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Antipruritic activity of the κ-opioid receptor agonist, TRK-820

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Abstract

The effects of the κ-opioid receptor agonist, TRK-820, (−)-17-(cyclopropylmethyl)-3, 14β-dihydroxy-4, 5α-epoxy-6β-[*N*-methyl-*trans*-3-(3-furyl) acrylamido] morphinan hydrochloride, on the itch sensation were compared with those of histamine H_1 receptor antagonists, using the mouse pruritogen-induced scratching model. Peroral administration of TRK-820 reduced the numbers of substance P- or histamine-induced scratches dose dependently. No obvious suppression of the spontaneous locomotor activity was observed at the doses used for the experiments, indicating that the inhibition of scratches was not due to the effect on general behavior. Furthermore, the scratching inhibitory activity of TRK-820 was dose dependently antagonized by the specific κ-opioid receptor antagonist, nor-binaltorphimine, suggesting that the inhibitory activity was mediated via κ-opioid receptors. Histamine H_1 receptor antagonists, chlorpheniramine and ketotifen, did not inhibit substance P-induced scratches, or did so only partially. Both antihistamines inhibited the histamine-induced scratches completely. These results suggest that TRK-820 has antipruritic activity which is mediated by κ-opioid receptors, and is effective in both antihistamine-sensitive and -resistant pruritus. © 2002 Published by Elsevier Science B.V.

Keywords: Pruritus; Itch; κ-Opioid receptor agonist; TRK-820

1. Introduction

One of the most common adverse effect of epidurally or intrathecally administered morphine, the μ-opioid receptor agonist, in humans is pruritus which is localized in the face, neck and upper thorax (Cousins and Mather, 1984; Ballantyne et al., 1988). On the other hand, the μ-opioid receptor antagonist, naloxone, blocks experimentally induced itching (Bernstein et al., 1982). Naloxone and naltrexone also suppress the itch sensation in patients with chronic cholestasis, chronic renal failure and atopic dermatitis (Bergasa et al., 1992; Peer et al., 1996; Metze et al., 1999). These observations suggest that the μ-opioid receptor system is involved in the itch sensation processing.

On the other hand, there is little information regarding whether compounds acting on κ-opioid receptors modulate the itch sensation in humans. In experimental animals, there was a suggestion that κ-opioid receptor agonists have antipruritic activity based on their inhibitory activity against bombesin-induced scratching behavior (Gmerek and Cowan, 1988). However, the physiological relevance of the stimulation remains unclear. It was reported recently that κ-opioid receptor agonists inhibit compound 48/80-induced scratching behavior (Cowan and Kehner, 1997; Kehner et al., 1999; Kamei and Nagase, 2001), which has been proposed as an animal itch model (Kuraishi et al., 1995). The fact that compound 48/80 causes histamine release from mast cells (Lowman et al., 1988; He et al., 1990) and that compound 48/80-induced scratching is inhibited by histamine H_1 receptor antagonists (Sugimoto et al., 1998; Kamei and Nagase, 2001) suggests that the experimental system mimics the antihistamine-sensitive pruritus in humans. Therefore, results indicate that the activation of κ-opioid receptors is effective against antihistamine-sensitive pruritus.

In clinical settings, antihistamine-resistant pruritus is important and is observed in patients with many symptoms such as atopic dermatitis, chronic cholestasis and chronic urticaria (Duncan et al., 1984; Wahlgren et al., 1990; Ponticelli and Bencini, 1995). Kuraishi and his colleagues

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reported that the administration of pruritogenic agent, substance P, induced scratching behavior, which mimicked the characteristics of itch-related scratches in humans (Kuraishi et al., 1995; Andoh et al., 1998). In addition, the substance P-induced scratching behavior is not inhibited by the histamine H_1 receptor antagonist (Kitagawa et al., 1997), and elicited responses even in mast cell-deficient mice. Taken together, these findings make it likely that substance P-induced scratches represent antihistamine-resistant pruritus.

