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Translational value of non-human primates in opioid research

Huiping Ding, **Mei-Chuan Ko**
Department of Physiology & Pharmacology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

Abstract

Preclinical opioid research using animal models not only provides mechanistic insights into the modulation of opioid analgesia and its associated side effects, but also validates drug candidates for improved treatment options for opioid use disorder. Non-human primates (NHPs) have served as a surrogate species for humans in opioid research for more than five decades. The translational value of NHP models is supported by the documented species differences between rodents and primates regarding their behavioral and physiological responses to opioid-related ligands and that NHP studies have provided more concordant results with human studies. This review highlights the utilization of NHP models in five aspects of opioid research, i.e., analgesia, abuse liability, respiratory depression, physical dependence, and pruritus. Recent NHP studies have found that (1) mixed mu opioid and nociceptin/orphanin FQ peptide receptor partial agonists appear to be safe, non-addictive analgesics and (2) mu opioid receptor- and mixed opioid receptor subtype-based medications remain the only two classes of drugs that are effective in alleviating opioid-induced adverse effects. Given the recent advances in pharmaceutical sciences and discoveries of novel targets, NHP studies are posed to identify the translational gap and validate therapeutic targets for the treatment of opioid use disorder. Pharmacological studies using NHPs along with multiple outcome measures (e.g., behavior, physiologic function, and neuroimaging) will continue to facilitate the research and development of improved medications to curb the opioid epidemic.

Keywords

Analgesia; Drug abuse; Itch; Macaque; Nociceptin/Orphanin FQ; Opioid receptor; Physical dependence; Respiratory depression; Spinal cord

1. Introduction

Recent marked increase in misuse and abuse of prescription and illicit opioids and the epidemic of opioid overdose mortality have unprecedentedly affected the United States

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[*]Corresponding author: Mei-Chuan Ko, Ph.D., Department of Physiology & Pharmacology, Wake Forest School of Medicine, 205 NRC, Medical Center Boulevard, Winston-Salem, NC 27157, USA. mko@wakehealth.edu (M.C. Ko).

Conflict of Interest
H.D. and M.C.K. declare that there is no conflict of interest.

(Brady et al., 2016; Volkow and Blanco, 2020). Although mu opioid peptide (**MOP**) receptor agonists remain the most widely used analgesics, their adverse effects such as abuse liability and respiratory arrest have contributed to escalating medical and economic burdens in the global community (Degenhardt et al., 2014; Rudd et al., 2016). Several scientific strategies have been initiated to develop safe and effective medications for pain and opioid addiction, indicating an urgent and unmet need for the treatment of opioid use disorder (Volkow and Blanco, 2020; Volkow and Collins, 2017).

Based on the International Union of Basic and Clinical Pharmacology Nomenclature Committee, there are four opioid receptor subtypes, i.e., MOP, delta opioid peptide (**DOP**), kappa opioid peptide (**KOP**), and nociceptin/orphanin FQ peptide (**NOP**) receptors, in the opioid receptor family (Cox et al., 2015). Although the NOP receptor is considered a subcategory of the opioid receptor family due to its atypical low affinity for the classical endogenous opioid peptides and insensitivity to naloxone antagonism, all four receptors share similar signal transduction pathways. These four receptors are 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 (Al-Hasani and Bruchas, 2011). However, these receptor subtypes have different anatomical distributions in the central nervous system. Other than shared therapeutic benefit analgesia, they exhibit distinct functional roles in regulating physiological functions and mood (Gavioli et al., 2019; Lutz and Kieffer, 2013; Mansour et al., 1988; Tejeda and Bonci, 2019).

This review highlights the functional profiles of opioid receptor-related ligands in non-human primates (**NHPs**). In specific, we discuss species differences in pharmacological profiles of opioid-related ligands between rodents and NHPs; and we summarize how NHP models are used to evaluate novel experimental compounds' functional profiles and efficacies to modulate MOP receptor agonist-associated adverse effects including abuse potential, respiratory depression, physical dependence, and pruritus.

2. Species differences between rodents and primates

NHPs, such as rhesus macaques (*Macaca mulatta*), cynomolgus macaques (*Macaca fascicularis*), vervet monkeys (*Chlorocebus aethiops sabaeus*), marmosets (*Callithrix jacchus*), and squirrel monkeys (*Saimiri sciureus*), are used as essential animal models in biomedical research due to their close genetic, physiological and behavioral similarities to humans when compared with other commonly used rodent models (Phillips et al., 2014). In particular, rhesus macaques play a critical role in modeling human diseases and biological responses that are not well simulated in rodents (Liao and Zhang, 2008; Seok et al., 2013). First whole-genome analysis of rhesus macaques revealed fundamental genetic similarities to the human genome (Rhesus Macaque Genome et al., 2007). Recently updated macaque reference genome assembly and annotation will advance the biomedical utility of rhesus macaques and facilitate the development of new genetic NHP models of human diseases (Warren et al., 2020). NHP brain and cellular imaging techniques further promote exciting opportunities to compare brain structure and neuro-connectivity and to study the neurobiological influence of chronic drug use for the translational impact (Izpisua Belmonte et al., 2015; Macknik et al., 2019). For instance, magnetic resonance imaging-based methodologies demonstrate that a large number of human and macaque striatal voxels were not matched to any mouse cortico-striatal circuit (e.g., mouse->human: 85% unassigned) (Balsters et al., 2020). In addition, positron emission tomography (PET) neuroimaging in NHPs defines in vivo biodistribution and pharmacokinetics of abused drugs and drug interactions. The longevity and complex social behaviors of NHPs and their similar drug metabolism to humans make PET imaging a powerful tool to conduct longitudinal translational studies in drug abuse research (Banks et al., 2017; Howell and Murnane, 2011). Furthermore, due to the similar functions of the hypothalamic-pituitary axis between macaques and humans, the effects of opioid use and stress on neuroendocrine functions could be modeled in NHPs (Fountas et al., 2018; Meyer and Hamel, 2014). For example, KOP receptor agonists increased the levels of prolactin, adrenocorticotropic hormone and cortisol in both NHPs and humans (Butelman et al., 2004a; Ko and Husbands, 2020; Pascoe et al., 2008; Ur et al., 1997).

