Differences between and combinations of opioids re-visited

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Purpose of review

Recent studies highlighting between-opioid differences in patient outcomes, opioid receptor interactions and animal study findings implicating a 'fine control' mechanism underpinning potential diversity in opioid receptor signalling that could potentially be exploited to develop novel opioid analgesics with improved tolerability are reviewed.

Recent findings

Recent clinical trials confirm the success of 'opioid rotation' for improving opioid tolerability and restoring analgesia in most patients who would otherwise experience intolerable side effects and poor pain relief. These findings suggest that individual strong opioids may interact, at least in part, with different opioid receptor subpopulations or modulate μ opioid receptor signalling in subtly different ways. Identification of novel μ opioid splice variants with different intron 1 sizes that heterodimerize with, and modulate the function of, native μ opioid receptors provide insight into potential diversity in opioid signalling. Oxycodone, unlike other strong opioids, does not cause potassium current desensitization nor does it displace [^{3}H]-morphine binding, consistent with its different in-vivo pharmacological profile to morphine. Opioid analgesic combinations administered as tethered bivalent ligands or admixture demonstrate good pain relief with improved side effect profiles.

Summary

Enhanced understanding of diversity in opioid signalling has the potential to produce novel strong opioid analgesics with improved tolerability.

Keywords

between-opioid differences, G protein-activated inwardly rectifying potassium current desensitization, morphine, opioid combinations, oxycodone

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Introduction

The fact that so few endogenous opioid peptides viz. endomorphins 1 and 2, β-endorphin, leu-enkephalin and met-enkephalin, dynorphin, with overlapping selectivities at μ opioid (MOP), δ opioid (DOP) and κ opioid (KOP) receptors as well as overlapping distribution patterns in the nervous system can differentially modulate a broad range of physiological functions including analgesia, meiosis, heart rate, thermoregulation, hormonal secretion, feeding, motivation/reward, locomotion, immune and stress responses, gastrointestinal transit and sedation [1] is a conundrum. This conundrum suggests that a poorly understood 'fine control' mechanism may underpin diversity in endogenous opioid signalling. It also raises the possibility that the desired and undesired effects of opioid analgesics may involve subtle 'between-opioid' differences in their interactions with this 'fine control' mechanism.

Between-opioid differences

It has long been appreciated by front-line clinicians that individual patients may respond better to one strong opioid analgesic than another, whether in terms of superior pain relief or improved tolerability or both. These clinical observations of between-opioid differences within individuals led to the practice of 'opioid rotation' whereby patients experiencing poor pain relief and intolerable opioid-related side effects to one strong opioid analgesic are rotated to another as a means of improving opioid tolerability and restoring satisfactory pain relief. As the traditional view is that all clinically available opioid analgesics produce their desired and undesired effects through activation of the MOP receptor, between-opioid differences in outcomes within individuals and between individuals are difficult to explain. Recent studies addressing between-opioid differences in clinical trial and animal study outcomes as well as differences in opioid receptor interactions are briefly reviewed herein.

Opioid rotation: recent prospective clinical trials

Three prospective clinical trials in this difficult to study target population have been published only recently.

Despite the limitations of their open-label designs, these trials [2•,3•,4] collectively show that rotation from one strong opioid to another is an effective means for restoring satisfactory analgesia with tolerable side effects in most patients who would otherwise experience intolerable side effects and poor pain relief, consistent with earlier anecdotal reports.

In the first of these studies [2•], 25 Japanese patients with chronic cancer pain who were experiencing intolerable side effects and inadequate analgesia with oral morphine were rotated to oral oxycodone. This allowed an approximately 1.7-fold increase in morphine equivalent dosage such that 84% (21/25) of patients achieved satisfactory pain relief with tolerable side effects at an average of 2.3 days and maintained up to 260 days [2•]. Four patients withdrew from the study: one for inadequate analgesia, two to adverse events and one withdrew consent [2•]. Patient acceptability was significantly greater ($P < 0.0004$) at the end of the study relative to study entry [2•].

