

## Basic opioid pharmacology

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### SUMMARY POINTS

- Opioids can be classified according to their mode of synthesis into alkaloids, semi-synthetic and synthetic compounds.
- There are three classical receptors (DOP, KOP and MOP). The novel NOP receptor is considered to be a non-opioid branch of the opioid receptor family.
- Opioids can either act as agonists, antagonists or partial agonists at these receptors.
- Opioid agonists bind to G-protein coupled receptors to cause cellular hyperpolarisation.
- MOP receptor agonists act in the central and peripheral nervous system to elicit analgesia.

### Introduction

Morphine is commonly considered to be the archetypal opioid analgesic and the agent to which all other painkillers are compared. For several thousand years, opioid-based analgesic agents have been used, in one form or another, to control pain. There is evidence to suggest that as long ago as 3000BC the opium poppy, *Papaver somniferum*, was cultivated for its active ingredients in what is now modern day Iraq. More recently, from the sixteenth to nineteenth centuries, laudanum (an alcoholic mix of opium and various ingredients) was frequently used as a popular remedy in European medicine. It was, however, not until morphine was isolated from opium in 1806 by Sertürner that modern opioid pharmacology was truly born. In 1847 the chemical formula for morphine was deduced and this, coupled with the invention of the hypodermic needle in 1853, led to the more precise and widespread clinical use of morphine<sup>1,2</sup>.

### Classification

Though morphine is the most widely known extract of *Papaver somniferum*, four naturally occurring alkaloids (plant derived amines) can be isolated from it: morphine, codeine, papaverine and thebaine. Of these alkaloids, morphine, codeine (a prodrug of morphine) and papaverine have found a place in clinical practice; morphine and codeine as analgesic agents and papaverine, a compound devoid of any pain killing properties, as a smooth muscle relaxant. Following Sertürner's isolation of morphine as the active component of the opium poppy, simple chemical manipulations of these basic opiate alkaloids began to yield a range of semi-synthetic opioids useful in clinical medicine (agents such as diamorphine, dihydrocodeine, buprenorphine, nalbuphine, naloxone and oxycodone). During the 20<sup>th</sup> century a number of synthetic opioids were also produced either by design or serendipitously. These synthetic compounds can be divided into four chemical groupings, the morphinan derivatives (levorphanol, butorphanol), the diphenylheptane derivatives (methadone, propoxyphene), the benzomorphan derivatives (pentazocine,

**Table 1.** Classification of opioids by synthetic process.

Naturally occurring	Semi-synthetic compounds	Synthetic compounds
Morphine Codeine Thebaine Papaverine	Heroin Dihydromorphine Buprenorphine Oxycodone	Pethidine Fentanyl Methadone Alfentanil Remifentanil

phenazocine) and the phenylpiperidine derivatives (pethidine, alfentanil, fentanyl, sufentanil and remifentanil) (Table 1)<sup>2,3</sup>.

Opioids can also be classified according to their effect at opioid receptors. In this manner opioids can be considered as agonists, partial agonists and antagonists. Agonists interact with a receptor to produce a maximal response from that receptor (analgesia following morphine administration is an example). Conversely antagonists bind to receptors but produce no functional response, while at the same time preventing an agonist from binding to that receptor (naloxone). Partial agonists bind to receptors but only elicit a partial functional response no matter the amount of drug administered (buprenorphine).

### Opioid receptors

In addition opioids can be categorized according to the type of opioid receptor at which they produce their effects. Classically there are considered to be three opioid receptors. These receptors are all G-protein coupled receptors, and were originally named mu (after morphine, its most commonly recognised exogenous ligand), delta (after *vas deferens*, the tissue within which it was first isolated) and kappa (after ketocyclazocine, the first ligand to act at this receptor). In 1996 the International Union of Pharmacology (IUPHAR) renamed the receptors OP1 (the delta receptor), OP2 (the kappa receptor) and OP3 (the mu receptor). In 2000 this nomenclature was again changed to DOP, KOP and MOP; this remains the current classification. (Table 2)<sup>1,4</sup>. Some authorities describe the existence of multiple subtypes of the three classical opioid receptors, but this is not a belief held by all researchers within the field. The classical opioid receptors are distributed widely within the central nervous system and to a lesser extent throughout the periphery, occupying sites within the *vas deferens*, knee joint, gastrointestinal tract, heart and immune system amongst others<sup>5</sup>.

