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Neuraxial Opioid-Induced Itch and Its Pharmacological Antagonism

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Abstract

Given its profound analgesic nature, neuraxial opioids are frequently used for pain management. Unfortunately, the high incident rate of itch/pruritus after spinal administration of opioid analgesics reported in postoperative and obstetric patients greatly diminishes patient satisfaction and thus the value of the analgesics. Many endeavors to solve the mystery behind neuraxial opioid-induced itch had not been successful, as the pharmacological antagonism other than the blockade of mu opioid receptors remains elusive. Nevertheless, as the characteristics of all opioid receptor subtypes have become more understood, more studies have shed light on the potential effective treatments. This review discusses the mechanisms underlying neuraxial opioid-induced itch and compares pharmacological evidence in nonhuman primates with clinical findings across diverse drugs. Both nonhuman primate and human studies corroborate that mixed mu/kappa opioid partial agonists seem to be the most effective drugs in ameliorating neuraxial opioid-induced itch while retaining neuraxial opioid-induced analgesia.

Keywords

Agonist; Analgesics; Antagonist; Antipruritics; Epidural; Intrathecal; Itch; Monkey; Mouse; Opioid receptor; Pain; Pruritus; Rat; Spinal cord

1 Neuraxial Opioids

1.1 Clinical Applications of Neuraxial Opioids

Neuraxial administration of drugs offers the techniques that deliver drugs in close proximity to the spinal cord, i.e., intrathecally into the cerebrospinal fluid or epidurally into the fatty tissues surrounding the dura. Neuraxial administration of opioids provides effective analgesia before and after a surgical procedure. The modern era of spinal opioid administration began with a report by Yaksh and Rudy in 1976, demonstrating analgesia in rats by intrathecal administration of morphine (Yaksh and Rudy 1976). In 1979, Wang et al. published the first controlled clinical study of intrathecally administered opioid in humans conducted in a double-blind placebo setting. Eight cancer patients were selected based on

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severe pain in the back and legs and failure to respond to systemic analgesics when given at reasonable dose levels and frequencies. Each patient received both morphine at either 0.5 mg or 1.0 mg dosage and the placebo saline. Injections were administered at the second or third lumbar interspace at various intervals ranging from 4 to 48 h, depending on each patient's response to the treatment. In the end, 17 injections of morphine and 12 injections of saline were administered in total. Three quarters of the patients reported long-lasting pain relief after being treated with intrathecal morphine, suggesting that there is a clear distinction between the analgesic effects of morphine and placebo saline (Wang et al. 1979). No sign of central nervous system depression was reported in this study; hence, it was concluded that intrathecally administered opioids were advantageous for relieving pain and free from compromising sensory and motor functions (Wang et al. 1979).

These findings encouraged further studies of intrathecally administered opioids to explore the possibilities in obstetrics and postoperative pain treatment. Later studies concluded that because of its selective blockade in pain conduction, i.e., an absence of sympathetic blockade, spinal opioid allows patients' motor functions to remain intact upon receiving treatment, rendering spinal opioid therapeutically advantageous over local anesthetics (Cousins and Mather 1984).

1.2 Side Effects of Neuraxial Opioids

The use of neuraxial opioids to relieve pain is not without its side effects, however. Itch/pruritus, nausea, vomiting, urinary retention, and respiratory depression are the prominent side effects. This review focuses on the discussion of itch/pruritus because it can sometimes become a more irritating problem than pain itself. Spinal opioid-induced pruritus is an unwanted itch sensation often seen in obstetric and postoperative patients, with an incidence of 20–100 % (Ganesh and Maxwell 2007; Krajnik and Zylicz 2001; Szarvas et al. 2003). The onset of pruritus begins shortly after analgesia, differing in severity and duration depending on different classes of opioids and the dosage used. This unpleasant sensation, causing a reflex or desire to scratch, may warrant the use of antipruritic drugs, which may in turn create hormonal changes in obstetric patients (Ganesh and Maxwell 2007; Szarvas et al. 2003).

The itch sensation caused by neuraxial opioid is not only disturbing to and inconvenient for patients but also a self-limiting factor as it reduces the efficacy of neuraxial opioids for pain relief (Ballantyne et al. 1988; Cousins and Mather 1984; Ganesh and Maxwell 2007; Szarvas et al. 2003). This long-standing troublesome problem associated with neuraxial opioid-induced itch has prompted many scientists and physicians to target studies on potential treatment options (Dominguez and Habib 2013; Ganesh and Maxwell 2007; Kumar and Singh 2013; Waxler et al. 2005). In an attempt to prevent or treat neuraxial opioid-induced itch, a wide variety of pharmacological agents have been evaluated in both animals and humans. However, there is not yet a widely accepted non-opioid drug for treating neuraxial opioid-induced itch. From the perspective of receptor mechanisms underlying opioid-induced itch, the purpose of this review is to discuss the treatment of neuraxial opioid-induced itch and its pharmacological antagonistic mechanisms through examining the evidence provided by preclinical and clinical studies from available literature to date.

