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Potential for Kappa Opioid Receptor Agonists to Engineer Non-Addictive Analgesics: A Narrative Review

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Abstract

A serious adverse effect of prescription opioid analgesics is addiction, both to these analgesics and to illicit drugs like heroin that also activate the mu opioid receptor (MOR). Opioid Use Disorder (OUD) and opioid overdose deaths represent a current American health crisis, and the prescription of opioid analgesics has contributed significantly to this crisis. While prescription opioids are highly effective analgesics, there currently exists no facile way to use them for extended periods without the risk of addiction. If addiction caused by MOR-targeting analgesics could be blocked by blending in a new "anti-addiction" ingredient that does not diminish analgesia and does not introduce its own therapeutically limiting side effects, then continued clinical use of prescription opioids for treating pain could be maintained (or even enhanced) instead of curtailed. In this narrative review, we contextualize this hypothesis, first with a brief overview of the current American opioid addiction crisis. The neurobiology of two key receptors in OUD development, MOR and the kappa opioid receptor (KOR), is then discussed to highlight the neuroanatomical features and circuitry in which signal transduction from these receptors lie in opposition – creating opportunities for pharmacological intervention in curtailing the addictive potential of MOR agonism. Prior findings with mixed MOR/KOR agonists are considered, before exploring new potential avenues such as biased KOR agonists. New pre-clinical data are highlighted demonstrating that the G protein-biased KOR agonist nalfurafine reduces the rewarding properties of MOR-targeting analgesics and enhances MOR-targeting analgesic-induced anti-nociception.

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Finally, we discuss the recent discovery that a Regulator of G protein Signaling (namely, RGS12) is a key component of signaling bias at KOR, presenting another drug discovery target towards identifying a single agent, or adjuvant to be added to traditional opioid analgesics, that could reduce or eliminate the addictive potential of the latter drug.

Brief History of the United States Opioid Epidemic

Opium, a powerful analgesic producing euphoria, has been used medicinally and recreationally since its first recorded harvest by Sumerians in 3400-BCE.[1] In the 1800's, Serturner isolated morphine, one of opium's active ingredients.[2] Morphine use increased with advent of the hypodermic needle[3] in 1853 and was extensive during the Civil-War, with subsequent addiction developing consistently enough to earn the name "the Army-Disease".[4] The addictive potential of rapid, systemic morphine administration via hypodermic needle, while overlooked by the medical community at the time, is demonstrated in the evidence of needle sharing[3] as early as 1914. Not long after morphine's medicalization began pursuit of a non-addictive substitute, including Wright's synthesis of diacetylmorphine.[2] Today, diacetylmorphine (heroin) is used illicitly, with lifetime use prevalence among Americans predicted to be >13%.[5] Without a non-addictive replacement, opioid analgesics were largely avoided outside of acute and cancer-related pain until claims in the 1980s that there was little risk of addiction when opioids were prescribed to patients without drug abuse histories.[2,6] Prescribing loosened thereafter, and pain was soon seen as "the fifth vital sign," with chronic-pain management becoming part of hospital accreditation.[7] Extended-release oxycodone constituted a major portion of the resultant increase in opioid prescriptions and was a central player in the rise in opioid use disorder (OUD); the extended release formulation was easily circumvented, allowing for large, instant oxycodone release.[8] In 2017, U.S. opioid prescriptions numbered 200-million, while OUD diagnoses exceeded 2.1-million[9].

OUD is defined[10] as "*…compulsive, prolonged self-administration…*" of opioids without legitimate medical purpose, or at higher doses than therapeutically required, despite "*… clinically significant impairment or distress.*" While OUD is commonly thought to involve heroin, 1.7-million of the 2.1-million-Americans diagnosed with OUD in 2017 were using prescription opioids.[9] While opioids for acute and cancer-related pain are regarded as standard and necessary, new persistent opioid use has been seen in up to 6.5% of post-surgical patients in recent studies.[11,12] The use of opioids for chronic-pain is contentious.[1] A recent meta-analysis found only a small reduction in pain and a small increase in functioning with opioid analgesics prescribed for chronic pain.[13] Long-term outpatient opioid prescriptions for chronic-pain constituted the majority of the increase in opioid prescriptions and carried with them increased abuse potential.[14] 8–12% of patients on long-term opioids for chronic-pain will develop OUD,[15,16] while 25% will engage in "aberrant medication-taking behaviors" such as opioid diversion.[15,16] Addiction to, and misuse of, prescription opioids are also linked to heroin use, with 80% of new heroin addicts reporting first abusing prescription opioids.[17] With strong correlation of the rise of OUD to prescription-rates, it is hoped that alterations in prescribing practices will help curb this rise.[16]

MOR, KOR, and Addiction

The opioid family of neuron signaling-inhibitory G protein-coupled receptors (GPCRs) not only includes “classical” mu and kappa opioid receptors (MOR and KOR), but also the delta opioid receptor (DOR) and the “non-classical” nociceptin-receptor.[18] While all modulate aspects of opioid-induced behaviors in rodents, MOR and KOR exhibit the strongest influence on the development of addiction.[19–22] Agonism of MOR, the primary target of opioid analgesics, produces both analgesia and euphoria.[19,20] KOR agonism produces analgesia as well (albeit more weakly), but also evokes clinically limiting effects like dysphoria and psychotomimesis.[23] Conversely, KOR antagonism is important to the multifactorial pharmacology of the partial MOR agonist and OUD therapeutic medication buprenorphine; while buprenorphine is considered an effective “anti-addiction” analgesic to prescribe to those in pain with a history of OUD,[24] it has also become a street drug in its own right.[25] Better understanding of the neurobiology and pharmacology of the two opioid receptors MOR and KOR, as they relate to analgesia as well as addiction development and maintenance, is warranted if KOR, in particular, is to be exploited in developing future anti-addiction pharmacotherapy.

