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Opioid Kappa Receptor Selective Agonist TRK-820 (Nalfurafine Hydrochloride)

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1. Introduction

TRK-820 (nalfurafine hydrochloride) is a selective opioid κ receptor agonist (Fig. 1) that was launched as an antipruritic for hemodialysis patients in Japan in 2009. In general, clinically used opioids, such as morphine, exhibit potent antinociceptive effects and simultaneous severe adverse effects, including drug dependence, derived from the opioid μ receptor. To develop analgesics without drug dependence, κ receptor agonists are investigated. However, conventional κ agonists, arylacetamide derivatives, showed aversive effects like psychotomimetic effects, and have not yet been used clinically. On the other hand, the novel κ agonist TRK-820 has no dependent or aversive properties. TRK-820, which has a structure different from arylacetamides, was first developed as an analgesic for postoperative pain, but the indication was changed to pruritus (Nakao & Mochizuki, 2009; Nagase & Fujii, 2011). The rational drug design and synthesis of the compound have been reported (Kawai et al., 2008; Nagase et al., 1998; Nagase & Fujii, 2011); therefore, in this chapter, we will focus on its pharmacological properties.

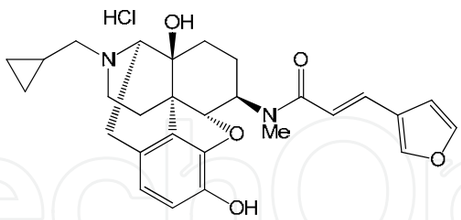


Fig. 1. Structure of nalfurafine hydrochloride (TRK-820)

2. Opioid receptor type selectivity (*In vitro*)

The binding affinities of TRK-820 were evaluated using various tritiated ligands and opioid receptors derived from various species (Table 1). The κ selectivity over the δ receptor (K_i ratio δ/κ) tended to be higher than over the μ receptor (K_i ratio μ/κ). Binding affinities for the L-type Ca^{2+} channel and 45 receptors, except the opioid receptors, were examined (Nakao & Mochizuki, 2009). Among the tested receptors, TRK-820 showed the strongest affinity for the muscarine M_1 receptor, but its K_i value was 1,700 nmol/L and approximately 7,000 times higher than that of the κ receptor. A comparison of the binding properties of TRK-820 and a conventional κ agonist, U-69,593, was noteworthy. In a competitive binding

K_i (nM)			K_i ratio		References
μ	δ	κ	μ/κ	δ/κ	
53	1200	3.5	15	343	Seki et al., 1999
5.2	161	0.075	69	2147	Wang, Y et al., 2005
0.71	49.9	0.36	2.0	139	Vanderah et al., 2008
2.21	484	0.244	9.1	1984	Nakao & Mochizuki, 2009
0.582	96.5	0.225	2.6	429	Nagase et al., 2010

Table 1. Binding affinities (K_i values) and selectivities (K_i ratios) of TRK-820 for the opioid receptors. Seki et al. used [^{3}H]bremazocine and the recombinant rat opioid receptors. Wang, Y et al. used [^{3}H]diprenorphine and recombinant rat μ, recombinant mouse δ, and recombinant human κ receptors. Vanderah et al. used [^{3}H]DAMDO, [^{3}H]*p*Cl-DPDPE, and [^{3}H]U-69,593 for the recombinant human μ, δ, and κ receptors, respectively. Nakao et al. used [^{3}H]diprenorphine and the recombinant human receptors. Nagase et al. used [^{3}H]DAMDO, [^{3}H]NTI, and [^{3}H]U-69,593 for the μ, δ, and κ receptors, respectively. Guinea pig forebrain or guinea pig cerebellum was used to assay the μ and δ receptor or κ receptor, respectively.

Assay	Selectivity		References
	μ/κ	δ/κ	
MVD	980	NC	Kawai et al., 2008
GPI	78.6	–	Kawai et al., 2008
cAMP (Sato et al.)	55	>6,667	Seki et al., 1999
cAMP (Nakao et al.)	203	2,610	Nakao & Mochizuki, 2009
[^{35}S]GTPγS	128	11,560	Wang, Y et al., 2005

Table 2. Selectivities of TRK-820 in various functional assays. Selectivity in MVD and GPI assays was obtained by *K*e ratios. The selectivity for the κ receptor over the δ receptor in the MVD assay was not calculated (NC) due to a lack of agonist activity for the δ receptor. The selectivity for the κ receptor over the δ receptor in the GPI assay was not obtained because GPI preparation contained only the μ and κ receptors. Seki et al. and Nakao et al. used the recombinant rat and human receptors in their assays, respectively. In the [^{35}S]GTPγS binding assay, recombinant rat μ, recombinant mouse δ, or recombinant human κ receptors were used.

assay using [^{3}H]TRK-820, TRK-820 completely replaced [^{3}H]TRK-820 binding, whereas U-69,593 did not replace it completely, with roughly 20% of [^{3}H]TRK-820 binding remaining. Moreover, Scatchard analysis of [^{3}H]TRK-820 and [^{3}H]U-69,593 binding using guinea pig cerebellum showed that TRK-820 had stronger binding affinity than U-69,593 (K_d values: 0.46±0.03 nM for [^{3}H]TRK-820, 1.17±0.14 nM for [^{3}H]U-69,593) and that the B_{max} value for [^{3}H]TRK-820 (284±43.3 fmol/mg protein) was significantly higher than the value for [^{3}H]U-69,593 (83.7±7.86 fmol/mg protein). Even in the presence of μ agonist DAMDO (100 nM) and δ agonist DPDPE (200 nM), the K_d and B_{max} values for [^{3}H]TRK-820 did not change (K_d = 0.51±0.03 nM, B_{max} = 265±27.2 fmol/mg protein) (Endoh et al., 2000). These results suggest that TRK-820 was selective ligand for the κ receptor and that its binding property for the κ receptor was different from that of the conventional κ agonist U-69,593. Many binding

assays are carried out using [^{3}H]U-69,593 because it is commercially available. However, the binding property of TRK-820 is difficult to be definitively evaluated because [^{3}H]TRK-820 is not available now.

TRK-820 was selective for the κ receptor, but the selectivity over the μ receptor was apparently not as high in the binding assays. Contrarily TRK-820 showed more selectivities for the κ receptor in functional assays: MVD (mouse vas deference) and GPI (guinea pig ileum) assay (Nagase et al., 1998), cAPM assay (Nakao & Mochizuki, 2009; Seki et al., 1999), and [^{35}S]GTPγS binding assay (Wang, Y et al., 2005) (Table 2). The results of the cAMP assay (IC_{50} (μ) = 8.3±1.4 nM, I_{max} (μ) = 69±3%, IC_{50} (δ) > 1,000 nM, I_{max} (δ) not determined, IC_{50} (κ) = 0.15±0.07 nM, I_{max} (κ) = 81±3% by Seki et al.; IC_{50} (μ) = 1.66±0.09 nM, I_{max} (μ) = 53.2±1.3%, IC_{50} (δ) = 21.3±1.0 nM, I_{max} (δ) = 77.9±1.6%, IC_{50} (κ) = 0.00816±0.00138 nM, I_{max} (κ) = 91.3±0.5% by Nakao et al.) indicated that TRK-820 was a selective and potent full agonist for the κ receptor and partial agonist for the μ and δ receptors. The potency for the δ receptor was very low (Nakao & Mochizuki, 2009; Seki et al., 1999). The [^{35}S]GTPγS binding assay provided similar results (EC_{50} (μ) = 3.2±1.3 nM, E_{max} (μ) = 54±7%, EC_{50} (δ) = 289±60 nM, E_{max} (δ) = 51±6%, EC_{50} (κ) = 0.025±0.003 nM, E_{max} (κ) = 93±5%) (Wang, Y et al., 2005). Mizoguchi et al. exhibited partial agonist activity of TRK-820 for the μ receptor in both *in vitro* and *in vivo* assays (Mizoguchi et al., 2003). TRK-820 concentration- or dose-dependently attenuated [^{35}S]GTPγS binding by DAMGO or antinociception induced by intracerebroventricular (i.c.v.) administration of DAMGO. On the other hand, the effects of morphine alone or a mixture with TRK-820 were investigated using a mouse acetic acid-induced writhing test or warm water (50 ^{o}C) tail-withdrawal assay in rhesus monkeys (Ko & Husbands, 2009; Nagase, 2010). Isobologram analysis of the results showed that additive or synergetic effects for TRK-820 in combination with morphine in the antinociceptive effect were observed, indicating that TRK-820 had no μ antagonist activity, at least no antagonism against analgesic activity induced by morphine. Why the effects of TRK-820 against DAMGO differed from those against morphine is not clear.

