THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: G PROTEIN-COUPLED RECEPTORS

Stephen P.H. Alexander*[1], Helen E. Benson[2], Elena Faccenda[2], Adam J. Pawson[2], Joanna L. Sharman[2], Michael Spedding[3], John A. Peters[4], Anthony J. Harmar[2] and CGTP Collaborators

*Author for correspondence; steve.alexander@guidetopharmacology.org
[1]*School of Life Sciences, University of Nottingham Medical School, Nottingham NG7 2UH, UK*
[2]*The University/BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh EH16 4TJ, UK*
[3]*Spedding Research Solutions SARL, Le Vésinet 78110, France*
[4]*Neuroscience Division, Medical Education Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK*

Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

G protein-coupled receptors are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An introduction to G protein-coupled receptors

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)(Mombaerts, 2004). The remaining ~350 non-sensory GPCRs mediate intercellular 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 (Overington *et al.*, 2006; Rask-Andersen *et al.*, 2011), although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs (Kolakowski, 1994) divided them, on the basis of sequence homology, into six classes. These classes and their prototype members were as follows: **Class A** (rhodopsin-like), **Class B** (secretin receptor family), **Class C** (metabotropic glutamate), **Class D** (fungal mating pheromone receptors), **Class E** (cyclic AMP receptors) and **Class F** (frizzled/smoothened). Of these, classes D and E are not found in vertebrates. An alternative classification scheme "GRAFS" (Schioth & Fredriksson, 2005) 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 (Page 1468) and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man (Mombaerts, 2004).

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 (Page 1469) 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 (Promel *et al.*, 2013).

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)) (Harmar, 2001).

GPCR families

Family	Class A (**R**hodopsin)	Class B (**S**ecretin)	Class C (**G**lutamate)	**A**dhesion	**F**rizzled
Receptors with known ligands	197[a]	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 Davenport *et al.* (2013) [b]Olender *et al.* (2008) ; [c]Mombaerts (2004); [d]Terakita (2005).

Acknowledgements

We are extremely grateful to the long list of collaborators who assisted in the construction of the Concise Guide to PHARMACOLOGY 2013/14 and to the website www.guidetopharmacology.org,, as well as to the Guides to Receptors and Channels. We are also extremely grateful for the financial contributions from the British Pharmacological Society, the International Union of Basic and Clinical Pharmacology and the Wellcome Trust (099156/Z/12/Z]), which support the website.

Conflict of interest

The authors state that there is no conflict of interest to disclose.

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *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**: 967–986. [PMID:23686350]

Harmar AJ. (2001) Family-B G-protein-coupled receptors. *Genome biology* **2**: REVIEWS3013. [PMID:11790261]

Kolakowski LF, Jr. (1994) GCRDb: a G-protein-coupled receptor database. *Receptors & channels* **2**: 1–7.

Mombaerts P. (2004) Genes and ligands for odorant, vomeronasal and taste receptors. *Nat Rev Neurosci* **5**: 263–278.

Olender T, Lancet D, Nebert DW. (2008) Update on the olfactory receptor (OR) gene superfamily. *Human genomics* **3**: 87–97.

Overington JP, Al-Lazikani B, Hopkins AL. (2006) How many drug targets are there? *Nat Rev Drug Discov* **5**: 993–996. [PMID:17139284]

Promel S, Langenhan T, Arac D. (2013) Matching structure with function: the GAIN domain of Adhesion-GPCR and PKD1-like proteins. *Trends Pharmacol Sci* **34**: 470–478. [PMID:23850273]
Rask-Andersen M, Almen MS, Schioth HB. (2011) Trends in the exploitation of novel drug targets. *Nat Rev Drug Discov* **10**: 579–590. [PMID:21804595]
Schioth HB, Fredriksson R. (2005) The GRAFS classification system of G-protein coupled receptors in comparative perspective. *Gen Comp Endocrinol* **142**: 94–101. [PMID:15862553]
Terakita A. (2005) The opsins. *Genome Biol* **6**: 213. [PMID:15774036]

List of records presented

1462 Orphan GPCRs
1471 5-Hydroxytryptamine receptors
1474 Acetylcholine receptors (muscarinic)
1476 Adenosine receptors
1478 Adhesion Class GPCRs
1480 Adrenoceptors
1484 Angiotensin receptors
1485 Apelin receptor
1486 Bile acid receptor
1487 Bombesin receptors
1488 Bradykinin receptors
1489 Calcitonin receptors
1491 Calcium-sensing receptors
1492 Cannabinoid receptors
1494 Chemerin receptor
1495 Chemokine receptors
1500 Cholecystokinin receptors
1501 Complement peptide receptors
1502 Corticotropin-releasing factor receptors
1503 Dopamine receptors
1505 Endothelin receptors
1506 Estrogen (G protein-coupled) receptor
1507 Formylpeptide receptors
1508 Free fatty acid receptors
1510 Frizzled Class GPCRs
1511 $GABA_B$ receptors
1513 Galanin receptors
1514 Ghrelin receptor
1515 Glucagon receptor family
1517 Glycoprotein hormone receptors
1518 Gonadotrophin-releasing hormone receptors
1519 GPR18, GPR55 and GPR119
1520 Histamine receptors
1521 Hydroxycarboxylic acid receptors
1522 Kisspeptin receptors
1523 Leukotriene, lipoxin and oxoeicosanoid receptors
1525 Lysophospholipid (LPA) receptors
1526 Lysophospholipid (S1P) receptors
1527 Melanin-concentrating hormone receptors
1528 Melanocortin receptors
1529 Melatonin receptors
1530 Metabotropic glutamate receptors
1532 Motilin receptor
1533 Neuromedin U receptors
1534 Neuropeptide FF/neuropeptide AF receptors
1535 Neuropeptide S receptor
1536 Neuropeptide W/neuropeptide B receptors
1537 Neuropeptide Y receptors
1538 Neurotensin receptors
1539 Opioid receptors
1541 Orexin receptors
1542 Oxoglutarate receptor
1543 P2Y receptors
1545 Parathyroid hormone receptors
1546 Peptide P518 receptor
1547 Platelet-activating factor receptor
1548 Prokineticin receptors
1549 Prolactin-releasing peptide receptor
1550 Prostanoid receptors
1552 Proteinase-activated receptors
1553 Relaxin family peptide receptors
1555 Somatostatin receptors
1556 Succinate receptor
1557 Tachykinin receptors
1558 Thyrotropin-releasing hormone receptors
1559 Trace amine receptor
1560 Urotensin receptor
1561 Vasopressin and oxytocin receptors
1562 VIP and PACAP receptors

Orphan GPCRs

Class A Orphans

Overview: Table 1 lists a number of putative GPCRs identified by IUPHAR [24], for which preliminary evidence for an endogenous ligand has been published, or for which there exists a potential link to a disease, or disorder. 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.

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 (see page 1519).

Table 1
Class A orphan GPCRs with putative endogenous ligands

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)	Selective agonists (pK_i)	Comment
GPR1	*GPR1*, P46091	–	chemerin (*RARRES2*, Q99969) (pK_d 8.28) [2]	–	–	Reported to act as a co-receptor for HIV [86].
GPR3	*GPR3*, P46089	G_s	–	–	–	sphingosine 1-phosphate was reported to be an endogenous agonist [97], but this finding was not replicated in subsequent studies [106]. Reported to activate adenylyl cyclase constitutively through G_s [21]. Gene disruption results in premature ovarian aging [55], reduced β-amyloid deposition [96] and hypersensitivity to thermal pain [81] in mice.
GPR4	*GPR4*, P46093	G_s	–	–	–	An initial report suggesting activation by lysophosphatidylcholine and sphingosylphosphorylcholine [111] has been retracted [112]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as protein-sensing receptors detecting acidic pH [17,85]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [113].
GPR6	*GPR6*, P46095	G_s	–	–	–	An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC_{50} value of 39nM) [36,97] was not repeated by β-arrestin PathHunter[TM] assays [90,106]. Reported to activate adenylyl cyclase constitutively through G_s and to be located intracellularly [75]. Gpr6-deficient mice showed reduced striatal cyclic AMP production *in vitro* and selected alterations in instrumental conditioning *in vitro*. [62].
GPR12	*GPR12*, P47775	–	–	–	–	Reports that sphingosine 1-phosphate was a ligand of GPR12 [35,97] have not been replicated in β-arrestin-based assays [90,106]. Gene disruption results in dyslipidemia and obesity [6].
GPR15	*GPR15*, P49685	–	–	–	–	Reported to act as a co-receptor for HIV [19]. In an infection-induced colitis model, Gpr15 knockout mice were more prone to tissue damage and inflammatory cytokine expression [47].

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)	Selective agonists (pK_i)	Comment
GPR17	*GPR17*, Q13304	–	LTC_4 (pEC_{50} 7.83 – 9.48) [16], LTD_4 (pEC_{50} 8.14 – 8.36) [16], UDP-glucose (pEC_{50} 5.92 – 9.52) [5,16], UDP-galactose (pEC_{50} 5.96 – 8.92) [5,16], UDP (pEC_{50} 5.97 – 8.8) [5,16]	–	–	Reported to be a dual leukotriene and UDP receptor [16]. 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 [17]. Reported to antagonize $CysLT_1$ receptor signalling in vivo and *in vitro* [65].
GPR20	*GPR20*, Q99678	–	–	–	–	Reported to inhibit adenylyl cyclase constitutively through $G_{i/o}$ [30]. GPR20 deficient mice exhibit hyperactivity characterised by increased total distance travelled in an open field test [8].
GPR22	*GPR22*, Q99680	$G_{i/o}$	–	–	–	Gene disruption results in increased severity of functional decompensation following aortic banding [1]. Identified as a susceptibility locus for osteoarthritis [23,46,98].
GPR26	*GPR26*, Q8NDV2	G_s	–	–	–	Has been reported to activate adenylyl cyclase constitutively through G_s [40]. Gpr26 knockout mice show increased levels of anxiety and depression-like behaviours [108].
GPR31	*GPR31*, O00270	–	12S-HETE (Selective) (pEC_{50} 9.55 - Mouse) [27]	–	–	–
GPR32	*GPR32*, O75388	Not yet established	resolvin D1 (Selective) (pEC_{50} 11.06) [51], LXA_4 (Selective) (pEC_{50} 9.7) [51]	[^{3}H]resolvin D1 (Agonist) ($2x10^{-10}$ M) [51]	–	resolvin D1 (more potently than LxA4) has been demonstrated to activate GPR32 in two publications [15,51]. The pairing was not replicated in a recent study based on β-arrestin recruitment [90]. GPR32 is a pseudogene in mice and rats.
GPR34	*GPR34*, Q9UPC5	G_i/G_o	lysophosphatidylserine (Selective) (pEC_{50} 6.57 – 6.89) [48,91]	–	–	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 β-arrestin recruitment [90]. Fails to respond to a variety of lipid-derived agents [106]. Gene disruption results in an enhanced immune response [59].
GPR35	*GPR35*, Q9HC97	–	2-oleoyl-LPA (pEC_{50} 7.3 – 7.52) [73], kynurenic acid (pEC_{50} 3.9 – 4.41) [90,99]	–	–	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 [53]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [73] but these results were not replicated in in a recent β-arrestin assay [90]. The phosphodiesterase inhibitor zaprinast [95] has become widely used as a surrogate agonist to investigate GPR35 pharmacology and signaliing [95]. GPR35 is also activated by the pharmaceutical adjunct pamoic acid [110].
GPR37	*GPR37*, O15354	G_i/G_o	–	–	neuropeptide head activator (pEC_{50} 7.96 – 8.48) [78]	Reported to associate and regulate the dopamine transporter [68] and to be a substrate for parkin [66]. Gene disruption results in altered striatal signalling [67].

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)	Selective agonists (pK_i)	Comment
GPR39	*GPR39*, O43194	G_q/G_{11}	Zn^{2+} [33]	–	–	Zn^{2+} has been reported to be a potent and efficacious agonist of human, mouse and rat GPR39 [105]. obestatin (*GHRL*, Q9UBU3), a fragment from the ghrelin precursor, was reported initially as an endogenous ligand, but subsequent studies failed to reproduce these findings. Has been reported to be down-regulated in adipose tissue in obesity-related diabetes [10]. Gene disruption results in obesity and altered adipocyte metabolism [77].
GPR50	*GPR50*, Q13585	–	–	–	–	GPR50 is structurally related to MT_1 and MT_2 melatonin receptors, with which it heterodimerises constitutively and specifically [57]. GPR50 knockout mice display abnormal thermoregulation and are much more likely than wild-type mice to enter fasting-induced torpor [3].
GPR61	*GPR61*, Q9BZJ8	G_s	–	–	–	GPR61 deficient mice exhibit obesity associated with hyperphagia [70]. Although no endogenous ligands have been identified, 5-(nonyloxy)tryptamine has been reported to be a low affinity inverse agonist [94].
GPR63	*GPR63*, Q9BZJ6	–	–	–	–	sphingosine 1-phosphate and dioleoylphosphatidic acid have been reported to be low affinity agonists for GPR63 [72] but this finding was not replicated in a β-arrestin-based assay [106].
GPR65	*GPR65*, Q8IYL9	G_s	–	–	–	GPR4, GPR65, GPR68 and GPR132 are now thought to function as proton-sensing receptors detecting acidic pH [17,85]. Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophlia in models of allergic airway disease [50].
GPR68	*GPR68*, Q15743	–	–	–	–	Gpr68 was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [103], but the original publication has been retracted [104]. GPR4, GPR65, GPR68 and GPR132 are now thought to function as protein-sensing receptors detecting acidic pH [17,85]. A family of 3,5-disubstituted isoxazoles were identified as agonists of GPR68 [82].
GPR75	*GPR75*, O95800	G_q/G_{11}	–	–	–	CCL5 (*CCL5*, P13501) was reported to be an agonist of GPR75 [37], but the pairing could not be repeated in a recent β-arrestin assay [90].
GPR84	*GPR84*, Q9NQS5	G_i/G_o	–	–	decanoic acid (pEC_{50} 5.0 – 5.4) [90,100], undecanoic acid (pEC_{50} 5.1) [100], lauric acid (pEC_{50} 5.05) [100]	Medium chain free fatty acids with carbon chain lengths of 9-14 activate GPR84 [92,100]. A surrogate ligand for GPR84, 6-n-octylaminouracil has also been proposed [92].
GPR87	*GPR87*, Q9BY21	–	LPA (pEC_{50} 7.44) [69,93]	–	–	–
GPR88	*GPR88*, Q9GZN0	–	–	–	–	Gene disruption results in altered striatal signalling [63].

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)	Selective agonists (pK_i)	Comment
GPR132	*GPR132*, Q9UNW8	G_s	–	–	–	GPR4, GPR65, GPR68 and GPR132 are now thought to function as protein-sensing receptors detecting acidic pH [17,85]. Reported to respond to lysophosphatidylcholine [41], but later retracted [102].
GPR149	*GPR149*, Q86SP6	–	–	–	–	Gpr149 knockout mice displayed increased fertility and enhanced ovulation, with increased levels of FSH receptor and cyclin D2 mRNA levels [20].
GPR183	*GPR183*, P32249	–	7α,25-dihydroxycholesterol (Selective) (pEC_{50} 8.1 – 9.85) [28,60], 7α,27-dihydroxycholesterol (Selective) (pEC_{50} 8.89) [60], 7β, 25-dihydroxycholesterol (Selective) (pEC_{50} 8.68) [60], 7β, 27-dihydroxycholesterol (Selective) (pEC_{50} 7.29) [60]	–	–	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 [28,60]. Gpr183-deficient mice show 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 [44,76].
LGR4	*LGR4*, Q9BXB1	–	R-spondin-2 (*RSPO2*, Q6UXX9) (Selective) (pEC_{50} 12.52) [9], R-spondin-1 (*RSPO1*, Q2MKA7) (Selective) (pEC_{50} 10.7) [9], R-spondin-3 (*RSPO3*, Q9BXY4) (Selective) (pEC_{50} 10.7) [9], R-spondin-4 (*RSPO4*, Q2I0M5) (Selective) (pEC_{50} 10.05) [9]	–	R-spondin-2 (*RSPO2*, Q6UXX9) (Selective) (pEC_{50} 12.52) [9], R-spondin-1 (*RSPO1*, Q2MKA7) (Selective) (pEC_{50} 10.7) [9], R-spondin-3 (*RSPO3*, Q9BXY4) (Selective) (pEC_{50} 10.7) [9], R-spondin-4 (*RSPO4*, Q2I0M5) (Selective) (pEC_{50} 10.05) [9]	LGR4 does not couple to heterotrimeric G proteins or to β-arrestin when stimulated by the R-spondins, indicating a unique mechanism of action. R-spondins bind to LGR4, which specifically associates with Frizzled and LRPs—proteins that are activated by the extracellular Wnt molecules and then trigger canonical Wnt signalling to increase gene expression [9,18,80]. Gene disruption leads to multiple developmental disorders [39,64,89,101].
LGR5	*LGR5*, O75473	–	R-spondin-2 (*RSPO2*, Q6UXX9) (Selective) (pEC_{50} 12.0) [9], R-spondin-1 (*RSPO1*, Q2MKA7) (Selective) (pEC_{50} 11.1) [9], R-spondin-3 (*RSPO3*, Q9BXY4) (Selective) (pEC_{50} 11.0) [9], R-spondin-4 (*RSPO4*, Q2I0M5) (Selective) (pEC_{50} 9.4) [9]	–	R-spondin-2 (*RSPO2*, Q6UXX9) (Selective) (pEC_{50} 12.0) [9], R-spondin-1 (*RSPO1*, Q2MKA7) (Selective) (pEC_{50} 11.1) [9], R-spondin-3 (*RSPO3*, Q9BXY4) (Selective) (pEC_{50} 11.0) [9], R-spondin-4 (*RSPO4*, Q2I0M5) (Selective) (pEC_{50} 9.4) [9]	The four R-spondins can bind to LGR4, LGR5, and LGR6, which specifically associate with Frizzled and LRPs—proteins that are activated by extracellular Wnt molecules- and then trigger canonical Wnt signalling to increase gene expression [9,18].
LGR6	*LGR6*, Q9HBX8	–	R-spondin-1 (*RSPO1*, Q2MKA7) (Selective) [9,18], R-spondin-2 (*RSPO2*, Q6UXX9) (Selective) [9,18], R-spondin-3 (*RSPO3*, Q9BXY4) (Selective) [9,18], R-spondin-4 (*RSPO4*, Q2I0M5) (Selective) [9,18]	–	–	–

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)	Selective agonists (pK_i)	Comment
MAS1	*MAS1*, P04201	G_q/G_{11}	angiotensin-(1-7) (*AGT*, P01019) (Selective) [84]	–	–	–
MRGPRD	*MRGPRD*, Q8TDS7	G_i/G_o	β-alanine (pEC_{50} 4.8) [87,90]	–	–	An endogenous peptide with a high degree of sequence similarity to angiotensin-(1-7) (*AGT*, P01019), alamandine, was shown to promote NO release in MrgD-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 [54]. Genetic ablation of MRGPRD+ neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [11].
MRGPRX1	*MRGPRX1*, Q96LB2	G_q/G_{11}	BAM8-22 (*PENK*, P01210) (Selective) (pEC_{50} 5.3 – 7.8) [13,56,90]	–	–	Reported to mediate the sensation of itch [61,88]. Reports that BAM8-22 (*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 [56] were replicated in an independent study using a β-arrestin recruitment assay [90].
MRGPRX2	*MRGPRX2*, Q96LB1	–	PAMP-20 (*ADM*, P35318) (Selective) [42]	–	PAMP-12 (human) (pEC_{50} 7.24 – 7.68) [42], CST-14 {Sp: Mouse, Rat} (pEC_{50} 6.9 – 7.6) [42,79,90]	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 [79], also confirmed in an independent study using a β-arrestin recruitment assay [90].
P2RY10	*P2RY10*, O00398	–	sphingosine 1-phosphate (Selective) (pEC_{50} 7.3) [69], LPA (Selective) (pEC_{50} 6.9) [69]	–	–	–
TAAR2	*TAAR2*, Q9P1P5	G_s	–	–	–	β-phenylethylamine > tryptamine [7] probable pseudogene in 10–15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [17] see Page 139.

Table 2
Class A Orphan GPCR with limited pharmacological or phenotypic profiles

Nomenclature	HGNC, UniProt	Principal transduction	Comment
GPR19	*GPR19*, Q15760	–	–
GPR21	*GPR21*, Q99679	$G_{q/11}$	Gpr21 knockout mice were resistant to diet-induced obesity, exhibiting an increase in glucose tolerance and insulin sensitivity and a modest lean phenotype [74].
GPR25	*GPR25*, O00155	–	–
GPR27	*GPR27*, Q9NS67	G_q/G_{11}	Knockdown of Gpr27 reduces endogenous mouse insulin promotor activity and glucose stimulated insulin secretion [52].
GPR33	*GPR33*, Q49SQ1	G_i/G_o	GPR33 is a pseudogene in most individuals, containing a premature stop codon within the coding sequence of the second intracellular loop [83].
GPR37L1	*GPR37L1*, O60883	G_i/G_o	–

Nomenclature	HGNC, UniProt	Principal transduction	Comment
GPR45	*GPR45*, Q9Y5Y3	–	–
GPR52	*GPR52*, Q9Y2T5	–	–
GPR62	*GPR62*, Q9BZJ7	–	–
GPR78	*GPR78*, Q96P69	G_s	GPR78 has been reported to be constitutively active, coupled to elevated cAMP production [40].
GPR82	*GPR82*, Q96P67	–	Mice with Gpr82 knockout have a lower body weight and body fat content associated with reduced food intake, decreased serum triglyceride levels, higher insulin sensitivity and glucose tolerance [22].
GPR83	*GPR83*, Q9NYM4	–	One isoform has been implicated in the induction of CD4(+)CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [29].
GPR85	*GPR85*, P60893	–	Proposed to regulate of hippocampal adult neurogenesis and neurogenesis-dependent learning and memory [14].
GPR135	*GPR135*, Q8IZ08	–	–
GPR139	*GPR139*, Q6DWJ6	G_q/G_{11}	–
GPR141	*GPR141*, Q7Z602	–	–
GPR142	*GPR142*, Q7Z601	–	–
GPR146	*GPR146*, Q96CH1	–	Yosten et al. demonstrated inhibition of proinsulin C-peptide (*INS*, P01308)-induced stimulation of cFos expression folllowing knockdown of GPR146 in KATOIII cells, suggesting proinsulin C-peptide as an endogenous ligand of the receptor [107].
GPR148	*GPR148*, Q8TDV2	–	–
GPR150	*GPR150*, Q8NGU9	–	–
GPR151	*GPR151*, Q8TDV0	–	GPR151 responded to galanin with an EC_{50} value of 2 μM, suggesting that the endogenous ligand shares structural features with galanin (*GAL*, P22466) [34].
GPR152	*GPR152*, Q8TDT2	–	–
GPR153	*GPR153*, Q6NV75	–	–
GPR160	*GPR160*, Q9UJ42	–	–
GPR162	*GPR162*, Q16538	–	–
GPR171	*GPR171*, O14626	–	GPR171 has been shown to be activated by endogenous peptide BigLEN. This receptor-peptide interaction is believed to be involved in regulating feeding and metabolism responses [26].
GPR173	*GPR173*, Q9NS66	–	–
GPR174	*GPR174*, Q9BXC1	G_s	Reported to respond to lysophosphatidylserine (pEC_{50} 7.1) [38].
GPR176	*GPR176*, Q14439	–	–
GPR182	*GPR182*, O15218	–	Rat GPR182 was first proposed as adrenomedullin receptor [43]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [45] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [31].
MAS1L	*MAS1L*, P35410	–	–
MRGPRX3	*MRGPRX3*, Q96LB0	G_q/G_{11}	–
MRGPRX4	*MRGPRX4*, Q96LA9	G_q/G_{11}	–
MRGPRE	*MRGPRE*, Q86SM8	–	–
MRGPRF	*MRGPRF*, Q96AM1	–	MRGPRF has been reported to respond to stimulation by angiotensin metabolites [25].

Nomenclature	HGNC, UniProt	Principal transduction	Comment
MRGPRG	*MRGPRG*, Q86SM5	–	–
OPN3	*OPN3*, Q9H1Y3	–	–
OPN5	*OPN5*, Q6U736	G_i/G_o	Evidence indicates OPN5 triggers a UV-sensitive G_i-mediated signalling pathway in mammalian tissues [49].
P2RY8	*P2RY8*, Q86VZ1	–	–

Table 3: Class C Orphans

Nomenclature	HGNC, UniProt
GPR156	*GPR156*, Q8NFN8
GPR158	*GPR158*, Q5T848
GPR179	*GPR179*, Q6PRD1
GPRC5A	*GPRC5A*, Q8NFJ5
GPRC5B	*GPRC5B*, Q9NZH0
GPRC5C	*GPRC5C*, Q9NQ84
GPRC5D	*GPRC5D*, Q9NZD1

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 [109], TRPM5 [109] and IP3 [32] 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 [58]. T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin [71].

Nomenclature	TAS1R1	TAS1R2	TAS1R3
HGNC, UniProt	*TAS1R1*, Q7RTX1	*TAS1R2*, Q8TE23	*TAS1R3*, Q7RTX0
Principal transduction	–	–	–

Taste 2 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- ($G\alpha t3$) and $G\alpha 14$-mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involvement of PLC$\beta 2$ [109], TRPM5 [109] and IP3 [32] 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.

Bitter: The composition and stoichiometry of bitter taste receptors is not yet established. Bitter receptors appear to separate into two groups, with very restricted ligand specificity or much broader responsiveness. For example, T2R5 responded to cycloheximide, but not 10 other bitter compounds [12], while T2R14 responded to at least eight different bitter tastants, including (-)-α-thujone and picrotoxinin [4].

Nomenclature	HGNC, UniProt
TAS2R1	*TAS2R1*, Q9NYW7
TAS2R3	*TAS2R3*, Q9NYW6
TAS2R4	*TAS2R4*, Q9NYW5
TAS2R5	*TAS2R5*, Q9NYW4
TAS2R7	*TAS2R7*, Q9NYW3
TAS2R8	*TAS2R8*, Q9NYW2
TAS2R8	*TAS2R8*, Q9NYW2
TAS2R9	*TAS2R9*, Q9NYW1
TAS2R10	*TAS2R10*, Q9NYW0
TAS2R13	*TAS2R13*, Q9NYV9
TAS2R14	*TAS2R14*, Q9NYV8
TAS2R16	*TAS2R16*, Q9NYV7
TAS2R19	*TAS2R19*, P59542
TAS2R20	*TAS2R20*, P59543
TAS2R42	*TAS2R42*, Q7RTR8
TAS2R30	*TAS2R30*, P59541
TAS2R31	*TAS2R31*, P59538
TAS2R39	*TAS2R39*, P59534
TAS2R40	*TAS2R40*, P59535
TAS2R50	*TAS2R50*, P59544
TAS2R43	*TAS2R43*, P59537
TAS2R46	*TAS2R46*, P59540
TAS2R41	*TAS2R41*, P59536
TAS2R60	*TAS2R60*, P59551
TAS2R38	*TAS2R38*, P59533

Other 7TM proteins

Nomenclature	HGNC, UniProt	Comment
GPR157	*GPR157*, Q5UAW9	GPR157 has ambiguous sequence similarities to several different GPCR families (class A, class B and the slime mould cyclic AMP receptor). Because of its distant relationship to other GPCRs, it cannot be readily classified.

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhanga CP, Bonner TI, Neubig RR *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**: 967–986. [PMID:23686350]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

5-Hydroxytryptamine receptors

Overview: 5-HT receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors [158] and subsequently revised [153]] are, with the exception of the ionotropic 5-HT_3 class, GPCR receptors where the endogenous agonist is 5-HT. 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 [124,216]. Most 5-HT receptors (except 5-ht_{1e} and $5\text{-ht}_{5a/5b}$) play specific roles mediating functional responses in different tissues (reviewed by [197,211].

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
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists (pK_i)	U92016A (9.7) [178], 8-OH-DPAT (8.4 – 9.4) [140,151,170,183,189,191,191–192], F15599 (8.6) [190]	L-694,247 (9.2) [149], CP94253 (8.7) [167], eletriptan (8.0) [184], sumatriptan (Partial agonist) (6.5 – 8.1) [149,172,183–184,187,194,215]	PNU109291 (9.1 - Gorilla) [143], L-694,247 (9.0) [217], eletriptan (8.9) [184], sumatriptan (8.0 – 8.7) [150,172,183–184,215]	BRL-54443 (8.7) [136]	BRL-54443 (8.9) [136], LY334370 (8.7) [213], LY573144 (8.7) [186], LY344864 (8.2) [195], eletriptan (8.0) [184], sumatriptan (7.2 – 7.9) [114–115,184,213]
Selective antagonists (pK_i)	NAD 299 (9.2) [161], WAY-100635 (7.9 – 9.2) [189,191], (S)-UH 301 (7.9) [189]	GR-55562 (pK_B 7.4) [159], SB 224289 (Inverse agonist) (8.2 – 8.6) [146,187,203], SB236057 (Inverse agonist) (8.2) [182]	SB 714786 (9.1) [214], BRL-15572 (7.9) [196]	–	–
Radioligands (K_d)	p-[^{18}F]MPPF, [^{11}C]WAY100635 (Antagonist), [^{3}H]NAD 299 (Antagonist) ($1.58\text{x}10^{-10}$ M) [160], [^{3}H]WAY100635 (Antagonist) ($3\text{x}10^{-10}$ M) [164], [^{3}H]F13640 (Agonist, Full agonist) ($1.4\text{x}10^{-9}$ M) [155], [^{3}H]8-OH-DPAT (Agonist, Full agonist) ($3.98\text{x}10^{-10}$ – $1\text{x}10^{-6}$ M) [122,162,188,191]	[^{11}C]AZ10419369, [^{3}H]N-methyl-AZ10419369 (Antagonist) ($3.7\text{x}10^{-10}$ M) [175], [^{125}I]GTI (Agonist) ($1.3\text{x}10^{-9}$ M - Rat) [130], [^{3}H]GR 125,743 (Antagonist) ($2.6\text{x}10^{-9}$ – $7.1\text{x}10^{-10}$ M) [149,218], [^{3}H]alniditan (Agonist, Full agonist) ($1\text{x}10^{-9}$ – $2.51\text{x}10^{-9}$ M) [171], [^{3}H]eletriptan (Agonist, Partial agonist) ($3\text{x}10^{-9}$ M) [184], [^{3}H]sumatriptan (Agonist, Partial agonist) ($1.1\text{x}10^{-8}$ M) [184]	[^{3}H]eletriptan (Agonist, Full agonist) ($9\text{x}10^{-10}$ M) [184], [^{125}I]GTI (Agonist) ($1.3\text{x}10^{-9}$ M - Rat) [130], [^{3}H]alniditan (Agonist, Full agonist) ($1.2\text{x}10^{-9}$ – $1.4\text{x}10^{-9}$ M) [171], [^{3}H]GR 125,743 (Antagonist) ($2.8\text{x}10^{-9}$ M) [218], [^{3}H]sumatriptan (Agonist, Full agonist) ($7\text{x}10^{-9}$ M) [184]	[^{3}H]5-HT (Agonist, Full agonist) ($6.31\text{x}10^{-9}$ – $7.94\text{x}10^{-9}$ M) [177,194]	[^{3}H]LY334370 (Agonist, Full agonist) ($3.98\text{x}10^{-10}$ M) [213], [^{125}I]LSD (Agonist) ($9.8\text{x}10^{-10}$ M - Mouse) [116]

Nomenclature	5-HT_{2A} receptor	5-HT_{2B} receptor	5-HT_{2C} receptor
HGNC, UniProt	*HTR2A*, P28223	*HTR2B*, P41595	*HTR2C*, P28335
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists (pK_i)	DOI (7.4 – 9.2) [131,185,205]	Ro 60-0175 (8.3) [166], BW723C86 (7.3 – 8.6) [119,166,201], DOI (7.6 – 7.7) [169,185,201],	Ro 60-0175 (7.7 – 8.2) [165–166], DOI (7.2 – 8.6) [142,185,201], lorcaserin (7.8) [209], WAY-163909 (6.7 – 8.0) [141]
Selective antagonists (pK_i)	ketanserin (8.1 – 9.7) [137,166,198], MDL-100,907 (pIC_{50} 6.5 – 9.3) [166,173,199]	RS-127445 (9.0 – 9.5) [128,166], EGIS-7625 (9.0) [168]	FR260010 (9.0) [152], SB 242084 (8.2 – 9.0) [163,166], RS-102221 (8.3 – 8.4) [129,166]
Radioligands (K_d)	[^{11}C]MDL100907, [^{18}F]altanserin (Antagonist), [^{3}H]RP62203 (Antagonist) ($1.3x10^{-10}$ M - Rat) [176], [^{3}H]ketanserin (Antagonist) ($2x10^{-10}$ – $2.9x10^{-9}$ M) [166,198]	[^{3}H]LSD (Agonist, Full agonist) ($2.1x10^{-9}$ M) [198], [^{3}H]mesulergine ($5x10^{-9}$ – $1x10^{-8}$ M), [^{3}H]5-HT (Agonist, Full agonist) ($8x10^{-9}$ M - Rat) [212], [^{125}I]DOI ($2x10^{-8}$ – $2.5x10^{-8}$ M)	[^{3}H]LSD (Agonist), [^{3}H]mesulergine (Antagonist, Inverse agonist) ($5x10^{-10}$ – $2.2x10^{-9}$ M) [144,198], [^{125}I]DOI ($6x10^{-9}$ – $2.5x10^{-8}$ M)

Nomenclature	5-HT_4 receptor	5-ht_{5a} receptor	5-ht_{5b} receptor	5-HT_6 receptor	5-HT_7 receptor
HGNC, UniProt	*HTR4*, Q13639	*HTR5A*, P47898	*HTR5BP*, P31387	*HTR6*, P50406	*HTR7*, P34969
Principal transduction	G_s	G_i/G_o	None identified	G_s	G_s
Selective agonists (pK_i)	ML 10302 (Partial agonist) (7.9 – 9.0) [121,123,179–181], BIMU 8 (7.3) [138], RS67506 (pEC_{50} 8.8 - Rat) [154]	–	–	E-6801 (Partial agonist) (8.7) [157], WAY-181187 (8.7) [202]	E55888 (8.6) [132]
Selective antagonists (pK_i)	RS 100235 (8.7 – 12.2) [138,200], SB 204070 (9.8 – 10.4) [120,179–180,210], GR 113808 (9.3 – 10.3) [117,120,123,138,180,200,210]	SB 699551 (8.2) [139]	–	SB399885 (9.0) [156], SB 271046 (8.9) [133], SB357134 (8.5) [134], Ro 63-0563 (7.9 – 8.4) [126,204]	SB269970 (8.6 – 8.9) [207], SB656104 (8.7) [145], SB 258719 (Inverse agonist) (7.5) [208]
Radioligands (K_d)	[^{123}I]SB 207710 ($8.6x10^{-11}$ M - Pig) [135], [^{3}H]GR 113808 (Antagonist) ($5x10^{-11}$ – $2x10^{-10}$ M) [117,120,181,210], [^{3}H]RS 57639 (Agonist) ($2x10^{-10}$ M - Guinea pig) [127], [^{11}C]SB207145 (Antagonist) ($2.8x10^{-9}$ M) [174]	[^{125}I]LSD (Agonist, Full agonist) ($2x10^{-10}$ M) [148], [^{3}H]5-CT (Agonist, Full agonist) ($2.5x10^{-9}$ M) [148]	[^{125}I]LSD, [^{3}H]5-CT	[^{3}H]5-CT (Agonist), [^{125}I]SB258585 (Antagonist) ($1x10^{-9}$ M) [156], [^{3}H]LSD (Agonist, Full agonist) ($2x10^{-9}$ M) [125], [^{3}H]Ro 63-0563 (Antagonist) ($5x10^{-9}$ M) [126]	[^{3}H]5-CT (Agonist) ($4x10^{-10}$ M) [207], [^{3}H]SB269970 (Antagonist) ($1.2x10^{-9}$ M) [207], [^{3}H]5-HT (Agonist, Full agonist) ($1x10^{-9}$ – $7.94x10^{-9}$ M) [118,206], [^{3}H]LSD (Agonist, Full agonist) ($2.51x10^{-9}$ – $3.16x10^{-9}$ M) [206]

Comments: Tabulated pK_i and K_D values refer to binding to human 5-HT receptors unless indicated otherwise. Unreferenced values are extracted from the **NC-IUPHAR database** (www.iuphar-db.org). The nomenclature of 5-HT_{1B}/5-HT_{1D} receptors has been revised [153]. 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. NAS181 is a selective antagonist of the rodent 5-HT_{1B} receptor. fananserin 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. The human 5-ht_{5A} receptor has been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells [193]. The human orthologue of the mouse 5-ht_{5b} receptor is non-functional due to interruption of the gene by stop codons. The 5-ht_{1e} receptor appears not to have been cloned from mouse, or rat, impeding definition of its function. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT_{1P}, has been described [147].

Further reading

Bockaert J, Claeysen S, Compan V, Dumuis A. (2011) 5-HT(4) receptors, a place in the sun: act two. *Curr Opin Pharmacol* **11**: 87–93. [PMID:21342787]

Codony X, Vela JM, Ramírez MJ. (2011) 5-HT(6) receptor and cognition. *Curr Opin Pharmacol* **11**: 94–100. [PMID:21330210]

Hartig PR, Hoyer D, Humphrey PP, Martin GR. (1996) Alignment of receptor nomenclature with the human genome: classification of 5-HT1B and 5-HT1D receptor subtypes. *Trends Pharmacol Sci* **17**: 103–5. [PMID:8936345]

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

Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, Saxena PR, Humphrey PP. (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev* **46**: 157–203. [PMID:7938165]

Leopoldo M, Lacivita E, Berardi F, Perrone R, Hedlund PB. (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, Massey BW. (2011) The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol* **11**: 59–67. [PMID:21420906]

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

Sargent BJ, Henderson AJ. (2011) Targeting 5-HT receptors for the treatment of obesity. *Curr Opin Pharmacol* **11**: 52–8. [PMID:21330209]

Acetylcholine receptors (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors, [224]) are GPCR of the Class A, rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42, its structural analogues AC-260584 and 77-LH-28-1, *N*-desmethylclozapine, TBPB and LuAE51090 have been described as functionally selective agonists of the M_1 receptor subtype *via* binding in a mode distinct from that utilized by non-selective agonists [220,235,237–238,246,253,256–257,259,259]. There are two pharmacologically characterised allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine, and the other binds KT 5720, WIN 62,577, WIN 51,708 and staurosporine [240–241].

Nomenclature	M_1 receptor	M_2 receptor	M_3 receptor	M_4 receptor	M_5 receptor
HGNC, UniProt	*CHRM1*, P11229	*CHRM2*, P08172	*CHRM3*, P20309	*CHRM4*, P08173	*CHRM5*, P08912
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{q/11}$	$G_{i/o}$	$G_{q/11}$
Selective antagonists (pK_i)	MT7 (11.0–11.1) [249], VU0255035 (7.8) [254]	–	–	MT3 (8.7) [234,250]	–
Selective allosteric regulators	BQCA (Positive) [244], brucine (Positive) [221], KT 5720 (Positive) [221], ML169 (Positive) [252], VU0029767 (Positive) [245], VU0090157 (Positive) [245]	–	N-chloromethyl-brucine (Positive) [221], WIN 62,577 (Positive) [221]	LY2033298 (Positive) [226], thiochrome (Positive) [221], VU0152099 (Positive) [222], VU0152100 (Positive) [222]	VU0238429 (Positive) [223]
Radioligands (K_d)	[^{11}C]butylthio-TZTP, [^{11}C]xanomeline, [^{18}F](R,R)-quinuclidinyl-4-fluoromethyl-benzilate, [^{3}H]QNB (Antagonist) (1.58×10^{-11}–2.51×10^{-11} M) [229,251], [^{3}H]N-methyl scopolamine (Antagonist) (5.01×10^{-11}–1.58×10^{-9} M) [225,228–229,230,232–234,236,239], [^{3}H]pirenzepine (Antagonist) (1.4×10^{-8} M) [263]	[^{18}F]FP-TZTP, [^{3}H]QNB (Antagonist) (2.51×10^{-11}–7.94×10^{-11} M) [251], [^{3}H]N-methyl scopolamine (Antagonist) (1.25×10^{-10}–5.01×10^{-7} M) [225,227,230,232–234,236, 239,262]	[^{3}H]QNB (Antagonist) (3.98×10^{-11} M) [251], [^{3}H]darifenacin (Antagonist) (3.16×10^{-10} M) [255], [^{3}H]N-methyl scopolamine (Antagonist) (3.98×10^{-11}–2.51×10^{-9} M) [225,227,230–232,234,236,239]	[^{3}H]QNB (Antagonist) (3.16×10^{-11}–2×10^{-10} M) [229,251], [^{3}H]N-methyl scopolamine (Antagonist) (6.3×10^{-11}–1.58×10^{-8} M) [225,227,229,230,232,234,236, 239,250,262]	[^{3}H]QNB (2×10^{-11}–6×10^{-11} M), [^{3}H]N-methyl scopolamine (Antagonist) (2×10^{-10}–7.94×10^{-9} M) [225,227,230,234,236,262]

Comments: LY2033298 and BQCA have also been shown to directly activate the M_4 and M_1 receptors, respectively, via an allosteric site [242–243,247–248]. The allosteric site for gallamine and strychnine on M_2 receptors can be labelled by [^{3}H]dimethyl-W84 [260]. McN-A-343 is a functionally selective partial agonist that appears to interact in a bitopic mode with both the orthosteric and an allosteric site on the M_2 muscarinic receptor [261]. THRX-160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M_2 receptors by binding both to the orthosteric and a nearby allosteric site [219,258].

Although numerous ligands for muscarinic acetylcholine receptors have been described, relatively few selective antagonists have been described, so it is common to assess the rank order of affinity of a number of antagonists of limited selectivity (e.g. 4-DAMP, darifenacin, pirenzepine) in order to identify the involvement of particular subtypes.

Further reading

Caulfield MP, Birdsall NJM. (1998) International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol Rev* **50**: 279–290. [PMID:9647869]

Eglen RM. (2012) Overview of muscarinic receptor subtypes. *Handb Exp Pharmacol* (**208**): 3–28. [PMID:22222692]

Gregory KJ, Sexton PM, Christopoulos A. (2007) Allosteric modulation of muscarinic acetylcholine receptors. *Curr Neuropharmacol* **5**: 157–167. [PMID:19305798]

Leach K, Simms J, Sexton PM, Christopoulos A. (2012) Structure-function studies of muscarinic acetylcholine receptors. *Handb Exp Pharmacol* (**208**): 29–48. [PMID:22222693]

Adenosine receptors

Overview: Adenosine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adenosine Receptors; [280]) are activated by the endogenous ligand adenosine (potentially inosine also at A_3 receptors). Crystal structures for the antagonist-bound and agonist-bound A_{2A} adenosine receptors have been described [287,323].

Nomenclature	A_1 receptor	A_{2A} receptor	A_{2B} receptor	A_3 receptor
HGNC, UniProt	*ADORA1*, P30542	*ADORA2A*, P29274	*ADORA2B*, P29275	*ADORA3*, P33765
Principal transduction	$G_{i/o}$	G_s	G_s	$G_{i/o}$
(Sub)family-selective agonists (pK_i)	NECA (5.3 – 8.2) [283,295,311,317,324]	NECA (6.9 – 8.7) [270,276,283,299,303,324]	NECA (5.7 – 6.9) [268,270,292,306,314,319,324]	NECA (7.5 – 8.4) [270,283,289,312,320,324]
Selective agonists (pK_i)	5-Cl-5-deoxy-(±)-ENBA (9.29) [279], GR79236 (8.51 - Rat) [288], cyclopentyladenosine (6.5 – 9.4) [274–275,283,285,288,295,311], CCPA (7.7 – 8.1) [288,308]	apadenoson (9.3) [310], CGS 21680 (6.7 – 8.1) [270,276,283,288,299,302–303,308]	Bay60-6583 (8.0 – 8.52) [277]	IB-MECA (8.7 – 9.2) [278,281,302,320], Cl-IB-MECA (8.0 – 8.9) [271,289,298]
(Sub)family-selective antagonists (pK_i)	XAC (pK_d 7.5) [279], CGS 15943 (8.46) [309]	XAC (8.4 – 9.0) [276,302], CGS 15943 (7.7 – 9.4) [276,299,302,309]	XAC (pA_2 7.9) [265], CGS 15943 (pA_2 7.8) [265], XAC (6.9 – 8.8) [268,292–293,302,306,314], CGS 15943 (6.0 – 8.1) [267,292–293,302,309,314]	CGS 15943 (7.0 – 7.9) [301–302,309,320], XAC (7.0 – 7.4) [302,312,320]
Selective antagonists (pK_i)	PSB36 (9.9 - Rat) [264], SLV320 (9.0) [297], DPCPX (7.4 – 9.2) [275,286,308,311,322]	SCH442416 (8.4 – 10.3) [313,316], ZM-241385 (8.8 – 9.1) [309], SCH 58261 (8.3 – 9.2) [276,303,309]	PSB-0788 (9.4) [269], PSB603 (9.26) [269], MRS1754 (8.8) [292,300], PSB1115 (7.27) [284]	MRS1220 (8.2 – 9.2) [289,301,315,325], VUF5574 (8.39) [318], MRS1523 (7.7) [304], MRS1191 (7.5) [289,294,305]
Radioligands (K_d)	[^{3}H]CCPA (Agonist, Full agonist) (6.31×10^{-10} M) [302,311], [^{3}H]DPCPX (Antagonist) (6×10^{-10} – 1.2×10^{-9} M) [274,278,302,309,311,317]	[^{3}H]ZM 241385 (Antagonist) (8×10^{-10} – 1.8×10^{-9} M) [266,282], [^{3}H]CGS 21680 (Agonist, Full agonist) (1.6×10^{-8} – 2.2×10^{-8} M) [291,321]	[^{3}H]MRS1754 (Antagonist) (1.58×10^{-10} M) [292]	[^{125}I]AB-MECA (Agonist, Full agonist) (6×10^{-10} – 1×10^{-9} M) [309,320]

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 [290]. DPCPX also exhibits antagonism at A_{2B} receptors (pK_i ca. 7,[265,302]). 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 [302]. [^{3}H]CGS 21680 is relatively selective for A_{2A} receptors, but may also bind to other sites in cerebral cortex [273,296]. [^{3}H]NECA binds to other non-receptor elements, which also recognise adenosine [307]. 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 [272].

Further reading

Fredholm BB, IJzerman AP, Jacobson KA, Linden J, Müller CE. (2011) International Union of Basic and Clinical Pharmacology. LXXXI. Nomenclature and classification of adenosine receptors–an update. *Pharmacol Rev* **63**: 1–34. [PMID:21303899]

Göblyös A, Ijzerman AP. (2011) Allosteric modulation of adenosine receptors. *Biochim Biophys Acta* **1808**: 1309–1318. [PMID:20599682]

Headrick JP, Peart JN, Reichelt ME, Haseler LJ. (2011) Adenosine and its receptors in the heart: regulation, retaliation and adaptation. *Biochim Biophys Acta* **1808**: 1413–1428. [PMID:21094127]

Lasley RD. (2011) Adenosine receptors and membrane microdomains. *Biochim Biophys Acta* **1808**: 1284–1289. [PMID:20888790]

Mundell S, Kelly E. (2011) Adenosine receptor desensitization and trafficking. *Biochim Biophys Acta* **1808**: 1319–1328. [PMID:20550943]

Ponnoth DS, Jamal Mustafa S. (2011) Adenosine receptors and vascular inflammation. *Biochim Biophys Acta* **1808**: 1429–1434. [PMID:20832387]

Wei CJ, Li W, Chen JF. (2011) Normal and abnormal functions of adenosine receptors in the central nervous system revealed by genetic knockout studies. *Biochim Biophys Acta* **1808**: 1358–1379. [PMID:21185258]

Adhesion Class GPCRs

Overview: Adhesion GPCRs are structurally identified on the basis of a large extracellular region, similar to the Class B GPCR, but which is linked to the 7TM region by a "stalk" motif containing a GPCR proteolytic site. The N-terminus often shares structural homology with proteins such as lectins and immunoglobulins, leading to the term adhesion GPCR [326,331].

Nomenclature	HGNC, UniProt	Comment
BAI1	*BAI1*, O14514	BAI1 is reported to respond to phosphatidylserine [329].
BAI2	*BAI2*, O60241	–
BAI3	*BAI3*, O60242	–
CD97	*CD97*, P48960	–
CELSR1	*CELSR1*, Q9NYQ6	–
CELSR2	*CELSR2*, Q9HCU4	–
CELSR3	*CELSR3*, Q9NYQ7	–
ELTD1	*ELTD1*, Q9HBW9	–
EMR1	*EMR1*, Q14246	–
EMR2	*EMR2*, Q9UHX3	–
EMR3	*EMR3*, Q9BY15	–
EMR4P	*EMR4P*, Q86SQ3	–
GPR56	*GPR56*, Q9Y653	Reported to bind tissue transglutaminase 2 [330] and collagen, which activates the $G_{12/13}$ pathway [328].
GPR64	*GPR64*, Q8IZP9	–
GPR97	*GPR64*, Q8IZP9	–
VLGR1	*GPR98*, Q8WXG9	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [327].
GPR110	*GPR110*, Q5T601	–
GPR111	*GPR111*, Q8IZF7	–
GPR112	*GPR112*, Q8IZF6	–
GPR113	*GPR113*, Q8IZF5	–
GPR114	*GPR114*, Q8IZF4	–
GPR115	*GPR115*, Q8IZF3	–
GPR116	*GPR116*, Q8IZF2	–
GPR123	*GPR123*, Q86SQ6	–
GPR124	*GPR124*, Q96PE1	–
GPR125	*GPR125*, Q8IWK6	–
GPR126	*GPR126*, Q86SQ4	–
GPR128	*GPR128*, Q96K78	–
GPR133	*GPR133*, Q6QNK2	–
GPR144	*GPR144*, Q7Z7M1	–

Nomenclature	HGNC, UniProt	Comment
LPHN1	*LPHN1*, O94910	–
LPHN2	*LPHN2*, O95490	–
LPHN3	*LPHN3*, Q9HAR2	–

Adrenoceptors

Overview: α_1-Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; [340]) are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline with equal potency. phenylephrine, methoxamine and cirazoline are agonists selective for α_1-adrenoceptors relative to α_2-adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are antagonists considered selective for α_1-adrenoceptors relative to α_2-adrenoceptors. [^{3}H]prazosin (0.25 nM) and [^{125}I]HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. The α_{1A}-adrenoceptor antagonist (+)-niguldipine also has high affinity for L-type Ca^{2+} channels. The conotoxin ρ-TIA acts as a negative allosteric modulator at the α_{1B}-adrenoceptor [396], while the snake toxin ρ-Da1a acts as a selective competitive antagonist at the α_{1A}-adrenoceptor [386]. Fluorescent derivatives of prazosin (Bodipy PL-prazosin – QAPB) are increasingly used to examine cellular localisation of α_1-adrenoceptors. The vasoconstrictor effects of selective α1-adrenoceptor agonists have led to their use as nasal decongestants; antagonists are used to treat hypertension (doxazosin, prazosin) and benign prostatic hyperplasia (alfuzosin, tamsulosin). The combined α_1- and β_2-adrenoceptor antagonist carvedilol is widely 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 possess α_1-adrenoceptor blocking properties that are believed to contribute to side effects such as orthostatic hypotension and extrapyramidal effects.

Nomenclature	α_{1A}-adrenoceptor	α_{1B}-adrenoceptor	α_{1D}-adrenoceptor
HGNC, UniProt	*ADRA1A*, P35348	*ADRA1B*, P35368	*ADRA1D*, P25100
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists (pK_i)	dabuzalgron (7.4) [339], A61603 (pIC_{50} 7.8–8.4) [355,369]	–	–
Selective antagonists (pK_i)	silodosin (10.4) [397], tamsulosin (10.0–10.7) [343,346,355,397,410], (+)-niguldipine (9.1–10.0) [355,397], ρ-Da1a (9.22) [386], SNAP5089 (8.8–9.4) [360,371,409]	–	BMY-7378 (8.7–9.1) [342,413]

Comments: *Adrenoceptors, α_1:* The clone originally called the α_{1C}-adrenoceptor corresponds to the pharmacologically defined α_{1A}-adrenoceptor [361]. Some tissues possess α_{1A}-adrenoceptors (termed $\alpha\alpha1_L$-adrenoceptors [355,381]) that display relatively low affinity in functional and binding assays for prazosin (pK_i < 9) indicative of different receptor states or locations. α_{1A}-adrenoceptor C-terminal splice variants form homo- and heterodimers, but fail to generate a functional α_{1L}-adrenoceptor [387]. A study suggests that the &alpha$_{1L}$-adenoceptor phenotype may result from the interaction of α_{1A}-adrenoceptors with cysteine-rich epidermal growth factor-like domain 1α (CRELD1α) [382–383,404]. α_{1D}-Adrenoceptors form heterodimers with α_{1B}- or β_2-adrenoceptors that show increased cell-surface expression [402]. Heterodimers formed between α_{1D}- and α_{1B}-adrenoceptors have distinct functional properties [359]. Recombinant α_{1D}-adrenoceptors have been shown in some heterologous systems to be mainly located intracellularly but cell-surface localization is attained by truncation of the N-terminus, or by co-expression of α1B- or β2-adrenoceptors to form heterodimers [359,402]. In smooth muscle of native blood vessels all three α_1-adrenoceptor subtypes are located on the surface and intracellularly [377–378].

Signalling is predominantly via $G_{q/11}$ but α_1-adrenoceptors also couple to $G_{i/o}$, G_s and $G_{12/13}$. Several ligands activating α_{1A}-adrenoceptors display ligand directed signalling bias. For example, oxymetazoline is a full agonist for extracellular acidification rate (ECAR) and a partial agonist for Ca^{2+} release but does not stimulate cAMP production. Phenylephrine is biased toward ECAR versus Ca^{2+} release or cAMP accumulation but not between Ca^{2+} release and cAMP accumulation [351]. There are also differences between subtypes in coupling efficiency to different pathways – *e.g.* in some systems coupling efficiency to Ca^{2+} signalling is $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$, but for MAP kinase signalling is $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$. In vascular smooth muscle, potency of agonists is related to the predominant subtype, α_{1D}- conveying greater sensitivity than α1A-adrenoceptors [354].

Adrenoceptors, α_2: α_2-Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; [340]) are activated by endogenous agonists with a relative potency of (-)-adrenaline > (-)-noradrenaline. UK14304 (brimonidine) and BHT920 are agonists selective for α_2-adrenoceptors relative to α_1-adrenoceptors, rauwolscine (9.0) and yohimbine (9.0) are antagonists selective for α_2-adrenoceptors relative to α_1-adrenoceptors. [^{3}H]rauwolscine (1 nM), [^{3}H]UK14304 (5 nM) and [^{3}H]RX821002 (0.5 nM and 0.1 nM at α_{2C}) are relatively selective radioligands. There is species variation in the pharmacology of the α_{2A}-adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine α_{2A}-adrenoceptors compared to the human receptor. These α_{2A} orthologues are sometimes referred to as α_{2D}-adrenoceptors. Multiple mutations of α_2-adrenoceptors have been described, some of which are associated with alterations in function. Presynaptic α_2-adrenoceptors are widespread in the nervous system and regulate many functions, hence the multiplicity of actions. The effects of classical (not subtype selective) α_2-adrenoceptor agonists such as clonidine, guanabenz and UK14304 (brimonidine) on central baroreflex control (hypotension and bradycardia), hypnotic, analgesic, seizure modulation and platelet aggregation are mediated by α_{2A}-adrenoceptors. clonidine has been used as an antihypertensive and also to counteract opioid withdrawal. Actions on imidazoline receptors may contribute to the pharmacological effects of clonidine. α_2-Adrenoceptor agonists such as dexmedetomidine have been widely used as sedatives and analgesics in veterinary medicine (also xylazine) and are now used frequently in humans. α_2-Adrenoceptor antagonists are relatively little used therapeutically although yohimbine has been used to treat erectile dysfunction and several anti-depressants (cyanopindolol, mirtazepine) that block α_2-adrenoceptors may work through this mechanism. The roles of α_{2B} and α_{2C}-adrenoceptors are less clear but 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.

Nomenclature	α_{2A}-adrenoceptor	α_{2B}-adrenoceptor	α_{2C}-adrenoceptor
HGNC, UniProt	*ADRA2A*, P08913	*ADRA2B*, P18089	*ADRA2C*, P18825
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists (pK_i)	oxymetazoline (Partial agonist) (8.0) [365,403], guanfacine (7.1) [374]	–	–
Selective antagonists (pK_i)	BRL 44408 (8.2–8.77) [403,414]	imiloxan (7.3 - Rat) [379]	JP1302 (pK_B 7.8) [392]

Comments: ARC-239 (pKi 8.0) and prazosin (pKi 7.5) show selectivity for α_{2B}- and $\alpha 2_C$-adrenoceptors over α_{2A}-adrenoceptors.oxymetazoline is a reduced efficacy agonist and is one of many α_2-adrenoceptor agonists that are imidazolines or closely related compounds. Other binding sites for imidazolines, distinct from α_2-adrenoceptors, and structurally distinct from the 7TM adrenoceptors, have been identified and classified as I_1, I_2 and I_3 sites; catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands for these sites, evoking hypotensive effects *in vivo*. I_1-imidazoline receptors are involved in central inhibition of sympathetic tone, I_2-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I_3-imidazoline receptors regulate insulin secretion from pancreatic β-cells. α_{2A}-adrenoceptor stimulation reduces insulin secretion from β-islets [412], 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 [391].

α_{2A}- and α_{2c}-adrenoceptors form homodimers [398]. 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 [398,401,405]. Signalling by α_2-adrenoceptors is primarily via $G_{i/o}$, however the α_{2A}-adrenoceptor also couples to G_s [350]. Imidazoline compounds display bias at the α_{2A}-adrenoceptor when assayed by [^{35}S] GTPγS binding compared to inhibition of cAMP accumulation [384]. The noradrenaline reuptake inhibitor desipramine acts directly on the α_{2A}-adrenoceptor, promoting internalisation via recruitment of β-arrestin without activating G proteins [345].

Adrenoceptors, β: β-Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, [340]) are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. isoprenaline is a synthetic agonist 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. (-)-noradrenaline, xamoterol and (-)-Ro 363 are agonists that 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 and L 755507 activate human β_3-adrenoceptors [393]. β_3-Adrenoceptors are relatively resistant to blockade by propranolol (pK_i 5.8–7.0), but can be blocked by high concentrations of bupranolol (pK_i 8.65,[394]). SR59230A has reasonably high affinity at β_3-adrenoceptors [375], but does not discriminate well between the three β-adrenoceptor subtypes [341] and has been reported to have lower affinity for the β_3-adrenoceptor in some circumstances [368]. [^{125}I]-cyanopindolol, [^{125}I]-hydroxybenzylpindolol and [^{3}H]-alprenolol are high affinity radioligands widely used to label β_1- and β_2-adrenoceptors and β_3-adrenoceptors can be labelled with higher concentrations (nM) of [^{125}I]-cyanopindolol in the presence of appropriate concentrations of β_1- and β_2-adrenoceptor antagonists. Fluorescent ligands such as BODIPY-TMR-CGP12177 are also increasingly being used to track β-adrenoceptors at the cellular level [335]. Somewhat selective β_1-adrenoceptor selective agonists (denopamine, dobutamine) are used short-term to treat cardiogenic shock but, in the longer term, reduce survival. β_1-Adrenoceptor-preferring antagonists are used to treat hypertension (atenolol, betaxolol, bisoprolol, metoprolol and nebivolol), cardiac arrhythmias (atenolol, bisoprolol, esmolol) and cardiac failure (metoprolol, nebivolol). Cardiac failure is also succesfully treated with carvedilol which blocks both β_1- and β_2-adrenoceptors, as well as α_1-adrenoceptors. β_2-Adrenoceptor-selective agonists are powerful bronchodilators widely used to treat respiratory disorders. There are both short (salbutamol, terbutaline) and long acting drugs (formoterol, salmeterol). Although many first generation β-adrenoceptor antagonists (propranolol) block both β_1- and β_2-adrenoceptors there are no β_2-adrenoceptor-selective antagonists used therapeutically. Although potentially useful for the treatment of obesity, there are no β_3-adrenoceptor-selective agonists used for this purpose currently. Several β_3-adrenoceptor agonists (mirabegron, amibegron and solabegron) are used to control overactive bladder syndrome.

Nomenclature	β_1-adrenoceptor	β_2-adrenoceptor	β_3-adrenoceptor
HGNC, UniProt	*ADRB1*, P08588	*ADRB2*, P07550	*ADRB3*, P13945
Principal transduction	G_s	G_s	G_s
Rank order of potency	(-)-noradrenaline > (-)-adrenaline	(-)-adrenaline > (-)-noradrenaline	(-)-noradrenaline = (-)-adrenaline
Endogenous agonists (pK_i)	noradrenaline (6.0) [356]	–	–
Selective agonists (pK_i)	(-)-Ro 363 (8.0) [380], xamoterol (Partial agonist) (7.0) [364], denopamine (Partial agonist) (5.8) [364,400]	formoterol (pEC_{50} 10.08) [334], salmeterol (pEC_{50} 9.9) [334], zinterol (pEC_{50} 9.48) [334], procaterol (pEC_{50} 8.43) [334]	carazolol (8.7) [376], BRL 37344 (6.4–7.0) [338,348,362,376], CGP 12177 (Partial agonist) (6.1–7.3) [338,373,376,380], CL316243 (5.2) [411], L 755507 (pEC_{50} 10.1) [334], L742791 (pEC_{50} 8.8) [408], SB251023 (pEC_{50} 7.14 - Mouse) [363]
Selective antagonists (pK_i)	CGP 20712A (8.5–9.2) [332,341,373], betaxolol (8.8) [373], atenolol (6.7–7.6) [332,366,373]	ICI 118551 (Inverse agonist) (9.2–9.5) [332,335,373]	L-748337 (8.4) [341], SR59230A (6.9–8.4) [341,347,362]
Radioligands (K_d)	[^{125}I]ICYP (Antagonist, it is necessary to use an excess of a β_2-AR-selective ligand such as ICI 118551 to allow visualisation of β_1-AR binding in native tissue) ($4.99x10^{-12}$–$3.28x10^{-11}$ M) [373,395]	[^{125}I]ICYP (Antagonist, it is necessary to use an excess of a β_1-AR-selective ligand such as CGP20712A to allow visualisation of β_2-AR binding in native tissues) ($7.9x10^{-12}$ M) [373,395]	[^{125}I]ICYP (Agonist, Partial agonist) ($1.58x10^{-10}$–$6.31x10^{-10}$ M) [373,380,385,395,399]
Comment	The agonists indicated have less than two orders of magnitude selectivity [334].	–	Agonist SB251023 has a pEC_{50} of 6.9 for the splice variant of the mouse β_3 receptor, β_{3b} [363].

Comments: Radioligand binding with [^{125}I]ICYP can be used to define β_1- or β_2-adrenoceptors when conducted in the presence of a 'saturating' concentration of either a β_1- or β_2-adrenoceptor-selective antagonist. [^{3}H]CGP12177 or [^{3}H]dihydroalprenolol can be used in place of [^{125}I]ICYP. Binding of a fluorescent analogue of CGP 12177 to β_2-adrenoceptors in living cells has been described [336]. [^{125}I]ICYP at higher (nM) concentrations can be used to label β_3-adrenoceptors in systems where there are few if any other β-adrenoceptor subtypes.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 and L 755507 activate human β3-adrenoceptors [394]. The β_3-adrenoceptor has an intron in the coding region, but splice variants have only been described for the mouse [352], where the isoforms display different signalling characteristics [363]. There are 3 β-adrenoceptors in turkey (termed the tβ, tβ3c and tβ4c) that have a pharmacology that differs from the human β-adrenoceptors [333]. The 'putative β_4-adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP 12177 and other nonconventional partial agonists at β_1-adrenoceptors,

since 'putative β_4-adrenoceptor'-mediated agonist effects of CGP 12177 are absent in mice lacking β_1-adrenoceptors [367,370]. Numerous polymorphisms have been described for the three β-adrenoceptors; some are associated with alterations in agonist-evoked signalling, trafficking, altered diseases susceptibility and/or altered responses to pharmacotherapy.