Analgesia

Clinical success with MOR-targeting analgesics arises from activity at both spinal and supraspinal sites. MOR localizes to presynaptic terminals of primary nociceptive afferents transmitting pain signals into the spinal cord,[26] as well as post-synaptic soma of secondary nociceptive efferents transmitting pain signals to higher brain centers.[26] MOR activation also modulates pain signals through activity in the periaqueductal gray (PAG),[27–29] a midbrain region that controls numerous functions, from fear and anxiety responses to blood pressure.[27–30]

The PAG modulates pain by controlling projections from midbrain nuclei to the dorsal horn of the spinal cord, a descending pathway that inhibits nociception.[27–30] This pathway begins in the PAG, where glutamatergic neurons projecting to serotonergic and noradrenergic cell bodies in the rostral-ventromedial-medulla (RVM) remain under tonic inhibition by a local GABAergic circuit.[27–30] Activation of MORs located on PAG GABAergic neurons disinhibits the glutamatergic projection neurons, in turn stimulating serotonergic and noradrenergic neurons of the RVM.[27] These RVM neurons then project to the dorsal horn, wherein release of serotonin and norepinephrine inhibits transmission of nociceptive signals.[27] In this way, MOR-targeting analgesics prevent nociceptive transmission through actions at receptors in the dorsal horn and indirectly through modulation of regulatory projections.

The role of KOR in spinal analgesia is similar to MOR activation outcomes, as the distribution of KOR resembles that of MOR[26] and KOR activation inhibits transmission of nociceptive signals through the dorsal horn.[26,31] However, the role of KOR remains unclear in the PAG and descending pain-inhibitory circuit. For example, microinjection of the KOR-agonist pentazocine into the PAG produces analgesia against noxious heat but not against pressure, while fentanyl, a MOR-selective-agonist, produced analgesia against both pain modalities.[32] A second group, however, used a thermal stimulus to show that morphine (a MOR-selective-agonist), but not U50,488 (a KOR-selective-agonist), produced analgesia

when microinjected directly into the PAG.[33] In addition to being a KOR-agonist, pentazocine also acts as a partial-agonist of MOR, while U50,488 acts more selectively at KOR and not MOR.[34,35] This difference likely explains the dissimilarity in these two findings.

As a further complication, the distribution of MOR and KOR in these descending circuits remains unclear. While overlap may exist, as reported in some histological studies,[36] others report that MOR and KOR act in specific RVM neuron subpopulations,[37] and produce opposing analgesic effects[37] (as discussed below). While less potent for somatic pain, KOR-agonists display greater potency for visceral pain, in both pre-clinical studies[38] (Table 1) and in a clinical trial using a peripherally restricted KOR-agonist[39]. As the underlying mechanisms and circuitry of somatic and visceral pain differ,[40] it is possible that differences in MOR and KOR distribution play a role in their differing effects.

While both MOR and KOR produce analgesia through activities in the spinal cord and descending pain-modulatory pathways, MOR-agonists provide greater analgesia than KOR-agonists given functional divergence in higher brain centers. Compared with KOR-agonists, MOR-targeting analgesics retain broad applicability to nearly all types of pain, in part because of their ability to produce euphoria, thereby reducing the affective component of pain and preventing “agony” even when the conscious perception of a nociceptive stimulus remains.[41] This ability, however, also leads to the dramatic abuse potential of MOR-targeting analgesics. In contrast, KOR agonism produces anxiety and dysphoria, limiting the clinical utility of KOR-agonists and playing a major role in the cycle of addiction through its role in producing negative affect.

Euphoria and Dysphoria

Both MOR and KOR play central roles in the cycle of addiction. While MOR activation drives initial development of drug preference through its euphorigenic properties,[19,20] KOR activation reinforces habitual drug-taking through its dysphoric properties, producing negative affect and “emotional pain”.[19,42,43] In the CNS, MOR and KOR normally function in opposition to produce an affective homeostasis. When perturbed, however, this system may spiral to lower and lower set-points of negative affect, leading to the destructive cycle of drug-seeking known as addiction.

(i) Euphoria, reward, and MOR—While MOR is distributed widely throughout the brain, its highest levels are in regions involved in pain processing (*e.g.*, thalamus, PAG) and in motivated behavior (mesolimbic system),[44] with the latter playing the strongest role in addiction development. Endomorphins are considered to be the natural, MOR-binding opioids central to pain relief. Another class of endogenous MOR-ligand, β-endorphin, is produced in the hypothalamus as well as the nucleus tractus solitarius,[45] and is expressed throughout the brain as a homeostatic mechanism of reducing stress and producing reward in response to novel stimuli, stress, and exercise.[46] Elevations in β–endorphin increase mesolimbic dopamine release[47], produce place preference[48], and augment the reinforcing properties of xenobiotic chemicals (*e.g.*, drugs of abuse)[49,50] and natural rewards (*e.g.*, sex, food).[46,51] Conversely, β-endorphin ablation or deletion of *Oprm1* (*MOR* gene) in mice

increases anxiety[52], attenuates motivational drive to acquire natural rewards[53], and reduces sensitivity to reward-predictive cues or stimuli.[54] Ultimately, MOR signaling largely produces positive affect and motivated behavior through effects on the mesolimbic system.

The mesolimbic pathway comprises dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc), and plays key roles in reward prediction and encoding the incentive salience of naturally rewarding stimuli.[55] When encountering a rewarding stimulus, ranging from basic rewards (*e.g.*, food) to complex social rewards (*e.g.*, praise), VTA burst firing releases dopamine in the NAcc and produces positive reinforcement of the behavioral pattern that produced the rewarding stimulus.[56] VTA dopamine neurons remain under tonic inhibition by local GABAergic interneurons that express MOR.[57] Endogenous opioid release in this area serves to inhibit these GABAergic interneurons, leading to disinhibition of VTA dopaminergic projections to the NAcc, producing positive reinforcement.[57] This action on VTA MORs is the primary mechanism of opioid analgesic-induced reward.[55,57] Intra-VTA application of the MOR agonist DAMGO stimulates local dopamine release in wildtype mice, but not MOR knockout mice[58]; moreover, systemic administration of morphine increases dopamine release in the NAcc, but this effect is markedly reduced in MOR knockout mice[59]. Accordingly, morphine or heroin-induced locomotor activation[59,60], conditioned place preference[60,61], intravenous self-administration[62], and opioid dependence and withdrawal[63] are all abolished in MOR knockout mice. Pharmacological studies show that place preference for MOR-targeting analgesics is blocked in rats by administering a MOR antagonist directly into the VTA;[64] conversely, MOR-agonists are self-administered by rats when applied directly to the VTA.[65] While animals will self-administer MOR-agonists when applied to several other brain regions as well[66], their actions in the VTA are necessary and sufficient for the reinforcing properties of opioid analgesics.[55] Furthermore, disinhibition of dopamine release likely plays a role in the ability of MOR-targeting opioid analgesics to reduce the affective experience of pain, as decreased function of midbrain dopaminergic neurons leads to increased pain,[67] while dopaminergic agents can produce analgesia themselves (*e.g.*, ref.[68]). Mice lacking tyrosine hydroxylase (*i.e.*, dopamine-deficient mice) show reduced thermal anti-nociception in response to morphine,[69] supporting a role for dopaminergic signaling in the analgesic response to traditional opioid analgesics.