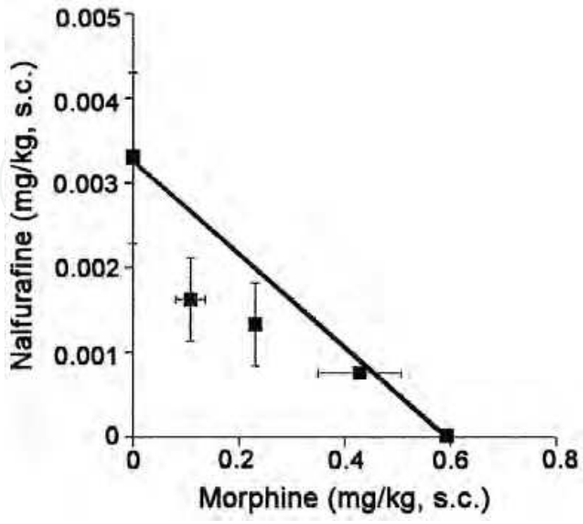


Fig. 2. Isobologram for the mixture of TRK-820- and morphine-induced antinociception in the mouse acetic acid-induced writhing test. Reprinted with permission from Nagase, 2010.

3. Analgesic effects

TRK-820 showed potent analgesic effects in some species (rodents and primates) with various stimuli: chemical, thermal, or mechanical stimuli and inflammatory, diabetic, herpetic, and postherpetic pain models. The antinociceptive effects of TRK-820 are summarized in Tables 3-7. Subcutaneous (s.c.) administration of TRK-820 produced dose-dependent and profound antinociceptive effects in the low temperature hot plate, tail flick, tail pressure, and tail pinch tests. However, TRK-820 was not as effective in high temperature hot plate tests (Table 3) (Endoh et al., 1999).

In a rat paw pressure test, TRK-820 given s.c. or intramuscularly (i.m.) induced dose-dependent and sufficient analgesic effects, which were suppressed by pre-treatment with selective κ antagonist nor-BNI (Table 3). The antinociceptive effect by TRK-820 (ED_{50} = 0.064 mg/kg, s.c.) was 170, 2, 20, and 78-fold more potent than U-50,488H, CI-977, morphine, and pentazocine, respectively (ED_{50} values : 11.0, 0.15, 1.3, and 5.0 mg/kg) (Endoh et al., 2000).

Compound	High temperture hot plate (55 °C)	Low temperature hot plate (51 °C)	Tail flick	Tail pressure	Tail pinch
TRK-820	32.0 % at 0.2	0.129	0.062	0.009	0.035
U-50,488H	63.8 % at 20	8.71	5.18	1.0	11.5
ICI-199,441	n.t.	0.065	0.042	0.024	0.051
U-69,593	n.t.	1.33	n.t.	0.48	2.8
CI-977	n.t.	n.t.	n.t.	n.t.	n.t.
PD-117302	n.t.	n.t.	n.t.	n.t.	n.t.
Pentazocine	44.6 % at 40	52.2	n.t.	n.t.	n.t.
Morphine	3.65	5.30	5.26	1.5	12.2

Compound	Paw pressure	Formalin test	Acetic acid-induced writhing test
TRK-820	0.064	0.0096	0.0033
U-50,488H	11.0	n.t.	1.16
ICI-199,441	0.074	0.0095	0.0071
CI-977	0.15	n.t.	0.0069
PD-117302	n.t.	n.t.	1.22
Pentazocine	5.0	n.t.	n.t.
Morphine	1.3	0.975	0.58

Table 3. ED_{50} values (mg/kg, s.c.) of the antinociceptive effects of some opioid agonists in various tests. U-50,488H, U-69,593, ICI-199,441, CI-977, and PD-117302 are conventional κ agonists. n.t. : not tested. Hot plate, tail flick, tail pressure, tail pinch, and acetic acid-induced writhing tests were performed in mice (Endoh et al., 1999). Paw pressure and formalin tests were performed in rats (Endoh et al., 2000).

In the formalin test, s.c. TRK-820 given 15 min prior to the formalin injection markedly inhibited the second phase of the nociceptive response induced by formalin in a dose-dependent manner. However, the analgesic effect of TRK-820 was low for the first phase of the formalin response. Similarly, a conventional κ agonist, ICI-199,441, also markedly inhibited the second phase. On the other hand, a μ agonist, morphine inhibited both phases in a dose-dependent manner. The antinociceptive potencies of TRK-820 and ICI-199,441 were almost equivalent (Table 3) (Endoh et al., 2000). A potent and dose-dependent antinociceptive effect of TRK-820 (i.m.) was also observed in cynomolgus monkeys. The analgesic effect of TRK-820 was 295 and 492-fold more potent than that of morphine in the 50 °C and 55 °C hot water tests, respectively, and 40 and 1000-fold more potent than that of U-50,488H and pentazocine in the 50 °C hot water test, respectively (Table 4) (Endoh et al., 2001).

Furthermore, the antinociceptive effects of TRK-820 administered s.c. and perorally (p.o.) were compared. The dose-dependent antinociception of TRK-820 (ED_{50} = 0.0033 mg/kg, s.c. and 0.032 mg/kg, p.o.) in the acetic acid-induced writhing test were inhibited by pre-treatment with nor-BNI. The antinociceptive effects induced by s.c. or p.o. administration of TRK-820 were 351 and 796-fold more potent than those induced by U-50,488H, respectively, and 175 and 187-fold more potent than those induced by morphine, respectively. Because the ED_{50} p.o./s.c. ratio for TRK-820 was the least among the tested compounds, TRK-820 was expected to be the most effective agent when administered p.o. (Table 5) (Endoh et al., 1999). Intravenous administration of TRK-820 was also reported to be effective in the same test (Vanderh et al., 2008).

The effect of repeated administration of some κ agonists and morphine on antinociceptive tolerance was examined by the acetic acid-induced writhing test in mice. After five

Compound	50 °C hot water	55 °C hot water
TRK-820	0.0078	0.012
Morphine	2.3	5.9
U-50,488H	0.31	n.t.
Pentazocine	> 10	n.t.

Table 4. ED_{50} values (mg/kg, i.m.) of antinociceptive effects induced by some opioid agonists in the hot water tail withdrawal test in cynomolgus monkeys. n.t. : not tested.

