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Pleiotropic Effects of Kappa Opioid Receptor-Related Ligands in Non-human Primates

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Abstract

The kappa opioid receptor (KOR)-related ligands have been demonstrated in preclinical studies for several therapeutic potentials. This chapter highlights (1) how non-human primates (NHP) studies facilitate the research and development of ligands targeting the KOR, (2) effects of the endogenous opioid peptide, dynorphin A-(1–17), and its analogs in NHP, and (3) pleiotropic effects and therapeutic applications of KOR-related ligands. In particular, synthetic ligands targeting the KOR have been extensively studied in NHP in three therapeutic areas, i.e., the treatment for itch, pain, and substance use disorders. As the KORs are widely expressed in the peripheral and central nervous systems, pleiotropic effects of KOR-related ligands, such as discriminative stimulus effects, neuroendocrine effects (e.g., prolactin release and stimulation of hypothalamic-pituitary-adrenal axis), and diuresis, in NHP are discussed. Centrally acting KOR agonists are known to produce adverse effects including dysphoria, hallucination, and sedation. Nonetheless, with strategic advances in medicinal chemistry, three classes of KOR-related agonists, i.e., peripherally restricted KOR agonists, mixed KOR/mu opioid receptor partial agonists, and G protein-biased KOR agonists, warrant additional NHP studies to improve our understanding of their functional efficacy, selectivity, and tolerability. Pharmacological studies in NHP which carry high translational significance will facilitate future development of KOR-based medications.

Keywords

Analgesics; Antipruritics; Drug abuse; Itch; Kappa opioid receptor; Macaque; Mu opioid receptor; Neuroendocrine function; Opioids; Pain; Spinal cord

1 The Dynorphin-Kappa Opioid Receptor System

In 1975, Avram Goldstein and his colleagues isolated and purified an endogenous opioid peptide named dynorphin A, a 17 amino acid polypeptide (Cox et al. 1975; Goldstein et al. 1981; Teschemacher et al. 1975). This peptide was described as “extraordinarily potent” (“dyn” from the Greek, dynamis (power) and “orphin” for endogenous morphine peptide)

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(Goldstein et al. 1981). Almost two decades later, the cognate receptor for this peptide family, i.e., kappa opioid receptor (*KOR*) (Cox et al. 2015), was cloned by different groups of investigators from rodents and humans (Meng et al. 1993; Yasuda et al. 1993; Zhu et al. 1995). Similar to the mu opioid receptor (*MOR*), the KOR is coupled to pertussis toxin-sensitive Gi/o proteins which inhibit adenylate cyclase and modulate the conductance of voltage-gated calcium channels and inward rectifying potassium channels (Bruchas and Chavkin 2010; Meng et al. 1993; Yasuda et al. 1993).

In the past few years, Positron Emission Tomography (*PET*) radiotracers for the KOR have been developed (Kim et al. 2013; Li et al. 2019). Although these newly developed KOR agonist and antagonist tracers do not have ideal selectivity at KOR over MOR and displayed binding discrepancies (Placzek et al. 2019), radiotracers for PET imaging of the KOR are valuable tools to investigate the functional roles of KOR and endogenous dynorphins in humans under different disease states, such as mood disorders and substance abuse disorders (de Laat et al. 2020). The dynorphin-KOR system has been extensively studied in the past four decades. Several articles have provided a comprehensive overview about the biological actions, medicinal chemistry, pharmacology, and therapeutic applications of this ligand-receptor system (Butelman and Kreek 2015; Chavkin and Koob 2016; Cunningham et al. 2011; Tejeda and Bonci 2019). Given a similar distribution of the KOR between human and NHP central nervous system (Peckys and Landwehrmeyer 1999; Sim-Selley et al. 1999; Simonin et al. 1995), this review highlights the functional profiles of KOR-related ligands in non-human primates (*NHP*). In particular, we discuss the therapeutic potential of KOR-related ligands based on findings from NHP studies which may facilitate the development of KOR-targeted ligands for different therapeutic applications.

