Opioid mechanisms and opioid drugs

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Abstract

The opioid system comprises four receptor subtypes: μ (MOP), κ (KOP), δ (DOP), now called the 'classical' opioid receptors, and the 'non-classical' nociceptin/orphanin FQ peptide (N/OFQ) receptor (NOP). Selective endogenous peptides, cleaved from larger precursor proteins, have been identified for all subtypes. Both classical and non-classical opioid receptors couple to inhibitory, pertussis toxin-sensitive G-proteins. Opioid receptors activate the same major intracellular pathways, which include: closing of voltage-sensitive calcium channels; opening of potassium channels and subsequent cellular hyperpolarization; and inhibition of cyclic AMP production through inhibition of the enzyme adenylate cyclase. All current, clinically used opioids work through activation of the MOP receptor. In an experimental setting, co-administration of MOP and DOP agonists has been shown to have a synergistic analgesic action. Administration of DOP-receptor antagonists has also been shown to reduce tolerance, physical dependence and other side effects of MOP-receptor agonists, without detriment to their analgesic action. In animal models NOP agonists are analgesic when administered spinally and have a pronociceptive/anti-analgesic (or anti-opioid) effect supraspinally. NOP knockout mice show a partial loss of tolerance to morphine and there is an up-regulation of N/OFQ production in chronic morphine tolerant mice. Analgesic tolerance that develops from repeated exposure to morphine is markedly attenuated in NOP knockout mice. The development of ligands with mixed action at MOP, DOP and NOP receptors offer new opportunities for opioid pharmacology.

Keywords G-protein-coupled receptor; MOP/DOP opioid receptor actions; NOP-receptor antagonist

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Learning objectives

After reading this article you should:

- know what the four subtypes of opioid receptor are and understand which receptor clinical drugs target
- have a basic understanding of the intracellular mechanisms by which opioid receptors work
- understand the main physiological effects from activation of the different subtypes of opioid receptor
- appreciate that there is interplay between the actions of the different subtypes of receptor and hence the value of drugs which target multiple receptor subtypes.

Opium and its derivatives have been used for centuries for medicinal and recreational purposes. Opiates refer to the non-peptide synthetic morphine-like drugs whilst the term opioid is more generic, encompassing all substances that produce morphine-like actions. Opioids can be loosely divided into four groups:

- naturally occurring endogenously produced opioid peptides (e.g. dynorphin and met-enkephalin)
- opium alkaloids such as morphine purified from the poppy *Papaver somniferum*
- semi-synthetic opioids (modifications to the natural morphine structure) such as diacetylmorphine (heroin)
- synthetic derivatives with structure unrelated to morphine, which include the phenylpiperidine series (e.g. pethidine and fentanyl), methadone series (e.g. methadone and dextropropoxyphene), benzomorphan series (e.g. pentazocine), and semi-synthetic thebaine derivatives (e.g. etorphine and buprenorphine).

Snyder and colleagues in 1973 published data showing specific binding of opioids, providing the first evidence of distinct receptors for these drugs. Multiple opioid receptor types were evident from initial studies, which showed: differences in opioid potency; selective antagonism; and stereospecificity of opiate actions. Opioid-receptor subtypes were defined from multiple studies characterizing drug action at distinct anatomical locations and through pharmacological profiles of opioids. 'Classical' opioid receptor definition is based in part on a sensitivity to naloxone and subtypes μ (MOP), κ (KOP) and δ (DOP) exist. Current International Union of Basic and Clinical Pharmacology (IUPHAR) nomenclature is included in parenthesis and will be used for the remainder of this article. Low-stringency hybridization screening using opioid receptor probes led to the discovery of a fourth 'opioid-like receptor' initially named LC132 (rat), MOR-3 (mouse) and ORL1 (human). Following the deorphanizing of the receptor and the identification of endogenous ligand, nociceptin/orphanin FQ (N/OFQ), the receptor was classified as a 'non-opioid' branch of the opioid receptor family, owing to a lack of sensitivity to naloxone whilst sharing significant sequence homology with the classical opioid receptors. The current nomenclature for this fourth opioid receptor subtype is nociceptin/orphanin FQ (N/OFQ) peptide receptor (NOP).

All receptors are G-protein coupled and share the same general structure: seven linked transmembrane spanning domains, an extracellular N-terminus and intracellular C-terminal tail. Based on alignment of their amino acid sequences, all four subtypes have an overall homology of about 60%; however, this

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increases to more than 80% in the second, third and seventh transmembrane domains.

Isoforms of all opioid receptors have been suggested based largely on pharmacological grounds, which sees the differential effect of a drug *in vivo* when compared to *in vitro* responses or incomplete tolerance profiles seen when alternating drugs acting at the same receptor. There is no evidence for multiple genes encoding opioid-receptor subtypes, opioids are encoded by single genes which when removed, as in knock-out animals, results in all those responses associated with the respective receptor becoming absent. The putative isoforms of receptors reported are accounted for in part by the alternative splicing of a single gene resulting in alternative receptor protein structures and therefore pharmacology, for the MOP receptor 15 splice variants have been reported with some distinct regional distribution within the CNS. The exact nature of the pharmacologically described subtypes remains the subject of debate.