Compound	s.c.	p.o.	ED_{50} p.o./s.c. ratio
TRK-820	0.0033	0.032	9.7
U-50,488H	1.16	25.5	22.0
CI-977	0.0069	> 1.0	> 145
ICI-199441	0.0071	0.3	42.3
PD-117302	1.22	33.0	27.0
Morphine	0.58	6.01	10.4

Table 5. ED_{50} values (mg/kg, s.c. or p.o.) for antinociceptive effects induced by some opioid agonists in the acetic acid-induced writhing test in mice.

administrations of TRK-820 (0.1-0.8 mg/kg, s.c.), U-50,488H (10-80 mg/kg, s.c.), ICI-199,441 (0.025-0.2 mg/kg, s.c.), or morphine (1.25-10 mg/kg, s.c.) over three days, the development of tolerance to the antinociception induced by each compound at a fixed dose was assessed and tolerance ED_{50} was calculated. Comparing the ratio of tolerance ED_{50} to acute antinociceptive ED_{50} of each compound, TRK-820 was found to develop the least tolerance to antinociception (Table 6) (Suzuki et al., 2004).

An analgesic effect of TRK-820 (i.m.) was also examined using rats with arthritis induced by adjuvant. TRK-820 dose-dependently produced potent and equivalent antinociceptive activity in both arthritic and normal rats in the paw pressure test. Similar results were obtained when morphine was injected i.m. However, the analgesic effect of a conventional κ agonist, ICI-199,441, in the arthritic rats was less potent than in normal rats (Table 7) (Endoh et al., 2000).

Compound	Tolerance ED_{50}	Acute antinociceptive ED_{50}	Ratio of tolerance ED_{50}/acute antinociceptive ED_{50}
TRK-820	0.54	0.0033	163.6
U-50,488H	30.7	1.16	26.5
ICI-199,441	0.078	0.0071	11.0
Morphine	5.72	0.58	9.9

Table 6. ED_{50} values (mg/kg, s.c.) for tolerance and antinociceptive effects induced by some opioid agonists in the acetic acid-induced writhing test.

Compound	Normal rat	Arthritic rat	ED50 ratio of arthritic rat/ normal rat
TRK-820	0.055	0.095	1.7
ICI-199,441	0.047	0.24	5.1
Morphine	1.1	1.1	1.0

Table 7. ED_{50} values (mg/kg, i.m.) for antinociceptive effects induced by some opioid agonists in the paw pressure test in normal and arthritic rats.

In streptozotocin-induced diabetic mice, the antinociceptive effects induced by several κ agonists, including TRK-820, were compared in the tail flick test. Intrathecal (i.t.) and i.c.v. administration of TRK-820 produced dose-dependent antinociceptive effects in both diabetic and non-diabetic mice. However, antinociception induced by TRK-820 administered i.t. or i.c.v. in diabetic mice were less potent than antinociception in non-diabetic mice. However, the antinociceptive effects of CI-977 administered i.t., but not i.c.v., in diabetic mice were less potent than those in non-diabetic mice. On the other hand, the antinociceptive effects of ICI-199,441 and R-84760 injected i.c.v., but not i.t., in diabetic mice were less potent than those in non-diabetic mice. These results indicate that the antinociceptive effects of κ agonists in diabetic mice are altered in a region-specific manner in the central nervous system and by chemotypes of κ agonists (Ohsawa et al., 2005).

In acute herpetic and postherpetic pain models induced by herpes simplex virus type-1 infection in mice, TRK-820 dose-dependently and remarkably inhibited the allodynia and hyperalgesia stimulated by von Frey filaments (Takasaki et al., 2004, 2006). The effects of TRK-820, but not morphine, were not significantly different between herpetic and postherpetic pain (Takasaki et al., 2006). TRK-820 (0.1 mg/kg, s.c.) almost completely relieved both allodynia and hyperalgesia in herpetic pain, whereas a high dose of morphine (20 mg/kg, s.c.) did not produce complete inhibition. However, TRK-820 (0.01-0.1 mg/kg, s.c.) did not affect the spontaneous locomotor activity of normal mice (Takasaki et al., 2004). Moreover, repeated administration of TRK-820 (0.1 mg/kg, p.o., twice daily) produced constant inhibition of allodynia and hyperalgesia in herpetic pain. The effects of the fourth administration with TRK-820 were not significantly different from those of the first administration. On the other hand, the effects of morphine rapidly decreased after repeated administration (20 mg/kg, p.o., twice daily). The effects of the third and fourth administration of morphine were significantly weaker than those of the first administration. Pre-treatment with morphine (20 mg/kg, p.o., three times) did not affect the antinociceptive effect of TRK-820 (0.1 mg/kg, p.o.), whereas the effect of morphine (20 mg/kg, p.o.) was significantly reduced (Takasaki et al., 2006). These results indicate that TRK-820 is effective on both herpetic and postherpetic pain in mice. In addition, the analgesic dose of TRK-820 did not develop acute tolerance and induced cross-tolerance to morphine in herpetic pain.

4. Antipruritic effects

4.1 Preclinical studies

The p.o. administration of TRK-820 dose-dependently inhibited scratching behavior induced by histamine in mice, which is one of the representative pruritogenic substances, without obvious suppression of spontaneous locomotor activity. The antiscratching activity of TRK-820 with ED_{50} 7.3 μg/kg was antagonized by nor-BNI (Togashi et al., 2002). TRK-820 was effective in scratching induced by the other pruritogenic substances: substance P (Togashi et al., 2002; Umeuchi et al., 2003; Utsumi et al., 2004), chloroquine (Inan & Cowan, 2004), compound 48/80 (Wang, Y et al., 2005), agmatin (Inan & Cowan, 2006a), and 5'-GNTI (Inan et al., 2009a, 2011) (Table 8). 5'-GNTI-induced scratching was suppressed by both pre-treatment and post-treatment with TRK-820. Tolerance did not develop to the antiscratching effect of TRK-820 in the subchronic study (Inan et al., 2009a).

Pruritogenic substance	Antipruritic effect	References
Histamine	ED_{50} = 7.3 μg/kg, p.o.	Togashi et al., 2002
Substance P	ED_{50} = 19.6 μg/kg, p.o.	Togashi et al., 2002
Chloroquine	TRK-820 (120 μg/kg, p.o.) suppressed the scratching almost completely	Inan & Cowan, 2004
Compound 48/80	ED_{50} = 6.64 μg/kg, s.c.	Wang, Y et al., 2005
Agmatin	TRK-820 (0.02 mg/kg, s.c.) was effective	Inan & Cowan, 2006a
5'-GNTI	TRK-820 (20 μg/kg, s.c.) suppressed the scratching almost completely	Inan et al., 2009a

Table 8. The antipruritic effects of TRK-820 against itching behaviors induced by various pruritogenic substances.

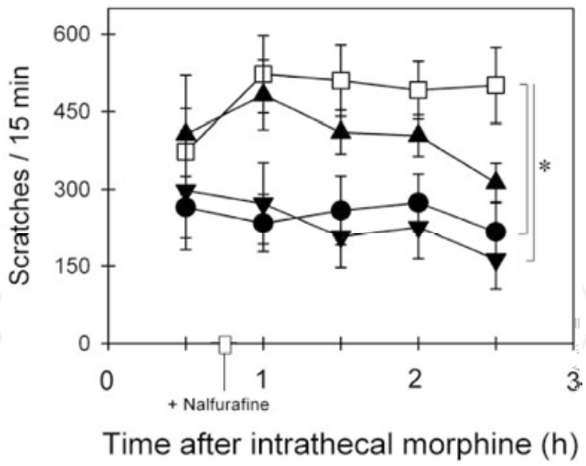


Fig. 3. Effects of TRK-820 on scratching induced by i.t. administration of morphine in rhesus monkeys. TRK-820 (0 (□), 0.1 (▲), 0.3 (●), and 1 (▼) μg/kg, i.m.) was given 45 min after the administration of morphine (0.03 mg, i.t.). * $p < 0.05$ between vehicle and time points 1 and 2.5 h. Reprinted with permission from Ko & Husbands, 2009.