In this study, we examined, for the first time, the effectiveness of κ-opioid receptor agonists against antihistamine-resistant pruritus in the animal model. A novel κ-opioid receptor agonist, TRK-820, (−)-17-(cyclopropylmethyl)-3, 14β-dihydroxy-4, 5α-epoxy-6β-[*N*-methyl-*trans*-3-(3-furyl) acrylamido] morphinan hydrochloride (Nagase et al., 1998), was employed to evaluate the ability of the κ-opioid receptor agonist to suppress antihistamine-resistant pruritus. TRK-820 reduced the number of substance P-induced scratches dose dependently in mice, and the scratching inhibitory activity was antagonized by the κ-opioid receptor antagonist, nor-binaltorphimine. These findings suggest that the κ-opioid receptor agonist, TRK-820, has the ability to suppress antihistamine-resistant pruritus via κ-opioid receptor-mediated mechanisms.

2. Materials and methods

2.1. Animals

Male ICR mice (Japan SLC, Japan) aged 4–5 weeks were used. The animals were housed 5 per cage under a controlled 12-h light–dark cycle and allowed free access to food pellets and tap water. One day before testing, the rostral part of the back of each mouse was shaved.

2.2. Drugs

Substance P (Peptide Institute, Japan) and histamine (Wako, Japan), which were used to induce the scratching behavior, were dissolved in phosphate-buffered saline, pH 7.4 (PBS; Gibco BRL, USA). TRK-820 (Toray Industries, Japan) was dissolved in distilled water containing 5% D-mannitol, ketotifen (Sigma, USA) was dissolved in distilled water containing 10% dimethyl sulfoxide, and nor-binaltor-

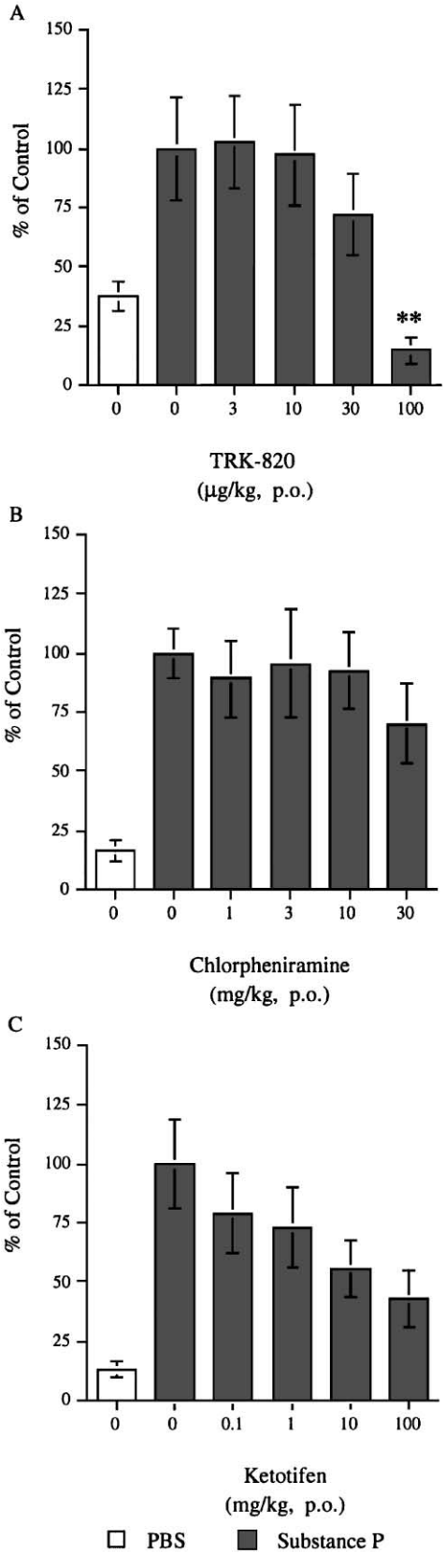

Fig. 1. Effects of TRK-820, chlorpheniramine or ketotifen on the substance P-induced scratching behavior in mice. The ICR strain mouse was given a p.o. administration of TRK-820 (A), chlorpheniramine (B) or ketotifen (C), and 30 (A) or 60 (B,C) min later, substance P (250 nmol/site) or PBS was injected intradermally. Immediately after the intradermal injection of substance P or PBS, the number of scratchings was recorded and counted over a 30-min period. The scratching number of the vehicle and substance P-injected group is shown as 100% in the vertical axes. Each value represents the mean ± S.E.M. ($n=8$). ** $P<0.01$ when compared with the vehicle and substance P-injected group (Dunnett's test).

phimine (synthesized by Toray Industries) and chlorpheniramine (Wako) were dissolved in distilled water.