In the second study [3•], 42 patients experiencing inadequate analgesia and intolerable side effects when receiving high dose oral morphine were rotated to transdermal buprenorphine. After a follow-up period of 10 weeks to 1 year, the proportion experiencing good/very good pain relief and good/very good sleep quality increased significantly ($P < 0.05$) from 5 to 76% and from 14 to 74%, respectively, at dosages of 52.5 μg/h for most patients with a few requiring 70 μg/h [3•]. For 10 patients with cancer, buprenorphine dosage increased during the follow-up period likely due to disease progression, whereas for the remaining 32 patients who did not have cancer, dosage remained stable for up to a year [3•]. Constipation was significantly reduced after rotation, with the number of patients requiring a laxative decreasing from 16/42 with high-dose morphine to 1/42 with transdermal buprenorphine [3•]. The relative contribution of the transdermal delivery route vis-à-vis its partial μ agonist/κ antagonist properties to improved constipation requires further investigation. Local irritation occurred in approximately 12% of patients rotated to transdermal buprenorphine but no additional serious adverse effects were reported [3•].

In 50 outpatients with cancer pain who were experiencing inadequate analgesia (60%) or intolerable side effects (gastrointestinal 32%; central 26%), rotation from oral morphine, tramadol or oxycodone, transdermal fentanyl or sublingual buprenorphine to oral sustained-release hydromorphone was successful in 64% of patients [4]. The morphine equivalent doses increased from 109 to 138 mg/day and concomitant analgesics and coanalgesics remained unmodified [4].

Potential factors contributing to clinical success of opioid rotation

The clinical success of opioid rotation likely involves pharmacokinetic and/or pharmacodynamic factors both of which may be subject to pharmacogenomic influence.

Pharmacodynamic factors

In-vitro studies documenting between-opioid differences in pharmacological profiles are briefly reviewed in the following sections.

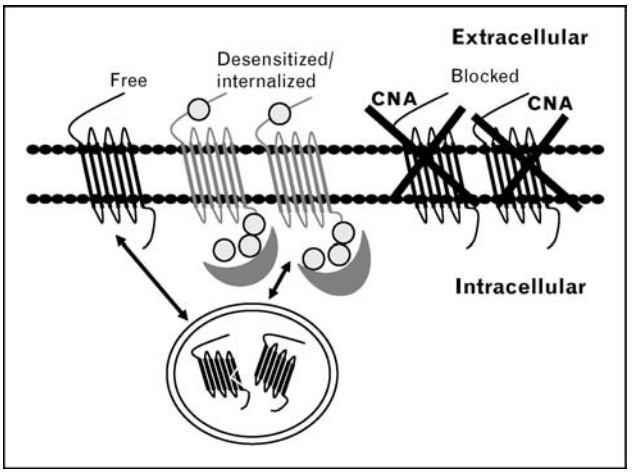
Oxycodone does not desensitize G protein-activated inwardly rectifying potassium currents

A recent study [5••] showed that a saturating concentration of oxycodone does not desensitize G protein activated inwardly rectifying potassium (GIRK) currents in slices of rat brain locus coeruleus tissue briefly exposed to the irreversible opioid antagonist, β-chlornaltrexamine, in contrast to multiple other opioid agonists tested (Fig. 1). This finding highlights that oxycodone is different from other opioid analgesics [5••] and suggests that it may interact, at least in part, with a different population of opioid receptors or modulate MOP receptor signalling in a subtly different way from other opioids.