This model above, however, is not without complications. Destroying dopaminergic projections from the VTA to the anterior cingulate cortex, for example, blocks acquisition of place preference to morphine administered to rodents either systemically or directly into the VTA, implicating mesocortical circuitry in opioid reinforcement.[70] In addition, while dopamine antagonists block acquisition of morphine-induced place preference, the potency of this effect varies with antagonist specificity across the various dopamine receptor subtypes.[71] More confounding still are findings that dopamine-deficient mice[69] still display place preference for morphine, implicating factors beyond dopaminergic signaling in producing opioid reward.

While the intricacies of dopamine signaling in addiction require further inquiry, the initial phase of opioid addiction development -- acute reward and euphoria -- remain best explained by disinhibition of mesolimbic circuitry. The potent ability of opioids to disinhibit this

circuitry underpins both their profound analgesic effects and their devastating propensity to incentivize compulsive use. Given its power, the brain employs potent means to regulate this mesolimbic circuitry, none linked more tightly to the cycle of addiction than KOR.

(ii) Dysphoria, altered set-points, and KOR—While KOR distribution mirrors that of MOR in many regions, oppositional localization in specific regions produces a profound difference in the ultimate effects of KOR stimulation *vs* MOR stimulation (Table 1).[44] MOR agonist-induced reward and analgesia are maintained in KOR knockout mice[63,72] and prodynorphin knockout mice[73,74]; conversely, KOR agonist-induced G protein coupling, analgesia, and aversion are unaffected by MOR ablation[75,76], supporting that the physiological effects of MOR and KOR are distinct and separable. While MOR stimulation produces euphoria, KOR activation produces dysphoria, a negative affective state that includes components of anxiety, anhedonia, and depression.[22,77] Dynorphin, the endogenous KOR-ligand neuropeptide cleaved to six different lengths from the precursor prodynorphin, is produced in the hypothalamus,[45] the amygdala,[78] and direct pathway GABAergic medium spiny neurons of the striatum[79] (among other regions), and is released in response to stress.[77] Unlike β-endorphin, dynorphin plays the role of a negative homeostatic regulator, producing the negative experiences of stress[80] and modulating the central effects of corticotropin releasing factor (CRF), a major hormonal regulator of the stress response.[80] The areas most heavily implicated in producing this negative state include the VTA-to-NAcc circuit, along with the amygdala and dorsal raphe nucleus (DRN), the latter being the brain's major serotonergic nucleus.[81] In each of these regions, KOR activation produces effects largely in opposition to those of MOR, culminating in the overall negative affective state of dysphoria.

In the mesolimbic system, KOR activation reduces dopamine release, with KOR expressed on both the cell bodies of dopaminergic VTA neurons (Figure 1), as well as the presynaptic terminals of these neurons within the NAcc of mice.[82,83] This distribution is different in the rat brain, with KORs located on the terminals of NAcc projections, but only on the bodies of VTA neurons projecting to the medial prefrontal cortex and amygdala,[84] and this distribution may vary within the human brain as well. In both the NAcc and VTA, KOR activation acts in negative feedback regulation of mesolimbic dopamine release, restoring homeostatic function within this circuit. When dopamine D1 receptor-expressing neurons within the NAcc are stimulated by dopamine, they release both dynorphin and GABA from axonal projections terminating in the VTA to reduce the firing rate of the dopaminergic neurons located therein.[85,86] Disinhibition of this circuitry by MOR-agonists produces reward, whereas inhibition by KOR-agonists produces the opposite (*i.e.*, aversion, as measured in rodents using conditioned place aversion [CPA][82,83]); as a result, KOR-agonists do not support self-administration in rats or rhesus monkeys[87,88]. Prior studies[82,83] strongly link these aversive properties of KOR-agonists to actions on mesolimbic dopamine neurons. For example, systemic administration of a KOR agonist produces place aversion in wildtype mice, but not constitutive or dopamine neuron-specific KOR knockout mice.[83] More recent work demonstrates that dynorphin/KOR microcircuits within the NAcc shell mediate negative affect engendered by inflammatory pain[89], and that discrete subpopulations of

dynorphin/KOR-expressing neurons in the ventral and dorsal NAcc shell differentially drive KOR-mediated aversion and 'paradoxical' reward, respectively.[90]

KOR actions in the amygdala appear to modulate fear and anxiety related behaviors, possibly through modulation of local GABAergic neurotransmission and long-term potentiation.[91] Fear conditioning in rats is reported to increase *Oprk1* mRNA in this region, and local KOR inhibition reduces this response.[92] In addition, KOR antagonism in the amygdala blocks the anxiogenic effects of a natural stressor (repeated forced swimming) or of intra-amygdalar CRF injection.[93] The DRN also plays a central role in mediating the affective response to KOR-agonists. KOR stimulation in this region reduces extracellular serotonin,[94] likely through increasing serotonin transporter levels via a p38α mitogen-activated protein kinase (MAPK)-dependent mechanism,[95] an effect seen in mice after both local KOR-agonist administration and social defeat stress[95]. Furthermore, while the KOR-agonist U50,488H did not produce place aversion in mice lacking KOR, viral re-expression of KORs on DRN neurons projecting to the NAcc restored U50,488H CPA in these KOR-deficient mice[96].