2 Effects of Dynorphins in Non-human Primates

Dynorphins in different chain lengths have been administered through different delivery routes to characterize their functional roles in NHP. Following intravenous administration, dynorphin A-(1–17) decreased food-maintained operant behavior which was not mediated by KOR. Unlike the prototypical KOR agonist U69,593 producing antinociception, systemic dynorphin A-(1–17) produced mild antinociceptive effects (Butelman et al. 1999c). Nonetheless, both dynorphin A-(1–17) and U69,593 increased serum levels of prolactin and such neuroendocrine effects were antagonized by an opioid antagonist quadazocine (Butelman et al. 1999c). These findings suggest that systemic dynorphin A-(1–17) produced both opioid and non-opioid effects in NHP. On the other hand, dynorphin A-(1–17) coadministered with capsaicin into the tail of the monkey produced peripheral antiallodynic effects, which could be blocked by a KOR antagonist (Ko et al. 2000). This early study provides the first functional evidence that activation of peripheral KORs in primates could be a viable therapeutic target for alleviating peripherally elicited pain. Indeed, KORs are present in rodent and human dorsal root ganglion (*DRG*) neurons and dynorphin A-(1–17) suppressed evoked Ca^{2+} transient in human DRG neurons (Ji et al. 1995; Moy et al. 2020; Snyder et al. 2018).

Unlike β-endorphin, intrathecal administration of dynorphin A-(1–17) did not produce antihyperalgesic effects in NHP. Nevertheless, dynorphin A-(1–17) dose-dependently

attenuated robust itch scratching responses elicited by intrathecal β-endorphin and gastrin-releasing peptide (Lee and Ko 2015). The inhibitory effect of dynorphin A-(1–17) on centrally elicited scratching supports the notion that patients suffering from chronic itch may have a decreased activity of the endogenous dynorphin-KOR system (Inan and Cowan 2005; Kardon et al. 2014). Importantly, a recent study demonstrates that plasma dynorphin A-(1–17) level inversely correlated with the pruritus severity in patients with chronic liver disease (Moniaga et al. 2019). These findings document a pivotal role of the dynorphin-KOR system in regulating itch sensation.

As noted, the effects of dynorphin A-(1–13) were also studied, but not as extensively as dynorphin A-(1–17). Intravenous administration of dynorphin A-(1–13) produced antinociception which was due to its partial KOR agonist activities (Butelman et al. 1995). Subcutaneous administration of dynorphin A-(1–13) with local capsaicin injection in the NHP tail also produced antiallodynic effects (Ko et al. 1999a). In addition, a synthetic dynorphin A-(1–8) analog, E-2078, was found to be stable without biotransformation products in human and NHP blood samples (Yu et al. 1997). Subcutaneous or intramuscular administration of E-2078 did not produce antinociception in NHP. Following intravenous administration, E-2078 produced non-KOR-mediated antinociceptive effects (Butelman et al. 1999d). Interestingly, E-2078 produced other KOR-mediated effects, including diuresis, sedation, KOR agonist-like discriminative effects, and increased serum prolactin levels (Butelman et al. 2004, 1999b). Overall, dynorphin A-(1–17) and E-2078 did not produce equivalent antinociceptive effects to non-peptidic KOR agonists, except with local administration peripherally. Thus, although dynorphin A-(1–17) and E-2078 produced other KOR-mediated effects, their functional profiles are not identical to prototypical, synthetic KOR agonists, U50,488 and U69,593, across different outcome measures in NHP. Future studies are warranted to determine whether metabolism (e.g., dynorphin A-(2–17)), site of action, degree of CNS exposure, and other mechanisms (e.g., *N*-methyl-D-aspartate receptor) contribute to non-opioid effects of dynorphin A-(1–17) and E-2078.

