Effects of Atypical κ-Opioid Receptor Agonists on Intrathecal Morphone-Induced Itch and Analgesia in Primates

Mei-Chuan Ko and Stephen M. Husbands

Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan (M.-C.K.); Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom (S.M.H.); and Department of Psychology, Institute of Neuroscience, and Research Center for Mind, Brain, and Learning, National Cheng Chi University, Taipei, Taiwan (M.-C.K.)

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ABSTRACT

itch/pruritus is the most common side effect associated with spinal administration of morphine given to humans for analgesia. The aim of this study was to investigate the effectiveness of κ-opioid receptor (KOR) agonists with diverse chemical structures as antipruritics and to elucidate the receptor mechanism underlying the antipruritic effect in monkeys. In particular, previously proposed non-KOR-1 agonists, including nalfurafine (TRK-820, 17-cyclopentylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan), bremazocine (2-ethyl-1,2,3,4,5,6-hexahydro-3-[1-hydroxycyclopropyl]-methyl]-11,11-dimethyl-2,6-methano-3-benzazocin-8-ol), and GR 89696 [4-[3,4-dichloro(NH2)]viny]acetyl]-3-(1-pyrrolidinylmethyl)-1-piperazinocarboxylic acid methyl ester, or GR 89696 did not antagonize systemic morphine-induced antinociception and respiratory depression. The dose-addition analysis revealed that there is no subadditivity for nalfurafine in combination with morphine in the antinociceptive effect. Furthermore, the KOR antagonist study revealed that antiscratching effects of both nalfurafine and a prototypical KOR agonist, U-50488H [trans-3,4-dichloro-N-methyl]-N-(2-[1-pyrrolidinyl]-cyclohexyl)-benzeneacetamide, could be blocked completely by a selective KOR antagonist, nor-binaltorphimine (3 mg/kg). These findings suggest that the agonist action on KOR mainly contributes to the effectiveness of these atypical KOR agonists as antipruritics, and there is no evidence for KOR subtypes or μ-opioid antagonist action underlying the effects of these KOR agonists. This mechanism-based study further supports the clinical potential of KOR agonists as antipruritics under the context of spinal opioid analgesia.

Spinal administration of μ-opioid receptor agonists is an important method for pain management. In particular, it is a widely used therapy for obstetric analgesia (Cousins and Mathers, 1984; DeBalli and Breen, 2003). However, itch/pruritus is the most common side effect of spinal opioid administration, and it reduces the value of spinal opioids for pain relief (Cousins and Mathers, 1984; Ganesh and Maxwell, 2007). Previous studies have demonstrated that the same μ-opioid receptors mediate both analgesic and itch/scratching responses in primates (Ko and Naughton, 2000; Ko et al., 2004). Therefore, opioid receptor antagonists such as naloxone are not ideal antipruritics to be used under this context because such compounds can reverse opioid analgesia concurrently (Rawal et al., 1986; Cohen et al., 1992; Wang et al., 1998). It is important to identify specific pharmacological agents that can inhibit spinal opioid-induced itch without attenuating analgesia.

The κ-opioid receptor (KOR) seems to be a promising target because several studies suggest that KOR agonists are potentially useful as antipruritics. For example, scratching was a prominent withdrawal sign in monkeys treated chronically with and withdrawn from a selective KOR agonist, U-50488H (Gmerik et al., 1987). Many withdrawal symptoms from opioids appear to be opposite to the acute effects of agonist administration (Heishman et al., 1989; Kishioka et al., 1998). It is important to identify specific pharmacological agents that can inhibit spinal opioid-induced itch without attenuating analgesia.

