49, 359, 1476], [^{125}I]N-biotin-[Ahx^0, Bpa^3]U-II (human) [541]

Comments: In the human vasculature, human urotensin-II (*UTS2*, O95399) elicits both vasoconstrictor (pD_2 9.3-10.1, [1476]) and vasodilator (pIC$_{50}$ 10.3-10.4, [2239]) responses.

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 [652]**) 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 [506].

Further reading on Vasopressin and oxytocin receptors

Carter CS *et al.* (2020) Is Oxytocin "Nature's Medicine"? *Pharmacol Rev* **72**: 829-861 [PMID:32912963]

Gulliver D *et al.* (2019) Targeting the Oxytocin System: New Pharmacotherapeutic Approaches. *Trends Pharmacol Sci* **40**: 22-37 [PMID:30509888]

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]

Russell JA. (2018) Fifty Years of Advances in Neuroendocrinology. *Brain Neurosci Adv* **2**: 2398212818812014 [PMID:32166160]

Nomenclature	V_{1A} receptor	V_{1B} receptor
HGNC, UniProt	*AVPR1A*, P37288	*AVPR1B*, P47901
Potency order of endogenous ligands	vasopressin (*AVP*, P01185) > oxytocin (*OXT*, P01178) [29, 379, 446, 1688, 2042, 2289, 2336]	vasopressin (*AVP*, P01185) > oxytocin (*OXT*, P01178) [29, 379, 519, 803, 1688, 2042, 2289, 2337]
Selective agonists	selepressin [1297], F180 [56, 446]	d[Leu^4]LVP [1841], d[Cha^4]AVP [519, 803]
Antagonists	conivaptan (pK_i 8.2–8.4) [2289, 2290]	nelivaptan (pK_i 8.4–9.3) [803, 2126]
Selective antagonists	relcovaptan (pK_i 8.1–9.3) [29, 446, 803, 2289, 2336], d$(CH_2)_5$[Tyr(Me)^2,Arg^8]VP (pK_i 9)	–
Labelled ligands	[^{125}I]OH-LVA (Antagonist) (pK_d 10.3–10.4) [390, 446], [^{3}H]AVP (human, mouse, rat) (Agonist) [248, 390, 2289, 2290, 2336], [^{3}H]d$(CH_2)_5$[Tyr(Me)^2]AVP (Antagonist) (pK_d 9)	[^{3}H]AVP (human, mouse, rat) (Agonist) [519, 2042, 2289, 2290, 2337]

Nomenclature	V_2 receptor	OT receptor
HGNC, UniProt	*AVPR2*, P30518	*OXTR*, P30559
Potency order of endogenous ligands	vasopressin (*AVP*, P01185) > oxytocin (*OXT*, P01178) [29, 379, 390, 1841, 2124, 2289, 2602]	oxytocin (*OXT*, P01178) > vasopressin (*AVP*, P01185) [29, 390, 391, 420, 803, 1060, 1182]
Selective agonists	VNA932 [620], OPC-51803 [1688], d[Val^4,DArg^8]VP	[Thr^4,Gly^7]OT [391, 591, 1060]
Antagonists	–	L-371,257 (pK_i 8.8) [803]
Selective antagonists	conivaptan (pK_i 9.4) [462], tolvaptan (pK_i 9.4) [2602], satavaptan (pK_i 8.4–9.3) [29, 447, 2123, 2124, 2289], lixivaptan (Inverse agonist) (pK_i 8.9–9.2) [39, 2124], d$(CH_2)_5$[D-Ile^2,Ile^4]AVP (pK_i 6.9–8.4) [447, 2124], mozavaptan (Inverse agonist) (pK_i 7.4–8.1) [447, 2124, 2289, 2337, 2602]	retosiban (pK_i 9–9.2) [1386, 1543], SSR126768A (pK_i 8.8–9.1) [2125], desGlyNH$_2$-d$(CH_2)_5$[Tyr(Me)^2,Thr^4,Orn^8]OT (pK_i 8.5), L-372662 (pK_i 8.4) [148]
Labelled ligands	[^{3}H]AVP (human, mouse, rat) (Agonist) [447, 1688, 2289, 2290, 2602], [^{3}H]dDAVP (Agonist) [1508], [^{3}H]desGly-NH$_2$[D-Ile^2,Ile^4]VP (pK_d 8.6)	[^{125}I]d$(CH_2)_5$[Tyr(Me)^2,Thr^4,Orn^8,Tyr-NH$_2$^{9}]OVT (Antagonist) (pK_d 10), [^{3}H]OT (human, mouse, rat) (Agonist) [390, 680, 1060, 1182], [^{111}In]DOTA-dLVT (pK_d 8.3) [389]