Oxycodone does not displace [^{3}H]-morphine in rat brain membranes

Consistent with the afore-mentioned findings [5••], recent radioligand binding studies show that oxycodone

Figure 1 Schematic diagram adapted from [5••] showing brief exposure to β-chlornaltrexamine irreversibly alkylates and hence removes a significant number of opioid receptors from the total available



The net result is three pools of opioid receptors viz. those removed by β-chlornaltrexamine, those that are internalized/desensitized by prior opioid agonist exposure and hence protected from irreversible alkylation by β- chlornaltrexamine and those re-cycled to the cell surface after internalization producing recovery from desensitization. Opioid agonist-specific differences were found in the pools of active/free receptors relative to those that were desensitized or internalized [5••].

displaces [^{3}H]-morphine from rat brain membranes with low affinity ($K_i = 357$ nmol/l) in contrast to the high affinity displacement by morphine ($K_i = 1.2$ nmol/l) [6••]. Oxycodone does not significantly displace either [^{3}H]-DPDPE or [^{3}H]-U69593 [6••,7] showing that it is not an agonist at either δ opioid or κ_1 opioid receptors. However, as oxycodone displaced the κ_2 selective ligand, [^{3}H]-bremazocine with relatively high affinity from rat brain membranes irreversibly depleted of μ opioid and δ opioid binding sites, and this displacement was blocked by the κ_{2b} ligand, leu-enkephalin, these findings suggest that oxycodone is a κ_{2b} opioid agonist [6••].

Between-opioid comparisons: human and animal studies

Multiple recent investigations outlined in the following sections collectively show that morphine, oxycodone and/or M6G have distinctly different in-vivo profiles under various experimental conditions [6••,8•,9••,10•].

Between-opioid differences in antinociceptive profiles of morphine and oxycodone in patients with chronic pancreatitis

It is widely accepted that oral oxycodone has an analgesic potency, approximately 1.5 times that of morphine in humans. In a recent randomized, double-blinded controlled trial [9••] in 10 patients with chronic pancreatitis, application of acute noxious mechanical, thermal and electrical pain stimuli to the skin, muscles and oesophagus resulted in marked differences in the antinociceptive profiles of oxycodone and morphine. Single 15-mg oral doses of oxycodone increased the pain threshold to mechanical stimulation applied to the skin and muscles of these patients, whereas 2-fold larger doses of morphine (30 mg) were no more effective than placebo [9••]. Oxycodone produced significant relief of thermal pain in the oesophagus, whereas morphine did not [9••]. Although both opioids produced significant relief of mechanically induced pain in the oesophagus, oxycodone was more potent [9••]. Significant between-opioid differences in the antinociceptive profiles of oxycodone and morphine in patients with chronic on-going visceral pain support the notion that these two opioids produce their analgesic and/or other effects by distinctly different mechanisms.

Between-opioid differences in clinical outcomes: combining opioid analgesics

Additional evidence that morphine and oxycodone likely produce their pharmacological effects by different opioid receptor populations comes from the success of a recent prospective, randomized, double-blind parallel group clinical trial [11••] in 40 patients that underwent elective lumbar discectomy. Briefly, perioperative administration of controlled-release oxycodone (20 mg) or placebo for six doses at 12-hourly intervals commencing the night before surgery [11••] reduced postoperative i.v. patient-controlled analgesia (PCA) consumption of morphine equivalents for 48 h postsurgery and produced superior pain relief at rest, on coughing and on mobilization relative to patients administered oral placebo and IV PCA morphine [11••]. Patients administered oral oxycodone and IV PCA morphine also had less postoperative nausea and vomiting and a shorter time to first bowel motion [11••].

Together, the afore-mentioned recent in-vitro and clinical data support the notion that oxycodone and morphine activate different opioid receptor populations to produce pain relief. This view is supported by several recent studies in rodent models of neuropathic pain [6••,8•,10•] that are reviewed in the next section.

Between-opioid comparisons in rodent neuropathic pain models

Comparison of the antinociceptive effects of subcutaneous bolus doses of morphine, oxycodone and M6G in mice with a partial chronic constriction injury (CCI) of the sciatic nerve showed that although oxycodone was equipotent in CCI-operated and sham-operated mice, morphine and M6G were considerably less potent in CCI-operated relative to sham-operated mice [10•]. After central routes of administration, the pattern of between-opioid differences changed with the antinociceptive potency of M6G, but not morphine or oxycodone, being significantly lower in CCI-operated compared with sham-operated mice [10•].