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ABBREVIATIONS: KOR, κ-opioid receptor; U-50488H, trans-(±)-3,4-dichloro-N-methyl-N-(2-[1-pyrrolidinyl]-cyclohexyl)-benzeneacetamide; nalfurafine (TRK-820), 17-cyclopentylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan; nor-BNI, nor-binaltorphimine; bremsazocine, (±)-6-ethyl-1,2,3,4,5,6-hexahydro-3-[1-hydroxycyclopropyl]methyl]-11,11-dimethyl-2,6-methano-3-benzazocin-8-ol; GR 89696, 4-[3,4-dichlorophenyl]acetyl]-3-(1-pyrrolidinylmethyl)-1-piperazinocarboxylic acid methyl ester.
al., 2000). Excessive scratching activity observed during KOR withdrawal indicates that acute administration of KOR agonists may have antipruritic effects. Animal studies seem to support this notion because systemic administration of KOR agonists inhibited scratching evoked by pruritogenic agents without interfering with locomotor activity in rodents (Cowan and Gmerek, 1986; Togashi et al., 2002). In addition, KOR agonists can prevent or reverse intrathecal morphine-induced itch/scratching responses without interfering with intrathecal morphine analgesia in monkeys (Ko et al., 2003a). More importantly, animal studies have led to a successful clinical trial of a novel KOR agonist, nalfurafine (TRK-820), in hemodialysis patients suffering from uremic pruritus, supporting the therapeutic potential of KOR agonists as antipruritics (Wikström et al., 2005).

It is interesting that KOR antagonist studies have indicated that KOR-mediated antinoceceptive effects may occur through two KOR subtypes. This distinction between KOR-1 and non-KOR-1 agonists is derived primarily from the differential susceptibility of KOR agonists to a KOR antagonist, nor-binaltorphimine (nor-BNI), and other opioid receptor antagonists, such as naltrexone in primates (Butelman et al., 1993; Ko et al., 1998). Prototypical KOR-1 agonists such as U-50488H are more sensitive to the antagonist effects of nor-BNI and naltrexone (Butelman et al., 1993; Ko et al., 1998). In contrast, other KOR agonists, including nalfurafine, bremazocine, and GR 89696, are less sensitive to the antagonist effects of nor-BNI and naltrexone (Butelman et al., 1993, 2001; Ko et al., 1998). Endoh et al. (2001) also demonstrated that KOR-1 agonists are less sensitive to the antagonist effects of nor-BNI and naltrexone.

The first part of the study was to determine the effectiveness of these atypical KOR agonists as antipruritics and to elucidate the receptor mechanisms underlying the antipruritic actions of these KOR agonists.

Intrathecal administration of a single dose of morphine produces both itch/scratching and antinoceceptive simultaneously in monkeys (Ko and Naughton, 2000; Ko et al., 2003a). This finding parallels closely with the behavioral effects of spinal administration of morphine in humans (Bailey et al., 1993; Palmer et al., 1999). It is valuable to investigate the effectiveness of these atypical KOR agonists as antipruritics and their mechanisms underlying the antipruritic actions of these KOR agonists under this context.

### Materials and Methods

#### Subjects

Eighteen adult intact male and female rhesus monkeys (*Macaca mulatta*) with body weights ranging between 6.5 and 12.1 kg were used. The monkeys were housed individually with free access to water and were fed approximately 25 to 30 biscuits (Purina Monkey Chow;Ralston Purina, St. Louis, MO) and fresh fruit daily. No monkey had exposure to any opioid receptor agonist or antagonist 1 month before the present study. The monkeys were housed in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care. The studies were conducted in accordance with the University Committee on the Use and Care of Animals in the University of Michigan (Ann Arbor, MI) and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the United States National Institutes of Health (Institute of Laboratory Animal Resources, 1996).

#### Procedures

##### Scratching Responses

Scratching responses, inferred to be a response to an itch sensation (Ko and Naughton, 2000; Ko et al., 2004), were recorded on videotapes while the monkeys were in their home cages. Each recording session was conducted for 15 min/test session. A scratch was defined as one short-duration (<1 s) episode of scraping contact of the forepaw or hind paw on the skin surface of other body parts. Scratches occurred repetitively at the same location. Scratching responses were scored by trained individuals who were blinded to experimental conditions. In addition, sedation was evaluated by cumulative time for eye closure or lying down at the bottom of the cage.