The effects of KOR activation within these brain regions suggests that the dynorphin/KOR system is central in mediating the aversive effects of stress.[21,43,96] Dynorphin levels increase during stress[97], and blockade of KOR or genetic deletion of *Oprk1* in mice prevents the pro-depressive and anxiogenic effects of forced swim, social defeat, and foot-shock stressors.[80,93,95] Systemic KOR-agonist administration produces place aversion[83] and depressive-like phenotypes in forced swim and intra-cranial self-stimulation (ICSS) assays.[98] By producing these negative affective states, the dynorphin/KOR system also figures heavily into the addictive cycle. Stressful stimuli reinstate extinguished drug-seeking behaviors in both place preference and self-administration paradigms.[99] Pre-treating mice with the KOR-antagonist nor-binaltorphimine (norBNI), or genetic deletion of either *Oprk1* or *Pdyn*, prevents reinstatement of conditioned place preference (CPP) for cocaine by foot shock or forced swim stressors, as well as to a single administration of U50,488H[100]. In addition, CPP for cocaine increased in mice exposed to forced swim stress prior to conditioning, an effect blocked by norBNI pre-treatment.[101]

In light of its role in regulating limbic function and mediating stress, KOR should be viewed as central to the "Allostatic Model"[102] that contextualizes addiction as a pathologically altered homeostatic set point, or "allostasis".[103] The dynorphin/KOR system contributes to allostasis largely through modulating dopamine tone within the mesolimbic system.[42,43] As described above, MOR-targeting analgesics increase dopaminergic tone in the NAcc, a property common to nearly all drugs-of-abuse[20]. Repeated use increases production of cAMP response element binding protein within the NAcc[85] and subsequent upregulation of dynorphin.[43,85,86] With cessation of opioid use, this elevated dynorphin tone leads to dysphoria, increasing the hedonic valence of the drug and increasing susceptibility to relapse in an attempt to attain the now pathologically altered homeostatic set point.[42,43,102]

In summary, while activation of MOR or KOR produces analgesia in response to stressful stimuli, the psychological functions of these receptors diverge dramatically and represent the opposing faces of opioid addiction. The drive to alleviate pain placed the profound effects of

MOR stimulation at the forefront of medicine in the early 2000s. Now, because of the resultant OUD crisis spawned by these powerful MOR-targeting analgesics, KOR antagonists sit among NIDA's ten most wanted drugs for the treatment of OUD,[104] specifically with the thought that KOR antagonism during OUD might reduce endogenous dynorphin signaling, and its contribution of stress, to drug-seeking behaviors and addiction reinstatement. In a separate means of exploiting pharmacological manipulation of KOR signaling towards a clinical benefit, KOR agonism has the potential to create blended KOR-agonist/MOR-agonist "combination" analgesics that diminish or eliminate the risk of acquiring OUD while on analgesics in the first place.

New approaches for improving opioid analgesics

Searches for a non-addictive analgesic began nearly the moment Serturner first isolated morphine in the 1800's.[2] Many opioids are sold today as combinations – also containing non-steroidal anti-inflammatories to reduce the dose of opioid necessary to treat pain, otherwise known as "dose sparing".[105] Other combination therapies, such as Suboxone (buprenorphine/naloxone), focus on preventing improper opioid use by compounding them with opioid antagonists active only when taken through improper routes.[24] While many approaches are currently being investigated, from targeting little-understood MOR splice-variants[106] to designing opioids that function only in the presence of inflammation,[107] the following sections focus on two widely studied and promising avenues: combination therapies activating multiple opioid receptors, and the utilization of "biased agonism."

Combining MOR and KOR activation

In the 1990s, researchers began utilizing the analgesic and non-reinforcing properties of KOR-agonists to augment traditional MOR-agonists. While KOR-agonists alone proved less potent in producing analgesia,[108] combining fentanyl (MOR-agonist) with U69,593 (KOR-agonist; Table 2) showed additive analgesic effects in rhesus monkeys while also reducing self-administration.[109] Furthermore, combining MOR and KOR-agonists prevented liabilities of opioid tolerance, hyperalgesia, and respiratory depression.[110,111] While pre-clinical experiments demonstrated utility of combined MOR and KOR agonism, enthusiasm waned after early clinical experiments utilizing mixed MOR/KOR-agonists. While nalbuphine (KOR-agonist and MOR partial agonist) demonstrated efficacy in reducing CPP to morphine in pre-clinical studies, suggesting a benefit against addiction induction,[112] human studies demonstrated dose-dependent increases in dysphoria, curtailing clinical utility.[113] Pentazocine (similar to nalbuphine) and butorphanol (KOR-agonist yet MOR-antagonist) also demonstrated classic dysphoric effects of traditional KOR-agonists in humans at higher doses,[23,113–116] limiting therapeutic potential.

Of note, however, is one report[117] that co–administration of the MOR and KOR-antagonist naltrexone with pentazocine in human subjects "unmasks" the KOR-related dysphoric effects of pentazocine at lower doses, but blocks both MOR-dependent and KOR-dependent effects at higher doses. As the antagonist naltrexone possesses greater affinity for MOR than KOR, these results support the premise that MOR agonism can mitigate KOR agonism-related dysphoria to some degree. While a single compound (like a mixed MOR/KOR-

agonist) is generally considered a more attractive drug candidate than a dual-drug formulation, this study[117] suggests that relative activity at each opioid receptor plays a critical role in the interaction between these two receptor systems. Studies in patients receiving methadone maintenance therapy demonstrate that administering nalbuphine, pentazocine, or butorphanol can precipitate withdrawal,[118–120] indicating that none of these three, mixed-action drugs achieves activity at MOR comparable to methadone, perhaps due to incomplete agonism. While new mixed MOR/KOR drugs under development may possess more favorable activity profiles, such as the 6β-naltrexamines and orvinols,[121] a co-administration paradigm may allow for greater control over relative activity at each receptor.

The recent rise of OUD has reinvigorated interest in KOR-agonists. A peripherally restricted KOR-agonist -- CR845/difelikefalin -- is currently in Phase III trials.[122] In addition to peripheral restriction of KOR agonism (*i.e.*, to provide analgesia without concomitant CNS-centered dysphoria), pre-clinical research is also focused on utilizing a newer concept in pharmacology: "biased agonism." This approach utilizes variations in the efficacy of different compounds to engage various aspects of intracellular machinery downstream of receptor stimulation.

Biased Agonism: All the good and none of the bad?