In long-term studies undertaken in the streptozotocin diabetic rat model of painful diabetic neuropathy, morphine hyposensitivity developed in a temporal manner with the antiallodynic efficacy of morphine abolished by approximately 3 months after diabetes induction and it remaining abolished for at least 6 months [6••]. In contrast, the antiallodynic efficacy of single subcutaneously bolus doses of oxycodone was maintained for at least 6 months though with a 3–4-fold decrease in potency [6••].

Following intrathecal administration of bolus doses of oxycodone and morphine to CCI rats, antiallodynia and antinociception were produced in the ipsilateral (injured side) and contralateral (noninjured) hindpaws, respectively [6••]. Intrathecal pretreatment with the selective κ opioid antagonist, norbinaltorphimine, at 24 h prior to opioid testing abolished oxycodone, but not morphine, antinociception [6••], suggesting that oxycodone's effects are mediated by a population of κ opioid receptors in agreement with earlier work [12]. In short-term studies [8•] in streptozotocin diabetic mice, norbinaltorphimine pretreatment abolished oxycodone antinociception, whereas in nondiabetic mice norbinaltorphimine

produced only partial attenuation. In the same study [8•], pretreatment of diabetic and nondiabetic mice with the selective μ opioid antagonist, naloxonazine, reportedly produced almost complete attenuation of antinociception.

Although the afore-mentioned rodent data show between-opioid and between-model differences in the pharmacological profiles of morphine and oxycodone in various neuropathic pain models, there are some discrepancies and a recent study [13••] sounds a note of caution with regard to interpretation of in-vivo animal data generated using 'selective' opioid antagonists as 'selectivity' appears to be both dose and route-dependent.

Opioid receptor antagonist selectivity: dose and route-dependent selectivity differences

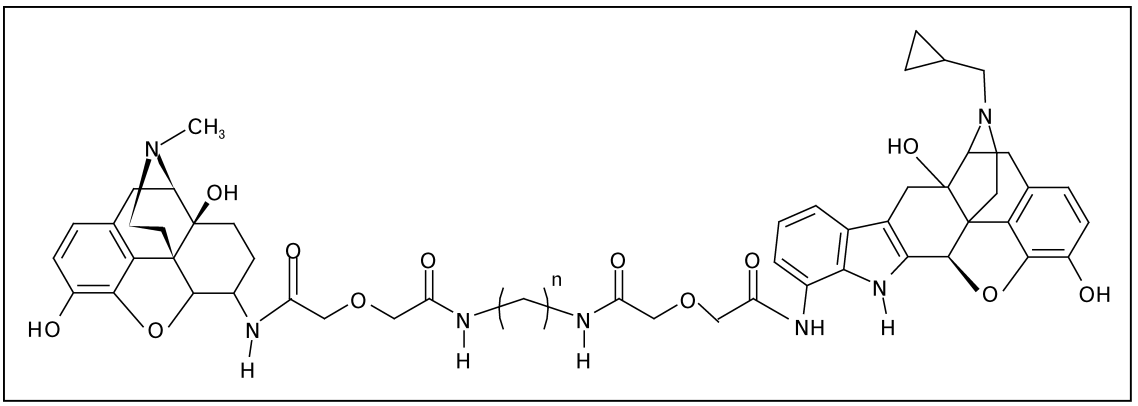
Apart from the requirement for norbinaltorphimine to be administered at least 6 h prior to agonist administration for κ opioid receptor selectivity to be evident, Lunzer and Portoghese [13••] recently showed significant route-dependent and dose-dependent selectivity differences for 'selective' KOP and DOP receptor antagonists. The most dramatic examples are the antagonism of DPDPE (δ_1 selective agonist) and bremazocine (κ_2 agonist) by norbinaltorphimine where the intracerebroventricular/intrathecal potency ratios were 12 and 40, respectively [13••]. On the basis of the proposed allosteric interactions between δ opioid and κ opioid receptor heterodimers in the central nervous system, these findings suggest that between-study differences in route-dependent and dose-dependent effects of norbinaltorphimine may reflect tissue-specific differences in densities of κ opioid, δ opioid and putative δ–κ opioid receptor complexes [13••].