Mounting evidence indicates that the dynorphin-KOR system is involved in negative affect derived from pain, drug abuse, and neuropsychiatric disorders (Koob and Volkow 2016; Liu et al. 2019; Massaly et al. 2019; Tejeda and Bonci 2019). It is important to investigate how elevated dynorphin level in the supraspinal regions modulates behavior and mood in humans and NHP. With the advance of surgical techniques, an intrathecal catheter can be implanted and placed in the cisterna magna of NHP for supraspinal drug delivery (Ding et al. 2015). The intracisternal administration of neuropeptides mimics the “volume transmission” of endogenous peptides transported to multiple sites in the brain (Veening et al. 2012). Future NHP studies with intracisternal administration of dynorphin A-(1–17) may improve our understanding of the supraspinal dynorphin-KOR system and the functional efficacy of KOR antagonists for modulating dynorphin-mediated effects in primates under different states.

To our knowledge, synthetic ligands targeting the KOR have been extensively studied in NHP as potential treatments in three therapeutic areas, i.e., for (1) itch (pruritus), (2) pain, and (3) substance use disorders. As the KOR is widely expressed in the peripheral and central nervous systems of humans and NHP (Peckys and Landwehrmeyer 1999; Sim-Selley

et al. 1999; Simonin et al. 1995), we also highlight the pleiotropic effects of KOR-related ligands in NHP.

3 Kappa Opioid Receptor Agonists as Antipruritics

3.1 Systemic Effects

The antipruritic effect of KOR agonists was first reported by Alan Cowan in the mid-1980s (Cowan and Gmerek 1986). The KOR seems a prominent therapeutic target for inhibiting itch because a series of rodent studies demonstrate that systemic administration of KOR agonists attenuated pruritogen-elicited scratching behavior (Cowan et al. 2015; Cowan and Ko 2020; Gmerek and Cowan 1984). That this response was consistent across chemical series confirmed that it was a property of KOR agonists and not compound specific.

One key relevant finding was that scratching behavior was a prominent withdrawal sign in NHP treated chronically with and withdrawn from a selective KOR agonist, U50,488 (Gmerek et al. 1987). Many withdrawal symptoms from opioids appear to be opposite to the acute effects of agonist administration (Ding et al. 2016; Ko et al. 2006; Martin and Eades 1964). Excessive scratching activity observed in NHP during withdrawal from the KOR agonist treatment suggests that acute administration of KOR agonists might have antipruritic effects. The first NHP study seemed to support this notion, as systemic administration of U50,488 dose-dependently prevented or attenuated morphine-induced scratching without inducing sedation (Ko et al. 2003b). Other NHP studies further demonstrated that non-antinociceptive doses of KOR agonists, such as nalfurafine, bremazocine, and GR89,696, attenuated intrathecal morphine-induced scratching without interfering with antinociception, supporting the potential clinical use of KOR agonists as antipruritics in the context of spinal opioid analgesia (Ko and Husbands 2009; Wakasa et al. 2004). Interestingly, systemic butorphanol, an opioid partial agonist, effectively blocked morphine-induced itch while maintaining morphine analgesia, through both MOR and KOR partial agonist actions (Lee et al. 2007). These findings encourage the development of opioid partial agonists with dual actions at both MOR and KOR as analgesics with fewer side effects.

More importantly, these animal studies led to a successful clinical trial of nalfurafine in hemodialysis patients suffering from uremic pruritus (Wikstrom et al. 2005). In 2009, nalfurafine was approved for clinical use as an antipruritic in Japan (Kumagai et al. 2012, 2010). However, antipruritic efficacy of a KOR agonist may be compromised by its narrow therapeutic window following systemic administration, i.e., its therapeutic effect could be associated with supraspinal KOR-mediated adverse effects, such as dysphoria and sedation (Butelman et al. 2001; Ko et al. 1999b; Pfeiffer et al. 1986). Recently, a G protein-biased KOR agonist, triazole 1.1, has been demonstrated to suppress scratching behavior without causing sedation and dysphoria in mice (Brust et al. 2016). Systemic triazole 1.1 at a single dose partially attenuated oxycodone-induced scratching without producing sedation and motor-impairing effects in NHP (Huskinson et al. 2020). It is important to have a side-by-side comparison with nalfurafine over a wide dose range to determine to what degree the therapeutic window of triazole 1.1 is wider than nalfurafine across different KOR-mediated effects in NHP.