2.3. Observation of the scratching behavior

The scratching behavior was observed according to the method described already (Kuraishi et al., 1995). Briefly, 30 min before testing, the mice were placed in a cage for acclimation. Immediately after an intradermal (i.d.) injection of substance P or histamine, the mice were returned to the same cages and behavior was recorded for 30 min using a video camera under unmanned conditions. Each recording was played back to count scratches. The number of scratches toward the injection site with their hind paws was counted and that of other sites such as ears and face was disregarded. Mice generally showed several scratches for about 1 s, such that a series of such behavior was counted as one scratch event. A volume of 50 μl of substance P or histamine was injected i.d. into the rostral part of the back. Test compounds were administered p.o. 30 or 60 min before the injection of pruritogen. Nor-binaltorphimine was administered s.c. 24 h before the TRK-820 injection, as described (Endoh et al., 1992).

2.4. Evaluation of the spontaneous locomotor activity

Spontaneous locomotor activity was evaluated by the wheel running test, as described (Misslin et al., 1988). Immediately following administration of the test compound, the mice were placed in the wheel of the apparatus and the number of rotations was recorded using a counter, for 60 min. The apparatus consisted of a running wheel with a central perforated metal band (6 cm wide) enclosed at each side by a circular Plexiglas sheet.

2.5. Data processing

Statistical significance was analyzed using comparisons made by repeated measures, using one-way or two-way analysis of variance, and post host hoc Dunnett's or unpaired *t*-test; $P < 0.05$ was considered significant. The percent of control was calculated as follows: (numbers of scratches)/(mean of the scratches in the pruritogen and vehicle instead of test compound-injected group) × 100. The ED_{50} value was defined as the dose required to produce 50% reduction of the