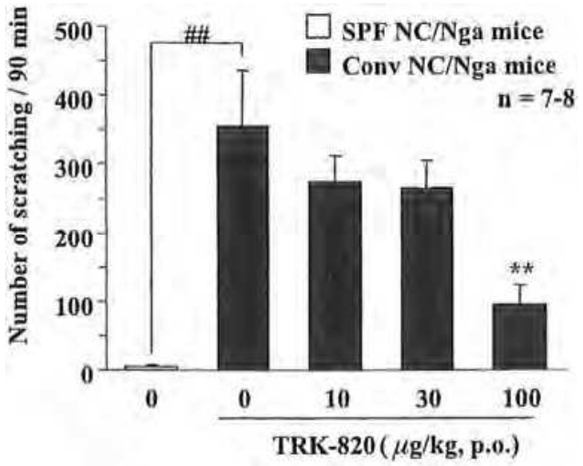


Fig. 4. Effects of TRK-820 on scratching behaviors observed in NC/Nag mice maintained in a conventional environment. $^{\#\#}p < 0.01$, Welch test. $^{**}p < 0.01$ compared to NC/Nag mice not treated with TRK-820, parametric Dunnett multiple comparison test. Reprinted with permission from Nakao et al., 2008.

Although epidural or i.t. administration of a μ agonist like morphine is an important method for pain management, an itching sensation is the most common side effect (Ballantyne et al., 1988; Cousins & Mather, 1984). The effect of TRK-820 on morphine-induced scratching in mice or primates was also evaluated (Ko & Husbands, 2009; Utsumi et al., 2004; Wakasa et al., 2004). Intramuscular administration of TRK-820 (0.3–1 μg/kg) dose-dependently attenuated scratching induced by morphine (i.t.) in rhesus monkeys without affecting antinociception by morphine (Fig. 3) (Ko & Husbands, 2009).

TRK-820 reportedly exhibited antipruritic effects on spontaneous scratching behavior in aged MRL/*lpr* mice (a possible model for pruritus in autoimmune disease) (Umeuchi et al.,

2005) or NC/Nag mice maintained in a conventional environment (an animal model for atopic dermatitis) (Nakao et al., 2008), and scratching behavior secondary to cholestasis induced chronic ethynylestradiol injections in rats (Inan & Cowan, 2006b). Interestingly, TRK-820 was effective in scratching behaviors observed in conventional NC/Nag mice, which were considered a model of atopic dermatitis (Fig. 4).

4.2 Clinical studies

Wikström et al. (2005) and Kumagai et al. (2010) reported the results of randomized, double-blind, placebo-controlled clinical studies in which TRK-820 was administered to patients undergoing hemodialysis intravenously or orally (Fig. 5). In these studies, TRK-820 exhibited significant antipruritic effects without severe adverse drug reactions. These outcomes suggest that TRK-820 can be considered a safe agent.

TRK-820 is prescribed in Japan as an antipruritic for hemodialysis. Very recently, Kumagai et al. reported that TRK-820 has been prescribed for approximately 18,000 hemodialysis patients and effective in 70 to 80% (Kumagai et al., 2011).

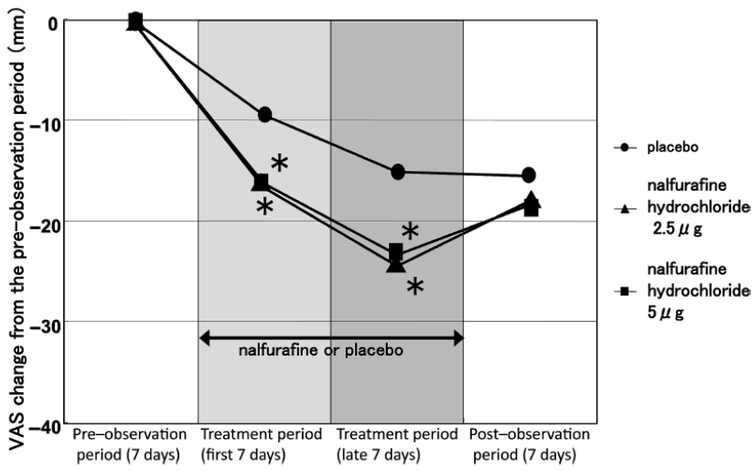


Fig. 5. Changes in VAS (visual analogue scale) values from the pre-observation period. All symbols show the mean values of VAS changes. *$p < 0.025$ compared to placebo, one-sided ANCOVA. Reprinted from Nagase & Fujii, 2011 with permission from Springer Science+Business Media. The VAS test consisted of a 100-mm horizontal line without scale markings. The patients were asked to mark the intensity of itching on the scale, with the right end of the line (100 mm) indicating the strongest possible itching and the left end (0 mm) indicating no itching.

5. Effects of TRK-820 on drug dependence

5.1 Effects of TRK-820 in the conditioned place preference (CPP) test

The μ agonists have a rewarding effect, which accounts for the abuse of morphine by humans. In animal models, the rewarding effects of μ agonists have been evaluated by the conditioned place preference (CPP) and self-administration paradigms (Di Chiara & North, 1992). In contrast to μ agonists, conventional κ agonists such as U-50,488H and U-69,593 generally lack

a rewarding effect (Dykstra et al., 1997). However in the CPP test, animals avoid an environment associated with the administration of the κ agonists, indicating that these drugs have aversive effects (Barr et al., 1994; Funada et al., 1993). In contrast to conventional κ agonists, such as U-50,488H, TRK-820 (3.0-30 μg/kg, s.c.) did not induce significant place aversion in mice at doses producing significant antinociception (Fig. 6) (Nagase, 2010). Notably, TRK-820 exhibited neither preferential nor aversive properties. Recently, the peroral administration of TRK-820 (5.0 μg/day) was reported to show no signs of psychological or physical dependence in an open-labeled clinical trial for one year (Nagase & Fujii, 2011).

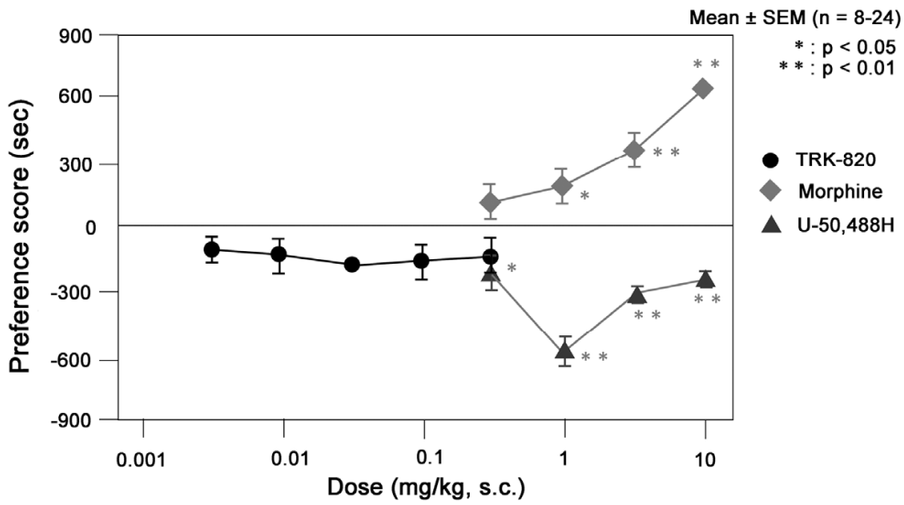


Fig. 6. The effect of TRK-820 in the CPP test. Reprinted with permission from Nagase, 2010.