Another viable strategy is to develop peripherally acting KOR agonists (Cowan et al. 2015). Although such agonists have not been studied in NHP models of itch, a recently completed phase 3 trial report showed that treatment with intravenous CR845 (difelikefalin), a peripherally restricted KOR agonist, for 12 weeks resulted in a marked and rapid reduction in itch intensity and improved itch-related quality of life in hemodialysis patients with chronic kidney disease-associated pruritus, compared with placebo treatment (Fishbane et al. 2020). These treatment outcomes are very encouraging as there were no adverse events of dysphoria and hallucination reported in the difelikefalin group. It is crucial for NHP experiments to investigate and compare the functional efficacy and side-effect profiles of nalfurafine, triazole 1.1, and difelikefalin against peripherally versus centrally elicited itch in a broader context as general antipruritics.

3.2 Intrathecal Effects

Given that the spinal delivery of drugs could minimize the degree of supraspinal KOR-mediated adverse effects, intrathecal administration of KOR-related agonists may change the therapeutic window. Recent studies demonstrate that a subpopulation of spinal interneurons expressing dynorphin A tonically inhibits itch in mice (Kardon et al. 2014). However, intrathecal administration of dynorphin A only partially attenuated scratching activities elicited by intrathecal β-endorphin (Lee and Ko 2015), indicating that there are other ligand-receptor systems in the spinal cord regulates MOR-mediated itch. In general, both NHP and human studies support that mixed MOR/KOR partial agonists are effective in ameliorating spinal opioid-induced itch while maintaining spinal opioid-induced analgesia (Ko 2015).

Despite these exciting findings, the functional efficacy, selectivity, and tolerability of KOR-related agonists as spinal antipruritics in NHP remain unknown. MOR antagonists and gastrin-releasing peptide receptor antagonists are selective antipruritics because both classes of drugs are effective in alleviating central MOR- and gastrin-releasing peptide receptor-mediated itch, respectively (Ding et al. 2015; Lee and Ko 2015). If KOR agonists are found to be effective against peripherally and centrally elicited itch in NHP, such pharmacological evidence will facilitate the development of KOR-related ligands as *spinal antipruritics* and may benefit a large population of patients affected by different types of itch.

4 Kappa Opioid Receptor Agonists as Analgesics

4.1 Centrally Acting Kappa Opioid Receptor Agonists

Ample evidence indicates that KOR-related agonists exert antinociceptive and anti-hypersensitive effects in rodents against a variety of pain modalities (Vanderah 2010; Zöllner and Stein 2007). The first NHP study documents that KOR agonists such as U50,488 produced antinociceptive effects manifested by increased tail-withdrawal latencies to acute noxious stimulus, 50 °C water (Dykstra et al. 1987). However, these antinociceptive doses of KOR agonists also produced stupor and discriminative stimulus effects, indicating that observed antinociception is accompanied by KOR-mediated interoceptive effects such as dysphoria and psychotomimesis (Chavkin and Koob 2016; Clark and Abi-Dargham 2019; Pfeiffer et al. 1986). Subsequently, numerous NHP studies have reported similar findings, i.e., doses of KOR agonists alleviating acute pain also produced sedation, which were

higher than doses that produced discriminative stimulus effects (Butelman et al. 2001, 1993; Ko et al. 1998; Negus et al. 2008). Although KOR agonists are relatively more potent in attenuating capsaicin-induced allodynia and carrageenan- evoked inflammatory pain than acute noxious stimulus (Butelman et al. 2003; Ko et al. 1999a; Sukhtankar et al. 2014), the antiallodynic potency of KOR agonists is similar to their potency in producing discriminative stimulus effects (Butelman et al. 2002; Dykstra et al. 1987). Future studies are warranted to investigate if G protein-biased KOR agonists could display a window between antiallodynic doses and doses eliciting negative interoceptive effects in NHP.