2 Mechanisms of Neuraxial Opioid-Induced Itch

2.1 The Molecular Basis

The molecular mechanism of neuraxial opioid-induced itch has been somewhat unveiled by a recent study (Liu et al. 2011). Liu et al. conducted a series of elegant experiments, demonstrating the uncoupling of morphine-induced itch and morphine-induced analgesia in the mouse spinal cord. The mu opioid receptor (MOP) isoform MOP1D is required for intrathecal morphine-induced itch. MOP1D heterodimerizes with gastrin-releasing peptide receptor (GRPR) in the spinal cord, together relaying itch neurotransmission. In particular, MOP agonist-induced scratching responses were nearly abolished in GRPR knockout mice and intrathecal morphine-induced scratching was inhibited by coadministration with a GRPR antagonist (Liu et al. 2011). However, the presence of MOP1D in the rat spinal cord has been questioned (Oldfield et al. 2008). A recent study in monkeys showed that the GRPR antagonist could not attenuate scratching responses elicited by intrathecal administration of an MOP-preferring ligand, β-endorphin, but the same GRPR antagonist significantly attenuated intrathecal gastrin-releasing peptide-induced scratching (Ko 2013). Although the identification of MOP1D in mice implicates that there may be a possible groundbreaking analgesic treatment without causing the pruritic side effect (Liu et al. 2011), future studies are warranted to investigate whether these exciting findings can be translated to other species and advanced to the clinical setting.

As promising as the separation of morphine-induced itch and morphine-induced analgesia implies, rodents subjected to intrathecal morphine did not display profound scratching activities. It is worth noting the dramatic differences in the scratching activities elicited by intrathecal morphine between rodents and primates. Both the magnitude and duration of intrathecal morphine-induced scratching in mice are very mild, i.e., 15 scratching bouts as peak activity 10 min after injection and the increased scratching activity only lasted for 10–15 min (Liu et al. 2011). As compared to scratching responses elicited by intrathecal vehicle or saline, mice display a similar profile of scratching activity which made other researchers conclude that intrathecal morphine failed to elicit scratching responses in mice (Sukhtankar and Ko 2013). Intrathecal morphine over a wide dose range also failed to elicit scratching responses in rats (Lee et al. 2003). Nevertheless, intrathecal morphine elicited profound scratching responses in nonhuman primates, i.e., approximately 600 scratches within a 15-min bin/time sampling and such profound scratching lasted for several hours (Ko and Naughton 2000; Ko et al. 2004). Such dramatic species differences in intrathecal morphine-induced scratching may affect the interpretations of the pharmacological and neurobiological findings.

2.2 The Cellular Basis

The cellular mechanisms of neuraxial opioid-induced itch have been elucidated in depth by pharmacological studies in nonhuman primates. First, microinjection of a kappa opioid receptor (KOP) agonist, U-50488H, or a delta opioid receptor (DOP) agonist, DPDPE, into the medullary dorsal horn did not evoke facial scratching in monkeys (Thomas et al. 1992). Second, intrathecal administration of U-50488H and a DOP agonist, SNC80, produced moderate antinociception, but both ligands did not produce scratching in monkeys (Ko et al.

2003a). Third, intrathecal administration of a nociceptin/orphanin FQ peptide receptor (NOP) agonist produced full antinociceptive effects without eliciting scratching (Ko et al. 2006). Fourth, the antagonist potency of nalmefene, an MOP-preferring antagonist, validates that MOP mainly mediates intrathecal morphine-induced itch scratching (Ko and Naughton 2000). Last, pretreatment with an MOP antagonist (clocinnamox), rather than a DOP antagonist (naltrindole) or a KOP antagonist (nor-binaltorphimine), blocked intrathecal morphine-induced scratching (Ko et al. 2004). Taken together, these findings clearly demonstrate that the MOP, but not other opioid receptor subtypes, mainly mediates neuraxial opioid-induced itch in primates.

There is a well-known theory for opioid-induced itch. As pain inhibits itch, opioid analgesics elicit itch sensation by providing pain relief, i.e., removal of pain unmasks itch sensation (Ikoma et al. 2006; McMahon and Koltzenburg 1992). However, functional evidence from pharmacological studies does not support this notion. By using receptor-selective ligands, pharmacological approaches allow researchers to elucidate the function of each opioid receptor subtype in modulating pain and itch sensations. The DOP, KOP, and NOP agonists produce analgesic properties across diverse pain modalities following intrathecal and systemic administration (Brandt et al. 2001; Butelman and Kreek 2013; Butelman et al. 1993; Hu et al. 2010; Ko et al. 2009; Sukhtankar et al. 2014). Interestingly, these three types of opioid receptor agonists do not elicit scratching responses over a wide antinociceptive dose range (Ko et al. 2004, 2009; Sukhtankar et al. 2014). These findings clearly demonstrate that only MOP agonists produce analgesic effects accompanied by itch scratching responses. Other opioid receptor subtypes, DOP, KOP, and NOP, do not mediate neuraxial opioid-induced itch. It is important to further investigate physiological properties of sensory neurons expressing MOP and/or other opioid receptor subtypes in the spinal cord. More importantly, opioid-induced analgesia and itch can be distinguished at the receptor level. From the perspective of developing novel neuraxial opioids, it is promising to reveal that spinal administration of NOP agonists produces morphine-comparable analgesic effects without evoking itch in nonhuman primates (Hu et al. 2010; Ko and Naughton 2009; Ko et al. 2006). Such important findings will facilitate future advances of spinal analgesics (Lin and Ko 2013; Molinari et al. 2013; Schröder et al. 2014).

