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Update on opioid pharmacology

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Summary

- Opioids bind to G-protein-coupled receptors.
- Opioid analgesia is a result of direct inhibition of peripheral and dorsal horn nociceptive neurons and activation of descending inhibitory pathways.
- Knowledge of the pharmacological differences between opioids is relevant to effective analgesia and patient safety.

INTRODUCTION

Opioid analgesics are the gold standard in systemic analgesia for severe acute pain. There are many different compounds in clinical use around the world. Cost, regulations and clinical setting dictate their availability. There is intra-patient and inter-patient variability in response to opioids. Incomplete cross-tolerance occurs when a patient is switched from one opioid to another, the clinical implication being that equivalent opioid doses need to be reduced when commencing a new opioid to avoid overdose. Knowledge of the pharmacological differences between opioids can be applied to select the appropriate drug for the relevant clinical setting and minimise the impact of side-effects. Over the last 20 years more information regarding the pharmacodynamics and pharmacokinetics in terms of opioid receptor dimers and oligomers, second messenger system effects and genotyping has come to light.

Opioid analgesics exert their pharmacological actions through the μ-opioid receptor, MOP, with some also having κ-opioid receptor, KOP activity.

OPIOID RECEPTORS

Classic opioid receptors

The opioid receptor is a G-protein-coupled (GPCR) with seven transmembrane regions. Opioid receptors are currently classified into:

1. δ-opioid receptors, DOP (named after the tissue it was first isolated from, vas **d**eferens);
2. κ-opioid receptors, KOP (named after the first ligand, **k**etocyclazine);
3. μ-opioid receptors, MOP (named after morphine, proposed 1976, cloned 1993).

The receptors were temporarily renamed in 1996 by the International Union of Pharmacology (IUPHAR) as OP1, OP2 and OP3. Prior to this they were known as DOR, KOR and MOR. Owing to the large body of literature using the Greek nomenclature, IUPHAR has recommended that the original δ, κ and μ nomenclature can be used interchangeably with DOP, KOP and MOP. Their actions are listed in Table 1.

Location

These receptors are located within the central nervous system in midbrain and brainstem areas associated with descending modulatory pathways and in the dorsal horn of the spinal cord. There are also peripheral sites including the vas deferens, knee joint, gastrointestinal tract, heart and immune system.

Opioid analgesia

Activation of midbrain opioid receptors indirectly stimulates descending inhibitory pathways. These descending pathways involve serotonergic and noradrenergic transmission, which results in inhibition of nociceptive traffic in the substantia gelatinosa of the dorsal horn of the spinal cord. In addition, opioids can act directly on nociceptive neurons in the dorsal horn and periphery.

Nociceptin receptor

This receptor, known as NOP, was discovered in 1984. Its endogenous ligand is nociceptin/orphanin FQ. Unlike the classical opioid receptors, it does not bind naloxone, which has led to the suggestion that it should not be classified as part of the opioid receptor family. It does, however, have a very similar structure and intracellular mechanisms.

Although, to date, only three types of opioid receptors have been cloned (DOP, KOP and MOP), at least 13 different opioid receptor subtypes were characterised using pharmacological methods over 10 years ago. Research is ongoing to discover the reason for this discrepancy. Postulated explanations are:

- There are splice variants of the receptor (however, expression is low in the central nervous system and

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Table 1. *Actions mediated by opioid receptors*

Receptor	Action
DOP	Spinal and supraspinal analgesia, reduced gastric motility
KOP	Spinal analgesia, diuresis, dysphoria
MOP	Analgesia, sedation, itch, bradycardia, respiratory depression, inhibition of gastrointestinal transit, opioid tolerance and hyperalgesia, endocrine effects including regulating prolactin, growth hormone, testosterone, and other hormones, and immunological effects
NOP	Spinal analgesia and hyperalgesia and allodynia, supraspinally pronociceptive/antianalgesic due to inhibition of opioid tone

the intracellular C-terminal domain of the receptor is affected rather than the ligand-binding, extracellular N-terminal).

- Functional heterodimeric opioid receptors such as DOP-KOP and DOP-MOP may exist.
- Ligand-directed GPCR signalling may produce differential effects on second messenger systems such as β-arrestin, i.e. biased agonism.