4.2 Peripherally Acting Kappa Opioid Receptor Agonists

The functional efficacy and side-effect profile of peripherally acting KOR agonists have been demonstrated in animal models and in clinical trials (Albert-Vartanian et al. 2016; Little 2013). The most promising peptidic KOR agonist difelikefalin, which is highly hydrophilic, limiting its ability to cross the blood-brain barrier, has shown its analgesic efficacy in hysterectomy and bunionectomy patients without sedation and hallucination. As noted, like any other KOR agonists, difelikefalin increases urine output and prolactin release in humans (Albert-Vartanian et al. 2016). To our knowledge, there is no published NHP study on difelikefalin.

ICI204,448 is the only peripherally acting KOR agonist that has been studied in NHP models. Similar to spiradoline, a centrally acting KOR agonist from the same structural family, ICI204,448 dose-dependently prolonged the food pellet retrieval latency, caused sedation, and increased prolactin levels. These findings suggest that not all the in vivo effects of systemic ICI204,448 are necessarily mediated peripherally in NHP (Butelman et al. 1999b). Nonetheless, it is pivotal to conduct NHP studies to characterize the functional efficacy of peripherally restricted KOR agonists like difelikefalin against different pain modalities and the potential therapeutic window by using well-documented central and peripheral KOR-mediated outcome measures (Butelman et al. 1999b, 2001; Ko et al. 1999b).

5 Kappa Opioid Receptor-Related Ligands for the Treatment of Substance Use Disorders

5.1 Effects of Kappa Opioid Receptor-Related Agonists

Given that KORs are expressed at numerous sites in the reward neurocircuitry and activation of KORs inhibited dopamine release in the nucleus accumbens (Darcq and Kieffer 2018; Spanagel et al. 1992) and medial prefrontal cortex (Tejeda et al. 2013), KOR agonists are expected to attenuate the rewarding and reinforcing effects of abused drugs. Indeed, across different operant schedules of reinforcement, KOR agonists reduced self-administration of drug and non-drug reinforcers in NHP (Cosgrove and Carroll 2002; Negus et al. 1997). However, food-maintained responding was usually decreased at doses that decreased drug self-administration, indicating lack of selectivity between drugs of abuse and natural rewards (Cosgrove and Carroll 2002; Mello and Negus 1998).

Both MOR and KOR are dynamically involved in drug abuse, dependence, and relapse (Darcq and Kieffer 2018; Karkhanis et al. 2017). Given that MOR and KOR agonists produce opposing effects on dopaminergic neurons (e.g., euphoria versus dysphoria) (Darcq and Kieffer 2018; Freeman et al. 2014; Negus et al. 2008), a viable strategy is to develop compounds with mixed KOR/MOR agonist activities as a treatment option for substance use disorders (Bidlack and Knapp 2013; Greedy et al. 2013). A cyclazocine analog, 8-carboxamidocyclazocine, with mixed KOR/MOR agonist actions, produced only mild sedation, but it did not show improved selectivity for inhibiting cocaine-versus food-maintained responding in NHP (Stevenson et al. 2004). However, another study reported that other mixed KOR/MOR agonists such as MCL-101 produced selective and sustained decreases in cocaine self-administration (Bowen et al. 2003). The efficacies of these mixed KOR/MOR agonists at the MOR relative to buprenorphine are not clear. Nonetheless, it is known that the mild-to-moderate reinforcing effects of buprenorphine, a low-efficacy partial MOR agonist, can be decreased by activating additional receptors such as nociceptin/orphanin FQ peptide receptors (NOR) (Ding et al. 2016). Compounds with mixed NOR/MOR low-efficacy partial agonist activities display improved side-effect profiles and effectively block drug abuse-related effects in NHP (Ding et al. 2018; Flynn et al. 2019; Kiguchi et al. 2019). In a similar approach, future studies using compounds with mixed KOR/MOR *low-efficacy* partial agonist activities in different ratios of efficacy at KOR versus MOR will advance our understanding of the functional role of KOR in modulating reinforcing effects of abused drugs.

