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Review Article

Hot topics in opioid pharmacology: mixed and biased opioids

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Summary

Analgesic design and evaluation have been driven by the desire to create high-affinity high-selectivity mu (μ)-opioid peptide (MOP) receptor agonists. Such ligands are the mainstay of current clinical practice, and include morphine and fentanyl. Advances in this sphere have come from designing pharmacokinetic advantage, as in rapid metabolism for remifentanil. These produce analgesia, but also the adverse-effect profile that currently defines this drug class: ventilatory depression, tolerance, and abuse liability. The MOP receptor is part of a family, and there are significant functional interactions between other members of the family (delta [δ]-opioid peptide [DOP], kappa [κ]-opioid peptide [KOP], and nociceptin/orphanin FQ receptor [NOP]). Experimentally, MOP agonism and DOP antagonism produce anti-nociception (animals) with no tolerance, and low doses of MOP and NOP ligands synergise to antinociceptive advantage. In this latter context, the lack of effect of NOP agonists on ventilation is an additional advantage. Recent development has been to move towards low-selectivity multifunctional 'mixed ligands', such as cebranopadol, or ligand mixtures, such as Targinact®. Moreover, the observation that β-arrestin coupling underlies the side-effect profile for MOP ligands (from knockout animal studies) led to the discovery of biased (to G-protein and away from β-arrestin intracellular signalling) MOP ligands, such as oliceridine. There is sufficient excitement in the opioid field to suggest that opioid analgesics without significant side-effects may be on the horizon, and the 'opioid Holy Grail' might be in reach.

Keywords: analgesia; biased agonists; novel analgesics; opioid receptors; opioids

G-protein-coupled receptors (GPCRs) represent a target for more than one-third of the US Food and Drug Administration (FDA)-approved blockbuster drugs, such as analgesics, antihistamines, neuroleptics, and many cardiovascular drugs. One important GPCR class is the opioid receptor family. Opioid receptors are classified as mu (μ)-opioid peptide (MOP), delta (δ)-opioid peptide (DOP), and kappa (κ)-opioid peptide (KOP), which are the classical naloxone-sensitive members of the family.[1] In addition, there is a non-classical member of the family: the nociceptin/orphanin FQ (N/OFQ) receptor (NOP). This latter receptor is not sensitive to naloxone.[2] Opioid receptors couple to G_i/G_o G-proteins to enhance the efflux of K^+ (producing hyperpolarisation in neurones), closing voltage-gated Ca^{2+} channels (to reduce transmitter release in neurones) and inhibiting adenylyl cyclase to reduce cyclic adenosine monophosphate formation (affecting membrane repolarisation). Signalling is switched off using the β-arrestin pathway (Fig. 1). Via these coordinated cellular events,[1–4] all members of the family are capable of producing analgesia (anti-nociception in non-

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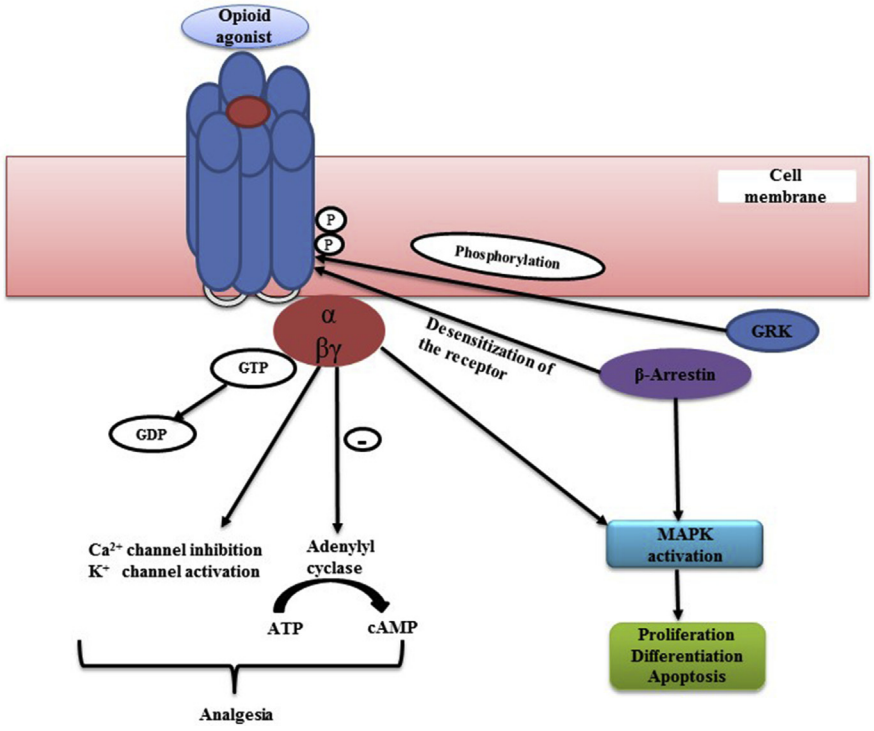