Evidently, species differences contributes to different results and interpretations regarding the receptor functions and drug effects. For instance, functional outcomes of drugs targeting serotonin system and neurobiology of serotonin receptors are markedly different between rats and NHPs (Li et al., 2010). There is now an extensive body of literature documenting that neuroanatomical, neurochemical, and neuropharmacological aspects of opioid and non-opioid receptors are comparable between humans and NHPs (Bianchi et al., 2012; Hawkinson et al., 2007; Phillips et al., 2014; Yu et al., 2019). In addition, humans and NHPs have the same thresholds for detecting a variety of stimuli and the nervous systems responsible for the somatosensory functions in the two species are fundamentally similar (Courtine et al., 2007; Kenshalo et al., 1989; LaMotte and Campbell, 1978; Rozsa et al., 1985). While rodent studies play a pivotal role in discovering novel targets as potential therapeutics, NHP studies establish a translational bridge toward human studies.

Rhesus macaques have been used for behavioral and pharmacological studies on opioids for more than five decades (Ding et al., 2020; Goldberg et al., 1969; Thompson and Schuster, 1964). Mounting evidence indicates that humans and NHPs have similar responses to opioid-related ligands (Lin and Ko, 2013; Mello et al., 1993; Woods and Winger, 1987). However, there are many examples that behavioral and physiological responses to opioid-related ligands in rodents cannot be translated to NHPs. Herein we briefly discuss four ligands to illustrate a translational gap.

First, a major metabolite of naltrexone, 6β-naltrexol, was demonstrated as a neutral MOP receptor antagonist in mice (Raehal et al., 2005). Unlike classic opioid antagonist naloxone, neutral antagonists do not alter basal MOP receptor signaling and could be used to block MOP receptor-medicated agonist and inverse agonist actions (Connor and Traynor, 2010; Wang et al., 2001). 6β-naltrexol did not significantly precipitate withdrawal in morphine-dependent mice and it reduced naloxone-precipitated withdrawal signs in mice (Raehal et al., 2005). In contrast, 6β-naltrexol precipitated withdrawal in morphine-dependent NHPs and it enhanced naltrexone-precipitated withdrawal symptoms in NHPs (Ko et al., 2006a). These findings indicate that the constitutive activities of the MOP receptor are different between rodents and primates and no neutral MOP receptor antagonist has yet been found in primates. Second, in searching for alternatives to buprenorphine, BU72 was identified with high affinity and efficacy for MOP receptors and it displayed a wide window between antinociception and respiratory depression in mice (Neilan et al., 2004). However, the antinociceptive dose of BU72 rapidly caused respiratory depression and arrest in NHPs, raising a safety concern that was not manifested in mice (Neilan et al., 2004). Third, while KOP receptor agonists produce antipruritic effects across species (Cowan and Ko, 2020; Inan and Cowan, 2020), a prototypical KOP receptor antagonist, nor-binaltorphimine, elicited robust scratching responses in mice, indicating a tonic inhibition of itch by endogenous KOP dynorphins (Kamei and Nagase, 2001; Kardon et al., 2014). In contrast, nor-binaltorphimine did not elicit scratching responses in NHPs following systemic and intrathecal administration (Ko et al., 2003; Lee et al., 2007), indicating different tonic activities of endogenous dynorphins between rodents and primates. Fourth, a NOP receptor-selective antagonist, J-113397, enhanced buprenorphine-induced antinociception in mice, indicating that activation of NOP receptors counteracted MOP receptor-mediated antinociception (Lutfy et al., 2003). However, J-113397 did not modulate buprenorphine-induced antinociception in NHPs. Instead, NOP receptor agonists synergistically enhanced MOP receptor agonist-induced antinociception in different NHP pain models (Cremeans et al., 2012; Hu et al., 2010). These findings clearly indicate that NOP receptor activation has opposite pain modulation between rodents and primates. Collectively, these examples pinpoint a critical need of NHP models to validate the functional profiles of ligand-receptor systems discovered in rodents and translate the therapeutic profiles of newly developed compounds to future human studies.