Another viable strategy is to develop G protein signaling-biased KOR agonists. Effects of triazole 1.1 (Brust et al. 2016) alone and against the reinforcing effects of abused drugs have not been studied in NHP yet. As both MOR and KOR oppositely modulate dopaminergic neurons (Darcq and Kieffer 2018; Spanagel et al. 1992), it is important to know if G protein-biased MOR and KOR agonists have decreased euphoric and dysphoric effects, respectively. Two reported G protein-biased MOR agonists such as TRV130 and PZM21 produced oxycodone-like reinforcing effects in rodents and NHP (Ding et al. 2020; Zamarripa et al. 2018), indicating that biasing an agonist towards G protein signaling pathways does not change MOR-dopamine receptor-mediated interoceptive effects. As noted, the in vitro assay amplification and the degree of biased agonism may confound how investigators determine which ligands are biased enough (Gillis et al. 2020). Whether such G protein-biased signaling would change KOR-dopamine receptor-mediated interoceptive effects remains to be determined. Intriguingly, low intrinsic efficacy for G protein activation may also contribute to an improved side-effect profile of G protein-biased MOR agonists (Azevedo-Neto et al. 2020; Gillis et al. 2020). It is pivotal to further investigate the similarities and differences between triazole 1.1 and KOR agonists with partial versus full efficacy in NHP.

5.2 Effects of Kappa Opioid Receptor Antagonists

Mounting evidence shows that enhanced KOR signaling during drug dependency and withdrawal may contribute to the anhedonic component of the addiction process, indicating that KOR antagonists may show greater therapeutic effects than agonist-based treatments (Chavkin and Koob 2016; Karkhanis et al. 2017). To our knowledge, there are only

two NHP studies conducted to examine the effectiveness of the KOR antagonist, nor-binaltorphimine (norBNI), against drug abuse-related effects. Acute injection of norBNI at a single dose of 3 mg/kg (30 min before the session) reduced ethanol-reinforced responding and ethanol intake (Williams and Woods 1998). However, on the next day, ethanol intake returned to levels similar to those at baseline or after saline pretreatment (Williams and Woods 1998). Given the long duration of KOR antagonism by norBNI extending to several weeks in NHP (Butelman et al. 1998; Ko et al. 1999b), its acute attenuation of ethanol intake may not be mediated via KOR blockade. The other NHP study shows that norBNI did not alter cocaine choice or extended-access cocaine intake (Hutsell et al. 2016). In the past decade, several short-acting selective KOR antagonists have been synthesized and characterized (Carroll and Carlezon Jr. 2013; Guerrero et al. 2019). Currently, there are numerous human studies initiated to investigate the therapeutic potential of KOR antagonists. A recent human study shows that an orally active KOR antagonist, CERC-501 (also called LY-2456302, JNJ-67953964, and aticaprant), did not affect cigarette craving, nicotine withdrawal, and subjective effects of smoking, indicating ineffectiveness of CERC-501 in the treatment of nicotine use disorder (Jones et al. 2020). To date, there are no positive findings from NHP or human studies regarding the functional efficacy of KOR antagonists in the context of substance use disorder-related endpoints. Nonetheless, future studies may explore the functional efficacy of newly developed KOR antagonists in NHP under different states (e.g., withdrawal and relapse) (Gerak et al. 2016; Kiguchi et al. 2020; Ko et al. 2006).

6 Pleiotropic Effects of Kappa Opioid Receptor-Related Ligands

As the KOR is widely expressed in the central and peripheral nervous systems (Ko et al. 2003a; Peckys and Landwehrmeyer 1999; Sim-Selley et al. 1999), it is not surprising that KOR agonists and antagonists produce pleiotropic effects in NHP and humans. Other than the abovementioned antipruritic and analgesic effects and as a potential treatment for substance use disorders, a few KOR-mediated effects in NHP are briefly discussed herein.