2.3 Animal Models with Translational Values

By using intrathecal administration, animal studies have shown that intrathecal morphine elicited scratching responses of different magnitudes and temporal patterns between rodents and nonhuman primates (Ko and Naughton 2000; Kuraishi et al. 2000; Lee et al. 2003; Liu et al. 2011; Sukhtankar and Ko 2013). Perhaps, the most important characteristic of intrathecal morphine is that it simultaneously provides pain relief and elicits itch sensation in patients. To the best of our knowledge, the nonhuman primate model can simulate this therapeutic profile very well. Intrathecal morphine over a wide dose range (10–320 μg) produced antinociceptive effects and it also produced profound scratching responses for several hours in rhesus monkeys (Ko and Naughton 2000; Ko et al. 2004). These observations closely parallel the behavioral effects and physiological relevance of spinal morphine in humans (Bailey et al. 1993; Palmer et al. 1999; Waxler et al. 2005).

Accordingly, nonhuman primates can serve as a translational bridge to explore and validate potential drugs that may be effective in treating neuraxial opioid-induced itch in humans.

Recently, several studies using in vivo electrophysiology have shed light on regulation of pain and itch sensations by sensory neurons. Moser and Giesler (2013) have identified trigeminothalamic tract (VTT) neurons in anesthetized rats that are differentially affected by morphine. Briefly, intrathecal morphine increased the ongoing activity of pruriceptive VTT neurons but inhibited the ongoing activity and responses to noxious stimuli in nociceptive VTT neurons. In addition, the spinothalamic tract (STT) responds to pruritogens with activation that reflects the time course of histamine-induced itch sensation in humans (Andrew and Craig 2001; Davidson et al. 2007; Simone et al. 2004). More interestingly, the responses of STT neurons to histamine were inhibited by scratching the skin, indicating a neural correlate of scratching-induced relief and the importance of spinal processing in controlling itch neurotransmission (Davidson et al. 2009). These observations pinpoint pruriceptive STT neurons being positioned within a plastic circuitry that can provide a locus for pharmacological management of itch (Davidson et al. 2009, 2012). Future research integrating both pharmacological and electrophysiological approaches in both rodents and nonhuman primates will advance our understanding of how the spinal neural circuits regulate MOP-mediated itch and analgesia. Based on the current literature, several pharmacological studies in nonhuman primates have been conducted to evaluate the effectiveness of diverse ligands in treating intrathecal morphine-induced scratching in adult rhesus monkeys (Table 1). These summarized findings in nonhuman primates are discussed and compared in the sections below (pharmacological antagonism) in terms of effectiveness of opioid- and non-opioid-related ligands in treating neuraxial opioid-induced itch in adult patients.

3 Pharmacological Antagonism by Opioid-Related Ligands

3.1 Mu Opioid Receptor Antagonists

As most opioid analgesics used in the clinics are MOP agonists, it is expected that MOP antagonists are effective in treating neuraxial opioid-induced itch in patients (Dominguez and Habib 2013; Ganesh and Maxwell 2007; Kumar and Singh 2013; Waxler et al. 2005). A systematic review of randomized trials involving obstetric patients indicated that intravenous naloxone (0.25–2.4 μg/kg/h) was effective in managing opioid-induced itch (Kjellberg and Tramer 2001). However, MOP antagonists are not widely useful in patients receiving neuraxial opioids for pain relief because MOP antagonists reverse or shorten neuraxial opioid-induced analgesia (Abboud et al. 1990; Cohen et al. 1992; Rawal et al. 1986; Wang et al. 1998).

Antagonist studies in nonhuman primates demonstrate that pretreatment with a single dose of nalmefene (32 μg/kg) was equally potent to block intrathecal morphine-induced itch scratching and antinociception (Ko and Naughton 2000). In this study, the in vivo pK_B analysis was used to verify functional receptor populations underlying the actions of intrathecal morphine. The same dose of nalmefene produced approximately tenfold rightward shifts in each subject's dose–response curves of intrathecal morphine for scratching and antinociception. Accordingly, nalmefene pK_B values were similar for both

endpoints, indicating that intrathecal morphine-induced scratching and antinociception are mediated by the same MOP population in primates (Ko and Naughton 2000). These findings indicate a narrow window between reversal of itch and analgesia by MOP antagonists and support the clinical findings that MOP antagonists such as naloxone and nalmefene may not be ideal drugs for treating pruritus in obstetric patients. Nevertheless, the MOP antagonist is one of the treatment options for ameliorating cholestatic pruritus, which may be caused by elevated levels of endogenous opioid peptides (Bergasa 2008; Jones and Bergasa 1992).

3.2 Opioid Receptor Partial Agonists

Both nalbuphine and butorphanol are opioid receptor partial agonists that have been used clinically as analgesics with limited abuse liability (Preston and Jasinski 1991). The radioligand binding assay suggests that both drugs have reasonable binding affinity for both MOP and KOP sites in monkey brain membranes, although nalbuphine has a higher selectivity for MOP over KOP (Butelman et al. 1998). In the cell lines expressing MOP or KOP, both drugs displayed low-mid efficacy as measured by the stimulation of [^{35}S]GTPγS binding, i.e., low-mid intrinsic activity (Emmerson et al. 1996; Remmers et al. 1999; Zhu et al. 1997). Interestingly, due to its low efficacy, nalbuphine displays partial MOP agonist actions with its context-dependent agonist/antagonist effects in nonhuman primate behavioral assays (Gerak et al. 1994; Gerak and France 1996). By contrast, butorphanol is characterized as a partial agonist acting at both KOP and MOP sites by diverse in vivo assays in nonhuman primates (Butelman et al. 1995; Lee et al. 2007; Vivian et al. 1999).