INTRACELLULAR EVENTS

Once a ligand has bound an opioid receptor, the associated intracellular G-protein is activated. The α-subunit exchanges bound GDP for GTP and the βγ-subunit dissociates and is free to interact with intracellular second messenger systems and ion channels. With classical opioid receptor binding there is a decrease in cyclic adenosine monophosphate (cAMP) production as adenylate cylase is inhibited and also potassium conductance is increased with a reduction in calcium conductance through the cell membrane. This causes cell hyperpolarisation and reduced neuronal excitability with reduced neurotransmitter release. This is a tenable mechanism for the clinical effects of opioids but it is surprisingly unproven to date.

Other second messenger systems are coupled to activation of opioid receptors such as mitogen-activated protein (MAP) kinases and the phospholipase C-mediated cascade, leading to the formation of inositol triphosphate and diacyl glycerol.

The concept of ligand-directed GPCR signalling has recently been proposed (Figure 1). GPCR activation can lead to either equal/unbiased signalling or unequal/biased signalling through G-protein and β-arrestin-mediated intracellular signalling pathways. The implication is that analgesia and adverse effects may be differentially transduced by these two pathways. In β-arrestin knockout mice the anti-nociceptive effect of morphine was enhanced and prolonged whereas respiratory depression, constipation and naloxone induced withdrawals were attenuated.

LONG-TERM OPIOID ADMINISTRATION

Prolonged exposure to opioids leads to multiple adaptations in second messenger signalling systems that may be responsible for tolerance, sensitisation and withdrawal symptoms.

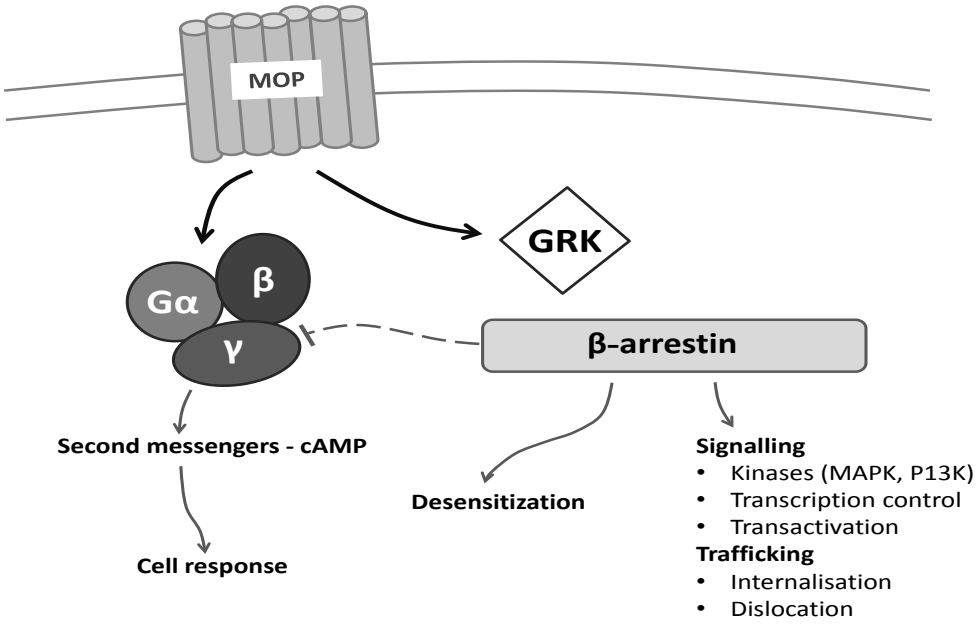

Figure 1. *Opioid receptor and intracellular cascade. MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; GRK, G-protein-coupled receptor kinase*

Intracellular protein kinases are responsible for an acute phosphorylation of the MOP and DOP opioid receptors, which results in tolerance to the effects of an agonist.

Internalisation of receptors is common to all GPCRs and is controlled by mechanisms separate from the agonist receptor interaction. GPCR kinases (GRK) phosphorylate agonist-bound receptors, promoting interactions with β-arrestins, which interfere with G-protein coupling and promote receptor internalisation. Receptor internalisation can have divergent responses – either receptor degradation, causing loss of function, or receptor dephosphorylation and recycling to the cell surface, leading to enhanced signalling.