5.2 The effects of TRK-820 on morphine and cocaine-induced rewarding effects

The mechanism of μ agonist-induced rewarding effects is outlined below. The activation of the μ receptor on γ-aminobutyric acid-containing interneurons is likely to disinhibit ventrotegmental area dopaminergic neurons, thereby increasing dopamine release in their terminal areas, including the nucleus accumbens (N.Acc). On the other hand, the activation of the κ receptor decreases dopamine release in the N.Acc (Di Chiara & Imperato, 1988; Spanagel et al., 1992). Therefore, κ agonists may be useful for treating morphine dependence. Indeed, the pretreatment with U-50,488H attenuated the morphine-induced place preference in mice (Funada et al., 1993). TRK-820 also significantly suppressed the place preference produced by morphine, and the effect of TRK-820 was antagonized by pre-treatment with nor-BNI (3.0 mg/kg, s.c.) in mice (Tsuji et al., 2001). In addition, TRK-820 was effective in reducing the rewarding effect produced by cocaine. TRK-820 (20 and 40 μg/kg, i.p.), at doses producing no aversive or sedative effects, suppressed the rewarding effect of cocaine (4.0 mg/kg, i.p.) in rats (Mori et al., 2002). U-50,488H and U-69,593 exhibited similar effects as TRK-820 (Shippenberg et al., 1996; Suzuki et al., 1992). Drug discrimination procedures provide relevant information about neuropharmacological mechanisms underlying the subjective effects of abused drugs, including cocaine, methamphetamine, and opioids, in animals. Therefore, the procedures are potentially useful for identifying candidate therapeutics for the management of drug abuse (Schuster & Johanson, 1988). Pre-treatment with TRK-820 (10 and 20 μg/kg, s.c.) significantly

shifted the dose-response curve for cocaine (10 mg/kg, i.p.) to the right without changing the response rate. This attenuating effect of TRK-820 was completely reversed by pre-treatment with nor-BNI (10 mg/kg, s.c.) (Mori et al., 2002).

5.3 Effects of TRK-820 on the morphine withdrawal response

In humans, withdrawal from the chronic administration of opioids such as morphine results in characteristic behaviors, including anxiety, nausea, insomnia, hot and cold flashes, muscle aches, perspiration, and diarrhea. Such symptoms would pose clinical problems in patients receiving long-term treatment with opioids for pain relief. Rodents that are physically dependent on morphine elicit characteristic signs (jumping, wet dog shakes, rearing, diarrhea, ptosis, and forepaw tremor) when administrated naloxone. The withdrawal signs precipitated by naloxone are used as an index of the physical dependence on morphine. The effects of κ agonists TRK-820 and U-50,488H on the development of physical dependence on morphine were reported. Co-injection of TRK-820 (0.003-0.03 mg/kg, s.c.) during chronic morphine treatment dose-dependently suppressed naloxone-precipitated body weight loss, and the other withdrawal signs in morphine-dependent mice treated with TRK-820 (0.03 mg/kg, s.c.) were significantly fewer than those in untreated mice. In contrast to TRK-820, co-injection of U-50,488H (1.0-10 mg/kg, s.c.) did not inhibit naloxone-precipitated body weight loss and other withdrawal signs (Tsuji et al., 2000).

5.4 The effect of TRK-820 on the nicotine-withdrawal response

Nicotine withdrawal produces characteristic syndromes, including irritability, anxiety, depression, and craving for nicotine. Pre-treatment with TRK-820 (10 and 30 μg/kg, s.c.) or U-50,488H (0.01-1.0 mg/kg, s.c.) has been reported to decrease dose-dependently mecamylamine-precipitated nicotine-withdrawal aversion in nicotine-dependent rats (Ise et al., 2002).

6. Comparison of pharmacological properties between TRK-820 and conventional κ agonists

We described in the previous sections some pharmacological properties of TRK-820 that are different from conventional κ agonists, arylacetamides such as U-50,488H and U-69,593: binding properties (section 2) and exhibition of no preferential and no aversive effect in the CPP paradigm (section 5). As described below, drug discrimination procedures indicate conclusive difference between TRK-820 and arylacetamides.

6.1 Discriminative tests

Drug discrimination procedures have shown that the properties of TRK-820 differ from those of conventional κ agonists, such as U-50,488H. In the cross-substitution tests using rats, U-50,488H (1.0-3.0 mg/kg) substituted for the discriminative stimulus effects of TRK-820 (40 μg/kg, i.p.), whereas TRK-820 (10-76 μg/kg) did not completely substitute for those of U-50,488H (3.0 mg/kg, i.p.). E-2078 (0.3-3.0 mg/kg), but not R-84760 (0.01-0.3 mg/kg), substituted for the discriminative stimulus effects of both TRK-820 and U-50,488H. KT-90 (0.03-3.0 mg/kg), CI-977 (1-30 mg/kg), or ICI-199441 (3.0-56 mg/kg) substituted for the discriminative stimulus effects of U-50,488H, but not for those of TRK-820 (Mori et al., 2004).

In this study, cross-substitution between the discriminative effects of U-50,488H and TRK-820 was not observed. The κ agonists tested in this study, except E-2078, tended to substitute for the discriminative stimulus effects of U-50,488H rather than those of TRK-820. These results suggest that U-50,488H and TRK-820 have differential properties. Furthermore, non-competitive NMDA antagonists phencyclidine (PCP, 0.5-2.0 mg/kg) and MK-801 (10-80 μg/kg) dose-dependently generalized to the discriminative stimulus effects of U-50,488H (3.0 mg/kg, i.p.) in the cross-substitution tests. On the other hand, PCP and MK-801 at doses that generalized to the discriminative stimulus effects of U-50,488H did not generalize to those of TRK-820 (40 μg/kg, i.p.) (Mori et al., 2006). The outcomes clearly indicate different properties between TRK-820 and U-50,488H.

7. Other pharmacological effects

7.1 The effect of TRK-820 on a rat model of schizophrenia

The effects of TRK-820 on hyperlocomotion and stereotyped behaviors (head-weaving, sniffing, and turning) induced by PCP were evaluated. These behaviors are thought to resemble the schizophrenia-like effects in humans. TRK-820 (10–100 μg/kg, s.c.) dose-dependently inhibited PCP (10 mg/kg, i.p.)-induced hyperlocomotion, and this effect was antagonized with nor-BNI (20 mg/kg, s.c.). PCP-induced stereotyped behaviors were also inhibited by treatment with TRK-820 in a dose-dependent manner. These findings that TRK-820 potentially ameliorates abnormal behaviors induced by PCP suggest its therapeutic potential against the symptoms of schizophrenia (Yoshikawa et al., 2009).