G protein-coupled receptors regulate diverse physiological processes and represent the target of greater than a third of all FDA approved drugs.[123] GPCRs contain seven transmembrane domains that couple to an intracellular, heterotrimeric complex of Gα, Gβ and Gγ subunits.[124] The Gα subunit associates with guanine nucleotide diphosphate (GDP) in the resting (inactive) conformation. When bound by agonist, the activated GPCR catalyzes exchange of GDP for guanine nucleotide triphosphate (GTP), at which point the Gα·GTP subunit dissociates from the Gβγ heterodimer.[124] Both the Gα GTP and Gβγ complexes initiate distinct signaling cascades that vary depending upon the receptor and the cellular context[124]; all opioid receptors couple to the inhibitory $G_{i/o}$ class of Gα proteins.[31] The $G_{i/o}$ heterotrimer, when activated, generally functions to inhibit cAMP production, as well as increase potassium conductance (hyperpolarizing the cell) and inhibit calcium conductance (preventing vesicular release of neurotransmitters).[27] Opioid receptor activation inhibits neuronal function through these G protein-dependent mechanisms.

In addition to G protein-dependent signaling, GPCRs also initiate signaling through a different class of proteins -- the β-arrestins.[125] Activated GPCRs often recruit G protein-receptor kinases (GRKs),[124] which phosphorylate the GPCR, subsequently leading to β-arrestin recruitment.[124,125] As their name implies, β-arrestin proteins arrest further G protein activation, and also can lead to subsequent receptor internalization. The internalized β-arrestin/GPCR complex then activates signaling pathways distinct from those activated by G proteins.[125,126] When a particular GPCR agonist activates either the G protein- or β-arrestin-dependent pathway to a greater extent than the other, this agonist is considered "biased" towards that pathway.[125] Physiological and behavioral effects classically associated with activation of specific GPCRs may occur to a greater or lesser extent upon application of biased agonists.[82,126] The possibility of discovering novel KOR agonists that minimize the adverse effects currently preventing their utility as adjuvants to conventional opioid

analgesics has led to a recent surge in research focused on biased KOR compounds and biased KOR signal transduction.

(i) G protein-biased KOR agonists—G protein-dependent signaling downstream of KOR activation produces analgesia via inhibiting pain transmission through the dorsal horn of the spinal cord.[26,31] Conversely, β-arrestin2 signaling is implicated in the therapeutically limiting dysphoric effects of KOR agonists.[82,127,128] As discussed above, natural stressors (such as forced swim) activate KOR in mice; the dysphoric component of this stress can be prevented by pharmacological inhibition of p38 MAPK downstream of KOR-initiated β–arrestin2 signaling,[128] or by preventing β-arrestin2 recruitment to activated KOR through deletion of *Adrbk2* (encoding the upstream G protein-receptor kinase βARK2/GRK3).[127] Furthermore, deletion of *Mapk14* (encoding p38α-MAPK) from dopamine neurons prevents conditioned place aversion (CPA) to the unbiased KOR agonist U50,488.[82] These results and others have spurred investigations into developing a “non-dysphoric” replacement of traditional MOR-targeting opioid analgesics with a single KOR agonist that is biased toward G protein signal transduction.

A G protein-biased KOR-agonist named triazole 1.1 was found to have reduced dysphoric liabilities in pre-clinical tests:[98] triazole 1.1 did not suppress ICSS thresholds, reduce NAcc dopamine release, nor inhibit novelty-induced locomotion at doses producing analgesia equivalent to U50,488. These results support the hypothesis that a G protein-biased KOR agonist will not produce the sedative and dysphoric effects that have limited the clinical utility of traditional, unbiased KOR agonists. However, another G protein-biased KOR-agonist, RB-64, was observed to produce CPA in both wild-type and β-arrestin2-deficient mice without inhibiting novelty-induced locomotion in either genotype.[129]

Because newer, G protein-biased KOR-agonists are thought to bias against eliciting dysphoric effects, we recently re-tested the hypothesis that co-administration of a G protein-biased KOR activator with a traditional opioid analgesic reduces the rewarding property of the latter drug without reducing its desired analgesic effect and without eliciting untoward dysphoria. We first profiled several G protein-biased KOR agonists,[130] including triazole 1.1 and nalfurafine, against an unbiased KOR agonist (U50,488). Based on our recent analyses[130] (summarized in Fig. 2), we agree that triazole 1.1 is G protein-biased, but also highlight that other G protein-biased compounds (*e.g.*, nalfurafine, EOM Sal B) have even greater G protein-bias *in vitro* and, therefore, decreased potential to elicit dysphoria in clinical usage. In particular, nalfurafine has high translational potential as an “anti-addiction” adjuvant for existing MOR-targeting analgesics, given nalfurafine’s safe usage in Japan since 2009 to treat uremic pruritis[131,132] without producing psychotomimesis or undue sleep disturbances (either insomnia or somnolence).[132] Most importantly, nalfurafine is also known to be free of abuse potential.[131]

Using co-administration in C57BL/6J mice, nalfurafine was observed to reduce CPP for morphine, yet enhance morphine-induced supraspinal analgesia, the latter suggesting that nalfurafine addition to an opioid analgesic could also lead to a reduction of dose of the latter.[130] Testing in male rhesus monkeys has further demonstrated that nalfurafine elicits a reduced degree of sedative-like and motor-impairing effects compared to typical KOR-

agonists,[133] and furthermore reduces self-administration of oxycodone, in rhesus monkeys, in mice, and in rats[134–136] – hopeful signs that nalfurafine could be used as an "anti-addiction" adjuvant to traditional opioid analgesics. Newer KOR agonists with G protein signaling bias are also being created with this anti-addiction application in mind (*e.g.*, USPTO-application US20200131162A1 "Synthesis of 20-nor-salvinorin-A" published 2020-04-30).