Fig. 1. Intracellular pathways that follow agonist binding to opioid receptors. Following agonist binding to an opioid receptor conformation changes in the receptor take place and the activation (via GDP – GTP exchange at the G-protein) of different signalling pathways. Predominantly left side of the figure: G-protein signalling pathways, by which opioid receptors cause the dissociation of G-protein into α and β/γ subunits leading to the inactivation of calcium channels, activation of potassium channels (reducing the excitability of the cell membrane), inhibition of adenylate cyclase and stimulation of mitogen associated protein kinases (MAPKs) cascades. Bias towards G-protein signalling has been linked to anti-nociceptive profile. Predominantly right side of the figure: β-arrestin signalling pathways, G-protein receptor kinases phosphorylate active G-protein coupled receptors enabling the recruitment of β-arrestins leading to the internalisation/desensitisation of opioid receptors and the activation of mitogen associated protein kinases (MAPKs) cascades. Bias towards β-arrestin has been linked to side effect profile.

humans) to varying degrees with differences in sites of action.[3,4] (Table 1). In addition, opioid receptors couple to mitogen-activated protein kinases, including extracellular signal-regulated protein kinases 1 and 2, p38, and Jun N-terminal kinase, via G-protein and independent β-arrestin pathways (Fig. 1).

Despite all members of the family being capable of producing analgesia, the mainstay in the clinic is usually agonists

Table 1 Opioid receptor classification and basic characteristics. cAMP, cyclic adenosine monophosphate; DOP, delta (δ)-opioid peptide; E1/2, endomorphin 1 and 2; KOP, kappa (κ)-opioid peptide; MAPK, mitogen-activated protein kinase; MOP, mu (μ)-opioid peptide; NOP, nociceptin/orphanin FQ.

	MOP	DOP	KOP	NOP
Other terminology	Mu: μ	Delta: δ	Kappa: κ	ORL-1
Evidence for subtypes	No	No	No	No
G-protein coupling	Yes: G_i	Yes: G_i	Yes: G_i	Yes: G_i
Crystal structure	Yes	Yes	Yes	Yes
Signalling (all)	K^+ channel activation, Ca^{2+} channelinhibition, MAPK activation, and inhibition of cAMP formation			
Arrestin recruitment	Yes	Yes	Yes	Yes
Natural	ligand E1/2[†]	Enkephalin	Dynorphin	N/OFQ
Analgesia	Yes	Yes	Yes	Yes
Clinical ligand	Morphine	None	None[‡]	None[¶]
Naloxone sensitivity[§]	Yes	Yes	Yes	No

[†] No precursor has yet been identified.
[‡] Buprenorphine as activity at KOP.
[¶] Cebranopadol is close to the clinic.
[§] MOP/DOP/KOP are defined as classical opioid receptors because of naloxone sensitivity.

for the MOP receptor with some emerging examples discussed next. These include drugs, such as morphine, fentanyl, and oxycodone. Attendant with the desired analgesic response, opioids have a poor side-effect profile: ventilatory depression, nausea and vomiting, constipation, tolerance, and dependence to name the most important. Tolerance sets up a vicious cycle of dose escalation (especially in palliative care), and dependence is a worldwide problem linked to premature death and criminality.

Opioid receptors are members of a family, and like all families, there are important interactions that have the potential for clinical exploitation. Opioid receptors interact with each other in both a physical sense (dimers) and at a systems level.[5] As such, the search for analgesics with a reduced side-effect profile has shifted away from selective MOP agonists to poorly selective 'dirty' opioids acting at multiple sites. In this review, we address the question: should analgesic research be focused on high-affinity MOP selective agonists, or on the design and characterisation of non-selective mixed molecules? We build on previous reviews from Dietis and colleagues[5] and Calo and Lambert[6] to cover selected preclinical development, and clinical use of molecule mixtures and mixed opioid/non-opioid ligands, and explore the potential for biased agonism to drive analgesia with reduced side-effects. In addition, we present cautionary tales that arise when animal (usually rodents) studies are used to predict human efficacy.

As a background, a reminder of basic pharmacological profile descriptors is provided in Figure 2. In its simplest form, a ligand can interact with a receptor to produce an effect (agonist) or block an effect (antagonist). An agonist that produces the maximum possible effect (loosely defined as efficacy) in a particular tissue is a full agonist; anything with lower efficacy is a partial agonist. Antagonists have no efficacy in this context, and some molecules reduce basal activity (or tone), known as *inverse agonists* (effect inverse of a classical agonist). *Potency* is the concentration or dose range over which a ligand produces its effect (the x-axis in Fig. 2).