All β-adrenoceptors couple to G_s (activating adenylyl cyclase and elevating cAMP levels), but it is also clear that they activate other G proteins such as G_i and many other G protein-independent signalling pathways, including β-arrestins, which may in turn lead to activation of mitogen-activated protein kinases. Many antagonists at β_1- and β_2-adrenoceptors are agonists at β_3-adrenoceptors (CL316243, CGP 12177 and carazolol). Many 'antagonists' that block agonist-stimulated cAMP accumulation, for example carvedilol and bucindolol, are able to activate mitogen-activated protein kinase pathways [337,353,357–358,393–394] and thus display 'protean agonism'. bupranolol appears to act as a neutral antagonist in most systems so far examined. Agonists also display biased signalling at the β_2-adrenoceptor via G_s or β-arrestins [349].

The X-ray crystal structures have been described of the agonist bound [406] and antagonist bound forms of the β_1- [407], agonist-bound [344] and antagonist-bound forms of the β_2-adrenoceptor [388,390], as well as a fully active agonist-bound, G_s protein-coupled β_2-adrenoceptor [389]. carvedilol and bucindolol bind to an extended site of the β_1-adrenoceptor involving contacts in TM2, 3, and 7 and extracellular loop 2 that may facilitate coupling to β-arrestins [407]. Compounds displaying β-arrestin-biased signalling at the β_2-adrenoceptor also have a greater effect on the conformation of TM7, whereas full agonists for G_s coupling promote movement of TM5 and TM6 [372].

Further reading

Baker JG, Hill SJ, Summers RJ. (2011) Evolution of β-blockers: from anti-anginal drugs to ligand-directed signalling. *Trends Pharmacol Sci* **32**: 227–234. [PMID:21429598]

Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, Molinoff PB, Ruffolo RR Jr, Trendelenburg AU. (1994) International Union of Pharmacology nomenclature of adrenoceptors. *Pharmacol Rev* **46**: 121–136. [PMID:7938162]

Cazzola M, Calzetta L, Matera MG. (2011) β(2) -adrenoceptor agonists: current and future direction. *Br J Pharmacol* **163**: 4–17. [PMID:21232045]

Daly CJ, McGrath JC. (2011) Previously unsuspected widespread cellular and tissue distribution of β-adrenoceptors and its relevance to drug action. *Trends Pharmacol Sci* **32**: 219–226. [PMID:21429599]

Evans BA, Sato M, Sarwar M, Hutchinson DS, Summers RJ. (2010) Ligand-directed signalling at beta-adrenoceptors. *Br J Pharmacol* **159**: 1022–1038. [PMID:20132209]

Gilsbach R, Hein L. (2012) Are the pharmacology and physiology of α_2 adrenoceptors determined by α_2-heteroreceptors and autoreceptors respectively?. *Br J Pharmacol* **165**: 90–102. [PMID:21658028]

Jensen BC, O'Connell TD, Simpson PC. (2011) Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. *J Mol Cell Cardiol* **51**: 518–528. [PMID:21118696]

Kobilka BK. (2011) Structural insights into adrenergic receptor function and pharmacology. *Trends Pharmacol Sci* **32**: 213–218. [PMID:21414670]

Michel MC, Harding SE, Bond RA. (2011) Are there functional β_3-adrenoceptors in the human heart?. *Br J Pharmacol* **162**: 817–822. [PMID:20735409]

Michel MC, Ochodnicky P, Homma Y, Igawa Y. (2011) β-adrenoceptor agonist effects in experimental models of bladder dysfunction. *Pharmacol Ther* **131**: 40–49. [PMID:21510978]

Nishimune A, Yoshiki H, Uwada J, Anisuzzaman AS, Umada H, Muramatsu I. (2012) Phenotype pharmacology of lower urinary tract α(1)-adrenoceptors. *Br J Pharmacol* **165**: 1226–1234. [PMID:21745191]

Vasudevan NT, Mohan ML, Goswami SK, Naga Prasad SV. (2011) Regulation of β-adrenergic receptor function: an emphasis on receptor resensitization. *Cell Cycle* **10**: 3684–3691. [PMID:22041711]

Walker JK, Penn RB, Hanania NA, Dickey BF, Bond RA. (2011) New perspectives regarding β(2)-adrenoceptor ligands in the treatment of asthma. *Br J Pharmacol* **163**: 18–28. [PMID:21175591]

Angiotensin receptors

Overview: The actions of angiotensin II (*AGT*, P01019) (Ang II) are mediated by AT_1 and AT_2 receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; [424]), which have around 30% sequence similarity. Endogenous ligands are angiotensin II (*AGT*, P01019) and angiotensin III (*AGT*, P01019) (Ang III), while angiotensin I (*AGT*, P01019) is weakly active in some systems.

Nomenclature	AT_1 receptor	AT_2 receptor
HGNC, UniProt	*AGTR1*, P30556	*AGTR2*, P50052
Principal transduction	$G_{q/11}$	G_i/G_o, Tyr & Ser/Thr phosphatases
Selective agonists (pK_i)	L-162313 (pIC_{50} 7.85–7.92) [433]	[p-aminoPhe6]ang II (pK_d 9.1–9.4 - Rat) [426,434], CGP42112 (pIC_{50} 9.63) [417]
Selective antagonists (pK_i)	candesartan (pIC_{50} 9.5–9.7) [436], irbesartan (pIC_{50} 8.7–8.8) [436], valsartan (pIC_{50} 8.61) [425], eprosartan (pIC_{50} 8.4–8.8) [429], EXP3174 (pIC_{50} 7.4–9.5) [435–436], losartan (pIC_{50} 7.4–8.7) [426,435]	PD123319 (pK_d 8.7–9.2) [426–427,440], PD123177 (pIC_{50} 8.5–9.5 - Rat) [419,422,428]
Radioligands (K_d)	[^{3}H]eprosartan (Antagonist), [^{3}H]A81988 (Antagonist) (5.7x10^{-10} M - Rat) [430], [^{3}H]L158809 (Antagonist) (6.6x10^{-10} M - Rat) [421], [^{125}I]EXP985 (Antagonist) (1.49x10^{-9} M - Rat) [423], [^{3}H]losartan (Antagonist) (6.2x10^{-9} M - Rat) [420], [^{3}H]valsartan (Antagonist) (IC_{50} 1x10^{-9} – 1.58x10^{-9} M) [437]	[^{125}I]CGP42112 (Agonist, Full agonist) (2.51x10^{-11} M) [426,438–439]

Comments: AT_1 receptors are predominantly coupled to $Gq_{/11}$, however they are also linked to arrestin recruitment and stimulate G protein-independent arrestin signalling [431]. 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.

There is also evidence for an AT_4 receptor that specifically binds angiotensin IV (*AGT*) 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) [432]. The AT_1 and bradykinin B2 receptors have been proposed to form a heterodimeric complex [416]. The antagonist activity of CGP42112 has also been reported [415]. 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 [418].

Further reading

de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. (2000) International Union of Pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev* **52**: 415–472. [PMID: 10977869]

Ellis B, Li XC, Miguel-Qin E, Gu V, Zhuo JL. (2012) Evidence for a functional intracellular angiotensin system in the proximal tubule of the kidney. *Am J Physiol Regul Integr Comp Physiol* **302**: R494–R509. [PMID:22170616]

MacKenzie A. (2011) Endothelium-derived vasoactive agents, AT1 receptors and inflammation. *Pharmacol Ther* **131**: 187–203. [PMID:21115037]

Patel BM, Mehta AA. (2012) Aldosterone and angiotensin: Role in diabetes and cardiovascular diseases. *Eur J Pharmacol* **697**: 1–12. [PMID:23041273]

Putnam K, Shoemaker R, Yiannikouris F, Cassis LA. (2012) The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. *Am J Physiol Heart Circ Physiol* **302**: H1219–H1230. [PMID:22227126]

Sevá Pessôa B, van der Lubbe N, Verdonk K, Roks AJ, Hoorn EJ, Danser AH. (2013) Key developments in renin-angiotensin-aldosterone system inhibition. *Nat Rev Nephrol* **9**: 26–36. [PMID:23165302]

Apelin receptor

Overview: The apelin receptor (APJ, nomenclature as agreed by NC-IUPHAR on apelin receptors, [449]) 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 [450].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Endogenous agonists (pK_i)	Radioligands (K_d)
apelin receptor	*APLNR*, P35414	$G_{i/o}$	[Pyr^{1}]apelin-13 ≥ apelin-13 > apelin-36 [443,450]	apelin-13 (Selective) (pIC_{50} 8.8 – 9.5) [443–444,448], apelin-17 (Selective) (pIC_{50} 7.9 – 9.02) [442,448], apelin-36 (Selective) (pIC_{50} 8.2 – 8.6) [443–444,446,448], [Pyr^{1}]apelin-13 (Selective) (pIC_{50} 7.0 – 8.8) [446,448]	[^{125}I][Nle^{75},Tyr^{77}]apelin-36 (human) (Agonist, Full agonist) (6.3x10^{-12} M) [446], [^{125}I][Glp^{65}Nle^{75},Tyr^{77}]apelin-13 (Agonist, Full agonist) (2.23x10^{-11} M) [444], [^{125}I](Pyr^{1})apelin-13 (Agonist, Full agonist) (3x10^{-10} M) [445], [^{125}I]apelin-13 (Agonist, Full agonist) (7x10^{-10} M) [443], [^{3}H](Pyr^{1})[Met(0)11]-apelin-13 (Agonist, Full agonist) (2.7x10^{-9} M) [448]

Comments: Potency order determined for heterologously expressed human APJ receptor (pD_2 values range from 9.5 to 8.6). APJ may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function [441]. A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* [447], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant APJ receptor [443].

Further reading

Chandrasekaran B, Dar O, McDonagh T. (2008) The role of apelin in cardiovascular function and heart failure. *Eur J Heart Fail* **10**: 725–732. [PMID:18583184]

Cheng B, Chen J, Bai B, Xin Q. (2012) Neuroprotection of apelin and its signaling pathway. *Peptides* **37**: 171–173. [PMID:22820556]

Davenport AP, Pitkin SL, Maguire JJ. (2007) Apelins. *in Encyclopedic Reference of Molecular Pharmacology Edited by* Offermanns S, Rosenthal W Springer. 201–206

Japp AG, Newby DE. (2008) The apelin-APJ system in heart failure: pathophysiologic relevance and therapeutic potential. *Biochem Pharmacol* **75**: 1882–1892. [PMID:18272138]

Langelaan DN, Bebbington EM, Reddy T, Rainey JK. (2009) Structural insight into G-protein coupled receptor binding by apelin. *Biochemistry* **48**: 537–548. [PMID:19123778]

Pitkin SL, Maguire JJ, Bonner TI, Davenport AP. (2010) International Union of Basic and Clinical Pharmacology. LXXIV. Apelin receptor nomenclature, distribution, pharmacology, and function. *Pharmacol Rev* **62**: 331–342. [PMID:20605969]

Bile acid receptor

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

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Selective agonists (p*K*$_i$)
GPBA receptor	*GPBAR1*, Q8TDU6	G_s [454]	lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid [452,454]	betulinic acid (pEC_{50} 5.98) [451], oleanolic acid (pEC_{50} 5.65) [455]

Comments: The triterpenoid natural product betulinic acid has also been reported to inhibit inflammatory signalling through the NFκB pathway [456]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [457]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [453].

Further reading

Fiorucci S, Cipriani S, Baldelli F, Mencarelli A. (2010) Bile acid-activated receptors in the treatment of dyslipidemia and related disorders. *Prog Lipid Res* **49**: 171–185. [PMID:19932133]

Fiorucci S, Mencarelli A, Palladino G, Cipriani S. (2009) Bile-acid-activated receptors: targeting TGR5 and farnesoid-X-receptor in lipid and glucose disorders. *Trends Pharmacol Sci* **30**: 570–580. [PMID:19758712]

Keitel V, Häussinger D. (2012) Perspective: TGR5 (Gpbar-1) in liver physiology and disease. *Clin Res Hepatol Gastroenterol* **36**: 412–419. [PMID:22521118]

Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B. (2009) Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev* **89**: 147–191. [PMID:19126757]

Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. (2011) The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. *J Hepatol* **54**: 1263–1272. [PMID:21145931]

Tiwari A, Maiti P. (2009) TGR5: an emerging bile acid G-protein-coupled receptor target for the potential treatment of metabolic disorders. *Drug Discov Today* **14**: 523–530. [PMID:19429513]

Bombesin receptors

Overview: Bombesin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, [462]) are activated by the endogenous ligands gastrin-releasing peptide (*GRP*, P07492) (GRP), NMB (*NMB*, P08949) (NMB) and GRP-(18–27) (*GRP*, P07492) (previously named neuromedin C). bombesin is a tetradecapeptide, originally derived from amphibians. These receptors couple primarily to the $G_{q/11}$ family of G proteins (but see also [463]). Activation of BB_1 and BB_2 receptors causes a wide range of physiological actions, including the stimulation of tissue growth, smooth–muscle contraction, secretion and many central nervous system effects [469]. A physiological role for the BB_3 receptor has yet to be fully defined although receptor knock-out experiments suggest a role in energy balance and the control of body weight [462].

Nomenclature	BB_1 receptor	BB_2 receptor	BB_3 receptor
HGNC, UniProt	*NMBR*, P28336	*GRPR*, P30550	*BRS3*, P32247
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Endogenous agonists (pK_i)	NMB (Selective) (8.1 – 10.3) [458,468]	gastrin-releasing peptide (Selective) (6.34 – 8.21) [458,468]	–
Selective antagonists (pK_i)	dNal-*cyc*(Cys-Tyr-dTrp-Orn-Val)-Nal-NH_2, PD 165929 (pK_d 8.2) [460], PD 168368 (pIC_{50} 9.24 – 9.6) [459], D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH_2 (pIC_{50} 6.22 – 6.56) [459,468]	[D-Phe^6,Cpa^{14},ψ13–14]bombesin-(6–14), JMV594 (pIC_{50} 8.7 - Mouse) [464,470], Ac-GRP-(20–26)-methylester (pIC_{50} 8.4 - Mouse) [461]	–
Selective agonists (pK_i)	–	–	[D-Tyr^6,Apa-4Cl^{11},Phe^{13},Nle^{14}]bombesin-(6–14) (8.1) [466]
Radioligands (K_d)	[^{125}I]BH-NMB, [^{125}I][Tyr^4]bombesin	[^{125}I]GRP (human), [^{125}I][D-Tyr^6]bombesin-(6–13)-methyl ester (Antagonist) ($5.3x10^{-10}$ M - Mouse) [465], [^{125}I][Tyr^4]bombesin (Agonist, Full agonist) ($6.31x10^{-9}$ M) [458]	[^{125}I][D-Tyr^6,β-Ala^{11},Phe^{13},Nle^{14}]bombesin-(6–14) (Agonist, Full agonist) ($1x10^{-8}$ – $3.98x10^{-9}$ M) [467]

Comments: All three subtypes may be activated by [D-Phe^6,β-Ala^{11},Phe^{13},Nle^{14}]bombesin-(6–14) [467]. [D-Tyr^6,Apa-4Cl^{11},Phe^{13},Nle^{14}]bombesin-(6–14) has more than 200-fold selectivity for BB_3 receptors over BB_1 and BB_2 [466].

Further reading

Jensen RT, Battey JF, Spindel ER, Benya RV. (2008) International Union of Pharmacology. LXVIII. Mammalian bombesin receptors: nomenclature, distribution, pharmacology, signaling, and functions in normal and disease states. *Pharmacol Rev* **60**: 1–42. [PMID:18055507]

Majumdar ID, Weber HC. (2011) Biology of mammalian bombesin-like peptides and their receptors. *Curr Opin Endocrinol Diabetes Obes* **18**: 68–74. [PMID:21042212]

Ohki-Hamazaki H, Iwabuchi M, Maekawa F. (2005) Development and function of bombesin-like peptides and their receptors. *Int J Dev Biol* **49**: 293–300. [PMID:15906244]

Roesler R, Henriques JA, Schwartsmann G. (2006) Gastrin-releasing peptide receptor as a molecular target for psychiatric and neurological disorders. *CNS Neurol Disord Drug Targets* **5**: 197–204. [PMID:16611092]

Weber HC. (2009) Regulation and signaling of human bombesin receptors and their biological effects. *Curr Opin Endocrinol Diabetes Obes* **16**: 66–71. [PMID:19115523]

Bradykinin receptors

Overview: Bradykinin (or kinin) receptors (nomenclature recommended by the NC-IUPHAR subcommittee on bradykinin (kinin) receptors, [478]) 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), T-kinin (*KNG1*, P01042) (Ile-Ser-BK), [Hyp^3]-BK (*KNG1*, P01042) and Lys-[Hyp^3]-bradykinin (*KNG1*, P01042). The variation in affinity or inactivity of B_2 receptor antagonists could reflect the existence of species homologues of B_2 receptors.

Nomenclature	B_1 receptor	B_2 receptor
HGNC, UniProt	*BDKRB1*, P46663	*BDKRB2*, P30411
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	[des-Arg^{10}]kallidin > [des-Arg^9]bradykinin = kallidin > bradykinin	kallidin > bradykinin >> [des-Arg^9]bradykinin, [des-Arg^{10}]kallidin
Endogenous agonists (pK_i)	[des-Arg^{10}]kallidin (*KNG1*, P01042) (Selective) (9.6 – 10.0) [471–472,477]	–
Selective agonists (pK_i)	[Sar,D-Phe^8,des-Arg^9]bradykinin (5.7) [477]	[Hyp^3,Tyr(Me)^8]BK, [Phe^8,ψ(CH$_2$-NH)Arg^9]BK
Selective antagonists (pK_i)	R 914 (pA_2 8.6) [474], R-715 (pA_2 8.5) [475], B-9958 (9.2 – 10.3) [473,480], [Leu^9,des-Arg^{10}]kallidin (9.1 – 9.3) [471–472]	icatibant (pA_2 8.4) [476], FR173657 (pA_2 8.2) [481], anatibant (8.2) [479]
Radioligands (K_d)	[^{3}H]Lys-[Leu^8][des-Arg^9]BK (Antagonist), [^{125}I]Hpp-desArg^{10}HOE140 (1x10^{-10} M), [^{3}H]Lys-[des-Arg^9]BK (Agonist, Full agonist) (4x10^{-10} M)	[^{125}I][Tyr^8]bradykinin, [^{3}H]BK (human, mouse, rat) (Agonist, Full agonist) (3.99x10^{-10} M - Mouse) [482], [^{3}H]NPC17731 (Antagonist) (3.9x10^{-10} – 7.7x10^{-10} M) [483–484]

Further reading

Campos MM, Leal PC, Yunes RA, Calixto JB. (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**: 646–651. [PMID:17056130]

Duchene J, Ahluwalia A. (2009) The kinin B(1) receptor and inflammation: new therapeutic target for cardiovascular disease. *Curr Opin Pharmacol* **9**: 125–131. [PMID:19124274]

Marceau F, Regoli D. (2004) Bradykinin receptor ligands: therapeutic perspectives. *Nat Rev Drug Discov* **3**: 845–852. [PMID:15459675]

Paquet JL, Luccarini JM, Fouchet C, Defrêne E, Loillier B, Robert C, Bélichard P, Cremers B, Pruneau D. (1999) Pharmacological characterization of the bradykinin B2 receptor: inter-species variability and dissociation between binding and functional responses. *Br J Pharmacol* **126**: 1083–1090. [PMID:10204994]

Thornton E, Ziebell JM, Leonard AV, Vink R. (2010) Kinin receptor antagonists as potential neuroprotective agents in central nervous system injury. *Molecules* **15**: 6598–6618. [PMID:20877247]

Calcitonin receptors

Overview: Calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors, [495,504]) are generated by the genes *CALCR* (which codes for the CT receptor (CTR),) and *CALCRL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR,). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying protein), which are single TM domain proteins of *ca.* 130 amino acids, identified as a family of three members; RAMP1, RAMP2 and RAMP3. There are splice variants of CTR; these in turn produce variants of the AMY receptor [504]. The endogenous agonists are the peptides CT (*CALCA*, P01258), α-CGRP (*CALCA*, P06881) (formerly known as CGRP-I), β-CGRP (*CALCB*, P10092) (formerly known as CGRP-II), AMY (*IAPP*, P10997) (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), AM (*ADM*, P35318) and AM2/IMD (*ADM2*, Q7Z4H4) (AM2/IMD). There are species differences in peptide sequences, particularly for the CTs. CTR-stimulating peptide (CRSP) is another member of the family with selectivity for the CTR but it is not expressed in humans [497]. BIBN4096BS (also known as olcegepant, *p*Ki~10.5) and MK-0974 (also known as telcagepant, *p*Ki~9) are the most selective antagonists available, having a high selectivity for CGRP receptors, with a particular preference for those of primate origin.

CLR by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, AM and AM2/IMD.

Nomenclature	CGRP receptor	AM_1 receptor	AM_2 receptor
Subunits	RAMP1 (Accessory protein), calcitonin receptor-like receptor	RAMP2 (Accessory protein), calcitonin receptor-like receptor	RAMP3 (Accessory protein), calcitonin receptor-like receptor
Principal transduction	G_s	G_s	G_s
Rank order of potency	α-CGRP > AM ≥ AM2/IMD > AMY ≥ CT (salmon)	AM > AMY > α-CGRP, AM2/IMD > CT (salmon)	AM ≥ AM2/IMD ≥ α-CGRP > AMY > CT (salmon)
Endogenous agonists (pK_i)	β-CGRP (9.9 – 11.0) [485,501], α-CGRP (9.7 – 10.0) [485,501]	AM (8.3 – 9.2) [485,501]	AM (8.3 – 9.0) [485,491]
Selective antagonists (pK_i)	BIBN4096BS (10.2 – 10.7) [489,493–494,500], MK-0974 (9.1) [506]	AM-(22-52) (human) (7.0 – 7.8) [485,494,501]	–
Radioligands (K_d)	$[^{125}I]$αCGRP (mouse, rat) (Agonist, Full agonist), $[^{125}I]$αCGRP (human) (Agonist, Full agonist) ($1x10^{-10}$ M)	$[^{125}I]$AM (rat) (Agonist, Full agonist) ($1x10^{-10}$ – $1x10^{-9}$ M)	$[^{125}I]$AM (rat) (Agonist, Full agonist) ($1x10^{-10}$ – $1x10^{-9}$ M)

Nomenclature	CT receptor	AMY_1 receptor	AMY_2 receptor	AMY_3 receptor
HGNC, UniProt	*CALCR*, P30988	–	–	–
Subunits	–	RAMP1 (Accessory protein), CT receptor	RAMP2 (Accessory protein), CT receptor	RAMP3 (Accessory protein), CT receptor
Principal transduction	G_s	G_s	G_s	G_s
Rank order of potency	CT (salmon) ≥ CT ≥ AMY, α-CGRP > AM, AM2/IMD	CT (salmon) ≥ AMY ≥ α-CGRP > AM2/IMD ≥ CT > AM	Poorly defined	CT (salmon) ≥ AMY > α-CGRP ≥ AM2/IMD ≥ CT > AM
Endogenous agonists (pK_i)	CT (Selective) (pEC_{50} 9.0 – 11.2) [486–487,492,498–499,503]	AMY	AMY	AMY
Radioligands (K_d)	$[^{125}I]$CT (salmon) (Agonist, Full agonist) ($1x10^{-10}$ M), $[^{125}I]$CT (human) (Agonist, Full agonist) ($1x10^{-10}$ – $1x10^{-9}$ M)	$[^{125}I]$BH-AMY (rat, mouse) (Agonist, Full agonist) ($1x10^{-10}$ – $1x10^{-9}$ M)	$[^{125}I]$BH-AMY (rat, mouse) (Agonist, Full agonist) ($1x10^{-10}$ – $1x10^{-9}$ M)	$[^{125}I]$BH-AMY (rat, mouse) (Agonist, Full agonist) ($1x10^{-10}$ – $1x10^{-9}$ M)

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 CT (*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 [488,492–493]. The insert negative (and major) human CTR splice variant ($hCT_{(a)}$) with RAMP1 (*i.e.* the $AMY_{1(a)}$ receptor) has a high affinity for CGRP, unlike $hCT_{(a)}$–RAMP3 (*i.e.* $AMY_{3(a)}$ receptor) [488,492]. However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [507]. In particular, CGRP is a more potent agonist than AMY (*IAPP*, P10997) at increasing cAMP at the delta 47 hCT(a) receptor, when transfected with RAMP1 (to give the corresponding AMY1(a) receptor) in Cos 7 cells [505].

The ligands described represent the best available but their selectivity is limited, apart from BIBN4096BS and MK-0974. For example, AM has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM_2 receptors. AM2/IMD also has high affinity for the AM_2 receptor [496]. CGRP-(8-37) acts as an antagonist of CGRP (pK_i ~8) and inhibits some AM and AMY responses (pK_i ~6–7). It is weak at CT receptors. Salmon CT-(8-32) is an antagonist at both AMY and CT receptors. AC187, a salmon CT analogue, is also an antagonist at AMY and CT receptors. Human AM-(22-52) has some selectivity towards AM receptors, but with modest potency (pK_i ~7), limiting its use [494]. AM-(22-52) is slightly more effective at AM_1 than AM_2 receptors but this difference is not sufficient for this peptide to be a useful discriminator of the AM receptor subtypes.

Ligand responsiveness at CT and AMY receptors can be affected by receptor splice variation and can depend on the pathway being measured. Particularly for AMY receptors, relative potency can vary with the type and level of RAMP present and can be influenced by other factors such as G proteins [502,507].

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 [508]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, *ASL* (P04424) is important for the coupling of CLR to adenylyl cyclase [490].

[^{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. [^{125}I]-Tyr^0-CGRP is widely used as a radioligand for CGRP receptors.

Some early literature distinguished between $CGRP_1$ and $CGRP_2$ receptors. It is now clear that *CLCRL/RAMP1* represents the $CGRP_1$ subtype and is now known simply as the CGRP receptor [495]. The $CGRP_2$ receptor is now considered to have arisen from the actions of CGRP at AM_2 and AMY receptors. This term should not be used [495].

Further reading

Archbold JK, Flanagan JU, Watkins HA, Gingell JJ, Hay DL. (2011) Structural insights into RAMP modification of secretin family G protein-coupled receptors: implications for drug development. *Trends Pharmacol Sci* **32**: 591–600. [PMID:21722971]

Barwell J, Gingell JJ, Watkins HA, Archbold JK, Poyner DR, Hay DL. (2012) Calcitonin and calcitonin receptor-like receptors: common themes with family B GPCRs?. *Br J Pharmacol* **166**: 51–65. [PMID:21649645]

Hay DL, Poyner DR, Quirion R, International Union of Pharmacology. (2008) International Union of Pharmacology. LXIX. Status of the calcitonin gene-related peptide subtype 2 receptor. *Pharmacol Rev* **60**: 143–145. [PMID:18552275]

Hong Y, Hay DL, Quirion R, Poyner DR. (2011) The pharmacology of Adrenomedullin 2/Intermedin. *Br J Pharmacol* [Epub ahead of print]. [PMID:21658025]

Moore EL, Salvatore CA. (2011) Targeting a Family B GPCR/RAMP Receptor Complex: CGRP Receptor Antagonists and Migraine. *Br J Pharmacol* [Epub ahead of print]. [PMID:21871019]

Poyner DR, Sexton PM, Marshall I, Smith DM, Quirion R, Born W, Muff R, Fischer JA, Foord SM. (2002) International Union of Pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors. *Pharmacol Rev* **54**: 233–246. [PMID:12037140]

Calcium-sensing receptors

Overview: The calcium-sensing receptor (CaS, provisional nomenclature) responds to extracellular calcium and magnesium in the millimolar range and to gadolinium and some polycations in the micromolar range [509]. The sensitivity of CaS to primary agonists can be increased by aromatic L-amino acids [511] and also by elevated extracellular pH [520] or decreased extracellular ionic strength [521].

This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

Nomenclature	CaS receptor	$GPRC_6$ receptor
HGNC, UniProt	*CASR*, P41180	*GPRC6A*, Q5T6X5
Principal transduction	$G_{q/11}$, $G_{i/o}$, $G_{12/13}$ [523]	–
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) [511]	–
Cation rank order of potency	$Gd^{3+} > Ca^{2+} > Mg^{2+}$ [509]	–
Polyamine rank order of potency	spermine > spermidine > putrescine [522]	–
Selective allosteric regulators	NPS 89636 (Negative) [515], NPS R-568 (Positive) (pK_d 6.5) [517], calindol (Positive) (pK_d 6.0 – 6.5) [513], AC265347 (Positive) (pEC_{50} 7.6 – 8.1) [514], cinacalcet (Positive) (pEC_{50} 7.3) [516], calindol (Positive) (pEC_{50} 6.5) [518], NPS 2143 (Negative) (pIC_{50} 7.1 – 7.4) [515,525], calhex 231 (Negative) (pIC_{50} 6.4) [519]	–
Comment	2-benzylpyrrolidine derivatives of NPS 2143 are also negative allosteric modulators of the calcium sensing receptor [525].	$GPRC_6$ is a related G_q-coupled receptor which responds to basic amino acids [524][525].

Comments: Positive allosteric modulators of CaS are termed Type II calcimimetics and can suppress parathyroid hormone (PTH (*PTH*, P01270)) secretion [517]. Negative allosteric modulators are called calcilytics and can act to increase PTH (*PTH*, P01270) secretion [515].

The central role of CaS in the maintenance of extracellular calcium homeostasis is seen most clearly in patients with loss-of-function CaS mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaS null mice [510,512], which exhibit similar increases in PTH secretion and blood Ca^{2+} levels. A gain-of-function mutation in the CaS gene is associated with autosomal dominant hypocalcaemia.

Further reading

Breitwieser GE. (2012) Minireview: the intimate link between calcium sensing receptor trafficking and signaling: implications for disorders of calcium homeostasis. *Mol Endocrinol* **26**: 1482–1495. [PMID:22745192]

Brown EM. (2010) Clinical utility of calcimimetics targeting the extracellular calcium-sensing receptor (CaSR). *Biochem Pharmacol* **80**: 297–307. [PMID:20382129]

Khan MA, Conigrave AD. (2010) Mechanisms of multimodal sensing by extracellular Ca(2+)-sensing receptors: a domain-based survey of requirements for binding and signalling. *Br J Pharmacol* **159**: 1039–1050. [PMID:20136834]

Magno AL, Ward BK, Ratajczak T. (2011) The calcium-sensing receptor: a molecular perspective. *Endocr Rev* **32**: 3–30. [PMID:20729338]

Ward DT, Riccardi D. (2012) New concepts in calcium-sensing receptor pharmacology and signalling. *Br J Pharmacol* **165**: 35–48. [PMID:21627634]

Wellendorph P, Brauner-Osborne H. (2004) Molecular cloning, expression, and sequence analysis of GPRC6A, a novel family C G-protein-coupled receptor. *Gene* **335**: 37–46. [PMID:15194188]

Cannabinoid receptors

Overview: Cannabinoid receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Cannabinoid Receptors; [542]) 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 [526].

Nomenclature	CB_1 receptor	CB_2 receptor
HGNC, UniProt	*CNR1*, P21554	*CNR2*, P34972
Principal transduction	$G_{i/o}$	$G_{i/o}$
(Sub)family-selective agonists (pK_i)	CP55940 [550], Δ^9-tetrahydrocannabinol [550], HU-210 [530], WIN55212-2 [550]	CP55940 [550], Δ^9-tetrahydrocannabinol [550], HU-210 [530], WIN55212-2 [550]
Selective agonists (pK_i)	arachidonyl-2-chloroethylamide (8.9 - Rat) [533], arachidonylcyclopropylamide (8.7 - Rat) [533], O-1812 (8.5 - Rat) [528], *R*-(+)-methanandamide (7.7 - Rat) [537]	JWH-133 (8.5) [535,541], AM1241 (8.1) [555], L-759,633 (7.7 – 8.2) [531,548], L-759,656 (7.7 – 7.9) [531,548], HU-308 (7.6) [532]
Selective antagonists (pK_i)	rimonabant (7.9 – 8.7) [529–530,545,549,550], AM251 (8.1 - Rat) [539], AM281 (7.9 - Rat) [538], LY320135 (6.9) [529]	SR144528 (8.3 – 9.2) [546,548], AM630 (7.5) [548]
Radioligands (K_d)	[^{3}H]rimonabant (Antagonist) ($1x10^{-10}$ – $1.2x10^{-9}$ M - Rat) [527,534,536,543,547,551,554]	–

Comments: Both CB_1 and CB_2 receptors may be labelled with [^{3}H]CP55940 (0.5 nM; [550]) and [^{3}H]WIN55212-2 (2–2.4 nM; [552–553]). anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [540,556]. There is evidence for an allosteric site on the CB_1 receptor [544]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [542]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have been identified [542]. 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 [542].

Further reading

Alexander SP, Kendall DA. (2007) The complications of promiscuity: endocannabinoid action and metabolism. *Br J Pharmacol* **152**: 602–623. [PMID:17876303]

Bosier B, Muccioli GG, Hermans E, Lambert DM. (2010) Functionally selective cannabinoid receptor signalling: therapeutic implications and opportunities. *Biochem Pharmacol* **80**: 1–12. [PMID:20206137]

Bradshaw HB, Lee SH, McHugh D. (2009) Orphan endogenous lipids and orphan GPCRs: a good match. *Prostaglandins Other Lipid Mediat* **89**: 131–134. [PMID:19379823]

Centonze D, Finazzi-Agrò A, Bernardi G, Maccarrone M. (2007) The endocannabinoid system in targeting inflammatory neurodegenerative diseases. *Trends Pharmacol Sci* **28**: 180–187. [PMID:17350694]

Di Marzo V, Bisogno T, De Petrocellis L. (2007) Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. *Chem Biol* **14**: 741–756. [PMID:17656311]

Di Marzo V, Petrocellis LD. (2006) Plant, synthetic, and endogenous cannabinoids in medicine. *Annu Rev Med* **57**: 553–574. [PMID:16409166]

Di Marzo V, Petrosino S. (2007) Endocannabinoids and the regulation of their levels in health and disease. *Curr Opin Lipidol* **18**: 129–140. [PMID:17353660]

Fernández-Ruiz J, Romero J, Velasco G, Tolón RM, Ramos JA, Guzmán M. (2007) Cannabinoid CB2 receptor: a new target for controlling neural cell survival?. *Trends Pharmacol Sci* **28**: 39–45. [PMID:17141334]

Godlewski G, Offertáler L, Wagner JA, Kunos G. (2009) Receptors for acylethanolamides-GPR55 and GPR119. *Prostaglandins Other Lipid Mediat* **89**: 105–111. [PMID:19615459]

Hansen HS, Diep TA. (2009) N-acylethanolamines, anandamide and food intake. *Biochem Pharmacol* **78**: 553–560. [PMID:19413995]

Howlett AC, Reggio PH, Childers SR, Hampson RE, Ulloa NM, Deutsch DG. (2011) Endocannabinoid tone versus constitutive activity of cannabinoid receptors. *Br J Pharmacol* **163**: 1329–1343. [PMID:21545414]

Izzo AA, Sharkey KA. (2010) Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther* **126**: 21–38. [PMID:20117132]

Maccarrone M, Gasperi V, Catani MV, Diep TA, Dainese E, Hansen HS, Avigliano L. (2010) The endocannabinoid system and its relevance for nutrition. *Annu Rev Nutr* **30**: 423–440. [PMID:20645854]

McPartland JM, Glass M, Pertwee RG. (2007) Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *Br J Pharmacol* **152**: 583–593. [PMID:17641667]

Mechoulam R, Parker LA. (2013) The endocannabinoid system and the brain. *Annu Rev Psychol* **64**: 21–47. [PMID:22804774]

Miller LK, Devi LA. (2011) The highs and lows of cannabinoid receptor expression in disease: mechanisms and their therapeutic implications. *Pharmacol Rev* **63**: 461–470. [PMID:21752875]

O'Sullivan SE. (2007) Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol* **152**: 576–582. [PMID:17704824]

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K *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]

Ross RA. (2011) L-α-lysophosphatidylinositol meets GPR55: a deadly relationship. *Trends Pharmacol Sci* **32**: 265–269. [PMID:21367464]

Sharir H, Abood ME. (2010) Pharmacological characterization of GPR55, a putative cannabinoid receptor. *Pharmacol Ther* **126**: 301–313. [PMID:20298715]

Ueda N, Tsuboi K, Uyama T. (2010) Enzymological studies on the biosynthesis of N-acylethanolamines. *Biochim Biophys Acta* **1801**: 1274–1285. [PMID:20736084]

Chemerin receptor

Overview: The chemerin receptor is activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is the result of sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase [557–558]. In addition, 2 GPCRs for resolvin D1 (RvD1) have been identified, FPR2/ALX, the lipoxin A_4 receptor, and GPR32, an orphan receptor [559].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Selective agonists (pK_i)	Radioligands (K_d)	Comment
chemerin receptor	*CMKLR1*, Q99788	Not yet established	resolvin E1 > chemerin C-terminal peptide > 18R-HEPE > EPA [557]	resolvin E1	[^{3}H]resolvin E1 (Agonist) ($1.1x10^{-8}$ M) [557–558]	NC-IUPHAR has issued a recommendation for a formal nomenclature change for this receptor from *CMKLR1* to 'chemerin receptor' based on new pairings with chemerin [560–562].

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al*. (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacological reviews* **65**: 967–986.

Chemokine receptors

Overview: Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, [600–601]) comprise a large subfamily of 7TM proteins that bind one or more chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes. Chemokine receptors can be divided by function into two main groups: G protein-coupled chemokine receptors, which mediate leukocyte trafficking, and "Atypical chemokine receptors", which may signal through non-G protein-coupled mechanisms and act as chemokine scavengers to downregulate inflammation or shape chemokine gradients.

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. Listed are those human agonists with EC_{50} values <50 nM in either Ca^{2+} flux or chemotaxis assays at human recombinant G protein-coupled chemokine receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and microbial non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, but CCR5 is the only one demonstrated to play an essential role in HIV/AIDS pathogenesis. The tables include both standard chemokine receptor names [628] and the most commonly used aliases. Numerical data quoted are typically pK_i or pIC_{50} values from radioligand binding to heterologously expressed receptors.

Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
HGNC, UniProt	*CCR1*, P32246	*CCR2*, P41597	*CCR3*, P51677	*CCR4*, P51679	*CCR5*, P51681
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Endogenous agonists (pK_i)	CCL13, CCL8, CCL3 (7.8 – 10.2) [571,572,588,630], CCL23 (Selective) (8.9) [571], CCL7 (8.1) [571,583], CCL5 (6.8 – 8.2) [572,588], CCL14 (7.4) [571], CCL15 (Selective) (pIC_{50} 7.9) [573]	CCL16, CCL2 (pIC_{50} 9.3 – 10.2) [573,595,598,605,615], CCL13 (pIC_{50} 8.6 – 8.7) [595,615], CCL7 (pIC_{50} 8.4 – 8.7) [573,595,615], CCL11 (Partial agonist) (pIC_{50} 7.1 – 7.7) [595,605]	CCL28, CCL8, CCL7 (8.6 – 9.2) [575], CCL13 (pIC_{50} 8.7 – 10.3) [599,615], CCL11 (Selective) (pIC_{50} 8.7 – 9.0) [577,591,599,610,615], CCL24 (Selective) (pIC_{50} 8.0 – 9.4) [599,605], CCL15 (pIC_{50} 8.6) [573], CCL26 (Selective) (pIC_{50} 7.9 – 8.9) [591,599,605]	CCL22 (Selective) (pIC_{50} 9.2) [589], CCL17 (Selective) (pIC_{50} 8.7) [589]	CCL16, CCL4 (Selective) (9.4 – 9.6) [602,609], CCL5 (9.2 – 9.7) [566,602,609], CCL8 (9.3) [609], CCL3 (8.0 – 8.9) [602,609,630], CCL2 (7.5) [602], CCL14 (7.2) [602], CCL11 (pIC_{50} 7.7) [570]
Selective agonists (pK_i)	–	–	CCL11 {Sp: Mouse} (9.5 – 10.0) [575]	–	R5-HIV-1 gp120
Non-selective agonists (pK_i)	–	–	–	vMIP-III	–
Endogenous antagonists (pK_i)	CCL4 (Selective) (7.1 – 7.8) [571,572]	CCL26 (Selective) (pIC_{50} 8.5) [605]	CXCL10 (Selective), CXCL11 (*CXCL11*, O14625) (Selective), CXCL9 (Selective)	–	CCL7 (Selective) (7.5) [602]

Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
Selective antagonists (pK_i)	CP-481,715 (pK_d 8.0) [579], BX 471 (8.2 – 9.0) [593], 2b-1 (pIC_{50} 8.7) [603], UCB35625 (pIC_{50} 8.0) [610]	GSK Compound 34 (7.6)	banyu (I) (Inverse agonist) (8.5) [617], SB328437 (8.4), BMS compound 87b (8.1) [616]	–	MRK-1, vicriviroc (9.1) [613], aplaviroc (8.5) [596], ancriviroc (7.8 – 8.7) [596,604,613], TAK-779 (7.5) [596], E913 (pIC_{50} 8.7) [597], maraviroc (pIC_{50} 8.1) [602]
Radioligands (K_d)	[^{125}I]CCL7 (human) (Agonist, Full agonist) ($7x10^{-10}$ M) [568], [^{125}I]CCL3 (human) (Agonist, Full agonist) ($1.58x10^{-9}$ – $1x10^{-8}$ M) [568,580,611], [^{125}I]CCL5 (human) (Agonist, Full agonist) ($7x10^{-9}$ M) [611]	[^{125}I]CCL2 (Agonist, Full agonist), [^{125}I]CCL7 (human) (Agonist)	[^{125}I]CCL5 (human) (Agonist), [^{125}I]CCL7 (human) (Agonist), [^{125}I]CCL11 (human) (Antagonist) ($5.01x10^{-9}$ M) [617]	[^{125}I]CCL17 (Agonist, Full agonist), [^{125}I]CCL27 (Agonist)	[^{125}I]CCL3 (human) (Agonist), [^{125}I]CCL5 (human) (Agonist), [^{125}I]CCL8 (human) (Agonist), [^{125}I]CCL4 (human) (Agonist, Full agonist) ($2.51x10^{-10}$ M) [602]
Comment	–	–	–	Monoclonal antibody mogamulizumab selectively blocks CCR4	–

Nomenclature	CCR6	CCR7	CCR8	CCR9	CCR10
HGNC, UniProt	*CCR6*, P51684	*CCR7*, P32248	*CCR8*, P51685	*CCR9*, P51686	*CCR10*, P46092
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Endogenous agonists (pK_i)	beta-defensin 4A (*DEFB4A*, *DEFB4B*, O15263) (Selective) [625], CCL20 (pIC_{50} 7.9 – 8.5) [564–565,606]	CCL21 (Selective) (pIC_{50} 9.3) [627], CCL19 (Selective) (pIC_{50} 7.7 – 9.0) [626–627]	CCL8 (Mouse), CCL1 (Selective) (pIC_{50} 8.5 – 9.8) [574,585,590]	CCL25 (Selective)	CCL27 (Selective), CCL28 (Selective)
Selective agonists (pK_i)	–	–	vMIP-I (pIC_{50} 8.9 – 9.9) [574,590]	–	–
Selective antagonists (pK_i)	–	–	vMCC-I (pIC_{50} 9.4) [574]	–	–
Radioligands (K_d)	[^{125}I]CCL20 (Agonist, Full agonist) (~$1x10^{-10}$ M) [582]	[^{125}I]CCL19 (Agonist, Full agonist), [^{125}I]CCL21 (Agonist, Full agonist)	[^{125}I]CCL1 (human) (Agonist, Full agonist) ($2.13x10^{-10}$ – $1.2x10^{-9}$ M) [590,608]	[^{125}I]CCL25 (Agonist, Full agonist)	–

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6
HGNC, UniProt	*CXCR1*, P25024	*CXCR2*, P25025	*CXCR3*, P49682	*CXCR4*, P61073	*CXCR5*, P32302	*CXCR6*, O00574
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Endogenous agonists (pK_i)	CXCL8 (8.8 – 9.5) [569,584,592,622,623], CXCL6 (7.0) [624]	CXCL6 (pK_d 7.0) [624], CXCL8 (8.8 – 9.5) [569,584,592,622,623], CXCL1 (Selective) (8.4 – 9.7) [584,592,623], CXCL3 (Selective) (pIC_{50} 7.8 – 9.2) [563], CXCL2 (Selective) (pIC_{50} 7.0 – 9.1) [563], CXCL5 (Selective) (pIC_{50} 6.9 – 9.0) [563], CXCL7 (Selective) (pIC_{50} 6.3 – 9.3) [563]	CXCL11 (Selective) (10.4 – 10.5) [586], CXCL10 (Selective) (7.8 – 9.8) [586,619], CXCL9 (Selective) (7.3 – 8.3) [586,619]	SDF-1α (Selective) (pK_d 7.7 – 8.2) [587,594], SDF-1β (Selective) (pK_d 7.86) [587]	CXCL13 (Selective)	CXCL16 (Selective) (pK_d 9.0) [621]
Endogenous antagonists (pK_i)	–	–	CCL11 (Selective) (7.2) [619], CCL7 (Selective) (6.6) [619]	–	–	–
Selective agonists (pK_i)	–	–	–	X4-HIV-1 gp120, ALX40-4C (Partial agonist) (pIC_{50} 6.1) [629]	–	–
Non-selective agonists (pK_i)	–	vCXCL-1	–	–	–	–
Selective antagonists (pK_i)	–	SB 225002 (pIC_{50} 7.7) [620]	–	HIV-Tat, plerixafor (7.0) [629], T134 (pIC_{50} 8.4) [614]	–	–
Radioligands (K_d)	[^{125}I]CXCL8 (human) (Agonist, Full agonist) ($2.51x10^{-10}$ – $1.2x10^{-9}$ M) [584,607]	[^{125}I]CXCL1 (Agonist, Full agonist), [^{125}I]CXCL5 (Agonist, Full agonist), [^{125}I]CXCL7 (Agonist, Full agonist), [^{125}I]CXCL8 (human) (Agonist, Full agonist) ($3.98x10^{-10}$ – $1.02x10^{-9}$ M) [584,607]	[^{125}I]CXCL10 (Agonist, Full agonist), [^{125}I]CXCL11 (Agonist, Full agonist)	[^{125}I]SDF-1α (human) (Agonist, Full agonist) ($3.98x10^{-9}$ – $7.94x10^{-9}$ M) [576,587]	–	[^{125}I]CXCL16 (Agonist, Full agonist)

Nomenclature	CX_3CR1	XCR1	DARC
HGNC, UniProt	*CX3CR1*, P49238	*XCR1*, P46094	*DARC*, Q16570
Principal transduction	$G_{i/o}$	$G_{i/o}$	not defined
Endogenous agonists (pK_i)	CX_3CL1 (Selective) (pIC_{50} 8.9) [578]	XCL1 (Selective), XCL2 (Selective)	–
Endogenous ligands	–	–	CXCL5, CXCL6, CXCL8, CXCL11, CCL2, CCL5, CCL7, CCL11, CCL14, CCL17
Selective agonists (pK_i)	–	SEAP-XCL1	–
Radioligands (K_d)	[^{125}I]CX_3CL1 (human) (Agonist, Full agonist)	–	–
Comment	–	When fused with secreted alkaline phophatase (SEAP), XCL1 functions as a probe at XCR1	–

Nomenclature	ACKR2	ACKR3	ACKR4	CCRL2
HGNC, UniProt	*ACKR2*, O00590	*ACKR3*, P25106	*ACKR4*, Q9NPB9	*CCRL2*, O00421
Principal transduction	arrestin	arrestin	not defined	not defined
Endogenous agonists (pK_i)	–	CXCL11, SDF-1α (pEC_{50} 7.52 – 7.9) [581,612]	CCL19 (8.4) [618], CCL25 (7.6) [618], CCL21 (6.9) [618]	–
Endogenous ligands	CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL17, CCL22	–	–	chemerin C-terminal peptide, CCL19 [567]

Comments: Mouse Cxcr binds iodinated mouse KC (CXCL1) and mouse MIP-2 (CXCL2) with high affinity (mouse KC and MIP-2 are homologues of human CXCL1 (*CXCL1*, P09341), CXCL2 (*CXCL2*, P19875) and CXCL3 (*CXCL3*, P19876)), but shows low affinity for human IL-8 (CXCL8 (*IL8*, P10145)).

Specific chemokine receptors facilitate cell entry by microbes, such as ACKR1 for *Plasmodium vivax*, and CCR5 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 Herpesvirus-68), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers.

The CC chemokine family (CCL1–28) includes I309 (CCL1 (*CCL1*, P22362)), MCP-1 (CCL2 (*CCL2*, P13500)), MIP-1α (CCL3 (*CCL3*, P10147)), MIP-1β (CCL4 (*CCL4*, P13236)), RANTES (CCL5 (*CCL5*, P13501)), MCP-3 (CCL7 (*CCL7*, P80098)), MCP-2 (CCL8 (*CCL8*, P80075)), eotaxin (CCL11 (*CCL11*, P51671)), MCP-4 (CCL13 (*CCL13*, Q99616)), HCC-1 (CCL14 (*CCL14*, Q16627)), Lkn-1/HCC-2 (CCL15 (*CCL15*, Q16663)), TARC (CCL17 (*CCL17*, Q92583)), ELC (CCL19 (*CCL19*, Q99731)), LARC (CCL20 (*CCL20*, P78556)), SLC (CCL21 (*CCL21*, O00585)), MDC (CCL22 (*CCL22*, O00626)), MPIF-1 (CCL23 (*CCL23*, P55773)), eotaxin-2 (CCL24 (*CCL24*, O00175)), TECK (CCL25 (*CCL25*, O15444)), eotaxin (CCL26 (*CCL26*, Q9Y258)), eskine/CTACK (CCL27 (*CCL27*, Q9Y4X3)) and MEC (CCL28 (*CCL28*, Q9NRJ3)). The CXC chemokine family (CXCL1–17) includes GROα (CXCL1 (*CXCL1*, P09341)), GROβ (CXCL2 (*CXCL2*, P19875)), GROγ (CXCL3 (*CXCL3*, P19876)), platelet factor 4 (CXCL4 (*PF4*, P02776)), ENA78 (CXCL5 (*CXCL5*, P42830)), GCP-2 (CXCL6 (*CXCL6*, P80162)), NAP-2 (CXCL7 (*PPBP*, P02775)), IL-8 (CXCL8 (*IL8*, P10145)), MIG (CXCL9 (*CXCL9*, Q07325)), IP10 (CXCL10 (*CXCL10*, P02778)), I-TAC (CXCL11 (*CXCL11*, O14625)), SDF-1 (CXCL12, *i.e.* SDF-1α (*CXCL12*, P48061) and SDF-1β (*CXCL12*, P48061)), BLC (CXCL13 (*CXCL13*, O43927)), BRAK (CXCL14 (*CXCL14*, O95715)), mouse lungkine (CXCL15) SR-PSOX (CXCL16 (*CXCL16*, Q9H2A7)) and CXCL17 (*CXCL17*, Q6UXB2). The CX_3C chemokine (CX_3CL1 (*CX3CL1*, P78423)) is also known as fractalkine (neurotactin in the mouse). Like CXCL16 (*CXCL16*, Q9H2A7), and unlike other chemokines, CX_3CL1 (*CX3CL1*, P78423) is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (XCL1 (*XCL1*, P47992)) is also known as lymphotactin. Two chemokine receptor antagonists have now been approved by the FDA: the CCR5 antagonist maraviroc (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and the CXCR4 antagonist plerixafor (Plerixifor, from Sanofi) for hematopoietic stem cell mobilization with G-CSF (*CSF3*, P09919) in patients undergoing transplantation in the context of chemotherapy for lymphoma and multiple myeloma.

Further reading

Koelink PJ, Overbeek SA, Braber S, de Kruijf P, Folkerts G, Smit MJ, Kraneveld AD. (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**: 227–229. [PMID:12037138]

Murphy PM, Baggiolini M, Charo IF, Hebert CA, Horuk R, Matsushima K, Miller LH, Oppenheim JJ, Power CA. (2000) International Union of Pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev* **52**: 145–176. [PMID:10699158]

Muñoz LM, Lucas P, Holgado BL, Barroso R, Vega B, Rodríguez-Frade JM, Mellado M. (2011) Receptor oligomerization: a pivotal mechanism for regulating chemokine function. *Pharmacol Ther* **131**: 351–358. [PMID:21600920]

Scholten DJ, Canals M, Maussang D, Roumen L, Smit MJ, Wijtmans M, de Graaf C, Vischer HF, Leurs R. (2012) Pharmacological modulation of chemokine receptor function. *Br J Pharmacol* **165**: 1617–1643. [PMID:21699506]

Szpakowska M, Fievez V, Arumugan K, van Nuland N, Schmit JC, Chevigné A. (2012) Function, diversity and therapeutic potential of the N-terminal domain of human chemokine receptors. *Biochem Pharmacol* **84**: 1366–1380. [PMID:22935450]

White GE, Iqbal AJ, Greaves DR. (2013) CC chemokine receptors and chronic inflammation–therapeutic opportunities and pharmacological challenges. *Pharmacol Rev* **65**: 47–89. [PMID:23300131]

Cholecystokinin receptors

Overview: Cholecystokinin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on CCK receptors, [644]) are activated by the endogenous peptides cholecystokinin-4 (CCK-4 (*CCK*, P06307)), CCK-8 (*CCK*, P06307), CCK-33 (*CCK*, P06307) and gastrin (gastrin-17 (*GAST*, P01350)). There are only two distinct subtypes of CCK receptors, CCK_1 and CCK_2 receptors, 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 both CCK and gastrin peptides. These receptors have characteristic and distinct distributions, with both present in both the central nervous system and peripheral tissues.

Nomenclature	CCK_1 receptor	CCK_2 receptor
HGNC, UniProt	*CCKAR*, P32238	*CCKBR*, P32239
Principal transduction	$G_{q/11}/G_s$	G_s
Rank order of potency	CCK-8 >> gastrin-17, CCK-8 (desulphated) > CCK-4	CCK-8 ≥ gastrin-17, CCK-8 (desulphated), CCK-4
Endogenous agonists (pK_i)	–	CCK-8 (desulphated) (pIC_{50} 8.3 – 8.7) [14], CCK-4 (pIC_{50} 7.5) [636]
Selective agonists (pK_i)	A-71623 (pIC_{50} 8.4 - Rat) [2], JMV180 (pIC_{50} 8.3) [639], GW-5823 (pIC_{50} 7.6) [633]	RB-400 (9.1 - Rat) [3], PBC-264 (pIC_{50} 9.1 – Rat) [638], gastrin-17 (pIC_{50} 8.3 - Mouse) [634]
Selective antagonists (pK_i)	devazepide (pIC_{50} 9.7 - Rat) [8], T-0632 (pIC_{50} 9.6 - Rat) [650], PD-140548 (pIC_{50} 8.6 - Rat) [647], lintitript (pIC_{50} 8.3) [632], lorglumide (pIC_{50} 6.7 – 8.2 - Rat) [634,637]	YF-476 (pIC_{50} 9.7) [4,24], GV150013 (pIC_{50} 9.4) [651], L-740093 (pIC_{50} 9.2) [643], YM-022 (pIC_{50} 9.2) [643], JNJ-26070109 (pIC_{50} 8.5) [642], L-365260 (pIC_{50} 8.4) [640], RP73870 (pIC_{50} 8.0 - Rat) [641], LY262691 (pIC_{50} 7.5 - Rat) [646]
Radioligands(K_d)	[^{3}H]devazepide (Antagonist) ($2x10^{-10}$ M) [5]	[^{3}H]L365260 (Antagonist) ($2.9x10^{-9}$ – $5.7x10^{-9}$ M) [17], [^{3}H]PD140376 (Antagonist) (K_i $1x10^{-10}$ – $2x10^{-10}$ M – Guinea pig) [635], [^{125}I]PD142308 (Antagonist) (K_i $2.5x10^{-10}$ M), [^{125}I]-BDZ_2 (Antagonist) (K_i $3.98x10^{-9}$ M) [631], [^{125}I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist, Full agonist) (IC_{50} $1x10^{-9}$ M) [645], [^{125}I]gastrin (Agonist, Full agonist) (IC_{50} $1x10^{-9}$ M), [^{3}H]gastrin (Agonist, Full agonist) (IC_{50} $1x10^{-9}$ M)

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 misplicing has been commonly observed [648], 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 [649], with alternative donor sites in exon 4 resulting in long (452 amino acids) and short (447 amino acids) forms of the receptor differing by five residues in ICL3, however, no clear functional differences have been observed.

Further reading

Cawston EE, Miller LJ. (2010) Therapeutic potential for novel drugs targeting the type 1 cholecystokinin receptor. *Br J Pharmacol* **159**: 1009–1021. [PMID:19922535]

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

Dufresne M, Seva C, Fourmy D. (2006) Cholecystokinin and gastrin receptors. *Physiol Rev* **86**: 805–847. [PMID:16816139]

Herranz R. (2003) Cholecystokinin antagonists: pharmacological and therapeutic potential. *Med Res Rev* **23**: 559–605. [PMID:12789687]

Miller LJ, Gao F. (2008) Structural basis of cholecystokinin receptor binding and regulation. *Pharmacol Ther* **119**: 83–95. [PMID:18558433]

Noble F, Wank SA, Crawley JN, Bradwejn J, Seroogy KB, Hamon M, Roques BP. (1999) International Union of Pharmacology. XXI. Structure, distribution, and functions of cholecystokinin receptors. *Pharmacol Rev* **51**: 745–781. [PMID:10581329]

Complement peptide receptors

Formerly known as: Anaphylatoxin receptors

Overview: Complement peptide receptors (nomenclature as agreed by the NC-IUPHAR subcommittee on Complement peptide receptors, see [665]) are activated by the endogenous ~75 amino-acid anaphylatoxin polypeptides C3a (*C3*, P01024). C4a (*C4A*, P0C0L4) and C5a (*C5*, P01031), generated upon stimulation of the complement cascade.

Nomenclature	C3a receptor	$C5a_1$ receptor	$C5a_2$ receptor
HGNC, UniProt	*C3AR1*, Q16581	*C5AR1*, P21730	*C5AR2*, Q9P296
Principal transduction	$G_{i/o}$, G_z	$G_{i/o}$, G_z, G_{16} (Buhl *et al.*, 1993)	–
Rank order of potency	C3a > C5a [653]	C5a, C5a des-Arg (*C5*) > C3a [653]	–
Endogenous agonists (pK_i)	–	RP-S19 (*RPS19*, P39019) [675]	–
Selective agonists (pK_i)	E7 (pEC_{50} 8.7) [654]	*N*-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO_2H (pIC_{50} 7.6) [664,666]	–
Selective antagonists (pK_i)	SB290157 (pIC_{50} 7.6) [652]	CHIPS (pK_d 9.0) [670], W54011 (8.7) [672], AcPhe-Orn-Pro-D-Cha-Trp-Arg (pIC_{50} 7.9) [674], *N*-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO_2H (pIC_{50} 7.2) [666]	–
Radioligands (K_d)	[^{125}I]C3a (human) (Agonist, Full agonist) (3.85x10^{-9} M) [657]	[^{125}I]C5a (human) (Agonist, Full agonist) (2x10^{-9} M) [661]	[^{125}I]C5a (human) (Agonist, Full agonist)
Comment	–	–	Binds C5a complement factor, but appears to lack G protein signalling and has been termed a decoy receptor [671]

Comments: SB290157 has also been reported to have agonist properties at the C3a receptor [668]. The putative chemoattractant receptor termed $C5a_2$ (also known as GPR77, C5L2) binds [^{125}I]C5a with no clear signalling function, but has a putative role opposing inflammatory responses [656,658–659]. Binding to this site may be displaced with the rank order C5a des-Arg (*C5*)> C5a (*C5*, P01031) [656,669] while there is controversy over the ability of C3a (*C3*, P01024) and C3a des Arg (*C3*, P01024) to compete [660,662–663,669]. $C5a_2$ appears to lack G protein signalling and has been termed a decoy receptor [671]. However, $C5a_2$ does recruit β-arrestin after ligand binding, which might provide a signaling pathway for this receptor [655,673]. There are also reports of pro-inflammatory activity of $C5a_2$, mediated by HMGB1, but the signaling pathway that underlies this is currently unclear (reviewed in [667]).

Further reading

Ali H. (2010) Regulation of human mast cell and basophil function by anaphylatoxins C3a and C5a. *Immunol Lett* **128**: 36–45. [PMID:19895849]

Hajishengallis G. (2010) Complement and periodontitis. *Biochem Pharmacol* **80**: 1992–2001. [PMID:20599785]

Klos A, Wende E, Wareham KJ, Monk PN. (2013) International Union of Pharmacology. LXXXVII. Complement peptide C5a, C4a, and C3a receptors. *Pharmacol Rev* **65**: 500–543. [PMID:23383423]

Manthey HD, Woodruff TM, Taylor SM, Monk PN. (2009) Complement component 5a (C5a). *Int J Biochem Cell Biol* **41**: 2114–2117. [PMID:19464229]

Monk PN, Scola AM, Madala P, Fairlie DP. (2007) Function, structure and therapeutic potential of complement C5a receptors. *Br J Pharmacol* **152**: 429–448. [PMID:17603557]

Sacks SH. (2010) Complement fragments C3a and C5a: the salt and pepper of the immune response. *Eur J Immunol* **40**: 668–670. [PMID:20186746]

Corticotropin-releasing factor receptors

Overview: Corticotropin-releasing factor (CRF, nomenclature as recommended by the NC-IUPHAR sub-committee on Corticotropin-releasing Factor Receptors, [682]) receptors are activated by the endogenous peptides CRF (*CRH*, P06850), a 41 amino-acid peptide, urocortin 1 (*UCN*, P55089), 40 amino-acids), urocortin 2 (*UCN2*, Q96RP3), 38 amino-acids) and urocortin 3 (*UCN3*, Q969E3), 38 amino-acids). CRF1 and CRF2 receptors are activated non-selectively by CRF (*CRH*, P06850) and urocortin 1 (*UCN*, P55089). Binding to CRF receptors can be conducted using [^{125}I]Tyr^{0}-CRF or [^{125}I]Tyr0-sauvagine with K^{d} values of 0.1–0.4 nM. CRF1 and CRF2 receptors are non-selectively antagonized by α-helical CRF, D-Phe-CRF-(12-41) and astressin.

Nomenclature	CRF_1 receptor	CRF_2 receptor
HGNC, UniProt	*CRHR1*, P34998	*CRHR2*, Q13324
Principal transduction	G_s	G_s
Endogenous agonists	–	urocortin 2 (Selective) (pK_d 8.5 – 8.6) [679], urocortin 3 (Selective) (pK_d 7.9 – 8.0) [679]
Selective antagonists (pK_i)	SSR125543A (8.7) [681], antalarmin (8.3 – 9.0) [688], DMP696 (8.3 – 9.0) [683], NBI27914 (8.3 – 9.0) [677], R121919 (8.3 – 9.0) [689], CP 154,526 (pIC_{50} 9.3 – 10.4 - Rat) [685], CP376395 (pIC_{50} 8.3 - Rat) [678], CRA1000 (pIC_{50} 6.4 – 7.1) [676]	antisauvagine (pK_d 8.8 – 9.6) [680], K41498 (9.2) [684], K31440 (8.7 – 8.8) [687]

Comments: A CRF binding protein has been identified (*CRHBP*, P24387) to which both CRF and urocortin 1 bind with high affinities, which has been suggested to bind and inactivate circulating CRF [686].

Further reading

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

Gysling K. (2012) Relevance of both type-1 and type-2 corticotropin releasing factor receptors in stress-induced relapse to cocaine seeking behaviour. *Biochem Pharmacol* **83**: 1–5. [PMID:21843515]

Hauger RL, Grigoriadis DE, Dallman MF, Plotsky PM, Vale WW, Dautzenberg FM. (2003) International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacol Rev* **55**: 21–26. [PMID:12615952]

Valentino RJ, Bangasser D, Van Bockstaele EJ. (2013) Sex-biased stress signaling: the corticotropin-releasing factor receptor as a model. *Mol Pharmacol* **83**: 737–745. [PMID:23239826]

Zhu H, Wang J, Li J, Li S. (2011) Corticotropin-releasing factor family and its receptors: pro-inflammatory or anti-inflammatory targets in the periphery?. *Inflamm Res* **60**: 715–721. [PMID:21476084]

Dopamine receptors

Overview: Dopamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Dopamine Receptors, [723]) 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.