##### Antinoception

The warm water (50°C) tail-withdrawal assay was used to evaluate thermal antinoceptive effects of the test compound (Ko et al., 1998). In brief, monkeys were seated in primate restraint chairs, and the lower parts of their shaved tails (approximately 15 cm) were immersed in a thermal flask containing water maintained at 42, 46, or 50°C. Tail-withdrawal latencies were measured using a computerized timer by an experimenter who was blinded to experimental conditions. In each test session, monkeys were evaluated once with three temperatures given in a random order. If the monkeys did not remove their tails within 20 s (cutoff), the flask was removed, and a maximum time of 20 s was recorded. Test sessions began with determining a control value at each temperature. Subsequent tail-withdrawal latencies were determined at multiple time points after the drug administration.

##### Respiratory Function

The monkey was seated in a primate restraint chair, enclosed within a sound-attenuating chamber. A rectangular helmet (13.5 × 17.0 × 13.5 cm) was placed over the head of the monkey and sealed around its neck by two closely fitting latex shields. Gas (either air or a mixture of 5% CO2 in air) flowed into the helmet and was pumped out at a rate of 8 l/min. The breathing of the monkeys produced changes in pressure inside the helmet that were measured with a pressure transducer connected to a polygraph (Grass model 7; Grass Instruments, Quincy, MA), and the data were recorded on a polygraph trace and in a microprocessor (IBM personal computer; IBM, White Plains, NY) via an analog-to-digital converter. The apparatus was calibrated routinely with known quantities of air.

The polygraph integrator was connected to a computer, which analyzes the data collected over a 3-min period. The rate of breathing (f, respiratory frequency) was determined directly. The minute volume (V _m_ ) was determined from the integration of the plethysmograph system. When the test compound was given in a cumulative dosing procedure, the test session contained six consecutive cycles. Each cycle was 30 min, which included the first 23-min exposure to air alone and the remaining 7-min exposure to 5% CO2 mixed in air. Responses in the first two cycles were averaged as a control value. The test compound was administered intramuscularly in the beginning of each cycle for the remaining dosing injection cycles (i.e., from 3rd–6th cycle).

#### Experimental Designs

The first part of the study was to determine the intervention effectiveness of KOR agonists with diverse chemical structures (Fig. 1), nalfurafine, bremazocine, and GR 89696, as antipruritics in monkeys (n = 6). In particular, the dose-response studies were conducted to investigate whether these KOR agonists could block scratching responses subsequent to intrathecal administration of morphine. Nalfurafine (0.1–1 μg/kg), bremazocine
volved in both nal啡afine- and U-50488H-induced antinociception and respiratory depression were used to detect the potential μ-opioid receptor antagonist effects of these KOR agonists. Additional antagonist studies were conducted to elucidate whether potential μ-opioid receptor antagonist effects could mediate the antiscratching effects of nal啡afine. The dose-addition analysis was used to evaluate the drug interaction between nal啡afine and morphine, and it could be used to differentiate the additive effects from the subadditive effects (Tallarida, 2000). Initially, dose-response curves for subcutaneous nal啡afine- and morphine-induced antinociception were determined. Depending on the potency of nal啡afine, three mixtures of nal啡afine in combination with morphine were determined for their dose-response curves for antinociception. For the remainder, a selective KOR antagonist, nor-BNI, was used to determine the involvement of KOR in both nal啡afine- and U-50488H-induced antiscratching effects. After administration of nor-BNI (3 mg/kg i.m.), effects of nal啡afine (1 μg/kg) and U-50488H (100 μg/kg) on intrathecal morphine (0.03 mg) were investigated. Effects on scratching and respiratory depression were assessed. The dose and pretreatment time for nor-BNI were determined based on previous studies showing that KOR antagonist effects of nor-BNI were observed within the first 2 weeks after systemic administration in monkeys (Butelman et al., 1993; Ko et al., 2003a).

Data Analysis. Mean values (mean ± S.E.M.) were calculated from individual values for all behavioral endpoints. Comparisons were made for the same monkeys across all test sessions in the same experiment. Data were analyzed by a two-way analysis of variance followed by the Newman-Keuls test for multiple (post hoc) comparisons. The criterion for significance was set at p < 0.05. For the dose-addition analysis, individual tail-withdrawal latencies in 50°C water were first converted to percentage of maximum possible effect, [(test latency – control latency)/(cutoff latency – control latency)] × 100. ED₅₀ values were then calculated by least-squares regression with the portion of the dose-response curves spanning the 50% of maximal possible effect, and 95% confidence limits were also determined (p < 0.05). Finally, statistical evaluation of drug interactions between nal啡afine and morphine was conducted by comparing the experimentally determined ED₅₀ values for each mixture (Zₘ₉) with predicted additive ED₅₀ values (Zₐdd) as described by Tallarida (2000). In brief, Zₘ₉ values were determined empirically as described above. Zₐdd values were calculated individually for each monkey by using the equation, Zₐdd = fA + (1 – f)B, where A is the ED₅₀ for nal啡afine alone, B is the ED₅₀ for morphine alone, and f = 0.25, 0.5, 0.75 represents the fractional multiplier for three mixtures of nal啡afine in combination with morphine.