7.2 The effect of TRK-820 on dyskinesia symptoms in a parkinsonian rat model

The effects of TRK-820 on rotational behavior were investigated in unilateral 6-hydroxydopamine (6-OHDA)-treated rats (hemi-parkinsonian rats), and on dyskinesia produced by administering L-DOPA to hemi-parkinsonian rats for 3 weeks (dyskinesia rats). TRK-820 significantly ameliorated abnormal behavior in hemi-parkinsonian rats at 30 μg/kg (s.c.), and L-DOPA induced dyskinesia at 10 and 30 μg/kg (s.c.). This effect was antagonized by pretreatment with nor-BNI (20 mg/kg, s.c.). Additionally, co-administration of TRK-820 (3 and 10 μg/kg, s.c.) with L-DOPA for 3 weeks suppressed the development of L-DOPA-induced dyskinesia. TRK-820 may be a suitable drug for the treatment of parkinsonian patients with dyskinesia symptoms (Ikeda et al., 2009).

7.3 The diuretic effect of TRK-820 in rats

Diuresis is a well-recognized effect of conventional κ agonists in animals and humans. A diuretic effect of TRK-820 in rats has also been reported. TRK-820 (0.005-0.02 mg/kg, s.c.) dose-dependently induced a diuretic effect without developing tolerance, and this effect was inhibited by selective κ antagonist 5′-GNTI (Inan et al., 2009b).

7.4 The effects of TRK-820 on endothelial cell differentiation and development of vasculature

The roles of the opioid κ system in vascular development were investigated (Yamamizu et al., 2011). U-50,488H and TRK-820 significantly inhibited endothelial cell differentiation and vascular formation through the inhibition of cAMP/PKA signaling.

8. Conclusion

TRK-820 was a selective κ agonist. However, its pharmacological properties were different from those of conventional arylacetamide κ agonists, including U-50,488H. A noteworthy feature of TRK-820 was that it showed no preferential or aversive properties, whereas U-50,488H produced aversion. This disparity of properties between TRK-820 and arylacetamide κ agonists was reported to stem from the difference in κ receptor subtypes each compound interacted with: arylacetamide κ agonists would interact with κ_1 receptor subtype, whereas TRK-820 may interact with another κ receptor subtype (perhaps κ_3) (Endoh et al., 1999; 2000; 2001; Tsuji et al., 2000a; 2000b). Although opioid receptors have been classified historically into three types (μ, δ, and κ types) and further divided into several subtypes from the pharmacological viewpoint (Dhawan et al., 1996), only the three major types have been cloned (Satoh & Minami, 1995). Much evidence has been compiled indicating that various receptors, including opioid receptors, exist as homo- or hetero dimers of the receptors (George et al., 2000, 2002; Gomes et al., 2000, 2004; Devi, 2001; Levac et al., 2002; Wang, D et al., 2005), and receptor dimerization has been invoked to explain the discrepancy between widely varied pharmacologies and the identification of only three opioid receptor types. Therefore, the disparity of properties between TRK-820 and arylacetamide κ agonists may stem from the difference in receptor dimers each compound interacts with. Both TRK-820 and arylacetamide κ agonists are expected to be useful tools for the investigation of receptor dimerization and/or κ receptor subtype. As mentioned in section 2, a binding assay using [^{3}H]TRK-820 and [^{3}H]U-69,593 is thought to be a facile and useful method for achieving that purpose. However, [^{3}H]TRK-820 is not currently available.

In addition to antipruritic and antinociceptive effects, TRK-820 exhibited various pharmacological effects, such as the treatment of the symptoms of schizophrenia or dyskinesia symptoms of parkisonian patients, or remedy for drug addiction. Moreover, TRK-820 has been already launched in Japan. TRK-820 is expected not only to be developed with the other indication, such as symptoms of schizophrenia or parkinson's disease, but also to be utilized to investigate pharmacology *via* the κ receptor.

9. References

Ballantyne, J.C.; Loach, A. B. & Carr, D. B. (1988). Itching after epidural and spinal opiates, *Pain*, 33, 2, 149-160, ISSN 0304-3959.

Barr, G. A.; Wang, S.; Carden, S. (1994). Aversive properties of the *κ* opioid agonist U50,488 in the week-old rat pup, *Psychopharmacology*, 113, 3-4, 422-428, ISSN 0033-3158.

Cousins, M.J. & Mather, L.E. (1984). Intrathecal and Epidural Administration of Opioids, *Anesthesiology*, 61, 3, 276-310, ISSN 0003-3022.

Devi, L. A. (2001). Heterodimerization of G-protein-coupled receptors: pharmacology, signaling and trafficking, *Trends Pharmacol. Sci*., 22, 10, 532-537, ISSN 0165-6147.

Dhawan, B. N.; Cesselin, F.; Raghubir, R.; Reisine, T.; Bradley, P. B.; Portoghese, P. S. & Hamon, M. (1996). International Union of Pharmacology. XII. Classification of Opioid Receptors, *Pharmacol. Rev*., 48, 4, 567-592, ISSN 0031-6997.

Di Chiara, G.; Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats, *Proc. Natl. Acad. Sci. U. S. A.*, 85, 14, 5274-5278, ISSN 0027-8424.

Di Chiara, G.; North, R. A. (1992). Neurobiology of opiate abuse, *Trends Pharmacol. Sci.,* 13, 5, 185-193, ISSN 0165-6147.

Dykstra, L. A.; Preston, K. L.; Bigelow, G. E. (1997). Discriminative stimulus and subjective effects of opioids with *mu* and *kappa* activity: data from laboratory animals and human subjects, *Psychopharmacology,* 130, 1, 14-27, ISSN 0033-3158.

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, 16, 1685-1694, ISSN 0024-3205.

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, 2, 133-140. ISSN 0014-2999.

Endoh, T.; Tajima, A.; Izumimoto, N.; Suzuki, T.; Saitoh, A.; Suzuki, T.; Narita, M.; Kamei, J.; Tseng, L. F.; Mizoguchi, H.; Nagase, H. (2001). TRK-820, a Selective κ-Opioid Agonist, Produces Potent Antinociception in Cynomolgus Monkeys, *Jpn. J. Pharmacol.,* 85, 3, 282-290, ISSN 0021-5198.

Funada, M.; Suzuki, T.; Narita, M.; Misawa, M.; Nagase, H. (1993). Blockade of morphine reward through the activation of κ-opioid receptors in mice, *Neuropharmacology,* 32, 12, 1315-1323, ISSN 0028-3908.

George, S. R.; Fan, T.; Xie, Z.; Tse, R.; Tam, V.; Varghese, G. & O'Dowd, B. F. (2000). Oligomerization of *μ*- and *δ*-Opioid Receptors. GENERATION OF NOVEL FUNCTIONAL PROPERTIES, *J. Biol. Chem.*, 275, 34, 26128-26135, ISSN 0021-9258.

George, S. R.; O'Dowd, B. F. & Lee, S. P. (2002). G-protein-coupled receptor oligomerization and its potential for drug discovery, *Nat. Rev. Drug Discov.*, 1, 10, 808-820, ISSN 1474-1776.

Gomes, I.; Jordan, B. A.; Gupta, A.; Trapaidze, N.; Nagy, V. & Devi, L. A. (2000). Heterodimerization of *μ* and *δ* Opioid Receptors: A Role in Opiate Synergy, *J. Neurosci.*, 20, 22, RC110, ISSN 0270-6474.

Gomes, I.; Gupta, A.; Filipovska, J.; Szeto, H. H.; Pintar, J.E. & Devi, L. A. (2004). A role for heterodimerization of *μ* and *δ* opiate receptors in enhancing morphine analgesia, *Proc. Nat. Acad. U.S.A.*, 101, 14, 5135-5139 ISSN 0027-8424.

