Opioid receptors

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Key points

The opioid system comprises four subtypes of receptor: MOP, DOP, KOP and NOP.

Opioid receptors all have selective endogenous peptides.

Analgesia elicited by opioids used clinically act predominately via the MOP receptor.

NOP receptor antagonists have been shown to cause analgesia in animals.

Tolerance to classical opioids may be attenuated by NOP receptor antagonism.

Opium and its derivatives have been used for centuries, both in a medicinal and 'recreational' manner. Indeed, findings of fossilized opium poppy seeds dating as far back as 30 000 yr ago suggest the use of opium by Neanderthal man. In 1799, Friedrich Serturner discovered the major active ingredient of opium, which he named morphine and opioid pharmacology was born. Morphine and its derivates are used today for the treatment of acute and chronic pain. It is now understood that morphine and other opioid drugs act on an endogenous opioidergic system, which is not only involved in setting pain (nociceptive) threshold and controlling nociceptive processing but also participates in modulation of gastrointestinal, endocrine and autonomic function, as well as a possible role in cognition.

Evidence for the existence of multiple opioid receptor subtypes arose from work identifying the different anatomical location and pharmacological profiles of compounds that were eventually used to name them, i.e. *m*orphine (*m*u), *k*etocyclazocine (*k*appa) and vas *d*eferens (*d*elta). Recently, a fourth opioid-like receptor has been included in the opioid receptor family and is termed the nociceptin orphanin FQ peptide receptor. Receptor nomenclature has changed numerous times but current International Union of Pharmacology (IUPHAR) opinion is MOP (mu), KOP (kappa), DOP (delta) and NOP for the nociceptin orphanin FQ peptide receptor. All four are G-protein-coupled receptors sharing the similar seven transmembrane topology (Fig. 1). Other receptor subtypes have been suggested (e.g. sigma receptor) but have been dismissed based on a lack of naloxone sensitivity.

Cellular mechanisms of action

G-protein-coupled receptors, such as those for opioids, have no direct link with effector proteins; instead the message is relayed via a G-protein. Both classical opioid receptors (MOP/KOP/DOP) and the non-classical NOP opioid

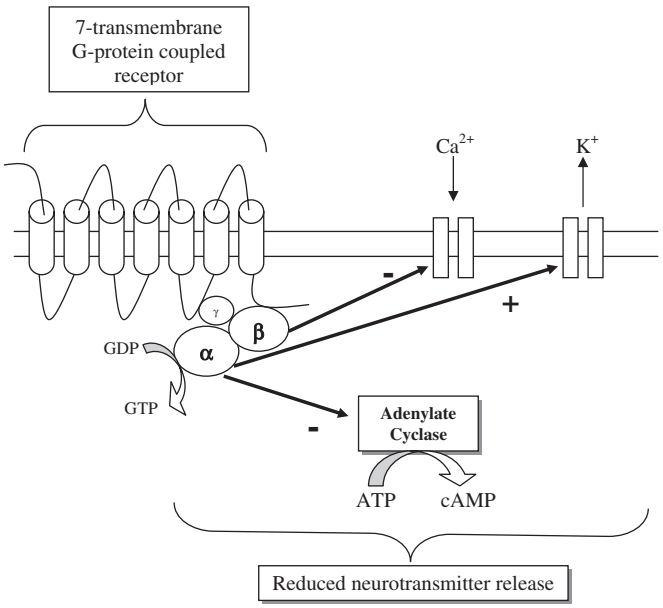

Fig. 1 Seven transmembrane structure of opioid G-protein-coupled receptor. Receptor activation by opioid receptor ligands leads to initiation of intracellular transduction pathways that include stimulation of potassium efflux, inhibition of VSCCs and inhibition of adenylyl cyclase. In this diagram the G-protein is denoted α, β, γ but the α-subunit interacts with K^+/Ca^{2+} channel and adenylate cyclase.

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receptor couple to inhibitory G-proteins. Activation of opioid receptors, for example MOP with morphine leads to: (i) closing of voltage sensitive calcium channels (VSCC); (ii) stimulation of potassium efflux leading to hyperpolarization; and (iii) reduced cyclic adenosine monophosphate (cAMP) production via inhibition of adenylyl cyclase. Overall, this results in reduced neuronal cell excitability leading to a reduction in transmission of nerve impulses along with inhibition of neurotransmitter release (Fig. 1).