Drugs. GR 89696 fumarate salt and U-50488H methanesulfonate salt (Sigma-Aldrich, St. Louis, MO), brema佐cine hydrochloride (RBI/Sigma, Natick, MA), nal啡afine hydrochloride (provided by Dr. S. M. Husbands, University of Bath, Bath, UK), nor-BNI dihydrochloride (Tocris Bioscience, Ellisville, MO), and morphine sulfate (Mallinckrodt, Hazelwood, MO) were dissolved in sterile water. Doses were presented in the compound forms listed above. For sys

Fig. 1. Structures of μ-opioid receptor agonists, brema佐cine, nal啡afine (TRK-820), and GR 89696.

**Fig. 2.** Effects of nal啡afine intervention on intrathecal morphine-induced itch/scratching and antinociception against 50°C water. Nal啡afine (micrograms per kilogram intramuscularly) was given 45 min after intrathecal administration of 0.03 mg of morphine. Each value represents mean ± S.E.M. (n = 6). Symbols represent different dosing conditions for the same monkeys. *+, significant difference from the vehicle condition between time points 1 and 2.5 h (p < 0.05).
temic administration, all compounds were administered at a volume of 0.1 ml/kg. For intrathecal administration, morphine was administered at a total volume of 1 ml. The detailed description for intrathecal drug delivery can be referred to Ko et al. (2003a).

Results

Figure 2 illustrates the effects of intramuscular nalfurafine on intrathecal morphine-induced scratching and antinociception. Nalfurafine intervention dose-dependently attenuated intrathecal morphine-induced scratching [F(3,15) = 7.0; p < 0.05]. Post hoc comparisons indicated that nalfurafine from 0.3 to 1 μg/kg significantly attenuated scratching between time points 1 and 2.5 h. Nalfurafine did not alter intrathecal morphine-induced antinociception [F(1,5) = 2.1; p > 0.05]. In addition, nalfurafine did not increase the sedation score [F(3,15) = 0.9; p > 0.05] under these conditions. Nalfurafine alone at the highest dose 1 μg/kg tested herein did not significantly increase scratching responses compared with the vehicle condition (data not shown).

Figure 3 illustrates the effects of intramuscular bremazocine on intrathecal morphine-induced scratching and antinociception. Bremazocine intervention dose-dependently attenuated intrathecal morphine-induced scratching [F(3,15) = 3.1; p < 0.05]. Post hoc comparisons indicated that bremazocine from 0.3 to 1 μg/kg significantly attenuated scratching between time points 1.5 and 2.5 h. Bremazocine did not alter intrathecal morphine-induced antinociception [F(1,5) = 2.5; p > 0.05]. In addition, bremazocine did not increase the sedation score [F(3,15) = 1.5; p > 0.05] under these conditions.

Figure 4 illustrates the effects of intramuscular GR 89696 on intrathecal morphine-induced scratching and antinociception. GR 89696 intervention dose-dependently attenuated intrathecal morphine-induced scratching [F(3,15) = 6.8; p < 0.05]. Post hoc comparisons indicated that 0.1 μg/kg GR 89696 significantly attenuated scratching between time points 1.5 and 2.5 h. GR 89696 did not alter intrathecal morphine-induced antinociception [F(1,5) = 0.5; p > 0.05]. In addition, GR 89696 did not increase the sedation score [F(3,15) = 1.4; p > 0.05] under these conditions.