(ii) RGS12 inhibitors?—β-arrestin proteins, as their name suggests, arrest G protein-mediated signaling from activated GPCRs. Another protein family – the 'Regulators of G-protein Signaling' (or RGS proteins) – also serve to extinguish GPCR signaling, but via a different mechanism: namely, acceleration of GTP hydrolysis by the Gα subunit to return the G proteins to their inactive, heterotrimeric state.[124] One particular member, RGS12, is enriched within the ventral striatum (vSTR); genetic ablation of *Rgs12* increases dopamine transporter (DAT) expression and dopamine uptake within the vSTR of mice.[137,138] (Similar CNS effects of RGS12 loss are also seen in changes to serotonin transporter expression and serotonin uptake[139]). The most likely direct targets for RGS12's inhibitory action are striatal presynaptic KORs, activation of which is known to attenuate striatal dopaminergic tone.[140] Given that *Oprk1* (*KOR)* and *Rgs12* mRNAs overlap in their CNS expression, and that KOR and RGS12 proteins co-immunoprecipitate as a complex from vSTR extracts,[137] it is likely that the increased DAT expression / function exhibited by RGS12-null mice is caused by removing a critical negative influence on signaling downstream of KOR activation. RGS12 overexpression markedly and selectively blunts G protein-dependent cAMP inhibition by KOR activation but greatly enhances β-arrestin recruitment to activated KOR.[137] (This same report[137] demonstrated that RGS12 does not interact with MOR in the same fashion: no co-immunoprecipitation was observed, nor the same degree of reducing MOR-agonist potency upon RGS12 overexpression). Consistent with the *in vitro* results suggesting an important role for RGS12 in blunting cAMP inhibition yet enhancing β-arrestin recruitment to activated KOR, RGS12 loss in mice enhances KOR-induced analgesia and attenuates KOR-induced CPA – G protein- and β–arrestin-dependent behaviors, respectively.[82,96,129] Given these data, we hypothesize that RGS12 is a hitherto unappreciated key regulator of KOR signaling, acting on both G protein- and β–arrestin-dependent signals to modulate the output of dynorphin/KOR signaling to dopamine reuptake and to the behavioral responses of both analgesia and aversion (Fig. 3). An inhibitor of RGS12, if discovered via compound screening (*e.g.*, ref.[141]), could therefore also have utility as an adjuvant to either a KOR agonist or traditional MOR-targeting analgesic, leading to a reduction in either KOR agonist-induced or dynorphin-induced dysphoria, respectively.

These recent studies have revealed the complexities, and potential promise, of signaling pathway-selective KOR-agonists and RGS12 inhibitors in reducing the deadly addiction liability of traditional MOR-targeting opioid analgesics. Specific G protein-biased KOR-agonists, such as triazole 1.1 and nalfurafine, may produce analgesia on their own without producing untoward dysphoria, and/or serve as additions to traditional opioid analgesics to lower their dose and reduce their addictive potential. A great deal more research into this field of behavioral pharmacology is required to disentangle the complexities of such biased KOR-agonists and their potential utility as replacements for, or adjuvants to, traditional

MOR-targeting analgesics. This further research on the pharmacotherapeutic utility of biased KOR agonism is especially important to transact in light of the recent challenges to the existence of (and utility of) biased agonism at MOR.[151]

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Glossary

Agonist	compound which activates receptor upon binding
Antagonist	compound which prevents receptor activation upon binding
Adrbk2	gene encoding GRK3
Arrb2	gene encoding β-arrestin2
BCE	before the common era
cAMP	cyclic adenosine monophosphate
CPA	conditioned place aversion
CPP	conditioned place preference
CRF	corticotropin releasing factor
DAT	dopamine transporter
DRN	dorsal raphe nucleus
EOM Sal B	an ethoxymethyl ether derivative of salvinorin A
GABA	the inhibitory neurotransmitter gamma-aminobutyric acid
GABAergic	pertaining to, or elaborating, the neurotransmitter GABA
GPCR	G protein-coupled receptor
G protein	guanine nucleotide-binding protein
GDP	guanosine diphosphate
GRK	G protein-coupled receptor kinase
GTP	guanosine triphosphate
ICSS	intra-cranial self-stimulation
KOR	kappa opioid receptor
MAPK	mitogen-activated protein kinase
MOR	mu opioid receptor

NAcc	nucleus accumbens
norBNI	the KOR antagonist nor-binaltorphimine
OPRK1	gene encoding KOR protein
OPRM1	gene encoding MOR protein
OUD	opioid use disorder
PAG	periaqueductal gray
PDYN	gene encoding dynorphin
RGS	regulator of G protein signaling
RGS12	regulator of G protein signaling type 12
RVM	rostral ventromedial medulla
SUD	substance use disorder
vSTR	ventral striatum
VTA	ventral tegmental area

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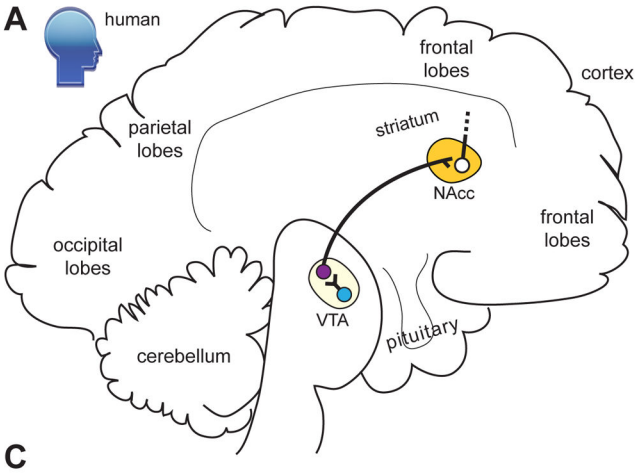

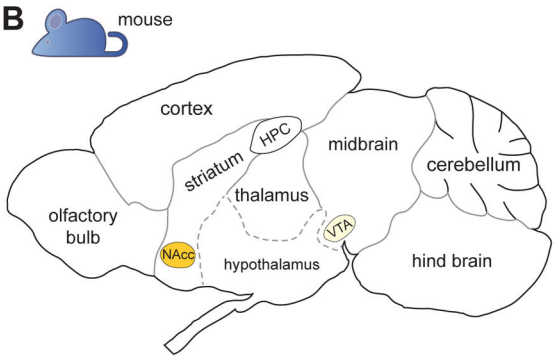

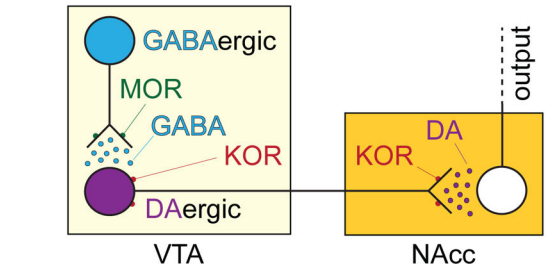

D

	human		mouse	
	MOR	KOR	MOR	KOR
basal ganglia	17.5	18.0	1.8	5.7
cortex	7.6	8.8	0.6	1.9
amygdala	7.0	15.9	0.9	2.7
hippocampus	2.6	4.5	0.7	0.8
hypothalamus	2.3	6.2	5.0	5.9
thalamus	0.5	1.6	1.8	2.3
midbrain	0.6	1.7	2.2	3.0
pons/medulla	5.2	3.1	1.2	1.7
cerebellum	37.9	2.2	0.2	0.1

