

Opioid Receptors

Key References

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Overview

Opioid receptors are distributed widely in brain and found in spinal cord and peripheral sensory and autonomic nerves. There are three well-characterized members of the opioid receptor family, designated by the Greek symbols δ , κ and μ . The more recently discovered ORL₁ receptor is placed with this family due to its high degree of structural homology. These receptors were renamed OP₁, OP₂, OP₃ and OP₄, respectively, by an International Union of Pharmacology (IUPHAR) nomenclature committee in 1996. This nomenclature has proved unpopular. The nomenclature (X-Opioid Peptide receptor) has been proposed giving μ , mu or MOP; δ , delta or DOP; κ , kappa or KOP and ORL₁ or NOP receptors. To keep matters straightforward the original nomenclature is used in the following discussion.

Opioid receptors are activated physiologically by the products of endogenous opioid peptide genes; proenkephalin (giving methionine- and leucine-enkephalin; Met-enk; Leu-enk, respectively), prodynorphin (dynorphins A and B and α -neo-endorphin) pro-opiomelanocortin (β -endorphin) and pronociceptin (nociceptin, also known as Orphanin FQ). Met-enk and Leu-enk have highest affinity for δ receptors, less affinity for μ , and very low affinity for κ receptors; the dynorphins have preferential affinity for κ receptors, but bind to the μ and δ types with high affinity; β -endorphin binds with high affinity to μ and δ receptors, but has little affinity for κ receptors. All the peptides are full agonists at their cognate receptors. Endomorphin-1 and -2, derived from an unknown precursor, are endogenous peptides with high selectivity for μ receptors. These peptides are unusual in that they are partial agonists. None of the proenkephalin, prodynorphin or pro-

opiomelanocortin peptide products or the endomorphins displays affinity for the ORL₁ receptor. Similarly, the ORL₁ receptor agonist nociceptin has no appreciable affinity for μ , δ or κ receptors.

The four receptor types have been cloned and shown to be 7-transmembrane receptors activating G proteins of the pertussis-toxin insensitive G $\alpha_{i/o}$ family, but including G α_z . Evidence for subtypes of μ , δ and κ opioid receptors exists, but the molecular basis for the observed functional and pharmacological differences is unclear. Putative δ_1 and δ_2 receptors are differentiated by several agonist and antagonist ligands. However, there is only one δ receptor gene, the protein product of which has properties of the putative δ_2 receptor. The distinction between the proposed μ_1 and μ_2 receptors is based largely on the apparent preferential blockade of the μ_1 type by the antagonist, naloxonazine. There is only one cloned μ receptor gene, corresponding to the putative μ_1 receptor, but several forms of the μ -receptor mRNA arising from alternative splicing have been reported. The receptors these encode differ at the end of the C-terminal tail and show subtle differences in the binding profile of opioid ligands; a role for the variants is not known.

The cloned κ receptor, with high affinity for U69593, is the κ_1 subtype. The proposed κ_2 and κ_3 subtypes are poorly defined in both molecular and pharmacological terms. A recent explanation for subtypes has evolved with the identification of opioid receptor heterodimers or hetero-oligomers that appear to have properties different from the monomeric receptors. An interesting addition to ligands that bind to the κ_1 receptor is the hallucinogen salvinorin-A. This is a highly efficacious and potent κ agonist, but is most

unusual in that it has no nitrogen atom. Endogenous opioid systems have a functional role in modulating pain perception; opioid agonists are therefore potent analgesics. Opioid receptors are also present in hypothalamus, where they influence temperature regulation and control of hormonal secretion. In the forebrain, endogenous opioids are involved in behavioral reinforcement and appear to play a role in anxiety and in the expression of emotions. Opioids influence gastrointestinal and autonomic nervous system function.