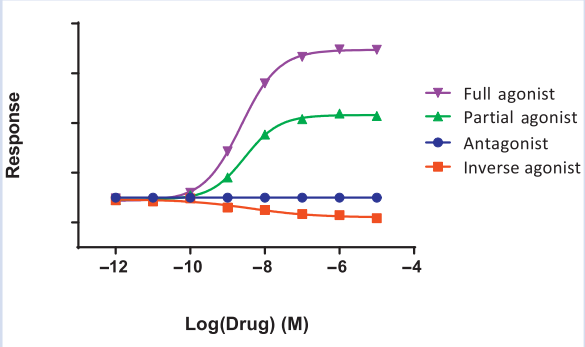

Fig. 2. Graphical representation of typical pharmacological 'behaviours'. A full agonist produces the maximal possible response (loosely describing efficacy) on the y-axis in arbitrary units. The green curve shows an agonist with lower maximum (efficacy), and this is a partial agonist. A neutral antagonist produces no response alone (but reverses the effects of an agonist). An inverse agonist reduces basal activity (often referred to as tone) and models an inverse sigmoid. Drug potency is depicted on the x-axis (Log[Drug]), and a typical measure would be the concentration or dose to produce 50% of the maximal response (EC_{50} or ED_{50}).

Mixed molecules and molecule mixtures

Morphine and oxycodone: MoxDuo

MoxDuo or Q8003 is a mixture of morphine and oxycodone (3:2), the rationale for which is the presumption from animal studies of co-administration opioid synergy and its potential to reduce the doses of the component drugs. Of note, both morphine and oxycodone are MOP agonists, but some interaction with κ_2 (for which there is little if any structural evidence[1]) is considered a bonus. In addition to analgesic synergy, a reduction in side-effect profile is also predicted. The majority of clinical studies were performed in bunionectomy patients.[7–9] In a Phase III double-blind randomised trial, Q8003 (morphine 12 mg:oxycodone 8 mg) was compared with the individual components. Of 522 patients randomised and 491 completed, 19 discontinued because of adverse events, but this was comparable across the groups. There was a statistically significant improvement in efficacy for Q8003 compared with morphine or oxycodone alone (assessed as sum of pain intensity differences), but there was no evidence for synergy. Moreover, there was no reduction in adverse events. As noted by Wolfe[10] in 2014 that contextualised a failed FDA application, the product failed to show synergy or safety advantage.

Targinact

Targinact is a mixture of oxycodone and naloxone that is administered orally. The mixture takes advantage of the extensive metabolism of naloxone. Naloxone undergoes first-pass metabolism via the oral route, such that it does not enter the CNS (in appreciable amounts). The actions of naloxone are therefore peripherally restricted by metabolism and act to prevent the actions of co-administered oxycodone on the gastrointestinal (GI) tract. Oxycodone enters the CNS to produce analgesia typical of a MOP agonist. The overall effects of Targinact would be predicted to be analgesia (central effect) without constipation (peripheral GI effect).[11] There are three index studies of note in moderate to severe chronic non-malignant and malignant pain where there was a significant improvement in bowel index (a measure of bowel function) compared with oxycodone.[12–14] Targinact appears to be a useful option in moderate to severe chronic pain that *can* be managed by opioids.

Tramadol and tapentadol

Tramadol and tapentadol are centrally acting analgesics and represent examples of bifunctional ligands; they are effectively non-selective. Both drugs have a dual mechanism of action: inhibition of catecholamine reuptake and MOP receptor agonism. Tramadol and tapentadol differ from the majority of examples in this review in that they target opioid and non-opioid sites. Both are MOP agonists, and both potentiate descending inhibitory control. Pain is processed via an afferent input into the spinal cord, spinal gating, ascension to the brain, and a descending inhibition circuit.[15] Analgesia is produced by reducing afferent inflow, spinal gating, and ascension to and processing in the brain. In addition, potentiating descending inhibition is analgesic. This latter pathway involves catecholamines, so blocking their uptake is analgesic, which is the presumed mechanism of analgesia produced by

antidepressants.[16] In the case of tramadol and tapentadol, analgesia is produced by a bifunctional (non-selective) action at MOP receptors and catecholamine reuptake, but there are important differences.[17–21] Tramadol is a chiral molecule, with the drug preparation being a racemic mixture with only one enantiomer being active. Tramadol has a low affinity at MOP receptors with the M1 metabolite of the drug having improved affinity (micromolar to nanomolar affinity); unfortunately, some patients are unable to metabolise tramadol. Tramadol inhibits the uptake of both norepinephrine and serotonin, and therefore, there is a possibility of central serotonin syndrome.[22,23]

Tapentadol is prepared as a single enantiomer that has higher affinity for MOP receptors and does not require metabolism. Moreover, there is a degree of selectivity for norepinephrine uptake. Both tramadol and tapentadol are effective in nociceptive, inflammatory, and neuropathic pain, although the efficacy of tramadol in neuropathic pain has been questioned.[24] Tapentadol immediate release improved pain intensity similar to oxycodone and was therefore classified as 'non-inferior' to oxycodone.[25] Responder rates were better with tapentadol compared with oxycodone, and there was a side-effect profile typical of MOP agonist. However, there was reduced nausea and vomiting compared with oxycodone.[25]