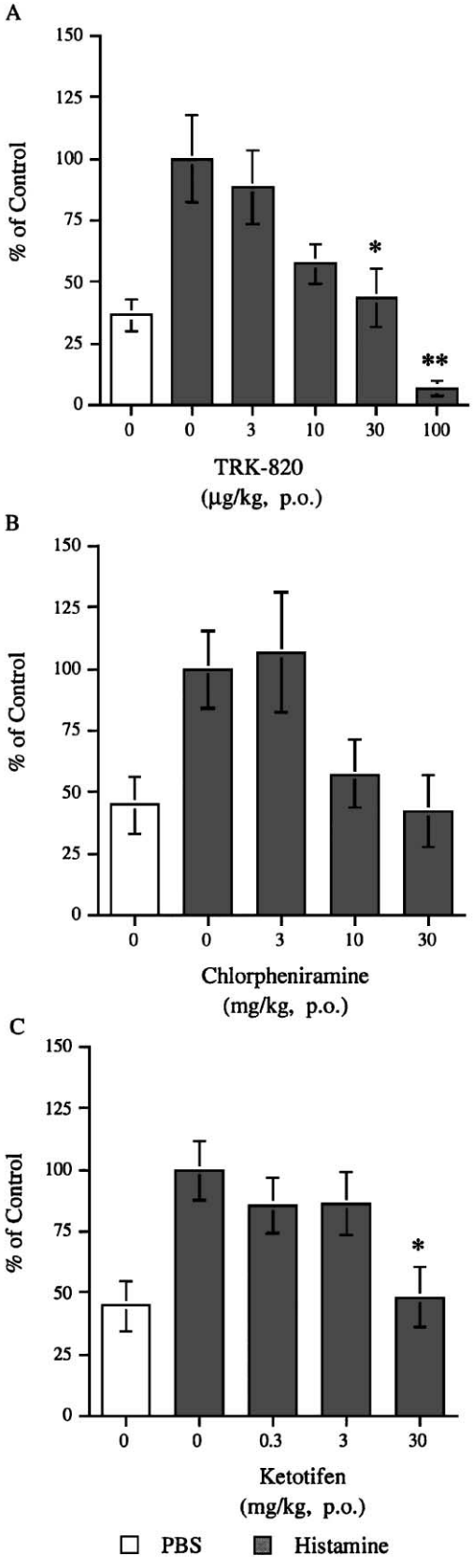

Fig. 2. Effects of TRK-820, chlorpheniramine or ketotifen on the histamine-induced scratching behavior in mice. The ICR strain mouse was given a p.o. administration of TRK-820 (A), chlorpheniramine (B) or ketotifen (C), and 30 (A) or 60 (B,C) min later, histamine (10 μg/site) or PBS was injected intradermally. Immediately after the intradermal injection of histamine or PBS, the number of scratchings was recorded and counted over a 30-min period. The scratching number of the vehicle and histamine-injected group is shown as 100% in the vertical axes. Each value represents the mean ± S.E.M. ($n = 7–12$). * $P < 0.05$, ** $P < 0.01$ when compared with the vehicle and histamine-injected group (Dunnett's test).

pruritogen-induced scratching numbers. The background scratching numbers, as obtained in the PBS-injected group, were subtracted from the scratching numbers of all pruritogen-injected groups and used for the calculations.

3. Results

3.1. Effects of TRK-820, chlorpheniramine or ketotifen on the substance P-induced scratching behavior

The effects of TRK-820, chlorpheniramine or ketotifen on the substance P-induced scratching are shown in Fig. 1. TRK-820, administered p.o. 30 min before the injection of substance P, dose dependently inhibited the scratching behavior and statistically significant inhibition was seen in the 100 μg/kg group (Fig. 1A). The ED_{50} value of TRK-820 was calculated as 19.6 μg/kg (95% confidence limits; 9.6–40.0 μg/kg). At the same time, the doses of TRK-820 affecting spontaneous locomotor activity were assessed in the mouse wheel running test. TRK-820, administered p.o. 30 min earlier, dose dependently suppressed running activity and the ED_{50} value was calculated as 102.8 μg/kg (95% confidence limits; 64.9–163.0 μg/kg).

Chlorpheniramine at doses of 1–30 mg/kg did not inhibit the substance P-induced scratching behavior (Fig. 1B). Ketotifen, administered p.o. 60 min before the injection of substance P, inhibited the scratching behavior dose dependently, but only moderate (66%) inhibition was observed with the highest dose, 100 mg/kg, used (Fig. 1C).

3.2. Effects of TRK-820, chlorpheniramine or ketotifen on the histamine-induced scratching behavior

The effects of TRK-820, chlorpheniramine or ketotifen on the histamine-induced scratching behavior are shown in Fig. 2. TRK-820, administered p.o. 30 min before the injection of histamine, dose dependently inhibited the scratching behavior and statistically significant inhibition was seen in the 30 and 100 μg/kg groups (Fig. 2A). The ED_{50} value of TRK-820 was calculated as 7.3 μg/kg (95% confidence limits; 4.2–12.6 μg/kg). Chlorpheniramine and ketotifen, administered 60 min earlier, also inhibited the scratching behavior dose dependently (Fig. 2B,C). The ED_{50} values of chlorpheniramine and ketotifen for the histamine-induced scratches were calculated as 8.5 mg/kg (95% confidence limits; 1.7–25.5 mg/kg) and 3.4 mg/kg (95% confidence limits; 0.5–20.3 mg/kg), respectively.