Nomenclature	D_1 receptor	D_5 receptor	D_2 receptor	D_3 receptor	D_4 receptor
HGNC, UniProt	*DRD1*, P21728	*DRD5*, P21918	*DRD2*, P14416	*DRD3*, P35462	*DRD4*, P21917
Principal transduction	G_s, G_{olf}	G_s	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
(Sub)family-selective agonists (pK_i)	A68930 (pEC_{50} 6.82) [712]	A68930 (pEC_{50} 6.6) [712]	quinpirole (4.9–7.7) [693,706,713,724–725,729]	quinpirole (6.4–8.0) [693,706,710,713,724–725,729]	quinpirole (7.5) [709,713,729]
Selective agonists (pK_i)	SKF-81297 (8.7 - Rat) [691], SKF-38393 (6.2–6.8) [726–727]	–	sumanirole (8.1) [705]	PD 128907 (7.6–7.7) [715,720]	PD168,077 (Partial agonist) (8.8 - Rat) [700], A412997 (8.1 - Rat) [711]
(Sub)family-selective antagonists (pK_i)	SKF-83556 (9.5) [726], SCH-23390 (7.4–9.5) [726–727], ecopipam (8.3) [728]	SKF-83556 (9.4) [726], SCH-23390 (7.5–9.5) [726], ecopipam (8.3) [726]	haloperidol (7.4–8.8) [695,704,706,724,728]	haloperidol (7.5–8.0) [695,724,728]	haloperidol (8.7) [703,728]
Selective antagonists (pK_i)	–	–	L-741,626 (7.9–8.5) [696,701], domperidone (7.9–8.4) [695,724], raclopride (8.0) [710]	S33084 (9.6) [708], nafadotride (9.52) [721], PG01037 (9.2) [697], NGB 2904 (8.8) [730], SB 277011-A (8.0) [716], (+)-S-14297 (7.9) [707]	L745870 (9.4) [701], sonepiprazole (8.9) [722], L741742 (8.5) [719]
(Sub)family-selective radioligands (K_d)	[^{3}H]SCH-23390 (Antagonist) ($3x10^{-10}$ M) [732]	[^{3}H]SCH-23390 (Antagonist) ($5.8x10^{-10}$ M) [717]	[^{3}H]spiperone (Antagonist) ($5.7x10^{-11}$ M - Rat) [692,699,731]	–	[^{3}H]spiperone (Antagonist) ($3x10^{-10}$ M) [698,729]
Radioligands (K_d)	[^{125}I]SCH23982 (Antagonist) ($3.5x10^{-10}$ M) [694]	[^{125}I]SCH23982 (Antagonist) ($8x10^{-10}$ M)	[^{3}H]raclopride (Antagonist) ($1.2x10^{-9}$ M - Rat) [702]	[^{3}H]spiperone (Antagonist) ($1.25x10^{-10}$ M - Rat) [699,731], [^{3}H]7-OH-DPAT (Agonist) ($2.7x10^{-10}$ M) [718], [^{3}H]PD128907 (Agonist) ($9.9x10^{-10}$ M) [690]	[^{125}I]L750667 (Antagonist) ($1.6x10^{-10}$ M) [713], [^{3}H]NGD941 (Antagonist) ($5x10^{-9}$ M) [714]
Comment	A68930 is an agonist with selectivity for D_1-like receptors [712]., SCH-23390 (pKi 9.5) [726], SKF-83556 (pKi 9.3) [726] and ecopipam (pKi 8.3) [728] are antagonists with selectivity for D_1-like receptors	A68930 is an agonist with selectivity for D_1-like receptors [712]., SCH-23390 (pKi 9.5) [726], SKF-83556 (pKi 9.3) [726] and ecopipam (pKi 8.3) [728] are antagonists with selectivity for D_1-like receptors	quinpirole is an agonist with selectivity for D_2-like receptors [729]	quinpirole is an agonist with selectivity for D_2-like receptors [729]	quinpirole is an agonist with selectivity for D_2-like receptors [729]

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.

Further reading

Beaulieu JM, Gainetdinov RR. (2011) The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* **63**: 182–217. [PMID:21303898]

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

Maggio R, Millan MJ. (2010) Dopamine D2-D3 receptor heteromers: pharmacological properties and therapeutic significance. *Curr Opin Pharmacol* **10**: 100–107. [PMID:19896900]

Ptácek R, Kuzelová H, Stefano GB. (2011) Dopamine D4 receptor gene DRD4 and its association with psychiatric disorders. *Med Sci Monit* **17**: RA215–RA220. [PMID:21873960]

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

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

Endothelin receptors

Overview: Endothelin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on endothelin receptors, [736]) are activated by the endogenous 21 amino-acid peptides endothelins 1–3 (ET-1 (*EDN1*, P05305), ET-2 (*EDN2*, P20800) and ET-3 (*EDN3*, P14138)).

Nomenclature	ET_A receptor	ET_B receptor
HGNC, UniProt	*EDNRA*, P25101	*EDNRB*, P24530
Principal transduction	$G_{q/11}$, G_s	$G_{q/11}$, $G_{i/o}$
Family selective agonists	ET-1 = ET-2 > ET-3 [744]	ET-1 = ET-2, ET-3
(Sub)family-selective antagonists (pK_i)	TAK 044 (pA_2 8.4 - Rat) [755], bosentan (pA_2 7.2 - Rat) [735], SB209670 (pK_B 9.4 - Rat) [739]	–
Selective agonists (pK_i)	–	sarafotoxin S6c (pK_d 8.8–9.8) [743,752], [$Ala^{1,3,11,15}$]ET-1 (pK_d 8.7–9.2) [747], BQ 3020 (9.7) [751], IRL 1620 (8.7) [754]
(Sub)family-selective antagonists (pK_i)	–	TAK 044 (pA_2 8.4 - Rat) [755], bosentan (pA_2 6.0 - Rat) [735], SB209670 (pK_B 9.4 - Rat) [739]
Selective antagonists (pK_i)	A127722 (pA_2 9.2–10.5) [749], BQ123 (pA_2 6.9–7.4) [744], ambrisentan (pA_2 7.1) [733], PD-156707 (pK_d 9.0–9.8) [745], FR139317 (Inverse agonist) (pIC_{50} 7.3–7.9) [744]	A192621 (pK_d 8.1) [753], BQ788 (pK_d 7.9–8.0) [752], IRL 2500 (pK_d 7.2) [752], RO4868443 (pIC_{50} 7.2) [734]
Radioligands (K_d)	[^{125}I]PD164333 (Antagonist) ($1.58x10^{-10}$–$2.5x10^{-10}$ M) [737], [^{3}H]S0139 (Antagonist) ($6x10^{-10}$ M), [^{125}I]PD151242 (Antagonist) ($7.9x10^{-10}$–$1x10^{-9}$ M) [738], [^{3}H]BQ123 (Antagonist) ($3.2x10^{-9}$ M) [742]	[^{125}I]IRL1620 (Agonist, Full agonist) ($7.9x10^{-11}$–$1.26x10^{-10}$ M) [748], [^{125}I][$Ala^{1,3,11,15}$]ET-1 (Agonist, Full agonist) ($2x10^{-10}$ M) [747], [^{125}I]BQ3020 (Agonist, Full agonist) ($1x10^{-10}$–$5x10^{-9}$ M) [740,747,750]

Comments: Splice variants of the ETA 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 [741]. Subtypes of the ET_B receptor have been proposed, although gene disruption studies in mice suggest that the heterogeneity results from a single gene product [746].

Further reading

Bagnato A, Rosanò L. (2008) The endothelin axis in cancer. *Int J Biochem Cell Biol* **40**: 1443–1451. [PMID:18325824]

Barr TP, Kam S, Khodorova A, Montmayeur JP, Strichartz GR. (2011) New perspectives on the endothelin axis in pain. *Pharmacol Res* **63**: 532–540. [PMID:21352917]

Davenport AP. (2002) International Union of Pharmacology. XXIX. Update on endothelin receptor nomenclature. *Pharmacol Rev* **54**: 219–226. [PMID:12037137]

Dhaun N, Webb DJ, Kluth DC. (2012) Endothelin-1 and the kidney–beyond BP. *Br J Pharmacol* **167**: 720–731. [PMID:22670597]

Kohan DE, Rossi NF, Inscho EW, Pollock DM. (2011) Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev* **91**: 1–77. [PMID:21248162]

Ling L, Maguire JJ, Davenport AP. (2013) Endothelin-2, the forgotten isoform: emerging role in the cardiovascular system, ovarian development, immunology and cancer. *Br J Pharmacol* **168**: 283–295. [PMID:22118774]

Nguyen A, Thorin-Trescases N, Thorin E. (2010) Working under pressure: coronary arteries and the endothelin system. *Am J Physiol Regul Integr Comp Physiol* **298**: R1188–R1194. [PMID:20237301]

Rubin LJ. (2012) Endothelin receptor antagonists for the treatment of pulmonary artery hypertension. *Life Sci* **91**: 517–521. [PMID:22884806]

Said N, Theodorescu D. (2012) Permissive role of endothelin receptors in tumor metastasis. *Life Sci* **91**: 522–527. [PMID:22846215]

Schneider MP, Boesen EI, Pollock DM. (2007) Contrasting Actions of Endothelin ET(A) and ET(B) Receptors in Cardiovascular Disease. *Annu Rev Pharmacol Toxicol* **47**: 731–759. [PMID:17002597]

Schorlemmer A, Matter ML, Shohet RV. (2008) Cardioprotective signaling by endothelin. *Trends Cardiovasc Med* **18**: 233–239. [PMID:19232951]

Speed JS, Pollock DM. (2013) Endothelin, kidney disease, and hypertension. *Hypertension* **61**: 1142–1145. [PMID:23608655]

Thorin E, Webb DJ. (2010) Endothelium-derived endothelin-1. *Pflugers Arch* **459**: 951–958. [PMID:19967386]

Estrogen (G protein-coupled) receptor

Overview: The G protein-coupled estrogen receptor (GPER, provisional nomenclature) was identified following observations of estrogen-evoked cAMP signalling in breast cancer cells [756], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [758]. There are observations of both cell-surface and intracellular expression of the GPER receptor [763–764].

Nomenclature	HGNC, UniProt	Principal transduction	Selective agonists (pK_i)	Selective antagonists (pK_i)	Radioligands (K_d)
GPER	*GPER1*, Q99527	G_s [761], $G_{i/o}$ [763]	G-1 (8.0) [757]	G36 (pIC_{50} 6.78–6.95) [760], G15 (pIC_{50} 6.7) [759]	[^{3}H]17β-estradiol (Agonist, Full agonist) ($2.7x10^{-9}$–$3.3x10^{-9}$ M) [764]

Comments: Antagonists at the nuclear estrogen receptor, such as fulvestrant and tamoxifen [761], as well as the flavonoid 'phytoestrogens' genistein and quercetin [762], are agonists at GPER receptors.

Further reading

Barton M. (2012) Position paper: The membrane estrogen receptor GPER–Clues and questions. *Steroids* **77**: 935–942. [PMID:22521564]

Filardo EJ, Thomas P. (2012) Minireview: G protein-coupled estrogen receptor-1, GPER-1: its mechanism of action and role in female reproductive cancer, renal and vascular physiology. *Endocrinology* **153**: 2953–2962. [PMID:22495674]

Hammond R, Gibbs RB. (2011) GPR30 is positioned to mediate estrogen effects on basal forebrain cholinergic neurons and cognitive performance. *Brain Res* **1379**: 53–60. [PMID:21138734]

Meyer MR, Prossnitz ER, Barton M. (2011) The G protein-coupled estrogen receptor GPER/GPR30 as a regulator of cardiovascular function. *Vascul Pharmacol* **55**: 17–25. [PMID:21742056]

Nilsson BO, Olde B, Leeb-Lundberg LM. (2011) G protein-coupled oestrogen receptor 1 (GPER1)/GPR30: a new player in cardiovascular and metabolic oestrogenic signalling. *Br J Pharmacol* **163**: 1131–1139. [PMID:21250980]

Prossnitz ER, Barton M. (2011) The G-protein-coupled estrogen receptor GPER in health and disease. *Nat Rev Endocrinol* **7**: 715–726. [PMID:21844907]

Formylpeptide receptors

Overview: The formylpeptide receptors, nomenclature agreed by NC-IUPHAR Subcommittee on the formyl peptide receptor family, [787]) respond to exogenous ligands such as the bacterial product fMet-Leu-Phe (fMLP) and endogenous ligands such as annexin I (*ANXA1*, P04083) , cathepsin G (*CTSG*, P08311), amyloid β42, serum amyloid A and spinorphin, derived from β-haemoglobin (*HBB*, P68871).

Nomenclature	FPR1	FPR2/ALX	FPR3
HGNC, UniProt	*FPR1*, P21462	*FPR2*, P25090	*FPR3*, P25089
Principal transduction	$G_{i/o}$, G_z	G_i [778]	–
Rank order of potency	fMet-Leu-Phe > cathepsin G (*CTSG*, P08311) > annexin I [776,783]	LXA_4=aspirin triggered lipoxin A4=ATLa2>LTC_4=LTD_4>>15-deoxy-LXA4>>fMet-Leu-Phe [765–766,768,770,784]	–
Selective agonists (pK_i)	fMet-Leu-Phe (pEC_{50} 10.1–10.2) [769,782]	–	–
Endogenous antagonists (pK_i)	spinorphin (Selective) (pIC_{50} 4.3) [777,780]	aspirin triggered lipoxin A4 (Selective), LXA_4 (Selective) (pEC_{50} ~12.0) [775], resolvin D1 (Selective) (pEC_{50} ~11.9) [775]	–
Endogenous agonists(pKi)	F2L (*HEBP1*, Q9NRV9) (Selective) (pEC_{50} 8.0–8.2) [779]	–	–
Selective antagonists (pK_i)	cyclosporin H (6.1–7.1) [785–786], t-Boc-FLFLF (6.0–6.5) [785]	ATLa2 [771]	–
Radioligands (K_d)	[^{3}H]fMet-Leu-Phe (Agonist, Full agonist) (5×10^{-10}–2.51×10^{-8} M) [774]	[^{3}H]LXA_4 (Agonist, Full agonist) (5×10^{-10}–7×10^{-10} M) [766–767]	–
Comment	A FITC-conjugated fMLP analogue has been used for binding to the mouse recombinant receptor [773]	The agonist activity of the lipid mediators described has been questioned [772,781], which may derive from batch-to-batch differences, partial agonism or biased agonism	–

Comments: Note that the data for FPR2ALX are also reproduced on the leukotriene receptor page.

Further reading

Dufton N, Perretti M. (2010) Therapeutic anti-inflammatory potential of formyl-peptide receptor agonists. *Pharmacol Ther* **127**: 175–188. [PMID:20546777]

Liu M, Zhao J, Chen K, Bian X, Wang C, Shi Y, Wang JM. (2012) G protein-coupled receptor FPR1 as a pharmacologic target in inflammation and human glioblastoma. *Int Immunopharmacol* **14**: 283–288. [PMID:22863814]

Rabiet MJ, Macari L, Dahlgren C, Boulay F. (2011) N-formyl peptide receptor 3 (FPR3) departs from the homologous FPR2/ALX receptor with regard to the major processes governing chemoattractant receptor regulation, expression at the cell surface, and phosphorylation. *J Biol Chem* **286**: 26718–26731. [PMID:21543323]

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

Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, Serhan CN, Murphy PM. (2009) International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev* **61**: 119–161. [PMID:19498085]

Free fatty acid receptors

Overview: Free fatty acid receptors (FFA, nomenclature as agreed by NC-IUPHAR Subcommittee on free fatty acid receptors, [792,814]) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (C14.0 (myristic acid), C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (linoleic acid), C18:3, (α-linolenic acid), C20:4 (arachidonic acid), C20:5,n-3 (EPA), C22:6,n-3 (docosahexaenoic acid)) activate FFA_1 [789,797,799] and FFA4 receptors [793,796,807], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA_2 [790,801,806] and FFA_3 [790,801] receptors. In addition, thiazolidinedione PPARγ agonists such as rosiglitazone activate FFA_1 (pEC_{50} 5.2; [800,811,813]) and small molecule allosteric modulators, such as 4-CMTB, have recently been characterised for FFA_2 [795,802,812].

Nomenclature	FFA1 receptor	FFA2 receptor	FFA3 receptor	FFA4 receptor
HGNC, UniProt	*FFAR1*, O14842	*FFAR2*, O15552	*FFAR3*, O14843	*FFAR4*, Q5NUL3
Principal transduction	$G_{q/11}$ [789,797,809,813]	$G_{q/11}$, $G_{i/o}$ [790,801,806,808]	$G_{i/o}$ [790,801,808,813]	$G_{q/11}$ [793,807,810,819]
Endogenous agonists (pK_i)	docosahexaenoic acid (pEC_{50} 5.4–6.0) [789,797]	–	–	α-linolenic acid (pEC_{50} 5.5) [810]
(Sub)family-selective agonists (pK_i)	α-linolenic acid (pEC_{50} 4.6–5.7) [789,797,799], myristic acid (pEC_{50} 4.5–5.1) [789,797,799], oleic acid (pEC_{50} 3.9–5.7) [789,797,799]	propanoic acid (pEC_{50} 3.0–4.9) [790,801,806,808], acetic acid (pEC_{50} 3.1–4.6) [790,801,806,808], *trans*-2-methylcrotonic acid (pEC_{50} 3.8) [808], butyric acid (pEC_{50} 2.9–4.6) [790,801,806,808], 1-methylcyclopropanecarboxylic acid (pEC_{50} 2.6) [808]	propanoic acid (pEC_{50} 3.9–5.7) [790,801,808,820], butyric acid (pEC_{50} 3.8–4.9) [790,801,808,820], 1-methylcyclopropanecarboxylic acid (pEC_{50} 3.9) [808], acetic acid (pEC_{50} 2.8–3.9) [790,801,808,820]	myristic acid (pEC_{50} 5.2) [819], oleic acid (pEC_{50} 4.7) [819]
Selective agonists (pK_i)	AMG-837 (pEC_{50} 8.5) [804], TUG-770 (pEC_{50} 8.2) [791], GW9508 (pEC_{50} 7.3) [788], TAK-875 (pEC_{50} 7.1) [817], linoleic acid (pEC_{50} 4.4–5.7) [789,797,799]	3-benzyl-4-(cyclopropyl-(4-(2,5-dichlorophenyl)thiazol-2-yl)amino)-4-oxobutanoic acid (pEC_{50} 7.1 - Rat) [794], (S)-4-CMTB (pEC_{50} 6.4) [795,802]	–	TUG-891 (pEC_{50} 7.0) [810], NCG21 (pEC_{50} 5.92) [816]
Selective antagonists (pK_i)	GW1100 (pIC_{50} 6.0) [788]	CATPB (pIC_{50} 6.5) [795]	–	–
Comment	Antagonist GW1100 has been shown to reduce [^{35}S]GTPγS binding in *FFAR1*-expressing cells [813]. GW1100 is also an oxytocin receptor antagonist [788]. TUG770 and GW9508 are both approximately 100 fold selective for FFA1 over FFA4 [788,791]. AMG837 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 [804,821]	–	Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [798]. *trans*-2-methylcrotonic acid is a weak agonist for FFA3, with a pEC of below 1 [808]	TUG891 exhibits 50–1000 fold selectivity for FFA4 over FFA1, dependent on the assay [810]. NGC21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [815]

Comments: Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [805], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [819]. The long FFA4 splice variant has not been identified in other primates or rodents to date [793,805].

GPR42 was originally described as a pseudogene within the family (ENSFM00250000002583), but the recent discovery of several polymorphisms suggests that some versions of GPR42 may be functional [803]. *GPR84* is a structurally-unrelated G protein-coupled receptor which has been found to respond to medium chain fatty acids [818].

Further reading

Hara T, Hirasawa A, Ichimura A, Kimura I, Tsujimoto G. (2011) Free fatty acid receptors FFAR1 and GPR120 as novel therapeutic targets for metabolic disorders. *J Pharm Sci* **100**: 3594–3601. [PMID:21618241]

Maslowski KM, Mackay CR. (2011) Diet, gut microbiota and immune responses. *Nat Immunol* **12**: 5–9. [PMID:21169997]

Milligan G, Stoddart LA, Smith NJ. (2009) Agonism and allosterism: the pharmacology of the free fatty acid receptors FFA2 and FFA3. *Br J Pharmacol* **158**: 146–153. [PMID:19719777]

Reimann F, Tolhurst G, Gribble FM. (2012) G-protein-coupled receptors in intestinal chemosensation. *Cell Metab* **15**: 421–431. [PMID:22482725]

Stoddart LA, Smith NJ, Milligan G. (2008) International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, –2, and –3: pharmacology and pathophysiological functions. *Pharmacol Rev* **60**: 405–417. [PMID:19047536]

Talukdar S, Olefsky JM, Osborn O. (2011) Targeting GPR120 and other fatty acid-sensing GPCRs ameliorates insulin resistance and inflammatory diseases. *Trends Pharmacol Sci* **32**: 543–550. [PMID:21663979]

Frizzled Class GPCRs

Overview: Receptors of the Class Frizzled (FZD, nomenclature as agreed by the NC-IUPHAR subcommittee [832]), are GPCRs originally identified in *Drosophila* [825], which are highly conserved across species. FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostatis. 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. β-Catenin-independent FZD signalling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of pertussis toxin-sensitive heterotrimeric G proteins [830], the elevation of intracellular calcium [833], activation of cGMP-specific PDE6 [822] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [828]. Furthermore, the phosphoprotein Disheveled constitutes a key player in WNT/FZD signalling. As with other GPCRs, members of the Frizzled family are functionally dependent on the β-arrestin scaffolding protein for internalization [826], β-catenin-dependent [823] and -independent [824,831] 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 (*SOST*, Q9BQB4)) or Dickkopf (DKK)), as well as modulatory (co)-receptors with positive Ryk, ROR1, ROR2 and Kremen, which may also function as independent signalling proteins.

Nomenclature	FZD_1	FZD_2	FZD_3	FZD_4	FZD_5	FZD_6	FZD_7	FZD_8	FZD_9	FZD_{10}	SMO
HGNC, UniProt	*FZD1*, Q9UP38	*FZD2*, Q14332	*FZD3*, Q9NPG1	*FZD4*, Q9ULV1	*FZD5*, Q13467	*FZD6*, O60353	*FZD7*, O75084	*FZD8*, Q9H461	*FZD9*, O00144	*FZD10*, Q9ULW2	*SMO*, Q99835

Comments: There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. Understanding of the coupling to G proteins is incomplete (see [827]). There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration–response relationships [829].

Ligands associated with FZD signalling ***WNTs***: Wnt-1 (*WNT1*, P04628), Wnt-2 (*WNT2*, P09544) (also known as Int-1-related protein), Wnt-2b (*WNT2B*, Q93097) (also known as WNT-13), Wnt-3 (*WNT3*, P56703), Wnt-3a (*WNT3A*, P56704), Wnt-4 (*WNT4*, P56705), Wnt-5a (*WNT5A*, P41221), Wnt-5b (*WNT5B*, Q9H1J7), Wnt-6 (*WNT6*, Q9Y6F9), Wnt-7a (*WNT7A*, O00755), Wnt-7b (*WNT7B*, P56706), Wnt-8a (*WNT8A*, Q9H1J5), Wnt-8b (*WNT8B*, Q93098), Wnt-9a (*WNT9A*, O14904) (also known as WNT-14), Wnt-9b (*WNT9B*, O14905) (also known as WNT-15 or WNT-14b), Wnt-10a (*WNT10A*, Q9GZT5), Wnt-10b (*WNT10B*, O00744) (also known as WNT-12), Wnt-11 (*WNT11*, O96014) and Wnt-16 (*WNT16*, Q9UBV4).

***Extracellular proteins that interact with FZDs*:** norrin (*NDP*, Q00604), R-spondin-1 (*RSPO1*, Q2MKA7), R-spondin-2 (*RSPO2*, Q6UXX9) , R-spondin-3 (*RSPO3*, Q9BXY4), 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), SOST (*SOST*, Q9BQB4), kremen 1 (*KREMEN1*, Q96MU8) and kremen 2 (*KREMEN2*, Q8NCW0)

Small exogenous ligands: Foxy-5, Box-5, UM206, and XWnt8 also known as mini-Wnt8.

Further reading

Dijksterhuis JP, Petersen J, Schulte G. (2013) WNT/Frizzled signaling: receptor-ligand selectivity with focus on FZD-G protein signaling and its physiological relevance. *Br J Pharmacol* [PMID:24032637]

King TD, Suto MJ, Li Y. (2012) The Wnt/β-catenin signaling pathway: a potential therapeutic target in the treatment of triple negative breast cancer. *J Cell Biochem* **113**: 13–18. [PMID:21898546]

King TD, Zhang W, Suto MJ, Li Y. (2012) Frizzled7 as an emerging target for cancer therapy. *Cell Signal* **24**: 846–851. [PMID:22182510]

Koval A, Purvanov V, Egger-Adam D, Katanaev VL. (2011) Yellow submarine of the Wnt/Frizzled signaling: submerging from the G protein harbor to the targets. *Biochem Pharmacol* **82**: 1311–1319. [PMID:21689640]

Schuijers J, Clevers H. (2012) Adult mammalian stem cells: the role of Wnt, Lgr5 and R-spondins. *EMBO J* **31**: 2685–2696. [PMID:22617424]

Schulte G. (2010) International Union of Basic and Clinical Pharmacology. LXXX. The class Frizzled receptors. *Pharmacol Rev* **62**: 632–667. [PMID:21079039]

Schulte G, Schambony A, Bryja V. (2010) beta-Arrestins - scaffolds and signalling elements essential for WNT/Frizzled signalling pathways?. *Br J Pharmacol* **159**: 1051–1058. [PMID:19888962]

$GABA_B$ receptors

Overview: Functional $GABA_B$ receptors (nomenclature agreed by NC-IUPHAR Subcommittee on $GABA_B$ receptors, [839,860]) are formed from the heterodimerization of two similar 7TM subunits termed $GABA_{B1}$ (*GABBR1*, Q9UBS5) and $GABA_{B2}$ (*GABBR2*, O75899) [839,843,859–860,866]. $GABA_B$ receptors are widespread in the CNS and regulate both pre- and post-synaptic 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. The $GABA_{B1}$ subunit when expressed alone is not transported to the cell membrane and is non-functional. 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) [837,839–840]. The $GABA_{B2}$ subunit also determines the rate of internalisation of the dimeric $GABA_B$ receptor [850]. 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 [839,849,859]. The two subunits interact by direct allosteric coupling [857], such that $GABA_{B2}$ increases the affinity of $GABA_{B1}$ for agonists and reciprocally $GABA_{B1}$ facilitates the coupling of $GABA_{B2}$ to G proteins [855,859]. $GABA_{B1}$ and $GABA_{B2}$ subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α-helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the $GABA_{B1}$ subunit but other domains of the proteins also contribute to their heteromerization [837,859]. 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 [841,858]. 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 [835,864] and reviewed by [861]. Four isoforms of the human $GABA_{B1}$ subunit have been cloned. The predominant $GABA_{B1(a)}$ and $GABA_{B1(b)}$ 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. $GABA_{B1(a)}$-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 $GABA_{B1(b)}$-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [862,868]. Isoforms generated by alternative splicing are $GABA_{B1(c)}$ that differs in the ECD, and $GABA_{B1(e)}$, which is a truncated protein that can heterodimerize with the $GABA_{B2}$ subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors [839]. Additional $GABA_{B1}$ subunit isoforms have been described in rodents and humans [856] and reviewed by [837].

Nomenclature	Principal transduction	Selective agonists (pK_i)	Selective antagonists (pK_i)	Radioligands (K_d)
$GABA_B$ receptor	$G_{i/o}$	3-APPA (5.2–7.2) [851], 3-APMPA (5.1) [869], CGP 44532 (pIC_{50} 8.6 - Rat) [846], (-)-baclofen (pIC_{50} 8.5 - Rat) [846]	CGP 62349 (8.5–8.9) [851,869], CGP 55845 (7.8) [869], SCH 50911 (5.5–6.0) [851,869], CGP 35348 (4.4) [869], 2-hydroxy-saclofen (pIC_{50} 4.1 - Rat) [853]	[^{3}H](R)-(-)-baclofen (Agonist), [^{3}H]CGP 62349 (Antagonist) ($9x10^{-10}$ M - Rat) [854], [^{125}I]CGP 64213 (Antagonist) ($1x10^{-9}$ M - Rat) [847], [^{125}I]CGP 71872 (Antagonist) ($1x10^{-9}$ M - Rat) [853], [^{3}H]CGP 54626 (Antagonist) (K_i $7.9x10^{-10}$ M - Rat) [852]

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 [839,845–846]. Radioligand K_D values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the $GABA_{B1}$ subunit [836]. 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 [845]. 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 [847]. In cerebellar Purkinje neurones, the interaction of Ca^{2+} with the $GABA_B$ receptor enhances the activity of $mGlu_1$, through functional cross-talk involving G-protein Gβγ subunits [863,865]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 and (+)-BHFF [834,837–838,845]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the $GABA_{B2}$ subunit [842,859]. In the presence of CGP7930, or GS39783, CGP 35348 and 2-hydroxy-saclofen behave as partial agonists [845]. 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 [844,867]. A similar phenotype has been found for $GABA_{B2}^{-/-}$ BALB/c mice [848].

Further reading

Benarroch EE. (2012) GABAB receptors: structure, functions, and clinical implications. *Neurology* **78**: 578–584. [PMID:22351795]

Bowery NG, Bettler B, Froestl W, Gallagher JP, Marshall F, Raiteri M, Bonner TI, Enna SJ. (2002) International Union of Pharmacology. XXXIII. Mammalian gamma-aminobutyric acid(B) receptors: structure and function. *Pharmacol Rev* **54**: 247–264. [PMID:12037141]

Gaiarsa JL, Kuczewski N, Porcher C. (2011) Contribution of metabotropic GABA(B) receptors to neuronal network construction. *Pharmacol Ther* **132**: 170–179. [PMID:21718720]

Gassmann M, Bettler B. (2012) Regulation of neuronal GABA(B) receptor functions by subunit composition. *Nat Rev Neurosci* **13**: 380–394. [PMID:22595784]

Ghose S, Winter MK, McCarson KE, Tamminga CA, Enna SJ. (2011) The GABAβ receptor as a target for antidepressant drug action. *Br J Pharmacol* **162**: 1–17. [PMID:20735410]

Pin JP, Neubig R, Bouvier M, Devi L, Filizola M, Javitch JA, Lohse MJ, Milligan G, Palczewski K, Parmentier M *et al*. (2007) International Union of Basic and Clinical Pharmacology. LXVII. Recommendations for the recognition and nomenclature of G protein-coupled receptor heteromultimers. *Pharmacol Rev* **59**: 5–13. [PMID:17329545]

Urwyler S. (2011) Allosteric modulation of family C G-protein-coupled receptors: from molecular insights to therapeutic perspectives. *Pharmacol Rev* **63**: 59–126. [PMID:21228259]

Galanin receptors

Overview: Galanin receptors (provisional nomenclature, [876]) 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 [874]; 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 [872] and porcine galanin-5–29 [885] and N-terminally extended forms (*e.g.* N-terminally seven and nine residue elongated forms of porcine galanin [873,885]) have been reported.

Nomenclature	GAL_1 receptor	GAL_2 receptor	GAL_3 receptor
HGNC, UniProt	*GALR1*, P47211	*GALR2*, O43603	*GALR3*, O60755
Principal transduction	$G_{i/o}$	$G_{i/o}$, $G_{q/11}$	$G_{i/o}$
Rank order of potency	galanin > galanin-like peptide [881]	galanin-like peptide ≥ galanin [881]	galanin-like peptide > galanin [878]
Selective agonists (pK_i)	–	[D-Trp^2]galanin-(1–29) (8.15 - Rat) [887], galanin(2–29) (rat/mouse) (7.25–8.72 - Rat) [882,891–893]	–
Selective antagonists (pK_i)	2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC_{50} 5.57) [884]	M871 (7.88) [889]	–

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 [880]. [^{125}I]-[Tyr^{26}]galanin binds to all three subtypes with K_d values ranging from 0.05 to 1 nM [875,886–888,892]. 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 [877,895]. 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 [890], spinal cord [894], locus coeruleus, hippocampus [870] and hypothalamus [871,879], but exhibit agonist activity at some peripheral sites [871,877]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL_1 receptors expressed endogenously in Bowes human melanoma cells [881], and at heterologously expressed recombinant GAL_1, GAL_2 and GAL_3 receptors [875,887–888]. Recent studies have 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 [883].

Further reading

Fang P, Sun J, Wang X, Zhang Z, Bo P, Shi M. (2013) Galanin participates in the functional regulation of the diabetic heart. *Life Sci* **92**: 628–632. [PMID:23376774]

Fang P, Yu M, Guo L, Bo P, Zhang Z, Shi M. (2012) Galanin and its receptors: a novel strategy for appetite control and obesity therapy. *Peptides* **36**: 331–339. [PMID:22664322]

Fang P, Yu M, Shi M, Zhang Z, Sui Y, Guo L, Bo P. (2012) Galanin peptide family as a modulating target for contribution to metabolic syndrome. *Gen Comp Endocrinol* **179**: 115–120. [PMID:22909974]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Lang R, Kofler B. (2011) The galanin peptide family in inflammation. *Neuropeptides* **45**: 1–8. [PMID:21087790]

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

Webling KE, Runesson J, Bartfai T, Langel U. (2012) Galanin receptors and ligands. *Front Endocrinol (Lausanne)* **3**: 146. [PMID:23233848]

Ghrelin receptor

Overview: Ghrelin receptors (nomenclature approved by NC-IUPHAR, [898]) are 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 [907]. Alternative splicing results in the formation of a second peptide, [des-Gln^{14}]ghrelin (*GHRL*, Q9UBU3) with equipotent biological activity [904]. A unique post-translational modification (octanoylation of Ser^{3}, catalysed by ghrelin O-acyltransferase (*MBOAT4*, Q96T53) [913] occurs in both peptides, essential for full activity in binding to the ghrelin receptors in the hypothalamus and pituitary; and the release of growth hormone release from the pituitary [906]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [897], 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 [902]. In cell systems, the ghrelin receptor is constitutively active [903], 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 [910].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Selective antagonists (pK_i)	Radioligands (K_d)
ghrelin receptor	*GHSR*, Q92847	$G_{q/11}$	ghrelin = [des-Gln^{14}]ghrelin [896,907]	GSK1614343 (pK_B 8.0 - Rat) [911], YIL781 (pK_B 8.0) [899], GSK1614343 (pIC_{50} 8.4) [912]	[^{125}I][His^{9}]ghrelin (human) (Agonist, Full agonist) (4x10^{-10} M) [905], [^{125}I][Tyr^{4}]ghrelin (human) (Agonist, Full agonist) (4x10^{-10} M) [909]

Comments: [des-octanoyl]ghrelin has been shown to bind (as [^{125}I]Tyr^{4}-des-octanoyl-ghrelin) and have effects in the cardiovascular system [896], 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; [901]). TZP101, 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 from the release of growth hormone [900]. A number of selective antagonists have been reported, including peptidomimetic [908] and non-peptide small molecules including GSK1614343 [911–912].

Further reading

Andrews ZB. (2011) The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci* **34**: 31–40. [PMID:21035199]

Angelidis G, Valotassiou V, Georgoulias P. (2010) Current and potential roles of ghrelin in clinical practice. *J Endocrinol Invest* **33**: 823–838. [PMID:21293171]

Briggs DI, Andrews ZB. (2011) Metabolic status regulates ghrelin function on energy homeostasis. *Neuroendocrinology* **93**: 48–57. [PMID:21124019]

Davenport AP, Bonner TI, Foord SM, Harmar AJ, Neubig RR, Pin JP, Spedding M, Kojima M, Kangawa K. (2005) International Union of Pharmacology. LVI. Ghrelin receptor nomenclature, distribution, and function. *Pharmacol Rev* **57**: 541–546. [PMID:16382107]

De Smet B, Mitselos A, Depoortere I. (2009) Motilin and ghrelin as prokinetic drug targets. *Pharmacol Ther* **123**: 207–223. [PMID:19427331]

De Vriese C, Delporte C. (2007) Influence of ghrelin on food intake and energy homeostasis. *Curr Opin Clin Nutr Metab Care* **10**: 615–619. [PMID:17693746]

Dezaki K, Sone H, Yada T. (2008) Ghrelin is a physiological regulator of insulin release in pancreatic islets and glucose homeostasis. *Pharmacol Ther* **118**: 239–249. [PMID:18433874]

Granata R, Baragli A, Settanni F, Scarlatti F, Ghigo E. (2010) Unraveling the role of the ghrelin gene peptides in the endocrine pancreas. *J Mol Endocrinol* **45**: 107–118. [PMID:20595321]

Nikolopoulos D, Theocharis S, Kouraklis G. (2010) Ghrelin: a potential therapeutic target for cancer. *Regul Pept* **163**: 7–17. [PMID:20382189]

Romero A, Kirchner H, Heppner K, Pfluger PT, Tschöp MH, Nogueiras R. (2010) GOAT: the master switch for the ghrelin system?. *Eur J Endocrinol* **163**: 1–8. [PMID:20421334]

Glucagon receptor family

Overview: The glucagon family of receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on the Glucagon receptor family, [926]) are activated by the endogenous peptide (27–44 aa) hormones glucagon, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glucose-dependent insulinotropic polypeptide, also known as gastric inhibitory polypeptide or GIP (*GIP*, P09681), GHRH (*GHRH*, P01286) and secretin (*SCT*, P09683). One common precursor (*GCG*, P01275) generates glucagon, GLP-1 and GLP-2 peptides [922].

Nomenclature	glucagon receptor	GLP-1 receptor	GLP-2 receptor	GIP receptor	GHRH receptor	secretin receptor
HGNC, UniProt	*GCGR*, P47871	*GLP1R*, P43220	*GLP2R*, O95838	*GIPR*, P48546	*GHRHR*, Q02643	*SCTR*, P47872
Principal transduction	G_s	G_s	G_s	G_s	G_s	G_s
Endogenous agonists (pK_i)	glucagon (Selective) (pEC_{50} 9.0) [929]	glucagon-like peptide-1-(7-37) (Selective) [919], glucagon-like peptide 1-(7-36) amide (Selective) (9.2) [923]	GLP-2 (Selective) (pIC_{50} 8.5) [932]	GIP (Selective) (pK_d 8.7) [938]	–	secretin (Selective) (pEC_{50} 9.7) [916]
Selective agonists (pK_i)	–	exendin-3 (P20394) [930], exendin-4 (8.7 – 9.0) [923]	–	–	BIM28011 [918], JI-38 (Rat) [924]	–
Selective antagonists (pK_i)	BAY27-9955 [928], des-His^1-[Glu^9]glucagon-NH_2 (pA_2 7.2 - Rat) [934–935], NNC 92-1687 (5.0) [925], L-168,049 (pIC_{50} 8.4) [915]	exendin-(9-39) (8.1) [923], GLP-1-(9-36) (pIC_{50} 6.91 - Rat) [927], T-0632 (pIC_{50} 4.7) [933]	–	[Pro^3]GIP	JV-1-36 (10.1 – 10.4 - Rat) [931,936–937], JV-1-38 (10.1 - Rat) [931,936–937]	[$(CH_2NH)^{4,5}$]secretin (5.3) [921]
Radioligands (K_d)	[^{125}I]glucagon (human, mouse, rat) (Agonist, Full agonist)	[^{125}I]exendin, [^{125}I]GLP-1-(7-37) (Agonist, Full agonist), [^{125}I]GLP-1-(7-36)-amide (Agonist, Full agonist) ($5x10^{-10}$ M) [923], [^{125}I]exendin-(9-39) (Antagonist) ($5x10^{-9}$ M) [923]	–	[^{125}I]GIP (Agonist, Full agonist) ($2.51x10^{-9}$ M - Rat) [920]	[^{125}I]GHRH (human) (Agonist, Full agonist) ($2.8x10^{-8}$ M - Rat) [914]	[^{125}I](Tyr^{10})secretin

Comments: The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems [917], although the physiological significance of this has yet to be established.

Further reading

Cho YM, Merchant CE, Kieffer TJ. (2012) Targeting the glucagon receptor family for diabetes and obesity therapy. *Pharmacol Ther* **135**: 247–278. [PMID:22659620]

Donnelly D. (2012) The structure and function of the glucagon-like peptide-1 receptor and its ligands. *Br J Pharmacol* **166**: 27–41. [PMID:21950636]

Jones BJ, Tan T, Bloom SR. (2012) Minireview: Glucagon in stress and energy homeostasis. *Endocrinology* **153**: 1049–1054. [PMID:22294753]

Mayo KE, Miller LJ, Bataille D, Dalle S, Göke B, Thorens B, Drucker DJ. (2003) International Union of Pharmacology. XXXV. The glucagon receptor family. *Pharmacol Rev* **55**: 167–194. [PMID:12615957]

Miller LJ, Dong M, Harikumar KG. (2011) Ligand Binding and Activation of the Secretin Receptor, a Prototypic Family B G Protein-Coupled Receptor. *Br J Pharmacol* [Epub ahead of print]. [PMID:21542831]

Rowland KJ, Brubaker PL. (2011) The "cryptic" mechanism of action of glucagon-like peptide-2. *Am J Physiol Gastrointest Liver Physiol* **301**: G1–G8. [PMID:21527727]

Willard FS, Bueno AB, Sloop KW. (2012) Small molecule drug discovery at the glucagon-like peptide-1 receptor. *Exp Diabetes Res* **2012**: 709893. [PMID:22611375]

Williams DL. (2009) Minireview: finding the sweet spot: peripheral versus central glucagon-like peptide 1 action in feeding and glucose homeostasis. *Endocrinology* **150**: 2997–3001. [PMID:19389830]

Glycoprotein hormone receptors

Overview: Glycoprotein hormone receptors (provisional nomenclature) 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 (*LHB*, *CGA*, P01229, P01215), hCG (*CGA*, *CGB*, P01233, P01215), *CGB2*/*CGB* or TSH (*TSHB*, *CGA*, P01222, P01215). 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 [950].

Nomenclature	FSH receptor	LH receptor	TSH receptor
HGNC, UniProt	*FSHR*, P23945	*LHCGR*, P22888	*TSHR*, P16473
Principal transduction	G_s	G_s, $G_{q/11}$ and G_i	All four families of G proteins can be activated by this receptor
Endogenous agonists (pK_i)	FSH (Selective)	hCG (Selective) (pK_d 9.9 – 11.8) [942,946], LH (Selective) (pIC_{50} 9.9 – 10.9) [942,946]	TSH (Selective)
Radioligands (K_d)	[^{125}I]FSH (human) (Agonist, Full agonist)	[^{125}I]CG (human) (Agonist, Full agonist), [^{125}I]LH (Agonist, Full agonist)	[^{125}I]TSH (Agonist, Full agonist)
Comment	Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders [939–941,953]. The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein [948].	Loss-of-function mutations of the LH receptor are associated with Leydig cell hypoplasia and gain-of-function mutations are associated with male-limited gonadotropin-independent precocious puberty (*e.g.* [944,951]) and Leydig cell tumours [945].	Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Grave's disease (*e.g.* [949]). Mutations of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas [947] and congenital hyperthyroidism [943]. TSH receptor loss-of-function mutations are associated with TSH resistance [952].

Further reading

Chiamolera MI, Wondisford FE. (2009) Minireview: Thyrotropin-releasing hormone and the thyroid hormone feedback mechanism. *Endocrinology* **150**: 1091–1096. [PMID:19179434]

George JW, Dille EA, Heckert LL. (2011) Current concepts of follicle-stimulating hormone receptor gene regulation. *Biol Reprod* **84**: 7–17. [PMID:20739665]

Gershengorn MC, Neumann S. (2012) Update in TSH receptor agonists and antagonists. *J Clin Endocrinol Metab* **97**: 4287–4292. [PMID:23019348]

Melamed P, Savulescu D, Lim S, Wijeweera A, Luo Z, Luo M, Pnueli L. (2012) Gonadotrophin-releasing hormone signalling downstream of calmodulin. *J Neuroendocrinol* **24**: 1463–1475. [PMID:22775470]

Menon KM, Menon B. (2012) Structure, function and regulation of gonadotropin receptors - a perspective. *Mol Cell Endocrinol* **356**: 88–97. [PMID:22342845]

Puett D, Angelova K, da Costa MR, Warrenfeltz SW, Fanelli F. (2010) The luteinizing hormone receptor: insights into structure-function relationships and hormone-receptor-mediated changes in gene expression in ovarian cancer cells. *Mol Cell Endocrinol* **329**: 47–55. [PMID:20444430]

Gonadotrophin-releasing hormone receptors

Overview: $GnRH_1$ and $GnRH_2$ receptors (provisonal nomenclature, also called Type I and Type II, respectively) have been cloned from numerous species (most of which express two or three types of GnRH receptor) and grouped phylogenetically [975]. Designated GnRH I (*GNRH1*, P01148) (to distinguish it from related peptides, such as GnRH II (*GNRH2*, O43555) (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH_2, also known as chicken GnRH-II) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH_2), also known as luteinising hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin. Receptors for all three ligands exist in amphibians but only GnRH I (*GNRH1*, P01148) and GnRH II (*GNRH2*, O43555) (and their cognate receptors) have been found in mammals [969,974]. $GnRH_1$ receptors are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I (*GNRH1*, P01148) and all lack the C-terminal tails found in other GPCR. $GnRH_2$ receptors all possess C-terminal tails and (where tested) are selective for GnRH II (*GNRH2*, O43555) (over GnRH I (*GNRH1*, P01148)). An alternative phylogenetic classification [970] divided these receptors into three classes and includes both GnRH I-selective mammalian and GnRH II-selective non-mammalian receptors as $GnRH_1$ receptors. Although thousands of peptide analogues of GnRH I (*GNRH1*, P01148) have been synthesised and several (agonists and antagonists) are used therapeutically [961], the potency of most of these peptides at $GnRH_2$ receptors is unknown.

Nomenclature	GnRH receptor	GnRH2 receptor
HGNC, UniProt	*GNRHR*, P30968	*GNRHR2*, Q96P88
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	GnRH I > GnRH II	GnRH II > GnRH I
Selective agonists (pK_i)	buserelin, goserelin, histrelin, nafarelin, triptorelin (9.3 – 9.5) [954], leuprolide (8.5 – 9.1) [976]	–
Selective antagonists (pK_i)	ganirelix, abarelix (9.1 – 9.5) [976], antide (9.0) [972], cetrorelix (8.8) [972]	trptorelix-1 [967]
Radioligands (K_d)	[^{125}I]GnRH I (human, mouse, rat) (Agonist, Full agonist), [^{125}I]buserelin (Agonist, Full agonist) ($4x10^{-8}$ M - Rat) [964]	[^{125}I]GnRH II (human) (Agonist, Full agonist)

Comments: $GnRH_1$ and $GnRH_2$ receptors couple primarily to $G_{q/11}$ [958] but coupling to G_s and G_i is evident in some systems [963]. $GnRH_2$ receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [955]. 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 [956,960,966,973]. In some human cancer cell models GnRH II (*GNRH2*, O43555) is more potent than GnRH I (*GNRH1*, P01148), implying mediation by GnRH2 receptors [959]. However, $GnRH_2$ receptors that are expressed by some primates are probably not expressed in humans because the human $GNRHR_2$ gene contains a frame shift and internal stop codon [971]. 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 [972]). Alternatively, there is evidence for multiple active GnRH receptor conformations [955,968,970] raising the possibility that $GnRH_1$ receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand specificity) than effects on $G_{q/11}$ in pituitary cells [968]. 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 [965]. GnRH receptor signalling may be dependent upon receptor oligomerisation [957,962].

Further reading

Bliss SP, Navratil AM, Xie J, Roberson MS. (2010) GnRH signaling, the gonadotrope and endocrine control of fertility. *Front Neuroendocrinol* **31**: 322–340. [PMID:20451543]

Bouligand J, Ghervan C, Trabado S, Brailly-Tabard S, Guiochon-Mantel A, Young J. (2010) Genetics defects in GNRH1: a paradigm of hypothalamic congenital gonadotropin deficiency. *Brain Res* **1364**: 3–9. [PMID:20887715]

Ciechanowska M, Lapot M, Mateusiak K, Przekop F. (2010) Neuroendocrine regulation of GnRH release and expression of GnRH and GnRH receptor genes in the hypothalamus-pituitary unit in different physiological states. *Reprod Biol* **10**: 85–124. [PMID:20668503]

Finch AR, Sedgley KR, Armstrong SP, Caunt CJ, McArdle CA. (2010) Trafficking and signalling of gonadotrophin-releasing hormone receptors: an automated imaging approach. *Br J Pharmacol* **159**: 751–760. [PMID:19888967]

Limonta P, Montagnani Marelli M, Mai S, Motta M, Martini L, Moretti RM. (2012) GnRH receptors in cancer: from cell biology to novel targeted therapeutic strategies. *Endocr Rev* **33**: 784–811. [PMID:22778172]

McArdle CA. (2012) Gonadotropin-releasing hormone receptor signaling: biased and unbiased. *Mini Rev Med Chem* **12**: 841–850. [PMID:22681250]

Navratil AM, Bliss SP, Roberson MS. (2010) Membrane rafts and GnRH receptor signaling. *Brain Res* **1364**: 53–61. [PMID:20836995]

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 [988].

Nomenclature	*GPR18*	*GPR55*	*GPR119*
HGNC, UniProt	*GPR18*, Q14330	*GPR55*, Q9Y2T6	*GPR119*, Q8TDV5
Principal transduction	$G_{i/o}$ [982]	$G_{12/13}$ [989]	G_s [984,987]
Rank order of potency	–	–	N-oleoylethanolamide, N-palmitoylethanolamine > SEA (anandamide is ineffective) [987]
Endogenous agonists (pK_i)	N-arachidonoylglycine [982]	2-arachidonoylglycerolphosphoinositol (Selective) [986], lysophosphatidylinositol (pEC_{50} 5.5 – 7.3) [978,985,990]	N-palmitoylethanolamine (Selective), SEA (Selective), N-oleoylethanolamide (Selective) (pEC_{50} 5.4 – 6.3) [977,987,990]
Selective agonists (pK_i)	–	AM251 (pEC_{50} 6.2 – 6.3) [978,980]	AS1269574 (pEC_{50} 5.6) [993], PSN632408 (pEC_{50} 5.3) [987], PSN375963 (pEC_{50} 5.1) [987]
Comment	The pairing of N-arachidonoylglycine with GPR18 was not replicated in two studies based on β-arrestin assays [990,992]	–	–

Comments: All listed endogenous agonists are remain currently as putative endogenous agonists.

GPR18 failed to respond to a variety of lipid-derived agents in an in vitro screen [992], but has been reported to be activated by Δ^9-tetrahydrocannabinol [983]. GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB_1 receptor antagonists/inverse agonists [988]. It has been reported lysophosphatidylinositol acts at other sites [991]. CID-16020046 has been described as a selective antagonist at GPR55 [979,981], although it has not yet been fully characterized. It has also been suggested oleoyllysophosphatidylcholine acts, at least in part, through GPR119 [984]. Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with N-oleoylethanolamide-mediated responses suggests additional mechanisms of action [984].

Further reading

Alexander SP. (2012) So what do we call GPR18 now?. *Br J Pharmacol* **165**: 2411–2413. [PMID:22014123]

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhanga CP, Bonner TI, Neubig RR *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**: 967–986. [PMID:23686350]

Hansen HS, Rosenkilde MM, Holst JJ, Schwartz TW. (2012) GPR119 as a fat sensor. *Trends Pharmacol Sci* **33**: 374–381. [PMID:22560300]

McHugh D. (2012) GPR18 in Microglia: implications for the CNS and endocannabinoid system signalling. *Br J Pharmacol* [Epub ahead of print]. [PMID:22563843]

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K *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]

Ross RA. (2011) L-α-lysophosphatidylinositol meets GPR55: a deadly relationship. *Trends Pharmacol Sci* **32**: 265–269. [PMID:21367464]

Yamashita A, Oka S, Tanikawa T, Hayashi Y, Nemoto-Sasaki Y, Sugiura T. (2013) The actions and metabolism of lysophosphatidylinositol, an endogenous agonist for GPR55. *Prostaglandins Other Lipid Mediat* [Epub ahead of print]. [PMID:23714700]

Zhao P, Abood ME. (2013) GPR55 and GPR35 and their relationship to cannabinoid and lysophospholipid receptors. *Life Sci* **92**: 453–457. [PMID:22820167]

Histamine receptors

Overview: Histamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Histamine Receptors, [1003]) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues (see [1003]).

Nomenclature	H_1 receptor	H_2 receptor	H_3 receptor	H_4 receptor
HGNC, UniProt	*HRH1*, P35367	*HRH2*, P25021	*HRH3*, Q9Y5N1	*HRH4*, Q9H3N8
Principal transduction	$G_{q/11}$	G_s	$G_{i/o}$	$G_{i/o}$
Selective agonists (pK_i)	methylhistaprodifen (6.4) [1025], histaprodifen (5.7) [1013]	amthamine (pEC_{50} 6.4) [1008]	immethridine (9.1) [1007], methimepip (9.0) [1006]	clobenpropit (Partial agonist) (7.4 – 8.3) [1000,1013–1015,1019], 4-methylhistamine (7.3 – 8.2) [1001,1013], VUF 8430 (7.5) [1012]
Selective antagonists (pK_i)	pyrilamine (Inverse agonist) (8.7 – 9.0) [995,1023], triprolidine (8.5 – 9.0) [995,1017]	tiotidine (7.5 - Rat) [994], ranitidine (7.1) [1010]	clobenpropit (8.4 – 9.4) [997,1000,1011,1014,1016,1028–1029], A331440 (8.5) [1002], iodophenpropit (8.2 – 8.7) [1028–1029], thioperamide (7.1 – 7.7) [997,999–1000,1011,1016,1028–1029]	JNJ 7777120 (7.8 – 8.3) [1013,1026–1027]
Radioligands (K_d)	[^{11}C]pyrilamine, [^{11}C]doxepin (Antagonist) (1x10^{-9} M) [1004], [^{3}H]pyrilamine (Antagonist, Inverse agonist) (7.9x10^{-10} – 4x10^{-9} M) [998,1017,1024–1025]	[^{125}I]aminopotentidine (Antagonist) (2x10^{-9} M - Rat) [1009], [^{3}H]tiotidine (Antagonist) (2.2x10^{-9} – 2x10^{-8} M) [1018]	[^{123}I]iodoproxyfan (Antagonist) (6.3x10^{-11} M) [1011], [^{125}I]iodophenpropit (Antagonist) (6x10^{-10} M - Rat) [1005], [^{3}H](*R*)-α-methylhistamine (Agonist, Full agonist) (6x10^{-10} M) [1014], *N*-[^{3}H]α-methylhistamine (Agonist, Full agonist) (1x10^{-9} M - Mouse) [996]	[^{3}H]JNJ 7777120 (Antagonist) (3.6x10^{-9} M) [1027]

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 [1014,1020–1022,1030]. Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H_4 receptor [1013]. [^{3}H]histamine has been used to label the H_4 receptor in heterologous expression systems.

Further reading

Berlin M, Boyce CW, Ruiz Mde L. (2011) Histamine H3 receptor as a drug discovery target. *J Med Chem* **54**: 26–53. [PMID:21062081]

Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM, Schunack W, Levi R, Haas HL. (1997) International Union of Pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev* **49**: 253–278. [PMID:9311023]

Leurs R, Vischer HF, Wijtmans M, de Esch IJ. (2011) En route to new blockbuster anti-histamines: surveying the offspring of the expanding histamine receptor family. *Trends Pharmacol Sci* **32**: 250–257. [PMID:21414671]

Marson CM. (2011) Targeting the histamine H4 receptor. *Chem Rev* **111**: 7121–7156. [PMID:21842846]

Passani MB, Blandina P. (2011) Histamine receptors in the CNS as targets for therapeutic intervention. *Trends Pharmacol Sci* **32**: 242–249. [PMID:21324537]

Schwartz JC. (2011) The histamine H3 receptor: from discovery to clinical trials with pitolisant. *Br J Pharmacol* **163**: 713–721. [PMID:21615387]

Hydroxycarboxylic acid receptors

Formerly known as: Nicotinic acid receptor family

Overview: The hydroxycarboxylic acid family of receptors (ENSFM00500000271913, nomenclature as agreed by NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors, [1037]) 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 [1040,1044–1045]. 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 [1044–1045].

Nomenclature	HCA_1 receptor	HCA_2 receptor	HCA_3 receptor
HGNC, UniProt	*HCAR1*, Q9BXC0	*HCAR2*, Q8TDS4	*HCAR3*, P49019
Principal transduction	$G_{i/o}$ [1031,1034,1036].	$G_{i/o}$ [1040,1044–1045]	$G_{i/o}$ [1040,1045]
Endogenous agonists (pK_i)	L-lactic acid (Selective) (pEC_{50} 1.3 – 2.89) [1032,1034,1036,1041]	β-D-hydroxybutyric acid (pEC_{50} 3.1) [1042]	3-hydroxyoctanoic acid (pEC_{50} 5.1) [1031]
Selective agonists (pK_i)	3,5-dihydroxybenzoic acid (pEC_{50} 3.72) [1035]	MK 6892 (pEC_{50} 7.8) [1039], MK 1903 (pEC_{50} 7.56) [1033], nicotinic acid (pEC_{50} 6.0 – 7.2) [1040,1044–1045], acipimox (pEC_{50} 5.2 – 5.6) [1040,1045], monomethylfumarate (pEC_{50} 5.03) [1043]	1-isopropylbenzotriazole-5-carboxylic acid (pEC_{50} 6.4) [1038]
Radioligands (K_d)	–	[^{3}H]nicotinic acid (Agonist, Full agonist) ($5.01x10^{-8}$ – $1x10^{-7}$ M) [1040,1044–1045]	–

Comments: Further closely-related GPCR include the 5-oxoeicosanoid receptor (*OXER1*, Q8TDS5) and *GPR31* (O00270).

Further reading

Blad CC, Ahmed K, IJzerman AP, Offermanns S. (2011) Biological and pharmacological roles of HCA receptors. *Adv Pharmacol* **62**: 219–250. [PMID:21907911]

Chapman MJ, Redfern JS, McGovern ME, Giral P. (2010) Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* **126**: 314–345. [PMID:20153365]

Gille A, Bodor ET, Ahmed K, Offermanns S. (2008) Nicotinic acid: pharmacological effects and mechanisms of action. *Annu Rev Pharmacol Toxicol* **48**: 79–106. [PMID:17705685]

Hanson J, Gille A, Offermanns S. (2012) Role of HCA_2 (GPR109A) in nicotinic acid and fumaric acid ester-induced effects on the skin. *Pharmacol Ther* **136**: 1–7. [PMID:22743741]

Offermanns S, Colletti SL, Lovenberg TW, Semple G, Wise A, IJzerman AP. (2011) International Union of Basic and Clinical Pharmacology. LXXXII: Nomenclature and Classification of Hydroxycarboxylic Acid Receptors (GPR81, GPR109A, and GPR109B). *Pharmacol Rev* **63**: 269–290. [PMID:21454438]

Vosper H. (2009) Niacin: a re-emerging pharmaceutical for the treatment of dyslipidaemia. *Br J Pharmacol* **158**: 429–441. [PMID:19627285]

Kisspeptin receptors

Overview: The kisspeptin receptor (nomenclature agreed by NC-IUPHAR committee on kisspeptin receptors, Kirby *et al.*, 2010 [1047]), 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.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Selective agonists (pK_i)	Selective antagonists (pK_i)	Radioligands (K_d)
kisspeptin receptor	*KISS1R*, Q969F8	$G_{q/11}$ [1048,1050]	kisspeptin-10 (Selective) (8.6–10.4) [1048,1051], kisspeptin-54 (Selective) (8.8–9.5) [1048,1051], kisspeptin-13 (Selective) (8.4) [1048]	4-fluorobenzoyl-FGLRW-NH2 (pEC_{50} 9.2) [1053], [dY]^{1}KP-10 (pIC_{50} 8.4 - Mouse) [1046]	peptide 234 [1052]	[^{125}I]kisspeptin-14 (human) [1049], [^{125}I]Tyr^{45}-kisspeptin-15 (Agonist, Full agonist) (1×10^{-10} M) [1051], [^{125}I]kisspeptin-13 (human) (Agonist, Full agonist) (2×10^{-10} M) [1049], [^{125}I]kisspeptin-10 (human) (Agonist, Full agonist) (1.9×10^{-9} M) [1048]

Further reading

Colledge WH. (2009) Kisspeptins and GnRH neuronal signalling. *Trends Endocrinol Metab* **20**: 115–121. [PMID:19097915]

Hameed S, Jayasena CN, Dhillo WS. (2011) Kisspeptin and fertility. *J Endocrinol* **208**: 97–105. [PMID:21084385]

Jayasena CN, Dhillo WS, Bloom SR. (2009) Kisspeptins and the control of gonadotropin secretion in humans. *Peptides* **30**: 76–82. [PMID:18656511]

Kirby HR, Maguire JJ, Colledge WH, Davenport AP. (2010) International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. *Pharmacol Rev* **62**: 565–578. [PMID:21079036]

Mead EJ, Maguire JJ, Kuc RE, Davenport AP. (2007) Kisspeptins: a multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. *Br J Pharmacol* **151**: 1143–1153. [PMID:17519946]

Millar RP, Roseweir AK, Tello JA, Anderson RA, George JT, Morgan K, Pawson AJ. (2010) Kisspeptin antagonists: unraveling the role of kisspeptin in reproductive physiology. *Brain Res* **1364**: 81–89. [PMID:20858467]

Moulédous L, Mollereau C, Zajac JM. (2010) Opioid-modulating properties of the neuropeptide FF system. *Biofactors* **36**: 423–429. [PMID:20803521]

Oakley AE, Clifton DK, Steiner RA. (2009) Kisspeptin signaling in the brain. *Endocr Rev* **30**: 713–743. [PMID:19770291]

Takayanagi Y, Onaka T. (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]

Tena-Sempere M. (2010) Kisspeptin signaling in the brain: recent developments and future challenges. *Mol Cell Endocrinol* **314**: 164–169. [PMID:19464345]

Yang HY, Tao T, Iadarola MJ. (2008) Modulatory role of neuropeptide FF system in nociception and opiate analgesia. *Neuropeptides* **42**: 1–18. [PMID:17854890]

Leukotriene, lipoxin and oxoeicosanoid receptors

Overview: Leukotriene receptors (nomenclature agreed by NC-IUPHAR subcommittee on Leukotriene Receptors, [1057]) are activated by the endogenous ligands leukotriene B_4 (LTB_4), LTC_4, LTD_4, LTE_4, 12R-HETE and 12S-HETE. $CysLT_1$ and $CysLT_2$ are co-expressed by most myeloid cells. However, the function of $CysLT_2$ remains unclear. $CysLT_2$ has been demonstrated to exert a suppressive influence on $CysLT_1$ expression, suggesting an autoregulatory function which is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking $CysLT_2$ receptors [1073].

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-S-transferase/LTC_4 synthase, γ-glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator-activated receptor α (PPARα, [1076]) and the FPR2/ALX lipoxin receptor [1061], complicating the interpretation of radioligand binding and functional studies (*e.g.* LTC_4 is rapidly converted in many systems to LTD_4). Metabolic inhibitors (*e.g.* serine–borate complex) reduce this problem but can also have nonspecific effects.