Both nalbuphine and butorphanol are effective in alleviating neuraxial opioid-induced itch (Table 2). In particular, systemic nalbuphine between 3 and 10 mg seems effective in decreasing the incidence of pruritus in most of the clinical studies. However, with a high dose of nalbuphine (20 mg), Morgan et al. (1991) did not find pruritus relief by nalbuphine. Butorphanol seems less popular than nalbuphine for treating opioid-induced itch probably due to potential drowsiness following systemic administration. Nevertheless, several studies have shown a decreased incidence of pruritus without other side effects when butorphanol was administered with morphine epidurally in pediatric patients (Bailey et al. 1994; Gunter et al. 2000; Lawhorn et al. 1995; Lawhorn and Brown 1994). A recent systematic review also indicates the potential benefits of using butorphanol to prevent neuraxial morphine-induced itch and decrease pain intensity and postoperative nausea and vomiting without increasing other side effects (Du et al. 2013). Importantly, a pharmacological study demonstrates that butorphanol's partial agonist actions at both MOP and KOP sites contribute to its antipruritic actions, i.e., low-efficacy ligands antagonize high-efficacy ligand's action in producing itch sensation (Lee et al. 2007). Compared with MOP antagonists, opioid receptor partial agonists seem to have an advantage for ameliorating itch while retaining analgesia (Dominguez and Habib 2013; Ganesh and Maxwell 2007; Kumar and Singh 2013; Waxler et al. 2005). These observations are in line with preclinical studies demonstrating that butorphanol is effective in alleviating MOP agonist-induced itch without reversing analgesia in nonhuman primates (Lee et al. 2007). Due to butorphanol's unique pharmacological profile, i.e., partial agonist actions at both MOP and KOP sites, dermatologists are very interested in developing a transdermal formulation of butorphanol for the treatment of chronic itch (Dawn and Yosipovitch 2006; Lim et al. 2008).

3.3 Kappa Opioid Receptor Agonists

Numerous preclinical and clinical studies have indicated that KOP is a viable therapeutic target for potential antipruritics (Cowan and Gmerek 1986; Ko et al. 2003b; Kumagai et al. 2010, 2012). Original studies in rodents showed that systemic administration of KOP agonists inhibited scratching activity evoked by pruritogens such as bombesin-related peptides (Gmerek and Cowan 1983, 1984). In particular, KOP agonists inhibited scratching behavior without interfering with locomotor activity in rodents (Inan et al. 2009; Togashi et al. 2002; Wang et al. 2005). Recent studies have identified a subset of inhibitory interneurons regulating itch in the dorsal horn of mouse spinal cord (Ross et al. 2010). It will be important to investigate the role of KOP modulating these inhibitory interneurons. Furthermore, pharmacological studies in nonhuman primates have demonstrated that KOP agonists, at nonsedating doses, can attenuate intrathecal morphine-induced scratching without affecting antinociception (Ko and Husbands 2009; Ko et al. 2003b). These findings facilitated the development of a KOP agonist, nalfurafine, as an antipruritic. To date, two clinical trials have reported that nalfurafine is a safe and effective antipruritic in hemodialysis patients suffering from uremic pruritus (Kumagai et al. 2010, 2012).

KOP agonists produce several effects opposite to those of MOP agonists in primates. For example, MOP agonists produce euphoria, whereas KOP agonists produce dysphoria (Kumor et al. 1986; Walsh et al. 2001); MOP agonists produce antidiuretic effects, while KOP agonists produce diuresis (Peters et al. 1987; Weiskopf et al. 1987). Although there is no selective KOP agonist approved for treating neuraxial opioid-induced itch, it seems promising to develop KOP-related ligands, especially mixed KOP/MOP agonists for this purpose or as spinal analgesics. Clinically used mixed KOP/MOP agonists such as butorphanol and pentazocine have a low incidence of pruritus and are effective in treating spinal morphine-induced itch (Abboud et al. 1989; Ackerman et al. 1989; Lawhorn et al. 1991; Tamdee et al. 2009). In addition, butorphanol produces neither euphoria nor dysphoria in humans and it does not cause diuresis (Butelman et al. 1995; Dershwitz et al. 1991). These findings strengthen the notion that mixed KOP/MOP agonists may have a therapeutic advantage over selective MOP agonists. It will be important to further develop novel opioid agonists with dual actions at both KOP and MOP sites with different degrees of intrinsic efficacy and advance the medicine of neuraxial opioids.

4 Pharmacological Antagonism by Non-Opioid Ligands

4.1 Serotonin 5-HT3 Receptor Antagonists

The effectiveness of a 5-HT3 receptor antagonist, ondansetron, in treating neuraxial opioid-induced itch varies across different clinical studies (Table 3). Several studies showed that intravenous ondansetron (4–8 mg) was effective in decreasing the incidence of pruritus in patients receiving either epidural or intrathecal morphine, fentanyl, or combination of MOP agonists. However, several other studies concluded that ondansetron was ineffective in treating itch in most of the patients receiving intrathecal fentanyl or combination of MOP agonists (Bonnet et al. 2008). It will be important to investigate whether fentanyl, sufentanil, or a combination of MOP agonists elicits a higher intensity of itch as both fentanyl and sufentanil have been characterized in the agonist stimulation of [^{35}S]GTPγS binding as full

MOP agonists with higher intrinsic activity as compared to morphine (Emmerson et al. 1996).