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$(CH_2)_5$[D-Ile^2,Ile^4]AVP and [^{3}H]desGly-NH$_2$[D-Ile^2,Ile^4]VP) exhibit low affinity at human V_2 receptors [34]. Similarly, desmopressin (dDVAP) is more V_2 selective in the rat than in the human [2042]. The gene encoding the V_2 receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [177]. Agonist d[Cha^4]AVP is selective only for the human and bovine V_{1B} receptors [519], while d[Leu^4]LVP has high affinity for the rat V_{1b} receptor [1841]. There are a group of V_{1B} receptor antagonists - TASP0233278, TASP0380325 and TASP0434299 that exhibit good selectivity profiles (human, rat) [1016, 1213]. Knockouts of vasopressin and oxytocin receptors have system-specific 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).

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 [871, 872]**) are activated by the endogenous peptides VIP (*VIP*, P01282), PACAP-38 (*ADCYAP1*, P18509), PACAP-27 (*ADCYAP1*, P18509), peptide histidine isoleucineamide (PHI {Mouse, Rat}), peptide histidine methionineamide (PHM (*VIP*, P01282)) and peptide histidine valine (PHV (*VIP*, P01282)). $VPAC_1$ and $VPAC_2$ receptors display comparable affinity for the PACAP peptides, PACAP-27 (*ADCYAP1*, P18509) and PACAP-38 (*ADCYAP1*, P18509), and VIP (*VIP*, P01282), whereas PACAP-27 (*ADCYAP1*, P18509) and PACAP-38 (*ADCYAP1*, P18509) are >100 fold more potent than VIP (*VIP*, P01282) as agonists of most isoforms of the PAC_1 receptor. However, one splice variant of the human PAC_1 receptor has been reported to respond to PACAP-38 (*ADCYAP1*, P18509), PACAP-27 (*ADCYAP1*, P18509) and VIP (*VIP*, P01282) with comparable affinity [482]. PG 99-465 [1633] 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 [530]. 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 [1647]. Two deletion variants of maxadilan, M65 [2388] and Max.d.4 [1648] have been reported to be PAC_1 receptor antagonists, but these peptides have not been extensively characterised.

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**: 265-70 [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]

Nomenclature	PAC_1 receptor	$VPAC_1$ receptor	$VPAC_2$ receptor
HGNC, UniProt	*ADCYAP1R1*, P41586	*VIPR1*, P32241	*VIPR2*, P41587
Potency order of endogenous ligands	PACAP-27 (*ADCYAP1*, P18509), PACAP-38 (*ADCYAP1*, P18509) ≫ VIP (*VIP*, P01282)	VIP (*VIP*, P01282), PACAP-27 (*ADCYAP1*, P18509), PACAP-38 (*ADCYAP1*, P18509) ≫ GHRH (*GHRH*, P01286), PHI {Pig}, secretin (*SCT*, P09683)	VIP (*VIP*, P01282), PACAP-38 (*ADCYAP1*, P18509), PACAP-27 (*ADCYAP1*, P18509) > PHI {Pig} ≫ GHRH (*GHRH*, P01286), secretin (*SCT*, P09683)
Selective agonists	maxadilan [530], maxadilan [530]	[Lys^{15},Arg^{16},Leu^{27}]VIP-(1-7)/GRF-(8-27)-NH_2 [1627], [$Ala^{11,22,28}$]VIP [1729]	Ro 25-1553 [788, 1098, 1627], Ro 25-1392 [2581]
Selective antagonists	–	PG 97-269 (pIC_{50} 8.7) [787, 1098]	–
Labelled ligands	[^{125}I]PACAP-27 (Agonist) [1878]	[^{125}I]VIP (human, mouse, rat) (Agonist) [1729], [^{125}I]PACAP-27 (Agonist)	[^{125}I]VIP (human, mouse, rat) (Agonist) [1729], [^{125}I]PACAP-27 (Agonist)

Comments: Subtypes of PAC_1 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 [2420], or from alternative splicing of PAC_1 receptor mRNA [2223].

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