Nomenclature	BLT_1 receptor	BLT_2 receptor	$CysLT_1$ receptor	$CysLT_2$ receptor
HGNC, UniProt	*LTB4R*, Q15722	*LTB4R2*, Q9NPC1	*CYSLTR1*, Q9Y271	*CYSLTR2*, Q9NS75
Principal transduction	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	LTB_4 >20-hydroxy-LTB_4 >>12R-HETE [1103]	12-HHT > LTB_4 > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE > 20-hydroxy-LTB_4 [1085,1103]	LTD_4 > LTC_4 > LTE_4 [1077,1093]	LTC_4 ≥ LTD_4 >> LTE_4 [1068,1082,1099]
Endogenous agonists (pK_i)	–	12S-HETE (Partial agonist) (pEC_{50}<7.52) [1103]	–	–
Selective antagonists (pK_i)	U75302 (6.4) [1055], CP105696 (pIC_{50} 8.1) [1095]	LY255283 (pIC_{50} 6.0–7.1) [1069,1103]	ICI198615 (8.4–8.6), SR2640 (8.7), sulukast (8.3), zafirlukast (pIC_{50} 8.59–8.74) [1077,1093], montelukast (pIC_{50} 8.31–8.64) [1077,1093], pobilukast (pIC_{50} 7.52) [1093]	BAYu9773 (pA_2 6.8–7.7 - Rat) [1100]
Radioligands (K_d)	[^{3}H]LTB4 (Agonist, Full agonist) (1.5×10^{-10} M) [1102], [^{3}H]CGS23131 (Antagonist) (1.3×10^{-8} M) [1072]	[^{3}H]LTB4 (2×10^{-10} – 2.3×10^{-8} M)	[^{3}H]ICI-198615 (Antagonist, in human lung parenchyma) (2.5×10^{-11} M) [1092], [^{3}H]LTD_4 (Agonist) (2×10^{-11} – 9.3×10^{-9} M)	[^{3}H]LTD_4 (Agonist, Full agonist, K_{d1} and K_{d-2} in COS-7 cells) (3.98×10^{-10} – 5.01×10^{-8} M) [1068]

Nomenclature	FPR2/ALX	OXE receptor
HGNC, UniProt	*FPR2*, P25090	*OXER1*, Q8TDS5
Principal transduction	G_i [1078]	$G_{i/o}$ [1070–1071,1074,1083]
Rank order of potency	LXA_4=aspirin triggered lipoxin A4=ATLa2>LTC_4=LTD_4>>15-deoxy-LXA4>>fMet-Leu-Phe [1060–1061,1063,1065,1098]	5-oxo-ETE, 5-oxo-C20:3, 5-oxo-ODE > 5-oxo-15-HETE > 5S-HPETE > 5S-HETE [1070,1074,1086]
Endogenous agonists (pK_i)	aspirin triggered lipoxin A4 (Selective), LXA_4 (Selective) (pEC_{50} ~12.0) [1075], resolvin D1 (Selective) (pEC_{50} ~11.9) [1075]	5-oxo-ETE (Selective) (pEC_{50} 8.3–8.5) [1064,1084,1086,1089,1094]
Selective antagonists (pK_i)	ATLa2 [1066]	–
Radioligands (K_d)	[^{3}H]LXA_4 (Agonist, Full agonist) (5×10^{-10} – 7×10^{-10} M) [1061–1062]	[^{3}H]5-oxo-ETE (Agonist) (3.8×10^{-9} M) [1084]
Comment	The agonist activity of the lipid mediators described has been questioned [1067,1088], which may derive from batch-to-batch differences, partial agonism or biased agonism.	–

Comments: BAYu9773 is an antagonist at $CysLT_1$ (6.8–7.7) and a reduced efficacy agonist at $CysLT_2$ receptors. The $CysLT_1$ and $CyLT_2$ receptors also respond to uracil nucleotides [1080–1081]. GPR17 has been described as a 'dualistic' receptor responding to both uracil nucleotides and cysteinyl leukotrienes, responses which may be inhibited by antagonists of either P2 or CysLT receptors [1059].

Lipoxin A4 receptors (FPR2/ALX, nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors; [1101]) are 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 [1058] as well as annexin I (*ANXA1*, P04083) (ANXA1) and its *N*-terminal peptides [1087]. 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 [1090]. Furthermore, FPR2/ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A [1096–1097].

Oxoeicosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoeicosanoid Receptors; [1056]) 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.

Note that the data for FPR2/ALX are also reproduced on the Formylpeptide receptor pages. A receptor selective for LXB_4 has been suggested from functional studies [1054,1079,1091]. Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and EPA, acted as receptor antagonists [1070].

Further reading

Ariel A, Serhan CN. (2007) Resolvins and protectins in the termination program of acute inflammation. *Trends Immunol* **28**: 176–183. [PMID:17337246]

Baker N, O'Meara SJ, Scannell M, Maderna P, Godson C. (2009) Lipoxin A4: anti-inflammatory and anti-angiogenic impact on endothelial cells. *J Immunol* **182**: 3819–3826. [PMID: 19265161]

Brink C, Dahlén SE, Drazen J, Evans JF, Hay DW, Rovati GE, Serhan CN, Shimizu T, Yokomizo T. (2004) International Union of Pharmacology XLIV. Nomenclature for the Oxoeicosanoid Receptor. *Pharmacol Rev* **56**: 149–157. [PMID:15001665]

Brink C, Dahlen SE, Drazen J, Evans JF, Hay DW, Nicosia S, Serhan CN. (2003) International Union of Pharmacology XXXVII. Nomenclature for leukotriene and lipoxin receptors. *Pharmacol Rev* **55**: 195–227. [PMID:12615958]

Grant GE, Rokach J, Powell WS. (2009) 5-Oxo-ETE and the OXE receptor. *Prostaglandins Other Lipid Mediat* **89**: 98–104. [PMID:19450703]

Kohli P, Levy BD. (2009) Resolvins and protectins: mediating solutions to inflammation. *Br J Pharmacol* **158**: 960–971. [PMID:19594757]

Ryan A, Godson C. (2010) Lipoxins: regulators of resolution. *Curr Opin Pharmacol* **10**: 166–172. [PMID:20226737]

Serhan CN, Chiang N. (2008) Endogenous pro-resolving and anti-inflammatory lipid mediators: a new pharmacologic genus. *Br J Pharmacol* **153**: S200–S215. [PMID:17965751]

Serhan CN, Chiang N, Van Dyke TE. (2008) Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* **8**: 349–361. [PMID:18437155]

Serhan CN, Yacoubian S, Yang R. (2008) Anti-inflammatory and proresolving lipid mediators. *Annu Rev Pathol* **3**: 279–312. [PMID:18233953]

Uddin M, Levy BD. (2010) Resolvins: Natural agonists for resolution of pulmonary inflammation. *Prog Lipid Res* [Epub ahead of print]. [PMID:**20887750**]

Xu ZZ, Ji RR. (2011) Resolvins are potent analgesics for arthritic pain. *Br J Pharmacol* **164**: 274–277. [PMID:21418190]

Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, Serhan CN, Murphy PM. (2009) International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev* **61**: 119–161. [PMID:19498085]

Lysophospholipid (LPA) receptors

Overview: Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid Receptors; [1104]) are activated by the endogenous lipid derivative LPA. Originally identified as members of the endothelial differentiation gene (*edg*) family along with sphingosine 1-phosphate receptors, the gene names have recently been updated to *LPAR1*, etc. to reflect the receptor function of these proteins. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Radioligand binding has been conducted in heterologous expression systems using [^{3}H]LPA (*e.g.* [1107]). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding, and therefore the relationship between recombinant and endogenously expressed receptors is unclear. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. Independent validation by multiple groups has been reported in the peer-reviewed literature for all six LPA receptors described in the tables, including further validation using a distinct read-out via a novel TGFα "shedding" assay [1111]. LPA has also been described to be an agonist at other orphan GPCRs (PSP24, GPR87 and GPR35), as well as at the nuclear hormone PPARγ receptors [1117,1119], although the physiological significance of these observations remain unclear.

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
Principal transduction	$G_{i/o}$, $G_{q/11}$, $G_{12/13}$	$G_{i/o}$, $G_{q/11}$, $G_{12/13}$	$G_{i/o}$, $G_{q/11}$, G_s	$G_{i/o}$, $G_{q/11}$, G_s, $G_{12/13}$ [1115]	G_q, $G_{12/13}$ [1114,1116]	$G_{12/13}$ [1112,1122]
Selective agonists (pK_i)	–	dodecylphosphate (pEC_{50} 6.2) [1121], decyl dihydrogen phosphate (pEC_{50} 5.4) [1121], GRI977143 (pEC_{50} 4.48) [1113]	OMPT (pEC_{50} 7.17) [1108]	–	–	–
Selective antagonists (pK_i)	AM966 (pIC_{50} 7.8) [1120]	H2L5186303 (7.68) [1105]	dioctanoylglycerol pyrophosphate (5.5–7.0) [1106,1118]	–	–	–

Comments: Ki16425 [1118], dodecylphosphate [1121], VPC12249 [1110] and VPC32179 [1109] have antagonist activity at LPA_1 and LPA_3 receptors. The selectivity of these antagonists is less than two orders of magnitude. None of the currently available chemical tools have validated specificity *in vivo*.

Further reading

Blaho VA, Hla T. (2011) Regulation of mammalian physiology, development, and disease by the sphingosine 1-phosphate and lysophosphatidic acid receptors. *Chem Rev* **111**: 6299–6320. [PMID:21939239]

Choi JW, Herr DR, Noguchi K, Yung YC, Lee CW, Mutoh T, Lin ME, Teo ST, Park KE, Mosley AN, Chun J. (2010) LPA receptors: subtypes and biological actions. *Annu Rev Pharmacol Toxicol* **50**: 157–186. [PMID:20055701]

Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH. (2010) International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* **62**: 579–587. [PMID:21079037]

Mutoh T, Rivera R, Chun J. (2012) Insights into the pharmacological relevance of lysophospholipid receptors. *Br J Pharmacol* **165**: 829–844. [PMID:21838759]

Schober A, Siess W. (2012) Lysophosphatidic acid in atherosclerotic diseases. *Br J Pharmacol* **167**: 465–482. [PMID:22568609]

Yanagida K, Ishii S. (2011) Non-Edg family LPA receptors: the cutting edge of LPA research. *J Biochem* **150**: 223–232. [PMID:21746769]

Lysophospholipid (S1P) receptors

Overview: Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid receptors; [1128]) are activated by the endogenous lipid derivatives sphingosine 1-phosphate (S1P) and with lower apparent affinity, sphingosylphosphorylcholine (SPC). Originally identified as members of the endothelial differentiation gene (*edg*) family along with lysophosphatidic acid receptors, the gene names have been updated to S1PR1, etc. to reflect the receptor function of these proteins. Most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms; S1P has also been described to act at intracellular sites [1142], still awaiting precise definition. Previously-proposed SPC (or lysophophosphatidylcholine) receptors – G2A, TDAG8, OGR1 and GPR4 – are lacking confirmation of these roles [1130]. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [^{32}P]S1P (*e.g* [1137]). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding. Targeted deletion of several S1P receptors and key enzymes involved in S1P biosynthesis or degradation has clarified signalling pathways and physiological roles. A crystal structure of an $S1P_1$-T4 fusion protein has recently been described [1132].

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
Principal transduction	$G_{i/o}$	G_q, $G_{12/13}$, G_s	G_q, $G_{i/o}$, G_s	$G_{i/o}$, $G_{12/13}$, G_s	$G_{i/o}$, $G_{12/13}$
Rank order of potency	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate > sphingosylphosphorylcholine [1124,1137]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate > sphingosylphosphorylcholine [1124,1137]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate > sphingosylphosphorylcholine [1137]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate > sphingosylphosphorylcholine [1143]	sphingosine 1-phosphate > dihydrosphingosine 1-phosphate > sphingosylphosphorylcholine [1133]
Selective agonists (pK_i)	SEW2871 (5.5 – 7.7) [1140], AUY954 (pEC_{50} 8.92) [1139]	–	–	–	–
Selective antagonists (pK_i)	W146 (7.7) [1141]	JTE-013 (pIC_{50} 7.77) [1138]	–	–	–

Comments: The immunomodulator fingolimod (FTY720) can be phosphorylated *in vivo* [1123] to generate a relatively potent agonist with activity at $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$ receptors [1125,1134], although its biological activity appears to involve functional antagonism [1127,1129,1136]. This compound has received world-wide approval as the first oral therapy for relapsing forms of Multiple Sclerosis, with a novel mechanism of action involving modulation of S1P receptors in both the immune and nervous systems [1126,1129,1131]. VPC23019 and VPC44116 have antagonist activity at $S1P_1$ and $S1P_3$ receptors [1135].

Further reading

Blaho VA, Hla T. (2011) Regulation of mammalian physiology, development, and disease by the sphingosine 1-phosphate and lysophosphatidic acid receptors. *Chem Rev* **111**: 6299–6320. [PMID:21939239]

Chi H. (2011) Sphingosine-1-phosphate and immune regulation: trafficking and beyond. *Trends Pharmacol Sci* **32**: 16–24. [PMID:21159389]

Choi JW, Gardell SE, Herr DR, Rivera R, Lee CW, Noguchi K, Teo ST, Yung YC, Lu M, Kennedy G *et al*. (2011) FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc Natl Acad Sci USA* **108**: 751–756. [PMID:21177428]

Choi JW, Lee CW, Chun J. (2008) Biological roles of lysophospholipid receptors revealed by genetic null mice: an update. *Biochim Biophys Acta* **1781**: 531–539. [PMID:18407842]

Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH. (2010) International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* **62**: 579–587. [PMID:21079037]

Maceyka M, Harikumar KB, Milstien S, Spiegel S. (2012) Sphingosine-1-phosphate signaling and its role in disease. *Trends Cell Biol* **22**: 50–60. [PMID:22001186]

Mutoh T, Rivera R, Chun J. (2012) Insights into the pharmacological relevance of lysophospholipid receptors. *Br J Pharmacol* **165**: 829–844. [PMID:21838759]

O'Sullivan C, Dev KK. (2013) The structure and function of the S1P1 receptor. *Trends in Pharmacological Sciences* **34**: 401–412. [PMID:23763867]

Pyne S, Pyne NJ. (2011) Translational aspects of sphingosine 1-phosphate biology. *Trends Mol Med* **17**: 463–472. [PMID:21514226]

Spiegel S, Milstien S. (2011) The outs and the ins of sphingosine-1-phosphate in immunity. *Nat Rev Immunol* **11**: 403–415. [PMID:21546914]

Melanin-concentrating hormone receptors

Overview: Melanin-concentrating hormone (MCH) receptors (provisional nomenclature, [1148]) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDML-RCMLGRVYRPCWQV) generated from a precursor (*PMCH*, P20382), which also produces neuropeptide EI and neuropeptide GE.

Nomenclature	MCH_1 receptor	MCH_2 receptor
HGNC, UniProt	*MCHR1*, Q99705	*MCHR2*, Q969V1
Principal transduction	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$ [1150–1152]
Rank order of potency	melanin-concentrating hormone (human) > MCH (salmon)	melanin-concentrating hormone (human) = MCH (salmon) [1150]
Selective antagonists (pK_i)	SNAP-7941 (pA_2 9.2) [1145], GW803430 (pIC_{50} 9.3) [1149], T-226296 (pIC_{50} 8.3) [1153], ATC0175 (pIC_{50} 7.9–8.1) [1147]	–
Radioligands (K_d)	[^{3}H]MCH (human, mouse, rat) (Agonist, Full agonist) [1146], [^{125}I]S36057 (Antagonist) ($3.2x10^{-10}$–$6.3x10^{-10}$ M) [1144], [^{125}I][Phe^{13},Tyr^{19}]MCH (Agonist, Full agonist) ($7x10^{-10}$ M) [1146]	–

Comments: The MCH_2 receptor appears to be a non-functional pseudogene in rodents [1154].

Further reading

Boughton CK, Murphy KG. (2012) Can Neuropeptides Treat Obesity? A review of neuropeptides and their potential role in the treatment of obesity. *Br J Pharmacol* [Epub ahead of print]. [PMID:23121386]

Chung S, Parks GS, Lee C, Civelli O. (2011) Recent updates on the melanin-concentrating hormone (MCH) and its receptor system: lessons from MCH1R antagonists. *J Mol Neurosci* **43**: 115–121. [PMID:20582487]

Eberle AN, Mild G, Zumsteg U. (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, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Parker JA, Bloom SR. (2012) Hypothalamic neuropeptides and the regulation of appetite. *Neuropharmacology* **63**: 18–30. [PMID:22369786]

Melanocortin receptors

Overview: Melanocortin receptors (provisional nomenclature, [1158]) are activated by members of the melanocortin family (α-MSH, β-MSH and γ-MSH derived from a common precursor, pro-opiomelanocortin (*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 (*AGRP*, O00253)).

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
Principal transduction	G_s	G_s	G_s	G_s	G_s
Rank order of potency	α-MSH > β-MSH > ACTH, γ-MSH	ACTH	γ-MSH, β-MSH > ACTH, α-MSH	β-MSH > α-MSH, ACTH > γ-MSH	α-MSH > β-MSH > ACTH > γ-MSH
Selective agonists (pK_i)	–	–	[D-Trp^8]γ-MSH (pIC_{50} 8.2) [1159]	MK-0493 [1162], THIQ (pIC_{50} 8.9) [1166]	–
Selective antagonists (pK_i)	–	–	PG-106 (pIC_{50} 6.7) [1160]	HS014 (8.5) [1165], MBP10 (pIC_{50} 10.0) [1155]	–
Radioligands (K_d)	[^{125}I]NDP-MSH (Agonist, Full agonist) ($3.3x10^{-10}$ M) [1161]	[^{125}I]ACTH-(1–24)	[^{125}I]SHU9119 (Antagonist) [1163], [^{125}I]NDP-MSH (Agonist, Full agonist) ($2x10^{-10}$ M) [1161]	[^{125}I]SHU9119 (Antagonist) ($7x10^{-10}$ M) [1163], [^{125}I]NDP-MSH (Agonist, Full agonist) ($1.2x10^{-9}$–$4x10^{-9}$ M) [1161,1164]	[^{125}I]NDP-MSH (Agonist, Full agonist) ($2.8x10^{-9}$ M) [1161]

Comments: Polymorphisms of the MC1 receptor have been linked to variations in skin pigmentation. Defects of the MC2 receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC4 receptor have been linked to obesity [1156–1157].

Further reading

Beaumont KA, Wong SS, Ainger SA, Liu YY, Patel MP, Millhauser GL, Smith JJ, Alewood PF, Leonard JH, Sturm RA. (2011) Melanocortin MC_1 receptor in human genetics and model systems. *Eur J Pharmacol* **660**: 103–110. [PMID:21199646]

Cooray SN, Clark AJ. (2011) Melanocortin receptors and their accessory proteins. *Mol Cell Endocrinol* **331**: 215–221. [PMID:20654690]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Holloway PM, Smith HK, Renshaw D, Flower RJ, Getting SJ, Gavins FN. (2011) Targeting the melanocortin receptor system for anti-stroke therapy. *Trends Pharmacol Sci* **32**: 90–98. [PMID:21185610]

Hruby VJ, Cai M, Cain J, Nyberg J, Trivedi D. (2011) Design of novel melanocortin receptor ligands: multiple receptors, complex pharmacology, the challenge. *Eur J Pharmacol* **660**: 88–93. [PMID:21208601]

Loos RJ. (2011) The genetic epidemiology of melanocortin 4 receptor variants. *Eur J Pharmacol* **660**: 156–164. [PMID:21295023]

Meimaridou E, Hughes CR, Kowalczyk J, Chan LF, Clark AJ, Metherell LA. (2013) ACTH resistance: genes and mechanisms. *Endocr Dev* **24**: 57–66. [PMID:23392095]

Renquist BJ, Lippert RN, Sebag JA, Ellacott KL, Cone RD. (2011) Physiological roles of the melanocortin MC_3 receptor. *Eur J Pharmacol* **660**: 13–20. [PMID:21211527]

Yang Y. (2011) Structure, function and regulation of the melanocortin receptors. *Eur J Pharmacol* **660**: 125–130. [PMID:21208602]

Melatonin receptors

Overview: Melatonin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on melatonin receptors, [1170]) are activated by the endogenous ligands melatonin and N-acetylserotonin.

Nomenclature	MT_1 receptor	MT_2 receptor
HGNC, UniProt	*MTNR1A*, P48039	*MTNR1B*, P49286
Principal transduction	$G_{i/o}$	$G_{i/o}$
Selective agonists (pK_i)	–	5-methoxy-luzindole (Partial agonist) (9.6) [1171], IIK7 (pIC_{50} 10.3) [1183]
Selective antagonists (pK_i)	–	K185 (9.3) [1175,1183], 4P-PDOT (8.8–9.3) [1167,1171], DH97 (8.0) [1184]
Radioligands (K_d)	2-[^{125}I]MLT (Agonist, Full agonist) (2.13×10^{-11} – 1.19×10^{-10} M) [1167,1171], [^{3}H]melatonin (Agonist, Full agonist) (1.3×10^{-10} – 4×10^{-10} M) [1169]	2-[^{125}I]MLT (Agonist, Full agonist) (1.07×10^{-10} – 1.86×10^{-10} M) [1167,1171], [^{3}H]melatonin (Agonist, Full agonist) (2.8×10^{-10} – 9.12×10^{-10} M) [1169]

Comments: melatonin, 2-iodo-melatonin, S20098 (agomelatine), GR 196429, LY 156735 and ramelteon [1176] 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) [1185]. luzindole is an MT_1/MT_2 melatonin receptor-selective competitive antagonist with some selectivity for the MT2 receptor [1172]. MT_1/MT_2 heterodimers present different pharmacological profiles from MT_1 and MT_2 receptors [1168].

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 [1178]. Pharmacological investigations of MT_3 binding sites have primarily been conducted in hamster tissues. At this site, N-acetylserotonin [1174,1177–1178,1182] and 5MCA-NAT [1182] appear to function as agonists, while prazosin [1177] functions as an antagonist. A suggested physiological function of the MT_3 receptor is in the control of intraocular pressure in rabbits [1181]. The *MT*$_3$ binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (*NQO2*, P16083 [1179–1180]). *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 [1173] although melatonin does not bind to GPR50 receptors.

Further reading

Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. (2012) Melatonin and its analogs in insomnia and depression. *J Pineal Res* **52**: 365–375. [PMID:21951153]

Dardente H. (2012) Melatonin-dependent timing of seasonal reproduction by the pars tuberalis: pivotal roles for long daylengths and thyroid hormones. *J Neuroendocrinol* **24**: 249–266. [PMID:22070540]

Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP, Olcese J. (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacol Rev* **62**: 343–380. [PMID:20605968]

Hickie IB, Rogers NL. (2011) Novel melatonin-based therapies: potential advances in the treatment of major depression. *Lancet* **378**: 621–631. [PMID:21596429]

Korkmaz A, Rosales-Corral S, Reiter RJ. (2012) Gene regulation by melatonin linked to epigenetic phenomena. *Gene* **503**: 1–11. [PMID:22569208]

Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R. (2008) Melatonin in the skin: synthesis, metabolism and functions. *Trends Endocrinol Metab* **19**: 17–24. [PMID:18155917]

Metabotropic glutamate receptors

Overview: Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors, [1243]) are activated by the endogenous ligands L-glutamic acid, L-serine-O-phosphate (L-SOP), N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are (1*S*,3*R*)-ACPD and L-CCG-I, which show limited selectivity for Group II receptors. An example of an antagonist selective for mGlu receptors is LY341495, which blocks $mGlu_2$ and $mGlu_3$ at low nanomolar concentrations, $mGlu_8$ at high nanomolar concentrations, and $mGlu_3$, $mGlu_4$, $mGlu_5$ and $mGlu_7$ in the micromolar range [1210]. Three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G-protein effector coupling: 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). Group I mGlu receptors may be activated by 3,5-DHPG and (*S*)-3HPG [1190] and antagonized by (*S*)-hexylhomoibotenic acid [1221]. Group II mGlu receptors may be activated by LY389795 [1229], LY379268 [1229], LY354740 [1244,1254], DCG-IV and (2*R*,3*R*)-APDC [1245], and antagonised by eGlu (4.3, [1207] and LY307452 [1200,1253]. Group III mGlu receptors may be activated by (*R*,*S*)-4-PPG [1203].

In addition to orthosteric ligands that directly interact with the glutamate recognition site directly, allosteric modulators have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Nomenclature	$mGlu_1$ receptor	$mGlu_5$ receptor
HGNC, UniProt	*GRM1*, Q13255	*GRM5*, P41594
Principal transduction	$G_{q/11}$	$G_{q/11}$
Selective agonists (pKi)	–	(S)-(+)-CBPG (Partial agonist) (pEC_{50} 4.3 - Rat) [1225], CHPG (pIC_{50} 3.4) [1232]
Selective antagonists (pKi)	AIDA (pA_2 4.2) [1231], 3-MATIDA (pIC_{50} 5.2-Rat) [1230], LY367385 (pIC_{50} 5.1) [1196], (S)-(+)-CBPG (pIC_{50} 4.2-Rat) [1225], (S)-TBPG (pIC_{50} 4.2-Rat) [1197]	ACDPP (pIC_{50} 6.9) [1188]
Selective allosteric regulators	PHCCC (Positive), Ro67-7476 (Positive) (pK_i 7.5–7.9 - Rat) [1213], Ro01-6128 (Positive) (pK_i 7.5–7.7 - Rat) [1213], Ro67-4853 (Positive) (pK_i 5.1 - Rat) [1213], JNJ16259685 (Negative) (pIC_{50} 8.9) [1217], A-841720 (Negative) (pIC_{50} 8.0) [1255], 3,5-dimethyl PPP (Negative) (pIC_{50} 7.8-Rat) [1227], YM298198 (Negative) (pIC_{50} 7.8-Rat) [1214], BAY 367620 (Negative) (pIC_{50} 6.8–8.0-Rat) [1193,1216], EM-TBPC (Negative) (pIC_{50} 6.9-Rat) [1223], LY456236 (Negative) (pIC_{50} 6.9) [1218], CPCCOEt (Negative) (pIC_{50} 5.2–5.8) [1220]	MTEP (Negative) (pK_i 7.8) [1191], VU-1545 (Positive) (pEC_{50} 8.0) [1198], CDPPB (Positive) (pEC_{50} 7.6–8.0) [1211,1219], MPEP (Negative) (pIC_{50} 7.4–7.7) [1202,1204], fenobam (Negative) (pIC_{50} 7.2) [1241], DFB (Positive) (pIC_{50} 5.6–8.5) [1236–1237], CPPHA (Positive) (pIC_{50} 6.3) [1237], SIB-1757 (Negative) (pIC_{50} 6.0–6.4) [1202,1252], SIB-1893 (Negative) (pIC_{50} 5.9–6.5) [1202,1252]

Nomenclature	$mGlu_2$ receptor	$mGlu_3$ receptor
HGNC, UniProt	*GRM2*, Q14416	*GRM3*, Q14832
Principal transduction	$G_{i/o}$	$G_{i/o}$
Selective antagonists (pKi)	PCCG-4 (pIC_{50} 5.1 - Rat) [1239]	–
Selective allosteric regulators	biphenylindanone A (Positive) (pEC_{50} 7.0) [1189], CBiPES (Positive) (pEC_{50} 7.0) [1209], Ro64-5229 (Negative) (pIC_{50} 7.0 - Rat) [1215], 4-MPPTS (Positive) (pIC_{50} 5.8) [1187,1208–1209,1242]	–
Endogenous agonists (pKi)	–	NAAG (Selective) (4.7) [1246]

Nomenclature	$mGlu_4$ receptor	$mGlu_6$ receptor	$mGlu_7$ receptor	$mGlu_8$ receptor
HGNC, UniProt	*GRM4*, Q14833	*GRM6*, O15303	*GRM7*, Q14831	*GRM8*, O00222
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Endogenous agonists (pKi)	–	–	–	L-SOP (pIC_{50} 6.2–7.2) [1224,1254]
Non-selective agonists (pKi)	L-AP4 (pEC_{50} 6.5) [1254], L-SOP (pEC_{50} 5.9) [1254]	–	L-SOP (pEC_{50} 4.5) [1254], L-AP4 (pEC_{50} 3.8) [1254]	L-AP4 (pIC_{50} 7.0–7.2) [1224]
Selective agonists (pKi)	LSP4-2022 [1205]	1-benzyl-APDC (pEC_{50} 4.7 - Rat) [1250], homo-AMPA (pEC_{50} 4.1) [1192]	LSP4-2022 (pEC_{50} 4.96) [1205]	(*S*)-3,4-DCPG (pEC_{50} 7.5) [1248]
Non-selective antagonists (pKi)	MAP4 (4.6 - Rat) [1206]	MAP4 (pIC_{50} 3.5 - Rat) [1240]	–	MPPG (pIC_{50} 4.33) [1254]
Selective antagonists (pKi)	–	THPG [1249]	–	–
Non-selective allosteric regulators	SIB-1893 (Positive) (pEC_{50} 6.3–6.8) [1226], MPEP (Positive) (pEC_{50} 6.3–6.6) [1226], PHCCC (Positive) (pEC_{50} 4.5) [1222]	–	AMN082 (Positive) (pEC_{50} 6.5–6.8) [1228]	–
Selective allosteric regulators	VU0361737 (Positive) (pEC_{50} 6.6) [1199], VU0155041 (Positive) (pEC_{50} 6.1) [1235]	–	MMPIP (Negative) (pIC_{50} 6.1–7.6 - Rat) [1234,1247]	–
Comment	pEC50 values for MPEP and SIB-1893 were obtained in the presence of L-AP4 [1226]	–	–	–

Comments: The activity of NAAG as an agonist at $mGlu_3$ receptors was questioned on the basis of contamination with glutamate [1194,1201], but this has been refuted [1233].

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [^{3}H]R214127 [1216] and [^{3}H]YM298198 [1214] at $mGlu_1$ receptors and [^{3}H]M-MPEP [1202] and [^{3}H]methoxymethyl-MTEP [1186] at $mGlu_5$ receptors. Although a number of radioligands have been used to examine binding using native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (*e.g.* human *versus* rat or mouse) of the 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 [1251], and is an antagonist at all group-III mGluRs with an IC50 of 30μM. A potential novel metabotrophic 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 metabotrophic glutamate receptors), but resistant to LY341495 [1195]. There are also reports of a distinct metabotrophic glutamate receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification [1212,1238].

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

All selective antagonists at metabotropic glutamate receptors are competitive.

Further reading

Bradley SJ, Challiss RA. (2012) G protein-coupled receptor signalling in astrocytes in health and disease: a focus on metabotropic glutamate receptors. *Biochem Pharmacol* **84**: 249–259. [PMID:22531220]

Flor PJ, Acher FC. (2012) Orthosteric versus allosteric GPCR activation: the great challenge of group-III mGluRs. *Biochem Pharmacol* **84**: 414–424. [PMID:22554564]

Julio-Pieper M, Flor PJ, Dinan TG, Cryan JF. (2011) Exciting times beyond the brain: metabotropic glutamate receptors in peripheral and non-neural tissues. *Pharmacol Rev* **63**: 35–58. [PMID:21228260]

Nicoletti F, Bockaert J, Collingridge GL, Conn PJ, Ferraguti F, Schoepp DD, Wroblewski JT, Pin JP. (2011) Metabotropic glutamate receptors: from the workbench to the bedside. *Neuropharmacology* **60**: 1017–1041. [PMID:21036182]

Schoepp DD, Alexander SP, Beart P, Conn PJ, Lodge D, Nakanishi S *et al*. (2000) Metabotropic glutamate receptors. *in* IUPHAR Compendium of Receptor Characterization and Classification *Edited by* Watson SP, Girdlestone D IUPHAR Press. 195–208.

Wood MR, Hopkins CR, Brogan JT, Conn PJ, Lindsley CW. (2011) "Molecular switches" on mGluR allosteric ligands that modulate modes of pharmacology. *Biochemistry* **50**: 2403–2410. [PMID:21341760]

Motilin receptor

Overview: Motilin receptors (provisional nomenclature, [1261]) are activated by a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a motilin-associated peptide (*MLN*, P12872). These receptors are also suggested to be responsible for the gastrointestinal prokinetic effects of certain macrolide antibiotics (often called motilides; *e.g.* erythromycin), although for many of these molecules the evidence is sparse.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Selective agonists (pK_i)	Selective antagonists (pK_i)	Radioligands (K_d)	Comment
motilin receptor	*MLNR*, O43193	$G_{q/11}$[1259–1260]	motilin (8.4 – 8.7) [1258,1265–1267]	GSK962040 (pEC_{50} 7.9) [1275], mitemcinal (pEC_{50} 7.5 – 7.8 - Rabbit) [1263,1273], azithromycin (pEC_{50} 5.5) [1256], mitemcinal (pIC_{50} 8.1 – 8.2 - Rabbit) [1257], ABT-229 (pIC_{50} 7.2) [1274], erythromycin-A (pIC_{50} 5.5 – 6.5) [1260,1274]	MA-2029 (pA_2 9.2) [1271], GM-109 (pA_2 7.2 – 7.5 - Rabbit) [1257,1272], GM-109 (pIC_{50} 8.0 - Pig) [1262]	[^{125}I]motilin (human) (Agonist, Full agonist) ($1x10^{-10}$ M) [1260]	Note that for the complex macrolide structures, selectivity of action has often not been rigorously examined and other actions are possible (*e.g.* P2X inhibition by erythromycin; [1277]). Small molecule motilin receptor agonists are now described [1264,1270,1276].

Comments: In laboratory rodents, the gene encoding the motilin percursor appears to be absent, while the receptor appears to be a pseudogene. Functions of motilin (*MLN*, P12872) are not usually detected in rodents, although brain and other responses to motilin (*MLN*, P12872) and the macrolide ABT-229 have been reported and the mechanism of these actions are obscure [1268–1269].

Further reading

De Smet B, Mitselos A, Depoortere I. (2009) Motilin and ghrelin as prokinetic drug targets. *Pharmacol Ther* **123**: 207–223. [PMID:19427331]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Sanger GJ, Wang Y, Hobson A, Broad J. (2012) Motilin: Toward a new understanding of the gastrointestinal neuropharmacology and therapeutic use of motilin receptor agonists. *Br J Pharmacol* [Epub ahead of print]. [PMID:23189978]

Takeshita E, Matsuura B, Dong M, Miller LJ, Matsui H, Onji M. (2006) Molecular characterization and distribution of motilin family receptors in the human gastrointestinal tract. *J Gastroenterol* **41**: 223–230. [PMID:16699856]

Neuromedin U receptors

Overview: Neuromedin U receptors (provisional nomenclature, [1279]) are activated by the endogenous 25 amino acid peptide neuromedin U (NMU-25 (*NMU*, P48645), NMU), a peptide originally isolated from pig spinal cord [1285]. 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 (NMS-33 (*NMS*, Q5H8A3)) has also been identified as an endogenous agonist [1286]. NMS-33 is, as its name suggests, a 33 amino-acid product of a precursor protein derived from a single gene and contains an amidated C-terminal heptapeptide identical to NMU. NMS-33 appears to activate NMU receptors with equivalent potency to NMU-25.

Nomenclature	NMU1 receptor	NMU2 receptor
HGNC, UniProt	*NMUR1*, Q9HB89	*NMUR2*, Q9GZQ4
Principal transduction	$G_{q/11}$ [1278,1280]	$G_{q/11}$ [1278,1281]
Selective antagonists (pK_i)	–	R-PSOP (pK_B 7.04) [1283]

Comments: NMU1 and NMU2 couple predominantly to $G_{q/11}$ although there is evidence of good coupling to $G_{i/o}$ [1278,1281,1282]. NMU1 and NMU2 can be labelled with [^{125}I]-NMU and [^{125}I]-NMS (of various species, *e.g.* [1284]), BODIPY® TMR-NMU or Cy3B-NMU-8 [1278]. A range of radiolabelled (^{125}I-), fluorescently labelled (*e.g.* Cy3, Cy5, rhodamine and FAM) and biotin labelled versions of NMU-25 (*NMU*, P48645) and NMS-33 (*NMS*, Q5H8A3) are now commercially available.

Further reading

Brighton PJ, Szekeres PG, Willars GB. (2004) Neuromedin U and its receptors: structure, function, and physiological roles. *Pharmacol Rev* **56**: 231–248. [PMID:15169928]

Budhiraja S, Chugh A. (2009) Neuromedin U: physiology, pharmacology and therapeutic potential. *Fundam Clin Pharmacol* **23**: 149–157. [PMID:19645813]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Mitchell JD, Maguire JJ, Davenport AP. (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**: 2985–2987. [PMID:19549882]

Neuropeptide FF/neuropeptide AF receptors

Overview: A single propeptide precursor (*NPFF*, O15130) generates the octapeptides NPFF (FLFQPQRF-NH_2, neuropeptide FF or F-8-F-amide) and NPSF (SLAAPQRF-NH_2, neuropeptide SF) and the octadecapeptide NPAF (AGEGLSSPFWSLAAPQRF-NH_2, neuropeptide AF or A-18-F-amide). NPFF and NPAF were originally isolated from bovine brain [1298].

Nomenclature	NPFF1 receptor	NPFF2 receptor
HGNC, UniProt	*NPFFR1*, Q9GZQ6	*NPFFR2*, Q9Y5X5
Principal transduction	$G_{q/11}$	$G_{i/o}$ [1293]
Rank order of potency	FMRF, NPFF > NPAF > NPSF, QRFP, PrRP-31 (*PRLH*) [1287]	NPAF, NPFF > PrRP-31 (*PRLH*) > FMRF, QRFP (*QRFP*, P83859) > NPSF [1287]
Endogenous agonists (pK_i)	RFRP-3 (*NPVF*, Q9HCQ7) (Selective) (9.2 – 9.3) [1288–1289,1292], NPFF (*NPFF*, O15130) (Selective) (8.5 – 9.9) [1287–1288,1292]	NPFF (Selective) (9.7) [1288,1291]
Selective agonists (pK_i)	–	dNPA (10.6) [1294–1295], AC263093 (pEC_{50} 5.2 – 5.9) [1290]
Selective antagonists (pK_i)	AC262620 (7.7 – 8.1) [1290], AC262970 (7.4 – 8.1) [1290], RF9 (7.2) [1296]	–
Radioligands (K_d)	[^{125}I]NPFF (Agonist, Full agonist) [1287], [^{125}I]Y-RFRP-3 (Agonist, Full agonist) (8x10^{-9} M) [1288], [^{3}H]NPVF (Agonist, Full agonist) (2.65x10^{-9} M) [1297]	[^{125}I]NPFF (Agonist, Full agonist) [1287], [^{125}I]EYF (Agonist, Full agonist) (6.3x10^{-11} M) [1292], [^{3}H]EYF (Agonist, Full agonist) (5.4x10^{-10} M) [1297]

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, [1296]).

Further reading

Moulédous L, Mollereau C, Zajac JM. (2010) Opioid-modulating properties of the neuropeptide FF system. *Biofactors* **36**: 423–429. [PMID:20803521]

Vyas N, Mollereau C, Chevé G, McCurdy CR. (2006) Structure-activity relationships of neuropeptide FF and related peptidic and non-peptidic derivatives. *Peptides* **27**: 990–996. [PMID:16490282]

Yang HY, Tao T, Iadarola MJ. (2008) Modulatory role of neuropeptide FF system in nociception and opiate analgesia. *Neuropeptides* **42**: 1–18. [PMID:17854890]

Neuropeptide S receptor

Overview: The neuropeptide S receptor (NPS, provisional nomenclature, [1300]) responds to the 20 amino-acid peptide neuropeptide S derived from the precursor (*NPS*, P0C0P6).

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)
NPS receptor	*NPSR1*, Q6W5P4	G_s, $G_{q/11}$ [1301–1302]	NPS (pEC_{50} 8.0) [1303]	[^{125}I]Tyr^{10}NPS (human) (Agonist, Full agonist) (3.3x10^{-10} M) [1303]

Comments: Polymorphisms in the NPS receptor have been suggested to be associated with asthma [1302] and irritable bowel syndrome [1299].

Further reading

Cannella N, Kallupi M, Ruggeri B, Ciccocioppo R, Ubaldi M. (2013) The role of the neuropeptide S system in addiction: focus on its interaction with the CRF and hypocretin/orexin neurotransmission. *Prog Neurobiol* **100**: 48–59. [PMID:23041581]

Dal Ben D, Antonini I, Buccioni M, Lambertucci C, Marucci G, Thomas A, Volpini R, Cristalli G. (2011) Neuropeptide S receptor: recent updates on nonpeptide antagonist discovery. *ChemMedChem* **6**: 1163–1171. [PMID:21452188]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Guerrini R, Salvadori S, Rizzi A, Regoli D, Calo' G. (2010) Neurobiology, pharmacology, and medicinal chemistry of neuropeptide S and its receptor. *Med Res Rev* **30**: 751–777. [PMID:19824051]

Pape HC, Jüngling K, Seidenbecher T, Lesting J, Reinscheid RK. (2010) Neuropeptide S: a transmitter system in the brain regulating fear and anxiety. *Neuropharmacology* **58**: 29–34. [PMID:19523478]

Reinscheid RK. (2008) Neuropeptide S: anatomy, pharmacology, genetics and physiological functions. *Results Probl Cell Differ* **46**: 145–158. [PMID:18204825]

Neuropeptide W/neuropeptide B receptors

Overview: The neuropeptide BW receptor 1 (NPBW1) is activated by two 23-amino-acid peptides, neuropeptide W (NPW-23 (*NPW*, Q8N729)) and neuropeptide B (NPB-23 (*NPB*, Q8NG41)) [1305,1309]. C-terminally extended forms of the peptides (NPW-30 (*NPW*, Q8N729) and NPB-29 (*NPB*, Q8NG41)) also activate NPBW1 [1304]. Unique to both forms of NPB is the N-terminal bromination of the first tryptophan residue. des-Br-NPB-23 (*NPB*, Q8NG41) and des-Br-NPB-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 NPB and NPW [1304].

Nomenclature	NPBW1 receptor	NPBW2 receptor
HGNC, UniProt	*NPBWR1*, P48145	*NPBWR2*, P48146
Principal transduction	$G_{i/0}$ [1307]	$G_{i/0}$ [1307]
Rank order of potency	NPB-29 > NPB-23 > NPW-23 > NPW-30 [1304]	NPW-23 > NPW-30 > NPB-29 > NPB-23 [1304]
Selective agonists (pK_i)	Ava3 (9.37–9.43) [1306], Ava5 (8.8–9.0) [1306]	–
Radioligands (K_d)	[^{125}I]NPW-23 (human) (Agonist) (4.4x10^{-10} M) [1310]	[^{125}I]NPW-23 (human) (Agonist) (1.99x10^{-8} M) [1309]

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 [1308].

Further reading

Date Y, Mondal MS, Kageyama H, Ghamari-Langroudi M, Takenoya F, Yamaguchi H, Shimomura Y, Mori M, Murakami N, Shioda S *et al*. (2010) Neuropeptide W: an anorectic peptide regulated by leptin and metabolic state. *Endocrinology* **151**: 2200–2210. [PMID:20189998]

Hondo M, Ishii M, Sakurai T. (2008) The NPB/NPW neuropeptide system and its role in regulating energy homeostasis, pain, and emotion. *Results Probl Cell Differ* **46**: 239–256. [PMID:18204824]

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

Singh G, Davenport AP. (2006) Neuropeptide B and W: neurotransmitters in an emerging G-protein-coupled receptor system. *Br J Pharmacol* **148**: 1033–1041. [PMID:16847439]

Neuropeptide Y receptors

Overview: Neuropeptide Y (NPY) receptors (nomenclature agreed by NC-IUPHAR on Neuropeptide Y Receptors, [1325]) are activated by the endogenous peptides NPY (*NPY*, P01303), NPY 3–36 (*NPY*, P01303), peptide YY (PYY (*PYY*, P10082)), PYY-(3–36) (*PYY*, P10082) and pancreatic polypeptide (PP (*PPY*, P01298)). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine recepter (originally named LESTR, [1323]). 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 [1321]. Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the relative potency of PP (*PPY*, P01298) is greater at the rat Y_4 receptor than at the human receptor [1317]. 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.

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
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Rank order of potency	NPY > PYY >> PP	NPY > PYY >> PP	PP > NPY = PYY	NPY > PYY > PP	NPY = PYY > PP
Endogenous agonists (pK_i)	–	NPY 3–36 (Selective), PYY-(3–36) (9.2–9.7) [1318,1320]	PP (8.7–10.9) [1311,1324,1327,1329]	–	–
Selective agonists (pK_i)	[Leu^{31},Pro^{34}]PYY (human), [Pro^{34}]NPY, [Pro^{34}]PYY (human), [Leu^{31},Pro^{34}]NPY (pEC$_{50}$ 7.1) [1314]	–	–	[Ala^{31},Aib^{32}]NPY (pig) (pIC$_{50}$ 8.2) [1313]	–
Selective antagonists (pK_i)	BIBP3226 (8.1–8.2) [1319,1326], BIBO3304 (pIC$_{50}$ 9.5) [1328]	BIIE0246 (pIC$_{50}$ 8.5) [1315], JNJ-5207787 (pIC$_{50}$ 6.9–7.1) [1312]	–	L-152,804 (7.6) [1322]	–
Radioligands (K_d)	[^{125}I][Leu^{31},Pro^{34}]NPY (Agonist, Full agonist), [^{3}H]BIBP3226 (Antagonist) (2.1x10^{-9} M)	[^{125}I]PYY-(3–36) (human) (Agonist, Full agonist)	[^{125}I]PP (human) (Agonist, Full agonist)	[^{125}I][cPP(1–7), NPY(19–23), Ala^{31}, Aib^{32}, Gln^{34}]hPP (Agonist) (5x10^{-10}–7x10^{-10} M – Rat) [1316]	–

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 [1319]. NPY-(13–36) is Y_2 selective relative to Y_1 and Y_5 receptors. PYY-(3–36) (*PYY*, P10082) is Y_2 selective relative to Y_1 receptors.

Further reading

Bowers ME, Choi DC, Ressler KJ. (2012) Neuropeptide regulation of fear and anxiety: Implications of cholecystokinin, endogenous opioids, and neuropeptide Y. *Physiol Behav* **107**: 699–710. [PMID:22429904]

Decressac M, Barker RA. (2012) Neuropeptide Y and its role in CNS disease and repair. *Exp Neurol* **238**: 265–272. [PMID:23022456]

Michel MC, Beck-Sickinger AG, Cox H, Doods HN, Herzog H, Larhammar D, Quirion R, Schwartz TW, Westfall TC. (1998) XVI. International Union of Pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY and pancreatic polypeptide receptors. *Pharmacol Rev* **50**: 143–150. [PMID:9549761]

Morales-Medina JC, Dumont Y, Quirion R. (2010) A possible role of neuropeptide Y in depression and stress. *Brain Res* **1314**: 194–205. [PMID:19782662]

Zengin A, Zhang L, Herzog H, Baldock PA, Sainsbury A. (2010) Neuropeptide Y and sex hormone interactions in humoral and neuronal regulation of bone and fat. *Trends Endocrinol Metab* **21**: 411–418. [PMID:20202858]

Zhang L, Bijker MS, Herzog H. (2011) The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. *Pharmacol Ther* **131**: 91–113. [PMID:21439311]

Neurotensin receptors

Overview: Neurotensin receptors (provisional nomenclature, [1330]) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (*NTS*, P30990), which also generates neuromedin N, an agonist at the NTS_2 receptor. A nonpeptide antagonist, SR142948A, shows high affinity (pK_i~9) at both NTS_1 and NTS_2 receptors [1331]. [^{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.

Nomenclature	NTS_1 receptor	NTS_2 receptor
HGNC, UniProt	*NTSR1*, P30989	*NTSR2*, O95665
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	neurotensin > neuromedin N [1332]	neurotensin = neuromedin N [1335]
Selective agonists (pK_i)	JMV449 [1338]	levocabastine (6.8) [1335,1337]
Selective antagonists (pK_i)	SR48692 (pIC_{50} 7.5–8.2) [1331]	–
Radioligands (K_d)	[^{3}H]SR48692 (Antagonist) ($3.2x10^{-9}$ M – Rat) [1333]	–

Comments: neurotensin (*NTS*, P30990) appears to be a low-efficacy agonist at the NTS_2 receptor [1339], while the NTS_1 receptor antagonist SR48692 is an agonist at NTS2 receptors [1339]. An additional protein, provisionally termed NTS3 (also known as NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation [1336]. It has been reported to interact with the NTS_1 receptor [1334] and has been implicated in hormone trafficking and/or neurotensin uptake.

Further reading

Dupouy S, Mourra N, Doan VK, Gompel A, Alifano M, Forgez P. (2011) The potential use of the neurotensin high affinity receptor 1 as a biomarker for cancer progression and as a component of personalized medicine in selective cancers. *Biochimie* **93**: 1369–1378. [PMID:21605619]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Kalafatakis K, Triantafyllou K. (2011) Contribution of neurotensin in the immune and neuroendocrine modulation of normal and abnormal enteric function. *Regul Pept* **170**: 7–17. [PMID:21549161]

Stolakis V, Kalafatakis K, Botis J, Zarros A, Liapi C. (2010) The regulatory role of neurotensin on the hypothalamic-anterior pituitary axons: emphasis on the control of thyroid-related functions. *Neuropeptides* **44**: 1–7. [PMID:19878995]

Tanganelli S, Antonelli T, Tomasini MC, Beggiato S, Fuxe K, Ferraro L. (2012) Relevance of dopamine D(2)/neurotensin NTS1 and NMDA/neurotensin NTS1 receptor interaction in psychiatric and neurodegenerative disorders. *Curr Med Chem* **19**: 304–316. [PMID:22335510]

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 (N/OFQ (*PNOC*, Q13519)); endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter names for the opioid receptors, μ, δ and κ, are well established, and IUPHAR considers these names most appropriate [1352]. The human N/OFQ receptor is considered 'opioid-related' rather than opioid because while it exhibits a high degree of structural homology with the conventional opioid receptors [1368], it displays a distinct pharmacology.

Nomenclature	δ receptor	κ receptor	μ receptor	NOP receptor
HGNC, UniProt	*OPRD1*, P41143	*OPRK1*, P41145	*OPRM1*, P35372	*OPRL1*, P41146
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Rank order of potency	–	–	–	N/OFQ >> dynorphin A
Principal endogenous agonists	β-endorphin, [Leu]enkephalin, [Met]enkephalin	big dynorphin, dynorphin A	β-endorphin, [Met]enkephalin, [Leu]enkephalin, endomorphin-1, endomorphin-2	–
Endogenous agonists (pK_i)	–	–	endomorphin-2 (Selective) (8.5 – Rat) [1388], endomorphin-1 (8.3) [1353,1388]	N/OFQ (Selective) (9.7–10.4) [1341,1365–1367,1372]
Selective agonists (pK_i)	[D-Ala^2]deltorphin I (pK_d 9.35) [1350,1382], [D-Ala^2]deltorphin II (8.8) [1351], DPDPE (8.8) [1369,1384], SNC80 (7.2) [1345,1376]	enadoline (9.6) [1357,1370], U69593 (9.5) [1363,1384], U50488 (7.8–9.7) [1348,1373,1379,1384,1386,1392–1393], salvinorin A (7.8–8.7) [1343,1377]	sufentanil (9.9) [1385], DAMGO (9.3) [1355,1384], PL017 (8.2) [1347,1384]	N/OFQ-(1–13)-NH_2 (10.1–10.4) [1341,1354,1365,1372], Ro64-6198 (9.6) [1358]
Selective antagonists (pK_i)	naltriben (10.0) [1381,1384], naltrindole (9.7) [1375,1384], TIPPψ (Inverse agonist) (9.0) [1378,1384]	nor-binaltorphimine (8.9–11.0) [1373–1374,1379,1384,1392–1393], GNTI (9.74–9.9) [1359,1373,1383]	CTAP (8.6) [1347,1384]	UFP-101 (10.2) [1346], SB 612111 (9.5) [1391], J-113397 (pIC_{50} 8.3) [1361]
Radioligands (K_d)	[^{3}H]deltorphin II [1344], [^{3}H]DPDPE [1340], [^{3}H]naltriben (Antagonist) [1364], [^{3}H]naltrindole (Antagonist) [1387]	[^{3}H]CI977 [1380], [^{3}H]U69593 (Agonist, Full agonist) ($2x10^{-9}$–$1.6x10^{-9}$ M) [1363,1373,1379]	[^{3}H]DAMGO (Agonist, Full agonist) [1390], [^{3}H]PL017 (Agonist) [1356]	[^{3}H]N/OFQ (Agonist, Full agonist) ($6.3x10^{-11}$ M) [1349,1367]

Comments: Subtypes of μ (μ1, μ2), δ (δ1, δ2) and κ (κ1, κ2, κ3) receptor have been proposed based primarily on binding studies with poorly selective ligands or results from *in vivo* studies. Only three naloxone-sensitive opioid receptors have been cloned, and while the μ-receptor in particular may be subject to extensive alternative splicing, these putative isoforms have not been definitively correlated with any of the proposed subtypes. Opioid receptor subtypes may reflect heterodimerization of opioid receptors with each other or with other GPCR [1360], but evidence for heterodimers in native cells is equivocal. 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 [1389]. Opioid receptor subtypes may reflect heterodimerization of opioid receptors with each other or with other GPCR, and while there is increasing evidence for heterodimers in native cells, the consequences this heterodimerization has for signalling remains largely unknown. For μ-opioid receptors at least, dimerization does not seem to be required for signalling [1362].

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 [1371] and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists [1342]. Pathway bias for agonists makes general rank orders of potency and efficacy somewhat obsolete, and they have, therefore, been removed from the table. As ever, the mechanisms underlying the acute and long term regulation of opiod receptor function are the subject of intense investigation and debate.

Further reading

Butelman ER, Yuferov V, Kreek MJ. (2012) κ-opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. *Trends Neurosci* **35**: 587–596. [PMID:22709632]

Dang VC, Christie MJ. (2012) Mechanisms of rapid opioid receptor desensitization, resensitization and tolerance in brain neurons. *Br J Pharmacol* **165**: 1704–1716. [PMID:21564086]

Kelly E. (2011) The subtleties of μ-opioid receptor phosphorylation. *Br J Pharmacol* **164**: 294–297. [PMID:21449916]

Pradhan AA, Befort K, Nozaki C, Gavériaux-Ruff C, Kieffer BL. (2011) The delta opioid receptor: an evolving target for the treatment of brain disorders. *Trends Pharmacol Sci* **32**: 581–590. [PMID:21925742]

Pradhan AA, Smith ML, Kieffer BL, Evans CJ. (2012) Ligand-directed signalling within the opioid receptor family. *Br J Pharmacol* **167**: 960–969. [PMID:22708627]

Williams JT, Ingram SL, Henderson G, Chavkin C, von Zastrow M, Schulz S, Koch T, Evans CJ, Christie MJ. (2013) Regulation of μ-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev* **65**: 223–254. [PMID:23321159]

Orexin receptors

Overview: Orexin receptors (nomenclature as agreed by NC-IUPHAR, see [1395]) 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 [1407]. Binding to both receptors may be accomplished with [^{125}I]orexin A (human, mouse, rat) [1397].

Nomenclature	OX_1 receptor	OX_2 receptor
HGNC, UniProt	*HCRTR1*, O43613	*HCRTR2*, O43614
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	orexin-A > orexin-B	orexin-A = orexin-B
Selective agonists (pK_i)	–	[Ala^{11}, D-Leu^{15}]orexin-B (pEC_{50} 9.9) [1394]
Selective antagonists (pK_i)	SB-334867 (7.4 – 7.5) [1402,1404], SB-408124 (7.2 – 7.6) [1399,1402]	N-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulphonyl)-amino]-N-pyridin-3-ylmethyl-acetamide (9.0) [1401] , 1-(2,4-dibromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1394,1396]dioxan-5-yl)-urea (7.9 – 8.6) [1403] , TCS-OX2-29 (7.4) [1396]

Comments: The primary coupling of orexin receptors to $G_{q/11}$ proteins is rather speculative and based on the strong activation of phospholipase C. Coupling of both receptors to $G_{i/o}$ and G_s has also been reported [1398,1406]; for most cellular responses observed, the G protein pathway is unknown. The rank order of endogenous agonist potency may depend on the cellular signal transduction machinery. The synthetic [Ala^{11}, D-Leu^{15}]orexin-B may show poor OX_2 receptor selectivity [1405].

Loss-of-function mutations in the gene encoding the OX_2 receptor underlie canine hereditary narcolepsy [1400].

Further reading

Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G. (2010) Role of orexin/hypocretin in reward-seeking and addiction: implications for obesity. *Physiol Behav* **100**: 419–428. [PMID:20338186]

Gotter AL, Roecker AJ, Hargreaves R, Coleman PJ, Winrow CJ, Renger JJ. (2012) Orexin receptors as therapeutic drug targets. *Prog Brain Res* **198**: 163–188. [PMID:22813974]

Gotter AL, Webber AL, Coleman PJ, Renger JJ, Winrow CJ. (2012) International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. *Pharmacol Rev* **64**: 389–420. [PMID:22759794]

Laburthe M, Voisin T. (2012) The orexin receptor OX(1)R in colon cancer: a promising therapeutic target and a new paradigm in G protein-coupled receptor signalling through ITIMs. *Br J Pharmacol* **165**: 1678–1687. [PMID:21627633]

Sakurai T, Mieda M. (2011) Connectomics of orexin-producing neurons: interface of systems of emotion, energy homeostasis and arousal. *Trends Pharmacol Sci* **32**: 451–462. [PMID:21565412]

Scammell TE, Winrow CJ. (2011) Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol* **51**: 243–266. [PMID:21034217]

Sharf R, Sarhan M, Dileone RJ. (2010) Role of orexin/hypocretin in dependence and addiction. *Brain Res* **1314**: 130–138. [PMID:19699189]

Oxoglutarate receptor

Overview: the oxoglutarate receptor (NC-IUPHAR recommended nomenclature, see Davenport *et al.*, 2004) has been suggested to respond to one of the intermediates of the citric acid cycle [1408].

Nomenclature	HGNC gene symbol	UniProtKB AC	Principal transduction	Endogenous agonists (pK_i)
oxoglutarate receptor	*OXGR1*	Q96P68	G_q [1408]	α-ketoglutaric acid (pEC_{50} 3.3 – 4.49) [1408–1409]

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacological reviews* **65**: 967–986.

P2Y receptors

Overview: P2Y receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, [1410–1411]) are activated by the endogenous ligands ATP, ADP, UTP, UDP 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 'UTP-preferring (or ATP-, *etc*.) P2Y receptor' or '$P2Y_1$-like', *etc*., until further, as yet undefined, corroborative criteria can be applied.

Nomenclature	$P2Y_1$ receptor	$P2Y_2$ receptor	$P2Y_4$ receptor	$P2Y_6$ receptor
HGNC, UniProt	*P2RY1*, P47900	*P2RY2*, P41231	*P2RY4*, P51582	*P2RY6*, Q15077
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	ADP>ATP	UTP=ATP	UTP>ATP (at rat recombinant receptors, UTP = ATP)	UDP>>UTP>ATP
Endogenous agonists (pK_i)	–	–	–	UDP (pEC_{50} 6.5) [1423]
Selective agonists (pK_i)	MRS2365 (pEC_{50} 9.4) [1421], ADPβS (pEC_{50} 7.3) [1459], 2MeSADP (pIC_{50} 5.4 – 7.0) [1458,1461]	2-thioUTP (pEC_{50} 7.3) [1426], PSB1114 (pEC_{50} 6.9) [1427], Ap_4A (pEC_{50} 6.1) [1419,1457], UTPγS (pEC_{50} 5.8) [1443], MRS2768 (pEC_{50} 5.7) [1441]	UTPγS [1444], MRS4062 (pEC_{50} 7.6) [1448]	MRS2957 (pEC_{50} 7.9) [1447], 5-iodoUDP (pEC_{50} 7.82) [1416], 3-phenacyl-UDP (pEC_{50} 7.2) [1426]
Selective antagonists (pK_i)	MRS2500 (8.8 – 9.1) [1420,1438], MRS2279 (7.9) [1461], MRS2179 (7.0 – 7.1) [1418,1461], 2,2′-pyridylisatogen tosylate (6.8) [1429]	AR-C118925XX (pIC_{50} ~6.0) [1436]	ATP (pK_d 6.2) [1437]	MRS2578 (pIC_{50} 7.4) [1445]
Radioligands (K_d)	[^{35}S]ADPβS (Agonist), [^{3}H]2MeSADP (Agonist), [^{3}H]MRS2279 (Antagonist) ($8x10^{-9}$ M) [1461]	–	–	–

Nomenclature	$P2Y_{11}$ receptor	$P2Y_{12}$ receptor	$P2Y_{13}$ receptor	$P2Y_{14}$ receptor
HGNC, UniProt	*P2RY11*, Q96G91	*P2RY12*, Q9H244	*P2RY13*, Q9BPV8	*P2RY14*, Q15391
Principal transduction	G_s, $G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{q/11}$
Rank order of potency	ATP>UTP	ADP>>ATP	ADP>>ATP	UDP-glucose
Endogenous agonists (pK_i)	–	ADP (5.9) [1432], ATP (5.2) [1432]	–	–
Selective agonists (pK_i)	NAADP [1452], NAD [1453], AR-C67085 (pEC_{50} 8.52) [1413,1424], NF546 (pEC_{50} 6.27) [1449]	2MeSADP (9.2) [1432]	–	MRS2690 (pEC_{50} 6.64 – 7.31) [1430,1442]
Selective antagonists (pK_i)	NF157 (7.35) [1460], NF340 (pIC_{50} 6.4 – 7.1) [1449]	PSB-0739 (7.6) [1414], ARL66096 (pIC_{50} 7.95) [1433–1434]	MRS2211 (pIC_{50} 5.97) [1439]	–
Radioligands (K_d)	–	[^{3}H]PSB-0413 (Antagonist) ($3.16x10^{-9}$ – $4.57x10^{-9}$ M) [1425,1455], [^{3}H]2MeSADP (Agonist, Full agonist) (IC_{50} $2.5x10^{-10}$ – $3.16x10^{-8}$ M) [1459]	–	–

Comments: AR-C69931MX (cangrelor) shows selectivity for $P2Y_{12}$ and $P2Y_{13}$ receptors compared with other P2Y receptors [1446,1459]. NF157 also has antagonist activity at $P2X_1$ receptors [1460]. UDP has been reported to be an antagonist at the $P2Y_{14}$ receptor [1428].

An orphan GPCR suggested to be a '$P2Y_{15}$' receptor [1435] appears not to be a genuine nucleotide receptor [1411], but rather responds to dicarboxylic acids [1431]. Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a $p2y_3$ receptor (ENSGALG00000017327), couples to the $G_{q/11}$ family of G proteins and shows the rank order of potency ADP > UTP > ATP = UDP [1462]. In addition, human sources have yielded a clone with a preliminary identification of p2y5 (*LPAR6*, P43657) and contradictory evidence of responses to ATP [1440,1463]. This protein is now classified as LPA_4, a receptor for lysophosphatidic acid (LPA) [1456,1464]. The clone clone termed p2y9 (*LPAR4*, 99677, [1454]). The clone p2y7 (*NOP9*, Q86U38), originally suggested to be a P2Y receptor [1412], has been shown to encode a leukotriene receptor [1465]. A P2Y receptor that was initially termed a p2y8 receptor (P79928) has been cloned from *Xenopus* laevis; it shows the rank order of potency ADPβS > ATP = UTP = GTP = CTP = TTP = ITP > ATPγS and elicits a Ca^{2+}-dependent Cl- current in Xenopus oocytes [1417]. The p2y10 clone (*P2RY10*, O00398) lacks functional data. Diadenosine polyphosphates also have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap_4A > Ap5a > Ap3a, coupling via $G_{q/11}$ [1419]. P2Y-like receptors have recently been described on mitochondria [1415]. CysLT1 and CysLT2 leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes LTC_4 and LTD_4 [1450–1451]; Human GPR17 (13304) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes as well as UDP and UDP-glucose [1422]. Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and cangrelor [1422].

Further reading

Abbracchio MP, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Miras-Portugal MT, King BF, Gachet C, Jacobson KA, Weisman GA, Burnstock G. (2003) Characterization of the UDP-glucose receptor (re-named here the P2Y14 receptor) adds diversity to the P2Y receptor family. *Trends Pharmacol Sci* **24**: 52–55. [PMID:12559763]

Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C, Jacobson KA *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]

Burnstock G. (2007) Purine and pyrimidine receptors. *Cell Mol Life Sci* **64**: 1471–1483. [PMID:17375261]

Burnstock G. (2008) Purinergic signalling and disorders of the central nervous system. *Nat Rev Drug Discov* **7**: 575–590. [PMID:18591979]

Erlinge D, Burnstock G. (2008) P2 receptors in cardiovascular regulation and disease. *Purinergic Signal* **4**: 1–20. [PMID:18368530]

Jacobson KA, Ivanov AA, de Castro S, Harden TK, Ko H. (2009) Development of selective agonists and antagonists of P2Y receptors. *Purinergic Signalling* **5**: 75–89. [PMID:18600475]

Parathyroid hormone receptors

Overview: The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor (PTH_1 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)). The parathyroid hormone 2 receptor (PTH_2 receptor) is activated by the precursor-derived peptide TIP39 (39 amino acids, *PTH2*, Q96A98). [^{125}I]PTH may be used to label both PTH_1 and PTH_2 receptors.

Nomenclature	PTH1 receptor	PTH2 receptor
HGNC, UniProt	*PTH1R*, Q03431	*PTH2R*, P49190
Principal transduction	G_s, $G_{q/11}$	G_s, $G_{q/11}$
Rank order of potency	PTH = PTHrP	TIP39, PTH >> PTHrP
Endogenous agonists (pK_i)	–	TIP39 (pIC_{50} 7.6 – 9.2) [1468–1469]
Selective agonists (pK_i)	PTHrP-(1-34) (pIC_{50} 7.8 – 8.1 - Rat) [1467], PTH-(1-34) (human) (pIC_{50} 7.4) [1466]	–

Comments: Although PTH (*PTH*, P01270) is an agonist at human PTH_2 receptors, it fails to activate the rodent orthologues. TIP39 (*PTH2*, Q96A98) is a weak antagonist at PTH_1 receptors [1470].