Mixed MOP/DOP agonists

A particular experimental example worthy of further mention is the interacation between MOP and DOP. A significant demonstration to reveal how a mixed opioid approach could be beneficial in terms of analgesia with a reduced tolerance profile was a study by Zhu and colleagues using DOP knockout (KO) mice, a genetic approach in which the gene encoding for the DOP receptor is removed. In wildtype mice, naturally expressing DOP, analgesic responses to morphine were lost following 5 days fixed drug administration, however, in DOP KO animals the same daily administration of morphine for 8 days failed to reveal tolerance. The study underlies the importance of DOP receptor expression in the development of morphine tolerance[26]. Pharmacological approaches, using MOP agonists and DOP antagonists also produce anti-nociception in animal models with a reducion in the development of tolerance. When mice are implanted with a morphine pellet, tolerance develops such that more morphine is required to produce the same degree of antinociception, this can be reversed by adminitration of the selective DOP antagonist, naltrindole[27]. Moreover, in a similar protocol but replacing DOP antagonism with antisense DOP knockdown Kest and colleagues[28] demonstrated that, where there is less DOP (a form of genetic DOP 'antagonism'), tolerance to morphine was again reduced. In a more elegant experiment Nitsche and colleagues[29] used DOP and ppENK (pre-pro-Enkephalin) knockout animals; ppENK is the precursor for the natural peptide ligand for DOP. In wild type animals tolerance to morphine rapidly developed; this was absent in animals that lacked either ppENK (the ability to activate DOP) or the DOP receptor itself.

A series of compounds that act as MOP agonists and DOP antagonists was used to elucidate the pharmacological characteristics required for the optimal production of anti-nociception without the development of tolerance and dependence.[30] A simple combination of MOP agonist activity with DOP antagonist activity was not sufficient to prevent the development of tolerance. High binding affinity at DOP receptors was deemed to protect against tolerance; however, compound efficacy *in vitro* or *in vivo* did not relate to a lack of tolerance development.[30]

Collectively, these data underscore a powerful receptor interaction with important functional consequences. Sadly, there are no mixed MOP agonist:DOP antagonist drugs or drug combinations currently in the clinic.

Buprenorphine

Buprenorphine, a semi-synthetic multifunctional opioid that can be derived from the naturally occurring alkaloid of the opium poppy, thebaine, is a mixed opioid already in clinical use. Buprenorphine is approved in the treatment of opioid dependency and as an analgesic, and has a mixed opioid pharmacology consisting of partial agonist activity at MOP and NOP receptors with low partial agonist activity at KOP and DOP receptors, as reported by some groups,[31,32] whilst others report DOP antagonism and KOP inverse agonism.[33]

Much of the early detailed pharmacological data characterising buprenorphine came from studies in rodents, defining what has now become a trademark characteristic of the drug, a bell-shaped dose–response curve.[34–36] This was observed with specific antinociceptive paradigms: in the mouse tail-flick pain model, the intensity of nociceptive stimuli determined whether or not a bell-shaped curve to the drug was evident. When low stimulus intensity was used, a ceiling effect for the antinociceptive action of buprenorphine is observed; however, when a higher-intensity stimulus is used, a bell-shaped curve is apparent, with greater anti-nociception observed at 1 mg kg^{-1} compared with 0.3 mg kg^{-1}, and lower anti-nociception at 3 mg kg^{-1} compared with buprenorphine 1 mg kg^{-1}.[34,35] In rodent models of acute and chronic pain, the drug had full analgesic efficacy for acute thermal and visceral pain, and for chronic inflammatory and neuropathic pain. Interestingly, for pain models using a chemical stimulus, a bell shape is not seen, highlighting the nature of the painful stimulus, rather than intensity, as influential in the shape of the dose–response curve.[36]

The ceiling effect to buprenorphine antinociceptive action is easily explained by its partial agonist activity. However, the bell-shaped response curve is more complex and proposed to be the result of mixed opioid activity, resulting in the activation of the NOP receptor, which leads to the suppression of MOP-mediated anti-nociception via the anti-opioid action of NOP receptor activation (see below), certainly in acute models of pain (Fig. 3). If this proposal is correct, NOP receptor antagonists should potentiate the anti-nociception of buprenorphine. This was shown in the mouse tail-flick assay using the NOP selective antagonist, J-113397.[35,37] The antagonism of the NOP receptor, or its absence in KO mice, leads to buprenorphine having a steeper dose–response curve and a full agonist profile.