3. Analgesia

3.1. NHP pain models

In order to evaluate the analgesic effects of opioids, NHP researchers commonly use the warm water tail-withdrawal assay (Dykstra and Woods, 1986), which is similar to thermal stimuli used in rodents (Deuis et al., 2017), for basic pharmacological explorations. However, this assay is not highly relevant to human clinical pain, as it measures an evoked response from a noxious stimulus, i.e., sensory dimension with minimum affective component. In contrast, patients experience pain without overt stimulation. Clinical pain is multi-dimensional and accompanied by affective changes and comorbidities, a phenomenon that is not accounted for in the acute thermal nociceptive assay (Gracely et al., 1978; Mao, 2012). Nonetheless, this assay allows researchers to determine to what degree opioid-related ligands can prolong the NHP's tail-withdrawal latency and whether detected antinociceptive doses produce any adverse effects. In general, following systemic administration, MOP receptor agonists produced thermal antinociceptive effects, which were accompanied by respiratory depression, scratching activity, and/or disruption of food-maintained operant behavior (France et al., 1992; Ko et al., 2002b; Negus et al., 2003). KOP receptor agonists produced antinociceptive effects at doses that induced sedation, diuresis, and discriminative stimulus effects (i.e., dysphoria and psychotomimesis) (Butelman et al., 2001; Butelman et al., 1993b; Dykstra et al., 1987; Ko et al., 1999b). This finding is consistent with other studies, showing that centrally-penetrating KOP receptor agonists produced sedative and psychotomimetic effects in humans (Pfeiffer et al., 1986; Walsh et al., 2001). DOP receptor agonists could not produce antinociception; instead, causing convulsions in NHPs (Negus et al., 1998; Sukhtankar et al., 2014). NOP receptor agonists produced antinociceptive effects at doses that did not cause respiratory depression and sedation (Ko et al., 2009; Podlesnik et al., 2011). However, NOP receptor agonists did not consistently increase the NHP's tail-withdrawal latency across different groups of NHPs (Kiguchi and Ko, 2019). It is worth noting if NHPs are not well adapted to the NHP chair and the measurement of the tail-withdrawal responses, higher doses of opioid agonists are required to suppress NHP's tail-withdrawal responses. Consequently, observed antinociceptive doses of opioids are higher than clinically used doses and do not display behavioral selectivity, i.e., antinociceptive doses also suppress other behaviors (Cowan and Ko, 2020; Kiguchi and Ko, 2019). Moreover, the analgesic effects of MOP, KOP, DOP, and NOP receptor agonists against different pain modalities (e.g., mechanical and neuropathic pain) warrant further investigation.

NHP researchers further developed other pain models to better assess the analgesic action of opioids. For example, capsaicin evokes pain sensation by activating the transient receptor potential vanilloid type 1, which is implicated in humans under diverse pain states (Brito et al., 2014). Capsaicin-induced allodynia has been utilized as a pain model in humans to evaluate and distinguish the analgesic efficacy of different classes of drugs (Eisenach et al., 2000; Park et al., 1995). In similar contexts, capsaicin-induced thermal allodynia in NHPs has been used to distinguish central versus peripheral sites of action (Butelman et al., 2004b; Ko et al., 1998; 1999a; Ko and Woods, 1999) and compare the antiallodynic efficacy among opioid and non-opioid ligands (Butelman et al., 2003; Ko et al., 2002a; Ko et al., 2000). Furthermore, carrageenan causes inflammation via cyclooxygenase-1/2 enzyme-mediated prostaglandin release (Dirig et al., 1998). Carrageenan-induced inflammatory pain in NHPs lasted for more than 6 hours post-injection and it is sensitive to detect potential antihyperalgesia of nonsteroidal anti-inflammatory drugs (NSAIDs), endogenous and synthetic opioids (Lee and Ko, 2015; Sukhtankar et al., 2014). These chemical-induced pain models document that opioid-related ligands are more potent in attenuating allodynia-/hyperalgesia-like responses in NHPs and their effective doses are close to clinically used doses (Kiguchi and Ko, 2019; Sukhtankar et al., 2014).

3.2. Strategies to enhance opioid analgesia

Pharmacological studies in NHP have identified viable strategies to develop safer opioid analgesics and/or to produce opioid-sparing effect, i.e., decreasing exposure to classic MOP receptor agonists. For example, NOP receptor agonists have been demonstrated to synergistically enhance the antinociceptive effects of MOP receptor agonists without causing respiratory depression and pruritus (Cremeans et al., 2012; Hu et al., 2010). Compounds with mixed MOP/NOP receptor agonist activities potently produced antinociceptive effects with fewer side effects, such as reinforcing effects (abuse potential), respiratory depression, pruritus, physical dependence and slower tolerance development (Ding et al., 2016; Ding et al., 2018b; Kiguchi et al., 2019). More importantly, a mixed NOP/opioid receptor agonist, cebranopadol, produced effective analgesia in patients with acute or chronic pain and showed reduced side effects including lower drug-liking effect, respiratory depression, and physical dependence (Calo and Lambert, 2018; Kiguchi et al., 2020b; Tzschentke et al., 2019). These findings exemplify that NHP studies represent a translational bridge and show functional similarities of ligands with mixed MOP/NOP receptor agonist activities between NHPs and humans.