Further reading

Datta NS, Abou-Samra AB. (2009) PTH and PTHrP signaling in osteoblasts. *Cell Signal* **21**: 1245–1254. [PMID:19249350]

Dobolyi A, Palkovits M, Usdin TB. (2010) The TIP39-PTH2 receptor system: unique peptidergic cell groups in the brainstem and their interactions with central regulatory mechanisms. *Prog Neurobiol* **90**: 29–59. [PMID:19857544]

Gesty-Palmer D, Chen M, Reiter E, Ahn S, Nelson CD, Wang S, Eckhardt AE, Cowan CL, Spurney RF, Luttrell LM, Lefkowitz RJ. (2006) Distinct beta-arrestin- and G protein-dependent pathways for parathyroid hormone receptor-stimulated ERK1/2 activation. *J Biol Chem* **281**: 10856–10864. [PMID:16492667]

Guerreiro PM, Renfro JL, Power DM, Canario AV. (2007) The parathyroid hormone family of peptides: structure, tissue distribution, regulation, and potential functional roles in calcium and phosphate balance in fish. *Am J Physiol Regul Integr Comp Physiol* **292**: R679–R696. [PMID:17023665]

Kraenzlin ME, Meier C. (2011) Parathyroid hormone analogues in the treatment of osteoporosis. *Nat Rev Endocrinol* [Epub ahead of print]. [PMID:21750510]

Mierke DF, Mao L, Pellegrini M, Piserchio A, Plati J, Tsomaia N. (2007) Structural characterization of the parathyroid hormone receptor domains determinant for ligand binding. *Biochem Soc Trans* **35** (Pt 4): 721–723. [PMID:17635133]

Naveh-Many T. (2010) Minireview: the play of proteins on the parathyroid hormone messenger ribonucleic Acid regulates its expression. *Endocrinology* **151**: 1398–1402. [PMID:20032048]

Silva BC, Bilezikian JP. (2011) New approaches to the treatment of osteoporosis. *Annu Rev Med* **62**: 307–322. [PMID:21054170]

Silver J, Naveh-Many T. (2009) Phosphate and the parathyroid. *Kidney Int* **75**: 898–905. [PMID:19129794]

Vilardaga JP, Romero G, Friedman PA, Gardella TJ. (2011) Molecular basis of parathyroid hormone receptor signaling and trafficking: a family B GPCR paradigm. *Cell Mol Life Sci* **68**: 1–13. [PMID:20703892]

Peptide P518 receptor

Overview: The peptide P518 receptor is also known as the QRFP receptor and responds to the endogenous peptide agonist QRFP.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Radioligands (K_d)
QRFP receptor	*QRFPR*, Q96P65	$G_{q/11}$, $G_{i/o}$ [1471]	QRFP26 (*QRFP*) (pEC_{50} 8.15) [1472], QRFP (*QRFP*, P83859) (pIC_{50} 7.8 – 9.28 – Rat) [1471,1474]	[^{125}I]QRFP (human) (Agonist, Full agonist) ($5.01x10^{-11}$ – $1.58x10^{-8}$ M) [1471,1473–1474]

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

Further reading

Fukusumi S, Fujii R, Hinuma S. (2006) Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. *Peptides* **27**: 1073–1086. [PMID:16500002]

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, see [1475]) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1479] and lysophosphatidylcholine [1482]. It may also be activated by bacterial lipopolysaccharide [1481].

Nomenclature	HGNC, UniProt	Principal transduction	Selective agonists (pK_i)	Selective antagonists (pK_i)	Radioligands (K_d)
PAF receptor	*PTAFR*, P25105	$G_{q/11}$, G_i, G_o	mc-PAF	SR 27417 (10.3) [1478], L659989 (8.1), ginkgolide B (6.4), apafant (5.2 – 7.5) [1483–1484], CV-6209 (pIC_{50} 8.1 – 8.3) [1477,1480]	[^{3}H]PAF (Agonist, Full agonist) ($1.6x10^{-9}$ – $1.3x10^{-9}$ M) [1476,1480]

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

Further reading

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Grigg J. (2012) The platelet activating factor receptor: a new anti-infective target in respiratory disease?. *Thorax* **67**: 840–841. [PMID:22802333]

Petho G, Reeh PW. (2012) Sensory and signaling mechanisms of bradykinin, eicosanoids, platelet-activating factor, and nitric oxide in peripheral nociceptors. *Physiol Rev* **92**: 1699–1775. [PMID:23073630]

Sirangelo I, Irace G, Balestrieri ML. (2013) Amyloid toxicity and platelet-activating factor signaling. *J Cell Physiol* **228**: 1143–1148. [PMID:23169529]

Yost CC, Weyrich AS, Zimmerman GA. (2010) The platelet activating factor (PAF) signaling cascade in systemic inflammatory responses. *Biochimie* **92**: 692–697. [PMID:20167241]

Prokineticin receptors

Overview: Prokineticin receptors (provisional nomenclature, [1486]) 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, [1491]) is a potent, non-selective agonist at prokineticin receptors [1488], while Bv8, an orthologue of PROK2 from amphibians (*Bombina sp.*, [1489]), is equipotent at recombinant PK_1 and PK_2 receptors [1490], and has high potency in macrophage chemotaxis assays, which are lost in PK_1-null mice [1485].

Nomenclature	PKR_1	PKR_2
HGNC, UniProt	*PROKR1*, Q8TCW9	*PROKR2*, Q8NFJ6
Principal transduction	$G_{q/11}$ [1487–1488]	$G_{q/11}$ [1487–1488]
Rank order of potency	prokineticin-2 > prokineticin-1 [1487–1488,1492]	prokineticin-2 > prokineticin-1 [1487–1488,1492]

Further reading

Balasubramanian R, Plummer L, Sidis Y, Pitteloud N, Martin C, Zhou QY, Crowley WF. (2011) The puzzles of the prokineticin 2 pathway in human reproduction. *Mol Cell Endocrinol* **346**: 44–50. [PMID:21664414]

Boulberdaa M, Urayama K, Nebigil CG. (2011) Prokineticin receptor 1 (PKR1) signalling in cardiovascular and kidney functions. *Cardiovasc Res* **92**: 191–198. [PMID:21856786]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Martin C, Balasubramanian R, Dwyer AA, Au MG, Sidis Y, Kaiser UB, Seminara SB, Pitteloud N, Zhou QY, Crowley Jr WF. (2011) The role of the prokineticin 2 pathway in human reproduction: evidence from the study of human and murine gene mutations. *Endocr Rev* **32**: 225–246. [PMID:21037178]

Negri L, Lattanzi R, Giannini E, Melchiorri P. (2007) Bv8/Prokineticin proteins and their receptors. *Life Sci* **81**: 1103–1116. [PMID:17881008]

Prolactin-releasing peptide receptor

Overview: The precursor (*PRLH*, P81277) for PrRP generates 31 and 20-amino-acid versions. QRFP (*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 [1495] derived from a FMRFamide-related peptide precursor (*NPVF*, Q9HCQ7), which is cleaved to generate neuropeptide NPSF (*NPFF*, O15130), neuropeptide RFRP-1 (*NPVF*, Q9HCQ7), neuropeptide RFRP-2 (*NPVF*, Q9HCQ7) and neuropeptide RFRP-3 (*NPVF*, Q9HCQ7) (neuropeptide NPVF).

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Endogenous agonists (pK_i)	Endogenous antagonists (pK_i)	Radioligands (K_d)
PRRP receptor	*PRLHR*, P49683	$G_{q/11}$ [1497]	PrRP-20, PrRP-31 [1497]	PrRP-20 (Selective) (9.0–9.6) [1494,1497], PrRP-31 (Selective) (9.0–9.2) [1494,1497]	NPY (*NPY*, P01303) (Selective) (5.4) [1496]	[^{125}I]PrRP31 [1493], [^{125}I]PrRP-20 (human) (Agonist, Full agonist) (2.6×10^{-11}–5.7×10^{-10} M) [1497]

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

Further reading

Samson WK, Taylor MM. (2006) Prolactin releasing peptide (PrRP): an endogenous regulator of cell growth. *Peptides* **27**: 1099–1103. [PMID:16500730]

Takayanagi Y, Onaka T. (2010) Roles of prolactin-releasing peptide and RFamide related peptides in the control of stress and food intake. *FEBS J* **277**: 4998–5005. [PMID:21126313]

Prostanoid receptors

Overview: Prostanoid receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors, [1512]) are activated by the endogenous ligands prostaglandins PGD_2, PGE_2 , $PGF_{2\alpha}$, PGH_2, prostacyclin [PGI_2] and thromboxane A_2. 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.

Nomenclature	DP_1 receptor	DP_2 receptor	FP receptor	IP_1 receptor	TP receptor
HGNC, UniProt	*PTGDR*, Q13258	*PTGDR2*, Q9Y5Y4	*PTGFR*, P43088	*PTGIR*, P43119	*TBXA2R*, P21731
Principal transduction	G_s	$G_{i/o}$	$G_{q/11}$	–	$G_{q/11}$
Rank order of potency	PGD_2 >> PGE_2 > $PGF_{2\alpha}$ > PGI_2, thromboxane A_2	PGD_2 >> $PGF_{2\alpha}$, PGE_2 > PGI_2, thromboxane A_2	$PGF_{2\alpha}$ > PGD_2 > PGE_2 > PGI_2, thromboxane A_2	PGI_2 >> PGD_2, PGE_2, $PGF_{2\alpha}$ > thromboxane A_2	thromboxane A_2 = PGH_2 >> PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2
Selective agonists (pK_i)	L-644,698 (9.0–9.3) [1563–1564], BW 245C (8.4–9.4) [1506,1563–1564], SQ-27986 (8.0) [1545], RS 93520 (Partial agonist) (7.5) [1545], ZK118182 (7.3) [1545]	15(*R*)-15-methyl-PGD_2 (8.9) [1518,1533,1552], 13,14-dihydro-15-keto-PGD_2 (7.4–8.5) [1518,1544,1552]	fluprostenol (8.6) [1498], latanoprost (free acid form) (8.6) [1498], AL12180 (pEC_{50} 7.7–7.9) [1547]	cicaprost (7.8) [1498], AFP-07 (pIC_{50} 8.5) [1508], BMY 45778 (pIC_{50} 8.0) [1520]	I-BOP (pK_d 8.94–9.32) [1532], U46619 (7.5) [1498], STA_2 (pIC_{50} 6.38–7.06) [1502]
Selective antagonists (pK_i)	laropiprant (10.1) [1550], BWA868C (8.6–9.3) [1506,1517,1563], S-5751 (8.8) [1501]	ramatroban (7.4) [1552] , CAY 10471 (pIC_{50} 8.92) [1543,1556]	AS604872 (7.5) [1510]	RO3244794 (pA_2 8.5) [1503], RO1138452 (8.7) [1503]	ifetroban (8.4–10.0) [1538], GR 32191 (8.3–9.4) [1502,1528], SQ-29548 (8.1–9.1) [1498,1554,1559], ONO 3708 (7.4–8.9) [1522]
Radioligands (K_d)	[^{3}H]PGD_2 (Agonist, Full agonist) (1.3×10^{-8} – 3×10^{-10} M) [1559,1563]	[^{3}H]PGD_2 (Agonist, Full agonist) (1.6×10^{-8} – 6×10^{-9} M) [1530,1548]	[^{3}H]$PGF_{2\alpha}$ (Agonist, Full agonist) (7.9×10^{-9} – 1×10^{-9} M) [1498–1499,1559], [^{3}H](+)-fluprostenol (Agonist) (3.4×10^{-8} M)	[^{3}H]iloprost (Agonist, Full agonist) (2×10^{-8} – 1×10^{-9} M) [1498,1505,1559]	[^{125}I]BOP (Agonist, Full agonist) (2×10^{-9} M) [1534], [^{125}I]SAP (Antagonist) (2×10^{-8} – 5×10^{-10} M) [1536], [^{3}H]SQ-29548 (Antagonist) (4×10^{-8} – 6.3×10^{-9} M) [1498,1559]

Nomenclature	EP_1 receptor	EP_2 receptor	EP_3 receptor	EP_4 receptor
HGNC, UniProt	*PTGER1*, P34995	*PTGER2*, P43116	*PTGER3*, P43115	*PTGER4*, P35408
Principal transduction	$G_{q/11}$	G_s	$G_{i/o}$	G_s
Rank order of potency	$PGE_2 > PGF_{2\alpha}$, $PGI_2 > PGD_2$, thromboxane A_2	$PGE_2 > PGF_{2\alpha}$, $PGI_2 > PGD_2$, thromboxane A_2	$PGE_2 > PGF_{2\alpha}$, $PGI_2 > PGD_2$, thromboxane A_2	$PGE_2 > PGF_{2\alpha}$, $PGI_2 > PGD_2$, thromboxane A_2
Selective agonists (pK_i)	17-phenyl-ω-trinor-PGE_2 (8.1) [1546], ONO-DI-004 (6.8 - Mouse) [1553]	ONO-AE1-259 (8.5 - Mouse) [1553], butaprost (free acid form) (5.9–7.0) [1498,1549], CP-533536 (pIC_{50} 7.3 - Rat) [1507]	SC46275 (pEC_{50} 8.74 - Rat) [1519], ONO-AE-248 (pEC_{50} 5.64–6.7) [1514,1527]	L902688 (pEC_{50} 8.05–10.3) [1515,1525], ONO-AE1-329 (pEC_{50} 7.66–7.8) [1514–1515], CP734432 (pIC_{50} 8.7) [1540]
Selective antagonists (pK_i)	ONO-8711 (9.2) [1557], SC-51322 (7.9) [1498], GW848687X (pIC_{50} 8.6) [1516]	–	L-798,106 (9.52–9.62) [1521,1551], ONO-AE3-240 (pIC_{50} 8.8 - Mouse) [1500]	MK-2894 (9.25) [1498,1504,1511], CP-533536 (8.6) [1535], ONO-AE3-208 (8.5), EP_4A (7.6–8.5) [1529,1565], BGC201531 (7.9) [1531], GW 627368 (7.0–7.1) [1559–1560], ER819762 (pIC_{50} 7.15) [1509]
Radioligands (K_d)	[^{3}H]PGE_2 (Agonist, Full agonist) (1×10^{-9} – 2.5×10^{-8} M) [1498,1546,1559]	[^{3}H]PGE_2 (Agonist, Full agonist) (1.25×10^{-8} – 1.99×10^{-8} M) [1498,1559]	[^{3}H]PGE_2 (Agonist, Full agonist) (3×10^{-10} – 7×10^{-9} M) [1498,1559]	[^{3}H]PGE_2 (Agonist, Full agonist) (2.4×10^{-8} – 3×10^{-10} M) [1498,1513,1558–1559]

Comments: ramatroban is also a TP receptor antagonist. cicaprost exhibits moderate EP_4 receptor agonist potency [1498]. iloprost also binds to EP_1 receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail [1542].

17-phenyl-ω-trinor-PGE_2 also shows agonist activity at EP_3 receptors. sulprostone also has affinity for EP_1 receptors. butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1526], IP [1555,1561] and TP [1524] receptors. mRNA for the EP_1 and EP_3 receptors undergo alternative splicing to produce two [1539] and at least six variants, respectively, which can interfere with signalling [1539] or generate complex patterns of G-protein ($G_{i/o}$, $G_{q/11}$, G_s and $G_{12,13}$) coupling (*e.g.* [1523,1537]). The possibility of additional receptors for the isoprostanes has been suggested [1541]. Receptors (prostamide F, which as yet lack a molecular correlate) that preferentially recognize PGF2-1-ethanolamide and its analogues (*e.g.* bimatoprost) have been identified, together with moderate-potency antagonists (*e.g.* AGN 211334) [1562].

The free acid form of AL-12182, AL-12180, used in *in vitro* studies, has a EC_{50} value of 15nM which is the concentration of the compound giving half-maximal stimulation of IP turnover in HEK-293 cells expressing the human FP receptor [1547].

References given alongside the TP receptor agonists I-BOP [1532] and STA_2 [1502] use human platelets as the source of TP receptors for competition radio-ligand binding assays to determine the indicated activity values.

Further reading

af Forselles KJ, Root J, Clarke T, Davey D, Aughton K, Dack K, Pullen N. (2011) In vitro and in vivo characterization of PF-04418948, a novel, potent and selective prostaglandin EP_2 receptor antagonist. *Br J Pharmacol* **164**: 1847–1856. [PMID:21595651]

Billot X, Chateauneuf A, Chauret N, Denis D, Greig G, Mathieu MC, Metters KM, Slipetz DM, Young RN. (2003) Discovery of a potent and selective agonist of the prostaglandin EP4 receptor. *Bioorg Med Chem Lett* **13**: 1129–1132. [PMID:12643927]

Félétou M, Huang Y, Vanhoutte PM. (2010) Vasoconstrictor prostanoids. *Pflugers Arch* **459**: 941–950. [PMID:20333529]

Félétou M, Vanhoutte PM, Verbeuren TJ. (2010) The thromboxane/endoperoxide receptor (TP): the common villain. *J Cardiovasc Pharmacol* **55**: 317–332. [PMID:20422736]

Schuligoi R, Sturm E, Luschnig P, Konya V, Philipose S, Sedej M, Waldhoer M, Peskar BA, Heinemann A. (2010) CRTH2 and D-type prostanoid receptor antagonists as novel therapeutic agents for inflammatory diseases. *Pharmacology* **85**: 372–382. [PMID:20559016]

Woodward DF, Jones RL, Narumiya S. (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]

Yang C, Liu X, Cao Q, Liang Q, Qiu X. (2011) Prostaglandin E receptors as inflammatory therapeutic targets for atherosclerosis. *Life Sci* **88**: 201–205. [PMID:21112342]

Proteinase-activated receptors

Overview: Proteinase-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Protease-activated Receptors, [1574]) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmasks a tethered ligand (TL) at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. TL sequences at human PAR1–4 are SFLLRN-NH2, SLIGKV-NH_2, TFRGAP-NH2 and GYPGQV-NH_2, respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation of Gαq-coupled calcium signaling, thereby preventing activation by activating proteinases but not by agonist peptides. Neutrophil elastase cleavage of PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [1581]. The role of such an action *in vivo* is unclear.

Nomenclature	PAR1	PAR2	PAR3	PAR4
HGNC, UniProt	*F2R*, P25116	*F2RL1*, P55085	*F2RL2*, O00254	*F2RL3*, Q96RI0
Principal transduction	$G_{q/11}/G_{i/o}/G_{12/13}$	$G_{q/11}/G_{i/o}$	Not known	$G_{q/11}/G_{i/o}$
Agonist proteases	thrombin (*F2*, P00734), activated protein C (*PROC*, P04070), matrix metalloproteinase 1 (*MMP1*, P45452), matrix metalloproteinase 13 (*MMP13*, P45452) [1569]	Trypsin, tryptase, TF/VIIa, Xa	thrombin (*F2*, P00734)	thrombin (*F2*, P00734), trypsin, cathepsin G (*CTSG*, P08311)
Selective agonists (pK_i)	TFLLR-NH_2 (pEC_{50} 5.41) [1573]	SLIGKV-NH_2 [1579], SLIGRL-NH_2 [1579], 2-furoyl-LIGRLO-amide (5.4) [1580], GB 110 (pEC_{50} 6.55) [1570],	–	AYPGKF-NH2, GYPGKF-NH2, GYPGQV-NH_2
Selective antagonists (pK_i)	SCH530348 (8.09) [1572], atopaxar (pIC_{50} 7.72) [1578], RWJ-56110 (pIC_{50} 6.36) [1568]	P2pal18s [1582], GB88 (pIC_{50} 5.7) [1583]	–	–
Radioligands (K_d)	[^{3}H]haTRAP (Agonist) ($1.5x10^{-8}$ M) [1566]	2-furoyl-LIGRL[N[^{3}H]propionyl]-O-NH_2 [1575], [^{3}H]2-furoyl-LIGRL-NH_2 (Agonist) [1576], trans-cinnamoyl-LIGRLO [N-[^{3}H]propionyl]-NH_2 [1567]	–	–

Comments: TFLLR-NH_2 is selective relative to the PAR_2 receptor [1571,1577]. thrombin (*F2*, P00734) is inactive at the PAR_2 receptor.

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).

2-Furoyl-LIGRLO-NH_2 activity was measured via calcium mobilisation in HEK 293 cells which constitutively coexpress human PAR_1 and PAR_2.

Further reading

Adams MN, Ramachandran R, Yau MK, Suen JY, Fairlie DP, Hollenberg MD, Hooper JD. (2011) Structure, function and pathophysiology of protease activated receptors. *Pharmacol Ther* **130**: 248–282. [PMID:21277892]

Canto I, Soh UJ, Trejo J. (2012) Allosteric modulation of protease-activated receptor signaling. *Mini Rev Med Chem* **12**: 804–811. [PMID:22681248]

García PS, Gulati A, Levy JH. (2010) The role of thrombin and protease-activated receptors in pain mechanisms. *Thromb Haemost* **103**: 1145–1151. [PMID:20431855]

Hollenberg MD, Compton SJ. (2002) International Union of Pharmacology. XXVIII. Proteinase-activated receptors. *Pharmacol Rev* **54**: 203–217. [PMID:12037136]

Ramachandran R, Noorbakhsh F, Defea K, Hollenberg MD. (2012) Targeting proteinase-activated receptors: therapeutic potential and challenges. *Nat Rev Drug Discov* **11**: 69–86. [PMID:22212680]

Soh UJ, Dores MR, Chen B, Trejo J. (2010) Signal transduction by protease-activated receptors. *Br J Pharmacol* **160**: 191–203. [PMID:20423334]

Vergnolle N. (2009) Protease-activated receptors as drug targets in inflammation and pain. *Pharmacol Ther* **123**: 292–309. [PMID:19481569]

Relaxin family peptide receptors

Overview: Relaxin family peptide receptors (RXFP, nomenclature as recommended by the NC-IUPHAR committee on relaxin family peptide receptors, [1584]) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: H1 relaxin (*RLN1*, P04808), H2 relaxin (*RLN2*, P04090), H3 relaxin (*RLN3*, Q8WXF3) (also known as INSL7), insulin-like peptide 3 (INSL3 (*INSL3*, P51460)) and INSL5 (*INSL5*, Q9Y5Q6).

Species homologues of relaxin have distinct pharmacology – H2 relaxin (*RLN2*, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [1611] and porcine relaxin may have a higher efficacy than H2 relaxin (*RLN2*, P04090) [1591]. H3 relaxin (*RLN3*, Q8WXF3) has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (*RLN3*, Q8WXF3) [1610]. At least two binding sites have been identified on the RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane domain [1591,1618]. The unique N-terminal LDLa module of RXFP1 and RXFP2 is essential for receptor signalling [1612].

Nomenclature	RXFP1 receptor	RXFP2 receptor	RXFP3 receptor	RXFP4 receptor
HGNC, UniProt	*RXFP1*, Q9HBX9	*RXFP2*, Q8WXD0	*RXFP3*, Q9NSD7	*RXFP4*, Q8TDU9
Principal transduction	G_s, $G_{\alpha oB}$, $G_{\alpha i3}$ [1590,1595,1599]	G_s, $G_{\alpha oB}$ [1590,1601]	$G_{i/o}$ [1606,1620]	$G_{i/o}$ [1604]
Rank order of potency	H2 relaxin > H3 relaxin >> INSL3 [1618]	INSL3 > H2 relaxin >> H3 relaxin [1601,1618]	H3 relaxin > H3 relaxin (B chain) [1604]	INSL5 = H3 relaxin > H3 relaxin (B chain) [1602–1603]
Endogenous antagonists (pK_i)	–	–	INSL5 (pIC_{50} 6.3) [1605]	–
Selective antagonists (pK_i)	LGR7-truncate [1612], B-R13/17K H2 relaxin (pEC_{50} 6.7) [1597],	(des 1-8) A-chain INSL3 analogue [1586], INSL3 B-chain analogue [1587], INSL3 B chain dimer [1616],	H3 relaxin analogue 3 [1613], R3(BΔ23-27)R/I5 chimeric peptide (pIC_{50} 9.2) [1600], R3-B1-22R (pIC_{50} 7.4) [1596]	R3(BΔ23-27)R/I5 chimeric peptide (pIC_{50} 8.64) [1600]
Radioligands (K_d)	[^{125}I]H2 relaxin (Agonist, Full agonist), [^{33}P]H2 relaxin (Agonist, Full agonist) ($5x10^{-10}$–$2x10^{-10}$ M) [1591,1618],	[^{125}I]INSL3 (human) (Agonist, Full agonist) ($1x10^{-10}$ M) [1608], [^{33}P]H2 relaxin (Agonist, Full agonist) ($1.06x10^{-9}$–$6.3x10^{-10}$ M) [1591,1618],	[^{125}I]H3 relaxin (Agonist, Full agonist) ($3x10^{-10}$ M) [1604], [^{125}I]H3-B/INSL5 A chimera (Agonist) ($5x10^{-10}$ M) [1602],	[^{125}I]H3 relaxin (Agonist, Full agonist) ($2x10^{-9}$–$2x10^{-10}$ M) [1603], [^{125}I]H3-B/INSL5 A chimera (Agonist) ($1.2x10^{-9}$ M) [1602],
Comment	europium-labelled H2 relaxin is a fluorescent ligand for this receptor (Kd=0.5 nM) [1614].	europium-labelled INSL3 is a fluorescent ligand for this receptor (Kd=1 nM) [1615].	europium-labelled H3-B/INSL5 A chimera is a fluorescent ligand for this receptor (Kd=5 nM) [1596].	europium-labelled H3-B/INSL5 A chimera is a fluorescent probe at this receptor (Kd=5 nM) [1596], europium-labelled mouse INSL5 is a fluorescent ligand at this receptor (Kd=5 nM) [1585].

Comments: H2 relaxin has recently successfully completed a Phase III clinical trial for the treatment of acute heart failure. 48 hr infusion of H2 relaxin reduced dyspnoea and 180 day mortality [1607]. Small molecule agonists active at RXFP1 receptors have been developed [1617,1622]. Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism [1588]. Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, most of which do not bind relaxin family peptides [1608]. Splice variants of RXFP1 encoding the N-terminal LDLa module act as antagonists of RXFP1 signalling [1610,1612]. cAMP elevation appears to be a major signalling pathway for RXFP1 and RXFP2 [1598–1599], but RXFP1 also activates MAP kinases, nitric oxide signalling and interacts with tyrosine kinases and glucocorticoid receptors [1594]. RXFP1 signalling involves lipid rafts, residues in the C-terminus of the receptor and activation of phosphatidylinositol-3-kinase [1595]. More recent studies provide evidence that RXFP1 is pre-assembled in signalosomes with other signalling proteins including $G\alpha_s$, $G\beta\gamma$ and adenyl cyclase 2 that display constitutive activity and are exquisitely sensitive to sub-picomolar concentrations of relaxin [1592]. The cAMP signalling pattern is highly dependent on the cell type in which RXFP1 is expressed [1593].

The receptor expression profiles suggest that RXFP3 is a neuropeptide receptor and RXFP4 a gut hormone receptor. The relaxin 3 RXFP3 system has roles in feeding and anxiety [1589,1609]. H3 relaxin (*RLN3*, Q8WXF3) acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 (*INSL5*, Q9Y5Q6) is an agonist at RXFP4 and a weak antagonist at RXFP3. Unlike RXFP1 and RXFP2 both

RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino-acids at the N-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes [1621]. RXFP3 couples to $G_{i/o}$ and inhibits adenylyl cyclase [1604,1619], and also causes Erk1/2 phosphorylation [1619]. Relatively little is known about RXFP4 signalling but like RXFP3 it couples to inhibitory G-proteins [1605]. Recent studies suggest that H2 relaxin (*RLN2*, P04090) also interacts with RXFP3 to cause a pattern of activation of signalling pathways that are a subset of those activated by H3 relaxin (*RLN3*, Q8WXF3). The two patterns of signaling observed in several cell types expressing RXFP3 are strong inhibition of forskolin-stimulated cAMP accumulation, ERK1/2 activation and nuclear factor NFκ-B reporter gene activation with H3 relaxin (*RLN3*, Q8WXF3), and weaker activity with H2 relaxin (*RLN2*, P04090), porcine relaxin, or insulin-like peptide 3 (INSL3 (*INSL3*, P51460)) and a strong stimulation of activator protein (AP)-1 reporter genes with H2 relaxin (*RLN2*, P04090), and weaker activation with H3 relaxin (*RLN3*, Q8WXF3) or porcine relaxin [1619]. Two pharmacologically distinct ligand binding sites were also identified on RXFP3-expressing cells using [^{125}I]H3-B/INSL5 A chimera which binds with high affinity with competition by H3 relaxin (*RLN3*, Q8WXF3) or a H3 relaxin (B chain) (*RLN3*, Q8WXF3) peptide, and [^{125}I]H2 relaxin which displays competition by H2 relaxin (*RLN2*, P04090), H3 relaxin (*RLN3*, Q8WXF3), or INSL3 (*INSL3*, P51460) and weakly by porcine relaxin. Thus at RXFP3, H2 relaxin (*RLN2*, P04090) is a biased ligand compared to the cognate ligand H3 relaxin (*RLN3*, Q8WXF3).

Further reading

Bathgate RA, Halls ML, van der Westhuizen ET, Callander GE, Kocan M, Summers RJ. (2013) Relaxin family peptides and their receptors. *Physiol Rev* **93**: 405–480. [PMID:23303914]

Bathgate RA, Ivell R, Sanborn BM, Sherwood OD, Summers RJ. (2006) International Union of Pharmacology LVII: recommendations for the nomenclature of receptors for relaxin family peptides. *Pharmacol Rev* **58**: 7–31. [PMID:16507880]

Callander GE, Bathgate RA. (2010) Relaxin family peptide systems and the central nervous system. *Cell Mol Life Sci* **67**: 2327–2341. [PMID:20213277]

Du XJ, Bathgate RA, Samuel CS, Dart AM, Summers RJ. (2010) Cardiovascular effects of relaxin: from basic science to clinical therapy. *Nat Rev Cardiol* **7**: 48–58. [PMID:19935741]

Ivell R, Kotula-Balak M, Glynn D, Heng K, Anand-Ivell R. (2011) Relaxin family peptides in the male reproductive system–a critical appraisal. *Mol Hum Reprod* **17**: 71–84. [PMID:20952422]

Kong RC, Shilling PJ, Lobb DK, Gooley PR, Bathgate RA. (2010) Membrane receptors: structure and function of the relaxin family peptide receptors. *Mol Cell Endocrinol* **320**: 1–15. [PMID:20138959]

van der Westhuizen ET, Halls ML, Samuel CS, Bathgate RA, Unemori EN, Sutton SW, Summers RJ. (2008) Relaxin family peptide receptors–from orphans to therapeutic targets. *Drug Discov Today* **13**: 640–651. [PMID:18675759]

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 approved by the NC-IUPHAR Subcommittee on Somatostatin Receptors**, [1628]). Activation of these receptors produces a wide range of physiological effects throughout the body including inhibiting the secretion of many hormones. The relationship of the cloned receptors to endogenously expressed receptors is not yet well established in some cases. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14 (*SST*, P61278)) and somatostatin-28 (SRIF-28 (*SST*, P61278)). Cortistatin (CST-14) has also been suggested to be an endogenous ligand for somatostatin receptors [1625].

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
Principal transduction	G_i	G_i	G_i	G_i	G_i
Selective agonists (pK_i)	L-797,591 (8.8) [1635], Des-Ala^{1,2,5}-[D-Trp^8,IAmp^9]SRIF (pIC_{50} 7.5) [1626]	L-054,522 (11.0) [1640], MK-678 (8.8 – 10.3) [1623,1634,1636–1638,1640], octreotide (8.7 – 9.9) [1623,1634,1636–1638,1640], BIM 23027 (pIC_{50} 10.85) [1624]	L-796,778 (7.6) [1635]	L-803,087 (9.2) [1635], NNC269100 (8.2) [1631]	L-817,818 (9.4) [1635], BIM 23268 (8.7) [1632], BIM 23052 (7.4 – 9.6) [1632,1636–1638]
Selective antagonists (pK_i)	SRA880 (pK_d 8.0 – 8.1) [1629]	[D-Tyr^8]CYN 154806 (pK_d 8.1 – 8.9) [1633]	NVP ACQ090 (7.9) [1630]	–	BIM 23627 (pIC_{50} 7.1) [1639]
Radioligands (K_d)	–	[^{125}I]Tyr^3 SMS 201-995 (Agonist, Full agonist) ($1.3x10^{-10}$ M) [1637–1638], [^{125}I]BIM23027 (Agonist, Full agonist) (IC_{50} $2.2x10^{-10}$ M - Rat) [1627]	–	–	[^{125}I]Tyr^3 SMS 201-995 (Agonist, Full agonist) ($2.3x10^{-10}$ M) [1637–1638]

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; BIM 23052 is said to be selective in rat but not human receptor [1634]. A number of nonpeptide subtype-selective agonists have been synthesised [1635].

Further reading

Ben-Shlomo A, Melmed S. (2010) Pituitary somatostatin receptor signaling. *Trends Endocrinol Metab* **21**: 123–133. [PMID:20149677]

Colao A, Auriemma RS, Lombardi G, Pivonello R. (2011) Resistance to somatostatin analogs in acromegaly. *Endocr Rev* **32**: 247–271. [PMID:21123741]

Csaba Z, Peineau S, Dournaud P. (2012) Molecular mechanisms of somatostatin receptor trafficking. *J Mol Endocrinol* **48**: R1–R12. [PMID:22159161]

Hoyer D, Epelbaum J, Feniuk W, Humphrey PPA, Meyerhof W, O'Carroll AM *et al*. (2000) Somatostatin receptors. *in* The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edn. *Edited by* Watson SP, Girdlestone D IUPHAR Media. 354–364.

Van Op den Bosch J, Adriaensen D, Van Nassauw L, Timmermans JP. (2009) The role(s) of somatostatin, structurally related peptides and somatostatin receptors in the gastrointestinal tract: a review. *Regul Pept* **156**: 1–8. [PMID:19362110]

Zatelli MC, degli Uberti E. (2009) The significance of new somatostatin analogs as therapeutic agents. *Curr Opin Investig Drugs* **10**: 1025–1031. [PMID:19777390]

Succinate receptor

Overview: the succinate receptor (NC-IUPHAR recommended nomenclature, see Davenport *et al.*, 2004) has been reported to respond to an intermediate of the citric acid cycle [1641].

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)
succinate receptor	*SUCNR1*, Q9BXA5	–	succinic acid (pEC_{50} 3.1–4.7) [1641–1642]

Further reading

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacological reviews* **65**: 967–986.

Tachykinin receptors

Overview: Tachykinin receptors (provisional nomenclature, [1658]) 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.

Nomenclature	NK_1 receptor	NK_2 receptor	NK_3 receptor
HGNC, UniProt	*TACR1*, P25103	*TACR2*, P21452	*TACR3*, P29371
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	substance P > neurokinin A > neurokinin B	neurokinin A > neurokinin B >> substance P	neurokinin B > neurokinin A > substance P
Selective agonists (pK_i)	[Pro^9]SP, septide (7.0–9.3) [1645,1663], [Sar^9,Met(O_2)^{11}]SP (pIC_{50} 9.7–9.9) [1673], substance P-OMe (pIC_{50} 7.4–7.5) [1673]	[βAla^8]neurokinin A-(4–10) (pK_d 6.0) [1656], GR64349 (pEC_{50} 8.4 – Rat) [1653], [Lys^5,Me-Leu^9,Nle^{10}]NKA-(4–10) (pIC_{50} 8.8–9.4 – Rat) [1667]	[Phe(Me)^7]neurokinin B (8.7–9.6) [1670–1671], senktide (7.1–8.6) [1670–1671,1673]
Selective antagonists (pK_i)	aprepitant (10.7) [1662], LY303870 (9.8–10.0) [1660], CP 99994 (9.3–9.7) [1643,1671], LY303870 (pIC_{50} 9.82) [1664], SR 140,333 (pIC_{50} 8.9–9.0) [1673], RP67580 (pIC_{50} 7.7) [1657]	GR159897 (pK_d 7.8–9.5) [1647,1656,1672], GR94800 (9.8) [1649], saredutant (9.4–9.7) [1643,1656,1671], MEN10627 (9.2), nepadutant (8.5–8.7) [1650,1652]	osanetant (8.4–9.7) [1643–1644,1651,1655,1665, 1668,1670–1671,1673], SB 223412 (7.4–9.0) [1646,1659,1670–1671], PD157672 (pIC_{50} 7.8) [1648]
Radioligands (K_d)	[^{125}I]SP (human, mouse, rat) (Agonist, Full agonist), [^{18}F]SPA-RQ (Antagonist), [^{3}H]BH-[Sar^9,Met(O_2)^{11}]SP, [^{3}H]SP (human, mouse, rat) (Agonist, Full agonist), [^{125}I]L703,606 (Antagonist) ($3x10^{-10}$ M), [^{125}I]BH-[Sar^9,Met(O_2)^{11}]SP (Agonist, Full agonist) ($1x10^{-9}$ M – Rat) [1674]	[^{125}I]NKA (human, mouse, rat), [^{3}H]GR100679, [^{3}H]SR48,968 (Antagonist) ($2x10^{-10}$ M – Rat) [1661]	[^{125}I][MePhe^7]NKB, [^{3}H]senktide, [^{3}H]SR142,801 (Antagonist) ($1.3x10^{-10}$ M)

Comments: The NK_1 receptor has also been described to couple to other G proteins [1669]. 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 suggestions for 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 [1654,1666].

Further reading

Commons KG. (2010) Neuronal pathways linking substance P to drug addiction and stress. *Brain Res* **1314**: 175–182. [PMID:19913520]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Pantaleo N, Chadwick W, Park SS, Wang L, Zhou Y, Martin B, Maudsley S. (2010) The mammalian tachykinin ligand-receptor system: an emerging target for central neurological disorders. *CNS Neurol Disord Drug Targets* **9**: 627–635. [PMID:20632965]

Rance NE, Krajewski SJ, Smith MA, Cholanian M, Dacks PA. (2010) Neurokinin B and the hypothalamic regulation of reproduction. *Brain Res* **1364**: 116–128. [PMID:20800582]

Rojas C, Slusher BS. (2012) Pharmacological mechanisms of 5-HT_3 and tachykinin NK_1 receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur J Pharmacol* **684**: 1–7. [PMID:22425650]

Tuluc F, Lai JP, Kilpatrick LE, Evans DL, Douglas SD. (2009) Neurokinin 1 receptor isoforms and the control of innate immunity. *Trends Immunol* **30**: 271–276. [PMID:19427266]

Thyrotropin-releasing hormone receptors

Overview: Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) 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 [1677]. [^{3}H]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.

Nomenclature	TRH_1 receptor	TRH_2 receptor
HGNC, UniProt	*TRHR*, P34981	*Trhr2*, Q9ERT2
Principal transduction	G_q	G_q
Selective antagonists (pK_i)	midazolam (5.49 - Rat) [1675], diazepam (5.15 - Rat) [1675], chlordiazepoxide (4.82 - Rat) [1675], chlordiazepoxide (4.7 - Mouse) [1676]	–
Comment	–	A class A G protein-coupled receptor: not present in man

Comments: The human orthologue of the rodent TRH_2 receptor has yet to be identified.

Further reading

Bílek R, Bičíková M, Šafařík L. (2011) TRH-like peptides. *Physiol Res* **60**: 207–215. [PMID:21114375]

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Nillni EA. (2010) Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Front Neuroendocrinol* **31**: 134–156. [PMID:20074584]

Trace amine receptor

Overview: Trace amine-associated receptors (nomenclature as agreed by NC-IUPHAR for trace amine receptors, [1680]) were initially discovered as a result of a search for novel 5-HT receptors [1678], where 15 mammalian orthologues were identified and divided into two families. The TA_1 receptor has been shown to have affinity for the endogenous trace amines tyramine, β-phenylethylamine and octopamine in addition to the classical amine dopamine [1678]. Emerging evidence suggests that TA_1 is a modulator of monoaminergic activity in the brain [1683] with TA_1 and dopamine D_2 receptors shown to form constitutive heterodimers when co-expressed [1679].

Nomenclature	HGNC, UniProt	Principal transduction	Rank order of potency	Radioligands (K_d)
TA_1 receptor	*TAAR1* (Hs), *Taar1* (Mm), *Taar1* (Rn), Q96RJ0	G_s	tyramine > β-phenylethylamine > octopamine = dopamine [1678]	[^{3}H]tyramine (Agonist, Full agonist) (2x10^{-8} M) [1678]

Comments: The product of the gene *TAAR2* (also known as GPR58) appears to respond to β-phenylethylamine > tyramine and to couple through G_s [1678] See Orphan GPCR (Page 1462).

TAAR3, in some individuals, and TAAR4 are pseudogenes in man, although functional in rodents. The signalling characteristics and pharmacology of TAA_5 (PNR, Putative Neurotransmitter Receptor: TAAR5, O14804), TAA_6 (Trace amine receptor 4, TaR-4: TAAR6, 96RI8), TAA_8 (Trace amine receptor 5, GPR102: TAAR8, Q969N4) and TAA_9 (trace amine associated receptor 9: TAAR9, 96RI9) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have been shown to have affinity for rodent cloned trace amine receptors, including TA_1 [1681]. An antagonist EPPTB has recently been described that has a pK_i of 9.1 at the mouse TA_1 but less than 5.3 for human TA_1 [1682].

Further reading

Burchett SA, Hicks TP. (2006) The mysterious trace amines: protean neuromodulators of synaptic transmission in mammalian brain. *Prog Neurobiol* **79**: 223–246. [PMID:16962229]

Grandy DK. (2007) Trace amine-associated receptor 1-Family archetype or iconoclast?. *Pharmacol Ther* **116**: 355–390. [PMID:17888514]

Maguire JJ, Parker WA, Foord SM, Bonner TI, Neubig RR, Davenport AP. (2009) International Union of Pharmacology. LXXII. Recommendations for trace amine receptor nomenclature. *Pharmacol Rev* **61**: 1–8. [PMID:19325074]

Miller GM. (2011) The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. *J Neurochem* **116**: 164–176. [PMID:21073468]

Sotnikova TD, Caron MG, Gainetdinov RR. (2009) Trace amine-associated receptors as emerging therapeutic targets. *Mol Pharmacol* **76**: 229–235. [PMID:19389919]

Zucchi R, Chiellini G, Scanlan TS, Grandy DK. (2006) Trace amine-associated receptors and their ligands. *Br J Pharmacol* **149**: 967–978. [PMID:17088868]

Urotensin receptor

Overview: The urotensin-II (U-II) receptor (UT, nomenclature as agreed by NC-IUPHAR, [1691,1694]) is activated by the endogenous dodecapeptide U-II (*UTS2*, O95399), originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [1685]. Several structural forms of U-II exist in fish and amphibians. The Goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* [1689,1700,1702–1703]. Human U-II (*UTS2*, O95399), an 11-amino-acid peptide [1689], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding [1686,1696]. This sequence is also conserved in the deduced amino-acid sequence of rat U-II (14 amino-acids) and mouse U-II (14 amino-acids), although the N-terminal is more divergent from the human sequence [1688]. A second endogenous ligand for UT has been discovered in rat [1707]. The urotensin II-related peptide (URP (*UTS2B*, Q765I0)), an octapeptide, is derived from a different gene, but shares the C-terminal sequence (CFWKYCV) common to U-II from other species. Identical sequences to rat URP (*UTS2B*, Q765I0) are predicted for the mature mouse and human peptides.

Nomenclature	HGNC, UniProt	Principal transduction	Endogenous agonists (pK_i)	Selective agonists (pK_i)	Selective antagonists (pK_i)	Radioligands (K_d)
UT receptor	*UTS2R*, Q9UKP6	$G_{q/11}$	U-II (8.6) [1692–1693,1695]	[Pen5]-U (4–11) (human) (9.7) [1695], U-II-(4–11) (human) (9.6) [1695], AC-7954 (6.6) [1690,1698], FL104 (pEC_{50} 5.8 – 7.5) [1697,1699]	urantide (8.3) [1704], SB-706375 (8.0) [1692], SB-611812 (6.6) [1705], palosuran (pIC_{50} 7.1) [1687]	[^{125}I]U-II (human) (Agonist, Full agonist) ($4x10^{-10}$ – $2.4x10^{-10}$ M) [1684,1701]

Comments: In human vasculature, human U-II (*UTS2*, O95399) elicits both vasoconstrictor (pD_2 9.3–10.1, [1701]) and vasodilator (pIC_{50} 10.3–10.4, [1706]) responses.

Further reading

Douglas SA, Ohlstein EH. (2000) Urotensin receptors. *in* The IUPHAR Receptor Compendium of Receptor Characterization and Classification. *Edited by* Girdlestone D IUPHAR Media Ltd. 365–372

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M, Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279–288. [PMID:15914470]

Guidolin D, Albertin G, Ribatti D. (2010) Urotensin-II as an angiogenic factor. *Peptides* **31**: 1219–1224. [PMID:20346384]

Hunt BD, Ng LL, Lambert DG. (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, Kinney WA. (2010) Urotensin-II receptor modulators as potential drugs. *J Med Chem* **53**: 2695–2708. [PMID:20043680]

Ross B, McKendy K, Giaid A. (2010) Role of urotensin II in health and disease. *Am J Physiol Regul Integr Comp Physiol* **298**: R1156–R1172. [PMID:20421634]

Vasopressin and oxytocin receptors

Overview: Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytoxcin receptors) are activated by the endogenous cyclic nonapeptides AVP (*AVP*, P01178) and oxytocin (*OXT*, P01178) (OT). These peptides are derived from precursors which also produce neurophysins (neurophysin I for OT; neurophysin II for AVP).

Nomenclature	V_{1A} receptor	V_{1B} receptor	V_2 receptor	OT receptor
HGNC, UniProt	*AVPR1A*, P37288	*AVPR1B*, P47901	*AVPR2*, P30518	*OXTR*, P30559
Principal transduction	$G_{q/11}$	$G_{q/11}$	G_s	$G_{q/11}$, $G_{i/o}$
Rank order of potency	AVP > oxytocin	AVP > oxytocin	AVP > oxytocin	oxytocin > AVP
Selective agonists (pK_i)	F180 (pK_d 7.9 – 8.3) [1711,1719]	d[Leu^4]LVP (9.8) [1731], d[Cha^4]AVP (9.0 – 9.7) [1721,1726], d[D-Pal^2]AVP (7.9) [1715,1721]	d[Val^4,DArg^8]VP, OPC-51803 (7.0) [1730], VNA932 (pIC_{50} 7.1) [1723]	[Thr^4,Gly^7]OT (8.2 – 8.4) [1718,1722,1727]
Selective antagonists (pK_i)	d$(CH_2)_5$[Tyr(Me)^2,Arg^8]VP (9.0), SR 49059 (8.1 – 9.3) [1708,1719, 1726,1732,1735,1738,1740–1742], conivaptan (8.2 – 8.4) [1738–1739]	SSR149415 (8.4 – 9.3) [1725–1726,1737]	tolvaptan (9.37) [1743], lixivaptan (Inverse agonist) (8.9 – 9.2) [1710,1735], SR 121463A (8.4 – 9.3) [1708,1719–1720,1734–1735,1738, 1742], d$(CH_2)_5$[D-Ile^2,Ile^4]AVP (6.9 – 8.4) [1735], OPC-31260 (Inverse antagonist) (7.6) [1744]	SSR126768A (8.82 – 9.05) [1736], L-371,257 (8.8) [1726], desGlyNH_2-d$(CH_2)_5$[Tyr(Me)^2,Thr^4,Orn^8]OT (8.5), L-372662 (8.4) [1712]
Radioligands (K_d)	[^{3}H]SR49059 (Antagonist), [^{125}I]OH-LVA (Antagonist) ($3.99x10^{-11}$ – $5x10^{-11}$ M) [1717,1719,1732], [^{3}H]AVP (Agonist, Full agonist) ($2.51x10^{-9}$ – $6.3x10^{-11}$ M) [1714,1717,1719–1720,1730, 1732,1733,1738–1743], [^{3}H]d$(CH_2)_5$[Tyr(Me)^2]AVP (Antagonist) ($1.1x10^{-9}$ M)	[^{3}H]SSR149415 (Antagonist), [^{3}H]AVP (Agonist, Full agonist) ($2.51x10^{-9}$ – $2.5x10^{-10}$ M) [1714,1717,1719–1720,1730, 1732,1733,1738–1743]	[^{3}H]AVP (Agonist, Full agonist) ($3.98x10^{-9}$ – $3.99x10^{-10}$ M) [1717,1719–1720,1730,1733, 1738–1739,1741–1743], [^{3}H]SR 121463A (Antagonist, Inverse agonist) ($4.1x10^{-9}$ – $5x10^{-10}$ M) [1720,1734], [^{3}H]desGly-NH_2[D-Ile^2,Ile^4]VP ($2.8x10^{-9}$ M), [^{3}H]dDAVP (Agonist, Full agonist) ($6.3x10^{-8}$ – $8x10^{-10}$ M) [1717,1720,1741]	[^{35}S]non-peptide OT antagonist (Antagonist) ($4.2x10^{-11}$ M) [1729], [^{125}I]d$(CH_2)_5$[Tyr(Me)^2,Thr^4,Orn^8,Tyr-NH_2^{9}]OVT (Antagonist) ($9x10^{-11}$ M), [^{3}H]OT (human, mouse, rat) (Agonist, Full agonist) [1717,1724,1727-1728], [^{111}In]DOTA-dLVT ($4.5x10^{-9}$ M) [1716]

Comments: 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 [1709]. Similarly, [^{3}H]d[D-Arg^8]VP is V_2 selective in the rat, not in the human [1733]. The gene encoding the V_2 receptor is polymorphic in man, underlying nephrogenic diabetes insipidus [1713]. d[Cha^4]AVP is selective only for the human and bovine V_{1b} receptors [1721], while d[Leu^4]LVP has high affinity for the rat V_{1b} receptor [1731].

Further reading

Bartz JA, Zaki J, Bolger N, Ochsner KN. (2011) Social effects of oxytocin in humans: context and person matter. *Trends Cogn Sci (Regul Ed)* **15**: 301–309. [PMID:21696997]

Knepper MA. (2012) Systems biology in physiology: the vasopressin signaling network in kidney. *Am J Physiol, Cell Physiol* **303**: C1115–C1124. [PMID:22932685]

Koshimizu TA, Nakamura K, Egashira N, Hiroyama M, Nonoguchi H, Tanoue A. (2012) Vasopressin V1a and V1b receptors: from molecules to physiological systems. *Physiol Rev* **92**: 1813–1864. [PMID:23073632]

Manning M, Misicka A, Olma A, Bankowski K, Stoev S, Chini B, Durroux T, Mouillac B, Corbani M, Guillon G. (2012) Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics. *J Neuroendocrinol* **24**: 609–628. [PMID:22375852]

Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci* **12**: 524–538. [PMID:21852800]

Neumann ID, Landgraf R. (2012) Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci* **35**: 649–659. [PMID:22974560]

VIP and PACAP receptors

Overview: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors, [1749]) are activated by the endogenous peptides VIP (*VIP*, P01282), PACAP-38 (*ADCYAP1*, P18509), PACAP-27 (*ADCYAP1*, P18509), peptide histidine isoleucineamide (PHI), peptide histidine methionineamide (PHM (*VIP*, P01282)) and peptide histidine valine (PHV (*VIP*, P01282)). "PACAP type II receptors" ($VPAC_1$ and $VPAC_2$ receptors) display comparable affinity for PACAP 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 [1745]. PG 99-465 [1752] 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 [1746]. 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 PACAP [1753]. Two deletion variants of maxadilan, M65 [1758] and Max.d.4 [1754] have been reported to be PAC_1 receptor antagonists, but these peptides have not been extensively characterised.

Nomenclature	$VPAC_1$ receptor	$VPAC_2$ receptor	PAC_1 receptor
HGNC, UniProt	*VIPR1*, P32241	*VIPR2*, P41587	*ADCYAP1R1*, P41586
Principal transduction	G_s	G_s	G_s
Rank order of potency	VIP, PACAP-27, PACAP-38 >> GHRH (*GHRH*, P01286), PHI, secretin (*SCT*, P09683)	VIP, PACAP-38, PACAP-27 > PHI >> GHRH (*GHRH*, P01286), secretin (*SCT*, P09683)	PACAP-27, PACAP-38 >> VIP
Selective agonists (pK_i)	[$Ala^{11,22,28}$]VIP (8.1) [1755], [Lys^{15},Arg^{16},Leu^{27}]VIP-(1–7)/GRF-(8–27)-NH_2 (pEC_{50} 8.3) [1751]	Ro 25-1392 (8.0) [1760], Ro 25-1553 (pEC_{50} 8.7) [1751], Ro 25-1553 (pEC_{50} 8.3) [1750], Ro 25-1553 (pIC_{50} 9.5) [1748], Ro 25-1553 (pIC_{50} 8.8) [1750], Ro 25-1553 (pIC_{50} 7.8) [1751]	maxadilan (pEC_{50} 10.3) [1746], maxadilan (pEC_{50} 6.2) [1746]
Selective antagonists (pK_i)	PG 97-269 (pIC_{50} 8.7) [1747], PG 97-269 (pIC_{50} 8.7) [1750], PG 97-269 (pIC_{50} 8.7) [1750], PG 97-269 (pIC_{50} 8.0) [1746], PG 97-269 (pIC_{50} 7.1) [1746]	–	–
Radioligands (K_d)	[^{125}I]PACAP-27 (Agonist), [^{125}I]VIP (Agonist) ($4x10^{-10}$ M) [1755]	[^{125}I]PACAP-27 (Agonist), [^{125}I]VIP (Agonist) ($7x10^{-10}$ M) [1755]	[^{125}I]PACAP-27 (Agonist) ($8.7x10^{-10}$ M) [1756]

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 [1759], or from alternative splicing of PAC_1 receptor mRNA [1757].

Further reading

Harmar AJ, Arimura A, Gozes I, Journot L, Laburthe M, Pisegna JR, Rawlings SR, Robberecht P, Said SI, Sreedharan SP, Wank SA, Waschek JA. (1998) International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. *Pharmacol Rev* **50**: 265–270. [PMID:9647867]

Harmar AJ, Fahrenkrug J, Gozes I, Laburthe M, May V, Pisegna JR, Vaudry D, Vaudry H, Waschek JA, Said SI. (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, Kiss P, Horvath G, Lubics A, Laszlo E, Tamas A, Racz B, Szakaly P. (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, Eiden LE. (2012) Is PACAP the major neurotransmitter for stress transduction at the adrenomedullary synapse?. *J Mol Neurosci* **48**: 403–412. [PMID:22610912]

References

1. Adams JW *et al*. (2008) *Am J Physiol Heart Circ Physiol* **295**: H509–H521. [PMID:18539757]
2. Barnea G *et al*. (2008) *Proc Natl Acad Sci USA* **105**: 64–69. [PMID:18165312]
3. Bechtold DA *et al*. (2012) *Curr Biol* **22**: 70–77. [PMID:22197240]
4. Behrens M *et al*. (2004) *Biochem Biophys Res Commun* **319**: 479–485. [PMID:15178431]
5. Benned-Jensen T, Rosenkilde MM. (2010) *Br J Pharmacol* **159**: 1092–1105. [PMID:20148890]
6. Bjursell M *et al*. (2006) *Biochem Biophys Res Commun* **348**: 359–366. [PMID:16887097]
7. Borowsky B *et al*. (2001) *Proc Natl Acad Sci U S A* **98**: 8966–8971. [PMID:11459929]
8. Brennan TJ *et al*. (2007) Transgenic mice containing GPCR5-1 gene disruptions. Patent number: US 2007/0074299 A1. Submitted on 08/08/2006. Issued on 29/03/2007.
9. Carmon KS *et al*. (2011) *Proc Natl Acad Sci USA* **108**: 11452–11457. [PMID:21693646]
10. Catalán V *et al*. (2007) *Clin Endocrinol (Oxf)* **66**: 598–601. [PMID:17371481]
11. Cavanaugh DJ *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 9075–9080. [PMID:19451647]
12. Chandrashekar J *et al*. (2000) *Cell* **100**: 703–711. [PMID:10761935]
13. Chen H, Ikeda SR. (2004) *J Neurosci* **24**: 5044–5053. [PMID:15163697]
14. Chen Q *et al*. (2012) *Eur J Neurosci* [Epub ahead of print]. [PMID:22697179]
15. Chiang N *et al*. (2012) *Nature* **484**: 524–528. [PMID:22538616]
16. Ciana P *et al*. (2006) *EMBO J* **25**: 4615–4627. [PMID:16990797]
17. Davenport AP *et al*. (2013) *Pharmacol Rev* **65**: 967–986. [PMID:23686350]
18. de Lau W *et al*. (2011) *Nature* **476**: 293–297. [PMID:21727895]
19. Edinger AL *et al*. (1997) *Proc Natl Acad Sci USA* **94**: 14742–14747. [PMID:9405683]
20. Edson MA *et al*. (2010) *Endocrinology* **151**: 358–368. [PMID:19887567]
21. Eggerickx D *et al*. (1995) *Biochem J* **309** (Pt 3): 837–843. [PMID:7639700]
22. Engel KM *et al*. (2011) *PLoS ONE* **6**: e29400. [PMID:22216272]
23. Evangelou E *et al*. (2011) *Ann Rheum Dis* **70**: 349–355. [PMID:21068099]
24. Foord SM *et al*. (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
25. Gembardt F *et al*. (2008) *Mol Cell Biochem* **319**: 115–123. [PMID:18636314]
26. Gomes I *et al*. (2013) *Proc Natl Acad Sci USA* [Epub ahead of print]. [PMID:24043826]
27. Guo Y *et al*. (2011) *J Biol Chem* **286**: 33832–33840. [PMID:21712392]
28. Hannedouche S *et al*. (2011) *Nature* **475**: 524–527. [PMID:21796212]
29. Hansen W *et al*. (2010) *Genes Immun* **11**: 357–361. [PMID:20200545]
30. Hase M *et al*. (2008) *J Biol Chem* **283**: 12747–12755. [PMID:18347022]
31. Hay DL *et al*. (2011) *Endocr Relat Cancer* **18**: C1–C14. [PMID:21051558]
32. Hisatsune C *et al*. (2007) *J Biol Chem* **282**: 37225–37231. [PMID:17925404]
33. Holst B *et al*. (2007) *Endocrinology* **148**: 13–20. [PMID:16959833]
34. Ignatov A *et al*. (2004) *Neuropharmacology* **46**: 1114–1120. [PMID:15111018]
35. Ignatov A *et al*. (2003) *J Neurosci* **23**: 907–914. [PMID:12574419]
36. Ignatov A *et al*. (2003) *Biochem Biophys Res Commun* **311**: 329–336. [PMID:14592418]
37. Ignatov A *et al*. (2006) *Br J Pharmacol* **149**: 490–497. [PMID:17001303]
38. Inoue A *et al*. (2012) *Nat Methods* **9**: 1021–1029. [PMID:22983457]
39. Jin C *et al*. (2008) *Invest Ophthalmol Vis Sci* **49**: 4245–4253. [PMID:18487371]
40. Jones PG *et al*. (2007) *Biochim Biophys Acta* **1770**: 890–901. [PMID:17363172]
41. Kabarowski JH *et al*. (2001) *Science* **293**: 702–705. [PMID:11474113]
42. Kamohara M *et al*. (2005) *Biochem Biophys Res Commun* **330**: 1146–1152. [PMID:15823563]
43. Kapas S *et al*. (1995) *J Biol Chem* **270**: 25344–25347. [PMID:7592696]
44. Kelly LM *et al*. (2011) *J Immunol* **187**: 3026–3032. [PMID:21844396]
45. Kennedy SP *et al*. (1998) *Biochem Biophys Res Commun* **244**: 832–837. [PMID:9535752]
46. Kerkhof HJ *et al*. (2010) *Arthritis Rheum* **62**: 499–510. [PMID:20112360]
47. Kim SV *et al*. (2013) *Science* **340**: 1456–1459. [PMID:23661644]
48. Kitamura H *et al*. (2012) *J Biochem* **151**: 511–518. [PMID:22343749]
49. Kojima D *et al*. (2011) *PLoS ONE* **6**: e26388. [PMID:22043319]
50. Kottyan LC *et al*. (2009) *Blood* **114**: 2774–2782. [PMID:19641187]
51. Krishnamoorthy S *et al*. (2010) *Proc Natl Acad Sci USA* **107**: 1660–1665. [PMID:20080636]
52. Ku GM *et al*. (2012) *PLoS Genet* **8**: e1002449. [PMID:22253604]
53. Kuc D *et al*. (2008) *Amino Acids* **35**: 503–505. [PMID:18235993]
54. Lautner RQ *et al*. (2013) *Circ Res* **112**: 1104–1111. [PMID:23446738]
55. Ledent C *et al*. (2005) *Proc Natl Acad Sci U S A* **102**: 8922–8926. [PMID:15956199]
56. Lembo PM *et al*. (2002) *Nat Neurosci* **5**: 201–209. [PMID:11850634]
57. Levoye A *et al*. (2006) *EMBO J* **25**: 3012–3023. [PMID:16778767]
58. Li X *et al*. (2002) *Prostaglandins Other Lipid Mediat* **67**: 173–180. [PMID:12013525]
59. Liebscher I *et al*. (2011) *J Biol Chem* **286**: 2101–2110. [PMID:21097509]
60. Liu C *et al*. (2011) *Nature* **475**: 519–523. [PMID:21796211]
61. Liu Q *et al*. (2009) *Cell* **139**: 1353–1365. [PMID:20004959]
62. Lobo MK *et al*. (2007) *Nat Neurosci* **10**: 1395–1397. [PMID:17934457]
63. Logue SF *et al*. (2009) *Mol Cell Neurosci* **42**: 438–447. [PMID:19796684]
64. Luo J *et al*. (2009) *Development* **136**: 2747–2756. [PMID:19605502]
65. Maekawa A *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 11685–11690. [PMID:19561298]
66. Marazziti D *et al*. (2009) *Autophagy* **5**: 741–742. [PMID:19398891]
67. Marazziti D *et al*. (2011) *FASEB J* **25**: 2071–2081. [PMID:21372109]
68. Marazziti D *et al*. (2007) *Proc Natl Acad Sci USA* **104**: 9846–9851. [PMID:17519329]
69. Murakami M *et al*. (2008) *Biochem Biophys Res Commun* **371**: 707–712. [PMID:18466763]
70. Nambu H *et al*. (2011) *Life Sci* **89**: 765–772. [PMID:21971119]
71. Nelson G *et al*. (2001) *Cell* **106**: 381–390. [PMID:11509186]
72. Niedernberg A *et al*. (2003) *Cell Signal* **15**: 435–446. [PMID:12618218]
73. Oka S *et al*. (2010) *Biochem Biophys Res Commun* **395**: 232–237. [PMID:20361937]
74. Osborn O *et al*. (2012) *J Clin Invest* **122**: 2444–2453. [PMID:22653059]
75. Padmanabhan S *et al*. (2009) *FEBS Lett* **583**: 107–112. [PMID:19059244]
76. Pereira JP *et al*. (2009) *Nature* **460**: 1122–1126. [PMID:19597478]
77. Petersen PS *et al*. (2011) *FASEB J* [Epub ahead of print]. [PMID:21784784]
78. Rezgaoui M *et al*. (2006) *J Cell Sci* **119**: 542–549. [PMID:16443751]
79. Robas N *et al*. (2003) *J Biol Chem* **278**: 44400–44404. [PMID:12915402]
80. Ruffner H *et al*. (2012) *PLoS ONE* **7**: e40976. [PMID:22815884]
81. Ruiz-Medina J *et al*. (2011) *Neuropharmacology* **61**: 43–50. [PMID:21352831]
82. Russell JL *et al*. (2012) *ACS Chem Biol* **7**: 1077–1083. [PMID:22462679]
83. Römpler H *et al*. (2005) *J Biol Chem* **280**: 31068–31075. [PMID:15987686]
84. Santos RA *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 8258–8263. [PMID:12829792]
85. Seuwen K *et al*. (2006) *J Recept Signal Transduct Res* **26**: 599–610. [PMID:17118800]
86. Shimizu N *et al*. (1999) *J Virol* **73**: 5231–5239. [PMID:10233994]
87. Shinohara T *et al*. (2004) *J Biol Chem* **279**: 23559–23564. [PMID:15037633]
88. Sikand P *et al*. (2011) *J Neurosci* **31**: 7563–7567. [PMID:21593341]
89. Song H *et al*. (2008) *J Biol Chem* **283**: 36687–36697. [PMID:18955481]
90. Southern C *et al*. (2013) *J Biomol Screen* **18**: 599–609. [PMID:23396314]
91. Sugo T *et al*. (2006) *Biochem Biophys Res Commun* **341**: 1078–1087. [PMID:16460680]
92. Suzuki M *et al*. (2013) *J Biol Chem* **288**: 10684–10691. [PMID:23449982]
93. Tabata K *et al*. (2007) *Biochem Biophys Res Commun* **363**: 861–866. [PMID:17905198]