The exact mechanism for ondansetron to alleviate itch is unknown. Although the 5-HT3 receptors can be identified in the spinal cord of rodents and primates (Laporte et al. 1996; Waeber et al. 1988), there is no anatomical evidence for the co-localization of the 5-HT3 receptor with MOP in the spinal cord or functional evidence for the interaction between the 5-HT3 receptor and MOP in any animal models. Since patients with cholestatic pruritus have elevated levels of endogenous opioids, there were several randomized controlled trials exploring the effects of ondansetron (Jones et al. 2007). It was concluded that ondansetron has negligible effect on cholestatic or uremic pruritus based on a recent systematic review (To et al. 2012). Figure 1 illustrates the effects of ondansetron on intrathecal morphine-induced scratching in monkeys. Intrathecal administration of morphine (32 μg) elicited profound scratching responses (i.e., ~600 scratches within a 15-min bin/time sampling) in rhesus monkeys (n = 8) (unpublished data from the Ko lab). Intravenous ondansetron (0.1–3.2 mg/kg) was given approximately 2 h after subjects received intrathecal morphine. Within these doses tested herein, ondansetron was ineffective in attenuating intrathecal morphine-induced scratching. A higher dose of ondansetron (10 mg/kg) caused extrapyramidal reactions in monkeys (i.e., involuntary head jerking, both legs were rigid and were in extensor spasm) which led to the termination of experiments.

4.2 Histamine H1 Receptor Antagonists

Although morphine can trigger the release of histamine from mast cells, clinical studies have indicated that antihistamines are not effective in relieving neuraxial opioid-induced itch (Dunteman et al. 1996; Horta et al. 2006). Pharmacological studies in nonhuman primates also found that an antihistamine, diphenhydramine, over a wide dose range could not attenuate intrathecal morphine-induced scratching (Ko et al. 2004). Moreover, other MOP agonists such as fentanyl and alfentanil do not stimulate histamine release (Hermens et al. 1985; Rosow et al. 1982), whereas they evoke itch/scratching in humans and nonhuman primates (Ellis et al. 1990; Ko et al. 2004). As tachyphylaxis develops quickly in response to histamine-induced itch, the role of histamine is minimal in both neuraxial opioid-induced itch and chronic itch. Nevertheless, the sedative effects of antihistamines may be helpful by providing needed sleep and interrupting the itch–scratch cycle while being barely effective in decreasing the severity of itch (Krajnik and Zylicz 2001; Szarvas et al. 2003).

4.3 Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) attenuate inflammatory pain by inhibiting cyclooxygenases and decreasing prostaglandin levels. Intravenous tenoxicam and rectal diclofenac have been reported to attenuate neuraxial opioid-induced itch (Colbert et al. 1999a, b). However, other studies using celecoxib and lornoxicam found no changes in the severity of pruritus (Gulhas et al. 2007; Lee et al. 2004). In the nonhuman primate inflammatory pain model, systemic administration of ketorolac (0.3–10 mg/kg) dose-dependently attenuated carrageenan-induced thermal allodynia/hyperalgesia (Sukhtankar et al. 2014). However, the same dose range of intravenous ketorolac did not attenuate scratching responses elicited by intrathecal morphine (32 μg) (unpublished data from the Ko

lab). Figure 2 compares the effects of ketorolac and nalmefene on intrathecal morphine-induced scratching in the same rhesus monkeys (n = 5). Either ketorolac (10 mg/kg) or nalmefene (32 μg/kg) was administered intravenously approximately 2 h after subjects received intrathecal morphine (32 μg). In this experimental setting, intravenous nalmefene, but not ketorolac, significantly attenuated scratching responses. Based on these results, NSAIDs may not be useful therapeutic agents to treat neuraxial opioid-induced itch. It seems unlikely that prostaglandins play a significant role as itch mediators associated with neuraxial opioids.

5 Conclusion

A variety of drugs have been evaluated in treating neuraxial opioid-induced itch. These diverse drugs, including gabapentin, dopamine D2 receptor antagonists, propofol, mirtazapine, and dexamethasone, have been discussed in recent review articles, but all have mixed results from a very limited number of clinical studies (Dominguez and Habib 2013; Ganesh and Maxwell 2007; Kumar and Singh 2013). As these drugs have not been extensively studied in nonhuman primates, there is no further discussion on the potential pharmacological antagonism of these drugs on neuraxial opioid-induced itch. Most importantly, accumulated pharmacological evidence in nonhuman primates (Table 1, Figs. 1 and 2) supports that (1) MOP antagonists and mixed KOP/MOP partial agonists are the most effective treatment options for managing neuraxial opioid-induced itch (Table 2) and (2) non-opioid ligands, including the 5-HT3 antagonist ondansetron, antihistamines, and NSAIDs, are not effective in treating neuraxial opioid-induced itch (Table 3). Collectively, these pharmacological studies indicate that rhesus monkeys may serve as a surrogate species for humans in preclinical studies to identify effective treatments for neuraxial opioid-induced itch.