Another strategy is to combine cannabinoid-related compounds with opioid analgesics. A series of NHP pharmacological studies demonstrates that cannabinoid receptor agonists, such as CP 55,940, WIN 55,212, and Δ9-tetrahydrocannabinol, enhanced the antinociceptive effects of MOP receptor agonists (Li et al., 2008; Maguire and France, 2014; Maguire et al., 2013). Importantly, these cannabinoid receptor agonists did not increase the respiratory depressant, discriminative stimulus, and reinforcing effects of MOP receptor agonists (Li et al., 2012; Maguire and France, 2018; Maguire et al., 2013; Weed et al., 2018). These findings support the notion that cannabinoid receptor agonists may produce opioid-sparing effects, i.e., to dispense opioid medications at lower doses, in humans (Abrams et al., 2011; Cooper et al., 2018; Lynch and Clark, 2003).

3.3. Limitations and opportunities of NHP analgesic studies

The development of chronic or neuropathic pain models in NHPs using surgical procedures is limited by ethical issues. Nonetheless, behavioral pharmacological studies in NHPs allow researcher to identify which ligand-receptor systems are involved in pain processing and how they are different from or similar to findings in rodents. NHP analgesic studies have used reflex-based assays for decades. Recently, an operant-based nociceptive assay has been developed in squirrel monkeys (Kangas and Bergman, 2014). This advance provides a valuable means to study how different classes of analgesics can restore the disruptive effects of nociceptive stimuli, rather than suppression of evoked nociceptive behavior. NHP investigators also found that neuroinflammation and dysregulation of multiple ligand-receptor systems involved in pain modulation appear to be permanent in the spinal cord of naturally occurring type 2 diabetic NHPs (Ding et al., 2018a; Kiguchi et al., 2017). This NHP disease model not only opens new avenues to study the functional roles of pain and neuroinflammation mediators, but also offers a valuable opportunity to explore potential treatments for diabetic neuropathy. Furthermore, rodent studies incorporating NHP data can enhance the translational relevance. For instance, nivolumab, a programmed cell death protein-1 (PD-1) inhibitor, attenuated morphine-induced antinociception in mice and NHPs, indicating that PD-1 regulates MOP receptor signaling in nociceptive neurons and anti-PD-1 immunotherapy may diminish opioid analgesia (Wang et al., 2020a). Through the assay improvement and studying neural substrates of NHPs under different states, NHP studies integrating multiple outcome measures will facilitate the research and development of innovative analgesics.

4. Abuse liability

Prescription and illicit opioids, primarily MOP receptor agonists, produce euphoria and are widely abused in our society. In the past few decades, the intravenous drug self-administration procedure is considered a gold standard to evaluate a drug’s abuse liability (i.e., reinforcing effect and strength) and potential medications for substance use disorders (Ator and Griffiths, 2003; Mello and Negus, 1996). In particular, NHP studies, not rodent models, have provided more concordant results with both human laboratory studies and clinical trials; and a series of empirical data supports the continued use of NHPs in drug abuse research (Banks et al., 2017; Ling et al., 2016; Wee et al., 2012; Weerts et al., 2007). Early NHP studies have demonstrated that MOP, not DOP, KOP, or NOP, receptor agonists produced reinforcing effects (Ko et al., 2009; Nakao et al., 2016; Negus et al., 1994). As KOP receptor activation decreases dopamine release in the nucleus accumbens (Spanagel et al., 1992), KOP receptor agonists are expected to counteract the reinforcing effects of abused drugs. However, KOP receptor agonists decreased self-administration of both drug and non-drug reinforcers in NHPs, indicating lack of functional selectivity (Cosgrove and Carroll, 2002; Mello and Negus, 1998).

Several treatment strategies have been initiated to tackle opioid abuse. First, anti-opioid immunopharmacotherapies have emerged as potential therapeutics for opioid use disorder. For example, fentanyl vaccines blunted the reinforcing effects of fentanyl in rats (Townsend et al., 2019). While fentanyl vaccines have great potential to prevent fentanyl from reaching the brain, it is not clear how NHPs would self-administer different MOP receptor agonists following fentanyl vaccine administration. It is challenging for a specific vaccine to protect individuals from experiencing reinforcing effects derived from abused opioids with diverse chemical structures or taking a much larger amount. Second, the development of G protein-biased MOP receptor agonists has emerged to mitigate MOP receptor-mediated adverse effects (Azzam et al., 2019). For example, a novel G protein-signalling biased MOP receptor agonist PZM21 produced antinociceptive effects without rewarding effects in mice (Manglik et al., 2016). However, PZM21 produced oxycodone-like reinforcing effects and strength in NHPs (Ding et al., 2020). Biased opioids may offer other advantages, but current studies in NHPs indicate they are not posed to be non-addictive analgesics.