94. Takeda S *et al*. (2004) *J Biochem* **135**: 597–604. [PMID:15173198]
95. Taniguchi Y *et al*. (2006) *FEBS Lett* **580**: 5003–5008. [PMID:16934253]
96. Thathiah A *et al*. (2009) *Science* **323**: 946–951. [PMID:19213921]
97. Uhlenbrock K *et al*. (2002) *Cell Signal* **14**: 941–953. [PMID:12220620]
98. Valdes AM, Spector TD. (2010) *Curr Opin Rheumatol* **22**: 139–143. [PMID:20090528]
99. Wang J *et al*. (2006) *J Biol Chem* **281**: 22021–22028. [PMID:16754668]
100. Wang J *et al*. (2006) *J Biol Chem* **281**: 34457–34464. [PMID:16966319]
101. Weng J *et al*. (2008) *Proc Natl Acad Sci USA* **105**: 6081–6086. [PMID:18424556]
102. Witte ON *et al*. (2005) *Science* **307**: 206. [PMID:15653487]
103. Xu Y *et al*. (2000) *Nat Cell Biol* **2**: 261–267. [PMID:10806476]
104. Xu Y *et al*. (2006) Retraction of: Xu Y, Zhu K, Hong G, Wu W, Baudhuin LM, Xiao Y, Damron DS. (2000) Nat Cell Biol. 2(5):261–267. *Nat Cell Biol* **8**: 299–. [PMID:16508674]
105. Yasuda H *et al*. (2007) *Biochem Biophys Res Commun* **354**: 154–159. [PMID:17214962]
106. Yin H *et al*. (2009) *J Biol Chem* **284**: 12328–12338. [PMID:19286662]
107. Yosten GL *et al*. (2013) *J Endocrinol* [Epub ahead of print]. [PMID:23759446]
108. Zhang LL *et al*. (2011) *Neuroscience* **196**: 203–214. [PMID:21924326]
109. Zhang Y *et al*. (2003) *Cell* **112**: 293–301. [PMID:12581520]
110. Zhao P *et al*. (2010) *Mol Pharmacol* **78**: 560–568. [PMID:20826425]
111. Zhu K *et al*. (2001) *J Biol Chem* **276**: 41325–41335. [PMID:11535583]
112. (2005) *J Biol Chem* **280**: 43280. [PMID:16498716]
113. Yang LV *et al*. (2007) *Mol Cell Biol* **27**: 1334–1347. [PMID:17145776]
114. Adham N *et al*. (1997) *Neuropharmacology* **36**: 569–576. [PMID:9225282]
115. Adham N *et al*. (1993) *Proc Natl Acad Sci U S A* **90**: 408–412. [PMID:8380639]
116. Amlaiky N *et al*. (1992) *J Biol Chem* **267**: 19761–19764. [PMID:1328180]
117. Bach T *et al*. (2001) *Naunyn Schmiedebergs Arch Pharmacol* **363**: 146–160. [PMID:11218067]
118. Bard JA *et al*. (1993) *J Biol Chem* **268**: 23422–23426. [PMID:8226867]
119. Beattie DT *et al*. (2004) *Br J Pharmacol* **143**: 549–560. [PMID:15466450]
120. Bender E *et al*. (2000) *J Neurochem* **74**: 478–489. [PMID:10646498]
121. Berque-Bestel I *et al*. (2003) *J Med Chem* **46**: 2606–2620. [PMID:12801225]
122. Blair JB *et al*. (2000) *J Med Chem* **43**: 4701–4710. [PMID:11101361]
123. Blondel O *et al*. (1998) *J Neurochem* **70**: 2252–2261. [PMID:9603189]
124. Bockaert J *et al*. (2006) *Cell Tissue Res* **326**: 553–572. [PMID:16896947]
125. Boess FG *et al*. (1997) *Mol Pharmacol* **52**: 515–523. [PMID:9284367]
126. Boess FG *et al*. (1998) *Mol Pharmacol* **54**: 577–583. [PMID:9730917]
127. Bonhaus DW *et al*. (1997) *Neuropharmacology* **36**: 671–679. [PMID:9225293]
128. Bonhaus DW *et al*. (1999) *Br J Pharmacol* **127**: 1075–1082. [PMID:10455251]
129. Bonhaus DW *et al*. (1977) *Neuropharmacology* **36**: 621–629. [PMID:9225287]
130. Boulenguez P *et al*. (1992) *J Neurochem* **58**: 951–959. [PMID:1738002]
131. Branchek T *et al*. (1990) *Mol Pharmacol* **38**: 604–609. [PMID:2233697]
132. Brenchat A *et al*. (2009) *Pain* **141**: 239–247. [PMID:19118950]
133. Bromidge SM *et al*. (1999) *J Med Chem* **42**: 202–205. [PMID:9925723]
134. Bromidge SM *et al*. (2001) *Bioorg Med Chem Lett* **11**: 55–58. [PMID:11140733]
135. Brown AM *et al*. (1993) *Br J Pharmacol* **110**: 10.
136. Brown AM *et al*. (1998) *British Journal of Pharmacology* **123**: 233.
137. Bryant HU *et al*. (1996) *Life Sci* **59**: 1259–1268. [PMID:8845011]
138. Claeysen S *et al*. (1997) *Neuroreport* **8**: 3189–3196. [PMID:9351641]
139. Corbett DF *et al*. (2005) *Bioorg Med Chem Lett* **15**: 4014–4018. [PMID:16002289]
140. De Vry J *et al*. (1998) *J Pharmacol Exp Ther* **284**: 1082–1094. [PMID:9495870]
141. Dunlop J *et al*. (2005) *J Pharmacol Exp Ther* **313**: 862–869. [PMID:15705738]
142. Egan C *et al*. (2000) *Synapse* **35**: 144–150. [PMID:10611640]
143. Ennis MD *et al*. (1998) *J Med Chem* **41**: 2180–2183. [PMID:9632349]
144. Fitzgerald LW *et al*. (1999) *J Neurochem* **72**: 2127–2134. [PMID:10217294]
145. Forbes IT *et al*. (2002) *Bioorg Med Chem Lett* **12**: 3341–3344. [PMID:12392747]
146. Gaster LM *et al*. (1998) *J Med Chem* **41**: 1218–1235. [PMID:9548813]
147. Gershon MD. (1999) *Aliment Pharmacol Ther* **13** Suppl 2: 15–30. [PMID:10429737]
148. Grailhe R *et al*. (2001) *Eur J Pharmacol* **418**: 157–167. [PMID:11343685]
149. Granas C, Larhammar D. (1999) *Eur J Pharmacol* **380**: 171–181. [PMID:10513577]
150. Hamblin MW, Metcalf MA. (1991) *Mol Pharmacol* **40**: 143–148. [PMID:1652050]
151. Hameg A *et al*. (2003) *Biochem Pharmacol* **65**: 435–440. [PMID:12527336]
152. Harada K *et al*. (2006) *Eur J Pharmacol* **553**: 171–184. [PMID:17074317]
153. Hartig PR *et al*. (1996) *Trends Pharmacol Sci* **17**: 103–105. [PMID:8936345]
154. Hegde SS, Eglen RM. (1996) *FASEB J* **10**: 1398–1407. [PMID:8903510]
155. Heusler P *et al*. (2010) *Naunyn Schmiedebergs Arch Pharmacol* **382**: 321–330. [PMID:20799027]
156. Hirst WD *et al*. (2006) *Eur J Pharmacol* **553**: 109–119. [PMID:17069795]
157. Holenz J *et al*. (2005) *J Med Chem* **48**: 1781–1795. [PMID:15771424]
158. Hoyer D *et al*. (1994) *Pharmacol Rev* **46**: 157–203. [PMID:7938165]
159. Hoyer D *et al*. (2002) *Pharmacol Biochem Behav* **71**: 533–554. [PMID:11888546]
160. Jerning E *et al*. (1998) *Eur J Pharmacol* **360**: 219–225. [PMID:9851589]
161. Johansson L *et al*. (1997) *J Pharmacol Exp Ther* **283**: 216–225. [PMID:9336327]
162. Kalipatnapu S *et al*. (2004) *Biosci Rep* **24**: 101–115. [PMID:15628665]
163. Kennett GA *et al*. (1997) *Neuropharmacology* **36**: 609–620. [PMID:9225286]
164. Khawaja X *et al*. (1997) *Life Sci* **60**: 653–665. [PMID:9048968]
165. Kimura Y *et al*. (2004) *Eur J Pharmacol* **483**: 37–43. [PMID:14709324]
166. Knight AR *et al*. (2004) *Naunyn Schmiedebergs Arch Pharmacol* **370**: 114–123. [PMID:15322733]
167. Koe BK *et al*. (1992) *Drug Development Research* **26**: 241–250.
168. Kovacs A *et al*. (2003) *Cardiovasc Drugs Ther* **17**: 427–434. [PMID:15107597]
169. Kursar JD *et al*. (1994) *Mol Pharmacol* **46**: 227–234. [PMID:8078486]
170. Lejeune F *et al*. (1997) *J Pharmacol Exp Ther* **280**: 1241–1249. [PMID:9067310]
171. Lesage AS *et al*. (1998) *Br J Pharmacol* **123**: 1655–1665. [PMID:9605573]
172. Leysen JE *et al*. (1996) *Mol Pharmacol* **50**: 1567–1580. [PMID:8967979]
173. Lopez-Gimenez JF *et al*. (2001) *Mol Pharmacol* **60**: 690–699. [PMID:11562430]
174. Madsen K *et al*. (2011) *Nucl Med Biol* **38**: 1085–1091. [PMID:21831646]
175. Maier DL *et al*. (2009) *J Pharmacol Exp Ther* **330**: 342–351. [PMID:19401496]
176. Malgouris C *et al*. (1993) *Eur J Pharmacol* **233**: 37–45. [PMID:8472747]
177. McAllister G *et al*. (1992) *Proc Natl Acad Sci U S A* **89**: 5517–5521. [PMID:1608964]
178. McCall RB *et al*. (1994) *J Pharmacol Exp Ther* **271**: 875–883. [PMID:7965808]
179. Mialet J *et al*. (2000) *Br J Pharmacol* **129**: 771–781. [PMID:10683202]
180. Mialet J *et al*. (2000) *Br J Pharmacol* **131**: 827–835. [PMID:11030734]
181. Mialet J *et al*. (2000) *Br J Pharmacol* **130**: 527–538. [PMID:10821780]
182. Middlemiss DN *et al*. (1999) *Eur J Pharmacol* **375**: 359–365. [PMID:10443589]
183. Millan MJ *et al*. (2000) *Synapse* **35**: 79–95. [PMID:10611634]
184. Napier C *et al*. (1999) *Eur J Pharmacol* **368**: 259–268. [PMID:10193663]
185. Nelson DL *et al*. (1999) *Naunyn Schmiedebergs Arch Pharmacol* **359**: 1–6. [PMID:9933142]
186. Nelson DL *et al*. (2010) *Cephalalgia* **30**: 1159–1169. [PMID:20855361]
187. Newman-Tancredi A *et al*. (2000) *Mol Pharmacol* **58**: 1042–1049. [PMID:11040052]
188. Newman-Tancredi A *et al*. (1999) *Naunyn Schmiedebergs Arch Pharmacol* **359**: 447–453. [PMID:10431754]
189. Newman-Tancredi A *et al*. (1998) *Eur J Pharmacol* **355**: 245–256. [PMID:9760039]

190. Newman-Tancredi A *et al*. (2009) *Br J Pharmacol* **156**: 338–353. [PMID:19154445]
191. Newman-Tancredi A *et al*. (1998) *Naunyn Schmiedebergs Arch Pharmacol* **357**: 205–217. [PMID:9550290]
192. Newman-Tancredi A *et al*. (1992) *Biochem J* **285**: 933–938. [PMID:1386736]
193. Noda M *et al*. (2003) *J Neurochem* **84**: 222–232. [PMID:12558985]
194. Parker EM *et al*. (1996) *J Neurochem* **67**: 2096–2103. [PMID:8863519]
195. Phebus LA *et al*. (1997) *Life Sci* **61**: 2117–2212. [PMID:9395253]
196. Price GW *et al*. (1997) *Naunyn Schmiedebergs Arch Pharmacol* **356**: 312–320. [PMID:9303567]
197. Ramage AG, Villalón CM. (2008) *Trends Pharmacol Sci* **29**: 472–481. [PMID:19086344]
198. Rashid M *et al*. (2003) *Life Sci* **73**: 193–207. [PMID:12738034]
199. Reavill C *et al*. (1999) *Br J Pharmacol* **126**: 572–574. [PMID:10188965]
200. Rivail L *et al*. (2004) *Br J Pharmacol* **143**: 361–370. [PMID:15351779]
201. Schaerlinger B *et al*. (2003) *Br J Pharmacol* **140**: 277–284. [PMID:12970106]
202. Schechter LE *et al*. (2008) *Neuropsychopharmacology* **33**: 1323–1335. [PMID:17625499]
203. Selkirk JV *et al*. (1998) *Br J Pharmacol* **125**: 202–208. [PMID:9776361]
204. Sleight AJ *et al*. (1998) *Br J Pharmacol* **124**: 556–562. [PMID:9647481]
205. Sleight AJ *et al*. (1996) *Biochem Pharmacol* **51**: 71–76. [PMID:8534270]
206. Stam NJ *et al*. (1997) *FEBS Lett* **413**: 489–494. [PMID:9303561]
207. Thomas DR *et al*. (2000) *Br J Pharmacol* **130**: 409–417. [PMID:10807680]
208. Thomas DR *et al*. (1998) *Br J Pharmacol* **124**: 1300–1306. [PMID:9720804]
209. Thomsen WJ *et al*. (2008) *J Pharmacol Exp Ther* **325**: 577–587. [PMID:18252809]
210. Van den Wyngaert I *et al*. (1997) *J Neurochem* **69**: 1810–1819. [PMID:9349523]
211. Villalón CM, Centurión D. (2007) *Naunyn Schmiedebergs Arch Pharmacol* **376**: 45–63. [PMID:17703282]
212. Wainscott DB *et al*. (1993) *Mol Pharmacol* **43**: 419–426. [PMID:8450835]
213. Wainscott DB *et al*. (2005) *Naunyn Schmiedebergs Arch Pharmacol* **371**: 169–177. [PMID:15900510]
214. Ward SE *et al*. (2005) *J Med Chem* **48**: 3478–3480. [PMID:15887956]
215. Weinshank RL *et al*. (1992) *Proc Natl Acad Sci USA* **89**: 3630–3634. [PMID:1565658]
216. Werry TD *et al*. (2008) *Pharmacol Ther* **119**: 7–23. [PMID:18554725]
217. Wurch T *et al*. (1998) *Mol Pharmacol* **54**: 1088–1096. [PMID:9855638]
218. Xie Z *et al*. (1999) *FEBS Lett* **456**: 63–67. [PMID:10452531]
219. Antony J *et al*. (2009) *FASEB J* **23**: 442–450. [PMID:18842964]
220. Avlani VA *et al*. (2010) *Mol Pharmacol* **78**: 94–104. [PMID:20413650]
221. Birdsall NJ, Lazareno S. (2005) *Mini Rev Med Chem* **5**: 523–543. [PMID:15974931]
222. Brady AE *et al*. (2008) *J Pharmacol Exp Ther* **327**: 941–953. [PMID:18772318]
223. Bridges TM *et al*. (2009) *J Med Chem* **52**: 3445–3448. [PMID:19438238]
224. Caulfield MP, Birdsall NJM. (1998) *Pharmacol Rev* **50**: 279–290. [PMID:9647869]
225. Cembala TM *et al*. (1998) *Br J Pharmacol* **125**: 1088–1094. [PMID:9846649]
226. Chan WY *et al*. (2008) *Proc Natl Acad Sci USA* **105**: 10978–10983. [PMID:18678919]
227. Cheng K *et al*. (2002) *J Pharmacol Exp Ther* **303**: 29–35. [PMID:12235229]
228. Christopoulos A *et al*. (1998) *Mol Pharmacol* **53**: 1120–1130. [PMID:9614217]
229. Christopoulos A, Wilson K. (2001) *Brain Res* **915**: 70–78. [PMID:11578621]
230. Hirose H *et al*. (2001) *J Pharmacol Exp Ther* **297**: 790–797. [PMID:11303071]
231. Huang F *et al*. (2001) *AAPS PharmSci* **3**: E30-E30. [PMID:12049493]
232. Jakubik J *et al*. (1997) *Mol Pharmacol* **52**: 172–179. [PMID:9224827]
233. Jakubik J *et al*. (2006) *Mol Pharmacol* **70**: 656–666. [PMID:16675658]
234. Jolkkonen M *et al*. (1994) *FEBS Lett* **352**: 91–94. [PMID:7925952]
235. Jones CK *et al*. (2008) *J Neurosci* **28**: 10422–10433. [PMID:18842902]
236. Khattar SK *et al*. (2006) *Biotechnol Lett* **28**: 121–129. [PMID:16369696]
237. Langmead CJ *et al*. (2008) *Br J Pharmacol* **154**: 1104–1115. [PMID:18454168]
238. Langmead CJ *et al*. (2006) *Mol Pharmacol* **69**: 236–246. [PMID:16207821]
239. Lazareno S, Birdsall NJM. (1995) *Mol Pharmacol* **48**: 362–378. [PMID:7651370]
240. Lazareno S *et al*. (2000) *Mol Pharmacol* **58**: 194–207. [PMID:10860942]
241. Lazareno S *et al*. (2002) *Mol Pharmacol* **62**: 1492–1505. [PMID:12435818]
242. Leach K *et al*. (2011) *Mol Pharmacol* **79**: 855–865. [PMID:21300722]
243. Leach K *et al*. (2010) *Neuropsychopharmacology* **35**: 855–869. [PMID:19940843]
244. Ma L *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 15950–15955. [PMID:19717450]
245. Marlo JE *et al*. (2009) *Mol Pharmacol* **75**: 577–588. [PMID:19047481]
246. May LT *et al*. (2007) *Mol Pharmacol* **72**: 463–476. [PMID:17525129]
247. Nawaratne V *et al*. (2010) *J Biol Chem* **285**: 19012–19021. [PMID:20406819]
248. Nawaratne V *et al*. (2008) *Mol Pharmacol* **74**: 1119–1131. [PMID:18628403]
249. Näsman J *et al*. (2000) *Biochem Biophys Res Commun* **271**: 435–439. [PMID:10799315]
250. Olianas MC *et al*. (1999) *J Pharmacol Exp Ther* **288**: 164–170. [PMID:9862767]
251. Peralta EG *et al*. (1987) *EMBO J* **6**: 3923–3929. [PMID:3443095]
252. Reid PR *et al*. (2011) *Bioorg Med Chem Lett* **21**: 2697–2701. [PMID:21194936]
253. Sams AG *et al*. (2010) *J Med Chem* **53**: 6386–6397. [PMID:20684563]
254. Sheffler DJ *et al*. (2009) *Mol Pharmacol* **76**: 356–368. [PMID:19407080]
255. Smith CM, Wallis RM. (1997) *J Recept Signal Transduct Res* **17**: 177–184. [PMID:9029489]
256. Spalding TA *et al*. (2006) *Mol Pharmacol* **70**: 1974–1983. [PMID:16959945]
257. Spalding TA *et al*. (2002) *Mol Pharmacol* **61**: 1297–1302. [PMID:12021390]
258. Steinfeld T *et al*. (2007) *Mol Pharmacol* **72**: 291–302. [PMID:17478612]
259. Sur C *et al*. (2003) *Proc Natl Acad Sci U S A* **100**: 13674–13679. [PMID:14595031]
260. Tränkle C *et al*. (2003) *Mol Pharmacol* **64**: 180–190. [PMID:12815174]
261. Valant C *et al*. (2008) *J Biol Chem* **283**: 29312–29321. [PMID:18723515]
262. Wang SZ, El-Fakahany EE. (1993) *J Pharmacol Exp Ther* **266**: 237–243. [PMID:7687290]
263. Watson M *et al*. (1984) *Brain Res* **290**: 179–182. [PMID:6546354]
264. Abo-Salem OM *et al*. (2004) *J Pharmacol Exp Ther* **308**: 358–366. [PMID:14563788]
265. Alexander SP *et al*. (1996) *Br J Pharmacol* **119**: 1286–1290. [PMID:8937736]
266. Alexander SP, Millns PJ. (2001) *Eur J Pharmacol* **411**: 205–210. [PMID:11164377]
267. Auchampach JA *et al*. (2009) *J Pharmacol Exp Ther* **329**: 2–13. [PMID:19141710]
268. Beukers MW *et al*. (2000) *Mol Pharmacol* **58**: 1349–1356. [PMID:11093773]
269. Borrmann T *et al*. (2009) *J Med Chem* **52**: 3994–4006. [PMID:19569717]
270. Bosch MP *et al*. (2004) *J Med Chem* **47**: 4041–4053. [PMID:15267242]
271. Brambilla R *et al*. (2000) *Naunyn Schmiedebergs Arch Pharmacol* **361**: 225–234. [PMID:10731034]
272. Briddon SJ *et al*. (2004) *Proc Natl Acad Sci USA* **101**: 4673–4678. [PMID:15070776]
273. Cunha RA *et al*. (1996) *Naunyn Schmiedebergs Arch Pharmacol* **353**: 261–271. [PMID:8692280]
274. Dalpiaz A *et al*. (1998) *Biochem Pharmacol* **56**: 1437–1445. [PMID:9827575]
275. de Ligt RA *et al*. (2005) *Eur J Pharmacol* **510**: 1–8. [PMID:15740718]
276. Dionisotti S *et al*. (1997) *Br J Pharmacol* **121**: 353–360. [PMID:9179373]
277. Eckle T *et al*. (2007) *Circulation* **115**: 1581–1590. [PMID:17353435]
278. Feoktistov I *et al*. (2001) *Biochem Pharmacol* **62**: 1163–1173. [PMID:11705449]
279. Franchetti P *et al*. (2009) *J Med Chem* **52**: 2393–2406. [PMID:19317449]
280. Fredholm BB *et al*. (2001) *Pharmacol Rev* **53**: 527–552. [PMID:11734617]
281. Gallo-Rodriguez C *et al*. (1994) *J Med Chem* **37**: 636–646. [PMID:8126704]
282. Gao ZG *et al*. (2000) *Biochem Pharmacol* **60**: 661–668. [PMID:10927024]
283. Gao ZG *et al*. (2004) *Biochem Pharmacol* **68**: 1985–1993. [PMID:15476669]

284. Hayallah AM *et al.* (2002) *J Med Chem* **45**: 1500–1510. [PMID:11906291]
285. Heitman LH *et al.* (2006) *Br J Pharmacol* **147**: 533–541. [PMID:16444290]
286. Iredale PA *et al.* (1994) *Br J Pharmacol* **111**: 1252–1256. [PMID:8032613]
287. Jaakola VP *et al.* (2008) *Science* **322**: 1211–1217. [PMID:18832607]
288. Jacobson KA, Gao ZG. (2006) *Nat Rev Drug Discov* **5**: 247–264. [PMID:16518376]
289. Jacobson KA *et al.* (1997) *Neuropharmacology* **36**: 1157–1165. [PMID:9364471]
290. Jacobson MA *et al.* (1995) *Genomics* **27**: 374–376. [PMID:7558011]
291. Jarvis MF *et al.* (1989) *J Pharmacol Exp Ther* **251**: 888–893. [PMID:2600819]
292. Ji X *et al.* (2001) *Biochem Pharmacol* **61**: 657–663. [PMID:11266650]
293. Ji XD, Jacobson KA. (1999) *Drug Des Discov* **16**: 217–226. [PMID:10624567]
294. Jiang JL *et al.* (1996) *J Med Chem* **39**: 4667–4675. [PMID:8917655]
295. Jockers R *et al.* (1994) *J Biol Chem* **269**: 32077–32084. [PMID:7798201]
296. Johansson B, Fredholm BB. (1995) *Neuropharmacology* **34**: 393–403. [PMID:7566470]
297. Kalk P *et al.* (2007) *Br J Pharmacol* **151**: 1025–1032. [PMID:17558436]
298. Kim HO *et al.* (1994) *J Med Chem* **37**: 3614–3621. [PMID:7932588]
299. Kim J *et al.* (1995) *J Biol Chem* **270**: 13987–13997. [PMID:7775460]
300. Kim YC *et al.* (2000) *J Med Chem* **43**: 1165–1172. [PMID:10737749]
301. Kim YC *et al.* (1996) *J Med Chem* **39**: 4142–4148. [PMID:8863790]
302. Klotz K-N *et al.* (1998) *Naunyn Schmiedebergs Arch Pharmacol* **357**: 1–9. [PMID:9459566]
303. Kull B *et al.* (1999) *Biochem Pharmacol* **57**: 65–75. [PMID:9920286]
304. Li AH *et al.* (1998) *J Med Chem* **41**: 3186–3201. [PMID:9703464]
305. Liang BT *et al.* (2010) Adenosine A_3 receptors in muscle protection. in Adenosine Receptors from Cell Biology to Pharmacology Edited by Borea P Springer. 257–280 [ISBN:9789048131440]
306. Linden J *et al.* (1999) *Mol Pharmacol* **56**: 705–713. [PMID:10496952]
307. Lorenzen A *et al.* (1996) *Biochem Pharmacol* **52**: 1375–1385. [PMID:8937447]
308. Obiefuna PC *et al.* (2005) *J Pharmacol Exp Ther* **315**: 329–336. [PMID:16020631]
309. Ongini E *et al.* (1999) *Naunyn Schmiedebergs Arch Pharmacol* **359**: 7–10. [PMID:9933143]
310. Peirce SM *et al.* (2001) *Am J Physiol Heart Circ Physiol* **281**: H67–H74. [PMID:11406470]
311. Rivkees SA *et al.* (1999) *J Biol Chem* **274**: 3617–3621. [PMID:9920910]
312. Salvatore CA *et al.* (1993) *Proc Natl Acad Sci USA* **90**: 10365–10369. [PMID:8234299]
313. Shinkre BA *et al.* (2010) *Bioorg Med Chem Lett* **20**: 5690–5694. [PMID:20801028]
314. Stewart M *et al.* (2004) *Biochem Pharmacol* **68**: 305–312. [PMID:15194002]
315. Sullivan GW *et al.* (2001) *Br J Pharmacol* **132**: 1017–1026. [PMID:11226132]
316. Todde S *et al.* (2000) *J Med Chem* **43**: 4359–4362. [PMID:11087559]
317. Townsend-Nicholson A, Schofield PR. (1994) *J Biol Chem* **269**: 2373–2376. [PMID:8300561]
318. van Muijlwijk-Koezen JE *et al.* (2000) *J Med Chem* **43**: 2227–2238. [PMID:10841801]
319. Varani K *et al.* (2005) *Biochem Pharmacol* **70**: 1601–1612. [PMID:16219300]
320. Varani K *et al.* (2000) *Mol Pharmacol* **57**: 968–975. [PMID:10779381]
321. Wan W *et al.* (1990) *J Neurochem* **55**: 1763–1771. [PMID:2213023]
322. Weyler S *et al.* (2006) *ChemMedChem* **1**: 891–902. [PMID:16902942]
323. Xu F *et al.* (2011) *Science* **332**: 322–327. [PMID:21393508]
324. Yan L *et al.* (2003) *Expert Opin Emerg Drugs* **8**: 537–576. [PMID:14662005]
325. Yates L *et al.* (2006) *Auton Autacoid Pharmacol* **26**: 191–200. [PMID:16553647]
326. Fredriksson R *et al.* (2003) *Mol Pharmacol* **63**: 1256–1272. [PMID:12761335]
327. Jacobson SG *et al.* (2008) *Hum Mol Genet* **17**: 2405–2415. [PMID:18463160]
328. Luo R *et al.* (2011) *Proc Natl Acad Sci USA* **108**: 12925–12930. [PMID:21768377]
329. Park D *et al.* (2007) *Nature* **450**: 430–434. [PMID:17960134]
330. Xu L *et al.* (2006) *Proc Natl Acad Sci U S A* **103**: 9023–9028. [PMID:16757564]
331. Yona S *et al.* (2008) *Trends Biochem Sci* **33**: 491–500. [PMID:18789697]
332. Baker JG. (2005) *Br J Pharmacol* **144**: 317–322. [PMID:15655528]
333. Baker JG. (2010) *PLoS ONE* **5**: e15487. [PMID:21152092]
334. Baker JG. (2010) *Br J Pharmacol* **160**: 1048–1061. [PMID:20590599]
335. Baker JG *et al.* (2003) *Mol Pharmacol* **64**: 679–688. [PMID:12920204]
336. Baker JG *et al.* (2003) *Br J Pharmacol* **139**: 232–242. [PMID:12770928]
337. Baker JG *et al.* (2003) *Mol Pharmacol* **64**: 1357–1369. [PMID:14645666]
338. Blin N *et al.* (1993) *Mol Pharmacol* **44**: 1094–1104. [PMID:7903415]
339. Blue DR *et al.* (2004) *BJU Int* **93**: 162–170. [PMID:14678390]
340. Bylund DB *et al.* (1994) *Pharmacol Rev* **46**: 121–136. [PMID:7938162]
341. Candelore MR *et al.* (1999) *J Pharmacol Exp Ther* **290**: 649–655. [PMID:10411574]
342. Carroll WA *et al.* (2001) *Bioorganic & Medicinal Chemistry Letters* **11**: 1119–1121. [PMID:11354357]
343. Chang DJ *et al.* (1998) *FEBS Lett* **422**: 279–283. [PMID:9490024]
344. Cherezov V *et al.* (2007) *Science* **318**: 1258–1265. [PMID:17962520]
345. Cottingham C *et al.* (2011) *J Biol Chem* **286**: 36063–36075. [PMID:21859713]
346. Daniels DV *et al.* (1999) *Eur J Pharmacol* **370**: 337–343. [PMID:10334511]
347. De Ponti F *et al.* (1996) *Br J Pharmacol* **117**: 1374–1376. [PMID:8730727]
348. Dolan JA *et al.* (1994) *J Pharmacol Exp Ther* **269**: 1000–1006. [PMID:7912272]
349. Drake MT *et al.* (2008) *J Biol Chem* **283**: 5669–5676. [PMID:18086673]
350. Eason MG, Liggett SB. (1995) *J Biol Chem* **270**: 24753–24760. [PMID:7559592]
351. Evans BA *et al.* (2011) *Mol Pharmacol* **79**: 298–307. [PMID:20978120]
352. Evans BA *et al.* (1999) *Br J Pharmacol* **127**: 1525–1531. [PMID:10455305]
353. Evans BA *et al.* (2010) *Br J Pharmacol* **159**: 1022–1038. [PMID:20132209]
354. Flacco N *et al.* (2013) *Br J Pharmacol* **169**: 413–425. [PMID:23373597]
355. Ford APDW *et al.* (1997) *Br J Pharmacol* **121**: 1127–1135. [PMID:9249248]
356. Frielle T *et al.* (1988) *Proc Natl Acad Sci U S A* **85**: 9494–9498. [PMID:2849109]
357. Galandrin S, Bouvier M. (2006) *Mol Pharmacol* **70**: 1575–1584. [PMID:16901982]
358. Galandrin S *et al.* (2008) *Mol Pharmacol* **74**: 162–172. [PMID:18403719]
359. Hague C *et al.* (2004) *J Pharmacol Exp Ther* **309**: 388–397. [PMID:14718583]
360. Hieble JP. (2000) *Pharmaceutica Acta Helvetiae* **74**: 163–171. [PMID:10812954]
361. Hieble JP *et al.* (1995) *Pharmacol Rev* **47**: 267–270. [PMID:7568329]
362. Hoffmann C *et al.* (2004) *Naunyn Schmiedebergs Arch Pharmacol* **369**: 151–159. [PMID:14730417]
363. Hutchinson DS *et al.* (2002) *Br J Pharmacol* **135**: 1903–1914. [PMID:11959793]
364. Isogaya M *et al.* (1999) *Mol Pharmacol* **56**: 875–885. [PMID:10531390]
365. Jasper JR *et al.* (1998) *Biochem Pharmacol* **55**: 1035–1043. [PMID:9605427]
366. Joseph SS *et al.* (2004) *Naunyn Schmiedebergs Arch Pharmacol* **369**: 525–532. [PMID:15060759]
367. Kaumann AJ *et al.* (2001) *Naunyn Schmiedebergs Arch Pharmacol* **363**: 87–93. [PMID:11191841]
368. Kaumann AJ, Molenaar P. (1996) *Br J Pharmacol* **118**: 2085–2098. [PMID:8864547]
369. Knepper SM *et al.* (1995) *J Pharmacol Exp Ther* **274**: 97–103. [PMID:7616455]
370. Konkar AA *et al.* (2000) *Mol Pharmacol* **57**: 252–258. [PMID:10648634]
371. Leonardi A *et al.* (1997) *J Pharmacol Exp Ther* **281**: 1272–1283. [PMID:9190863]
372. Liu JJ *et al.* (2012) *Science* **335**: 1106–1110. [PMID:22267580]
373. Louis SN *et al.* (1999) *Eur J Pharmacol* **367**: 431–435. [PMID:10079020]
374. MacLennan SJ *et al.* (1997) *Br J Pharmacol* **121**: 1721–1729. [PMID:9283709]
375. Manara L *et al.* (1996) *Br J Pharmacol* **117**: 435–442. [PMID:8821531]
376. Mejean A *et al.* (1995) *Eur J Pharmacol* **291**: 359–366. [PMID:8719421]

377. Methven L *et al.* (2009) *Br J Pharmacol* **158**: 209–224. [PMID:19572943]
378. Methven L *et al.* (2009) *Br J Pharmacol* **158**: 1663–1675. [PMID:19888965]
379. Michel AD *et al.* (1990) *Br J Pharmacol* **99**: 560–564. [PMID:1970500]
380. Molenaar P *et al.* (1997) *Br J Pharmacol* **120**: 165–176. [PMID:9117106]
381. Morishima S *et al.* (2007) *J Urol* **177**: 377–381. [PMID:17162094]
382. Nishimune A *et al.* (2010) *J Pharmacol Sci* **113**: 169–181. [PMID:20508391]
383. Nishimune A *et al.* (2012) *Br J Pharmacol* **165**: 1226–1234. [PMID:21745191]
384. Pauwels PJ *et al.* (2003) *J Pharmacol Exp Ther* **305**: 1015–1023. [PMID:12649300]
385. Popp BD *et al.* (2004) *Eur J Pharmacol* **484**: 323–331. [PMID:14744619]
386. Quinton L *et al.* (2010) *Br J Pharmacol* **159**: 316–325. [PMID:20015090]
387. Ramsay D *et al.* (2004) *Mol Pharmacol* **66**: 228–239. [PMID:15266013]
388. Rasmussen SG *et al.* (2011) *Nature* **469**: 175–180. [PMID:21228869]
389. Rasmussen SG *et al.* (2011) *Nature* **477**: 549–555. [PMID:21772288]
390. Rosenbaum DM *et al.* (2011) *Nature* **469**: 236–240. [PMID:21228876]
391. Rosengren AH *et al.* (2010) *Science* **327**: 217–220. [PMID:19965390]
392. Sallinen J *et al.* (2007) *Br J Pharmacol* **150**: 391–402. [PMID:17220913]
393. Sato M *et al.* (2007) *Mol Pharmacol* **72**: 1359–1368. [PMID:17717109]
394. Sato M *et al.* (2008) *Mol Pharmacol* **74**: 1417–1428. [PMID:18684840]
395. Sato Y *et al.* (1996) *Eur J Pharmacol* **315**: 363–367. [PMID:8982677]
396. Sharpe IA *et al.* (2003) *J Biol Chem* **278**: 34451–34457. [PMID:12824165]
397. Shibata K *et al.* (1995) *Mol Pharmacol* **48**: 250–258. [PMID:7651358]
398. Small KM *et al.* (2006) *Biochemistry* **45**: 4760–4767. [PMID:16605244]
399. Strosberg AD. (1997) *Annu Rev Pharmacol Toxicol* **37**: 421–450. [PMID:9131260]
400. Suzuki T *et al.* (1993) *J Pharmacol Exp Ther* **267**: 785–790. [PMID:7902433]
401. Tan M *et al.* (2009) *J Biol Chem* **284**: 6270–6281. [PMID:19126537]
402. Uberti MA *et al.* (2005) *J Pharmacol Exp Ther* **313**: 16–23. [PMID:15615865]
403. Uhlén S *et al.* (1994) *J Pharmacol Exp Ther* **271**: 1558–1565. [PMID:7996470]
404. Ventura S. (2012) *Br J Pharmacol* **165**: 1223–1225. [PMID:21913893]
405. Vilardaga JP *et al.* (2008) *Nat Chem Biol* **4**: 126–131. [PMID:18193048]
406. Warne T *et al.* (2011) *Nature* **469**: 241–244. [PMID:21228877]
407. Warne T *et al.* (2008) *Nature* **454**: 486–491. [PMID:18594507]
408. Weber AE *et al.* (1998) *Bioorg Med Chem Lett* **8**: 2111–2116. [PMID:9873496]
409. Wetzel JM *et al.* (1995) *J Med Chem* **38**: 1579–1581. [PMID:7752182]
410. Williams TJ *et al.* (1999) *Br J Pharmacol* **127**: 252–258. [PMID:10369480]
411. Yanagisawa T *et al.* (2000) *Tohoku J Exp Med* **192**: 181–193. [PMID:11249148]
412. Yang J *et al.* (2012) *J Biol Chem* **287**: 24795–24806. [PMID:22645144]
413. Yoshio R *et al.* (2001) *Jpn J Pharmacol* **86**: 189–195. [PMID:11459121]
414. Young P *et al.* (1989) *Eur J Pharmacol* **168**: 381–386. [PMID:2573535]
415. (1988) *Ann N Y Acad Sci* **547**: 1–541. [PMID:3071214]
416. AbdAlla S *et al.* (2000) *Nature* **407**: 94–98. [PMID:10993080]
417. Bosnyak S *et al.* (2011) *Clin Sci* **121**: 297–303. [PMID:21542804]
418. Cappelli A *et al.* (2004) *J Med Chem* **47**: 2574–2586. [PMID:15115399]
419. Chang RS, Lotti VJ. (1990) *Mol Pharmacol* **37**: 347–351. [PMID:2314387]
420. Chansel D *et al.* (1993) *Eur J Pharmacol* **247**: 193–198. [PMID:8282008]
421. Chen TB *et al.* (1992) *Mol Pharmacol* **42**: 1077–1082. [PMID:1480133]
422. Chiu AT *et al.* (1989) *Biochem Biophys Res Commun* **165**: 196–203. [PMID:2590220]
423. Chiu AT *et al.* (1992) *Biochem Biophys Res Commun* **188**: 1030–1039. [PMID:1445340]
424. de Gasparo M *et al.* (2000) *Pharmacol Rev* **52**: 415–472. [PMID:10977869]
425. de Gasparo M, Whitebread S. (1995) *Regul Pept* **59**: 303–311. [PMID:8577935]
426. de Gasparo M *et al.* (1994) Heterogeneity of angiotensin receptor subtypes. *In* Medicinal Chemistry of the Renin-Angiotensin System. *Edited by* Timmermanns PBMWM, Wexler RR Elsevier. 269–294 [ISBN:0444820531]
427. Dudley DT *et al.* (1990) *Mol Pharmacol* **38**: 370–377. [PMID:2402226]
428. Dudley DT, Summerfelt RM. (1993) *Regul Pept* **44**: 199–206. [PMID:8469774]
429. Edwards RM *et al.* (1992) *J Pharmacol Exp Ther* **260**: 175–181. [PMID:1309870]
430. Hancock AA *et al.* (1994) *Eur J Pharmacol* **267**: 49–54. [PMID:8206129]
431. Luttrell LM, Gesty-Palmer D. (2010) *Pharmacol Rev* **62**: 305–330. [PMID:20427692]
432. Moeller I *et al.* (1997) *J Neurochem* **68**: 2530–2537. [PMID:9166749]
433. Perlman S *et al.* (1995) *J Biol Chem* **270**: 1493–1496. [PMID:7829475]
434. Speth RC, Kim KH. (1990) *Biochem Biophys Res Commun* **169**: 997–1006. [PMID:2194459]
435. Timmermans PBMWM *et al.* (1993) *Pharmacol Rev* **45**: 205–251. [PMID:8372104]
436. Vanderheyden PML *et al.* (1999) *Br J Pharmacol* **126**: 1057–1065. [PMID:10193788]
437. Verheijen I *et al.* (2000) *Fundam Clin Pharmacol* **14**: 577–585. [PMID:11206708]
438. Whitebread S *et al.* (1989) *Biochem Biophys Res Commun* **163**: 284–291. [PMID:2775266]
439. Whitebread SE *et al.* (1991) *Biochem Biophys Res Commun* **181**: 1365–1371. [PMID:1764088]
440. Wiest SA *et al.* (1991) *J Cardiovasc Pharmacol* **17**: 177–184. [PMID:1709220]
441. Cayabyab M *et al.* (2000) *J Virol* **74**: 11972–11976. [PMID:11090199]
442. El Messari S *et al.* (2004) *J Neurochem* **90**: 1290–1301. [PMID:15341513]
443. Fan X *et al.* (2003) *Biochemistry* **42**: 10163–10168. [PMID:12939143]
444. Hosoya M *et al.* (2000) *J Biol Chem* **275**: 21061–21067. [PMID:10777510]
445. Katugampola SD *et al.* (2001) *Br J Pharmacol* **132**: 1255–1260. [PMID:11250876]
446. Kawamata Y *et al.* (2001) *Biochim Biophys Acta* **1538**: 162–171. [PMID:11336787]
447. Lee DK *et al.* (2005) *Endocrinology* **146**: 231–236. [PMID:15486224]
448. Medhurst AD *et al.* (2003) *J Neurochem* **84**: 1162–1172. [PMID:12603839]
449. Pitkin SL *et al.* (2010) *Pharmacol Rev* **62**: 331–342. [PMID:20605969]
450. Tatemoto K *et al.* (1998) *Biochem Biophys Res Commun* **251**: 471–476. [PMID:9792798]
451. Genet C *et al.* (2010) *J Med Chem* **53**: 178–190. [PMID:19911773]
452. Kawamata Y *et al.* (2003) *J Biol Chem* **278**: 9435–9440. [PMID:12524422]
453. Londregan AT *et al.* (2013) *Med Chem Lett* **23**: 1407–1411. [PMID:23337601]
454. Maruyama T *et al.* (2002) *Biochem Biophys Res Commun* **298**: 714–719. [PMID:12419312]
455. Sato H *et al.* (2007) *Biochem Biophys Res Commun* **362**: 793–798. [PMID:17825251]
456. Takada Y, Aggarwal BB. (2003) *J Immunol* **171**: 3278–3286. [PMID:12960358]
457. Vassileva G *et al.* (2006) *Biochem J* **398**: 423–430. [PMID:16724960]
458. Benya RV *et al.* (1995) *Mol Pharmacol* **47**: 10–20. [PMID:7838118]
459. González N *et al.* (2009) *Peptides* **30**: 1473–1486. [PMID:19463875]
460. Hall MD *et al.* (1996) *Bioorganic and Medicinal Chemistry Letters* **6**: 2617–2622.
461. Heimbrook DC *et al.* (1989) *J Biol Chem* **264**: 11258–11262. [PMID:2544588]
462. Jensen RT *et al.* (2008) *Pharmacol Rev* **60**: 1–42. [PMID:18055507]
463. Jian X *et al.* (1999) *J Biol Chem* **274**: 11573–11581. [PMID:10206964]
464. Llinares M *et al.* (1999) *J Pept Res* **53**: 275–283. [PMID:10231715]
465. Mantey S *et al.* (1993) *Mol Pharmacol* **43**: 762–774. [PMID:7684815]
466. Mantey SA *et al.* (2004) *J Pharmacol Exp Ther* **310**: 1161–1170. [PMID:15102928]
467. Mantey SA *et al.* (1997) *J Biol Chem* **272**: 26062–26071. [PMID:9325344]
468. Ryan R *et al.* (1999) *J Pharmacol Exp Ther* **290**: 1202–1211. [PMID:10454496]
469. Tokita K *et al.* (2002) *Mol Pharmacol* **61**: 1435–1443. [PMID:12021405]
470. Tokita K *et al.* (2001) *J Biol Chem* **276**: 36652–36663. [PMID:11463790]
471. Austin CE *et al.* (1997) *J Biol Chem* **272**: 11420–11425. [PMID:9111052]
472. Bastian S *et al.* (1997) *Br J Pharmacol* **122**: 393–399. [PMID:9313952]

473. Gera L *et al.* (2006) *J Pharmacol Exp Ther* **317**: 300–308. [PMID:16368899]
474. Gobeil F *et al.* (1999) *Hypertension* **33**: 823–829. [PMID:10082494]
475. Gobeil F *et al.* (1996) *Hypertension* **28**: 833–839. [PMID:8901831]
476. Gobeil F *et al.* (1996) *Br J Pharmacol* **118**: 289–294. [PMID:8735629]
477. Jones C *et al.* (1999) *Eur J Pharmacol* **374**: 423–433. [PMID:10422787]
478. Leeb-Lundberg LM *et al.* (2005) *Pharmacol Rev* **57**: 27–77. [PMID:15734727]
479. Pruneau D *et al.* (1999) *Immunopharmacology* **43**: 187–194. [PMID:10596852]
480. Regoli D *et al.* (1998) *Eur J Pharmacol* **348**: 1–10. [PMID:9650825]
481. Rizzi A *et al.* (1997) *Hypertension* **29**: 951–956. [PMID:9095082]
482. Windischhofer W, Leis HJ. (1997) *J Bone Miner Res* **12**: 1615–1625. [PMID:9333122]
483. Zhang SP, Codd EE. (1998) *Life Sci* **62**: 2303–2314. [PMID:9651119]
484. Zhang SP *et al.* (2001) *Int Immunopharmacol* **1**: 955–965. [PMID:11379050]
485. Aiyar N *et al.* (2001) *Mol Cell Biochem* **224**: 123–133. [PMID:11693189]
486. Albrandt K *et al.* (1995) *Endocrinology* **136**: 5377–5384. [PMID:7588285]
487. Armour SL *et al.* (1999) *J Pharmacol Toxicol Methods* **42**: 217–224. [PMID:11033437]
488. Christopoulos G *et al.* (1999) *Mol Pharmacol* **56**: 235–242. [PMID:10385705]
489. Doods H *et al.* (2000) *Br J Pharmacol* **129**: 420–423. [PMID:10711339]
490. Evans BN *et al.* (2000) *J Biol Chem* **275**: 31438–31443. [PMID:10903324]
491. Fraser NJ *et al.* (1999) *Mol Pharmacol* **55**: 1054–1059. [PMID:10347248]
492. Hay DL *et al.* (2005) *Mol Pharmacol* **67**: 1655–1665. [PMID:15692146]
493. Hay DL *et al.* (2006) *Mol Pharmacol* **70**: 1984–1991. [PMID:16959943]
494. Hay DL *et al.* (2003) *Br J Pharmacol* **140**: 477–486. [PMID:12970090]
495. Hay DL *et al.* (2008) *Pharmacol Rev* **60**: 143–145. [PMID:18552275]
496. Hong Y *et al.* (2011) *Br J Pharmacol* [Epub ahead of print]. [PMID:21658025]
497. Katafuchi T *et al.* (2003) *J Biol Chem* **278**: 12046–12054. [PMID:12556539]
498. Kuwasako K *et al.* (2003) *Biochem Biophys Res Commun* **301**: 460–464. [PMID:12565884]
499. Leuthauser K *et al.* (2000) *Biochem J* **351**: 347–351. [PMID:11023820]
500. Mallee JJ *et al.* (2002) *J Biol Chem* **277**: 14294–14298. [PMID:11847213]
501. McLatchie LM *et al.* (1998) *Nature* **393**: 333–339. [PMID:9620797]
502. Morfis M *et al.* (2008) *Endocrinology* **149**: 5423–5431. [PMID:18599553]
503. Muff R *et al.* (1999) *Endocrinology* **140**: 2924–2927. [PMID:10342886]
504. Poyner DR *et al.* (2002) *Pharmacol Rev* **54**: 233–246. [PMID:12037140]
505. Qi T *et al.* (2013) *Br J Pharmacol* **168**: 644–657. [PMID:22946511]
506. Salvatore CA *et al.* (2008) *J Pharmacol Exp Ther* **324**: 416–421. [PMID:18039958]
507. Tilakaratne N *et al.* (2000) *J Pharmacol Exp Ther* **294**: 61–72. [PMID:10871296]
508. Walker CS *et al.* (2010) *Trends Pharmacol Sci* **31**: 476–483. [PMID:20633935]
509. Brown EM *et al.* (1993) *Nature* **366**: 575–580. [PMID:8255296]
510. Chang W *et al.* (2008) *Sci Signal* **1**: ra1. [PMID:18765830]
511. Conigrave AD *et al.* (2000) *Proc Natl Acad Sci USA* **97**: 4814–4819. [PMID:10781086]
512. Ho C *et al.* (1995) *Nat Genet* **11**: 389–394. [PMID:7493018]
513. Kessler A *et al.* (2004) *Bioorg Med Chem Lett* **14**: 3345–3349. [PMID:15149704]
514. Ma JN *et al.* (2011) *J Pharmacol Exp Ther* **337**: 275–284. [PMID:21239511]
515. Nemeth EF *et al.* (2001) *J Pharmacol Exp Ther* **299**: 323–331. [PMID:11561095]
516. Nemeth EF *et al.* (2004) *J Pharmacol Exp Ther* **308**: 627–635. [PMID:14593085]
517. Nemeth EF *et al.* (1998) *Proc Natl Acad Sci U S A* **95**: 4040–4045. [PMID:9520489]
518. Petrel C *et al.* (2004) *J Biol Chem* **279**: 18990–18997. [PMID:14976203]
519. Petrel C *et al.* (2003) *J Biol Chem* **278**: 49487–49494. [PMID:14506236]
520. Quinn SJ *et al.* (2004) *J Biol Chem* **279**: 37241–37249. [PMID:15201280]
521. Quinn SJ *et al.* (1998) *J Biol Chem* **273**: 19579–19586. [PMID:9677383]
522. Quinn SJ *et al.* (1997) *Am J Physiol* **273**: C1315–C1323. [PMID:9357776]
523. Ward DT, Riccardi D. (2012) *Br J Pharmacol* **165**: 35–48. [PMID:21627634]
524. Wellendorph P *et al.* (2005) *Mol Pharmacol* **67**: 589–597. [PMID:15576628]
525. Yang W *et al.* (2005) *Bioorg Med Chem Lett* **15**: 1225–1228. [PMID:15686947]
526. Alexander SP, Kendall DA. (2007) *Br J Pharmacol* **152**: 602–623. [PMID:17876303]
527. Breivogel CS *et al.* (1997) *J Pharmacol Exp Ther* **282**: 1632–1642. [PMID:9316881]
528. Di Marzo V *et al.* (2001) *Biochem Biophys Res Commun* **281**: 444–451. [PMID:11181068]
529. Felder CC *et al.* (1998) *J Pharmacol Exp Ther* **284**: 291–297. [PMID:9435190]
530. Felder CC *et al.* (1995) *Mol Pharmacol* **48**: 443–450. [PMID:7565624]
531. Gareau Y *et al.* (1996) *Bioorg Med Chem Lett* **6**: 189–194.
532. Hanus L *et al.* (1999) *Proc Natl Acad Sci USA* **96**: 14228–14233. [PMID:10588688]
533. Hillard CJ *et al.* (1999) *J Pharmacol Exp Ther* **289**: 1427–1433. [PMID:10336536]
534. Hirst RA *et al.* (1996) *Neurosci Lett* **220**: 101–104. [PMID:8981483]
535. Huffman JW *et al.* (1999) *Bioorg Med Chem* **7**: 2905–2914. [PMID:10658595]
536. Jung M *et al.* (1997) *J Neurochem* **68**: 402–409. [PMID:8978752]
537. Khanolkar AD *et al.* (1996) *J Med Chem* **39**: 4515–4519. [PMID:8893848]
538. Lan R *et al.* (1999) *AAPS Pharmsci* **1**: E4-null. [PMID:11741201]
539. Lan R *et al.* (1999) *J Med Chem* **42**: 769–776. [PMID:10052983]
540. O'Sullivan SE. (2007) *Br J Pharmacol* **152**: 576–582. [PMID:17704824]
541. Pertwee RG. (2000) *Expert Opin Investig Drugs* **9**: 1553–1571. [PMID:11060760]
542. Pertwee RG *et al.* (2010) *Pharmacol Rev* **62**: 588–631. [PMID:21079038]
543. Petitet F *et al.* (1996) *Neuroreport* **7**: 789–792. [PMID:8733746]
544. Price MR *et al.* (2005) *Mol Pharmacol* **68**: 1484–1495. [PMID:16113085]
545. Rinaldi-Carmona M *et al.* (1994) *FEBS Lett* **350**: 240–244. [PMID:8070571]
546. Rinaldi-Carmona M *et al.* (1998) *J Pharmacol Exp Ther* **284**: 644–650. [PMID:9454810]
547. Rinaldi-Carmona M *et al.* (1996) *Life Sci* **58**: 1239–1247. [PMID:8614277]
548. Ross RA *et al.* (1999) *Br J Pharmacol* **126**: 665–672. [PMID:10188977]
549. Ruiu S *et al.* (2003) *J Pharmacol Exp Ther* **306**: 363–370. [PMID:12663689]
550. Showalter VM *et al.* (1996) *J Pharmacol Exp Ther* **278**: 989–999. [PMID:8819477]
551. Sim LJ *et al.* (1996) *J Neurosci* **16**: 8057–8066. [PMID:8987831]
552. Slipetz DM *et al.* (1995) *Mol Pharmacol* **48**: 352–361. [PMID:7651369]
553. Song ZH, Bonner TI. (1996) *Mol Pharmacol* **49**: 891–896. [PMID:8622639]
554. Thomas BF *et al.* (1998) *J Pharmacol Exp Ther* **285**: 285–292. [PMID:9536023]
555. Yao BB *et al.* (2006) *Br J Pharmacol* **149**: 145–154. [PMID:16894349]
556. Zygmunt PM *et al.* (1999) *Nature* **400**: 452–457. [PMID:10440374]
557. Arita M *et al.* (2005) *J Exp Med* **201**: 713–722. [PMID:15753205]
558. Arita M *et al.* (2007) *J Immunol* **178**: 3912–3917. [PMID:17339491]
559. Krishnamoorthy S *et al.* (2010) *Proc Natl Acad Sci USA* **107**: 1660–16605. [PMID:20080636]
560. Luangsay S *et al.* (2009) *J Immunol* **183**: 6489–6499. [PMID:19841182]
561. Meder W *et al.* (2003) *FEBS Lett* **555**: 495–499. [PMID:14675762]
562. Zabel BA *et al.* (2005) *J Immunol* **174**: 244–251. [PMID:15611246]
563. Ahuja SK, Murphy PM. (1996) *J Biol Chem* **271**: 20545–20550. [PMID:8702798]
564. Ai LS, Liao F. (2002) *Biochemistry* **41**: 8332–8341. [PMID:12081481]
565. Baba M *et al.* (1997) *J Biol Chem* **272**: 14893–14898. [PMID:9169459]
566. Baba M *et al.* (1999) *Proc Natl Acad Sci USA* **96**: 5698–5703. [PMID:10318947]
567. Barnea G *et al.* (2008) *Proc Natl Acad Sci USA* **105**: 64–69. [PMID:18165312]
568. Ben-Baruch A *et al.* (1995) *J Biol Chem* **270**: 22123–22128. [PMID:7545673]
569. Bertini R *et al.* (2004) *Proc Natl Acad Sci U S A* **101**: 11791–11796. [PMID:15282370]
570. Blanpain C *et al.* (1999) *Blood* **94**: 1899–1905. [PMID:10477718]

571. Chou CC *et al.* (2002) *Br J Pharmacol* **137**: 663–675. [PMID:12381680]
572. Combadiere C *et al.* (1995) *J Biol Chem* **270**: 29671–29675. [PMID:8530354]
573. Coulin F *et al.* (1997) *Eur J Biochem* **248**: 507–515. [PMID:9346309]
574. Dairaghi DJ *et al.* (1999) *J Biol Chem* **274**: 21569–21574. [PMID:10419462]
575. Daugherty BL *et al.* (1996) *J Exp Med* **183**: 2349–2354. [PMID:8642344]
576. Di Salvo J *et al.* (2000) *Eur J Pharmacol* **409**: 143–154. [PMID:11104827]
577. Duggal P *et al.* (2003) *Genes Immun* **4**: 245–250. [PMID:12761559]
578. Garin A *et al.* (2003) *J Immunol* **171**: 5305–5312. [PMID:14607932]
579. Gladue RP *et al.* (2003) *J Biol Chem* **278**: 40473–40480. [PMID:12909630]
580. Gong X *et al.* (1997) *J Biol Chem* **272**: 11682–11685. [PMID:9115216]
581. Gravel S *et al.* (2010) *J Biol Chem* [Epub ahead of print]. [PMID:20956518]
582. Greaves DR *et al.* (1997) *J Exp Med* **186**: 837–844. [PMID:9294138]
583. Habasque C *et al.* (2002) *Mol Hum Reprod* **8**: 419–425. [PMID:11994538]
584. Hall DA *et al.* (1999) *Br J Pharmacol* **126**: 810–818. [PMID:10188995]
585. Haskell CA *et al.* (2006) *Mol Pharmacol* **69**: 309–316. [PMID:16221874]
586. Heise CE *et al.* (2005) *J Pharmacol Exp Ther* **313**: 1263–1271. [PMID:15761110]
587. Hesselgesser J *et al.* (1998) *J Immunol* **160**: 877–883. [PMID:9551924]
588. Hesselgesser J *et al.* (1998) *J Biol Chem* **273**: 15687–15692. [PMID:9624164]
589. Imai T *et al.* (1998) *J Biol Chem* **273**: 1764–1768. [PMID:9430724]
590. Inngjerdingen M *et al.* (2001) *Blood* **97**: 367–375. [PMID:11154210]
591. Kitaura M *et al.* (1999) *J Biol Chem* **274**: 27975–27980. [PMID:10488147]
592. Lee J *et al.* (1992) *J Biol Chem* **267**: 16283–16287. [PMID:1379593]
593. Liang M *et al.* (2000) *J Biol Chem* **275**: 19000–19008. [PMID:10748002]
594. Loetscher P *et al.* (1998) *J Biol Chem* **273**: 22279–22283. [PMID:9712844]
595. Lüttichau HR *et al.* (2003) *J Biol Chem* **278**: 10928–10933. [PMID:12554737]
596. Maeda K *et al.* (2006) *J Biol Chem* **281**: 12688–12698. [PMID:16476734]
597. Maeda K *et al.* (2001) *J Biol Chem* **276**: 35194–35200. [PMID:11454872]
598. Mirzadegan T *et al.* (2000) *J Biol Chem* **275**: 25562–25571. [PMID:10770925]
599. Morokata T *et al.* (2005) *J Pharmacol Exp Ther* : -. [PMID:16339911]
600. Murphy PM. (2002) *Pharmacol Rev* **54**: 227–229. [PMID:12037138]
601. Murphy PM *et al.* (2000) *Pharmacol Rev* **52**: 145–176. [PMID:10699158]
602. Napier C *et al.* (2005) *Biochem Pharmacol* **71**: 163–172. [PMID:16298345]
603. Naya A *et al.* (2003) *Bioorg Med Chem* **11**: 875–884. [PMID:12614873]
604. Palani A *et al.* (2001) *J Med Chem* **44**: 3339–3342. [PMID:11585437]
605. Parody TR, Stone MJ. (2004) *Cytokine* **27**: 38–46. [PMID:15207250]
606. Power CA *et al.* (1997) *J Exp Med* **186**: 825–835. [PMID:9294137]
607. Richardson RM *et al.* (2003) *J Immunol* **170**: 2904–2911. [PMID:12626541]
608. Roos RS *et al.* (1997) *J Biol Chem* **272**: 17251–17254. [PMID:9211859]
609. Ruffing N *et al.* (1998) *Cell Immunol* **189**: 160–168. [PMID:9790730]
610. Sabroe I *et al.* (2000) *J Biol Chem* **275**: 25985–25992. [PMID:10854442]
611. Sarau HM *et al.* (1997) *J Pharmacol Exp Ther* **283**: 411–418. [PMID:9336350]
612. Southern C *et al.* (2013) *J Biomol Screen* **18**: 599–609. [PMID:23396314]
613. Strizki JM *et al.* (2005) *Antimicrob Agents Chemother* **49**: 4911–4919. [PMID:16304152]
614. Tamamura H *et al.* (1998) *Biochem Biophys Res Commun* **253**: 877–882. [PMID:9918823]
615. Uguccioni M *et al.* (1997) *J Clin Invest* **100**: 1137–1143. [PMID:9276730]
616. Wacker DA *et al.* (2002) *Bioorg Med Chem Lett* **12**: 1785–1789. [PMID:12067561]
617. Wan Y *et al.* (2002) *Eur J Pharmacol* **456**: 1–10. [PMID:12450563]
618. Watts AO *et al.* (2013) *J Biol Chem* **288**: 7169–7181. [PMID:23341447]
619. Weng Y *et al.* (1998) *J Biol Chem* **273**: 18288–18291. [PMID:9660793]
620. White JR *et al.* (1998) *J Biol Chem* **273**: 10095–10098. [PMID:9553055]
621. Wilbanks A *et al.* (2001) *J Immunol* **166**: 5145–5154. [PMID:11290797]
622. Wilson S *et al.* (2005) *J Biol Chem* **280**: 28663–28674. [PMID:15946947]
623. Wu L *et al.* (1996) *J Biol Chem* **271**: 31202–31209. [PMID:8940121]
624. Wuyts A *et al.* (1998) *Eur J Biochem* **255**: 67–73. [PMID:9692902]
625. Yang D *et al.* (1999) *Science* **286**: 525–528. [PMID:10521347]
626. Yoshida R *et al.* (1997) *J Biol Chem* **272**: 13803–13809. [PMID:9153236]
627. Yoshida R *et al.* (1998) *J Biol Chem* **273**: 7118–7122. [PMID:9507024]
628. Yoshie O, Zlotnik A. (2000) *Immunity* **2**: 121–127. [PMID:10714678]
629. Zhang WB *et al.* (2002) *J Biol Chem* **277**: 24515–24521. [PMID:11923301]
630. Zoffmann S *et al.* (2001) *J Med Chem* **44**: 215–222. [PMID:11170631]
631. Akgün E *et al.* (2009) *J Med Chem* **52**: 2138–2147. [PMID:19271701]
632. Gouldson P *et al.* (2000) *Eur J Pharmacol* **400**: 185–194. [PMID:10988332]
633. Henke BR *et al.* (1997) *J Med Chem* **40**: 2706–2725. [PMID:9276016]
634. Hughes J *et al.* (1990) *Proc Natl Acad Sci U S A* **87**: 6728–6732. [PMID:1975695]
635. Hunter JC *et al.* (1993) *Mol Pharmacol* **43**: 595–602. [PMID:8474432]
636. Ito M *et al.* (1993) *J Biol Chem* **268**: 18300–18305. [PMID:8349705]
637. Iwamoto Y *et al.* (1987) *Pancreas* **2**: 85–90. [PMID:2437574]
638. Jagerschmidt A *et al.* (1996) *Eur J Pharmacol* **296**: 97–106. [PMID:8720482]
639. Kennedy K *et al.* (1995) *Biochem Biophys Res Commun* **213**: 845–852. [PMID:7654246]
640. Lee YM *et al.* (1993) *J Biol Chem* **268**: 8164–8169. [PMID:7681836]
641. Lindström E *et al.* (1999) *Br J Pharmacol* **127**: 530–536. [PMID:10385255]
642. Morton MF *et al.* (2011) *J Pharmacol Exp Ther* **338**: 328–336. [PMID:21493750]
643. Nilsson I *et al.* (2002) *Regul Pept* **103**: 29–37. [PMID:11738246]
644. Noble F *et al.* (1999) *Pharmacol Rev* **51**: 745–781. [PMID:10581329]
645. Powers SP *et al.* (1988) *Int J Pept Protein Res* **31**: 429–434. [PMID:3410633]
646. Rasmussen SG *et al.* (2011) *Nature* **469**: 175–180. [PMID:21228869]
647. Singh L *et al.* (1995) *Eur J Pharmacol* **286**: 185–191. [PMID:8605955]
648. Smith JP *et al.* (2002) *Int J Mol Med* **10**: 689–694. [PMID:12429993]
649. Song I *et al.* (1993) *Proc Natl Acad Sci U S A* **90**: 9085–9089. [PMID:8415658]
650. Taniguchi H *et al.* (1996) *Eur J Pharmacol* **304**: 147–154. [PMID:8813597]
651. Ursini A *et al.* (2000) *J Med Chem* **43**: 3596–3613. [PMID:11020274]
652. Ames RS *et al.* (2001) *J Immunol* **166**: 6341–6348. [PMID:11342658]
653. Ames RS *et al.* (1996) *FEBS Lett* **395**: 157–159. [PMID:8898085]
654. Ames RS *et al.* (1997) *Immunopharmacology* **38**: 87–92. [PMID:9476119]
655. Bamberg CE *et al.* (2010) *J Biol Chem* **285**: 7633–7644. [PMID:20044484]
656. Cain SA, Monk PN. (2002) *J Biol Chem* **277**: 7165–7169. [PMID:11773063]
657. Chao TH *et al.* (1999) *J Biol Chem* **274**: 9721–9728. [PMID:10092660]
658. Gao H *et al.* (2005) *FASEB J* **19**: 1003–1005. [PMID:15784721]
659. Gavrilyuk V *et al.* (2005) *J Neurochem* **92**: 1140–1149. [PMID:15715664]
660. Honczarenko M *et al.* (2005) *Leukemia* **19**: 1682–1683; author reply 1684–5. [PMID:15990859]
661. Huey R, Hugli TE. (1985) *J Immunol* **135**: 2063–2068. [PMID:4020139]
662. Kalant D *et al.* (2003) *J Biol Chem* **278**: 11123–11129. [PMID:12540846]
663. Kalant D *et al.* (2005) *J Biol Chem* **280**: 23936–23944. [PMID:15833747]
664. Kawai M *et al.* (1992) *J Med Chem* **35**: 220–223. [PMID:1732540]
665. Klos A *et al.* (2013) *Pharmacol Rev* **65**: 500–543. [PMID:23383423]
666. Konteatis ZD *et al.* (1994) *J Immunol* **153**: 4200–4205. [PMID:7930622]
667. Li R *et al.* (2013) *FASEB J* **27**: 855–864. [PMID:23239822]
668. Mathieu MC *et al.* (2005) *Immunol Lett* **100**: 139–145. [PMID:16154494]