Superactivation of adenylyl cyclase occurs with a chronic administration of opioid agonists. The alteration in levels of cAMP brings about numerous secondary changes.

Opioid-induced hyperalgesia

Opioid-induced hyperalgesia is a paradoxical response to an opioid agonist resulting not in an analgesic or antinociceptive effect, but an increase in pain perception.

Evidence for the mechanism of opioid-induced hyperalgesia includes:

- upregulation of excitatory neurotransmitters such as substance P and CGRP in primary afferent fibres and the spinal cord;
- increased evoked release of excitatory transmitters in the spinal cord;
- upregulation of spinal dynorphin levels, promoting enhanced input from afferent nociceptors;
- activation of descending pan-facilitation from the rostroventral medulla;
- increased cholecystokinin (CCK) in the brainstem acting via descending pathways;

TRPV1 (transient receptor potential cation channel subfamily V member 1) receptor antagonists have been shown to reverse opioid-induced hyperalgesia;

- *N*-methyl-D-aspartate (NMDA) receptor mechanisms in keeping with central sensitisation;
- glial activation via Toll-like 4 receptors.

DUAL OPIOID THERAPY

Combinations of analgesics often yield pharmacological effects greater than the sum of the individual effects. This phenomenon is termed synergy. Methadone and morphine have been demonstrated to act synergistically in animal models of analgesia. Interestingly, the effects of these drugs on gastrointestinal transit did not show synergy.

GENETICS

Splice variants

A single gene (OPMR1) has been associated with MOP. Genes consist of exons and introns. In the normal situation the introns are spliced out so the combined exons can be transcripted into mRNA and then translated into receptor proteins. Alternative splicing (splice variants) is one way a single gene can produce a vast array of different proteins. Mice lacking exon 1 of MOP are insensitive to morphine ,and those lacking exon 2 are sensitive to morphine but do not have an antinociceptive response to diamorphine (heroin), fentanyl or morphine-6-glucuronide. The relevance of these findings to clinical variability is unclear at present.

Genetics come into play when metabolism of opioids is considered, and codeine is an interesting case. Codeine can be considered a pro-drug and is metabolised via three pathways in the liver. The product of cytochrome P 3A4 (CYP3A4) is norcodeine, whilst codeine-6-glucuronide is produced by UGT 2B7 (over 80% of codeine metabolism). Codeine-6-glucuronide has been postulated to be responsible for the analgesic effect of codeine, but the CYP2A6 pathway is widely accepted as the most important (despite being responsible for less than 5% of codeine metabolism). The product of the CYP2A6 pathway is morphine. There are several phenotypes of CYP2A6; codeine lacks efficacy in poor metabolisers, whereas in ultrarapid metabolisers there is increased formation of morphine, leading to a higher risk of toxicity. This is highlighted by a case report of the death from opioid toxicity of an infant of a breastfeeding mother. The mother was an ultrarapid metaboliser taking 60 mg of codeine a day.[1]

RECEPTOR DIMERISATION

Opioid receptors exist as single entities but can also exist as homodimers such as KOP–KOP or MOP–MOP and heterodimers such as DOP–MOP and DOP–KOP. This dimerisation alters the receptors' pharmacological properties, with affinity for highly selective agonists and antagonists being reduced. Partially selective agonists and endogenous opioids have a greater affinity for these dimeric complexes. These heterodimers may explain the variability in molecular and pharmacological properties of opioid receptors.

SOME SPECIFIC OPIOIDS

Morphine

Morphine is a phenanthrene derivative that is an agonist at MOP and KOP receptors. Along with codeine it is the on the WHO essential medicines list published in March 2011. Codeine may be removed from the WHO list in the next edition subject to review. It has a bioavailability of 15–50% due to an extensive first-pass metabolism.

It is 20–40% protein bound, predominantly to albumin ,and the volume of distribution (V_D) is 3.4–4.7 L kg^{-1}. Degree of analgesia and plasma concentration are not clearly related. Metabolism occurs in the liver to morphine-3-glucuronide and morphine-6-glucuronide and normorphine. Morphine-6-glucuronide has analgesic effects and morphine-3-glucuronide has effects on arousal. Excretion occurs predominantly in the urine as the glucuronide conjugates; 7–10% appears in the faeces as conjugates morphine. The clearance is 12–23 mL min^{-1} kg^{-1} and the elimination half life is 1.7–4.5 hours. The peak analgesic effect occurs 30–60 minutes after parenteral administration due to the low lipid solubility (slowing transit to the nervous system) and the duration of effect is 3–4 hours.