Third, compounds with mixed opioid actions may retain analgesia with reduced side effects. For example, by decreasing the dopaminergic activity, NOP receptor activation is known to reduce the rewarding effects of abused drugs in rodents (Ciccocioppo et al., 2019; Toll et al., 2016). Buprenorphine is a MOP receptor partial agonist with binding affinity at KOP and DOP receptors (Lewis, 1985; Spagnolo et al., 2008). As a buprenorphine analog, BU08028 shows buprenorphine-like MOP receptor efficacy with additional affinity and efficacy at NOP receptors (Cami-Kobeci et al., 2011). BU08028 displayed lower reinforcing strength than buprenorphine in NHPs (Ding et al., 2016). Other mixed MOP/NOP receptor partial agonists (AT-121 and BU10038) or full agonist (cebranopadol) in different chemical structures also produced antinociception with decreased reinforcing strength (Ding et al., 2018b; Kiguchi et al., 2019; Kiguchi and Ko, 2019). More importantly, AT-121 was further tested to show its effectiveness to attenuate oxycodone-, not food-, induced reinforcing effects in NHPs (Ding et al., 2018b). These findings support the notion that compounds with mixed MOP/NOP receptor partial agonist activities have relatively lower abuse potential and can be used to attenuate opioid abuse-related effects (Kiguchi et al., 2020b; Lin and Ko, 2013). In a similar approach, given that MOP and KOP receptors have opposite modulation of dopaminergic neurons (Spanagel et al., 1992), mixed MOP/KOP receptor agonists are worth to be investigated in NHP models. In particular, mixtures of KOP receptor agonists (nalfurafine and salvinorin A) with oxycodone showed reduced self-administration in NHPs (Zamarripa et al., 2020). It is important to develop compounds with mixed MOP/KOP receptor agonists in different efficacies at MOP versus KOP receptors (Bidlack and Knapp, 2013; Greedy et al., 2013) and investigate their functional efficacy, selectivity, and tolerability in NHP models.

Finally, MOP receptor antagonist-based compounds have been proven to be a potential treatment option based on studies in NHPs. For instance, BU10119 with mixed MOP/KOP receptor antagonist activities showed therapeutic potential for the treatment of neuropsychiatric disorders (Almatroudi et al., 2018). BU10119 was recently demonstrated to not only block MOP receptor agonist-induced reinforcing effects, but also attenuate heroin-primed reinstatement of extinguished responding in NHPs, indicating of relapse prevention (Maguire et al., 2020a). The limitation of BU10119 could be its naltrexone-like property to elicit withdrawal signs in morphine-dependent NHPs (Maguire et al., 2020a). Another compound is methocinnamox, which was initially characterized as a pseudo-irreversible MOP receptor antagonist with a long duration of action in mice (Broadbear et al., 2000). A single dose of methocinnamox selectively blocked the reinforcing effects of MOP receptor agonists for several days without changing the NHP’s physiological functions (Maguire et al., 2019). More importantly, repeated administration (i.e., once per 12 days for five injections) of methocinnamox significantly decreased fentanyl self-administration for more than two months in NHPs (Maguire et al., 2020b). These exciting findings indicate that methocinnamox could be a safe, effective, and long-acting treatment option for opioid use disorder. Other than four treatment strategies mentioned above, there are other targets and approaches (France et al., 2020; Rasmussen et al., 2019) that have not yet been evaluated in NHP models. Preclinical studies using NHPs will continue to facilitate the research and development of effective medications for opioid use disorder.

5. Respiratory depression

Opioid-induced respiratory depression is one of the most concerning complications in pain treatment with opioid analgesics and overdose in persons with opioid use disorder. Researchers have established different NHP models to study opioid receptor mechanisms underlying respiratory depression and test strategies to ameliorate the respiratory depressant effects of opioids. Previous model used head plethysmograph to measure respiratory endpoints in restrained, conscious NHPs (Butelman et al., 1993a; Butelman et al., 2001; France et al., 1992). Recently, implantation of telemetry device has made it practical to measure real-time respiratory parameters in freely moving NHPs (Ding et al., 2016). Utilization of these NHP models demonstrated that MOP receptor, but not KOP, DOP or NOP receptors, is the main contributor to opioid-induced respiratory depression (France et al., 1994; Ko et al., 2009; Negus et al., 1994). A single injection of fentanyl at 2-fold of its antinociceptive dose in NHPs produced a rapid and severe decrease in respiration rate, which was reversed by a MOP receptor antagonist naltrexone (Ding et al., 2016). This observation in NHPs recapitulates the rapid onset and severity of fentanyl overdose in humans (Grell et al., 1970; Kuczyńska et al., 2018). In contrast, in the same NHP telemetry model, novel compounds with mixed opioid partial agonist actions did not compromise respiratory functions (Ding et al., 2016; Ding et al., 2018b; Kiguchi et al., 2019). Therefore, NHPs provide a valuable tool to distinguish clinically used opioids and new investigational compounds in their impacts on the respiration system. More importantly, it allows researchers to validate strategies to prevent or reverse respiratory depression, which can be translated to human studies.