Endogenous and exogenous ligands

The endogenous opioid peptides are cleaved from four pro-hormone precursors: (i) pro-enkephalin, (ii) pro-opiomelancortin, (iii) pro-dynorphin, and (iv) pre-pro-N/OFQ (pp-noc). The endogenous DOP receptor peptides are met-enkephalin and leu-enkephalin, cleaved from proenkephalin.[1] Pro-dynorphin gives rise to the KOP receptor agonists dynorphin A and B whilst N/OFQ is from the polypeptide precursor pre-pro-N/OFQ. Pro-opiomelancortin encodes the peptide β-endorphin, which has agonist activity at all three classical opioid receptors. Presently, the precursor protein(s) for the endogenous MOP receptor peptides endomorphin 1 and 2 is unknown.[2]

The prototypical MOP agonist is the alkaloid morphine, extracted and purified from opium. Of the synthetic opioid agonists, whose structures bear no resemblance to morphine, fentanyl and remifentanil are the more potent compounds. Pentazocine and buprenorphine are partial agonists. Owing to the reduced efficacy of partial agonists, they are able to antagonize or reduce the responsiveness of a full agonist such as morphine when acting at the same receptor. This may result in an increase in the dose of full agonist required in order to compete against the partial agonist and restore the full agonists maximal response. Differences in the pharmacokinetics of a partial and full agonist could lead to overdose if the partial agonist were to be metabolized more rapidly than the full agonist.

A number of the opioid ligands lack specificity for a particular subtype of opioid receptor. For example, the endogenous peptide β-endorphin has agonist activity at all three classical opioid receptors. Buprenorphine has partial agonist activity at MOP and NOP receptors and, as a result, has a bell shaped response curve for its analgesic activity *in vivo* (i.e. at low and intermediate doses an analgesic response results), at higher doses the analgesic response may be decreased. The complex pharmacology of buprenorphine is explained by its agonist activity at both MOP, resulting in analgesia at low and intermediate doses, and NOP, resulting in an anti-opioid/anti-analgesic action at higher doses (see later). Some other opioid drugs have mixed actions at different opioid receptors. For example, pentazocine behaves as an antagonist at MOP receptors but a partial agonist at DOP and KOP receptors. Currently, there are no clinically selective drugs available that work via DOP, KOP or NOP receptors (see Table 1 for a list of exogenous and endogenous classical opioid receptor ligands).

Table 1 Endogenous opioid peptides, synthetic and semi-synthetic opioid agonists and antagonists, along with their selectivity for the different subtypes of opioid receptor. N/OFQ = nociceptin orphanin FQ; × = no affinity; ✓ = low affinity; ✓✓ = intermediate affinity; ✓✓✓ = high affinity. (Modified from Rang, Dale and Ritter[3])

Endogenous ligand	Receptor subtype			
	MOP	KOP	DOP	NOP
β-endorphin	✓✓✓	✓✓✓	✓✓✓	×
Endomorphin 1/2	✓✓✓	×	×	×
Leu-enkephalin	✓	×	✓✓✓	×
Met-enkephalin	✓✓	×	✓✓✓	×
Dynorphin A/B	✓✓	✓✓✓	✓	✓
N/OFQ	×	×	×	✓✓✓
Clinical Drugs				
Agonists				
Morphine	✓✓✓	✓	✓	×
Meperidine	✓✓✓	✓	✓	×
Diamorphine	✓✓✓	✓	✓	×
Fentanyl/remifentanil	✓✓✓	✓	×	×
Antagonist				
Naloxone	✓✓✓	✓✓	✓✓	×

Opioid receptor subtypes

MOP

The MOP receptor was the last of the classical opioid receptors to be cloned and is located throughout the central nervous system in areas involved in sensory and motor function including regions concerned with the integration and perception of these senses, for example cerebral cortex, amygdala (of the limbic system). High density of MOP receptors is found in the caudate putamen (of the basal ganglia). MOP receptors are located presynaptically on primary afferent neurons within the dorsal horn of the spinal cord where they inhibit glutamate release and hence transmission of nociceptive stimuli from C and Aδ fibres. The periaqueductal grey (PAG) is an area of the midbrain involved in the central control of nociceptive transmission. Efferent outflow from the PAG descends to the spinal cord where it acts to inhibit nociceptive transmission in afferent fibres, this pathway is known as the descending inhibitory control pathway. High densities of MOP receptor are found in the PAG and the analgesia of some opioids is proposed to come about from removal of an inhibitory γ-amino butyric acid (GABA)-ergic tone in this region of the brain. GABA is the main inhibitory transmitter in the brain and acts to reduce or prevent antinociceptive outflow from the PAG.

