Opioid and opioid-like

Overview: Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (met), [Leu]enkephalin (leu), β-endorphin (β-end), α-neo-dynorphin, dynorphin A (dynA), dynorphin B (dynB), Big dynorphin (Big dyn), nociceptin/orphanin FQ (N/OFQ) and endomorphin-1 and 2. The Greek letter names for the opioid receptors, μ, δ and κ, are well established, and IUPHAR considers these names most appropriate (Foord *et al.*, 2005). 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 (Mollereau *et al.*, 1994), it displays a distinct pharmacology.

Nomenclature	Delta opioid receptor	Kappa opioid receptor	Mu opioid receptor	N/OFQ receptor
Preferred abbreviation	δ	κ	μ	NOP
Other names	OP_1, DOP, DOR	OP_2, KOP, KOR	OP_3, MOP, MOR	ORL1, OP_4
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Rank order of potency	β-End = leu = met > dynA	Big dyn > dynA >> β-end > leu > met	β-End > dynA > met = leu	N/OFQ >> dynA
Selective agonists	DPDPE (Mosberg *et al.*, 1983), DSBULET (Delay-Goyet *et al.*, 1988), [$DAla^2$]deltorphin I or II (Erspamer *et al.*, 1989), SNC80 (Bilsky *et al.*, 1995)	U69593 (Lahti *et al.*, 1985), CI977 (Hunter *et al.*, 1990), Salvinorin A (Roth *et al.*, 2002)	Endomorphin-1 and 2 (Zadina *et al.*, 1997), morphine (Goldstein and Naidu, 1989), DAMGO (Handa *et al.*, 1981), sufentanil (Yeadon and Kitchen, 1988), PL017 (Costa *et al.*, 1992)	N/OFQ, N/OFQ-(1-13)-NH_2 (Guerrini *et al.*, 1997), Ro646198 (Jenck *et al.*, 2000), UFP112 (Rizzi *et al.*, 2007)
Selective antagonists	Naltrindole (Portoghese *et al.*, 1988), naltriben (Sofuoglu *et al.*, 1991)	Nor-binaltorphimine (Portoghese *et al.*, 1987), GNTI (Stevens *et al.*, 2000)	CTAP (Pelton *et al.*, 1986)	J113397 (8.3, Kawamoto *et al.*, 1999), SB612111 (8.5, Zaratin *et al.*, 2004), UFP101 (7.2, Calo' *et al.*, 2002)
Probes	[^{3}H]-DPDPE (Goldstein and Naidu, 1989), [^{3}H]-naltrindole (Yamamura *et al.*, 1992), [^{3}H]-deltorphin II (Gomes *et al.*, 2000), [^{3}H]-naltriben (Lever and Scheffel, 1998)	[^{3}H]-U69593 (Lahti *et al.*, 1985), [^{3}H]-CI977 (Simonin *et al.*, 2001)	[^{3}H]-DAMGO (Goldstein and Naidu, 1989), [^{3}H]-PL017 (Hawkins *et al.*, 1987)	[^{3}H]-N/OFQ (Dooley and Houghten, 1996), [^{3}H]-Leu-N/OFQ, [^{125}I]-Tyr^{14}-N/OFQ

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 isforms have not been definitively correlated with any of the proposed subtypes. Opioid receptor subtypes may reflect hetero-dimerization of opioid receptors with each other or with other 7TM receptors (Jordan and Devi, 1999), but evidence for heterodimers in native cells is equivocal. A distinct met-enkephalin receptor lacking structural resemblence to the opioid receptors listed has been identified (ENSG00000060491) and termed an opioid growth factor receptor (see Zagon *et al*., 2002).

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human μ receptors (see Oertel *et al*., 2009) and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists (Bruchas *et al*., 2007).

Abbreviations: **CI977**, (5*R*)-(5*α*,7*α*,8*β*)-(–)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxaspiro[4,5]dec-8-yl)-4-benzofuranacetamide hydrochloride; **CTAP**, D-Phe-*cyc*[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-NH_2; **DAMGO**, Tyr-DAla-Gly-[*N*MePhe]-NH$(CH_2)_2$; **DPDPE**, *cyc*[$DPen^2$, $DPen^5$]enkephalin; **DSBULET**, Tyr-DSer(OtBu)-Gly-Phe-Leu-Thr; **GNTI**, 5′-guanidinyl-17-(cyclopropylmethyl)-6,7-dehydro-4,5*α*-epoxy-3,14-dihydroxy-6,7-2′,3′-indolomorphinan; **ICI174864**, *N*,*N*-diallyl-Tyr-Aib-Phe-Leu-OH (Aib is aminoisobutyric acid); **J113397**, 1-[(3*r*,4*r*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one; **PL017**, [*N*-$MePhe^3$,$DPro^4$]morphiceptin; **Ro646198**, (1*S*,3*aS*)-8-(2,3,3*a*,4.5.6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one; **SB612111**, (–)-*cis*-1-methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol; **SNC80**, (+)-4-[(αR)-*α*-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide; **U69593**, 5*α*,7*α*,8*β*-(–)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxasipro(4,5)dec-8-yl)benzene acetamide; **UFP101**, [$Nphe^1$,Arg^{14},Lys^{15}]nociceptin-NH_2; **UFP112**, [(pF)$Phe^4Aib^7Arg^{14}Lys^{15}$]N/OFQ-$NH_2$

Further Reading

Bailey CP, Connor M (2005). Opioids: cellular mechanisms of tolerance and physical dependence. *Curr Opin Pharmacol* **5**: 60–68.
Ballantyne JC, Laforge KS (2007). Opioid dependence and addiction during opioid treatment of chronic pain. *Pain* **129**: 235–255.
Cahill CM, Holdridge SV, Morinville A (2007). Trafficking of δ-opioid receptors and other G-protein-coupled receptors: implications for pain and analgesia. *Trends Pharmacol Sci* **28**: 23–31.