3.3. Effect of nor-binaltorphimine on the scratching inhibition activity of TRK-820

To confirm that the scratching inhibitory activity of TRK-820 is mediated by κ-opioid receptors, the effect of the κ-opioid receptor antagonist, nor-binaltorphimine, on the activity of TRK-820 was examined. Pretreatment with nor-binaltorphimine at doses of 1–10 mg/kg suppressed the scratching inhibitory activity of TRK-820 dose dependently (Fig. 3). The numbers of scratches in the TRK-820-injected and in the corresponding vehicle-injected groups after pretreatment with 10 mg/kg of nor-binaltorphimine did not

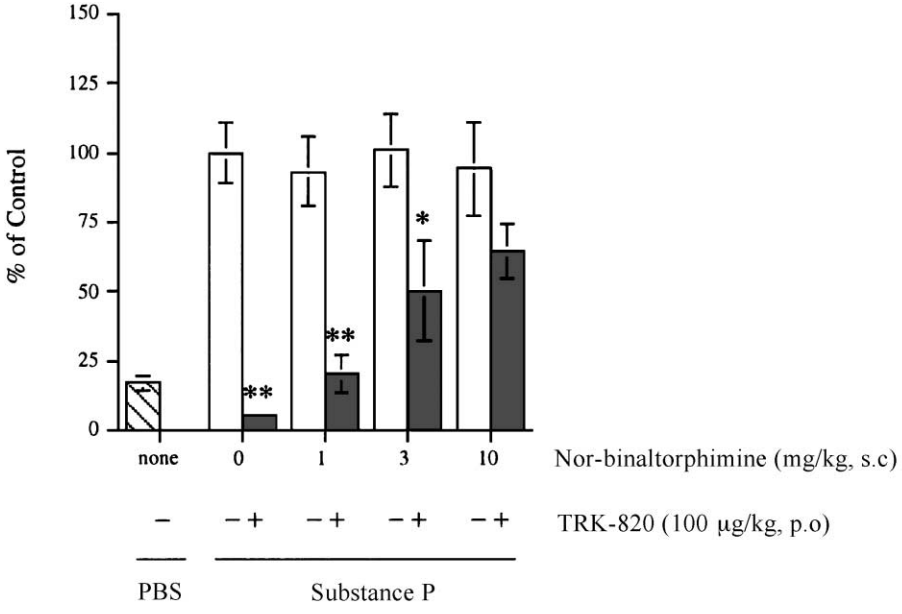

Fig. 3. Effect of nor-binaltorphimine on the scratching inhibitory activity of TRK-820. The ICR strain mouse was given a s.c. injection of nor-binaltorphimine. Next day, the mouse was given a p.o. administration of 100 μg/kg TRK-820 or vehicle, and 30 min later, substance P (250 nmol/site) or PBS was injected intradermally. Immediately after the intradermal injection of substance P or PBS, the number of scratchings was recorded and counted over a 30-min period. The scratching number of the vehicle and substance P-injected group is shown as 100% in the vertical axis. Each value represents the mean ± S.E.M. ($n = 8$). * $P < 0.05$, ** $P < 0.01$ when compared with the corresponding vehicle-injected group (unpaired t-test).

differ significantly. Nor-binaltorphimine pretreatment alone did not affect the numbers of scratches at any dose (Fig. 3).

4. Discussion

Pruritus can be defined as an unpleasant sensation that provokes the desire to scratch and is one of the important symptoms of skin diseases such as atopic dermatitis and urticaria. In addition to occurring in skin diseases, pruritus occurs in some patients with visceral disorders, including hepatic cholestasis, malignancy and chronic renal failure. Histamine H_1 receptor antagonists with or without antiallergic activity (an inhibition of mast cell degranulation) are mainly used to treat pruritus. However, neither type of antihistamine offers sufficient relief of most pruritus, such as atopic dermatitis, chronic cholestasis and chronic renal failure. To date, no drug effective in the full spectrum of pruritus has yet been described (Hägermark, 1992). In the present study, we evaluated the antipruritic activity of the κ-opioid receptor agonist, TRK-820, and compared it with the activity of the histamine H_1 receptor antagonists, ketotifen and chlorpheniramine, those with or without antiallergic effect, using the pruritogen-induced scratching behavior model in mice.