**Table 2.** Changes in the classification of the classical opioid receptors over time.

Pre-cloning	Post-cloning	IUPHAR 1996	IUPHAR 2000
δ	DOR	OP1	DOP
κ	KOR	OP2	KOP
μ	MOR	OP3	MOP

Soon after the discovery of the opioid receptors a series of endogenous ligands active at the receptors were discovered in brain extracts. Three pro-hormone precursors provide the parent compounds from which these endogenous ligands are derived. Proenkephalin is cleaved to form met-enkephalin and leu-enkephalin which bind to the DOP receptor. Dynorphin A and B are derived from prodynorphin and are agonists at the KOP receptor. Pro-opiomelanocortin (POMC) is the

parent compound for β-endorphin, an agonist at the MOP receptor, though it is capable of displaying agonist activity at all three classical opioid receptors<sup>1,3,6</sup>. Two further endogenous peptides act as agonists at the MOP receptor, endomorphin 1 and 2, but no precursor has yet been identified (Table 3). There is significant cross talk between the endogenous agonists and the three classical receptors.

In 1994 a fourth G-protein coupled endogenous opioid like receptor was found and subsequently named the nociceptin receptor (NOP). Rapidly after this discovery came the isolation from brain extracts of its endogenous ligand nociceptin/orphanin FQ (N/OFQ). This endogenous ligand is similarly derived from a precursor compound, in this instance from the polypeptide precursor pre-pro-nociceptin. Though the N/OFQ/NOP system does not bind naloxone, nor are its effects reversed by naloxone, it is a G-protein coupled receptor system that shares a marked similarity to the known amino acid sequences of the classical opioid receptors (the NOP receptor shows 80% homology to the KOP receptor)<sup>1,7</sup>. At a cellular level N/OFQ acts to produce similar actions to those described for the classical opioid receptors above. For these reasons it has been classified as the fourth opioid receptor; however, due to its lack of response to the classical opioid antagonist (naloxone) some pharmacologists have questioned the wisdom of this classification. IUPHAR considers the NOP receptor to be a non-opioid branch of the opioid receptor family<sup>4</sup>.

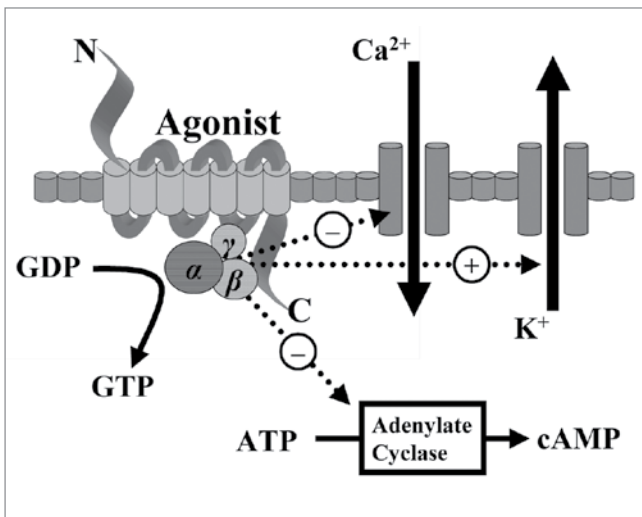
In clinical practice the stimulation of the differing opioid receptors produces a range of effects along with analgesia, which are often dependent upon the location of the receptor. Agonists binding to MOP receptors may cause analgesia but also sedation, respiratory depression, bradycardia, nausea and vomiting and a reduction in gastric motility. Similar activation of DOP receptors can cause spinal and supraspinal analgesia and reduce gastric motility, while KOP receptor stimulation may produce spinal analgesia, a diuresis and dysphoria. Spinally N/OFQ has been shown to produce analgesia and hyperalgesia, dependent upon the administered concentration, and allodynia. Supraspinally when administered intracerebrovascularily it is thought to produce a pro-nociceptive anti-analgesic effect, due to an inhibition of endogenous opioid tone<sup>1,8</sup>.

**Table 3.** Opioid receptors and their endogenous ligands and precursors.

Receptor	Precursor	Peptide
DOP	Pro-enkephalin	[Met]-enkephalin [Leu]-enkephalin
KOP	Pro-dynorphin	Dynorphin-A Dynorphin-B
MOP	POMC	β-Endorphin
	Unknown	Endomorphin-1 Endomorphin-2
NOP	Pre-pro-nociceptin	N/OFQ