I. Discriminative Stimulus Effects

Early drug discrimination studies have provided convincing evidence that KOR and MOR possess distinct interoceptive effects (i.e., dysphoric/hallucinogenic versus euphoric subjective effects) in NHP (Dykstra et al. 1987; Herling and Woods 1981; Pfeiffer et al. 1986). Interestingly, in the drug discrimination assay, NHP trained to discriminate salvinorin A generalized to centrally acting KOR agonists and such effects were mediated by KORs, not serotonergic 5HT2 receptors (Butelman et al. 2010). Salvinorin A is unique pharmacologically and chemically as it represents the first non-nitrogenous, naturally occurring KOR-selective agonist and the only known non-alkaloidal hallucinogen (Roth et al. 2002). Salvinorin A-containing products have been widely used for non-medical purposes and its related analogs in a new scaffold may lead to future development for KOR-based pharmacotherapy (Butelman and Kreek 2015; Roach and Shenvi 2018).

II. Sedation

Early NHP studies also find that sedation is a common adverse effect associated with KOR agonists (Dykstra et al. 1987). KOR agonist-induced sedation was mediated by supraspinal KORs, as intracisternal pretreatment with a long-acting KOR antagonist norBNI fully blocked such an effect for more than 4 weeks (Ko et al. 1999b). Centrally acting KOR agonists generally produce more robust sedation than peripherally acting KOR agonists, mixed KOR/MOR partial agonists, and agonists selective for other opioid receptor subtypes (Butelman et al. 1999b; Lee et al. 2007; Podlesnik et al. 2011; Sukhtankar et al. 2014). It will be important to determine and compare the electroencephalographic profiles at analgesic doses derived from different classes of opioid analgesics in NHP and humans (Malver et al. 2014).

III. Neuroendocrine Effects

Prolactin release from the anterior pituitary is under tonic inhibition by hypothalamic dopaminergic systems and KOR agonists increase prolactin levels by suppressing these dopaminergic neurons (Durham et al. 1996; Ur et al. 1997). Importantly, NHP studies find that increased serum prolactin level is a sensitive and quantitative neuroendocrine endpoint for the apparent efficacy of KOR agonists (Butelman et al. 1999a). As its site of action may be outside of the blood- brain barrier, prolactin release could be sensitive to the action of peripherally restricted KOR agonists (Butelman et al. 1999b). Indeed, all KOR-targeted agonists (i.e., peptides, centrally penetrating, and peripherally restricted agonists) increased the serum prolactin levels in NHP and humans (Albert-Vartanian et al. 2016; Butelman et al. 2001, 2002, 2004).

KOR agonists are also known to increase adrenocorticotropic hormone (ACTH) and cortisol levels in humans (Ur et al. 1997). A selective KOR agonist, U50,488, dose-dependently stimulates ACTH and cortisol release in both male and female NHP (Pascoe et al. 2008). This study demonstrates only KOR agonists, not MOR or delta opioid receptor agonists, can stimulate the hypothalamic-pituitary-adrenal axis activity. Unexpectedly, a KOR antagonist, norBNI, caused mild-to-moderate increases in ACTH and cortisol with unknown receptor mechanisms in NHP (Williams et al. 2003). As the stimulation of hypothalamic-pituitary-adrenal axis is highly associated with stress-related disorders (Ehlert et al. 2001; Stephens and Wand 2012), future NHP and human studies are warranted to investigate the potential adverse consequences from repeated use of KOR-related ligands including both agonists and antagonists.

IV. Diuresis

Human studies have documented the diuretic effects of KOR agonists (Albert-Vartanian et al. 2016; Peters et al. 1987; Reece et al. 1994). Similarly, KOR agonists potently increased the urine output in NHP (Butelman et al. 2001, 1999d; Dykstra et al. 1987). Pretreatment with intracisternal norBNI significantly blocked KOR agonist-induced diuresis in NHP for 20 weeks, indicating central KOR-mediated diuresis (Ko et al. 2003c). Further evidence suggests the sites of KOR-mediated diuresis could be both inside and outside of the blood-brain barrier, as more peripherally restricted KOR agonists also produce diuretic effects (Albert-Vartanian et al. 2016; Butelman et al. 1999d).