Substance P and histamine are recognized as the most common mediators of the itch sensations in humans (Hägermark et al., 1978; Fjellner and Hägermark, 1981). These mediators induce scratches in mice, which is regarded as an experimental itch model (Kuraishi et al., 1995; Kitagawa et al., 1997). Substance P is thought to induce scratches by acting on the peripheral terminal of sensory neurons directly through tachykinin NK_1 receptors (Andoh et al., 1998), rather than by the activation and degranulation of mast cells (Ebertz et al., 1987). In fact, the substance P-induced scratches were not, or only partly, inhibited by chlorpheniramine and ketotifen, respectively. (Fig. 1). On the other hand, and in agreement with the report that the histamine-induced scratches involved the activation of histamine receptors (Kitagawa et al., 1997; Inagaki et al., 1999), scratches were completely inhibited by chlorpheniramine and ketotifen (Fig. 2). Therefore, the substance P- and histamine-induced scratches are likely to represent two different types of pruritus.

TRK-820 dose dependently suppressed both the substance P- and histamine-induced scratching behavior. Therefore, it is possible that TRK-820 has antipruritic effects on both antihistamine-resistant and -sensitive pruritus in humans. In these experimental itch models, a compound that affects motor activity or has a muscle-relaxing effect may be regarded as having scratching inhibitory activity. Since κ-opioid receptor agonists have a sedative effect, it is possible that the assessment is affected by sedation. However, TRK-820 showed no apparent inhibition of spontaneous locomotor activity in mice at doses of up to 100 μg/kg. Furthermore, the sedative ED_{50} value of TRK-820 in the wheel running test was 5.2 to 14.1 times greater than the antipruritic ED_{50} values. Therefore, it is unlikely that the scratching inhibitory activity of TRK-820 involved the sedative effect.

In order to clarify whether this scratching inhibitory activity of TRK-820 is mediated via κ-opioid receptors, the effect of pretreatment with the κ-opioid receptor antagonist was examined. The pretreatment with nor-binaltorphimine dose dependently antagonized the scratching inhibitory activity of TRK-820 (Fig. 3). Kamei and Nagase (2001) recently reported that nor-binaltorphimine induced the scratching behavior immediately after administration, which might be an itch-associated response. On the other hand, no scratches were observed 24 h after the administration of nor-binaltorphimine in the present study, which is consistent with their report in which it disappeared within 2 h. Thus, it seems likely that nor-binaltorphimine acts as a selective κ-opioid receptor antagonist, not as a pruritogenic agent, when used with the present doses and schedule. Taken together, the results suggest that the scratching inhibitory activity of TRK-820 is mediated via κ-opioid receptors.

TRK-820 has been synthesized as a new type of κ-opioid receptor-selective agonist (Nagase et al., 1998). In vitro studies using mouse vas deferens, guinea pig ileum or Chinese hamster ovary (CHO) cells expressing recombinant rat μ-, δ-, or κ-opioid receptors (Seki et al., 1999), showed that TRK-820 had a potent κ-opioid receptor selective agonistic activity. The compound has potent antinociceptive activity in the mouse acetic acid writhing test (Endoh et al., 1999), rat formalin test (Endoh et al., 2000), and monkey hot-water tail-withdrawal procedure (Endoh et al., 2001). The most important characteristics of TRK-820 is that it induces far weaker aversive effects than do other κ-opioid receptor agonists in a conditioned place preference experiment (Tsuji et al., 2001). TRK-820 may have characteristics different from those of other κ-opioid agonists as suggested by several reports (Endoh et al., 1999; Tsuji et al., 2000a,b). In this study, we showed, for the first time, that the κ-opioid receptor agonist, TRK-820, had the ability to suppress not only antihistamine-sensitive but also antihistamine-resistant pruritus via κ-opioid receptors. Taken the findings together, it seems that TRK-820 may represent new entity of drugs to treat pruritus in humans, and over a wider spectrum than offered by preexisting drugs.