Figure 1. Schematic of relative locations of KOR and MOR receptors in the mesolimbic pathway of the human (A) and mouse (B) brains.

Panel **C** depicts activation of MORs on GABAergic interneurons of the VTA disinhibiting dopamine release and producing reward. Activation of KORs on dopaminergic neurons inhibits dopamine release, producing dysphoria. Panel D lists normalized mRNA expression levels for the transcripts encoding MOR and KOR in indicated regions of the human and mouse brains. Consensus Normalized eXpression (NX) values were generated as previously described by the Human Protein Atlas (https://www.proteinatlas.org/about/assays+annotation#normalization_rna).

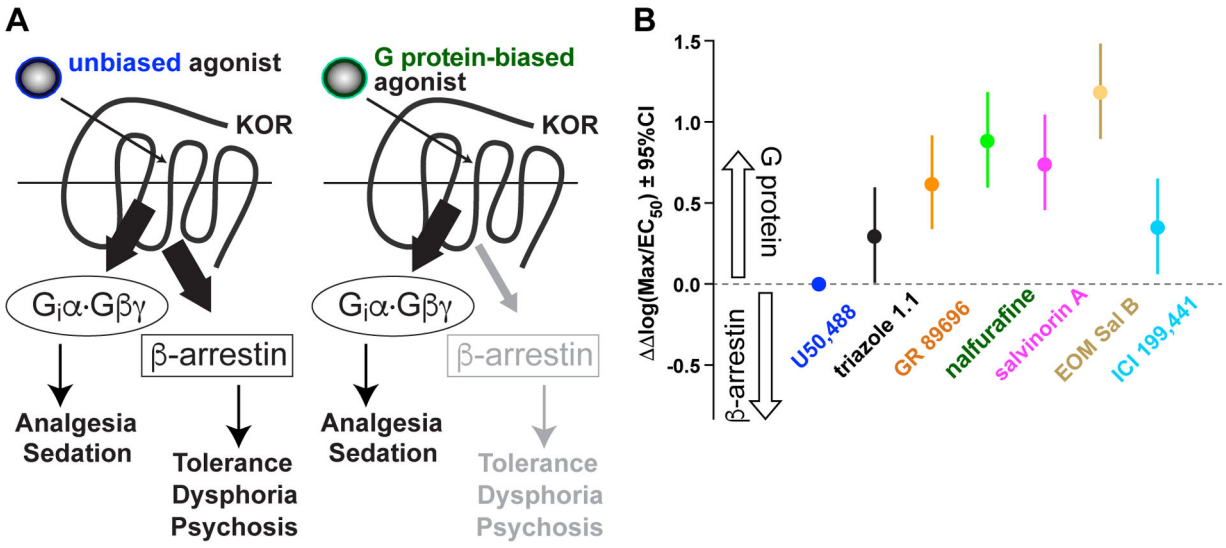

Figure 2. Triazole 1.1, nalfurafine, and EOM Sal B are G protein-biased KOR agonists.

(A) Unlike unbiased KOR agonists (*e.g.*, **(±)U50,488**), G protein-biased agonists have diminished potency in signaling to β–arrestin recruitment. (**B**) Summary of bias factors for each compound as obtained from maximal efficacy (E_{max} or "Max") and potency (EC_{50}) values. $\Delta\Delta\log(Max/EC_{50})$ values, with 95% confidence intervals (CIs), are plotted for each compound to indicate relative bias towards G protein signaling (*versus* U50,488). Bias factors in the plot of panel B are derived from ref.[130].