DeHaven-Hudkins DL, DeHaven RN, Little PJ, Techner LM (2008). The involvement of the μ-opioid receptor in gastrointestinal pathophysiology: therapeutic opportunities for antagonism at this receptor. *Pharmacol Ther* **117**: 162–187.
Fichna J, Janecka A, Costentin J, Do Rego JC (2007). The endomorphin system and its evolving neurophysiological role. *Pharmacol Rev* **59**: 88–123.
Henriksen G, Willoch F (2008). Imaging of opioid receptors in the central nervous system. *Brain* **131**: 1171–1196.
Kieffer BL, Evans CJ (2009). Opioid receptors: from binding sites to visible molecules *in vivo*. *Neuropharmacology* **56** (Suppl. 1): 205–212.
Koch T, Hollt V (2008). Role of receptor internalization in opioid tolerance and dependence. *Pharmacol Ther* **117**: 199–206.
Kuszak AJ, Pitchiaya S, Anand JP, Mosberg HI, Walter NG, Sunahara RK (2009). Purification and functional reconstitution of monomeric μ-opioid receptors: allosteric modulation of agonist binding by Gi2. *J Biol Chem* **284**: 26732–26741.
Lambert DG (2008). The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential. *Nat Rev Drug Discov* **7**: 694–710.
Oertel BG, Kettner M, Scholich K, Renne C, Roskam B, Geisslinger G *et al*. (2009). A common human micro-opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain. *J Biol Chem* **284**: 6530–6535.
Pineyro G, Archer-Lahlou E (2007). Ligand-specific receptor states: implications for opiate receptor signalling and regulation. *Cell Signal* **19**: 8–19.
Sadee W, Wang D, Bilsky EJ (2005). Basal opioid receptor activity, neutral antagonists, and therapeutic opportunities. *Life Sci* **76**: 1427–1437.
Somogyi AA, Barratt DT, Coller JK (2007). Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**: 429–444.
Wang Y, Van Bockstaele EJ, Liu-Chen LY (2008). *In vivo* trafficking of endogenous opioid receptors. *Life Sci* **83**: 693–699.
Zollner C, Stein C (2007). Opioids. *Handb Exp Pharmacol* **177**: 31–63.

References

Bilsky EJ *et al*. (1995). *J Pharmacol Exp Ther* **273**: 359–366.
Bruchas MR *et al*. (2007). *J Biol Chem* **282**: 29803–29811.
Calo' G *et al*. (2002). *Br J Pharmacol* **136**: 303–311.
Costa EM *et al*. (1992). *Life Sci* **50**: 73–81.
Delay-Goyet P *et al*. (1988). *J Biol Chem* **263**: 4124–4130.
Dooley CT, Houghten RA (1996). *Life Sci* **59**: L23–L29.
Erspamer V *et al*. (1989). *Proc Natl Acad Sci USA* **86**: 5188–5192.
Foord SM *et al*. (2005). *Pharmacol Rev* **57**: 279–288.
Goldstein A, Naidu A (1989). *Mol Pharmacol* **36**: 265–272.
Gomes I *et al*. (2000). *J Neurosci* **20**: RC110.
Guerrini R *et al*. (1997). *J Med Chem* **40**: 1789–1793.
Handa BK *et al*. (1981). *Eur J Pharmacol* **70**: 531–540.
Hawkins KN *et al*. (1987). *Eur J Pharmacol* **133**: 351–352.
Hunter JC *et al*. (1990). *Br J Pharmacol* **101**: 183–189.
Jenck F *et al*. (2000). *Proc Natl Acad Sci USA* **97**: 4938–4943.
Jordan BA, Devi LA (1999). *Nature* **399**: 697–700.
Kawamoto H *et al*. (1999). *J Med Chem* **42**: 5061–5063.
Lahti RA *et al*. (1985). *Eur J Pharmacol* **109**: 281–284.
Lever JR, Scheffel U (1998). *Eur J Pharmacol* **350**: 335–344.
Mollereau C *et al*. (1994). *FEBS Lett* **341**: 33–38.
Mosberg HI *et al*. (1983). *Proc Natl Acad Sci USA* **80**: 5871–5874.
Pelton JT *et al*. (1986). *J Med Chem* **29**: 2370–2375.
Portoghese PS *et al*. (1987). *J Med Chem* **30**: 1991–1994.
Portoghese PS *et al*. (1988). *Eur J Pharmacol* **146**: 185–186.
Rizzi A *et al*. (2007). *Peptides* **28**: 1240–1251.
Roth BL *et al*. (2002). *Proc Natl Acad Sci USA* **99**: 11934–11939.
Simonin F *et al*. (2001). *Eur J Pharmacol* **414**: 189–195.
Sofuoglu M *et al*. (1991). *J Pharmacol Exp Ther* **257**: 676–680.
Stevens WC *et al*. (2000). *J Med Chem* **43**: 2759–2769.
Yamamura MS *et al*. (1992). *Life Sci* **50**: L119–L124.
Yeadon M, Kitchen I (1988). *Neuropharmacology* **27**: 345–348.
Zadina JE *et al*. (1997). *Nature* **386**: 499–502.
Zagon IS *et al*. (2002). *Brain Res Rev* **38**: 351–376.
Zaratin PF *et al*. (2004). *J Pharmacol Exp Ther* **308**: 454–461.