It is important to recognise in analgesic development that rodents display noticeable behavioural and pharmacological differences to non-human primates, with the latter being more 'human' in their pain physiology and pharmacology. In primates, systemic buprenorphine dose dependently produces anti-nociception, ventilatory depression, and itch/scratching up to 0.1 mg kg^{-1}.[32] At a dose of 1 mg kg^{-1}, buprenorphine retains its antinociceptive action without increased ventilatory depression; it is this ceiling action regarding ventilatory depression that gives the drug such a favourable

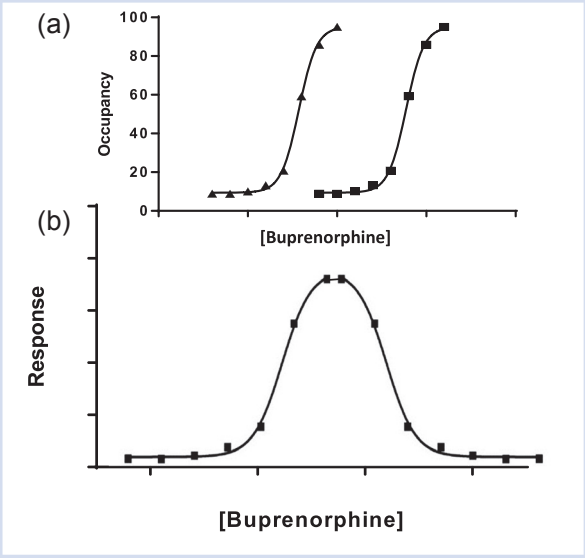

Fig. 3. Buprenorphine pharmacology. Graphical representation of the relationship between (a) buprenorphine mixed opioid receptor occupancy at mu (μ)-opioid peptide (MOP) (upper triangle) and nociceptin/orphanin FQ (NOP) (upper square) receptors, and (b) the bell-shaped analgesic response curve in rodents. Occupancy of MOP receptors at low concentrations of buprenorphine results in analgesia. As the concentration of buprenorphine is increased, occupancy at NOP receptors and via the anti-opioid action results in the falling analgesic response.

therapeutic window.[32] This suggests that much of the complex pharmacological dose–response curve data for buprenorphine are a rodent phenomenon.

In non-human primates, MOP and NOP antagonists have differing actions on buprenorphine-induced responses. Pretreatment with a MOP antagonist leads to a large rightward shift in the buprenorphine dose–response curve for a range of physiological responses, including anti-nociception, ventilatory depression, and itch/scratching. The degree of shift is similar to that seen with the antagonism of selective MOP agonists, suggesting that buprenorphine-induced anti-nociception, ventilatory depression, and itch/scratching in primates are from agonist activity at MOP receptors alone.[32] This is not unexpected given that the affinity of buprenorphine for NOP is significantly lower than at the classical opioid receptors: 77 nM at human NOP receptors compared with 1.5 nM at MOP receptors.[37]

Accounting for any possible NOP receptor element in buprenorphine action, the NOP antagonist, J-113397, at a dose capable of antagonising the actions of the NOP-selective agonist, Ro 64-6198, in primates, produced no shift in the dose–response curves of buprenorphine. Therefore, fundamentally different to rodent models, NOP receptors are not involved in the physiological responses to buprenorphine in primates.[32] A number of NOP agonists co-administered with buprenorphine lead to a synergistic antinociceptive response in primates. Unlike in rodents, NOP activation does not have an anti-opioid effect diminishing MOP-induced anti-nociception, but supports a potentiated antinociceptive action from the synergistic actions of combined NOP and MOP agonists.

Activation of the NOP receptor not only modulates the analgesic activity of opioids, but also the rewarding properties of a number of drugs of abuse.[38–40] In relation to the mixed opioid receptor activity of buprenorphine, when administered to Sardinian alcohol preferring rats at low doses, there was increased alcohol consumption, whilst at higher doses, alcohol consumption was attenuated.[41] In the presence of the NOP antagonist, UFP-101, the high dose buprenorphine reduction in alcohol consumption was absent. In these animal paradigms of reward, buprenorphine is seen to act through the MOP receptor at low doses, but at higher doses, there is activation of the NOP receptor with its anti-opioid effects leading to attenuated alcohol consumption.[41] Combining NOP activation with MOP activation (see below) may provide an effective way to attenuate opioid reward pathways, and may account for the reduced abuse liability of buprenorphine in humans.

Whilst buprenorphine acts with full analgesic efficacy, pharmacologically, it is a partial agonist at the MOP receptor, which could hold implications in chronic models of pain where opioid receptor expression is likely to change. Appreciation of drug intrinsic activity (efficacy) is important; opioid receptor densities vary from region to region, or in disease states, which could see a partial agonist acting as a full agonist for one response, say analgesia, but having a partial agonist activity for another, such as ventilatory depression. In rodent models of chronic pain, both inflammatory and neuropathic, where opioid receptor densities are likely to be unstable, buprenorphine proved a potent analgesic.[36] In the clinical setting, buprenorphine provides analgesia paralleling that seen with full MOP agonists, and without a ceiling effect, suggesting either a high partial intrinsic efficacy for buprenorphine or a large MOP receptor density in those neuronal populations/regions leading to analgesia. However, the ceiling effect for ventilatory depression induced by buprenorphine is suggestive that the latter is true and buprenorphine is a clear partial agonist.