669. Okinaga S *et al.* (2003) *Biochemistry* **42**: 9406–9415. [PMID:12899627]
670. Postma B *et al.* (2004) *J Immunol* **172**: 6994–7001. [PMID:15153520]
671. Scola AM *et al.* (2009) *Mol Immunol* **46**: 1149–1162. [PMID:19100624]
672. Sumichika H *et al.* (2002) *J Biol Chem* **277**: 49403–49407. [PMID:12384495]
673. Van Lith LH *et al.* (2009) *J Biomol Screen* **14**: 1067–1075. [PMID:19641221]
674. Wong AK *et al.* (1998) *J Med Chem* **41**: 3417–3425. [PMID:9719594]
675. Yamamoto T. (2000) *Pathol Int* **50**: 863–871. [PMID:11107061]
676. Chaki S *et al.* (1999) *Eur J Pharmacol* **371**: 205–211. [PMID:10357258]
677. Chen C *et al.* (1996) *J Med Chem* **39**: 4358–4360. [PMID:8893829]
678. Chen YL *et al.* (2008) *J Med Chem* **51**: 1385–1392. [PMID:18288792]
679. Dautzenberg FM *et al.* (2004) *Biochem Pharmacol* **68**: 1833–1844. [PMID:15450949]
680. Dautzenberg FM *et al.* (2001) *J Pharmacol Exp Ther* **296**: 113–120. [PMID:11123370]
681. Gully D *et al.* (2002) *J Pharmacol Exp Ther* **301**: 322–332. [PMID:11907190]
682. Hauger RL *et al.* (2003) *Pharmacol Rev* **55**: 21–26. [PMID:12615952]
683. He L *et al.* (2000) *J Med Chem* **43**: 449–456. [PMID:10669572]
684. Lawrence AJ *et al.* (2002) *Br J Pharmacol* **136**: 896–904. [PMID:12110614]
685. Lundkvist J *et al.* (1996) *Eur J Pharmacol* **309**: 195–200. [PMID:8874139]
686. Perkins AV *et al.* (1995) *J Endocrinol* **146**: 395–401. [PMID:7595134]
687. Rühmann A *et al.* (2002) *Peptides* **23**: 453–460. [PMID:11835994]
688. Webster EL *et al.* (1996) *Endocrinology* **137**: 5747–5750. [PMID:8940412]
689. Zobel AW *et al.* (2000) *J Psychiatr Res* **34**: 171–181. [PMID:10867111]
690. Akunne HC *et al.* (1995) *Life Sci* **57**: 1401–1410. [PMID:7674830]
691. Andersen PH, Jansen JA. (1990) *Eur J Pharmacol* **188**: 335–347. [PMID:1973652]
692. Bunzow JR *et al.* (1988) *Nature* **336**: 783–787. [PMID:2974511]
693. Burris KD *et al.* (1995) *Neuropsychopharmacology* **12**: 335–345. [PMID:7576010]
694. Dearry A *et al.* (1990) *Nature* **347**: 72–76. [PMID:2144334]
695. Freedman SB *et al.* (1994) *J Pharmacol Exp Ther* **268**: 417–426. [PMID:8301582]
696. Grundt P *et al.* (2007) *Bioorg Med Chem Lett* **17**: 745–749. [PMID:17095222]
697. Grundt P *et al.* (2007) *J Med Chem* **50**: 4135–4146. [PMID:17672446]
698. Hidaka K *et al.* (1995) *Neurosci Lett* **186**: 145–148. [PMID:7777184]
699. Hoare SR *et al.* (2000) *Br J Pharmacol* **130**: 1045–1059. [PMID:10882389]
700. Kortagere S *et al.* (2004) *Mol Pharmacol* **66**: 1491–1499. [PMID:15448188]
701. Kulagowski JJ *et al.* (1996) *J Med Chem* **39**: 1941–1942. [PMID:8642550]
702. Köhler C *et al.* (1985) *Biochem Pharmacol* **34**: 2251–2259. [PMID:4015674]
703. Lahti RA *et al.* (1993) *Eur J Pharmacol* **236**: 483–486. [PMID:8102973]
704. MacKenzie RG *et al.* (1994) *Eur J Pharmacol* **266**: 79–85. [PMID:7907989]
705. McCall RB *et al.* (2005) *J Pharmacol Exp Ther* **314**: 1248–1256. [PMID:15980060]
706. Mierau J *et al.* (1995) *Eur J Pharmacol* **290**: 29–36. [PMID:7664822]
707. Millan MJ *et al.* (1994) *Eur J Pharmacol* **260**: R3-R5. [PMID:7988633]
708. Millan MJ *et al.* (2000) *J Pharmacol Exp Ther* **293**: 1048–1062. [PMID:10869410]
709. Millan MJ *et al.* (2002) *J Pharmacol Exp Ther* **303**: 791–804. [PMID:12388666]
710. Millan MJ *et al.* (1995) *J Pharmacol Exp Ther* **275**: 885–898. [PMID:7473180]
711. Moreland RB *et al.* (2005) *Pharmacol Biochem Behav* **82**: 140–147. [PMID:16153699]
712. Nergårdh R *et al.* (2005) *Pharmacol Biochem Behav* **82**: 495–505. [PMID:16318870]
713. Patel S *et al.* (1996) *Mol Pharmacol* **50**: 1658–1664. [PMID:8967990]
714. Primus RJ *et al.* (1997) *J Pharmacol Exp Ther* **282**: 1020–1027. [PMID:9262371]
715. Pugsley TA *et al.* (1995) *J Pharmacol Exp Ther* **275**: 1355–1366. [PMID:8531103]
716. Reavill C *et al.* (2000) *J Pharmacol Exp Ther* **294**: 1154–1165. [PMID:10945872]
717. Ricci A, Amenta F. (1994) *J Neuroimmunol* **53**: 1–7. [PMID:8051291]
718. Ricci A *et al.* (1995) *J Neuroimmunol* **58**: 139–144. [PMID:7759603]
719. Rowley M *et al.* (1996) *J Med Chem* **39**: 1943–1945. [PMID:8642551]
720. Sautel F *et al.* (1995) *Neuroreport* **6**: 329–332. [PMID:7756621]
721. Sautel F *et al.* (1995) *J Pharmacol Exp Ther* **275**: 1239–1246. [PMID:8531087]
722. Schlachter SK *et al.* (1997) *Eur J Pharmacol* **322**: 283–286. [PMID:9098699]
723. Schwartz JC *et al.* (1998) Dopamine receptors. *In* The IUPHAR Compendium of Receptor Characterization and Classification. *Edited by* Girdlestone D IUPHAR media. 141–151
724. Sokoloff P *et al.* (1992) *Eur J Pharmacol* **225**: 331–337. [PMID:1354163]
725. Sokoloff P *et al.* (1990) *Nature* **347**: 146–151. [PMID:1975644]
726. Sunahara RK *et al.* (1991) *Nature* **350**: 614–619. [PMID:1826762]
727. Tiberi M, Caron MG. (1994) *J Biol Chem* **269**: 27925–27931. [PMID:7525564]
728. Tice MA *et al.* (1994) *Pharmacol Biochem Behav* **49**: 567–571. [PMID:7862709]
729. Van Tol HHM *et al.* (1991) *Nature* **350**: 610–614. [PMID:1840645]
730. Xi ZX, Gardner EL. (2007) *CNS Drug Rev* **13**: 240–259. [PMID:17627675]
731. Zhen J *et al.* (2010) *J Neurosci Methods* **188**: 32–38. [PMID:20122961]
732. Zhou QZ *et al.* (1990) *Nature* **347**: 76–86. [PMID:2168520]
733. Bolli MH *et al.* (2004) *J Med Chem* **47**: 2776–2795. [PMID:15139756]
734. Breu V *et al.* (1996) *FEBS Lett* **383**: 37–41. [PMID:8612786]
735. Clozel M *et al.* (1994) *J Pharmacol Exp Ther* **270**: 228–235. [PMID:8035319]
736. Davenport AP. (2002) *Pharmacol Rev* **54**: 219–226. [PMID:12037137]
737. Davenport AP *et al.* (1998) *Br J Pharmacol* **123**: 223–230. [PMID:9489609]
738. Davenport AP *et al.* (1994) *Br J Pharmacol* **111**: 4–6. [PMID:8012722]
739. Elliott JD *et al.* (1994) *J Med Chem* **37**: 1553–1557. [PMID:8201588]
740. Harland SP *et al.* (1995) *J Cardiovasc Pharmacol* **26**: S408-S411. [PMID:8587429]
741. Hatae N *et al.* (2007) *Mol Endocrinol* **21**: 1192–1204. [PMID:17312275]
742. Ihara M *et al.* (1995) *Eur J Pharmacol* **274**: 1–6. [PMID:7768260]
743. Kuc RE *et al.* (1995) *J Cardiovasc Pharmacol* **26**: S373-S375. [PMID:8587419]
744. Maguire JJ, Davenport AP. (1995) *Br J Pharmacol* **115**: 191–197. [PMID:7647976]
745. Maguire JJ *et al.* (1997) *J Pharmacol Exp Ther* **280**: 1102–1108. [PMID:9023329]
746. Mizuguchi T *et al.* (1997) *Br J Pharmacol* **120**: 1427–1430. [PMID:9113361]
747. Molenaar P *et al.* (1992) *Br J Pharmacol* **107**: 637–639. [PMID:1472961]
748. Nambi P *et al.* (1994) *J Pharmacol Exp Ther* **268**: 202–207. [PMID:8301559]
749. Opgenorth TJ *et al.* (1996) *J Pharmacol Exp Ther* **276**: 473–481. [PMID:8632312]
750. Peter MG, Davenport AP. (1996) *Br J Pharmacol* **117**: 455–462. [PMID:7881728]
751. Reynolds EE *et al.* (1995) *Biochem Biophys Res Commun* **209**: 506–512. [PMID:7733918]
752. Russell FD, Davenport AP. (1996) *Br J Pharmacol* **119**: 631–636. [PMID:8904635]
753. von Geldern TW *et al.* (1999) *J Med Chem* **42**: 3668–3678. [PMID:10479298]
754. Watakabe T *et al.* (1992) *Biochem Biophys Res Commun* **185**: 867–873. [PMID:1320877]
755. Watanabe T *et al.* (1995) *Br J Pharmacol* **114**: 949–954. [PMID:7780649]
756. Aronica SM *et al.* (1994) *Proc Natl Acad Sci USA* **91**: 8517–8521. [PMID:8078914]
757. Bologa CG *et al.* (2006) *Nat Chem Biol* **2**: 207–212. [PMID:16520733]
758. Carmeci C *et al.* (1997) *Genomics* **45**: 607–617. [PMID:9367686]
759. Dennis MK *et al.* (2009) *Nat Chem Biol* **5**: 421–427. [PMID:19430488]
760. Dennis MK *et al.* (2011) *J Steroid Biochem Mol Biol* **127**: 358–366. [PMID:21782022]
761. Filardo EJ *et al.* (2000) *Mol Endocrinol* **14**: 1649–1660. [PMID:11043579]
762. Maggiolini M *et al.* (2004) *J Biol Chem* **279**: 27008–27016. [PMID:15090535]
763. Revankar CM *et al.* (2005) *Science* **307**: 1625–1630. [PMID:15705806]
764. Thomas P *et al.* (2005) *Endocrinology* **146**: 624–632. [PMID:15539556]
765. Clish CB *et al.* (1999) *Proc Natl Acad Sci USA* **96**: 8247–8252. [PMID:10393980]

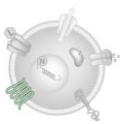
766. Fiore S *et al.* (1994) *J Exp Med* **180**: 253–260. [PMID:8006586]
767. Fiore S *et al.* (1992) *J Biol Chem* **267**: 16168–16176. [PMID:1322894]
768. Fiore S, Serhan CN. (1995) *Biochemistry* **34**: 16678–16686. [PMID:8527441]
769. Freer RJ *et al.* (1980) *Biochemistry* **19**: 2404–2410. [PMID:7387981]
770. Gronert K *et al.* (2001) *Am J Pathol* **158**: 3–9. [PMID:11141472]
771. Guilford WJ *et al.* (2004) *J Med Chem* **47**: 2157–2165. [PMID:15056011]
772. Hanson J *et al.* (2013) *Biochem Pharmacol* **85**: 1795–1802. [PMID:23643932]
773. He HQ *et al.* (2013) *Mol Pharmacol* **83**: 389–398. [PMID:23160941]
774. Koo C *et al.* (1982)*Biochem Biophys Res Commun* **106**: 442–449. [PMID:6285921]
775. Krishnamoorthy S *et al.* (2010) *Proc Natl Acad Sci USA* **107**: 1660–1665. [PMID:20080636]
776. Le Y *et al.* (2002) *Trends Immunol* **23**: 541–548. [PMID:12401407]
777. Liang TS *et al.* (2001) *J Immunol* **167**: 6609–6614. [PMID:11714831]
778. Maddox JF *et al.* (1997) *J Biol Chem* **272**: 6972–6978. [PMID:9054386]
779. Migeotte I *et al.* (2005) *J Exp Med* **201**: 83–93. [PMID:15623572]
780. Murphy PM *et al.* (1992) *J Biol Chem* **267**: 7637–7643. [PMID:1373134]
781. Planagumà A *et al.* (2013) *Clin Exp Immunol* **173**: 298–309. [PMID:23607720]
782. Showell HJ *et al.* (1976) *J Exp Med* **143**: 1154–1169. [PMID:1262785]
783. Sun R *et al.* (2004) *J Immunology* **173**: 428–436. [PMID:15210802]
784. Takano T *et al.* (1997) *J Exp Med* **185**: 1693–1704. [PMID:9151906]
785. Wenzel-Seifert K, Seifert R. (1993) *J Immunol* **150**: 4591–4599. [PMID:8387097]
786. Yan P *et al.* (2006) *J Immunology* **177**: 7050–7058. [PMID:17082621]
787. Ye RD *et al.* (2009) *Pharmacol Rev* **61**: 119–161. [PMID:19498085]
788. Briscoe CP *et al.* (2006) *Br J Pharmacol* **148**: 619–628. [PMID:16702987]
789. Briscoe CP *et al.* (2003) *J Biol Chem* **278**: 11303–11311. [PMID:12496284]
790. Brown AJ *et al.* (2003) *J Biol Chem* **278**: 11312–11319. [PMID:12496283]
791. Christiansen E *et al.* (2013) *ACS Med Chem Lett* **4**: 441–445. [PMID:23687558]
792. Davenport AP *et al.* (2013) *Pharmacol Rev* **65**: 967–986. [PMID:23686350]
793. Hirasawa A *et al.* (2005) *Nat Med* **11**: 90–94. [PMID:15619630]
794. Hudson BD *et al.* (2013) *J Biol Chem* **288**: 17296–17312. [PMID:23589301]
795. Hudson BD *et al.* (2012) *J Biol Chem* **287**: 41195–41209. [PMID:23066016]
796. Ichimura A *et al.* (2012) *Nature* **483**: 350–354. [PMID:22343897]
797. Itoh Y *et al.* (2003) *Nature* **422**: 173–176. [PMID:12629551]
798. Kimura I *et al.* (2011) *Proc Natl Acad Sci USA* **108**: 8030–8035. [PMID:21518883]
799. Kotarsky K *et al.* (2003) *Biochem Biophys Res Commun* **301**: 406–410. [PMID:12565875]
800. Kotarsky K *et al.* (2003) *Pharmacol Toxicol* **93**: 249–258. [PMID:14675457]
801. Le Poul E *et al.* (2003) *J Biol Chem* **278**: 25481–25489. [PMID:12711604]
802. Lee T *et al.* (2008) *Mol Pharmacol* **74**: 1599–1609. [PMID:18818303]
803. Liaw CW, Connolly DT. (2009) *DNA Cell Biol* **28**: 555–560. [PMID:19630535]
804. Lin DC *et al.* (2012) *Mol Pharmacol* **82**: 843–859. [PMID:22859723]
805. Moore K *et al.* (2009) *Comp Biochem Physiol B, Biochem Mol Biol* **154**: 419–426. [PMID:19723586]
806. Nilsson NE *et al.* (2003) *Biochem Biophys Res Commun* **303**: 1047–1052. [PMID:12684041]
807. Oh DY *et al.* (2010) *Cell* **142**: 687–698. [PMID:20813258]
808. Schmidt J *et al.* (2011) *J Biol Chem* **286**: 10628–10640. [PMID:21220428]
809. Schröder R *et al.* (2010) *Nat Biotechnol* **28**: 943–949. [PMID:20711173]
810. Shimpukade B *et al.* (2012) *J Med Chem* **55**: 4511–4515. [PMID:22519963]
811. Smith NJ *et al.* (2009) *J Biol Chem* **284**: 17527–17539. [PMID:19398560]
812. Smith NJ *et al.* (2011) *Mol Pharmacol* **80**: 163–173. [PMID:21498659]
813. Stoddart LA *et al.* (2007) *Mol Pharmacol* **71**: 994–1005. [PMID:17200419]
814. Stoddart LA *et al.* (2008) *Pharmacol Rev* **60**: 405–417. [PMID:19047536]
815. Sun Q *et al.* (2010) *Mol Pharmacol* **78**: 804–810. [PMID:20685848]
816. Suzuki T *et al.* (2008) *J Med Chem* **51**: 7640–7644. [PMID:19007110]
817. Tsujihata Y *et al.* (2011) *J Pharmacol Exp Ther* **339**: 228–237. [PMID:21752941]
818. Wang J *et al.* (2006) *J Biol Chem* **281**: 34457–34464. [PMID:16966319]
819. Watson SJ *et al.* (2012) *Mol Pharmacol* **81**: 631–642. [PMID:22282525]
820. Xiong Y *et al.* (2004) *Proc Natl Acad Sci U S A* **101**: 1045–1050. [PMID:14722361]
821. Xiong Y *et al.* (2013) *Mol Cell Endocrinol* **369**: 119–129. [PMID:23403053]
822. Ahumada A *et al.* (2002) *Science* **298**: 2006–2010. [PMID:12471263]
823. Bryja V *et al.* (2007) *Proc Natl Acad Sci USA* **104**: 6690–6695. [PMID:17426148]
824. Bryja V *et al.* (2008) *EMBO Rep* **9**: 1244–1250. [PMID:18953287]
825. Chan SD *et al.* (1992) *J Biol Chem* **267**: 25202–25207. [PMID:1334084]
826. Chen W *et al.* (2003) *Science* **301**: 1394–1397. [PMID:12958365]
827. Dijksterhuis JP *et al.* (2013) *Br J Pharmacol* [PMID:24032637]
828. Hansen C *et al.* (2009) *J Biol Chem* **284**: 27533–27543. [PMID:19651774]
829. Kikuchi A *et al.* (2009) *Trends Cell Biol* **19**: 119–129. [PMID:19208479]
830. Kilander MB *et al.* (2011) *Cell Signal* **23**: 550–554. [PMID:21070854]
831. Kim GH, Han JK. (2007) *EMBO J* **26**: 2513–2526. [PMID:17476309]
832. Schulte G. (2010) *Pharmacol Rev* **62**: 632–667. [PMID:21079039]
833. Slusarski DC *et al.* (1997) *Nature* **390**: 410–413. [PMID:9389482]
834. Adams CL, Lawrence AJ. (2007) *CNS Drug Rev* **13**: 308–316. [PMID:17894647]
835. Bartoi T *et al.* (2010) *J Biol Chem* **285**: 20625–20633. [PMID:20406808]
836. Belley M *et al.* (1999) *Bioorg Med Chem* **7**: 2697–2704. [PMID:10658574]
837. Bettler B *et al.* (2004) *Physiol Rev* **84**: 835–867. [PMID:15269338]
838. Binet V *et al.* (2004) *J Biol Chem* **279**: 29085–29091. [PMID:15126507]
839. Bowery NG *et al.* (2002) *Pharmacol Rev* **54**: 247–264. [PMID:12037141]
840. Bowery NG, Enna SJ. (2000) *J Pharmacol Exp Ther* **292**: 2–7. [PMID:10604925]
841. Comps-Agrar L *et al.* (2011) *EMBO J* **30**: 2336–2349. [PMID:21552208]
842. Dupuis DS *et al.* (2006) *Mol Pharmacol* **70**: 2027–2036. [PMID:16966477]
843. Emson PC. (2007) *Prog Brain Res* **160**: 43–57. [PMID:17499108]
844. Enna SJ, Bowery NG. (2004) *Biochem Pharmacol* **68**: 1541–1548. [PMID:15451397]
845. Froestl W. (2011) *Future Med Chem* **3**: 163–175. [PMID:21428811]
846. Froestl W, Mickel SJ. (1997) Chemistry of $GABA_B$ modulators. *In* The GABA Receptors. *Edited by* Enna SJ, Bowery NG Humana Press. 271–296 [ISBN:0896034585]
847. Galvez T *et al.* (2000) *Mol Pharmacol* **57**: 419–426. [PMID:10692480]
848. Gassmann M *et al.* (2004) *J Neurosci* **24**: 6086–6097. [PMID:15240800]
849. Geng Y *et al.* (2012) *Nat Neurosci* **15**: 970–978. [PMID:22660477]
850. Hannan S *et al.* (2011) *J Biol Chem* **286**: 24324–24335. [PMID:21724853]
851. Hirst WD *et al.* (2003) *Biochem Pharmacol* **65**: 1103–1113. [PMID:12663046]
852. Jones KA *et al.* (1998) *Nature* **396**: 674–679. [PMID:9872315]
853. Kaupmann K *et al.* (1997) *Nature* **386**: 239–246. [PMID:9069281]
854. Keir MJ *et al.* (1999) *Brain Res Mol Brain Res* **71**: 279–289. [PMID:10521582]
855. Kubo Y, Tateyama M. (2005) *Curr Opin Neurobiol* **15**: 289–295. [PMID:15922585]
856. Lee C *et al.* (2010) *PLoS ONE* **5**: e14044. [PMID:21124972]
857. Monnier C *et al.* (2011) *EMBO J* **30**: 32–42. [PMID:21063387]
858. Pin JP *et al.* (2009) *J Physiol (Lond)* **587** (Pt 22): 5337–5344. [PMID:19723778]
859. Pin JP *et al.* (2004) *Biochem Pharmacol* **68**: 1565–1572. [PMID:15451400]
860. Pin JP *et al.* (2007) *Pharmacol Rev* **59**: 5–13. [PMID:17329545]
861. Pinard A *et al.* (2010) *Adv Pharmacol* **58**: 231–255. [PMID:20655485]

862. Pérez-Garci E *et al*. (2006) *Neuron* **50**: 603–616. [PMID:16701210]
863. Rives ML *et al*. (2009) *EMBO J* **28**: 2195–2208. [PMID:19590495]
864. Schwenk J *et al*. (2010) *Nature* **465**: 231–235. [PMID:20400944]
865. Tabata T *et al*. (2004) *Proc Natl Acad Sci USA* **101**: 16952–16957. [PMID:15550547]
866. Ulrich D, Bettler B. (2007) *Curr Opin Neurobiol* **17**: 298–303. [PMID:17433877]
867. Vacher CM *et al*. (2006) *J Neurochem* **97**: 979–991. [PMID:16606363]
868. Vigot R *et al*. (2006) *Neuron* **50**: 589–601. [PMID:16701209]
869. Wood MD *et al*. (2000) *Br J Pharmacol* **131**: 1050–1054. [PMID:11082110]
870. Bartfai T *et al*. (1991) *Proc Natl Acad Sci USA* **88**: 10961–10965. [PMID:1720557]
871. Bartfai T *et al*. (1993) *Proc Natl Acad Sci USA* **90**: 11287–11291. [PMID:7504301]
872. Bersani M *et al*. (1991) *FEBS Lett* **283**: 189–194. [PMID:1710578]
873. Bersani M *et al*. (1991) *Endocrinology* **129**: 2693–2698. [PMID:1718731]
874. Evans HF, Shine J. (1991) *Endocrinology* **129**: 1682–1684. [PMID:1714839]
875. Fitzgerald LW *et al*. (1998) *J Pharmacol Exp Ther* **287**: 448–456. [PMID:9808667]
876. Foord SM *et al*. (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
877. Gu ZF *et al*. (1995) *J Pharmacol Exp Ther* **272**: 371–378. [PMID:7529309]
878. Lang R *et al*. (2005) *Neuropeptides* **39**: 179–184. [PMID:15944009]
879. Leibowitz SF, Kim T. (1992) *Brain Res* **599**: 148–152. [PMID:1283559]
880. Lu X *et al*. (2005) *Neuropeptides* **39**: 165–167. [PMID:15944007]
881. Ohtaki T *et al*. (1999) *J Biol Chem* **274**: 37041–37045. [PMID:10601261]
882. Pang L *et al*. (1998) *J Neurochem* **71**: 2252–2259. [PMID:9832122]
883. Saar I *et al*. (2013) *J Neurochem* [Epub ahead of print]. [PMID:23600864]
884. Scott MK *et al*. (2000) *Bioorg Med Chem* **8**: 1383–1391. [PMID:10896115]
885. Sillard R *et al*. (1992) *Peptides* **13**: 1055–1060. [PMID:1283627]
886. Skofitsch G *et al*. (1986) *Peptides* **7**: 1029–1042. [PMID:2436195]
887. Smith KE *et al*. (1997) *J Biol Chem* **272**: 24612–24616. [PMID:9305929]
888. Smith KE *et al*. (1998) *J Biol Chem* **273**: 23321–23326. [PMID:9722565]
889. Sollenberg UE *et al*. (2006) *International Journal of Peptide Research and Therapeutics* **12**: 115–119.
890. Ulman LG *et al*. (1993) *J Physiol (Lond)*, **464**: 491–499. [PMID:7693918]
891. Wang S *et al*. (1998) *FEBS Lett* **434**: 277–282. [PMID:9742938]
892. Wang S *et al*. (1997) *Mol Pharmacol* **52**: 337–343. [PMID:9281594]
893. Wang S *et al*. (1997) *J Biol Chem* **272**: 31949–31952. [PMID:9405385]
894. Wiesenfeld-Hallin Z *et al*. (1992) *Proc Natl Acad Sci USA* **89**: 3334–3337. [PMID:1373497]
895. Wynick D *et al*. (1993) *Proc Natl Acad Sci USA* **90**: 4231–4235. [PMID:7683428]
896. Bedendi I *et al*. (2003) *Eur J Pharmacol* **476**: 87–95. [PMID:12969753]
897. Bednarek MA *et al*. (2000) *J Med Chem* **43**: 4370–4376. [PMID:11087562]
898. Davenport AP *et al*. (2005) *Pharmacol Rev* **57**: 541–546. [PMID:16382107]
899. Esler WP *et al*. (2007) *Endocrinology* **148**: 5175–5185. [PMID:17656463]
900. Fraser GL *et al*. (2008) *Endocrinology* **149**: 6280–6288. [PMID:18719021]
901. Holst B *et al*. (2003) *Mol Endocrinol* **17**: 2201–2210. [PMID:12907757]
902. Holst B *et al*. (2009) *Mol Pharmacol* **75**: 44–59. [PMID:18923064]
903. Holst B *et al*. (2004) *J Biol Chem* **279**: 53806–53817. [PMID:15383539]
904. Hosoda H *et al*. (2000) *J Biol Chem* **275**: 21995–22000. [PMID:10801861]
905. Katugampola SD *et al*. (2001) *Br J Pharmacol* **134**: 143–149. [PMID:11522606]
906. Kojima M *et al*. (1999) *Nature* **402**: 656–660. [PMID:10604470]
907. Matsumoto M *et al*. (2001) *Biochem Biophys Res Commun* **287**: 142–146. [PMID:11549267]
908. Moulin A *et al*. (2013) *Amino Acids* **44**: 301–314. [PMID:22798076]
909. Muccioli G *et al*. (2001) *J Endocrinol Invest* **24**: RC7-RC9. [PMID:11314756]
910. Pantel J *et al*. (2006) *J Clin Invest* **116**: 760–768. [PMID:16511605]
911. Perdonà E *et al*. (2011) *Eur J Pharmacol* **650**: 178–183. [PMID:21034740]
912. Sabbatini FM *et al*. (2010) *ChemMedChem* **5**: 1450–1455. [PMID:20593439]
913. Yang J *et al*. (2008) *Cell* **132**: 387–396. [PMID:18267071]
914. Boulanger L *et al*. (2002) *Peptides* **23**: 43–50. [PMID:11814616]
915. Cascieri MA *et al*. (1999) *J Biol Chem* **274**: 8694–8697. [PMID:10085108]
916. Chow BK. (1995) *Biochem Biophys Res Commun* **212**: 204–211. [PMID:7612008]
917. Christopoulos A *et al*. (2003) *J Biol Chem* **278**: 3293–3297. [PMID:12446722]
918. Coy DH, Murphy WA. (1996) *Ann NY Acad Sci* **805**: 149–158. [PMID:8993400]
919. Dillon JS *et al*. (1993) *Endocrinology* **133**: 1907–1910. [PMID:8404634]
920. Gallwitz B *et al*. (1996) *Regul Pept* **63**: 17–22. [PMID:8795084]
921. Haffar BM *et al*. (1991) *J Biol Chem* **266**: 316–322. [PMID:1702423]
922. Irwin DM. (2001) *Regul Pept* **98**: 1–12. [PMID:11179772]
923. Jorgensen R *et al*. (2005) *Mol Endocrinol* **19**: 812–823. [PMID:15528268]
924. Kanashiro-Takeuchi RM *et al*. (2010) *Proc Natl Acad Sci USA* **107**: 2604–2609. [PMID:20133784]
925. Madsen P *et al*. (1998) *J Med Chem* **41**: 5150–5157. [PMID:9857085]
926. Mayo KE *et al*. (2003) *Pharmacol Rev* **55**: 167–194. [PMID:12615957]
927. Montrose-Rafizadeh C *et al*. (1997) *J Biol Chem* **272**: 21201–21206. [PMID:9261127]
928. Petersen KF, Sullivan JT. (2001) *Diabetologia* **44**: 2018–2024. [PMID:11719833]
929. Pohl SL *et al*. (1969) *Science* **164**: 566–567. [PMID:4305077]
930. Raufman JP *et al*. (1991) *J Biol Chem* **266**: 2897–2902. [PMID:1704369]
931. Schally AV, Varga JL. (1999) *Trends Endocrinol Metab* **10**: 383–391. [PMID:10542394]
932. Thulesen J *et al*. (2002) *Regul Pept* **103**: 9–15. [PMID:11738243]
933. Tibaduiza EC *et al*. (2001) *J Biol Chem* **276**: 37787–37793. [PMID:11498540]
934. Unson C, Merrifield RB. (1987) *Proc Natl Acad Sci USA* **84**: 4083–4087. [PMID:3035568]
935. Unson CG *et al*. (1989) *Peptides* **10**: 1171–1177. [PMID:2560175]
936. Varga JL, Rekasi Z. (1999) *Proc Natl Acad Sci USA* **96**: 692–697. [PMID:9892695]
937. Varga JL *et al*. (2004)*Proc Natl Acad Sci U S A* **101**: 1708–1713. [PMID:14755056]
938. Volz A *et al*. (1995) *FEBS Lett* **373**: 23–29. [PMID:7589426]
939. Aittomäki K *et al*. (1995) *Cell* **82**: 959–968. [PMID:7553856]
940. Beau I *et al*. (1998) *J Clin Invest* **102**: 1352–1359. [PMID:9769327]
941. Gromoll J *et al*. (1996) *J Clin Endocrinol Metab* **81**: 1367–1370. [PMID:8636335]
942. Jia XC *et al*. (1991) *Mol Endocrinol* **5**: 759–768. [PMID:1922095]
943. Kopp P *et al*. (1995) *N Engl J Med* **332**: 150–154. [PMID:7800007]
944. Latronico AC, Segaloff DL. (1999) *Am J Hum Genet* **65**: 949–958. [PMID:10486313]
945. Liu G *et al*. (1999) *N Engl J Med* **341**: 1731–1736. [PMID:10580072]
946. Müller T *et al*. (2003) *J Clin Endocrinol Metab* **88**: 2242–2249. [PMID:12727981]
947. Parma J *et al*. (1993) *Nature* **365**: 649–651. [PMID:8413627]
948. Quintana J *et al*. (1994) *J Biol Chem* **269**: 8772–8779. [PMID:8132609]
949. Rapoport B *et al*. (1998) *Endocr Rev* **19**: 673–716. [PMID:9861544]
950. Sairam MR. (1989) *FASEB J* **3**: 1915–1926. [PMID:2542111]
951. Shenker A. (2002) *Receptors Channels* **8**: 3–18. [PMID:12408104]
952. Sunthornthepvarakui T *et al*. (1995) *N Engl J Med* **332**: 155–160. [PMID:7528344]
953. Touraine P *et al*. (1999) *Mol Endocrinol* **13**: 1844–1854. [PMID:10551778]
954. Beckers T *et al*. (2001) *Biochem Biophys Res Commun* **289**: 653–663. [PMID:11726197]
955. Caunt CJ *et al*. (2004) *Endocrinology* **145**: 3594–3602. [PMID:15059960]
956. Cheng CK, Leung PC. (2005) *Endocr Rev* **26**: 283–306. [PMID:15561800]
957. Conn PM *et al*. (1982) *Endocrinology* **111**: 335–337. [PMID:6282571]

958. Grosse R *et al*. (2000) *J Biol Chem* **275**: 9193–9200. [PMID:10734055]
959. Gründker C *et al*. (2002) *Am J Obstet Gynecol* **187**: 528–537. [PMID:12237622]
960. Harrison GS *et al*. (2004) *Endocr Relat Cancer* **11**: 725–748. [PMID:15613448]
961. Kiesel LA *et al*. (2002) *Clin Endocrinol (Oxf)* **56**: 677–687. [PMID:12072036]
962. Kroeger KM *et al*. (2001) *J Biol Chem* **276**: 12736–12743. [PMID:11278883]
963. Krsmanovic LZ *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 2969–2974. [PMID:12591945]
964. Kuphal D *et al*. (1994) *Endocrinology* **135**: 315–320. [PMID:8013367]
965. Leaños-Miranda A *et al*. (2003) *J Clin Endocrinol Metab* **88**: 3360–3367. [PMID:12843188]
966. Limonta P *et al*. (2003) *Front Neuroendocrinol* **24**: 279–295. [PMID:14726258]
967. Maiti K *et al*. (2003) *Mol Cells* **16**: 173–179. [PMID:14651258]
968. Maudsley S *et al*. (2004) *Cancer Res* **64**: 7533–7544. [PMID:15492280]
969. Millar RP. (2005) *Anim Reprod Sci* **88**: 5–28. [PMID:16140177]
970. Millar RP *et al*. (2004) *Endocr Rev* **25**: 235–275. [PMID:15082521]
971. Morgan K *et al*. (2003) *Endocrinology* **144**: 423–436. [PMID:12538601]
972. Neill JD. (2002) *Endocrinology* **143**: 737–743. [PMID:11861490]
973. Schally AV, Nagy A. (2004) *Trends Endocrinol Metab* **15**: 300–310. [PMID:15350601]
974. Sealfon SC *et al*. (1997) *Endocr Rev* **18**: 180–205. [PMID:9101136]
975. Silver MR *et al*. (2005) *Endocrinology* **146**: 3351–3361. [PMID:15878963]
976. Struthers RS *et al*. (2007) *Endocrinology* **148**: 857–867. [PMID:17095587]
977. Chu ZL *et al*. (2010) *Mol Endocrinol* **24**: 161–170. [PMID:19901198]
978. Henstridge CM *et al*. (2010) *Br J Pharmacol* **160**: 604–614. [PMID:20136841]
979. Heynen-Genel S *et al*. (2010) Screening for Selective Ligands for GPR55 - Antagonists. *In* Probe Reports from the NIH Molecular Libraries Program. Bethesda (MD): National Center for Biotechnology Information.
980. Kapur A *et al*. (2009) *J Biol Chem* **284**: 29817–29827. [PMID:19723626]
981. Kargl J *et al*. (2013) *J Pharmacol Exp Ther* **346**: 54–66. [PMID:23639801]
982. Kohno M *et al*. (2006) *Biochem Biophys Res Commun* **347**: 827–832. [PMID:16844083]
983. McHugh D *et al*. (2011) *Br J Pharmacol* [Epub ahead of print]. [PMID:21595653]
984. Ning Y *et al*. (2008) *Br J Pharmacol* **155**: 1056–1065. [PMID:18724386]
985. Oka S *et al*. (2007) *Biochem Biophys Res Commun* **362**: 928–934. [PMID:17765871]
986. Oka S *et al*. (2009) *J Biochem* **145**: 13–20. [PMID:18845565]
987. Overton HA *et al*. (2006) *Cell Metab* **3**: 167–175. [PMID:16517404]
988. Pertwee RG *et al*. (2010) *Pharmacol Rev* **62**: 588–631. [PMID:21079038]
989. Ryberg E *et al*. (2007) *Br J Pharmacol* **152**: 1092–1101. [PMID:17876302]
990. Southern C *et al*. (2013) *J Biomol Screen* **18**: 599–609. [PMID:23396314]
991. Yamashita A *et al*. (2013) *Prostaglandins Other Lipid Mediat* [Epub ahead of print]. [PMID:23714700]
992. Yin H *et al*. (2009) *J Biol Chem* **284**: 12328–12338. [PMID:19286662]
993. Yoshida S *et al*. (2010) *Biochem Biophys Res Commun* **400**: 437–441. [PMID:20804735]
994. Beukers MW *et al*. (1997) *Br J Pharmacol* **122**: 867–874. [PMID:9384502]
995. Booth RG *et al*. (2002) *J Pharmacol Exp Ther* **302**: 328–336. [PMID:12065734]
996. Chen J *et al*. (2003) *Eur J Pharmacol* **467**: 57–65. [PMID:12706455]
997. Cogé F *et al*. (2001) *Biochem J* **355**: 279–288. [PMID:11284713]
998. De Backer MD *et al*. (1998) *Biochem J* **335**: 663–670. [PMID:9794809]
999. Esbenshade TA *et al*. (2004) *Biochem Pharmacol* **68**: 933–945. [PMID:15294456]
1000. Esbenshade TA *et al*. (2003) *J Pharmacol Exp Ther* **305**: 887–896. [PMID:12606603]
1001. Gbahou F *et al*. (2006) *Br J Pharmacol* **147**: 744–754. [PMID:16432504]
1002. Hancock AA *et al*. (2004) *Eur J Pharmacol* **487**: 183–197. [PMID:15033391]
1003. Hill SJ *et al*. (1997) *Pharmacol Rev* **49**: 253–278. [PMID:9311023]
1004. Ishiwata K *et al*. (2004) *Nucl Med Biol* **31**: 493–502. [PMID:15093820]
1005. Jansen FP *et al*. (1994) *Br J Pharmacol* **113**: 355–362. [PMID:7834183]
1006. Kitbunnadaj R *et al*. (2005) *J Med Chem* **48**: 2100–2107. [PMID:15771452]
1007. Kitbunnadaj R *et al*. (2004) *J Med Chem* **47**: 2414–2417. [PMID:15115383]
1008. Kraus A *et al*. (2009) *Chem Med Chem* **4**: 232–240. [PMID:19072936]
1009. Kühn B *et al*. (1996) *Mol Endocrinol* **10**: 1697–1707. [PMID:8961278]
1010. Leurs R *et al*. (1994) *Br J Pharmacol* **112**: 847–854. [PMID:7921611]
1011. Ligneau X *et al*. (2000) *Br J Pharmacol* **131**: 1247–1250. [PMID:11090094]
1012. Lim HD *et al*. (2006) *J Med Chem* **49**: 6650–6651. [PMID:17154494]
1013. Lim HD *et al*. (2005) *J Pharmacol Exp Ther* **314**: 1310–1321. [PMID:15947036]
1014. Liu C *et al*. (2001) *Mol Pharmacol* **59**: 420–426. [PMID:11179434]
1015. Liu C *et al*. (2001) *J Pharmacol Exp Ther* **299**: 121–130. [PMID:11561071]
1016. Lovenberg TW *et al*. (2000) *J Pharmacol Exp Ther* **293**: 771–778. [PMID:10869375]
1017. Moguilevsky N *et al*. (1994) *Eur J Biochem* **224**: 489–495. [PMID:7925364]
1018. Monczor F *et al*. (2003) *Mol Pharmacol* **64**: 512–520. [PMID:12869657]
1019. Morse KL *et al*. (2001) *J Pharmacol Exp Ther* **296**: 1058–1066. [PMID:11181941]
1020. Nakamura T *et al*. (2000) *Biochem Biophys Res Commun* **279**: 615–620. [PMID:11118334]
1021. Nguyen T *et al*. (2001) *Mol Pharmacol* **59**: 427–433. [PMID:11179435]
1022. Oda T *et al*. (2000) *J Biol Chem* **275**: 36781–36786. [PMID:10973974]
1023. Ratnala VR *et al*. (2004) *Eur J Biochem* **271**: 2636–2646. [PMID:15206929]
1024. Schotte A *et al*. (1996) *Psychopharmacology (Berl)* **124**: 57–73. [PMID:8935801]
1025. Seifert R *et al*. (2003) *J Pharmacol Exp Ther* **305**: 1104–1115. [PMID:12626648]
1026. Smits RA *et al*. (2006) *J Med Chem* **49**: 4512–4516. [PMID:16854056]
1027. Thurmond RL *et al*. (2004) *J Pharmacol Exp Ther* **309**: 404–413. [PMID:14722321]
1028. Wieland K *et al*. (2001) *J Pharmacol Exp Ther* **299**: 908–914. [PMID:11714875]
1029. Wulff BS *et al*. (2002) *Eur J Pharmacol* **453**: 33–41. [PMID:12393057]
1030. Zhu Y *et al*. (2001) *Mol Pharmacol* **59**: 434–441. [PMID:11179436]
1031. Ahmed K *et al*. (2009) *J Biol Chem* **284**: 21928–21933. [PMID:19561068]
1032. Ahmed K *et al*. (2010) *Cell Metab* **11**: 311–319. [PMID:20374963]
1033. Boatman PD *et al*. (2012) *J Med Chem* **55**: 3644–3666. [PMID:22435740]
1034. Cai TQ *et al*. (2008) *Biochem Biophys Res Commun* **377**: 987–991. [PMID:18952058]
1035. Liu C *et al*. (2012) *J Pharmacol Exp Ther* **341**: 794–801. [PMID:22434674]
1036. Liu C *et al*. (2009) *J Biol Chem* **284**: 2811–2822. [PMID:19047060]
1037. Offermanns S *et al*. (2011) *Pharmacol Rev* **63**: 269–290. [PMID:21454438]
1038. Semple G *et al*. (2006) *J Med Chem* **49**: 1227–1230. [PMID:16480258]
1039. Shen HC *et al*. (2010) *J Med Chem* **53**: 2666–2670. [PMID:20184326]
1040. Soga T *et al*. (2003) *Biochem Biophys Res Commun* **303**: 364–369. [PMID:12646212]
1041. Southern C *et al*. (2013) *J Biomol Screen* **18**: 599–609. [PMID:23396314]
1042. Taggart AK *et al*. (2005) *J Biol Chem* **280**: 26649–26652. [PMID:15929991]
1043. Tang H *et al*. (2008) *Biochem Biophys Res Commun* **375**: 562–565. [PMID:18722346]
1044. Tunaru S *et al*. (2003) *Nat Med* **9**: 352–355. [PMID:12563315]
1045. Wise A *et al*. (2003) *J Biol Chem* **278**: 9869–9874. [PMID:12522134]
1046. Curtis AE *et al*. (2010) *Am J Physiol Endocrinol Metab* **298**: E296–E303. [PMID:19934405]
1047. Kirby HR *et al*. (2010) *Pharmacol Rev* **62**: 565–578. [PMID:21079036]
1048. Kotani M *et al*. (2001) *J Biol Chem* **276**: 34631–34636. [PMID:11457843]
1049. Mead EJ *et al*. (2007) *Endocrinology* **148**: 140–147. [PMID:17023533]
1050. Muir AI *et al*. (2001) *J Biol Chem* **276**: 28969–28975. [PMID:11387329]
1051. Ohtaki T *et al*. (2001) *Nature* **411**: 613–617. [PMID:11385580]
1052. Roseweir AK *et al*. (2009) *J Neurosci* **29**: 3920–3929. [PMID:19321788]

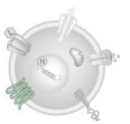
1053. Tomita K *et al.* (2008) *Biopolymers* **90**: 503–511. [PMID:18302161]
1054. Ariel A *et al.* (2003) *J Immunol* **170**: 6266–6272. [PMID:12794159]
1055. Boie Y *et al.* (1999) *Eur J Pharmacol* **380**: 203–213. [PMID:10513580]
1056. Brink C *et al.* (2004) *Pharmacol Rev* **56**: 149–157. [PMID:15001665]
1057. Bäck M *et al.* (2011) *Pharmacol Rev* **63**: 539–584. [PMID:21771892]
1058. Chiang N *et al.* (2000) *J Exp Med* **191**: 1197–1208. [PMID:10748237]
1059. Ciana P *et al.* (2006) *EMBO J* **25**: 4615–4627. [PMID:16990797]
1060. Clish CB *et al.* (1999) *Proc Natl Acad Sci USA* **96**: 8247–8252. [PMID:10393980]
1061. Fiore S *et al.* (1994) *J Exp Med* **180**: 253–260. [PMID:8006586]
1062. Fiore S *et al.* (1992) *J Biol Chem* **267**: 16168–16176. [PMID:1322894]
1063. Fiore S, Serhan CN. (1995) *Biochemistry* **34**: 16678–16686. [PMID:8527441]
1064. Grant GE *et al.* (2009) *Prostaglandins Other Lipid Mediat* **89**: 98–104. [PMID:19450703]
1065. Gronert K *et al.* (2001) *Am J Pathol* **158**: 3–9. [PMID:11141472]
1066. Guilford WJ *et al.* (2004) *J Med Chem* **47**: 2157–2165. [PMID:15056011]
1067. Hanson J *et al.* (2013) *Biochem Pharmacol* **85**: 1795–1802. [PMID:23643932]
1068. Heise CE *et al.* (2000) *J Biol Chem* **275**: 30531–30536. [PMID:10851239]
1069. Herron DK *et al.* (1992) *J Med Chem* **35**: 1818–1828. [PMID:1316967]
1070. Hosoi T *et al.* (2002) *J Biol Chem* **277**: 31459–31465. [PMID:12065583]
1071. Hosoi T *et al.* (2005) *Biochem Biophys Res Commun* **334**: 987–995. [PMID:16039985]
1072. Jackson RH *et al.* (1992) *J Pharmacol Exp Ther* **262**: 80–89. [PMID:1320692]
1073. Jiang Y *et al.* (2007) *Blood* **110**: 3263–3270. [PMID:17693579]
1074. Jones CE *et al.* (2003) *Mol Pharmacol* **63**: 471–477. [PMID:12606753]
1075. Krishnamoorthy S *et al.* (2010) *Proc Natl Acad Sci USA* **107**: 1660–1665. [PMID:20080636]
1076. Lin Q *et al.* (1999) *Biochemistry* **38**: 185–190. [PMID:9890897]
1077. Lynch KR *et al.* (1999) *Nature* **399**: 789–793. [PMID:10391245]
1078. Maddox JF *et al.* (1997) *J Biol Chem* **272**: 6972–6978. [PMID:9054386]
1079. Maddox JF, Serhan CN. (1996) *J Exp Med* **183**: 137–146. [PMID:8551217]
1080. Mellor EA *et al.* (2003) *Proc Natl Acad Sci USA* **100**: 11589–11593. [PMID:13679572]
1081. Mellor EA *et al.* (2001) *Proc Natl Acad Sci USA* **98**: 7964–7969. [PMID:11438743]
1082. Nothacker HP *et al.* (2000) *Mol Pharmacol* **58**: 1601–1608. [PMID:11093801]
1083. O'Flaherty JT *et al.* (2000) *J Immunol* **164**: 3345–3352. [PMID:10706729]
1084. O'Flaherty JT *et al.* (1998) *J Biol Chem* **273**: 32535–32541. [PMID:9829988]
1085. Okuno T *et al.* (2008) *J Exp Med* **205**: 759–766. [PMID:18378794]
1086. Patel P *et al.* (2008) *J Pharmacol Exp Ther* **325**: 698–707. [PMID:18292294]
1087. Perretti M *et al.* (2002) *Nat Med* **8**: 1296–1302. [PMID:12368905]
1088. Planagumà A *et al.* (2013) *Clin Exp Immunol* **173**: 298–309. [PMID:23607720]
1089. Powell WS *et al.* (1992) *J Biol Chem* **267**: 19233–19241. [PMID:1326548]
1090. Resnati M *et al.* (2002) *Proc Natl Acad Sci USA* **99**: 1359–1364. [PMID:11818541]
1091. Romano M *et al.* (1996) *J Immunol* **157**: 2149–2154. [PMID:8757340]
1092. Rovati GE *et al.* (1992) *Biochem Pharmacol* **44**: 1411–1415. [PMID:1329767]
1093. Sarau HM *et al.* (1999) *Mol Pharmacol* **56**: 657–663. [PMID:10462554]
1094. Schwenk U, Schröder JM. (1995) *J Biol Chem* **270**: 15029–15036. [PMID:7797484]
1095. Showell HJ *et al.* (1995) *J Pharmacol Exp Ther* **273**: 176–184. [PMID:7714764]
1096. Sodin-Semrl S *et al.* (2004) *Int J Immunopathol Pharmacol* **17**: 145–156. [PMID:15171815]
1097. Su SB *et al.* (1999) *J Exp Med* **189**: 395–402. [PMID:9892621]
1098. Takano T *et al.* (1997) *J Exp Med* **185**: 1693–1704. [PMID:9151906]
1099. Takasaki J *et al.* (2000) *Biochem Biophys Res Commun* **274**: 316–322. [PMID:10913337]
1100. Tudhope SR *et al.* (1994) *Eur J Pharmacol* **264**: 317–323. [PMID:7698171]
1101. Ye RD *et al.* (2009) *Pharmacol Rev* **61**: 119–161. [PMID:19498085]
1102. Yokomizo T *et al.* (1997) *Nature* **387**: 620–624. [PMID:9177352]
1103. Yokomizo T *et al.* (2001) *J Biol Chem* **276**: 12454–12459. [PMID:11278893]
1104. Chun J *et al.* (2010) *Pharmacol Rev* **62**: 579–587. [PMID:21079037]
1105. Fells JI *et al.* (2008) *Bioorg Med Chem* **16**: 6207–6217. [PMID:18467108]
1106. Fischer DJ *et al.* (2001) *Mol Pharmacol* **60**: 776–784. [PMID:11562440]
1107. Fukushima N *et al.* (1998) *Proc Natl Acad Sci USA* **95**: 6151–6156. [PMID:9600933]
1108. Hasegawa Y *et al.* (2003) *J Biol Chem* **278**: 11962–11969. [PMID:12554733]
1109. Heasley BH *et al.* (2004) *Bioorg Med Chem Lett* **14**: 2735–2740. [PMID:15125924]
1110. Heise CE *et al.* (2001) *Mol Pharmacol* **60**: 1173–1180. [PMID:11723223]
1111. Inoue A *et al.* (2012) *Nat Methods* **9**: 1021–1029. [PMID:22983457]
1112. Kimura T *et al.* (2011) *Cardiovasc Res* **92**: 149–158. [PMID:21632882]
1113. Kiss GN *et al.* (2012) *Mol Pharmacol* **82**: 1162–1173. [PMID:22968304]
1114. Kotarsky K *et al.* (2006) *J Pharmacol Exp Ther* **318**: 619–628. [PMID:16651401]
1115. Lee CW *et al.* (2007) *J Biol Chem* **282**: 4310–4317. [PMID:17166850]
1116. Lee CW *et al.* (2006) *J Biol Chem* **281**: 23589–23597. [PMID:16774927]
1117. McIntyre TM *et al.* (2003) *Proc Natl Acad Sci USA*. **100**: 131–136. [PMID:12502787]
1118. Ohta H *et al.* (2003) *Mol Pharmacol* **64**: 994–1005. [PMID:14500756]
1119. Simon MF *et al.* (2005) *J Biol Chem* **280**: 14656–14662. [PMID:15710620]
1120. Swaney JS *et al.* (2010) *Br J Pharmacol* **160**: 1699–1713. [PMID:20649573]
1121. Virag T *et al.* (2003) *Mol Pharmacol* **63**: 1032–1042. [PMID:12695531]
1122. Yanagida K *et al.* (2009) *J Biol Chem* **284**: 17731–17741. [PMID:19386608]
1123. Albert R *et al.* (2005) *J Med Chem* **48**: 5373–5377. [PMID:16078855]
1124. Ancellin N, Hla T. (1999) *J Biol Chem* **274**: 18997–19002. [PMID:10383399]
1125. Brinkmann V *et al.* (2002) *J Biol Chem* **277**: 21453–21457. [PMID:11967257]
1126. Choi JW *et al.* (2011) *Proc Natl Acad Sci USA* **108**: 751–756. [PMID:21177428]
1127. Chun J, Brinkmann V. (2011) *Discov Med* **12**: 213–228. [PMID:21955849]
1128. Chun J *et al.* (2010) *Pharmacol Rev* **62**: 579–587. [PMID:21079037]
1129. Cohen JA, Chun J. (2011) *Ann Neurol* **69**: 759–777. [PMID:21520239]
1130. Davenport AP *et al.* (2013) *Pharmacol Rev* **65**: 967–986. [PMID:23686350]
1131. Groves A *et al.* (2013) *J Neurol Sci* **328**: 9–18. [PMID:23518370]
1132. Hanson MA *et al.* (2012) *Science* **335**: 851–855. [PMID:22344443]
1133. Im DS *et al.* (2000) *J Biol Chem* **275**: 14281–14286. [PMID:10799507]
1134. Mandala S *et al.* (2002) *Science* **296**: 346–349. [PMID:11923495]
1135. Marsolais D, Rosen H. (2009) *Nat Rev Drug Discov* **8**: 297–307. [PMID:19300460]
1136. Noguchi K, Chun J. (2011) *Crit Rev Biochem Mol Biol* **46**: 2–10. [PMID:20979571]
1137. Okamoto H *et al.* (1998) *J Biol Chem* **273**: 27104–27110. [PMID:9765227]
1138. Osada M *et al.* (2002) *Biochem Biophys Res Commun* **299**: 483–487. [PMID:12445827]
1139. Pan S *et al.* (2006) *Chem Biol* **13**: 1227–1234. [PMID:17114004]
1140. Sanna MG *et al.* (2004) *J Biol Chem* **279**: 13839–13848. [PMID:14732717]
1141. Sanna MG *et al.* (2006) *Nat Chem Biol* **2**: 434–441. [PMID:16829954]
1142. Takabe K *et al.* (2008) *Pharmacol Rev* **60**: 181–195. [PMID:18552276]
1143. Van Brocklyn JR *et al.* (2000) *Blood* **95**: 2624–2629. [PMID:10753843]
1144. Audinot V *et al.* (2001) *Br J Pharmacol* **133**: 371–378. [PMID:11375253]
1145. Borowsky B *et al.* (2002) *Nat Med* **8**: 825–830. [PMID:12118247]
1146. Burgaud JL *et al.* (1997) *Biochem Biophys Res Commun* **241**: 622–629. [PMID:9434758]
1147. Chaki S *et al.* (2005) *J Pharmacol Exp Ther* **313**: 831–839. [PMID:15677346]
1148. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1149. Hertzog DL *et al.* (2006) *Bioorg Med Chem Lett* **16**: 4723–4727. [PMID:16870432]
1150. Hill J *et al.* (2001) *J Biol Chem* **276**: 20125–20129. [PMID:11274220]

1151. Mori M *et al.* (2001) *Biochem Biophys Res Commun* **283**: 1013–1018. [PMID:11355873]
1152. Rodriguez M *et al.* (2001) *Mol Pharmacol* **60**: 632–639. [PMID:11562423]
1153. Takekawa S *et al.* (2002) *Eur J Pharmacol* **438**: 129–135. [PMID:11909603]
1154. Tan CP *et al.* (2002) *Genomics* **79**: 785–792. [PMID:12036292]
1155. Bednarek MA *et al.* (2001) *J Med Chem* **44**: 3665–3672. [PMID:11606131]
1156. Chagnon YC *et al.* (1997) *Mol Med* **3**: 663–673. [PMID:9392003]
1157. Farooqi IS, O'Rahilly S. (2008) *Nat Clin Pract Endocrinol Metab* **4**: 569–577. [PMID:18779842]
1158. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1159. Grieco P *et al.* (2000) *J Med Chem* **43**: 4998–5002. [PMID:11150170]
1160. Grieco P *et al.* (2007) *Peptides* **28**: 1191–1196. [PMID:17482720]
1161. Kopanchuk S *et al.* (2005) *Eur J Pharmacol* **512**: 85–95. [PMID:15840392]
1162. Krishna R *et al.* (2009) *Clin Pharmacol Ther* **86**: 659–666. [PMID:19741604]
1163. Nickolls SA *et al.* (2003) *J Pharmacol Exp Ther* **304**: 1217–1227. [PMID:12604699]
1164. Schioth HB *et al.* (1995) *Eur J Pharmacol* **288**: 311–317. [PMID:7774675]
1165. Schiöth HB *et al.* (1998) *Br J Pharmacol* **124**: 75–82. [PMID:9630346]
1166. Sebhat IK *et al.* (2002) *J Med Chem* **45**: 4589–4593. [PMID:12361385]
1167. Audinot V *et al.* (2003) *Naunyn Schmiedebergs Arch Pharmacol* **367**: 553–561. [PMID:12764576]
1168. Ayoub MA *et al.* (2004) *Mol Pharmacol* **66**: 312–321. [PMID:15266022]
1169. Browning C *et al.* (2000) *Br J Pharmacol* **129**: 877–886. [PMID:10696085]
1170. Dubocovich ML *et al.* (2010) *Pharmacol Rev* **62**: 343–380. [PMID:20605968]
1171. Dubocovich ML *et al.* (1997) *Naunyn Schmiedebergs Arch Pharmacol* **355**: 365–375. [PMID:9089668]
1172. Dubocovich ML *et al.* (1998) *FASEB J* **12**: 1211–1220. [PMID:9737724]
1173. Dufourny L *et al.* (2008) *BMC Evol Biol* **8**: 105. [PMID:18400093]
1174. Eison AS, Mullins UL. (1993) *Life Sci* **53**: PL393-PL398. [PMID:8246675]
1175. Faust R *et al.* (2000) *J Med Chem* **43**: 1050–1061. [PMID:10737738]
1176. Kato K *et al.* (2005) *Neuropharmacology* **48**: 301–310. [PMID:15695169]
1177. Lucchelli A *et al.* (1997) *Br J Pharmacol* **121**: 1775–1781. [PMID:9283717]
1178. Molinari EJ *et al.* (1996) *Eur J Pharmacol* **301**: 159–168. [PMID:8773460]
1179. Nosjean O *et al.* (2000) *J Biol Chem* **275**: 31311–31317. [PMID:10913150]
1180. Nosjean O *et al.* (2001) *Biochem Pharmacol* **61**: 1369–1379. [PMID:11331072]
1181. Pintor J *et al.* (2003) *Br J Pharmacol* **138**: 831–836. [PMID:12642384]
1182. Popova JS, Dubocovich ML. (1995) *J Neurochem* **64**: 130–138. [PMID:7798906]
1183. Sugden D *et al.* (1999) *Reprod Nutr Dev* **39**: 335–344. [PMID:10420436]
1184. Teh MT, Sugden D. (1998) *Naunyn Schmiedebergs Arch Pharmacol* **358**: 522–528. [PMID:9840420]
1185. Ting KN *et al.* (1999) *Br J Pharmacol* **127**: 987–995. [PMID:10433507]
1186. Anderson JJ *et al.* (2002) *J Pharmacol Exp Ther* **303**: 1044–1051. [PMID:12438526]
1187. Barda DA *et al.* (2004) *Bioorg Med Chem Lett* **14**: 3099–3102. [PMID:15149652]
1188. Bonnefous C *et al.* (2005) *Bioorg Med Chem Lett* **15**: 1197–1200. [PMID:15686941]
1189. Bonnefous C *et al.* (2005) *Bioorg Med Chem Lett* **15**: 4354–4358. [PMID:16046122]
1190. Brabet I *et al.* (1995) *Neuropharmacology* **34**: 895–903. [PMID:8532171]
1191. Brodkin J *et al.* (2002) *Eur J Neurosci* **16**: 2241–2244. [PMID:12473093]
1192. Bräuner-Osborne H *et al.* (1996) *J Med Chem* **39**: 3188–3194. [PMID:8759641]
1193. Carroll FY *et al.* (2001) *Mol Pharmacol* **59**: 965–973. [PMID:11306677]
1194. Chopra M *et al.* (2009) *J Pharmacol Exp Ther* **330**: 212–219. [PMID:19389924]
1195. Chung DS *et al.* (1997) *J Pharmacol Exp Ther* **283**: 742–749. [PMID:9353394]
1196. Clark BP *et al.* (1997) *Bioorganic & Medicinal Chemistry Letters* **7**: 2777–2780.
1197. Costantino G *et al.* (2001) *Bioorg Med Chem* **9**: 221–227. [PMID:11249114]
1198. de Paulis T *et al.* (2006) *J Med Chem* **49**: 3332–3344. [PMID:16722652]
1199. Engers DW *et al.* (2009) *J Med Chem* **52**: 4115–4118. [PMID:19469556]
1200. Escribano A *et al.* (1998) *Bioorg Med Chem Lett* **8**: 765–770. [PMID:9871538]
1201. Fricker AC *et al.* (2009) *Neuropharmacology* **56**: 1060–1067. [PMID:19285517]
1202. Gasparini F *et al.* (2002) *Bioorg Med Chem Lett* **12**: 407–409. [PMID:11814808]
1203. Gasparini F *et al.* (1999) *J Pharmacol Exp Ther* **289**: 1678–1687. [PMID:10336568]
1204. Gasparini F *et al.* (1999) *Neuropharmacology* **38**: 1493–1503. [PMID:10530811]
1205. Goudet C *et al.* (2012) *FASEB J* **26**: 1682–1693. [PMID:22223752]
1206. Han G, Hampson DR. (1999) *J Biol Chem* **274**: 10008–10013. [PMID:10187777]
1207. Jane DE *et al.* (1996) *Neuropharmacology* **35**: 1029–1035. [PMID:9121605]
1208. Johnson MP *et al.* (2003) *J Med Chem* **46**: 3189–3192. [PMID:12852748]
1209. Johnson MP *et al.* (2005) *Psychopharmacology (Berl)* **179**: 271–283. [PMID:15717213]
1210. Kingston AE *et al.* (1998) *Neuropharmacology* **37**: 1–12. [PMID:9680254]
1211. Kinney GG *et al.* (2005) *J Pharmacol Exp Ther* **313**: 199–206. [PMID:15608073]
1212. Klein J *et al.* (1997) *Neuropharmacology* **36**: 305–311. [PMID:9175608]
1213. Knoflach F *et al.* (2001) *Proc Natl Acad Sci U S A* **98**: 13402–13407. [PMID:11606768]
1214. Kohara A *et al.* (2005) *J Pharmacol Exp Ther* **315**: 163–169. [PMID:15976016]
1215. Kolczewski S *et al.* (1999) *Bioorg Med Chem Lett* **9**: 2173–2176. [PMID:10465539]
1216. Lavreysen H *et al.* (2003) *Mol Pharmacol* **63**: 1082–1093. [PMID:12695537]
1217. Lavreysen H *et al.* (2004) *Neuropharmacology* **47**: 961–972. [PMID:15555631]
1218. Li L *et al.* (2002) *Neuropharmacology* **43**: 295.
1219. Lindsley CW *et al.* (2004) *J Med Chem* **47**: 5825–5828. [PMID:15537338]
1220. Litschig S *et al.* (1999) *Mol Pharmacol* **55**: 453–461. [PMID:10051528]
1221. Madsen U *et al.* (2005) *Neuropharmacology* **49** Suppl. 1: 114–119. [PMID:15996690]
1222. Maj M *et al.* (2003) *Neuropharmacology* **45**: 895–906. [PMID:14573382]
1223. Malherbe P *et al.* (2003) *J Biol Chem* **278**: 8340–8347. [PMID:12509432]
1224. Malherbe P *et al.* (1999) *Brain Res Mol Brain Res* **67**: 201–210. [PMID:10216218]
1225. Mannaioni G *et al.* (1999) *Neuropharmacology* **38**: 917–926. [PMID:10428410]
1226. Mathiesen JM *et al.* (2003) *Br J Pharmacol* **138**: 1026–1030. [PMID:12684257]
1227. Micheli F *et al.* (2003) *Bioorg Med Chem* **11**: 171–183. [PMID:12470711]
1228. Mitsukawa K *et al.* (2005) *Proc Natl Acad Sci U S A* **102**: 18712–18717. [PMID:16339898]
1229. Monn JA *et al.* (1999) *J Med Chem* **42**: 1027–1040. [PMID:10090786]
1230. Moroni F *et al.* (2002) *Neuropharmacology* **42**: 741–751. [PMID:12015200]
1231. Moroni F *et al.* (1997) *J Pharmacol Exp Ther* **281**: 721–729. [PMID:9152378]
1232. Mutel V *et al.* (2000) *J Neurochem* **75**: 2590–2601. [PMID:11080213]
1233. Neale JH. (2011) *J Neurochem* [Epub ahead of print]. [PMID:21740441]
1234. Niswender CM *et al.* (2010) *Mol Pharmacol* **77**: 459–468. [PMID:20026717]
1235. Niswender CM *et al.* (2008) *Mol Pharmacol* **74**: 1345–1358. [PMID:18664603]
1236. O'Brien JA *et al.* (2003) *Mol Pharmacol* **64**: 731–740. [PMID:12920211]
1237. O'Brien JA *et al.* (2004) *J Pharmacol Exp Ther* **309**: 568–577. [PMID:14747613]
1238. Pellegrini-Giampietro DE *et al.* (1996) *Br J Pharmacol* **118**: 1035–1043. [PMID:8799579]
1239. Pellicciari R *et al.* (1996) *J Med Chem* **39**: 2259–2269. [PMID:8667369]
1240. Pin JP, Acher F. (2002) *Curr Drug Targets CNS Neurol Disord* **1**: 297–317. [PMID:12769621]
1241. Porter RH *et al.* (2005) *J Pharmacol Exp Ther* **315**: 711–721. [PMID:16040814]
1242. Schaffhauser H *et al.* (2003) *Mol Pharmacol* **64**: 798–810. [PMID:14500736]
1243. Schoepp DD *et al.* (2000) Metabotropic glutamate receptors. *In* IUPHAR Compendium of Receptor Characterization and Classification. *Edited by* Watson SP, Girdlestone D IUPHAR Press. 195–208.
1244. Schoepp DD *et al.* (1997) *Neuropharmacology* **36**: 1–11. [PMID:9144636]