Ikeda, K.; Yoshikawa, S.; Kurokawa, T.; Yuzawa, N.; Nakao, K.; Mochizuki, H. (2009). TRK-820, a selective kappa opioid receptor agonist, could effectively ameliorate L-DOPA-induced dyskinesia symptoms in a rat model of Parkinson's disease, *Eur. J. Pharmacol.,* 620, 1-3, 42-48, ISSN 0014-2999.

Inan, S. & Cowan, A. (2004). Kappa opioid agonists suppress chloroquine-induced scratching in mice, *Eur. J. Pharmacol.,* 502, 3, 233-237. ISSN 0014-2999.

Inan, S. & Cowan, A. (2006a). AGMATINE-INDUCED STEREOTYPED SCRATCHING IN MICE IS ANTAGONIZED BY NALFURAFINE, A KAPPA OPIOID AGONIST, *Pharmacologist*, 48, 1, 38, ISSN 0031-7004.

Inan, S. & Cowan, A. (2006b). Nalfurafine, a kappa opioid receptor agonist, inhibits scratching behavior secondary to cholestasis induced by chronic ethynylestradiol injections in rats, *Pharmacol. Biochem. Behav.*, 85, 1, 39-43. ISSN 0091-3057.

Inan, S.; Dun, N. J. & Cowan, A. (2009a). NALFURAFINE PREVENTS 5'-GUANIDINONALTRINDOLE- AND COMPOUND 48/80-INDUCED SPINAL c-fos EXPRESSION AND ATTENUATES 5'-GUANIDINONALTRINDOLE-

ELICITED SCRATCHING BEHAVIOR IN MICE, *Neuroscience*, 163, 1, 23-33, ISSN 0306-4522.

Inan, S.; Lee, D. Y. -W; Liu-Chen, L. Y.; Cowan, A. (2009b). Comparison of the diuretic effects of chemically diverse kappa opioid agonists in rats: nalfurafine, U50,488H, and salvinorin A, *Naunyn Schmiedebergs Arch. Pharmacol.,* 379, 3, 263-270, ISSN 0028-1298.

Inan, S.; Dun, N. J. & Cowan, A. (2011). Investigation of gastrin-releasing peptide as a mediator for 5'-guanidinonaltrindole-induced compulsive scratching in mice, *Peptides*, 32, 2, 286-292, ISSN 0196-9781.

Ise, Y.; Narita, M.; Nagase, H.; Suzuki, T. (2002). Modulation of κ-opioidergic systems on mecamylamine-precipitated nicotine-withdrawal aversion in rats, *Neurosci. Lett.,* 323, 2, 164-166, ISSN 0304-3940.

Kawai, K.; Hayakawa, J.; Miyamoto, T.; Imamura, Y.; Yamane, S.; Wakita, H.; Fujii, H.; Kawamura, K.; Matsuura, H.; Izumimoto, N.; Kobayashi, R.; Endo, T. & Nagase, H. (2008). Design, synthesis, and structure–activity relationship of novel opioid κ-agonists, *Bioorg. Med. Chem.,* 16, 20, 9188-9201. ISSN 0968-0896.

Ko, M. –C. & Husbands, S. M. (2009). Effects of Atypical κ-Opioid Receptor Agonists on Intrathecal Morphine-Induced Itch and Analgesia in Primates, *J. Pharmacol. Exp. Ther.,* 328, 1, 193-200. ISSN 0022-3565.

Kumagai, H.; Ebata, T.; Takamori, K.; Muramatsu, T.; Nakamoto, H. & Suzuki, H. (2010). Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study, *Nephrol. Dial. Transplant.*, 25, 4, 1251-1257, ISSN 0931-0509.

Kumagai, H.; Yamamoto, K.; Kushiyama, T.; Higashi, Y.; Takechi, H. & Suzuki, H. (2011). A novel κ-receptor agonist, nalfurafine, for severe itch in hemodialysis patients, *Kidney and Dialysis*, 70, 4, 651-657, ISSN 0385-2156.

Levac, B. A. R.; O'Dowd, B. F. & George, S. R. (2002). Oligomerization of opioid receptors: generation of novel signaling units, *Curr. Opin. Pharmacol.*, 2, 1, 76-81, ISSN 1471-4892.

Mori, T.; Nomura, M.; Nagase, H.; Narita, M.; Suzuki, T. (2002). Effects of a newly synthesized κ-opioid receptor agonist, TRK-820, on the discriminative stimulus and rewarding effects of cocaine in rats, *Psychopharmacology,* 161, 1, 17-22, ISSN 0033-3158.

Mori, T.; Nomura, M.; Yoshizawa, K.; Nagase, H.; Narita, M.; Suzuki, T. (2004). Differential properties between TRK-820 and U-50,488H on the discriminative stimulus effects in rats, *Life Sci.,* 75, 20, 2473-2482, ISSN 0024-3205.

Mori, T.; Nomura, M.; Yoshizawa, K.; Nagase, H.; Sawaguchi, T.; Narita, M.; Suzuki, T. (2006). Generalization of NMDA-Receptor Antagonists to the Discriminative Stimulus Effects of κ-Opioid Receptor Agonists U-50,488H, but Not TRK-820 in Rats, *J. Pharmacol. Sci.,* 100, 2, 157-161, ISSN 1347-8613.

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, 2, 366-369. ISSN 0009-2363.

Nagase, H. (2010). Design and Synthesis of a Novel Antipruritic Drug, Nalfurafine Hydrochloride and Its Pharmacological Feature, *Jpn. J. Pharm. Palliat. Care Sci.* 3, 4, 115-122. ISSN 1882-9783.

Nagase, H.; Watanabe, A.; Nemoto, T.; Yamaotsu, N.; Hayashida, K.; Nakajima, M.; Hasebe, K.; Nakao, K.; Mochizuki, H.; Hirono, S. & Fujii, H. (2010). Drug design and synthesis of a novel κ opioid receptor agonist with an oxabicyclo[2.2.2]octane skeleton and its pharmacology, *Bioorg. Med. Chem. Lett.* 20, 1, 121-124. ISSN 0960-894X.

Nagase, H. & Fujii, H. (2011). Opioids in Preclinical and Clinical Trials, In: *Chemistry of Opioid*, Nagase, H. (Ed.), 29-62, Springer, ISBN 978-3-642-18106-1, Heidelberg.

Nakao, K.; Ikeda, K.; Kurokawa, T.; Togashi, Y.; Umeuchi, H.; Honda, T.; Okano, K. & Mochizuki, H. (2008). Effect of TRK-820, a selective κ opioid receptor agonist, on scratching behavior in an animal model of atopic dermatitis, *Jpn. J. Neuropsychopharmacol.*, 28, 2, 75-83, ISSN 1340-2544.

Nakao, K. & Mochizuki, H. (2009). NALFURAFINE HYDROCHLORIDE: A NEW DRUG FOR THE TREATMENT OF UREMIC PRURITUS IN HEMODIALYSIS PATIENTS, *Drugs Today* 45, 5, 323-329. ISSN 1699-3993.

Ohsawa, M.; Kamei, J. (2005). Modification of κ-Opioid Receptor Agonist-Induced Antinociception by Diabetes in the Mouse Brain and Spinal Cord, *J. Pharmacol. Sci.*, 98, 1, 25-32, ISSN 1347-8613.

Satoh, M. & Minami, M. (1995). MOLECULAR PHARMACOLOGY OF THE OPIOID RECEPTORS, *Pharmacol. Ther.*, 68, 3, 343-364, ISSN 0163-7258.

Schuster, C. R.; Johanson, C. E. (1988). Relationship between the discriminative stimulus properties and subjective effects of drugs, *Psychopharmacol. Ser.* 4, 161–175, ISBN 0931-6795.