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Abbreviations

DOP	Delta opioid receptor
GRPR	Gastrin-releasing peptide receptor
KOP	Kappa opioid receptor
MOP	Mu opioid receptor
NOP	Nociceptin/orphanin FQ peptide receptor

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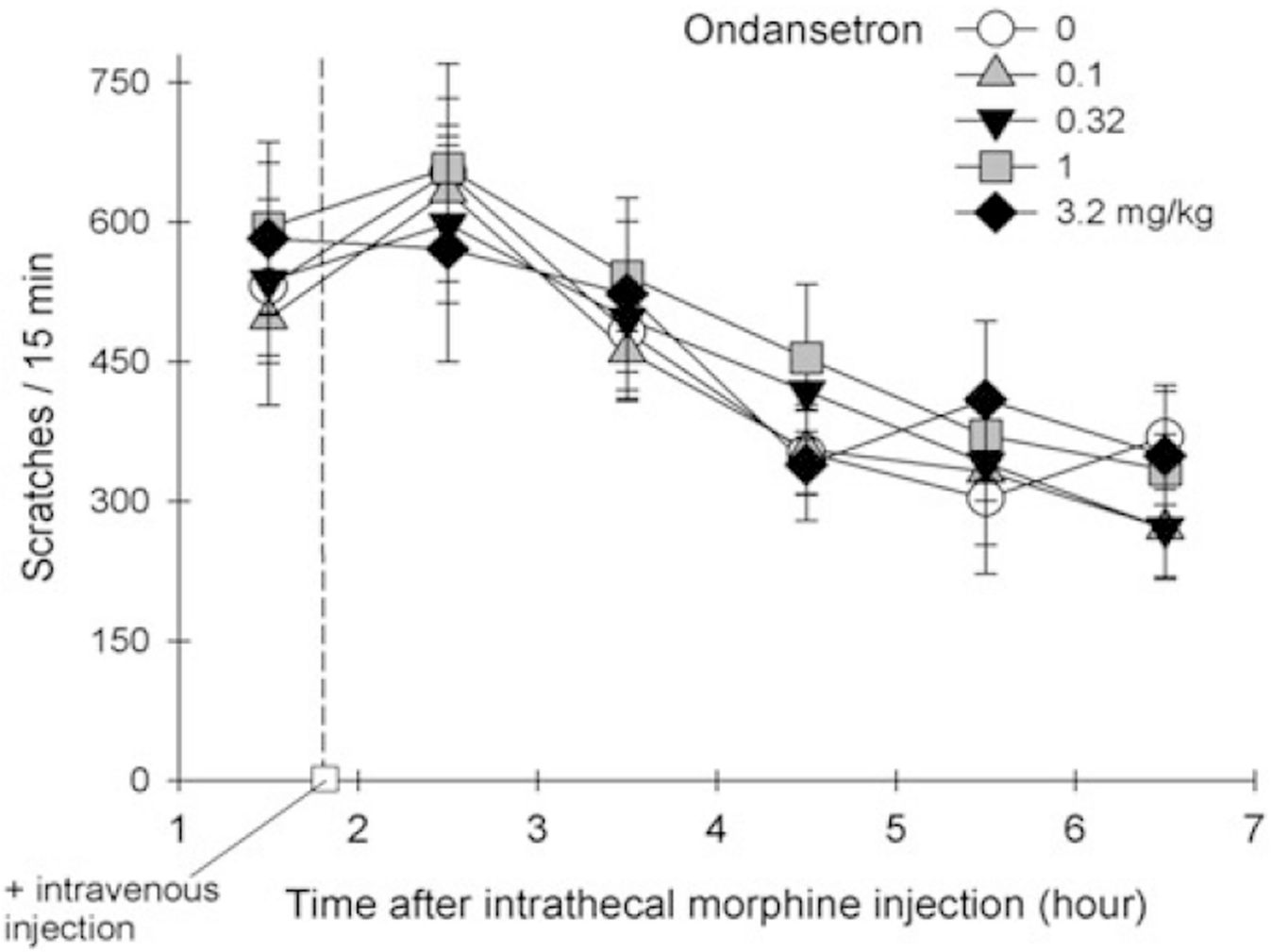

Fig. 1.

Effects of intravenous ondansetron on intrathecal morphine-induced itch scratching responses in rhesus monkeys. Each value represents means +/− S.E.M. (*n* = 8)