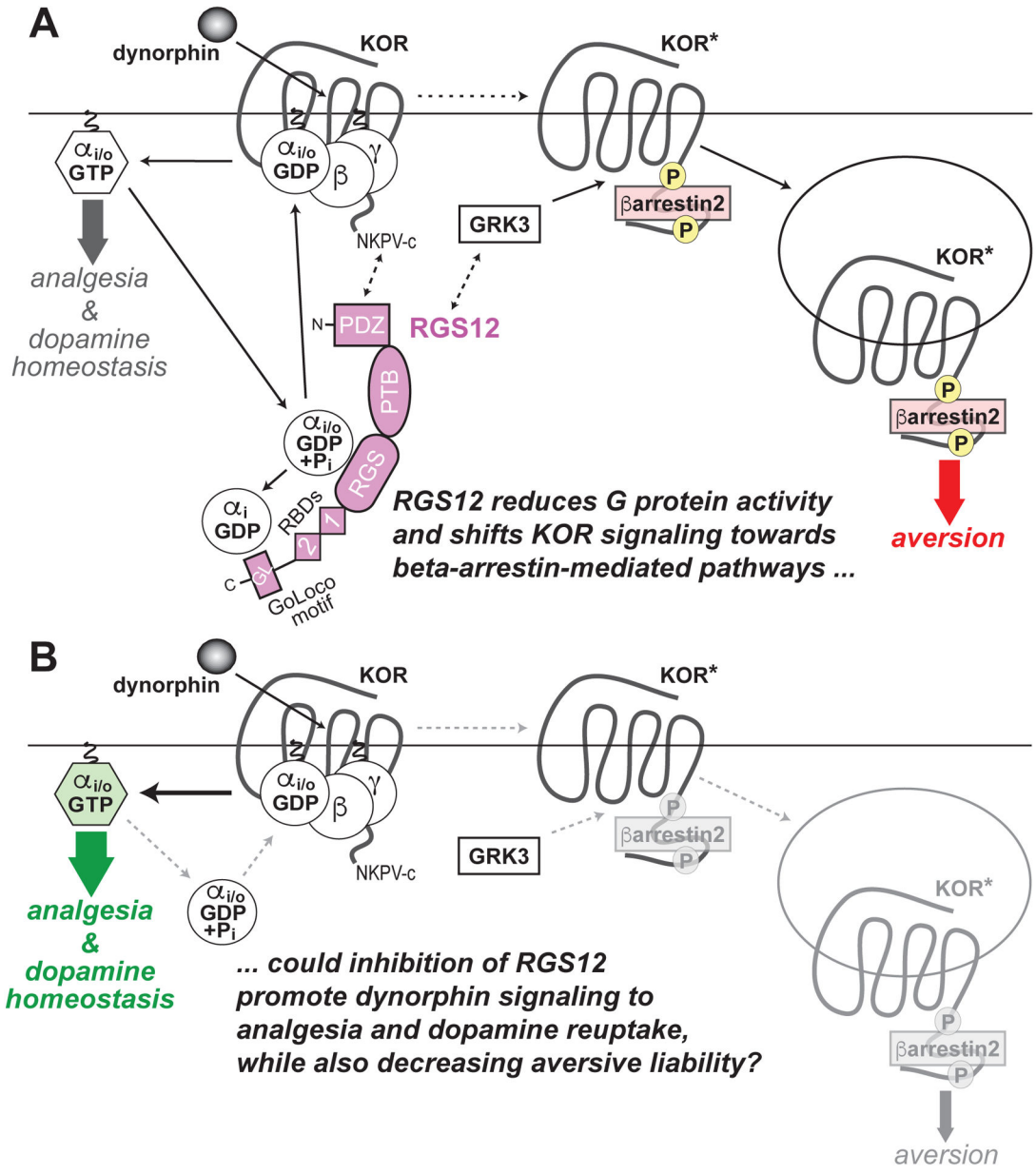

Figure 3. Model of RGS12 action in the differential behavioral outputs of kappa opioid receptor (KOR) signaling, as derived from recent published work using *Rgs12*-deficient mouse strains. [137,138] **(A)** Dynorphin-induced activation of KOR, as occurs during stress, dissociates $G_{i/o}$-coupled heterotrimers into free G protein subunits, evokes G protein-dependent signal transduction (*thick grey arrow*) and, ultimately, produces analgesia and also regulates dopamine homeostasis by the pre-synaptic dopamine transporter (DAT). RGS12 expression is known to reduce KOR-mediated G protein signaling via its central RGS domain (by accelerating GTP hydrolysis of $G\alpha_{i/o}$·GTP) and its C–terminal GoLoco motif (by trapping $G\alpha_i$·GDP). RGS12 also contains an N-terminal PDZ domain that likely interacts with the C-terminal PDZ domain docking site of KOR ('*NKPV-c*'). RGS12 also contains tandem Ras-binding domains (RBDs) that we previously established interact with activated H-Ras and Raf to enable MAPK/ERK scaffolding properties[150]. Agonist-stimulated KOR activation

also drives GRK3-dependent βarrestin2 recruitment, resulting in receptor internalization, βarrestin-dependent signal transduction (*thick red arrow*) and, ultimately, aversive behavior (in parallel to decreased extracellular dopamine). RGS12 expression augments KOR agonist-stimulated βarrestin recruitment independent of its GAP and GDI activity[137], suggesting that RGS12 modulates GRK3 activity on activated KOR (KOR*) and/or enhances βarrestin2 recruitment and/or function by as yet undetermined molecular mechanisms. **(B)** Loss of RGS12 in mice results in concomitant increases in KOR-mediated G protein signaling and decreases in βarrestin2 recruitment, thus resulting in enhanced KOR agonist-stimulated analgesia and enhanced DAT function causing enhanced dopamine reuptake (*thicker green arrow*), as well as an attenuation of KOR-stimulated aversion (*thinner grey arrow*), respectively.

Table 1.

Pre-clinical Effects of MOR and KOR Agonism

Type of Pain:	Effect of MOR Agonism	Effect of KOR Agonism	Relative Efficacy	References
Spinal	analgesia	Analgesia	MOR ≈ KOR	142
Supraspinal	analgesia; euphoria	analgesia; dysphoria	MOR ⋙ KOR	142
Inflammatory	analgesia	Analgesia	MOR ≈ KOR	142–146
Visceral	analgesia	Analgesia	MOR < KOR	72,147
Somatic	analgesia	Analgesia	MOR > KOR	142–144
Neuropathic	can worsen	Mixed	-	142–146

Table 2.

MOR and KOR Agonists and Their Selectivities[129,148,149]

Drug / Compound name:	Selectivity (estimated Ki [nM]) at the human receptor*			Approved for use?
	MOR	KOR	DOR	
β-Endorphin	1.18	31.7	1 to 5.4	*endogenous*
Dynorphin A	32	0.5	1,000	*endogenous*
Enkephalin	1.77	506.17	200 to 1,430	*endogenous*
Morphine	2.16	50 to >2,000	1,545 to 2,500	USA (FDA) for analgesia
Oxycodone	780	>2,000	>10,000	USA (FDA) for analgesia
Fentanyl	1	169.9	152 to >1,000	USA (FDA) for analgesia
Pentazocine	5.4	2.6	114.5	USA (FDA) for analgesia
Butorphanol	0.12	0.22	12	USA (FDA) for analgesia
Buprenorphine	0.85 (partial agonism)	0.71 (antagonism)	3.7 (antagonism)	USA (FDA) for OUD
Nalfurafine* (TRK-820)	3.2 to 5.2	0.025 to 0.075	161 to 289	Japan (MHLW) for pruritus
EOM Salvinorin B	>1	0.32	>1	no
ICI 199,441	54	0.04	24	no
U50,488	>1,000	0.16	645	no
U69,593	>1,000	1.53	>1,000	no
RB-64	>10,000	0.59	>10,000	no
Salvinorin A	>10,000	1.82	>1,000	no
Triazole 1.1	>10,000	0.25	>2,000	no

*Estimated nalfurafine Ki (nM) values are presented at the rat MOR, human KOR, and mouse DOR, respectively.