References

Andoh, T., Nagasawa, T., Satoh, M., Kuraishi, Y., 1998. Substance P induction of itch-associated response mediated by cutaneous NK_1 tachykinin receptors in mice. J. Pharmacol. Exp. Ther. 286, 1140–1145.

Ballantyne, J.C., Loach, A.B., Carr, D.B., 1988. Itching after epidural and spinal opiates. Pain 33, 149–160.

Bergasa, N.V., Talbot, T.L., Alling, D.W., Schmitt, J.M., Walker, E.C., Baker, B.L., Korenman, J.C., Park, Y., Hoofnagle, J.H., Jones, E.A., 1992. A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. Gastroenterology 102, 544–549.

Bernstein, J.E., Swift, R.M., Soltani, K., Lorincz, A.L., 1982. Antipruritic effect of an opiate antagonist, naloxone hydrochloride. J. Invest. Dermatol. 78, 82–83.

Cousins, M.J., Mather, L.E., 1984. Intrathecal and epidural administration of opioids. Anesthesiology 61, 276–310.

Cowan, A., Kehner, G.B., 1997. Antagonism by opioids of compound 48/80-induced scratching in mice. Br. J. Pharmacol. 122, 169P (Suppl).

Duncan, J.S., Kennedy, H.J., Trigger, D.R., 1984. Treatment of pruritus due to chronic obstructive liver disease. Br. Med. J. 289, 22.

Ebertz, J.M., Hirshman, C.A., Kettelkamp, N.S., Uno, H., Hanifin, J.M., 1987. Substance P-induced histamine release in human cutaneous mast cells. J. Invest. Dermatol. 88, 682–685.

Endoh, T., Matsuura, H., Tanaka, C., Nagase, H., 1992. Nor-binaltorphimine: a potent and selective κ-opioid receptor antagonist with long-lasting activity in vivo. Arch. Int. Pharmacodyn. Ther. 316, 30–42.

Endoh, T., Matsuura, H., Tajima, A., Izumimoto, N., Tajima, C., Suzuki, T., Saitoh, A., Suzuki, T., Narita, M., Tseng, L., Nagase, H., 1999. Potent antinociceptive effects of TRK-820, a novel κ-opioid receptor agonist. Life Sci. 65, 1685–1694.

Endoh, T., Tajima, A., Suzuki, T., Kamei, J., Suzuki, T., Narita, M., Tseng, L., Nagase, H., 2000. Characterization of the antinociceptive effects of TRK-820 in the rat. Eur. J. Pharmacol. 387, 113–140.

Endoh, T., Tajima, A., Izumimoto, N., Suzuki, T., Saitoh, A., Suzuki, T., Narita, M., Kamei, J., Tseng, L., Mizoguchi, H., Nagase, H., 2001. TRK-820, a selective κ-opioid agonist, produces potent antinociception in cynomolgus monkeys. Jpn. J. Pharmacol. 85, 282–290.

Fjellner, B., Hägermark, Ö., 1981. Studies on pruritogenic and histamine-releasing effects of some putative peptide neurotransmitters. Acta Dermatovenerol. (Stockholm) 61, 245–250.

Gmerek, D.E., Cowan, A., 1988. Role of opioid receptors in bombesin-induced grooming. Ann. N. Y. Acad. Sci. 525, 291–300.

Hägermark, Ö., 1992. Peripheral and central mediators of itch. Skin Pharmacol. 5, 1–8.

Hägermark, Ö., Hökfelt, T., Pernow, B., 1978. Flare and itch induced by substance P in human skin. J. Invest. Dermatol. 71, 233–235.

He, D., Esquenazi-Behar, S., Sorter, N.A., Lim, H.W., 1990. Mast-cell heterogeneity: functional comparison of purified mouse cutaneous and peritoneal mast cells. J. Invest. Dermatol. 94, 178–185.

Inagaki, N., Nakamura, N., Nagao, M., Musoh, K., Kawasaki, H., Nagai, H., 1999. Participation of histamine H_1 and H_2 receptors in passive cutaneous anaphylaxis-induced scratching behavior in ICR mice. Eur. J. Pharmacol. 367, 361–371.