Hydromorphone

Hydromorphone has similar pharmacokinetics and duration of action to morphine but is five times more potent with a slightly faster onset of action. Glucuronidation only occurs at position 3, making it better tolerated in patients with renal impairment because of the lack of an active metabolite.

Fentanyl, remifentanil and alfentanil

These opioids are MOP agonists that are commonly used in the peri-operative period. They display pharmacokinetic differences including increased lipid solubility compared with morphine, resulting in faster onset and offset. Remifentanil has a short, context-insensitive half-life of elimination due to metabolism by non-specific tissue and plasma esterases. Remifentanil has been used to generate an experimental model of hyperalgesia.

Buprenorphine

Buprenorphine is a synthetic derivative of the alkaloid thebaine. It acts as a partial agonist at MOP receptors and dissociates slowly, leading to prolonged analgesia compared with morphine. It has a high affinity for, but low intrinsic activity at, KOP receptors. Owing to significant first-pass metabolism the sublingual route is preferred. The bioavailability is highly variable even by the intramuscular route, at between 40% and 90%. The drug is 96% protein bound *in vitro* and the V_D is 3.2 L kg^{-1}. Metabolism occurs in the liver by dealkylation with subsequent conjugation to glucuronide – the polar conjugates then appear to be excreted in the bile and hydrolysed by bacteria in the gastrointestinal tract. Excretion occurs predominantly via the faeces as unchanged buprenorphine, with the remainder excreted in the urine as conjugated buprenorphine and dealkylated derivatives. The clearance is 1 L min^{-1}. The elimination half-life is 5 hours.

As it is a partial agonist, buprenorphine may antagonise the effect of morphine and may precipitate withdrawal in opioid-dependent patients. This tends to occur only at very high doses.

Methadone

Methadone is a synthetic opioid developed in 1942. It is a lipophilic basic drug (pK_a 9.2) and exists as a racemic mixture of two enantiomers, *R*-methadone and *S*-methadone. *R*-methadone is a potent MOP and DOP agonist. The *S*-methadone enantiomer is inactive as a MOP agonist but acts as an NMDA receptor antagonist. Following oral administration, time to peak plasma concentration is 2.5–3 hours. The oral bioavailability is high at around 85%. The V_D is high in humans at 4.2–9.2 L kg^{-1}. At physiological pH, 86% of methadone is bound to plasma proteins, predominantly α_1-acid glycoprotein. Unlike morphine, methadone is biotransformed in the liver rather than conjugated, and at daily doses of less than 55 mg the majority of the metabolites are cleared in the faeces. Methadone is metabolised by the cytochrome P450 enzymes. The main enzyme responsible for the N-demethylation of methadone is CYP3A4, with lesser involvement from CYP1A2 and CYP2D6. The main product of metabolism, 2-ethylidene-1,5-dimethyl-3,3-diphenylprrolidine (EDDP), is inactive. There are large interindividual variations in methadone pharmacology. Renal excretion is variable and pH dependent ,with excretion increasing as urine pH decreases. The elimination of methadone is biphasic. The α-phase is 8–12 hours and the β-elimination phase is even longer at 30–60 hours. Despite this long elimination period, the duration of analgesia is 8–12 hours, and for pain management the daily dose is often divided into two or three administrations. There is a real risk of accumulation and toxicity with repeated doses.

Tramadol and tapentadol

Tramadol is a partial MOP agonist with an additional serotonin and noradrenaline reuptake inhibition action and tapentadol is a MOP agonist with noradrenaline reuptake inhibition. Tramadol is metabolised to an active metabolite M1, which has greater affinity for MOP than it's parent compound.

CONCLUSION

No single mechanism adequately explains the intraindividual or interindividual variability observed with opioids. Available evidence suggests that a constellation of neurobiological, demographic, medical and patient specific factors all contribute to a determining a patient's response to a particular opioid. Opioids remain a key component in acute pain management and in cancer pain. Opioid use in chronic non-malignant pain is limited by tolerance and hyperalgesia.

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