One strategy to mitigate respiratory depression is to develop novel opioid agonists with reduced liability of respiratory depression. Mixed MOP/NOP receptor partial agonists showed potent antinociceptive effects without inducing respiratory depression (Ding et al., 2016; Ding et al., 2018b; Kiguchi et al., 2019). A mixed NOP/opioid receptor full agonist, cebranopadol, did not affect NHP's respiratory function at a dose 3 times higher than its antinociceptive dose, which is consistent with observations in human studies (Dahan et al., 2017; Kiguchi and Ko, 2019). These findings support the research strategy to develop MOP/NOP receptor agonists as innovative analgesics with improved safety profile in humans. The other strategy is to develop new agents that can prevent or reverse opioid-induced respiratory depression. Although the opioid receptor antagonist naloxone is a quick-acting antidote for opioid overdose, its short duration of action limits it clinical utility. A recent NHP study demonstrates that a novel opioid antagonist methocinnamox effectively attenuated and reversed the respiratory depressant effects of heroin (Gerak et al., 2019). The striking advantage of methocinnamox is its long duration of action which lasts for a few days. It is important to further compare the duration of protection against opioid-induced respiratory depression between methocinnamox and a slow release formulation of naltrexone (Vivitrol). Nevertheless, these recent NHP findings have encouraging implications about methocinnamox being able to provide sustained protection from opioid overdose.

Direct activation of TREK1 potassium channel downstream of the MOP receptor induced antinociception but not opioid-induced respiratory depression in rodents (Busserolles et al., 2020). It would be interesting to further investigate whether TREK1 activators produce similar effects in NHPs. Several other pharmaceutical agents, such as serotonin receptor agonist, nicotinic receptor agonist, monoclonal antibodies with high affinities for opioids, have been studied in rodents to show potential effectiveness in reducing opioid-induced respiratory depression (Baehr et al., 2020; Ren et al., 2015; 2020). However, their side effect profiles and lack of thorough studies of efficacies hinder the therapeutic use of these agents (Dahan et al., 2018). Future studies of these newly developed compounds and other countermeasures for opioid toxicity (France et al., 2020) in NHPs will provide functional evidence of their potential utilities in humans.

6. Physical dependence

Physical dependence on opioids tends to perpetuate compulsive drug use and is considered an important component of opioid use disorder (Brady, 1991; Kosten and Baxter, 2019). It is responsible for the emergence of spontaneous withdrawal upon abrupt discontinuation of opioids or rapid dose reduction (Pergolizzi et al., 2020; Volkow and McLellan, 2016). In addition, following acute or repeated exposure to MOP agonists, humans and NHPs quickly develop physical dependence which is revealed by emergence of withdrawal signs after administration of an opioid receptor antagonist (Azolosa et al., 1994; Heishman et al., 1990; Ko et al., 2006a). The neurobiological mechanism underlying opioid physical dependence and withdrawal could be the binding to opioid receptors in the locus coeruleus. Acute effects of opioids lead to the decreased level of cyclic adenosine monophosphate (cAMP) and reduced release of norepinephrine. Upon spontaneous or precipitated withdrawal, the cAMP level and neuronal firing rates in the locus coeruleus increase dramatically above normal levels, causing excessive release of norepinephrine and severe opioid withdrawal symptoms (Cao et al., 2010; Kosten and George, 2002; Rasmussen et al., 1990).

NHP models have been established to quantitate opioid withdrawal signs and investigate how different strategies could modulate opioid withdrawal. In early studies, withdrawal signs designated as lying down, avoiding contact, vocalizing, crawling, holding abdomen, salivation, and tremors were noted in NHPs receiving chronic administration of morphine (Aceto et al., 1998; Beardsley et al., 2004; Martin and Eades, 1964). Recently, NHPs implanted with telemetry device were established to study antagonist-precipitated withdrawal (Ding et al., 2016; Kiguchi et al., 2019). Naltrexone quickly increased respiratory rate, minute volume, heart rate, and blood pressure in morphine-treated NHPs, validating that respiratory and cardiovascular parameters are reliable and quantitative indicators of antagonist-precipitated withdrawal. In addition, suppression of food-maintained operant responding was established as additional quantitative measure of precipitated withdrawal signs along with changes in physiological parameters and behavioral signs (Maguire et al., 2020a).

The NHP model has demonstrated its value in distinguishing various opioid full agonists versus partial agonists in their potentials to produce physical dependence. For example, neither the NOP receptor agonists nor mixed MOP/NOP receptor partial agonists produced physical dependence (Ding et al., 2016; Ding et al., 2018b; Kiguchi et al., 2019). These results support the notion that unlike MOP receptor agonists, NOP-related agonists have less liability to develop physical dependence following the same period of repeated exposure. Given that physical dependence is one of the major concerns associated with the use of opioid analgesics (Saxon, 2013; Schuckit, 2016; Volkow and Blanco, 2020), the development of mixed MOP/NOP receptor partial agonists is a viable approach to curb the opioid epidemic.