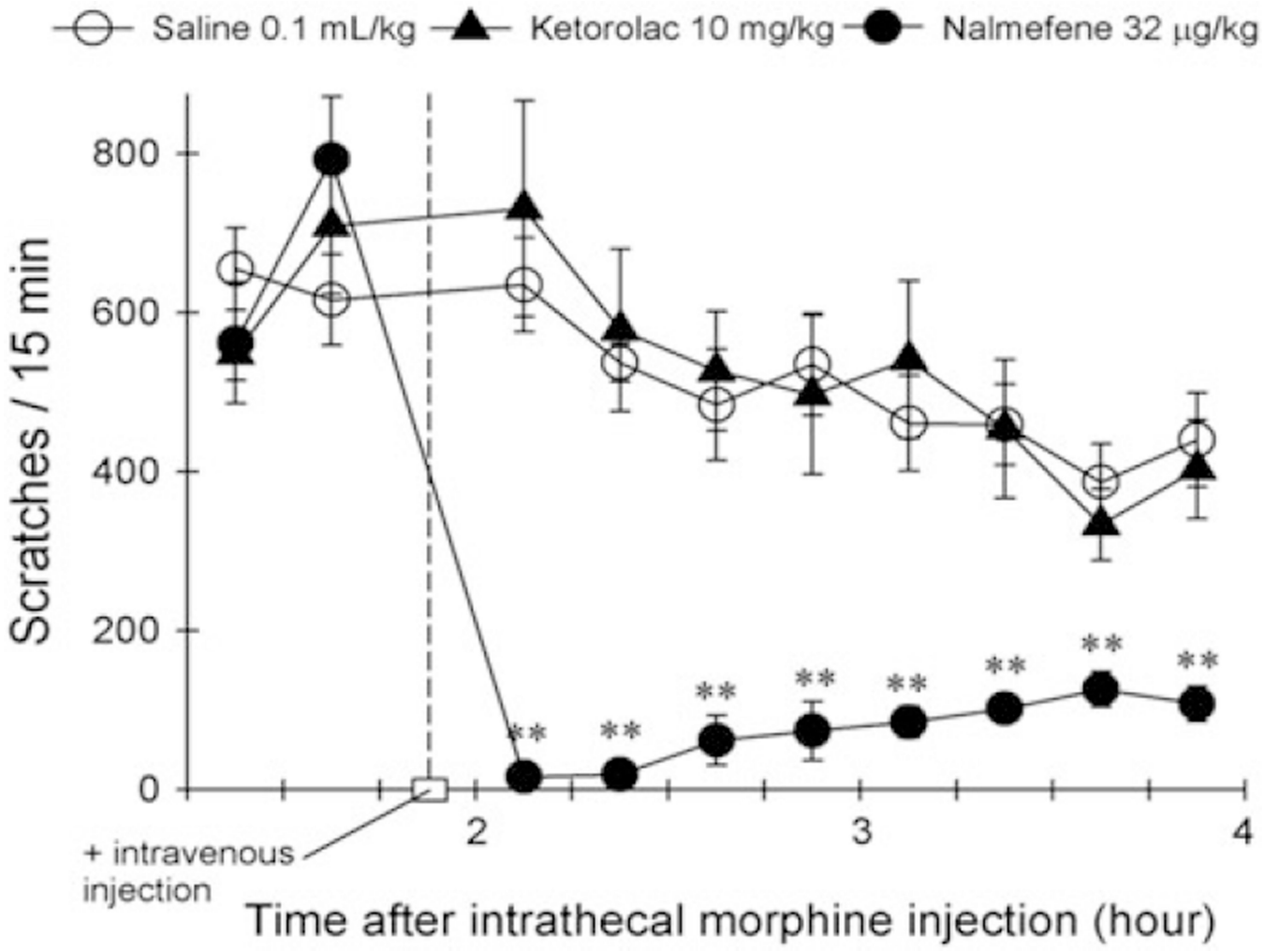

Fig. 2.

Effects of intravenous ketorolac and nalmefene on intrathecal morphine-induced itch scratching responses in rhesus monkeys. Each value represents mean +/− S.E.M. (*n* = 5). The *asterisks* represent significant differences from the saline condition

Table 1

Summary of preclinical studies evaluating the effectiveness of diverse ligands in managing neuraxial opioid-induced scratching in adult rhesus monkeys

Neuraxial opioids	Treatment drug and doses	Outcomes and conclusion	References
Intrathecal morphine 10–320 μg	Intravenous nalmefene (MOP antagonist) 10–32 μg/kg	Effective Scratching responses: ↓	Ko and Naughton (2000)
Intrathecal morphine 32 μg	Intramuscular clocinnamox (MOP antagonist) 0.1 mg/kg	Effective Scratching responses: ↓	Ko et al. (2004)
Intrathecal morphine 32 μg	Subcutaneous butorphanol (mixed KOP/MOP partial agonist) 10–32 μg/kg	Effective Scratching responses: ↓	Lee et al. (2007)
Intrathecal morphine 10–32 μg	Subcutaneous U-50488H (KOP agonist) 0.1–0.32 mg/kg	Effective Scratching responses: ↓	Ko et al. (2003b)
Intrathecal morphine 32 μg	Intramuscular nalfurafine (KOP agonist) 0.3–1 μg/kg	Effective Scratching responses: ↓	Ko and Husbands (2009)
Intrathecal morphine 32 μg	Intramuscular naltrindole (DOP antagonist) 1 mg/kg	Ineffective No change in scratching responses	Ko et al. (2004)
Intrathecal morphine 50 nmol	Intrathecal N/OFQ (NOP agonist) 10–100 nmol	Ineffective No change in scratching responses	Ko and Naughton (2009)
Intrathecal morphine 32 μg	Intravenous ondansetron (5HT3 antagonist) 0.1–3.2 mg/kg	Ineffective No change in scratching responses	Fig. 1
Intrathecal morphine 32 μg	Intramuscular diphenhydramine (antihistamine) 0.32–3.2 mg/kg	Ineffective No change in scratching responses	Ko et al. (2004)
Intrathecal morphine 32 μg	Intravenous ketorolac (NSAID) 1–10 mg/kg	Ineffective No change in scratching responses	Fig. 2

Note: ↓ = decrease/ inhibition, *MOP* mu opioid receptor, *KOP* kappa opioid receptor, *NOP* nociceptin/orphanin FQ peptide receptor, *DOP* delta opioid receptor, *NSAID* non-steroidal anti-inflammatory drug

Table 2

Summary of clinical studies evaluating the effectiveness of opioid receptor partial agonists in managing neuraxial opioid-induced pruritus in adult patients