V. Other Effects

KOR agonists have other therapeutic applications such as cardio-protection, anti-inflammation, neuroprotection, and potential treatment for multiple sclerosis (Beck et al. 2019). In addition, KOR antagonists have been proposed and developed as potential therapeutics for neuropsychiatric disorders such as depression and schizophrenia (Clark and Abi-Dargham 2019; Jacobson et al. 2020; Zhang et al. 2007). Although NHP researchers did not study these listed effects, such effects illustrate a vast diversity of potential therapeutics from KOR-related ligands.

7 Conclusion

Taken together, pharmacological profiles of KOR-related agonists in NHP have shown therapeutic potentials for treating itch, pain, and drug abuse. Figure 1 illustrates the functional profiles of four different classes of KOR-related ligands based on NHP and human studies. NHP models offer the most phylogenetically appropriate evaluation of opioid and non-opioid receptor functions and drug effects (Chen et al. 2013; Lin and Ko 2013; Phillips et al. 2014). We have often seen that exciting findings from rodents cannot be translated to primates. For example, a newly discovered G protein signaling-biased MOR agonist, PZM21, did not exert rewarding effects in mice (Manglik et al. 2016), while others found it to induce respiratory depression and develop tolerance to its analgesic effects (Hill et al. 2018). However, PZM21 produced oxycodone-like reinforcing effects and strength, i.e., the same degree of abuse liability, in NHP (Ding et al. 2020). With recent strategic advances in medicinal chemistry, three classes of KOR-related ligands, i.e., G protein-biased KOR agonists, mixed KOR/MOR partial agonists, and peripherally restricted KOR agonists, warrant additional NHP studies to improve our understanding of their functional efficacy, selectivity, and tolerability. Pharmacological studies in NHP will continue to provide a translational bridge and facilitate future drug development of KOR-based medications.

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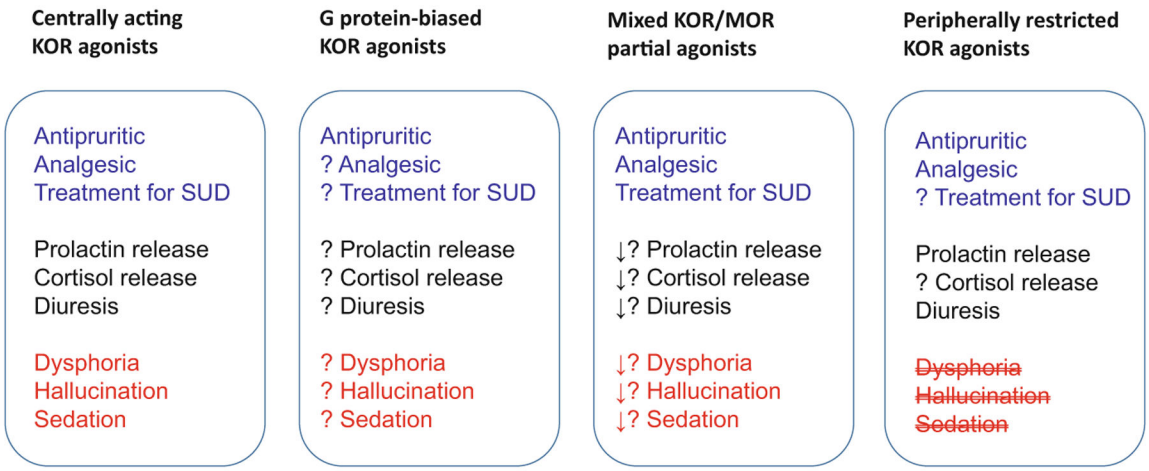

Fig. 1.

Simplified scheme to compare functional profiles of kappa opioid receptor-related ligands based on NHP and human studies. Noted, ? to be determined, ↓ decreased effect