The dose-response curves of morphine-induced antinociception in the presence of different KOR agonists (i.e., 0.1 ml/kg vehicle, 1 μg/kg nalfurafine, 1 μg/kg bremazocine, and 1 μg/kg GR 89696) are shown in Figure 5. The results indicate that all compounds tested significantly reduced scratching and antinociception compared with the vehicle condition. However, the extent of the reduction varied depending on the compound and dose used.
nor-BNI also significantly blocked the ability of 100 μg/kg GR 89696 to attenuate intrathecal morphine-induced scratching \( [F(2,10) = 16.2; p < 0.05] \).

**Discussion**

The first part of the study showed that systemic administration of atypical KOR agonists, nalfurafine (TRK-820), bremazocine, and GR 89696, potently attenuated intrathecal morphine-induced itch/scratching responses in a dose-dependent manner. It is important that intervention with these KOR agonists maintained intrathecal morphine-induced antinociception without producing sedation, supporting the notion of using KOR agonists for treating pruritus associated with spinal opioid analgesia in primates. It is worth noting that these KOR agonists used in the present study are extremely potent (i.e., in the unit of micrograms per kilogram), and these doses alone do not produce significant antinociceptive effects in monkeys (Butelman et al., 1993, 2001; Ko et al., 1998; Endoh et al., 2001). It may indicate that there are more KORs expressed in sensory neurons modulating itch sensation compared with those in nociceptors and/or that activation of KOR is more efficient in producing antipruritic actions than antinociceptive action. Nevertheless, it should be noted that these nonantinociceptive, nonsedative doses of KOR agonists did not completely suppress intrathecal morphine-elicited scratching. It is possible that distributions of morphine administered intrathecally and KOR agonists administered intramuscularly are not equivalent, and distinct sites of actions for both intrathecal morphine and intramuscular KOR agonists contribute to remaining scratching observed under this context. It will be interesting to examine whether intrathecal administration of morphine and KOR agonists together can produce maximal suppression of scratching responses in future studies.

The second part of the study demonstrated that antiscratching doses of these KOR agonists did not produce μ-opioid receptor antagonist effects. In particular, pretreatment with effective antiscratching doses of nalfurafine, bremazocine, or GR 89696 did not antagonize systemic mor-

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**Fig. 5.** Effects of pretreatment with κ-opioid receptor agonists on the dose-response curve of systemic morphine-induced respiratory depression. A single dose of the compound (micrograms per kilogram intramuscularly) was given 30 min before administration of the first dose of morphine (milligrams per kilogram intramuscularly). BL represents the effects of κ-opioid receptor agonists alone on the respiratory function of the subjects (i.e., the control value). Each value represents mean ± S.E.M. (n = 6).
Although these KOR agonists have moderate binding affinities, they have approximately 100-fold lower potency in stimulating /\mu/-opioid receptors compared with KOR measured by a functional guanosine 5’-3-O-(thio)triphosphate binding assay (Emmerson et al., 1994; Toll et al., 1998; Butelman et al., 2001; Wang et al., 2005). These findings may suggest that potential /\mu/-opioid antagonist effects of these KOR agonists can only be manifested at much higher doses in the guanosine 5’-3-O-(thio)triphosphate binding assay, and they cannot be detected in vivo in monkeys because of untoward effects elicited by high doses of KOR agonists (Butelman et al., 2001; Mizoguchi et al., 2003).

Because nalfurafine has been studied in the clinical trial (Wikström et al., 2005), additional pharmacological approaches were used to elucidate the receptor mechanisms underlying this compound’s antiscratching effects. The dose-addition analysis and its isobologram indicate that there were additive effects for nalfurafine in combination with morphine in producing antinociceptive effects. This finding strongly supports the notion that /\mu/-opioid antagonist effects of atypical KOR agonists identified from in vitro studies may not contribute to their behavioral effects observed herein (Butelman et al., 2001; Mizoguchi et al., 2003; Wang et al., 2005). More importantly, the KOR antagonist study revealed that antiscratching effects of both nalfurafine and U-50488H could be blocked completely by nor-BNI pretreatment. For comparison, a recent study has demonstrated that nor-BNI only acts as a diuretic and antiscratching effects of bremazocine in the same monkeys (Ko et al., 1999). In contrast, intracisternal nor-BNI at the same dose equally blocked both U-50488H- and bremazocine-induced diuresis for 20 weeks (Ko et al., 2003b). These findings may indicate that the KOR population required for producing antinociception is greater than that for diuretic and antiscratching effects in primates. Although functional KOR subtypes have been proposed based on different pharmacological studies (Butelman et al., 1993, 1998; Ko et al., 1998), both KOR-1 and non-KOR-1 agonists are equally active in a variety of behavioral assays in monkeys (France et al., 1994; Butelman et al., 2001; Ko et al., 2003b).