Neuraxial opioids	Treatment drugs and doses	Outcomes and conclusion	References
Epidural morphine 0.1 mg/kg	Intravenous nalbuphine 0.1 mg/kg	Effective Pruritus score: ↓	Penning et al. (1988)
Epidural morphine 5 mg	Intravenous nalbuphine 20 mg	Ineffective No change in the degree of pruritus	Morgan et al. (1991)
Epidural morphine 5 mg	Intravenous nalbuphine 5 mg	Effective Severity of pruritus: ↓	Cohen et al. (1992)
Epidural morphine 5 mg	Intravenous nalbuphine 2.5 mg/h	Effective Pruritus score: ↓	Kendrick et al. (1996)
Epidural morphine 3 mg/12 h	Intravenous nalbuphine 60 μg/kg/h	Effective Incidence of pruritus (13 %): ↓	Wang et al. (1998)
Epidural morphine 1.5 mg/12 h	Intramuscular nalbuphine 10 mg	Effective Incidence of pruritus (44 %): ↓ Severity of pruritus: ↓	Liao et al. (2011)
Intrathecal morphine 200 μg	Nalbuphine (no specified delivery route) 5–10–10 mg, stepwise	Effective VAS score of zero (83 %)	Alhashemi et al. (1997)
Intrathecal morphine 200 μg	Intravenous nalbuphine 3 mg	Effective Treatment success rate (83 %): ↑	Charuluxananan et al. (2001)
Intrathecal morphine 200 μg	Intravenous nalbuphine 4 mg	Effective Pruritus score: ↓ Request for pruritus treatment: ↓	Charuluxananan et al. (2003)
Intrathecal morphine 150 μg	Intravenous nalbuphine 2–3 mg	Effective % of successful treatment (87–97 %): ↑	Somrat et al. (1999)
Intrathecal fentanyl 50 μg	Intravenous nalbuphine 4 mg	Partially effective Incidence of pruritus (61 %)	Ben-David et al. (2002)
Epidural morphine 4 mg	Epidural butorphanol 3 mg	Effective % patients treated for pruritus (0 %): ↓	Lawhorn et al. (1991)
Epidural morphine 4 mg	Epidural butorphanol 3 mg	Effective Incidence of pruritus (20 %): ↓	Wittels et al. (1993)
Epidural morphine 3 mg	Epidural butorphanol 3 mg	Ineffective No change in VAS for pruritus	Gambling et al. (1994)
Epidural morphine 60 μg/kg	Epidural butorphanol 30 μg/kg	Effective Severity of pruritus: ↓	Bailey et al. (1994)
Intrathecal morphine 150 μg	Intravenous butorphanol 2 mg	Ineffective No change in the intensity of pruritus	Sakai et al. (2001)
Intrathecal morphine 100 μg	Intravenous butorphanol Bolus 1 mg with 0.2 mg/h	Effective Incidence of pruritus (13 %): ↓	Wu et al. (2012)

Note: *VAS* visual analog scale, ↓ = decrease/inhibition, ↑ = increase

Table 3

Summary of clinical studies evaluating the effectiveness of a 5-HT3 receptor antagonist, ondansetron, in managing neuraxial opioid-induced pruritus in adult patients

Neuraxial opioids	Treatment drug and doses	Outcomes and conclusion	References
Epidural morphine, 2 mg Intrathecal morphine, 0.2 mg	Intravenous ondansetron 8 mg	Effective Success rate (70 %): ↑	Borgeat and Stirnemann (1999)
Epidural morphine 3 mg	Intravenous ondansetron 4 mg	Effective Incidence of pruritus (28 %): ↓	Tzeng et al. (2003)
Intrathecal sufentanil 2.5 μg and morphine 100 μg	Intravenous ondansetron 8 mg	Ineffective No change in the frequency and severity of pruritus	Yazigi et al. (2002)
Intrathecal morphine 160 μg and fentanyl 15 μg	Intravenous ondansetron 8 mg	Ineffective No change in the incidence of pruritus	Sarvela et al. (2006)
Intrathecal morphine 250 μg	Intravenous ondansetron 4 mg	Effective Incidence of pruritus (34 %): ↓	Iatrou et al. (2005)
Intrathecal morphine 200 μg	Intravenous ondansetron 4–8 mg	Effective Request for pruritus treatment: ↓	Charuluxananan et al. (2003)
Intrathecal morphine 200 μg	Intravenous ondansetron 4 mg	Effective Treatment success rate (80 %): ↑	Charuluxananan et al. (2000)
Intrathecal morphine 200 μg	Intravenous ondansetron 4 mg Orally disintegrating tablets 8 mg	Effective Incidence of pruritus (56–66 %): ↓	Pirat et al. (2005)
Intrathecal morphine 150 μg	Intravenous ondansetron 0.1 mg/kg	Effective Incidence of pruritus (25 %): ↓	Yeh et al. (2000)
Intrathecal fentanyl 25 μg	Intravenous ondansetron 4–8 mg	Ineffective No change in the incidence and severity of pruritus	Wells et al. (2004)
Intrathecal fentanyl 25 μg	Intravenous ondansetron 8 mg	Effective Incidence of pruritus (39 %): ↓	Gurkan and Toker (2002)
Intrathecal fentanyl 25 μg	Intravenous ondansetron 8 mg	Effective Incidence of pruritus (6 %): ↓	Gulhas et al. (2007)
Intrathecal fentanyl 15 μg	Intravenous ondansetron 8 mg	Ineffective No change in the incidence of pruritus	Browning et al. (2013)
Intrathecal fentanyl 10 μg	Intravenous ondansetron 4–8 mg	Ineffective No change in the incidence and severity of pruritus	Korhonen et al. (2003)
Intrathecal sufentanil 10 μg	Intravenous ondansetron 8 mg	Ineffective No change in the incidence and severity of pruritus	Waxler et al. (2004)

Note: *VAS* visual analog scale, ↓ = decrease/inhibition, ↑ = increase