Another strategy for combating opioid withdrawal is to offer effective treatment options for suppressing withdrawal symptoms. In the clinic, opioid withdrawal is often managed by the utility of buprenorphine, a MOP receptor partial agonist (Gowing et al., 2017; Kosten and Baxter, 2019; Schuckit, 2016). Numerous clinical studies have documented that buprenorphine treatment can significantly reduce craving and relapse risk and suppress opioid withdrawal (Gowing et al., 2017; Kakko et al., 2019; Reimer et al., 2020). However, buprenorphine can acutely produce euphoric effects and mild-to-moderate physical dependence with prolonged use or precipitate withdrawal in individuals dependent on a higher efficacy MOP agonist; and it has the additional risk of diversion and misuse or abuse of medication (Eissenberg et al., 1996; Johanson et al., 2012; Lavonas et al., 2014; Saxon, 2013). Given the improved functional profiles of mixed MOP/NOP receptor partial agonists displayed in NHPs, it is important to determine and compare the effectiveness and potency of buprenorphine with those of BU08028 and AT-121 in alleviating opioid withdrawal in NHP models described above. Positive outcomes from such studies will open a new avenue of treatment for managing opioid withdrawal.

Besides the involvement of neurons in the underlying mechanisms of opioid withdrawal, interactions between glial cells and neurons are proposed to play an important role as well (Burma et al., 2017b). The microglial pannexin-1 channel was identified as a therapeutic target for opioid withdrawal in rodents. Pannexin-1-blocking peptide or the clinically used nonselective pannexin-1 channel blocker mefloquine or probenecid reduced the severity of opioid withdrawal without compromising antinociceptive effects (Burma et al., 2017a). Preclinical studies of pannexin-1 channel blockers in NHPs will shed light on their potential effectiveness in treating opioid dependence.

7. Pruritus

Pruritus (itch sensation) is a common side effect of spinal opioids often experienced by obstetric and postoperative patients. This problem significantly compromises the value of spinal opioid analgesics in providing pain relief (Ganesh and Maxwell, 2007). The neurobiological mechanisms of opioid-induced pruritus are not fully understood. Studies in laboratory animals and humans demonstrate that opioid-induced pruritus is mainly mediated by MOP receptors (Ko, 2015). While MOP receptors are expressed in both inhibitory and excitatory interneurons in the mouse spinal dorsal horn, a recent study demonstrates that intrathecal morphine elicited itch via MOP receptors on spinal inhibitory interneurons (Wang et al., 2020b).

To prevent or treat spinal opioid-induced itch, a variety of pharmacological agents have been evaluated in both preclinical animal models and clinical studies. In NHPs, intrathecal morphine simultaneously induced antinociception and robust scratching responses (Ko and Naughton, 2000). Unlike morphine, intrathecal administration of KOP, DOP, and NOP receptor agonists all produced antinociception without scratching responses, indicating that the MOP receptor, not other opioid receptor subtypes, mainly mediates spinal opioid-induced itch (Ko, 2014; Ko et al., 2006b). In addition, spinally elicited scratching response in NHPs is a valid in vivo endpoint for determining the efficacy of MOP receptor activation. For example, MOP receptor agonists with different intrinsic efficacy, such as DAMGO versus morphine, elicited different magnitudes of scratching activities (Ko et al., 2004). It is important to note that intrathecal morphine produces long-lasting itch sensation and pain relief for hours in humans and NHPs (Ko and Naughton, 2000; Palmer et al., 1999). However, intrathecal morphine only elicited mild and transient scratching lasting for 10–15 min or vehicle-like responses in rodents (Liu et al., 2011; Sukhtankar and Ko, 2013). Such drastic species differences between rodents and primates support the translational value of NHP models for the exploration and validation of drugs without itch sensation and drugs that can potentially treat spinal opioid-induced itch (Cowan and Ko, 2020; Ko, 2015).

Indeed, NHP studies have identified mixed MOP/NOP receptor agonists as a new class of analgesics without eliciting itch sensation (Kiguchi et al., 2020a). With regard to alleviating spinal-opioid induced itch, both opioid ligands and non-opioid ligands have been investigated for their effectiveness in NHPs (Ko, 2015). MOP antagonists equally blocked intrathecal morphine-induced itch scratching and antinociception (Ko and Naughton, 2000). It supports the clinical findings that MOP receptor antagonists are not ideal drugs for treating pruritus in obstetric patients (Dominguez and Habib, 2013; Ganesh and Maxwell, 2007). Compared with MOP antagonists, a mixed MOP/KOP receptor partial agonist, butorphanol, is effective in alleviating MOP agonist-induced itch without reversing analgesia in NHPs (Lee et al., 2007). These observations are in line with clinical studies demonstrating that mixed MOP/KOP receptor partial agonists could decrease incidence of pruritus without other side effects (Dominguez and Habib, 2013; Waxler et al., 2005). Furthermore, KOP receptor agonists, at non-sedating doses, can attenuate intrathecal morphine-induced scratching without affecting antinociception (Ko and Husbands, 2009; Ko et al., 2003). These findings facilitated the development of a KOP receptor agonist, nalfurafine, as an antipruritic. Clinical trials have reported that nalfurafine is a safe and effective antipruritic in hemodialysis patients suffering from uremic pruritus (Kumagai et al., 2012; Kumagai et al., 2010).