Major side-effects associated with MOP agonists include respiratory depression through a reduction in the sensitivity of central and peripheral chemoreceptors to hypercapnia. MOP agonists further inhibit gastrointestinal tract secretions and peristalsis, often causing constipation. MOP opioids also have effects on the cardiovascular system, thermoregulation, hormone secretion and immune function.

Studies using MOP receptor knockout mice have defined the role MOP plays tonically and when stimulated by exogenously applied ligands. MOP receptor knockout mice show increased sensitivity to thermal pain, implicating the receptor in this

mode of nociception. However, no change in threshold from pain elicited via mechanical stimuli was seen. None of the predicted effects or side-effects of morphine were seen in mice lacking the MOP receptor. There is no change in respiratory function demonstrating no tonic role in this system. Morphine did not produce analgesia or respiratory effects. This genetic approach confirms that both the wanted and unwanted effects of morphine are attributable to action at the MOP receptor.[4]

Whilst the main analgesic effects of opioids are elicited by central activation of opioid receptors, a number of the common side-effects, including reduced gastrointestinal motility, urinary retention and pruritus, are regulated by activation of peripherally located opioid receptors. The use of peripherally acting opioid receptor antagonists may reduce a number of these peripherally mediated side-effects, for example methylnaltrexone, a peripherally acting opioid antagonist, was shown in clinical trials to be effective at treating opioid-induced constipation.

DOP

The DOP receptor was the first to be cloned and is less widely distributed relative to the other opioid receptors. Highest densities are found in the olfactory bulb, cerebral cortex, nucleus accumbens and the caudate putamen. DOP receptors are located presynaptically on primary afferents where they inhibit the release of neurotransmitters. Through both spinal and supraspinal sites, the receptor is involved in the antinociceptive/analgesic actions of some opioids. However, DOP receptor agonists have also been shown to reduce gastrointestinal tract motility and cause respiratory depression.[5] Studies with DOP receptor knockout mice revealed that they display hyperlocomotor activity and it is assumed the receptor, under basal conditions, may dampen locomotor behaviour. DOP receptor knockout mice also displayed anxiogenic and depressive-like responses, suggesting that the receptor may act to regulate mood.

KOP

The kappa or KOP receptor was the second of the opioid receptor family to be cloned. The prototypical agonist of the kappa receptor is the non-peptide benzomorphan ketocyclazocine, the actions of which have been shown to be distinct from those elicited by stimulation of the MOP receptor, for example sedation without marked effects on heart rate. Two synthetic KOP receptor agonists, spiradoline (U-62,066E) and enadoline (CI-977) have undergone clinical trials for their analgesic actions.[6,7] Whilst spiradoline produced promising analgesia in animals, clinical data shows that spiradoline produces adverse effects such as diuresis, sedation and dysphoria at doses lower than those needed for analgesic effects. Enadoline produced similar side-effects including sedation, confusion and dizziness along with increased urinary output and feelings of depersonalization. The side-effects elicited by these and other KOP receptor agonists have, to date, limited their effective clinical use. However, it has been shown recently that KOP agonists (e.g. enadoline) may have neuroprotective actions via their ability to inhibit post ischaemic glutamate release.

The advantage of the KOP receptor agonists over other opioid ligands is that they do not cause respiratory depression. It must also be mentioned that KOP agonists also display an anti-opioid action attenuating analgesia elicited by endogenously released or exogenously administered MOP agonists. It has been hypothesized that this action is caused by a distinct distribution of KOP receptors on primary cells located within the nucleus raphe magnus (NRM), a group of cell bodies situated in the midbrain. The output from the NRM forms part of the descending inhibitory control pathway acting to dampen nociceptive transmission at the level of the spinal cord. The NRM consists of primary and secondary cells whose axons terminate in the spinal cord. It is suggested that secondary cell firing facilitates nociceptive transmission, whilst primary cells inhibit it. Analgesia elicited by exogenously applied opioids is mainly via agonist activity at the opioid receptor MOP. It has been shown that MOP receptors are situated only at secondary cells of the NRM. Inhibition of these secondary cells via MOP receptor stimulation results in presynaptic inhibition of GABA-ergic input to primary cells leading to their disinhibition (Fig. 2). This disinhibition, which equates to primary cell stimulation, results in analgesia elicited at the level of the spinal cord. KOP receptors are localised only on the primary cells of the NRM and the anti-analgesic effect of KOP receptor agonists is caused by inhibition of the primary cells thus preventing indirect stimulation mediated through the MOP receptor pathway.