**Intracellular events**

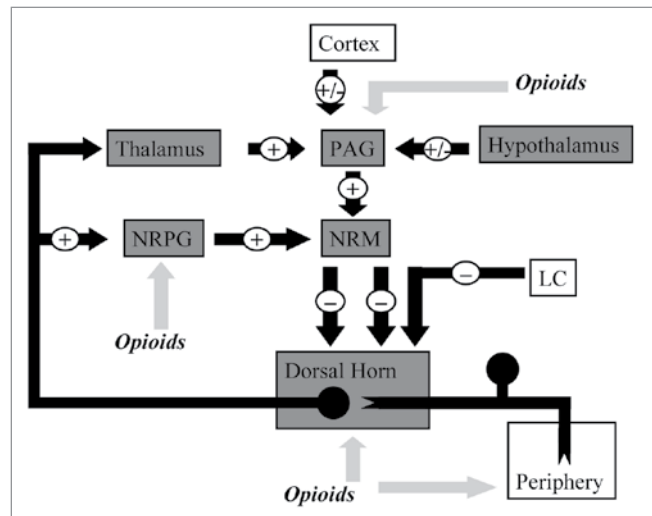
Though producing subtly different functional effects all of these receptors display similar cellular responses following receptor activation. Binding of an opioid agonist to a G-protein coupled opioid receptor on the transmembrane portion of the receptor causes the  $\alpha$  subunit of the G-protein to exchange its bound guanosine diphosphate (GDP) molecule with intracellular guanosine triphosphate (GTP). This then allows the  $\alpha$ -GTP complex to dissociate away from the  $\beta\gamma$  complex. Both of these complexes ( $\alpha$ -GTP and  $\beta\gamma$ ) are then free to interact with target proteins. In the case of a classical opioid agonist binding to its G-protein receptor, this results in the inhibition of adenylate cyclase. This in turn causes a reduction in intracellular cyclic adenosine monophosphate (cAMP) levels. Additionally these complexes interact with a number of ion channels, producing activation of potassium conductance and an inhibition of calcium conductance. The net effect of these changes is of a reduced intracellular cAMP, a hyperpolarisation of the cell in question and, for neuronal cells, reduced neurotransmitter release (Figure 1). In some cell types activation of opioid receptors can also paradoxically cause a release of calcium from intracellular stores, leading to an increase in the intracellular calcium concentration<sup>6,9</sup>.



**Figure 1.** Intracellular changes occurring following the binding of an opioid agonist to a G-protein coupled opioid receptor.

**Opioid mediated analgesia**

Opioid receptors are distributed throughout the central nervous system and within peripheral tissue of neural and non-neural origin. Centrally, the periaqueductal grey (PAG), locus cereleus and rostral ventral medulla show high concentrations of opioid receptors, while opioid receptors are also present in the substantia gelatinosa of the dorsal horn.



**Figure 2.** This figure shows schematically the descending inhibitory pathways. Areas shaded grey display a high expression of opioid receptors and their endogenous ligands. MOP agonists produce analgesia either by indirectly increasing neuronal traffic through the descending pathway at the NRPG and PAG, or by directly inhibiting nociceptive afferents in the periphery.

*PAG = Periaqueductal grey  
 NRPG = Nucleus reticularis paragigantocellularis  
 NRM = Nucleus raphe magnus  
 LC = Locus cereleus*

Within the central nervous system activation of MOP receptors in the midbrain is thought to be a major mechanism of opioid induced analgesia. Here MOP agonists act by indirectly stimulating descending inhibitory pathways which act upon the periaqueductal grey (PAG) and nucleus reticularis paragigantocellularis (NRPG) with the net effect of an activation of descending inhibitory neurones. This leads to greater neuronal traffic through the nucleus raphe magnus (NRM), increasing stimulation of 5-HT and enkephalin-containing neurones which connect directly with the substantia gelatinosa of the dorsal horn. This in turn results in a reduction of nociceptive transmission from the periphery to the thalamus. Exogenous and endogenous opioids can also exert a direct inhibitory effect upon the substantia gelatinosa (in the dorsal horn) and peripheral nociceptive afferent neurones, reducing nociceptive transmission from the periphery (Figure 2). This series of cellular events and mechanisms produces much of the analgesic effect commonly seen following the administration of MOP agonists.

**Clinical opioids**

All opioids used in clinical practice today work at the MOP receptor, though some have additional activity at one or more of the other opioid receptors. There are presently no agents available for medical use which are specific to just DOP, KOP or NOP receptors (agonists, antagonists or partial agonists).

Both codeine and morphine, two of the naturally occurring alkaloids present in the opium poppy, are MOP agonists commonly used as analgesic agents within the pain clinic. Codeine first needs to be metabolised by the body to morphine for it to display any activity. A percentage of the population lack the ability to perform this conversion and so derive limited pain relief from it. Morphine also has some action at both DOP and KOP receptors. Oxycodone, another commonly used analgesic, is a semi-synthetic derivative of thebaine. It has been used clinically for almost ninety years and mediates its analgesic properties through both MOP and KOP receptors. In contrast, buprenorphine is one of the few opioid partial agonists available for medical administration, working as a partial agonist at both the MOP and NOP receptors (it also has activity at DOP and KOP receptors)<sup>1,10</sup>. In practice this means that it produces analgesic effects at lower plasma concentrations via its interaction with the MOP receptor, but anti-analgesic effects at high doses through interactions with the NOP receptor. It is less sedating and produces less euphoria than a full MOP agonist. These properties make it a useful drug within the pain clinic as the potential for respiratory depression and overdose is reduced compared to MOP agonists.

Naloxone and naltrexone are antagonists at all three classical opioid receptors, attenuating or reversing the effects of agonists at all these sites. They do not however bind to the NOP receptor and therefore would not modulate the effects of any future NOP agonists or partial agonists.

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