Kamei, J., Nagase, H., 2001. Norbinaltorphimine, a selective κ-opioid receptor antagonist, induces an itch-associated response in mice. Eur. J. Pharmacol. 418, 141–145.

Kehner, G.B., Gaul, F., Zang, W.Y., Daubert, J.D., Cassel, J.A., DeHaven, R.N., DeHaven-Hudkins, D.L., Cowan, A., 1999. Stereoselective antipruritic effects of enadoline and GR 94839 in mice. FASEB J. 13, A801.

Kitagawa, K., Andoh, T., Nagasawa, T., Satoh, M., Kuraishi, Y., 1997. Different effects of antagonists to histamine and serotonin receptors on itch-related behavior induced by substance P, histamine and serotonin in mice. Jpn. J. Pharmacol. 73 (Suppl. 1) 93 pp.

Kuraishi, Y., Nagasawa, T., Hayashi, K., Satoh, M., 1995. Scratching behavior induced by pruritogenic but not algesiogenic agents in mice. Eur. J. Pharmacol. 275, 229–233.

Lowman, M.A., Rees, P.H., Benyon, R.C., Church, M.K., 1988. Human mast cell heterogeneity: histamine release from mast cells dispersed from skin, lung, adenoids, tonsils, and colon in response to IgE-dependent and nonimmunologic stimuli. J. Allergy Clin. Immunol. 81, 590–597.

Metze, D., Reimann, S., Beissert, S., Luger, T., 1999. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. J. Am. Acad. Dermatol. 41, 533–539.

Misslin, R., Belzung, C., Vogel, E., 1988. Interaction of RO 15-4513 and ethanol on the behaviour of mice: antagonistic or additive effects? Psychopharmacology 94, 392–396.

Nagase, H., Hayakawa, J., Kawamura, K., Kawai, K., Takezawa, Y., Matsuura, H., Tajima, C., Endo, T., 1998. Discovery of a structurally novel opioid κ-agonist derived from 4,5-epoxymorphinan. Chem. Pharm. Bull. 46, 366–369.

Peer, G., Kivity, S., Agami, O., Fireman, E., Silverberg, D., Blum, M., Iaina, A., 1996. Randomised crossover trial of naltrexone in uraemic pruritus. Lancet 348, 1552–1554.

Ponticelli, C., Bencini, P.L., 1995. Pruritus is dialysis patients: a neglected problem. Nephrol. Dial. Transplant 10, 2174–2176.

Seki, T., Awamura, S., Kimura, C., Ide, S., Sakano, K., Minami, M., Nagase, H., Satoh, M., 1999. Pharmacological properties of TRK-820 on cloned μ-, δ- and κ-opioid receptors and nociceptin receptor. Eur. J. Pharmacol. 376, 159–167.

Sugimoto, Y., Umakoshi, K., Nojiri, N., Kamei, C., 1998. Effects of histamine H_1 receptor antagonists on compound 48/80-induced scratching behavior in mice. Eur. J. Pharmacol. 351, 1–5.

Tsuji, M., Takeda, H., Matsumiya, T., Nagase, H., Yamazaki, M., Narita, M., Suzuki, T., 2000a. A novel κ-opioid receptor agonist, TRK-820, blocks the development of physical dependence on morphine in mice. Life Sci. 66, 353–358.

Tsuji, M., Yamazaki, M., Takeda, H., Matsumiya, T., Nagase, H., Tseng, L., Narita, M., Suzuki, T., 2000b. The novel κ-opioid receptor agonist TRK-820 has no effect on the development of antinociceptive tolerance to morphine in mice. Eur. J. Pharmacol. 394, 91–95.

Tsuji, M., Takeda, H., Matsumiya, T., Nagase, H., Narita, M., Suzuki, T., 2001. The novel κ-opioid receptor agonist TRK-820 suppresses the rewarding and locomotor-enhancing effects of morphine in mice. Life Sci. 68, 1717–1725.

Wahlgren, C.-F., Hägermark, Ö., Bergström, R., 1990. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. Br. J. Dermatol. 122, 545–551.