Mixed MOP/NOP ligands

There is growing interest in mixed MOP/NOP ligands based on a number of animal studies.[42] Low doses of N/OFQ and morphine that are ineffective as analgesics (and hence, have no side-effects) alone produce marked synergism.[43] In this context, it is also worth noting that NOP receptor activation is not associated with ventilatory depression.[2] There are published data on several mixed MOP/NOP ligands, including cebranopadol,[44] BU08028,[45] SR16435,[46] and AT-121[47] ; cebranopadol and AT-121 are described in more detail. Cebranopadol is a mixed opioid–NOP agonist for which there is a substantial basic profile and ongoing clinical evaluation. Basic profile is of a relatively high-affinity MOP and NOP agonist with partial agonism at the NOP receptor. Recent data suggest that cebranopadol is a MOP and particularly NOP G-protein biased agonist[48] (see below). Activation produces anti-nociception (in rodents) with higher potency in models of neuropathic pain, a massive advantage over current opioids. There are limited ventilatory effects, and tolerance develops very slowly: days with morphine and weeks with cebranopadol.[44] There are nine studies on cebranopadol that have been completed in patients with diabetic polyneuropathy, bunionectomy, chronic low back pain, osteoarthritis of the knee, and cancer[6] (clinicaltrials.org). The data outline early translation to the clinic and an innovative analgesic profile with significant efficacy in neuropathic pain.[6,49]

Very recently, a further mixed opioid–NOP agonist was introduced: AT-121. This ligand also displayed relatively high affinity for both MOP and NOP receptors, and a partial agonist profile at both receptors. In non-human primates, this molecule produced anti-nociception and suppressed the reinforcing effects of oxycodone. There was no ventilatory depression, opioid-induced hyperalgesia, or dependence. There are no clinical data available.[47]

Biased agonists

Signalling via GPCRs is initiated by a conformational change in the receptor leading to G-protein activation. Agonist efficacy driven by this interaction can be classified as full agonist, partial agonist, antagonist, or inverse agonist[50] (Fig. 2); a further descriptor for functional activity can be driven by ligand bias. Biased agonism (or functional selectivity) is the ability of a particular ligand to drive one signalling pathway over another (bias). In order to quantify bias of the ligand, the other (often experimental) sources of bias in the system, such as receptor (different expression in different experimental systems) and observational bias, should be removed or controlled.[51] There are several methods for bias quantification driven by selection of the reference unbiased comparator and the pathways under study.[52] Much of the literature on bias comes from the cardiovascular system, so we include a brief description.

Biased agonists and the cardiovascular system

Expression of GPCRs in the cardiovascular system is high, and a wide range of cardiovascular diseases are linked to GPCRs and their signalling pathways.[53] Well-characterised examples include Angiotensin II (AngII) type 1 receptor and β-adrenergic receptors, with roles in hypertension.[54,55] In addition to the classical GPCR/G-protein signalling, functional responses can be mediated by other transducers, such as β-arrestins and G-protein-coupled receptor kinases (GRKs) (Smith and colleagues[56]). β-Arrestins were initially shown to be responsible for the inhibition of β-adrenoceptor function; the name arrestin was coined to indicate a role in turning off receptor responsiveness.[57] There appears to be some advantage to driving signalling via the β-arrestin pathway (Table 2); this is the opposite in analgesic research where β-arrestin can support the adverse effect profile. G-protein biased ligands for AngII receptors cause vasoconstriction and fluid retention, whilst a β-arrestin-biased ligand (TRV120027) reduces arterial pressure and increases cardiac contractility. Carvedilol is a β1-AR β-arrestin-biased ligand that has a cardioprotective effect because it is believed that sustained β1-AR activation is cardiotoxic through increasing apoptosis, heart rate, and blood pressure via G_s signalling. Carvedilol also activates epidermal growth factor receptor (EGFR) through a β-arrestin pathway. EGFR has a significant role in nitric oxide production and eventually induces the relaxation of various vascular beds.[58–60]

Table 2 Examples of biased ligands for cardiovascular and opioid receptors.[53,56]

Ligand	Receptor	Signalling bias
Oliceridine (TRV130)	μ-Opioid	G-protein
TRV734	μ-Opioid	G-protein
Triazole 1.1	κ-Opioid	G-protein
RB-64	κ-Opioid	G-protein
PZM21	μ-Opioid	G-protein
Dmt-c[D-Lys-Phe-Asp]NH_2	μ- and δ-Opioid	β-Arrestin biased
Carvedilol	β_1-Adrenergic receptor	β-Arrestin biased
Alprenolol	β_1-Adrenergic receptor	β-Arrestin biased
ApoM+HDL-S1P	Sphingosine 1-phosphate receptor-1 ($S1P_1$)	β-Arrestin biased