Opioid Receptors

CURRENTLY ACCEPTED NAME	μ	δ	κ	ORL1
CURRENT IUPHAR NAME	OP ₃	OP ₁	OP ₂	OP ₄
SUGGESTED NAME	MOP	DOP	KOP	NOP
NAME OF CLONED RECEPTOR	MOR	DOR	KOR	ORL ₁
STRUCTURAL INFORMATION	400 aa (human)	372 aa (human)	380 aa (human)	372 aa (human)
SELECTIVE AGONISTS	DAMGO (E7384), Endomorphin-1 and -2 (E3273 , E3148), Fentanyl (F3886), Morphine (M8777)	DPDPE ^a (E3888), (-)-TAN-67 (SB205607) ^a (T5824), [D-Ala ² ,Glu ⁴]-Deltorphin (T0675), ^b DSLET, ^b BW373U86 (B8930), SNC80 (S2812)	U69593, U50488H, Enadoline (C1977), Salvinorin-A, Ethylketocyclazocine, ^c Bremazocine ^c	Nociceptin (Orphanin FQ) (O4011), Ro 64-6198
SELECTIVE ANTAGONISTS	β -FNA ^d (O003), MCAM, ^d CTAP (C6352), CTOP (P5296), Cyprodime (C153)	BNTX, ^a DALCE, ^{a,d} Naltriben ^b (N156), 5'-NTII, ^{b,d} TIPP(ψ) (T7075), Naltrindole (N115), ICI174864	nor-BNI (N1771), GNTI (G3416)	J-113397, [Nphe ¹]-Nociceptin(1-13)NH ₂ (N0524), [Phe ¹ ψ (CH ² -NH)-Gly ²]- Nociceptin (1-13)NH ₂ (N213 , N9908) ^f
ENDOGENOUS OPIOID PEPTIDES	β -Endorphin (E6261), Endomorphin-1 and -2 (E3273 , E3148), [Met ⁵]-Enkephalin (M6638), [Leu ⁵]-Enkephalin (G1885)	β -Endorphin (E6261), [Met ⁵]-Enkephalin (M6638), [Leu ⁵]-Enkephalin (G1885)	Dynorphin A (D8147)	Nociceptin (Orphanin FQ) (O4011)
NON-SELECTIVE OPIOID ANTAGONISTS	β -CNA ^d (O001), Naloxone (N7758), Naltrexone (N3136)	β -CNA ^d (O001), Naloxone (N7758), Naltrexone (N3136)	β -CNA ^d (O001), Naloxone (N7758), Naltrexone (N3136)	Not known
SIGNAL TRANSDUCTION MECHANISMS	G _{i/o} (cAMP modulation) G _{1/o} (K ⁺ channel open) G _o (Ca ²⁺ channel closed) G _{1/o} (MAP kinase)	G _{i/o} (cAMP modulation) G _{1/o} (K ⁺ channel open) G _o (Ca ²⁺ channel closed) G _{1/o} (MAP kinase)	G _{i/o} (cAMP modulation) G _{1/o} (K ⁺ channel open) G _o (Ca ²⁺ channel closed) G _{1/o} (MAP kinase)	G _i (cAMP modulation) G _{1/o} (K ⁺ channel open) G _o (Ca ²⁺ channel closed) G _{1/o} (MAP kinase)
RADIOLIGANDS OF CHOICE	[³ H]-DAMGO [³ H]-CTAP	[³ H]-DPDPE ^a [³ H]-Naltrindole	[³ H]-U69593 [³ H]-Bremazocine	[³ H]-Nociceptin (Orphanin FQ)
TISSUE EXPRESSION	CNS, including thalamus, nucleus accumbens, locus coeruleus, amygdala, spinal cord, ventral tegmental area, substantia nigra; GI tract	CNS, including nucleus accumbens, caudate putamen, pontine nuclei, olfactory tubercle, amygdala, spinal cord; GI tract, heart	CNS, including hypothalamus, nucleus accumbens, ventral tegmental area, substantia nigra, olfactory tubercle, amygdala, spinal cord; heart	CNS, including cortex, thalamus, amygdala, hippocampus periaqueductal grey, substantia nigra, spinal cord

FOOTNOTES

Opioid Receptors

PHYSIOLOGICAL FUNCTION	Antinociception, reward, respiratory function, GI motility	Antinociception, immune function, mood	Antinociception, water diuresis, dysphoria	Nociception/antinociception, learning and memory (negative regulator)
DISEASE RELEVANCE	Pain, drug abuse, diarrhea	Depression, pain, cardioprotection	Pruritis, pain	Pain

Abbreviations

nor-BNI: nor-Binaltorphimine

BNTX: (E)-7-Benzylidenenaltrexone

BW373U86: (\pm)-(1[S*]2 α ,5 β)-4-((2,5-Dimethyl-4-(2-propenyl)-1-piperazinyl)[3-hydroxyphenyl]methyl)-N,N-diethylbenzamide

β -**CNA:** β -Chlornaltrexamine

CTAP: D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH₂

CTOP: D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Phe-Thr-NH₂

DALCE: [D-Ala²,Leu⁵,Cys⁶]-Enkephalin

DAMGO: [D-Ala²,N-Me-Phe⁴,Gly-ol⁵]-Enkephalin

DPDPE: [D-Pen^{2,5}]-Enkephalin

DSLET: [D-Ser²,Leu⁵,Thr⁶]-Enkephalin

β -**FNA:** β -Funnaltrexamine

GNTI: 5'-Guanidinylnaltrindole

ICI 174864: N,N-Diallyl-Tyr-Aib-Aib-Phe-Leu

J-113397: 1-[(3R,4R)-1-Cycloocylomethyl-3-hydroxymethyl-4-piperidinyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one

MCAM: Methocinnomox

5'-NTII: Naltrindole 5'-isothiocyanate

Ro 64-6198: (1S,3aS)-8-(2,3,3a,4,5,6-Hexahydro-1H-phenalen-1-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

SNC80: (+)-4-[(α R)- α -((2S5R)-4-allyl-2,5-Dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide

(-)-**TAN-67:** (-)-2-Methyl-4 $\alpha\alpha$ -(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12 α -octahydroquinolino[2,3,3-q]isoquinoline

TIPP(η): H-Tyr-Tic η -[CH₂NH]Phe-Phe-OH.

U-69593: (+)-(5 α ,7 α ,8 β)-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide

U-50488: 3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide

FOOTNOTES

- a** Putative δ_1 ligands.
- b** Putative δ_2 ligands.
- c** Not selective but used to define "non- κ_1 " sites.
- d** These ligands bind irreversibly or pseudoirreversibly.
- e** Inverse agonist.
- f** Has agonist properties in some systems.