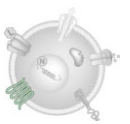
1245. Schoepp DD *et al.* (1996) *Neuropharmacology* **35**: 1661–1672. [PMID:9076745]
1246. Schweitzer C *et al.* (2000) *Neuropharmacology* **39**: 1700–1706. [PMID:10884552]
1247. Suzuki G *et al.* (2007) *J Pharmacol Exp Ther* **323**: 147–156. [PMID:17609420]
1248. Thomas NK *et al.* (2001) *Neuropharmacology* **40**: 311–318. [PMID:11166323]
1249. Thoreson WB *et al.* (1997) *Neuropharmacology* **36**: 13–20. [PMID:9144637]
1250. Tuckmantel W *et al.* (1997) *Bioorg Med Chem Lett* **7**: 601–606.
1251. Uyama Y *et al.* (1997) *Brain Res* **752**: 327–330. [PMID:9106476]
1252. Varney MA *et al.* (1999) *J Pharmacol Exp Ther* **290**: 170–181. [PMID:10381773]
1253. Wermuth CG *et al.* (1996) *J Med Chem* **39**: 814–816. [PMID:8632404]
1254. Wu S *et al.* (1998) *Brain Res Mol Brain Res* **53**: 88–97. [PMID:9473604]
1255. Zheng GZ *et al.* (2005) *J Med Chem* **48**: 7374–7388. [PMID:16279797]
1256. Broad J, Sanger GJ. (2013) *Br J Pharmacol* **168**: 1859–1867. [PMID:23190027]
1257. Clark MJ *et al.* (1999) *Clin Exp Pharmacol Physiol* **26**: 242–245. [PMID:10081621]
1258. Coulie B *et al.* (2001) *J Biol Chem* **276**: 35518–35522. [PMID:11461914]
1259. Depoortere I, Peeters TL. (1995) *Regul Pept* **55**: 227–235. [PMID:7761622]
1260. Feighner SD *et al.* (1999) *Science* **284**: 2184–2188. [PMID:10381885]
1261. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1262. Haramura M *et al.* (2002) *J Med Chem* **45**: 670–675. [PMID:11806718]
1263. Koga H *et al.* (1994) *Bioorganic and Medicinal Chemistry Letters* **4**: 1347–1352.
1264. Li JJ *et al.* (2004) *J Med Chem* **47**: 1704–1708. [PMID:15027861]
1265. Matsuura B *et al.* (2005) *J Pharmacol Exp Ther* **313**: 1101–1108. [PMID:15677347]
1266. Matsuura B *et al.* (2002) *J Biol Chem* **277**: 9834–9839. [PMID:11781320]
1267. Matsuura B *et al.* (2006) *J Biol Chem* **281**: 12390–12396. [PMID:16531413]
1268. McKee KK *et al.* (1997) *Genomics* **46**: 426–434. [PMID:9441746]
1269. Nieuwenhuijs VB *et al.* (1999) *Eur J Clin Invest* **29**: 33–40. [PMID:10092986]
1270. Sanger GJ *et al.* (2009) *Neurogastroenterol Motil* **21**: 657–664, e30–1. [PMID:19374732]
1271. Sudo H *et al.* (2008) *Eur J Pharmacol* **581**: 296–305. [PMID:18164286]
1272. Takanashi H *et al.* (1995) *J Pharmacol Exp Ther* **273**: 624–628. [PMID:7752063]
1273. Takanashi H *et al.* (2007) *Pharmacology* **79**: 137–148. [PMID:17183187]
1274. Thielemans L *et al.* (2005) *J Pharmacol Exp Ther* **313**: 1397–1405. [PMID:15764739]
1275. Westaway SM *et al.* (2009) *J Med Chem* **52**: 1180–1189. [PMID:19191554]
1276. Westaway SM, Sanger GJ. (2009) *Prog Med Chem* **48**: 31–80. [PMID:21544957]
1277. Zhao DM *et al.* (2000) *Am J Physiol Lung Cell Mol Physiol* **278**: L726–L736. [PMID:10749750]
1278. Brighton PJ *et al.* (2004) *Mol Pharmacol* **66**: 1544–1556. [PMID:15331768]
1279. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1280. Hedrick JA *et al.* (2000) *Mol Pharmacol* **58**: 870–875. [PMID:10999960]
1281. Hosoya M *et al.* (2000) *J Biol Chem* **275**: 29528–29532. [PMID:10887190]
1282. Hsu SH, Luo CW. (2007) *Am J Physiol Endocrinol Metab* **293**: E1021–E1029. [PMID:17652154]
1283. Liu JJ *et al.* (2009) *J Pharmacol Exp Ther* **330**: 268–275. [PMID:19369576]
1284. Meng T *et al.* (2008) *Acta Pharmacol Sin* **29**: 517–527. [PMID:18358099]
1285. Minamino N *et al.* (1985) *Biochem Biophys Res Commun* **130**: 1078–1085. [PMID:3839674]
1286. Mori K *et al.* (2005) *EMBO J* **24**: 325–335. [PMID:15635449]
1287. Gouardères C *et al.* (2007) *Neuropharmacology* **52**: 376–386. [PMID:17011599]
1288. Gouardères C *et al.* (2002) *Neuroscience* **115**: 349–361. [PMID:12421602]
1289. Gouardères C, Zajac JM. (2007) *Neurosci Res* **58**: 91–94. [PMID:17337079]
1290. Lameh J *et al.* (2010) *J Pharmacol Exp Ther* **334**: 244–254. [PMID:20354177]
1291. Mollereau C *et al.* (2001) *Br J Pharmacol* **133**: 1–4. [PMID:11325787]
1292. Mollereau C *et al.* (2002) *Eur J Pharmacol* **451**: 245–256. [PMID:12242085]
1293. Mollereau C *et al.* (2005) *Mol Pharmacol* **67**: 965–975. [PMID:15608144]
1294. Quelven I *et al.* (2005) *Eur J Pharmacol* **508**: 107–114. [PMID:15680260]
1295. Roussin A *et al.* (2005) *Biochem Biophys Res Commun* **336**: 197–203. [PMID:16129413]
1296. Simonin F *et al.* (2006) *Proc Natl Acad Sci U S A* **103**: 466–471. [PMID:16407169]
1297. Talmont F *et al.* (2009) *Neurochem Int* **55**: 815–819. [PMID:19682524]
1298. Yang HY *et al.* (1985) *Proc Natl Acad Sci U S A* **82**: 7757–7761. [PMID:3865193]
1299. D'Amato M *et al.* (2007) *Gastroenterology* **133**: 808–817. [PMID:17854592]
1300. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1301. Gupte J *et al.* (2004) *Proc Natl Acad Sci USA* **101**: 1508–1513. [PMID:14757815]
1302. Vendelin J *et al.* (2005) *Am J Respir Cell Mol Biol* **33**: 262–270. [PMID:15947423]
1303. Xu YL *et al.* (2004) *Neuron* **43**: 487–497. [PMID:15312648]
1304. Brezillon S *et al.* (2003) *J Biol Chem* **278**: 776–783. [PMID:12401809]
1305. Fujii R *et al.* (2002) *J Biol Chem* **277**: 34010–34016. [PMID:12118011]
1306. Kanesaka M *et al.* (2007) *J Pept Sci* **13**: 379–385. [PMID:17486669]
1307. Mazzocchi G *et al.* (2005) *J Clin Endocrinol Metab* **90**: 3466–3471. [PMID:15797961]
1308. Nagata-Kuroiwa R *et al.* (2011) *PLoS ONE* **6**: e16972. [PMID:21390312]
1309. Shimomura Y *et al.* (2002) *J Biol Chem* **277**: 35826–35832. [PMID:12130646]
1310. Singh G *et al.* (2004) *Brain Res* **1017**: 222–226. [PMID:15261118]
1311. Bard JA *et al.* (1995) *J Biol Chem* **270**: 26762–26765. [PMID:7592911]
1312. Bonaventure P *et al.* (2004) *J Pharmacol Exp Ther* **308**: 1130–1137. [PMID:14617685]
1313. Cabrele C *et al.* (2002) *Biochemistry* **41**: 8043–8049. [PMID:12069595]
1314. Cox HM, Tough IR. (1995) *Br J Pharmacol* **116**: 2673–2678. [PMID:8590988]
1315. Doods H *et al.* (1999) *Eur J Pharmacol* **384**: R3-R5. [PMID:10611450]
1316. Dumont Y *et al.* (2004) *Neuropeptides* **38**: 163–174. [PMID:15337369]
1317. Eriksson H *et al.* (1998) *Regul Pept* **75–76**: 29–37. [PMID:9802391]
1318. Gehlert DR *et al.* (1996) *Mol Pharmacol* **49**: 224–228. [PMID:8632753]
1319. Gerald C *et al.* (1996) *Nature* **382**: 168–171. [PMID:8700207]
1320. Gerald C *et al.* (1995) *J Biol Chem* **270**: 26758–26761. [PMID:7592910]
1321. Gregor P *et al.* (1996) *FEBS Lett* **381**: 58–62. [PMID:8641440]
1322. Kanatani A *et al.* (2000) *Biochem Biophys Res Commun* **272**: 169–173. [PMID:10872822]
1323. Loetscher M *et al.* (1994) *J Biol Chem* **269**: 232–237. [PMID:8276799]
1324. Lundell I *et al.* (1995) *J Biol Chem* **270**: 29123–29128. [PMID:7493937]
1325. Michel MC *et al.* (1998) *Pharmacol Rev* **50**: 143–150. [PMID:9549761]
1326. Sjödin P *et al.* (2006) *Biochem J* **393**: 161–169. [PMID:16097949]
1327. Tough IR *et al.* (2006) *J Pharmacol Exp Ther* **319**: 20–30. [PMID:16807358]
1328. Wieland HA *et al.* (1998) *Br J Pharmacol* **125**: 549–555. [PMID:9806339]
1329. Yan H *et al.* (1996) *Proc Natl Acad Sci U S A* **93**: 4661–4665. [PMID:8643460]
1330. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1331. Gully D *et al.* (1997) *J Pharmacol Exp Ther* **280**: 802–812. [PMID:9023294]
1332. Hermans E *et al.* (1997) *Br J Pharmacol* **121**: 1817–1823. [PMID:9283723]
1333. Labbé-Jullié C *et al.* (1995) *Mol Pharmacol* **47**: 1050–1056. [PMID:7746272]
1334. Martin S *et al.* (2002) *Gastroenterology* **123**: 1135–1143. [PMID:12360476]
1335. Mazella J *et al.* (1996) *J Neurosci* **16**: 5613–5620. [PMID:8795617]
1336. Nielsen MS *et al.* (1999) *J Biol Chem* **274**: 8832–8836. [PMID:10085125]
1337. Richard F *et al.* (2001) *Mol Pharmacol* **60**: 1392–1398. [PMID:11723247]
1338. Souazé F *et al.* (1997) *J Biol Chem* **272**: 10087–10094. [PMID:9092553]
1339. Vita N *et al.* (1998) *Eur J Pharmacol* **360**: 265–272. [PMID:9851594]
1340. Akiyama K *et al.* (1985) *Proc Natl Acad Sci USA* **82**: 2543–2547. [PMID:2986120]
1341. Bigoni R *et al.* (2002) *Naunyn Schmiedebergs Arch Pharmacol* **365**: 442–449. [PMID:12070757]
1342. Bruchas MR *et al.* (2007) *J Biol Chem* **282**: 29803–29811. [PMID:17702750]

1343. Béguin C *et al*. (2005) *Bioorg Med Chem Lett* **15**: 2761–2765. [PMID:15869877]
1344. Búzás B *et al*. (1992) *Life Sci* **50**: PL75–PL78. [PMID:1313131]
1345. Calderon SN *et al*. (1994) *J Med Chem* **37**: 2125–2128. [PMID:8035418]
1346. Calo G *et al*. (2002) *Br J Pharmacol* **136**: 303–311. [PMID:12010780]
1347. Chang KJ *et al*. (1983) *J Pharmacol Exp Ther* **227**: 403–408. [PMID:6313901]
1348. Chavkin C *et al*. (2004) *J Pharmacol Exp Ther* **308**: 1197–1203. [PMID:14718611]
1349. Dooley CT, Houghten RA. (1996) *Life Sci* **59**: PL23–PL29. [PMID:8684262]
1350. Erspamer V. (1988) *Ann N Y Acad Sci* **547**: 3–9. [PMID:3071223]
1351. Erspamer V *et al*. (1989) *Proc Natl Acad Sci USA* **86**: 5188–5192. [PMID:2544892]
1352. Foord SM *et al*. (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1353. Gong J *et al*. (1998) *FEBS Lett* **439**: 152–156. [PMID:9849897]
1354. Guerrini R *et al*. (1997) *J Med Chem* **40**: 1789–1793. [PMID:9191955]
1355. Handa BK *et al*. (1981) *Eur J Pharmacol* **70**: 531–540. [PMID:6263640]
1356. Hawkins KN *et al*. (1987) *Eur J Pharmacol* **133**: 351–352. [PMID:3030778]
1357. Hunter JC *et al*. (1990) *Br J Pharmacol* **101**: 183–189. [PMID:2178014]
1358. Jenck F *et al*. (2000) *Proc Natl Acad Sci U S A* **97**: 4938–4943. [PMID:10758169]
1359. Jones RM, Portoghese PS. (2000) *Eur J Pharmacol* **396**: 49–52. [PMID:10822054]
1360. Jordan BA, Devi L. (1999) *Nature* **399**: 697–700. [PMID:10385123]
1361. Kawamoto H *et al*. (1999) *J Med Chem* **42**: 5061–5063. [PMID:10602690]
1362. Kuszak AJ *et al*. (2009) *J Biol Chem* **284**: 26732–26741. [PMID:19542234]
1363. Lahti RA *et al*. (1985) *Eur J Pharmacol* **109**: 281–284. [PMID:2986999]
1364. Lever JR, Scheffel U. (1998) *Eur J Pharmacol* **350**: 335–344. [PMID:9696425]
1365. McDonald J *et al*. (2003) *Br J Pharmacol* **140**: 61–70. [PMID:12967935]
1366. Molinari S *et al*. (2012) *Br J Pharmacol* [Epub ahead of print]. [PMID:22827708]
1367. Mollereau C *et al*. (1996) *FEBS Lett* **395**: 17–21. [PMID:8849681]
1368. Mollereau C *et al*. (1994) *FEBS Lett* **341**: 33–38. [PMID:8137918]
1369. Mosberg HI *et al*. (1983) *Proc Natl Acad Sci USA* **80**: 5871–5874. [PMID:6310598]
1370. Neumeyer JL *et al*. (2003) *J Med Chem* **46**: 5162–5170. [PMID:14613319]
1371. Oertel BG *et al*. (2009) *J Biol Chem* **284**: 6530–6535. [PMID:19116204]
1372. Okawa H *et al*. (1999) *Br J Pharmacol* **127**: 123–130. [PMID:10369464]
1373. Payza K. (2003) *In* The Delta Receptor. *Edited by* Chang KJ CRC Press. 261–275 [ISBN:0824740319]
1374. Portoghese PS *et al*. (1987) *J Med Chem* **30**: 1991–1994. [PMID:2444704]
1375. Portoghese PS *et al*. (1988) *Eur J Pharmacol* **146**: 185–186. [PMID:2832195]
1376. Quock RM *et al*. (1997) *Eur J Pharmacol* **326**: 101–104. [PMID:9178661]
1377. Roth BL *et al*. (2002) *Proc Natl Acad Sci U S A* **99**: 11934–11939. [PMID:12192085]
1378. Schiller PW *et al*. (1993) *J Med Chem* **36**: 3182–3187. [PMID:8230106]
1379. Simonin F *et al*. (1995) *Proc Natl Acad Sci U S A* **92**: 7006–7010. [PMID:7624359]
1380. Simonin F *et al*. (2001) *Eur J Pharmacol* **414**: 189–195. [PMID:11239918]
1381. Sofuoglu M *et al*. (1991) *J Pharmacol Exp Ther* **257**: 676–680. [PMID:1851833]
1382. Stefano GB *et al*. (1992) *Proc Natl Acad Sci USA* **89**: 9316–9320. [PMID:1329092]
1383. Stevens WC *et al*. (2000) *J Med Chem* **43**: 2759–2769. [PMID:10893314]
1384. Toll L *et al*. (1998) *NIDA Res Monogr* **178**: 440–466. [PMID:9686407]
1385. Volpe DA *et al*. (2011) *Regul Toxicol Pharmacol* **59**: 385–390. [PMID:21215785]
1386. Vonvoigtlander PF *et al*. (1983) *J Pharmacol Exp Ther* **224**: 7–12. [PMID:6129321]
1387. Yamamura MS *et al*. (1992) *Life Sci* **50**: PL119–PL124. [PMID:1313133]
1388. Zadina JE *et al*. (1997) *Nature* **386**: 499–502. [PMID:9087409]
1389. Zagon IS *et al*. (2002) *Brain Res Brain Res Rev* **38**: 351–376. [PMID:11890982]
1390. Zajac JM, Roques BP. (1983) *Life Sci* **33** Suppl 1: 155–158. [PMID:6319853]
1391. Zaratin PF *et al*. (2004) *J Pharmacol Exp Ther* **308**: 454–461. [PMID:14593080]
1392. Zhu J *et al*. (1995) *Life Sci* **56**: PL201-PL207. [PMID:7869844]
1393. Zhu J *et al*. (1997) *J Pharmacol Exp Ther* **282**: 676–684. [PMID:9262330]
1394. Asahi S *et al*. (2003) *Bioorg Med Chem Lett* **13**: 111–113. [PMID:12467628]
1395. Gotter AL *et al*. (2012) *Pharmacol Rev* **64**: 389–420. [PMID:22759794]
1396. Hirose M *et al*. (2003) *Bioorg Med Chem Lett* **13**: 4497–4499. [PMID:14643355]
1397. Holmqvist T *et al*. (2001) *Neurosci Lett* **305**: 177–180. [PMID:11403934]
1398. Kukkonen JP, Åkerman KEO. (2005) Intracellular Signal Pathways Utilized by the Hypocretin/Orexin Receptors. *In* Hypocretins. Integrators of Physiological Signals. *Edited by* de Lecea L, Sutcliffe JG Verlag: Springer. 221–231 [ISBN:9780387254463]
1399. Langmead CJ *et al*. (2004) *Br J Pharmacol* **141**: 340–346. [PMID:14691055]
1400. Lin L *et al*. (1999) *Cell* **98**: 365–376. [PMID:10458611]
1401. Malherbe P *et al*. (2009) *Br J Pharmacol* **156**: 1326–1341. [PMID:19751316]
1402. Malherbe P *et al*. (2009) *Mol Pharmacol* **76**: 618–631. [PMID:19542319]
1403. McAtee LC *et al*. (2004) *Bioorg Med Chem Lett* **14**: 4225–4229. [PMID:15261275]
1404. Porter RA *et al*. (2001) *Bioorg Med Chem Lett* **11**: 1907–1910. [PMID:11459658]
1405. Putula J *et al*. (2011) *Neurosci Lett* **494**: 57–60. [PMID:21362456]
1406. Ramanjaneya M *et al*. (2009) *J Endocrinol* **202**: 249–261. [PMID:19460850]
1407. Sakurai T *et al*. (1998) *Cell* **92**: 573–585. [PMID:9491897]
1408. He W *et al*. (2004) *Nature* **429**: 188–193. [PMID:15141213]
1409. Southern C *et al*. (2013) *J Biomol Screen* **18**: 599–609. [PMID:23396314]
1410. Abbracchio MP *et al*. (2003) *Trends Pharmacol Sci* **24**: 52–55. [PMID:12559763]
1411. Abbracchio MP *et al*. (2006) *Pharmacol Rev* **58**: 281–341. [PMID:16968944]
1412. Akbar GK *et al*. (1996) *J Biol Chem* **271**: 18363–18367. [PMID:8702478]
1413. Balogh J *et al*. (2005) *J Mol Cell Cardiol* **39**: 223–230. [PMID:15893764]
1414. Baqi Y *et al*. (2009) *J Med Chem* **52**: 3784–3793. [PMID:19463000]
1415. Belous A *et al*. (2004) *J Cell Biochem* **92**: 1062–1073. [PMID:15258927]
1416. Besada P *et al*. (2006) *J Med Chem* **49**: 5532–5543. [PMID:16942026]
1417. Bogdanov YD *et al*. (1997) *J Biol Chem* **272**: 12583–12590. [PMID:9139711]
1418. Boyer JL *et al*. (1996) *Mol Pharmacol* **50**: 1323–1329. [PMID:8913364]
1419. Castro E *et al*. (1992) *Br J Pharmacol* **106**: 833–837. [PMID:1393282]
1420. Cattaneo M *et al*. (2004) *Biochem Pharmacol* **68**: 1995–2002. [PMID:15476670]
1421. Chhatriwala M *et al*. (2004) *J Pharmacol Exp Ther* **311**: 1038–43. [PMID:15345752]
1422. Ciana P *et al*. (2006) *EMBO J* **25**: 4615–27. [PMID:16990797]
1423. Communi D *et al*. (1996) *Biochem Biophys Res Commun* **222**: 303–308. [PMID:8670200]
1424. Communi D *et al*. (1999) *Br J Pharmacol* **128**: 1199–1206. [PMID:10578132]
1425. El-Tayeb A *et al*. (2005) *Bioorg Med Chem Lett* **15**: 5450–5452. [PMID:16213725]
1426. El-Tayeb A *et al*. (2006) *J Med Chem* **49**: 7076–7087. [PMID:17125260]
1427. El-Tayeb A *et al*. (2011) *J Med Chem* **54**: 2878–2890. [PMID:21417463]
1428. Fricks IP *et al*. (2008) *J Pharmacol Exp Ther* **325**: 588–594. [PMID:18252808]
1429. Gao ZG *et al*. (2004) *Biochem Pharmacol* **68**: 1985–1993. [PMID:15476669]
1430. Gao ZG *et al*. (2013) *Purinergic Signal* **9**: 31–40. [PMID:22825617]
1431. He W *et al*. (2004) *Nature* **429**: 188–193. [PMID:15141213]
1432. Herbert JM, Savi P. (2003) *Semin Vasc Med* **3**: 113–122. [PMID:15199474]
1433. Humphries RG *et al*. (1995) *Br J Pharmacol* **115**: 1110–1116. [PMID:7582510]
1434. Humphries RG *et al*. (1994) *Br J Pharmacol* **113**: 1057–1063. [PMID:7858849]
1435. Inbe H *et al*. (2004) *J Biol Chem* **279**: 19790–19799. [PMID:15001573]
1436. Kemp PA *et al*. (2004) *Am J Respir Cell Mol Biol* **31**: 446–455. [PMID:15231488]
1437. Kennedy C *et al*. (2000) *Mol Pharmacol* **57**: 926–931. [PMID:10779375]

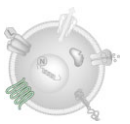


1438. Kim HS *et al.* (2003) *J Med Chem* **46**: 4974–4987. [PMID:14584948]
1439. Kim YC *et al.* (2005) *Biochem Pharmacol* **70**: 266–274. [PMID:15913566]
1440. King BF, Townsend-Nicholson A. (2000) *J Auton Nerv Syst* **81**: 164–170. [PMID:10869716]
1441. Ko H *et al.* (2008) *Bioorg Med Chem* **16**: 6319–6332. [PMID:18514530]
1442. Ko H *et al.* (2007) *J Med Chem* **50**: 2030–2039. [PMID:17407275]
1443. Lazarowski ER *et al.* (1995) *Br J Pharmacol* **116**: 1619–1627. [PMID:8564228]
1444. Lazarowski ER *et al.* (1996) *Br J Pharmacol* **117**: 203–209. [PMID:8825364]
1445. Mamedova LK *et al.* (2004) *Biochem Pharmacol* **67**: 1763–1770. [PMID:15081875]
1446. Marteau F *et al.* (2003) *Mol Pharmacol* **64**: 104–112. [PMID:12815166]
1447. Maruoka H *et al.* (2010) *J Med Chem* **53**: 4488–4501. [PMID:20446735]
1448. Maruoka H *et al.* (2011) *J Med Chem* **54**: 4018–4033. [PMID:21528910]
1449. Meis S *et al.* (2010) *J Pharmacol Exp Ther* **332**: 238–247. [PMID:19815812]
1450. Mellor EA *et al.* (2003) *Proc Natl Acad Sci USA* **100**: 11589–11593. [PMID:13679572]
1451. Mellor EA *et al.* (2001) *Proc Natl Acad Sci U S A* **98**: 7964–7969. [PMID:11438743]
1452. Moreschi I *et al.* (2008) *Cell Calcium* **43**: 344–355. [PMID:17707504]
1453. Moreschi I *et al.* (2006) *J Biol Chem* **281**: 31419–31429. [PMID:16926152]
1454. Noguchi K *et al.* (2003) *J Biol Chem* **278**: 25600–25606. [PMID:12724320]
1455. Ohlmann P *et al.* (2013) *Purinergic Signal* **9**: 59–66. [PMID:22892887]
1456. Pasternack SM *et al.* (2008) *Nat Genet* **40**: 329–334. [PMID:18297070]
1457. Patel K *et al.* (2001) *Eur J Pharmacol* **430**: 203–210. [PMID:11711032]
1458. Schachter JB, Harden TK. (1997) *Br J Pharmacol* **121**: 338–344. [PMID:9154346]
1459. Takasaki J *et al.* (2001) *Mol Pharmacol* **60**: 432–439. [PMID:11502873]
1460. Ullmann H *et al.* (2005) *J Med Chem* **48**: 7040–7048. [PMID:16250663]
1461. Waldo GL *et al.* (2002) *Mol Pharmacol* **62**: 1249–1257. [PMID:12391289]
1462. Webb TE *et al.* (1996) *Mol Pharmacol* **50**: 258–265. [PMID:8700132]
1463. Webb TE *et al.* (1996) *Biochem Biophys Res Commun* **219**: 105–110. [PMID:8619790]
1464. Yanagida K *et al.* (2009) *J Biol Chem* **284**: 17731–17741. [PMID:19386608]
1465. Yokomizo T *et al.* (1997) *Nature* **387**: 620–624. [PMID:9177352]
1466. Gardella TJ *et al.* (1996) *J Biol Chem* **271**: 19888–19893. [PMID:8702701]
1467. Gardella TJ *et al.* (1995) *J Biol Chem* **270**: 6584–6588. [PMID:7896796]
1468. Goold CP *et al.* (2001) *J Pharmacol Exp Ther* **299**: 678–690. [PMID:11602681]
1469. Hoare SR *et al.* (2000) *J Biol Chem* **275**: 27274–27283. [PMID:10854439]
1470. Jonsson KB *et al.* (2001) *Endocrinology* **142**: 704–709. [PMID:11159842]
1471. Fukusumi S *et al.* (2003) *J Biol Chem* **278**: 46387–46395. [PMID:12960173]
1472. Jiang Y *et al.* (2003) *J Biol Chem* **278**: 27652–27657. [PMID:12714592]
1473. Kuc RE *et al.* (2006) *Proceedings of the British Pharmacological Society* **4**: abst186.
1474. Takayasu S *et al.* (2006) *Proc Natl Acad Sci USA* **103**: 7438–7443. [PMID:16648250]
1475. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1476. Fukunaga K *et al.* (2001) *J Biol Chem* **276**: 43025–43030. [PMID:11560941]
1477. Goldring WP *et al.* (2005) *Bioorg Med Chem Lett* **15**: 3263–3266. [PMID:15922596]
1478. Herbert JM *et al.* (1993) *J Lipid Mediat* **7**: 57–78. [PMID:8395255]
1479. Marathe GK *et al.* (1999) *J Biol Chem* **274**: 28395–28404. [PMID:10497200]
1480. Nakamura M *et al.* (1991) *J Biol Chem* **266**: 20400–20405. [PMID:1657923]
1481. Nakamura M *et al.* (1992) *FEBS Lett* **314**: 125–129. [PMID:1333988]
1482. Ogita T *et al.* (1997) *Am J Physiol* **272** (1 Pt 2): H17–H24. [PMID:9038918]
1483. Parent JL *et al.* (1996) *J Biol Chem* **271**: 23298–23303. [PMID:8798529]
1484. Svetlov S, Nigam S. (1993) *Biochem Biophys Res Commun* **190**: 162–166. [PMID:8380690]
1485. (1988) *Ann N Y Acad Sci* **547**: 1–541. [PMID:3071214]
1486. Foord SM *et al.* (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1487. Lin DC *et al.* (2002) *J Biol Chem* **277**: 19276–19280. [PMID:11886876]
1488. Masuda Y *et al.* (2002) *Biochem Biophys Res Commun* **293**: 396–402. [PMID:12054613]
1489. Mollay C *et al.* (1999) *Eur J Pharmacol* **374**: 189–196. [PMID:10422759]
1490. Negri L *et al.* (2005) *Br J Pharmacol* **146**: 625–632. [PMID:16113687]
1491. Schweitz H *et al.* (1999) *FEBS Lett* **461**: 183–188. [PMID:10567694]
1492. Soga T *et al.* (2002) *Biochim Biophys Acta* **1579**: 173–179. [PMID:12427552]
1493. Ellacott KL *et al.* (2005) *Peptides* **26**: 675–681. [PMID:15752583]
1494. Engstrom M *et al.* (2003) *J Pharmacol Exp Ther* **305**: 825–832. [PMID:12606605]
1495. Hinuma S *et al.* (2000) *Nat Cell Biol* **2**: 703–708. [PMID:11025660]
1496. Lagerström MC *et al.* (2005) *Genomics* **85**: 688–703. [PMID:15885496]
1497. Langmead CJ *et al.* (2000) *Br J Pharmacol* **131**: 683–688. [PMID:11030716]
1498. Abramovitz M *et al.* (2000) *Biochim Biophys Acta* **1483**: 285–293. [PMID:10634944]
1499. Abramovitz M *et al.* (1994) *J Biol Chem* **269**: 2632–2636. [PMID:8300593]
1500. Amano H *et al.* (2003) *J Exp Med* **197**: 221–232. [PMID:12538661]
1501. Arimura A *et al.* (2001) *J Pharmacol Exp Ther* **298**: 411–419. [PMID:11454901]
1502. Armstrong RA *et al.* (1993) *Br J Pharmacol* **110**: 539–547. [PMID:8242228]
1503. Bley KR *et al.* (2006) *Br J Pharmacol* **147**: 335–345. [PMID:16331286]
1504. Blouin M *et al.* (2010) *J Med Chem* **53**: 2227–2238. [PMID:20163116]
1505. Boie Y *et al.* (1994) *J Biol Chem* **269**: 12173–12178. [PMID:7512962]
1506. Boie Y *et al.* (1995) *J Biol Chem* **270**: 18910–18916. [PMID:7642548]
1507. Cameron KO *et al.* (2009) *Bioorg Med Chem Lett* **19**: 2075–2078. [PMID:19250823]
1508. Chang CS *et al.* (1997) *Prostaglandins* **53**: 83–90. [PMID:9112287]
1509. Chen Q *et al.* (2010) *Br J Pharmacol* **160**: 292–310. [PMID:20423341]
1510. Cirillo R *et al.* (2007) *Am J Obstet Gynecol* **197**: 54.e1–e9. [PMID:17618756]
1511. Clark P *et al.* (2008) *J Pharmacol Exp Ther* **325**: 425–434. [PMID:18287210]
1512. Coleman RA *et al.* (1994) *Pharmacol Rev* **46**: 205–229. [PMID:7938166]
1513. Davis TL, Sharif NA. (2000) *Br J Pharmacol* **130**: 1919–1926. [PMID:10952683]
1514. Foudi N *et al.* (2011) *Br J Pharmacol* **163**: 826–834. [PMID:21323896]
1515. Foudi N *et al.* (2008) *Br J Pharmacol* **154**: 1631–1639. [PMID:18516068]
1516. Giblin GM *et al.* (2007) *Bioorg Med Chem Lett* **17**: 385–389. [PMID:17084082]
1517. Giles H *et al.* (1989) *Br J Pharmacol* **96**: 291–300. [PMID:2924081]
1518. Hata AN *et al.* (2003) *J Pharmacol Exp Ther* **306**: 463–470. [PMID:12721327]
1519. Hung GH *et al.* (2006) *Prostaglandins Leukot Essent Fatty Acids* **74**: 401–415. [PMID:16737803]
1520. Jones RL *et al.* (1997) *J Cardiovasc Pharmacol* **29**: 525–535. [PMID:9156364]
1521. Juteau H *et al.* (2001) *Bioorg Med Chem* **9**: 1977–1984. [PMID:11504634]
1522. Kattelman EJ *et al.* (1986) *Thromb Res* **41**: 471–481. [PMID:3008368]
1523. Kotani M *et al.* (1995) *Mol Pharmacol* **48**: 869–879. [PMID:7476918]
1524. Krauss AH *et al.* (1996) *Br J Pharmacol* **117**: 1171–1180. [PMID:8882612]
1525. Leduc M *et al.* (2009) *J Pharmacol Exp Ther* **331**: 297–307. [PMID:19584306]
1526. Liljebris C *et al.* (1995) *J Med Chem* **38**: 289–304. [PMID:7830272]
1527. Longrois D *et al.* (2012) *Eur J Pharmacol* **681**: 55–59. [PMID:22342278]
1528. Lumley P *et al.* (1989) *Br J Pharmacol* **97**: 783–794. [PMID:2527074]
1529. Machwate M *et al.* (2001) *Mol Pharmacol* **60**: 36–41. [PMID:11408598]
1530. Mathiesen JM *et al.* (2006) *Mol Pharmacol* **69**: 1441–1453. [PMID:16418339]
1531. Maubach KA *et al.* (2009) *Br J Pharmacol* **156**: 316–327. [PMID:19154437]
1532. Mayeux PR *et al.* (1991) *J Biol Chem* **266**: 13752–13758. [PMID:1830308]
1533. Monneret G *et al.* (2003) *J Pharmacol Exp Ther* **304**: 349–355. [PMID:12490611]
1534. Morinelli TA *et al.* (1989) *J Pharmacol Exp Ther* **251**: 557–562. [PMID:2530338]
1535. Murase A *et al.* (2008) *Life Sci* **82**: 226–232. [PMID:18155068]

1536. Naka M *et al*. (1992) *J Pharmacol Exp Ther* **262**: 632–637. [PMID:1386885]
1537. Negishi M *et al*. (1995) *J Biol Chem* **270**: 16122–161227. [PMID:7608175]
1538. Ogletree ML *et al*. (1993) *J Pharmacol Exp Ther* **264**: 570–578. [PMID:8437108]
1539. Okuda-Ashitaka E *et al*. (1996) *J Biol Chem* **271**: 31255–31261. [PMID:8940129]
1540. Prasanna G *et al*. (2009) *Exp Eye Res* **89**: 608–617. [PMID:19445930]
1541. Pratico D *et al*. (1996) *J Biol Chem* **271**: 14916–14924. [PMID:8663015]
1542. Raychowdhury MK *et al*. (1994) *J Biol Chem* **269**: 19256–19261. [PMID:8034687]
1543. Royer JF *et al*. (2007) *Allergy* **62**: 1401–1409. [PMID:17714552]
1544. Sawyer N *et al*. (2002) *Br J Pharmacol* **137**: 1163–1172. [PMID:12466225]
1545. Sharif NA *et al*. (2000) *J Pharmacol Exp Ther* **293**: 321–328. [PMID:10772998]
1546. Sharif NA, Davis TL. (2002) *J Pharm Pharmacol* **54**: 539–547. [PMID:11999132]
1547. Sharif NA *et al*. (2006) *J Ocul Pharmacol Ther* **22**: 291–309. [PMID:17076623]
1548. Shichijo M *et al*. (2003) *J Pharmacol Exp Ther* **307**: 518–525. [PMID:12975488]
1549. Stillman BA *et al*. (1999) *Mol Pharmacol* **56**: 545–551. [PMID:10462542]
1550. Sturino CF *et al*. (2007) *J Med Chem* **50**: 794–806. [PMID:17300164]
1551. Su X *et al*. (2008) *Am J Physiol Renal Physiol* **295**: F984–F994. [PMID:18632791]
1552. Sugimoto H *et al*. (2005) *Eur J Pharmacol* **524**: 30–37. [PMID:16256979]
1553. Suzawa T *et al*. (2000) *Endocrinology* **141**: 1554–1559. [PMID:10746663]
1554. Swayne GT *et al*. (1988) *Eur J Pharmacol* **152**: 311–319. [PMID:2975605]
1555. Takechi H *et al*. (1996) *J Biol Chem* **271**: 5901–5906. [PMID:8621463]
1556. Ulven T, Kostenis E. (2005) *J Med Chem* **48**: 897–900. [PMID:15715457]
1557. Watanabe K *et al*. (1999) *Cancer Res* **59**: 5093–5096. [PMID:10537280]
1558. Whittle BJ *et al*. (2012) *Biochem Pharmacol* **84**: 68–75. [PMID:22480736]
1559. Wilson RJ *et al*. (2006) *Br J Pharmacol* **148**: 326–339. [PMID:16604093]
1560. Wilson RJ, Giles H. (2005) *Br J Pharmacol* **144**: 405–415. [PMID:15655509]
1561. Wise H *et al*. (1995) *Eur J Pharmacol* **278**: 265–269. [PMID:7589166]
1562. Woodward DF *et al*. (2008) *Pharmacol Ther* **120**: 71–80. [PMID:18700152]
1563. Wright DH *et al*. (1998) *Br J Pharmacol* **123**: 1317–1324. [PMID:9579725]
1564. Wright DH *et al*. (1999) *Eur J Pharmacol* **377**: 101–115. [PMID:10448933]
1565. Young RN *et al*. (2004) *Heterocycles* **64**: 437–446.
1566. Ahn HS *et al*. (1997) *Mol Pharmacol* **51**: 350–356. [PMID:9203642]
1567. Al-Ani B *et al*. (1999) *J Pharmacol Exp Ther* **290**: 753–760. [PMID:10411588]
1568. Andrade-Gordon P *et al*. (1999) *Proc Natl Acad Sci USA* **96**: 12257–12262. [PMID:10535908]
1569. Austin KM *et al*. (2013) *Blood* **121**: 431–439. [PMID:23086754]
1570. Barry GD *et al*. (2010) *J Med Chem* **53**: 7428–7440. [PMID:20873792]
1571. Blackhart BD *et al*. (1996) *J Biol Chem* **271**: 16466–16471. [PMID:8663335]
1572. Chackalamannil S *et al*. (2008) *J Med Chem* **51**: 3061–3064. [PMID:18447380]
1573. Chung AW *et al*. (2002) *Br J Pharmacol* **135**: 1123–1132. [PMID:11877318]
1574. Hollenberg MD, Compton SJ. (2002) *Pharmacol Rev* **54**: 203–217. [PMID:12037136]
1575. Hollenberg MD *et al*. (2008) *J Pharmacol Exp Ther* **326**: 453–462. [PMID:18477767]
1576. Kanke T *et al*. (2005) *Br J Pharmacol* **145**: 255–263. [PMID:15765104]
1577. Kawabata A *et al*. (1999) *J Pharmacol Exp Ther* **288**: 358–370. [PMID:9862790]
1578. Kogushi M *et al*. (2011) *Eur J Pharmacol* **657**: 131–137. [PMID:21300059]
1579. Lee MC, Huang SC. (2008) *Neurogastroenterol Motil* **20**: 385–391. [PMID:18179608]
1580. McGuire JJ *et al*. (2004) *J Pharmacol Exp Ther* **309**: 1124–1131. [PMID:14976230]
1581. Ramachandran R *et al*. (2012) *Nat Rev Drug Discov* **11**: 69–86. [PMID:22212680]
1582. Sevigny LM *et al*. (2011) *Proc Natl Acad Sci USA* **108**: 8491–8496. [PMID:21536878]
1583. Suen JY *et al*. (2012) *Br J Pharmacol* **165**: 1413–1423. [PMID:21806599]
1584. Bathgate RA *et al*. (2006) *Pharmacol Rev* **58**: 7–31. [PMID:16507880]
1585. Belgi A *et al*. (2011) *Biochemistry* **50**: 8352–8361. [PMID:21866895]
1586. Büllesbach EE, Schwabe C. (2005) *J Biol Chem* **280**: 14586–14590. [PMID:15708846]
1587. Del Borgo MP *et al*. (2006) *J Biol Chem*: 727–729. [PMID:16547350]
1588. Ferlin A *et al*. (2003) *J Clin Endocrinol Metab* **88**: 4273–4279. [PMID:12970298]
1589. Ganella DE *et al*. (2012) *Behav Pharmacol* **23**: 516–525. [PMID:22854307]
1590. Halls ML *et al*. (2006) *Mol Pharmacol*: -. [PMID:16569707]
1591. Halls ML *et al*. (2005) *J Pharmacol Exp Ther* **313**: 677–687. [PMID:15649866]
1592. Halls ML, Cooper DM. (2010) *EMBO J* **29**: 2772–2787. [PMID:20664520]
1593. Halls ML *et al*. (2009) *Ann N Y Acad Sci* **1160**: 108–111. [PMID:19416169]
1594. Halls ML *et al*. (2007) *Br J Pharmacol* **150**: 677–691. [PMID:17293890]
1595. Halls ML *et al*. (2009) *Mol Pharmacol* **75**: 415–428. [PMID:19029286]
1596. Haugaard-Kedström LM *et al*. (2011) *J Am Chem Soc* **133**: 4965–4974. [PMID:21384867]
1597. Hossain MA *et al*. (2010) *Amino Acids* **39**: 409–416. [PMID:20043231]
1598. Hsu SY *et al*. (2000) *Mol Endocrinol* **14**: 1257–1271. [PMID:10935549]
1599. Hsu SY *et al*. (2002) *Science* **295**: 671–674. [PMID:11809971]
1600. Kuei C *et al*. (2007) *J Biol Chem* **282**: 25425–25435. [PMID:17606621]
1601. Kumagai J *et al*. (2002) *J Biol Chem* **277**: 31283–31286. [PMID:12114498]
1602. Liu C *et al*. (2005) *Mol Pharmacol* **67**: 231–240. [PMID:15465925]
1603. Liu C *et al*. (2003) *J Biol Chem* **278**: 50765–50770. [PMID:14522967]
1604. Liu C *et al*. (2003) *J Biol Chem* **278**: 50754–50764. [PMID:14522968]
1605. Liu C *et al*. (2005) *J Biol Chem* **280**: 292–300. [PMID:15525639]
1606. Matsumoto M *et al*. (2000) *Gene* **248**: 183–189. [PMID:10806363]
1607. Metra M *et al*. (2013) *J Am Coll Cardiol* **61**: 196–206. [PMID:23273292]
1608. Muda M *et al*. (2005) *Mol Hum Reprod* **11**: 591–600. [PMID:16051677]
1609. Ryan PJ *et al*. (2013) *Behav Brain Res* **244**: 142–151. [PMID:23380674]
1610. Scott DJ *et al*. (2005) *Ann N Y Acad Sci* **1041**: 13–16. [PMID:15956681]
1611. Scott DJ *et al*. (2005) *Ann N Y Acad Sci* **1041**: 8–12. [PMID:15956680]
1612. Scott DJ *et al*. (2006) *J Biol Chem* **281**: 34942–34954. [PMID:16963451]
1613. Shabanpoor F *et al*. (2012) *J Med Chem* **55**: 1671–1681. [PMID:22257012]
1614. Shabanpoor F *et al*. (2012) *Biochem Biophys Res Commun* **420**: 253–256. [PMID:22425984]
1615. Shabanpoor F *et al*. (2008) *Bioconjug Chem* **19**: 1456–1463. [PMID:18529069]
1616. Shabanpoor F *et al*. (2011) *Biopolymers* **96**: 81–87. [PMID:20560146]
1617. Shemesh R *et al*. (2008) *J Biol Chem* **283**: 34643–34649. [PMID:18854305]
1618. Sudo S *et al*. (2003) *J Biol Chem* **278**: 7855–7862. [PMID:12506116]
1619. van der Westhuizen ET *et al*. (2010) *Mol Pharmacol* **77**: 759–772. [PMID:20159943]
1620. Van Der Westhuizen ET *et al*. (2007) *Curr Drug Targets* **8**: 91–104. [PMID:17266534]
1621. Wilkinson TN *et al*. (2005) *BMC Evol Biol* **5**: 14. [PMID:15707501]
1622. Xiao J *et al*. (2013) *Nat Commun* **4**: 1953. [PMID:23764525]
1623. Bruns C *et al*. (1996) *Metabolism* **45**: 17–20. [PMID:8769372]
1624. Castro SW *et al*. (1996) *Br J Pharmacol* **117**: 639–646. [PMID:8646408]
1625. De Lecea L *et al*. (1996) *Nature* **381**: 242–245. [PMID:8622767]
1626. Erchegyi J *et al*. (2005) *J Med Chem* **48**: 507–514. [PMID:15658864]
1627. Holloway S *et al*. (1996) *Neuropharmacology* **35**: 1109–1120. [PMID:9121614]
1628. Hoyer D *et al*. (2000) Somatostatin receptors. *In* The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edn. *Edited by* Watson SP, Girdlestone D IUPHAR Media. 354–364.
1629. Hoyer D *et al*. (2004) *Neurosci Lett* **361**: 132–135. [PMID:15135911]
1630. Hoyer D *et al*. (2004) Soc Neuroscience Abs, : -.
1631. Liu S *et al*. (1998) *J Med Chem* **41**: 4693–4705. [PMID:9822540]



1632. Meyerhof W. (1998) *Rev Physiol Biochem Pharmacol* **133**: 55–108. [PMID:9600011]
1633. Nunn C *et al*. (2003) *Naunyn Schmiedebergs Arch Pharmacol* **367**: 1–9. [PMID:12616335]
1634. Patel YC, Srikant CB. (1994) *Endocrinology* **135**: 2814–2817. [PMID:7988476]
1635. Rohrer SP *et al*. (1998) *Science* **282**: 737–740. [PMID:9784130]
1636. Siehler S *et al*. (1998) *Naunyn Schmiedebergs Arch Pharmacol* **357**: 483–489. [PMID:9650799]
1637. Siehler S *et al*. (1998) *Eur J Pharmacol* **348**: 311–320. [PMID:9652348]
1638. Siehler S *et al*. (1999) *Naunyn Schmiedebergs Arch Pharmacol* **360**: 488–499. [PMID:10598788]
1639. Tulipano G *et al*. (2002) *Endocrinology* **143**: 1218–1224. [PMID:11897676]
1640. Yang L *et al*. (1998) *Proc Natl Acad Sci U S A* **95**: 10836–10841. [PMID:9724791]
1641. He W *et al*. (2004) *Nature* **429**: 188–193. [PMID:15141213]
1642. Southern C *et al*. (2013) *J Biomol Screen* **18**: 599–609. [PMID:23396314]
1643. Anthes JC *et al*. (2002) *Eur J Pharmacol* **450**: 191–202. [PMID:12206858]
1644. Beaujouan JC *et al*. (1997) *Eur J Pharmacol* **319**: 307–316. [PMID:9042606]
1645. Bellucci F *et al*. (2002) *Br J Pharmacol* **135**: 266–274. [PMID:11786503]
1646. Bennacef I *et al*. (2004) *Bioorg Med Chem* **12**: 4533–4541. [PMID:15265501]
1647. Beresford IJ *et al*. (1995) *Eur J Pharmacol* **272**: 241–248. [PMID:7713168]
1648. Boden P *et al*. (1996) *J Med Chem* **39**: 1664–1675. [PMID:8648606]
1649. Bradshaw CG *et al*. (1994) *J Med Chem* **37**: 1991–1995. [PMID:8027981]
1650. Catalioto RM *et al*. (1998) *Br J Pharmacol* **123**: 81–91. [PMID:9484857]
1651. Chung FZ *et al*. (1995) *Mol Pharmacol* **48**: 711–716. [PMID:7476898]
1652. Cialdai C *et al*. (2006) *Eur J Pharmacol* **549**: 140–148. [PMID:16979621]
1653. Deal MJ *et al*. (1992) *J Med Chem* **35**: 4195–4204. [PMID:1331460]
1654. Donaldson LF *et al*. (1996) *Biochem J* **320** (Pt 1): 1–5. [PMID:8947459]
1655. Emonds-Alt X *et al*. (1995) *Life Sci* **56**: PL27–PL32. [PMID:7830490]
1656. Emonds-Alt X *et al*. (1993) *Biochem Biophys Res Commun* **191**: 1172–1177. [PMID:7682062]
1657. Fong TM *et al*. (1992) *J Biol Chem* **267**: 25668–25671. [PMID:1281470]
1658. Foord SM *et al*. (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1659. Giardina GA *et al*. (1996) *J Med Chem* **39**: 2281–2284. [PMID:8691422]
1660. Gitter BD *et al*. (1995) *J Pharmacol Exp Ther* **275**: 737–744. [PMID:7473161]
1661. Grisshammer R *et al*. (1994) *Recept Channels* **2**: 295–302. [PMID:7719707]
1662. Hale JJ *et al*. (1998) *J Med Chem* **41**: 4607–4614. [PMID:9804700]
1663. Hastrup H, Schwartz TW. (1996) *FEBS Lett* **399**: 264–266. [PMID:8985159]
1664. Huang SC, Korlipara VL. (2010) *Expert Opin Ther Pat* **20**: 1019–1045. [PMID:20533894]
1665. Kamali F. (2001) *Curr Opin Investig Drugs* **2**: 950–956. [PMID:11757797]
1666. Krause JE *et al*. (1997) *Proc Natl Acad Sci USA* **94**: 310–315. [PMID:8990205]
1667. Matuszek MA *et al*. (1998) *Eur J Pharmacol* **352**: 103–109. [PMID:9718274]
1668. Oury-Donat F *et al*. (1995) *J Pharmacol Exp Ther* **274**: 148–154. [PMID:7616392]
1669. Roush ED, Kwatra MM. (1998) *FEBS Lett* **428**: 291–294. [PMID:9654151]
1670. Sarau HM *et al*. (2001) *Eur J Pharmacol* **413**: 143–150. [PMID:11226387]
1671. Sarau HM *et al*. (1997) *J Pharmacol Exp Ther* **281**: 1303–1311. [PMID:9190866]
1672. Smith PW *et al*. (1995) *J Med Chem* **38**: 3772–3779. [PMID:7562907]
1673. Tian Y *et al*. (1996) *J Biol Chem* **271**: 20250–20257. [PMID:8702757]
1674. Tousignant C *et al*. (1990) *Brain Res* **524**: 263–270. [PMID:1705465]
1675. Drummond AH *et al*. (1989) *Ann N Y Acad Sci* **553**: 197–204. [PMID:2566295]
1676. Straub RE *et al*. (1990) *Proc Natl Acad Sci U S A* **87**: 9514–9518. [PMID:2175902]
1677. Sun Y *et al*. (2003) *J Mol Endocrinol* **30**: 87–97. [PMID:12683933]
1678. Borowsky B *et al*. (2001) *Proc Natl Acad Sci U S A* **98**: 8966–8971. [PMID:11459929]
1679. Espinoza S *et al*. (2011) *Mol Pharmacol* **80**: 416–425. [PMID:21670104]
1680. Maguire JJ *et al*. (2009) *Pharmacol Rev* **61**: 1–8. [PMID:19325074]
1681. Scanlan TS *et al*. (2004) *Nat Med* **10**: 638–642. [PMID:15146179]
1682. Stalder H *et al*. (2011) *Bioorg Med Chem Lett* **21**: 1227–1231. [PMID:21237643]
1683. Xie Z, Miller GM. (2009) *Biochem Pharmacol* **78**: 1095–1104. [PMID:19482011]
1684. Ames RS *et al*. (1999) *Nature* **401**: 282–286. [PMID:10499587]
1685. Bern HA *et al*.(1985) *Recent Prog Horm Res* **41**: 533–552. [PMID:2864726]
1686. Brkovic A *et al*.(2003) *J Pharmacol Expl Ther* **306**: 1200–1209. [PMID:12807997]
1687. Clozel M *et al*. (2004) *J Pharmacol Exp Ther* **311**: 204–212. [PMID:15146030]
1688. Coulouarn Y *et al*. (1999) *FEBS Lett* **457**: 28–32. [PMID:10486557]
1689. Coulouarn Y *et al*. (1998) *Proc Natl Acad Sci USA* **95**: 15803–15808. [PMID:9861051]
1690. Croston GE *et al*. (2002) *J Med Chem* **45**: 4950–4953. [PMID:]
1691. Douglas SA, Ohlstein EH. (2000) Urotensin receptors. *In* The IUPHAR Receptor Compendium of Receptor Characterization and Classification. *Edited by* Girdlestone D IUPHAR Media Ltd. 365–372.
1692. Douglas SA *et al*. (2005) *Br J Pharmacol* **145**: 620–635. [PMID:15852036]
1693. Elshourbagy NA *et al*. (2002) *Br J Pharmacol* **136**: 9–22. [PMID:11976263]
1694. Foord SM *et al*. (2005) *Pharmacol Rev* **57**: 279–288. [PMID:15914470]
1695. Grieco P *et al*. (2002) *J Med Chem* **45**: 4391–4394. [PMID:12238917]
1696. Kinney WA *et al*. (2002) *Angew Chem Int Ed Engl* **41**: 2940–2944. [PMID:12203418]
1697. Lehmann F *et al*. (2009) *Bioorg Med Chem* **17**: 4657–4665. [PMID:19481466]
1698. Lehmann F *et al*. (2005) *Bioorg Med Chem* **13**: 3057–3068. [PMID:15781415]
1699. Lehmann F *et al*. (2007) *Eur J Med Chem* **42**: 276–285. [PMID:17112638]
1700. Liu Q *et al*. (1999) *Biochem Biophys Res Commun* **266**: 174–178. [PMID:10581185]
1701. Maguire JJ *et al*. (2000) *Br J Pharmacol* **131**: 441–446. [PMID:11015293]
1702. Mori M *et al*. (1999) *Biochem Biophys Res Commun* **265**: 123–129. [PMID:10548501]
1703. Nothacker H-P *et al*. (1999) *Nat Cell Biol* **1**: 383–385. [PMID:10559967]
1704. Patacchini R *et al*. (2003) *Br J Pharmacol* **140**: 1155–1158. [PMID:14645137]
1705. Rakowski E *et al*. (2005) *J Mol Cell Cardiol* **39**: 785–791. [PMID:16171813]
1706. Stirrat A *et al*. (2001) *Am J Physiol Heart Circ Physiol* **280**: H925–H928. [PMID:11158995]
1707. Sugo T, Mori M. (2008) *Peptides* **29**: 809–812. [PMID:17628210]
1708. Akerlund M *et al*. (1999) *Br J Obstet Gynaecol* **106**: 1047–1053. [PMID:10519430]
1709. Ala Y *et al*. (1998) *J Am Soc Nephrol* **9**: 1861–1872. [PMID:9773787]
1710. Albright JD *et al*. (1998) *J Med Chem* **41**: 2442–2444. [PMID:9651149]
1711. Andres M *et al*. (2002) *Br J Pharmacol* **135**: 1828–1836. [PMID:11934825]
1712. Bell IM *et al*. (1998) *J Med Chem* **41**: 2146–2163. [PMID:9622556]
1713. Bichet DG *et al*. (1998) *Proc Assoc Am Physicians* **110**: 387–394. [PMID:9756088]
1714. Breton C *et al*. (2001) *J Biol Chem* **276**: 26931–26941. [PMID:11337500]
1715. Cheng LL *et al*. (2004) *J Med Chem* **47**: 2375–2388. [PMID:15084136]
1716. Chini B *et al*. (2003) *Br J Cancer* **89**: 930–936. [PMID:12942128]
1717. Chini B *et al*. (1995) *EMBO J* **14**: 2176–2182. [PMID:7774575]
1718. Chini B *et al*. (1996) *FEBS letters* **397**: 201–206. [PMID:8955347]
1719. Cotte N *et al*. (2000) *Eur J Biochem* **267**: 4253–4263. [PMID:10866830]
1720. Cotte N *et al*. (1998) *J Biol Chem* **273**: 29462–29468. [PMID:9792651]
1721. Derick S *et al*. (2002) *Endocrinology* **143**: 4655–4664. [PMID:12446593]
1722. Elands J *et al*. (1988) *Am J Physiol* **254** (1 Pt 1): E31–E38. [PMID:2827511]
1723. Failli AA *et al*. (2006) *Bioorg Med Chem Lett* **16**: 954–959. [PMID:16297621]
1724. Fuchs AR *et al*. (1982) *Science* **215**: 1396–1398. [PMID:6278592]
1725. Griebel G *et al*. (2002) *Proc Natl Acad Sci U S A* **99**: 6370–6375. [PMID:11959912]
1726. Griffante C *et al*. (2005) *Br J Pharmacol* **146**: 744–751. [PMID:16158071]
1727. Jasper JR *et al*. (1995) *Life Sci* **57**: 2253–2261. [PMID:7475979]



1728. Kimura T *et al.* (1994) *Eur J Endocrinol* **131**: 385–390. [PMID:7921228]
1729. Lemaire W *et al.* (2002) *Eur J Pharmacol* **450**: 19–28. [PMID:12176104]
1730. Nakamura S *et al.* (2000) *Br J Pharmacol* **129**: 1700–1706. [PMID:10780976]
1731. Pena A *et al.* (2007) *J Med Chem* **50**: 835–847. [PMID:17300166]
1732. Phalipou S *et al.* (1997) *J Biol Chem* **272**: 26536–26544. [PMID:9334232]
1733. Saito M *et al.* (1997) *Biochem Pharmacol* **53**: 1711–1717. [PMID:9264324]
1734. Serradeil-Le Gal C *et al.* (1996) *J Clin Invest* **98**: 2729–2738. [PMID:8981918]
1735. Serradeil-Le Gal C *et al.* (2000) *Kidney Int* **58**: 1613–1622. [PMID:11012895]
1736. Serradeil-Le Gal C *et al.* (2004) *J Pharmacol Exp Therap* **309**: 414–424. [PMID:14722330]
1737. Serradeil-Le Gal C *et al.* (2002) *J Pharmacol Exp Ther* **300**: 1122–1130. [PMID:11861823]
1738. Tahara A *et al.* (1998) *Br J Pharmacol* **125**: 1463–1470. [PMID:9884074]
1739. Tahara A *et al.* (1998) *Naunyn Schmiedebergs Arch Pharmacol* **357**: 63–69. [PMID:9459574]
1740. Thibonnier M *et al.* (1994) *J Biol Chem* **269**: 3304–3310. [PMID:8106369]
1741. Thibonnier M *et al.* (1997) *Endocrinology* **138**: 4109–4122. [PMID:9322919]
1742. Tsukada J *et al.* (2001) *Br J Pharmacol* **133**: 746–754. [PMID:11429400]
1743. Yamamura Y *et al.* (1998) *J Pharmacol Exp Ther* **287**: 860–867. [PMID:9864265]
1744. Yamamura Y *et al.* (1992) *Br J Pharmacol* **105**: 787–791. [PMID:1387020]
1745. Dautzenberg FM *et al.* (1999) *J Neuroendocrinol* **11**: 941–949. [PMID:10583729]
1746. Dickson L *et al.* (2006) *Neuropharmacology* **51**: 1086–1098. [PMID:16930633]
1747. Gourlet P *et al.* (1997) *Peptides* **18**: 1555–1560. [PMID:9437716]
1748. Gourlet P *et al.* (1997) *Peptides* **18**: 403–408. [PMID:9145428]
1749. Harmar AJ *et al.* (1998) *Pharmacol Rev* **50**: 265–270. [PMID:9647867]
1750. Juarranz MG *et al.* (1999) *Mol Pharmacol* **56**: 1280–1287. [PMID:10570056]
1751. Moody TW *et al.* (2002) *J Mol Neurosci* **18**: 29–35. [PMID:11931347]
1752. Moreno D *et al.* (2000) *Peptides* **21**: 1543–1549. [PMID:11068102]
1753. Moro O, Lerner EA. (1997) *J Biol Chem* **272**: 966–970. [PMID:8995389]
1754. Moro O *et al.* (1999) *J Biol Chem* **274**: 23103–23110. [PMID:10438479]
1755. Nicole P (2000) *J Biol Chem* **275**: 24003–24012. [PMID:10801840]
1756. Pisegna JR *et al.* (2000) *Ann N Y Acad Sci* **921**: 195–201. [PMID:11193823]
1757. Spengler D *et al.* (1993) *Nature* **365**: 170–175. [PMID:8396727]
1758. Uchida D *et al.* (1998) *Ann N Y Acad Sci* **865**: 253–258. [PMID:9928019]
1759. Van Rampelbergh J *et al.* (1996) *Mol Pharmacol* **50**: 1596–1604. [PMID:8967982]
1760. Xia M *et al.* (1997) *J Pharmacol Exp Ther* **281**: 629–633. [PMID:9152366]