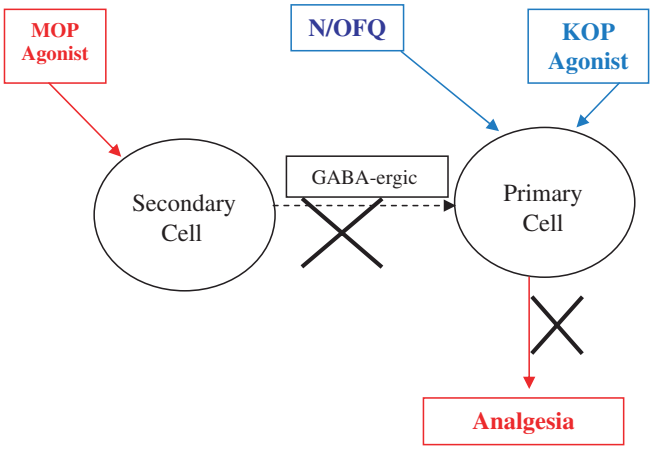

Fig. 2 In the NRM stimulation of primary cells is thought to induce analgesia via activation of descending inhibitory control pathways and release of endogenous opioids. MOP agonists cause analgesia via inhibiting secondary cells, the output from which is inhibitory (GABA) toward primary cells. Removal of this GABA-ergic tone disinhibits primary cells resulting in their activation and thus analgesia. KOP and NOP receptors are situated on primary cells and their anti-opioid action is from a direct inhibition of these cells, preventing MOP receptor mediated disinhibition. (Modified from Pan 2000[8]).

NOP

At the cellular level, N/OFQ produces similar actions to those of the classical opioids resulting in reduced neuronal excitability and inhibition of transmitter release. Initial studies concentrated on the role N/OFQ and NOP in pain. However, exogenous administration has been shown to have effects on locomotion, stress and anxiety, feeding, learning and memory, reward/addiction and urogenital activity.

N/OFQ has been shown under laboratory conditions to have a pronociceptive, anti-analgesic effect when applied supraspinally whilst spinally N/OFQ causes analgesia at high doses; low doses lead to hyperalgesia. N/OFQ anti-analgesic action is the hypothesised cause for the supraspinal pronociception effect, inhibiting either endogenous opioid tone or stress-induced analgesia produced during testing procedures in laboratory animals. N/OFQ anti-opioid effect is caused by NOP receptor localization on, and inhibition of, primary cells of the NRM, analogous to the KOP receptor pathway (Fig. 2).[8] It is believed that endogenous levels of N/OFQ may act to set threshold to pain, as NOP receptor antagonists have been shown to give rise to a long lasting analgesia with similar efficacy to morphine. NOP receptor antagonists may have a possible future as novel analgesics or maybe used as an adjuvant to reduce the amount of classical opioid drug required to produce analgesia. Consequently, this may reduce the side-effects encountered when using classical opioids.

The N/OFQ–NOP system is believed to play a role in the development of tolerance to morphine analgesia. NOP receptor 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. Studies in knockout mice confirmed that morphine tolerance to analgesia, but not acute response to morphine, was markedly attenuated. This action has also been confirmed through the actions of potent selective NOP antagonists, which also attenuate morphine tolerance. These findings suggest the N/OFQ–NOP system contributes to neuronal plasticity involved in the development of tolerance seen with chronic morphine exposure.

NOP receptors are localized on afferent fibres and N/OFQ has been evaluated for its acute urodynamic effects in patients suffering neurogenic detrusor overactivity incontinence. It was shown that N/OFQ elicited a robust acute inhibitory effect on the micturition reflex in this patient group. In summary, animal paradigms suggest that NOP receptor antagonists will be useful for the treatment of pain. Also, NOP receptor blockade may prove useful in reducing tolerance to opioids and/or reducing the dose of opioid ligand required to provide analgesia.

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See multiple choice questions 14–17.