Biased agonists and opioid receptors

Opioid receptors couple to multiple signalling pathways, and therefore, have 'pluridimensional efficacy'[61] (Table 1) and represent a target for the design of biased ligands[62] (Table 2). The proposal of targeting specific signalling transduction pathways in opioid receptors arose from an important study in 1999 by Bohn and colleagues.[63] They blocked the function of β-arrestin 2 protein in mice by gene deletion, which led to an improvement in the analgesic effect of morphine and less tolerance in comparison with wild-type animals as a result of effectively blocking the β-arrestin desensitisation process. Naloxone administration to both groups diminished the analgesic effect of morphine, whilst naltrindole and norbinaltorphimine administration acting at DOP and KOP receptors, respectively, were ineffective. These β-arrestin 2 KO animals also showed reduced morphine-induced constipation (animal models of GI transit) and ventilatory depression.[64] Bias in favour of G-protein signalling at the expense of β-arrestin signalling has the potential to produce analgesia with reduced side-effects (Fig. 4).

Oliceridine or TRV130

This is the first G-protein biased ligand which has been developed by Trevena pharmaceutical company. In 2013, DeWire and colleagues[65] found that TRV130 was superior to morphine in producing analgesia and side-effects. *In vitro* studies showed remarkable G-protein stimulation, a reduction of β-arrestin recruitment, and reduced internalisation of MOP receptors. TRV130 is a weak (partial) agonist for G-protein activation and is inactive in β-arrestin signalling, a similar profile to PZM21 (Azzam and Lambert, unpublished data). The results of *in vivo* studies showed a significant improvement in antinociceptive effects in TRV130-treated rats and mice, and a decrease in ventilatory depression and constipation. These data support the idea that the recruitment of β-arrestin is linked to the incidence of adverse effects of opioids, and also facilitates the identification of selective biased ligands.[65,66]

Ongoing clinical studies with TRV130 have been running since 2014. Most have revealed that i.v. TRV130 is well tolerated, and has the same or better analgesic effect as morphine with a prominent decrease in side-effects. TRV130 has passed through several phases of the clinical trials cycle.[67–70] Recently, Altarifi and colleagues show that TRV130 has sustained antinociceptive effects in repeated use and is resistant to antinociceptive tolerance, similar to previous data, while gastrointestinal function was inhibited. In addition, they found that repeated TRV130 use enhanced abuse liability similar to morphine, measured by an intracranial self-stimulation procedure (ICSS).[71]

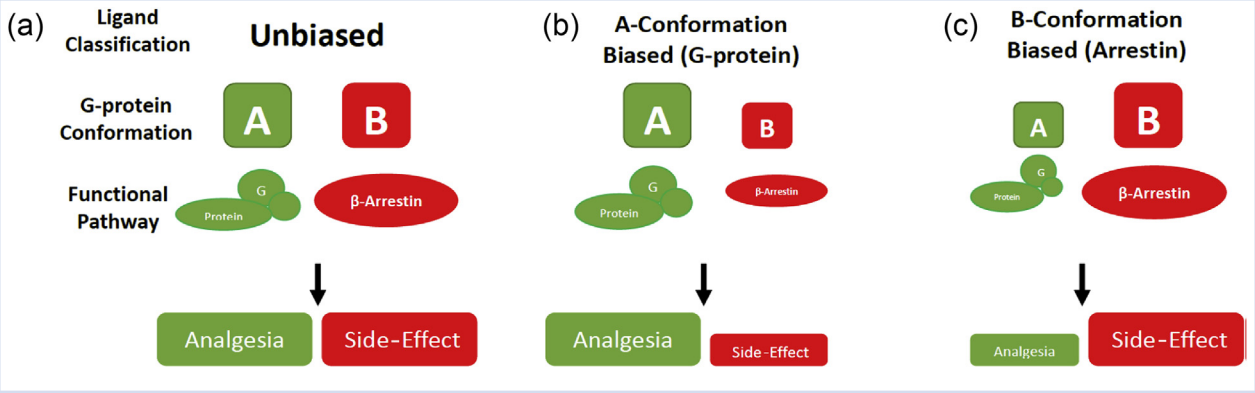

Fig. 4. Stylised diagram depicting biased agonism at the MOP receptor. Three possibilities are shown coupling to G-protein or β-arrestin. (a) An unbiased agonist that interacts equally with both pathways, and is predicted to produce analgesia and side-effects. (b) Bias to G-protein signalling is shown, which is predicted to show analgesia and reduced side-effects. (c) The opposite bias is depicted; β-arrestin bias is predicted to produce more side-effects and display reduced analgesic profile.