Opioid receptor complexes: potential for diversity in opioid signalling

MOP, DOP and KOP opioid receptors were cloned in the early 1990s, whereas earlier work using pharmacological methods had characterized at least 13 opioid receptor subtypes (μ_1, μ_2, μ_3, δ_1, δ_2, μ–δ complex, κ_{1a}, κ_{1b}, κ_{2a1}, κ_{2a2}, κ_{2b1}, κ_{2b2}, κ_3) [14,15]. In the last decade, multiple splice variants of the human, rat and mouse MOP receptor have been identified suggesting that splice variants may explain diversity in MOP signalling [15]. However, this proposal is controversial as MOP splice variants are generally low in abundance [16] and they differ primarily in their intracellular C-terminal domain rather than their extracellular N-terminal domain, such that the radioligand binding profiles of multiple μ opioid ligands at MOP splice variants are quite similar [15].

In support of the view that pharmacologically defined opioid receptor subtypes may represent opioid receptor complexes that have unique signalling properties, DOP–KOP [17] and DOP–MOP [18] opioid receptor heterodimers whose in-vitro radioligand binding and functional properties differ from those of the parent receptors were characterized almost a decade ago. More recently, two novel human MOR splice variants (SV1 and SV2) that contain exon 1 and a different size of intron 1 were shown to heterodimerize with the wild-type MOR and the heterodimers modulated ligand binding at the wild-type MOR [16]. If MOP, DOP and KOP splice variants hetero-oligomerize in a combinatorial fashion, enormous diversity in opioid receptor signalling becomes possible. However, this notion is highly speculative and in-vivo supporting evidence is sparse.

Figure 2 Bivalent opioid ligands targeted to the putative MOP–DOP opioid receptor heterodimer, comprising oxymorphone tethered to naltrindole by a spacer comprising 19–21 atoms



These bivalent opioid ligands produce potent antinociception with less physical dependence and a marked reduction in potential abuse liability relative to morphine [20••].

Bivalent opioid ligands targeting opioid receptor complexes: recent in-vivo findings

On the basis that antinociceptive tolerance to morphine does not develop in DOP knockout mice [19], multiple research groups have designed bivalent opioid ligands comprising a μ opioid receptor agonist tethered to a δ opioid receptor antagonist by a variable length spacer as a means of producing novel strong opioid analgesics with potentially fewer undesired effects. In 2007, Lenard *et al.* [20••] reported on the potential abuse liability of a series of bivalent opioid ligands (Fig. 2) comprising oxymorphone (μ selective opioid agonist) tethered to naltrindole (δ selective opioid antagonist) by spacers of 16, 19 or 21 atoms [20••]. Using a conditioned place preference-testing paradigm in mice, bivalent opioid ligands with spacers of 19 and 21 atoms had lower abuse liability than morphine [20••]. As these compounds reportedly target MOP–DOP heterodimeric opioid receptors selectively and they produce markedly less antinociceptive tolerance and physical dependence in mice [20••], bivalent opioid ligands appear promising for future development as novel strong analgesics with fewer undesired effects.

Conclusion

Between-opioid differences in opioid receptor interactions as well as human and animal study outcomes suggest the existence of a fine control mechanism underpinning diversity in opioid receptor signalling. In support of this view, recent studies show that bivalent opioid ligands targeted to the MOP–DOP opioid receptor complex produce potent antinociception with reduced potential abuse liability and less physical dependence. By extrapolation, diversity in opioid receptor signalling may be underpinned by a family of opioid receptor complexes, exploitation of which has the potential to produce a future generation of strong opioid analgesics with reduced adverse effects.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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