Previous studies have found differences in KOR-regulated desensitization and phosphorylation between human KOR and rat KOR (Li et al., 2002; Liu-Chen, 2004). The major difference of KOR in vivo between rodents and primates is that the KOR antagonist, nor-BNI, elicits scratching responses in mice (Kamei and Nagase, 2001), but it does not do so in monkeys (Ko et al., 2003a). nor-BNI only acts as a neutral KOR antagonist to block the behavioral effects of

**TABLE 1**

Predicted ED₅₀ values (Zₕₐ₅) and experimentally determined ED₅₀ values (Zₘᵢₓ) of mixtures of nalfurafine administered in combination with morphine in the antinociceptive assay in monkeys

<table>
<thead>
<tr>
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<th>Zₕₐ₅ (95% CL)</th>
<th>Zₘᵢₓ (95% CL)</th>
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<tbody>
<tr>
<td>Nalfurafine + morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0027:1, Nalfurafine/morphine</td>
<td>0.76 (0.43–1.37)</td>
<td>0.74 (0.43–1.29)</td>
</tr>
<tr>
<td>0.008:1, Nalfurafine/morphine</td>
<td>0.51 (0.29–0.92)</td>
<td>0.34 (0.22–0.52)</td>
</tr>
<tr>
<td>0.024:1, Nalfurafine/morphine</td>
<td>0.26 (0.15–4.6)</td>
<td>0.17 (0.11–0.26)</td>
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CL, confidence limit.
KOR agonists in primates (Butelman et al., 1993; Ko et al., 1999, 2003a). Nevertheless, both types of KOR agonists, such as nalfurafine and U-50488H, have been shown to have a broader application as antipruritics by using diverse pruritogenic agents across both rodents and primates (Togashi et al., 2002; Ko et al., 2003a; Wakasa et al., 2004; Wang et al., 2005; Inan and Cowan, 2006). An early study has shown that subcutaneous administration of nalfurafine could effectively suppress intracisternal morphine-induced scratching in mice (Umeuchi et al., 2003). However, as previously demonstrated, intrathecal morphine simultaneously produces both scratching and antinociception in monkeys, but not in rodents (Ko and Naughton, 2000; Ko et al., 2003a; Lee et al., 2003). The present study of KOR agonists as antipruritics in primates further extends the therapeutic application of KOR agonists under the context of spinal opioid analgesia (Ko et al., 2003a; Lee et al., 2007; the present study). More importantly, a recent study demonstrated that there are two separate populations of spinothalamic tract neurons responding to histamine versus nonhistaminergic pruritogenic agent, cowhage, in monkeys (Davidson et al., 2007). It will be important to conduct more translational research in primates to compare the effectiveness of KOR agonists against scratching responses evoked by different pruritogenic agents.

In summary, this study is the first to provide direct evidence and translational value that previously proposed non-KOR-1 agonists, nalfurafine, bremazocine, and GR 89696, are effective and very potent in blocking intrathecal morphine-induced itch/scratching responses without interfering with intrathecal morphine-induced analgesia in primates. The agonist action of KOR mainly contributes to the effectiveness of nalfurafine as an antipruritic, and there is no evidence in vivo for KOR subtypes or μ-opioid antagonist action underlying the antipruritic effects of nalfurafine. These findings further support the therapeutic potential of KOR agonists, regardless of their KOR-1 selectivity, as antipruritics in the context of spinal opioid analgesia.

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References


Ko and Husbands


Address correspondence to: Dr. Mei-Chuan Ko, Department of Pharmacology, University of Michigan Medical School, 1301 MSRB III, Ann Arbor, MI 48109-5632. E-mail: mko@umich.edu