In October 2018, the US FDA considered oliceridine, but was not convinced by the safety data and voted 8:7 against approval. Concerns were expressed by the Anesthetic and Analgesic Drug Products Advisory Committee regarding the adequacy of the suggested dosing strategy in treating moderate to severe pain, and a failure to show improvement over an active comparator. Further uncertainties surrounded the possible use of higher doses to establish adequate pain treatment and how this may lead to adverse events, QT prolongation, and ventilatory depression.

PZM21

PZM21 is another biased MOP agonist produced by computational docking of 3000 compounds. *In vivo* and *in vitro* studies revealed high selectivity for MOP receptors with weak KOP antagonist action. Also, G-protein activation is similar to TRV130 along with weak β-arrestin recruitment, even with co-expressed GRK.[72,73] PZM21 has low efficacy in G-protein activation, and depresses ventilation and induces tolerance similar to morphine in animal studies. In contrast to the previous results, PZM21 is similar to traditional ligands in the incidence of side-effects.[74]

With respect to TRV130 and PZM21 it is worth exploring the pharmacology a little more carefully. If both molecules are partial agonists and if the arrestin pathway is poorly amplified then an absolute lack of efficacy could be simply explained as partial agonist behaviour rather than resorting to the ascription of a bias label. This is currently speculation and will require rigorous experimental validation.

Other biased opioid agonists

SHR9352

Li and colleagues[75] have made structural changes to TRV130 to produce a highly efficacious new compound. SHR9352 has high affinity for MOP receptors compared with KOP and DOP receptors. Furthermore, it shows high selectivity towards G-protein activation and less β-arrestin recruitment *in vitro* and in animal studies.

Dmt-c[D-Lys-Phe-Asp]NH_2

Gach-Janczak and colleagues[76] described the cyclic peptide Dmt-c[D-Lys-Phe-Asp]NH_2 as the first MOP and DOP β-arrestin-biased ligand. It displays an enhanced antinociceptive profile in the hot-plate test, but decreased GI transit in animals. The improvement in analgesic effect might be attributable to the simultaneous activation of both MOP and DOP receptors, whilst GI side-effects might be attributed to β-arrestin recruitment.

Mitragynine pseudoindoxyl

Mitragynine pseudoindoxyl is a mixed MOP agonist/DOP antagonist, which has G-protein pathway signalling bias when assayed *in vitro*. In *in vivo* mouse models, the compound produced a potent antinociceptive response and importantly no reward or aversion along with diminished antinociceptive tolerance, ventilatory depression, and GI transit inhibition. These findings suggest that this combination of MOP agonism/DOP antagonism coupled with the non-recruitment of β-arrestin 2 may allow the antinociceptive responses to be separated from many of the common MOP agonist side-effects.[77]

SR-17018

Schmid and colleagues[78] tested a series of MOP compounds containing a piperidine core structure in a number of systems for functional selectivity between G-protein signalling and β-arrestin 2 recruitment. The *in vivo* antinociceptive efficacies of these compounds were compared with the ventilatory suppressant effects to determine the therapeutic window (i.e. best pain relief with least ventilatory depression). Compounds with β-arrestin 2 bias over G-protein signalling had a reduced therapeutic window relative to morphine (i.e. induction of ventilatory depression at lower doses). Compounds that had an improved and broader therapeutic window relative to morphine showed a bias for G-protein signalling relative to the recruitment of β-arrestin 2.[78,79] Of the series tested, SR-17018 showed the greatest G-protein signalling bias and a high

ED_{50} for ventilatory suppression. These findings reveal a positive association between the *in vitro* determined bias factor, degree of difference between G-protein signalling and β-arrestin 2 recruitment, therapeutic window, and ability to separate anti-nociception and ventilatory depression.[78]

Conclusions

Old pharmacological doctrine dictates that high-affinity, highly selective MOP agonists are the perfect analgesic, and in a sense, this is correct, as MOP agonism produces analgesia. However, MOP agonism also produces the side-effect profile that currently characterises (and villifies) opioids: ventilatory depression, tolerance, and abuse potential. Corbett and colleagues[80] described the quest for opioids without side-effects as the Holy Grail, but concluded that this is an exciting but vain quest. Maybe, 12 years on from the Corbett review we may be making progress but by utilising interactions between opioid receptors and designing non-selective and biased ligands.

Authors' contributions

Writing paper: all authors.
Revising paper: all authors.

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Declaration of interest

DGL is Chair of the Board of the *British Journal of Anaesthesia* and, in the past, has had funding from and held a consultancy with Grünenthal, the company that is developing cebranopadol. DGL is also a non-executive director of Cellomatics, a small or medium-sized enterprise contract research organisation. This review is based on a presentation at the 72nd New York State Society of Anesthesiologists, Post-Graduate Assembly in Anesthesiology meeting in New York City on December 9, 2018.

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