Endogenous opioid peptides

Hughes and Kosterlitz isolated the first endogenous opiates, two peptides (met-enkephalin and leu-enkephalin) that competed with morphine-like drugs for binding to receptors in the brain. Subsequent studies identified further endogenous opioids to include dynorphin A, dynorphin B, β-endorphin, endomorphin-1 and -2, and N/OFQ (Table 1).[1] Met- and leu-enkephalin showed preferential binding to DOP receptors, whilst dynorphin A and B favoured binding to KOP receptors, N/OFQ for NOP and endomorphin-1 and -2 for MOP. β-endorphin has activity at all three classical subtypes but shows some preference for MOP receptors. Opioid peptides are cleaved from larger precursors: β-endorphin from preproopiomelancortin; met- and leu-enkephalin from preproenkephalin; N/OFQ from pre-pro-nociceptin; and dynorphin A and B from preprodynorphin. The precursor(s) for endomorphin-1 and -2 are yet to be identified. The precursors contain other bioactive fragments within their sequences, and in the case of preproenkephalin multiple copies of their respective peptides (Table 1).[2]

Characteristics of the more common opioid peptides.

Precursor	Ligand	Peptide sequence
Unknown	Endomorphin-1	YPWF-NH_2
Unknown	Endomorphin-2	YPFF-NH_2
Pro-opiomelanocortin	β-endorphin	Y**GGF**MTSE**KS**QTPLVTL
		FKNAIIKNAYKKGE
Pro-enkephalin	Leu-enkephalin	Y**GGF**L
		Y**GGF**MRF
		Y**GGF**MRGL
	Met-enkephalin	Y**GGF**M
	Metorphamide	Y**GGF**MRRV-NH_2
Pro-dynorphin	Dynorphin A	Y**GGF**LRRIRPKL**K**WD**NQ**
	Dynorphin B	Y**GGF**LRRQFKVVT
	α-neoendorphin	Y**GGF**LRKYPK
	β-neoendorphin	Y**GGF**LRKYP
Pre-pro-nociceptin	N/OFQ	F**GGF**TGAR**KS**AR**K**LA**NQ**
	Nocistatin	TEPGLEEVGEIEQKQLQ

Standard single amino acid code is used. Note that endorphins, enkephalins and dynorphins share a common Tyr-Gly-Gly-Phe (YGGF) motif which enables binding to classical opioid receptors (modified from[1])

Table 1

Intracellular effectors

The four subtypes of opioid receptor couple to inhibitory, pertussis toxin sensitive G-proteins (e.g. $G_{i/o}$). Both recombinant and endogenously expressed opioid receptors activate the same major intracellular pathways, which include: closing of (predominantly) N and P/Q-type voltage-sensitive calcium channels; opening of potassium channels and subsequent cellular hyperpolarization; and inhibition of cyclic AMP (cAMP) production through the inhibition of the enzyme adenylyl cyclase.[2,3]

G-protein-coupled receptors (GPCRs) couple to heterotrimeric G-proteins, which are formed from three distinct subunits: α, β, and γ. There are numerous gene products encoding for the different subunits. GPCR activation, for example MOP with morphine, induces a conformational change in the receptor, which allows coupling to respective G-protein subtype(s), this will be a G-protein possessing a $G_{i/o}$ α-subunit. In their resting form G-proteins reside in a heterotrimeric complex (αβγ), with guanine diphosphate (GDP) in association with the α-subunit. G-protein association with its cognate receptor, upon ligand binding, leads to dissociation of GDP from the α subunit and binding of GTP followed by the dissociation of α-GTP from the βγ complex. Both α-GTP and βγ are able to affect different intracellular pathways through activation or inhibition of enzymes and ion channels. G-protein GTPase activity, which converts GTP into GDP, leads to cessation of signalling and reforming of the α-GDP subunit with βγ (Figure 1).

N/P-type voltage-sensitive calcium channels (VSCCs) are located at synaptic terminals and play a major role in transmitter release and therefore synaptic transmission. Some G-protein coupled receptors, including opioid receptors, negatively regulate VSCC, such that their activation inhibits calcium influx, preventing neurotransmitter release. Channel inhibition results from a positive shift in the voltage dependence of the channel coupled to a slowing of activation; the inhibition can be relieved by a strong depolarization. Classical opioid receptors have been shown to inhibit N-, P/Q-, L- and T-type calcium channels. However because of their location at presynaptic terminals, N- and P/Q-type channel modulation is thought to be of most importance. N-type and P/Q-types calcium currents are most sensitive to inhibition by N/OFQ. VSCC inhibition by opioids has been demonstrated in a variety of preparations, including the locus coeruleus, periaqueductal grey neurons and trigeminal ganglion neurons. Overall the effect of opioids on VSCCs leads to reduced transmitter release.[3]

G-protein inwardly rectifying potassium (GIRK) channels are activated by opioid receptors. GIRK channel opening is through an interaction with Gβγ subunits released from $G_{i/o}$ G-proteins and leads to membrane hyperpolarization through an efflux of potassium ions. The net effect is reduced neuronal excitability and, through opioid receptor location on nociceptive afferents, a concomitant reduction in nociceptive transmission. N/OFQ-mediated activation of GIRK channels has also been demonstrated at many central sites, including spinal cord, locus coeruleus, periaqueductal grey and hypothalamus.[4,5]