On the other hand, non-opioid ligands, such as serotonin 5-HT3 receptor antagonist (ondansetron), antihistamines, and NASIDs failed to attenuate intrathecal morphine-induced scratching in NHPs (Ko, 2015; Ko et al., 2004). These results to certain degree recapitulate the varied effectiveness of ondansetron and the ineffectiveness of antihistamines and NSAIDs in relieving spinal opioid-induced itch in clinical studies (Ko, 2015). Collectively, these pharmacological studies suggest that NHPs could serve as a surrogate species for humans in preclinical studies to identify effective treatments for spinal opioid-induced itch.

Furthermore, NHPs could also prove useful in studying the neurobiological mechanisms underlying spinal opioid-induced itch. In mice, intrathecal morphine-induced scratching was inhibited by co-administration with a gastrin-releasing peptide receptor (GRPR) antagonist (Liu et al., 2011). However, in NHPs, the GRPR antagonist could not attenuate spinal MOP agonist-elicited scratching activities (Lee and Ko, 2015). Recently, Wang et al demonstrated that intrathecal administration of neuropeptide Y suppressed morphine-induced itch in mice (Wang et al., 2020b). It will be interesting to examine whether neuropeptide Y plays a functional role in morphine-induced itch in NHPs as well. Rodent studies continue to provide mechanistic insights to the neurocircuitry for modulating itch (Kardon et al., 2014; Liu et al., 2011; Wang et al., 2020b). Future NHP studies can further define the functional profile of discovered ligand-receptor systems in sensory processing and determine if these targets modulate spinal opioid-induced itch in primates.

8. Conclusions

Similarities between NHPs and humans and species differences between rodents and NHPs in functional profiles of opioid-related pharmacological agents support the translational value of NHPs in opioid research (Banks et al., 2017; Kiguchi and Ko, 2019; Lin and Ko, 2013). Research in NHPs has led to the development of novel analgesic compounds that display improved side-effect profiles when compared with opioids currently used in the clinic. Furthermore, NHPs have served as a surrogate species to examine the therapeutic potentials of experimental compounds in the treatment of opioid use disorder. Figure 1 summarizes the main adverse effects of MOP receptor agonists discussed in this review and strategies to ameliorate such effects. Mixed MOP/NOP receptor partial agonists are being developed as safe, non-addictive analgesics (Kiguchi et al., 2020a). NHP studies have found that MOP receptor- or mixed opioid receptor subtype-based meditations, but not non-opioid ligands, show effectiveness in reducing opioid-induced adverse effects (Gerak et al., 2019; Kiguchi et al., 2020b; Maguire et al., 2020b). With recent advances in medicinal chemistry, there are other targets and treatment strategies (France et al., 2020; Rasmussen et al., 2019) which are worth investigating in NHP models. Behavioral pharmacological studies using NHPs will continue to facilitate the research and development of effective medications to address the challenges from the opioid crisis (Volkow and Collins, 2017).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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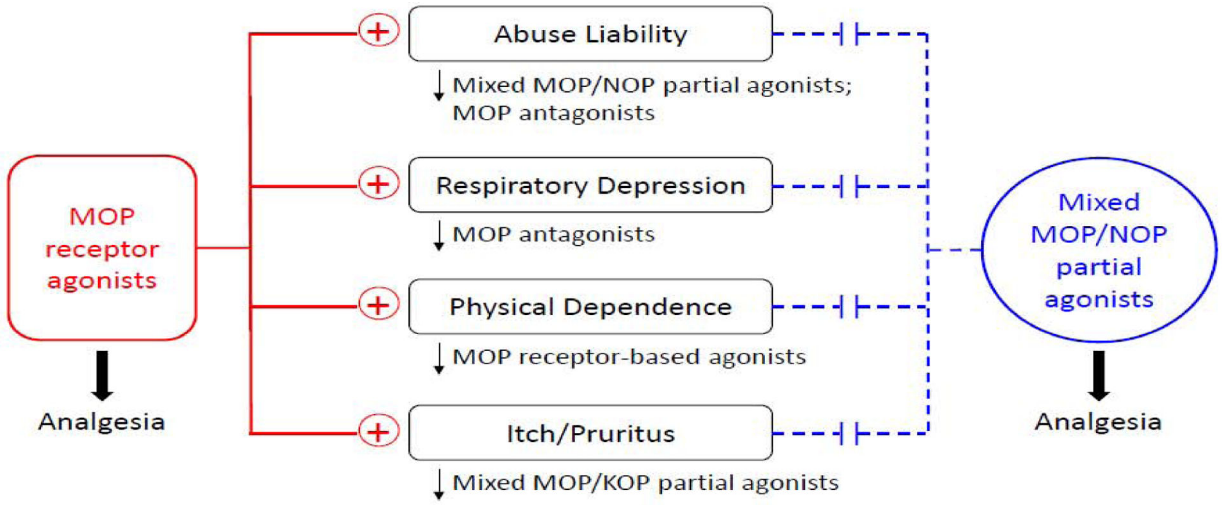

Figure 1.

Simplified scheme to summarize the functional profiles of two classes of opioid-related agonists based on human and/or non-human primate studies. + symbols represent the adverse effects associated with MOP receptor agonists. Dashed lines indicate reduced or lack of adverse effects associated with mixed MOP/NOP receptor partial agonists. ↓ symbols represent that the adverse effect can be ameliorated by a specific category of pharmacological agents.