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, 1-2, 159-167. ISSN 0014-2999.

Shippenberg, T. S.; LeFevour, A.; Heidbreder, C. (1996). κ-Opioid Rreceptor Agonists Prevent Sensitization to the Conditioned Rewarding Effects of Cocaine, *J. Pharmacol. Exp. Ther.*, 276, 2, 545-554, ISSN 0022-3565.

Spanagel, R.; Herz, A.; Shippenberg, T. S. (1992). Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway, *Proc. Natl. Acad. Sci. U. S. A.*, 89, 6, 2046-2050, ISSN 0027-8424.

Suzuki, T.; Shiozaki, Y.; Masukawa, Y.; Misawa, M.; Nagase, H. (1992). The Role of Mu- and Kappa-Opioid Receptors in Cocaine-Induced Conditioned Place Preference, *Jpn. J. Pharmacol.*, 58, 4, 435-442, ISSN 0021-5198.

Suzuki, T.; Izumimoto, N.; Takezawa, Y.; Fujimura, M.; Togashi, Y.; Nagase, H.; Tanaka, T.; Endoh, T. (2004). Effect of repeated administration of TRK-820, a κ-opioid receptor agonist, on tolerance to its antinociceptive and sedative actions, *Brain Res.*, 995, 2, 167-175, ISSN 0006-8993.

Takasaki, I.; Suzuki, T.; Sasaki, A.; Nakao, K.; Hirakata, M.; Okano, K.; Tanaka, T.; Nagase, H.; Shiraki, K.; Nojima, H.; Kuraishi, Y. (2004). Suppression of Acute Herpetic Pain Related Responses by the κ-Opioid Receptor Agonist (-)-17- Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-3-trans-3-(3-furyl)Acrylamido]

Morphinan Hydrochloride (TRK-820) in Mice, *J. Pharmacol. Exp. Ther.*, 309, 1, 36-41, ISSN 0022-3565.

Takasaki, I.; Nojima, H.; Shiraki, K.; Kuraishi, Y. (2006). Specific down-regulation of spinal μ-opioid receptor and reduced analgesic effects of morphine in mice with postherpetic pain, *Eur. J. Pharmacol.*, 550, 1-3, 62-67, ISSN 0014-2999.

Togashi, Y.; Umeuchi, H.; Okano, K.; Ando, N.; Yoshizawa, Y.; Honda, T.; Kawamura, K.; Endoh, T.; Utsumi, J.; Kamei, J.; Tanaka, T. & Nagase, H. (2002). Antipruritic activity of the κ-opioid receptor agonist, TRK-820, *Eur. J. Pharmacol.*, 435, 2-3, 259-264. ISSN 0014-2999.

Tsuji, M.; Yamazaki, M.; Takeda, H.; Matsumiya, T.; Nagase, H.; Tseng, L. F.; Narita, M. & Suzuki, T. (2000a). The novel κ-opioid receptor agonist TRK-820 has no affect on the development of antinociceptive tolerance to morphine in mice, *Eur. J. Pharmacol.*, 394, 1, 91-95. ISSN 0014-2999.

Tsuji, M.; Takeda, H.; Matsumiya, T.; Nagase, H.; Yamazaki, M.; Narita, M. & Suzuki, T. (2000b). A NOVEL κ-OPIOID RECEPTOR AGONIST, TRK-820, BLOCKS THE DEVELOPMENT OF PHYSICAL DEPENDENCE ON MORPHINE IN MICE, *Life Sci.*, 66, 25, PL353-358, ISSN 0024-3205.

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, 15, 1717-1725, ISSN 0024-3205.

Umeuchi, H.; Togashi, Y.; Honda, T.; Nakao, K.; Okano, K.; Tanaka, T. & Nagase, H. (2003). Involvement of central μ-opioid system in the scratching behavior in mice, and the suppression of it by the activation of κ-opioid system, *Eur. J. Pharmacol.*, 477, 1, 29-35. ISSN 0014-2999.

Umeuchi, H.; Kawashima, Y.; Aoki, C. A.; Kurokawa, T.; Nakao, K.; Itoh, M.; Kikuchi, K.; Kato, T.; Okano, K.; Gershwin, M. E. & Miyakawa, H. (2005). Spontaneous scratching behavior in MRL/*lpr* mice, a possible model for pruritus in autoimmune diseases, and antipruritic activity of a novel κ-opioid receptor agonist nalfurafine hydrochloride, *Eur. J. Pharmacol.*, 518, 2-3, 133-139. ISSN 0014-2999.

Utsumi, J.; Togashi, Y.; Umeuchi, H.; Okano, K.; Tanaka, T. & Nagase, H. (2004). Antipruritic Activity of a Novel κ-Opioid Receptor Agonist, TRK-820, In: *Itch: Basic Mechanisms and Therapy* Yosipovitch, G.; Greaves, M. W.; Fleischer A. B. Jr.; McGlone, F. (Ed.) 107-114. ISBN 0-8247-4747-X.

Vanderah, T. W.; Largent-Milnes, T.; Lai, J.; Porreca, F.; Houghten, R. A.; Menzaghi, F.; Wisniewski, K.; Stalewski, J.; Sueiras-Diaz, J.; Galyean, R.; Schteingart, C.; Junien, J. –L.; Trojnar, J.; Riviere, P. J. –M.(2008). Novel D-amino acid tetrapeptides produce potent antinociception by selectively acting at peripheral κ-opioid receptors, *Eur. J. Pharmacol.*, 583, 1, 62-72, ISSN 0014-2999.

Wakasa, Y.; Fujiwara, A.; Umeuchi, H.; Endoh, T.; Okano, K.; Tanaka, T. & Nagase, H. (2004). Inhibitory effects of TRK-820 on systemic skin scratching induced by morphine in rhesus monkeys, *Life Sci.*, 75, 24, 2947-2957, ISSN 0024-3205.

Wang, D.; Sun, X.; Bohn, L. M. & Sadée, W. (2005). Opioid Receptor Homo- and Heterodimerization in Living Cells by Quantitative Bioluminescence Resonance Energy Transfer, *Mol. Pharmacol.*, 67, 6, 2173-2184, ISSN 0026-895X.

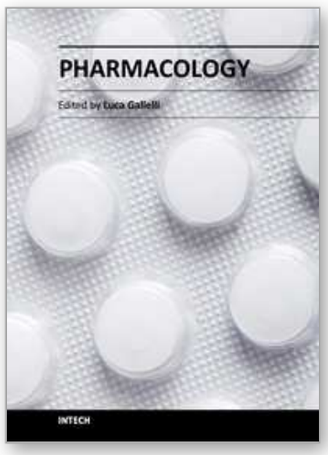
Wang, Y.; Tang, K.; Inan, S.; Siebert, D.; Holzgrabe, U.; Lee, D. Y. W.; Huang, P.; Li, J. –G.; Cowan, A. & Liu-Chen, L. –Y. (2005). Comparison of Pharmacological Activities of

Three Distinct κ Ligands (Salvinorin A, TRK-820 and 3FLB) on κ Opioid Receptors in Vitro and Their Antipruritic and Antinociceptive Activities in Vivo, *J. Pharmacol. Exp. Ther.*, 312, 1, 220-230. ISSN 0022-3565.

Wikström, B.; Gellert, R.; Ladefoged, S. D.; Danda, Y.; Akai, M.; Ide, K.; Ogasawara, M.; Kawashima, Y.; Ueno, K.; Mori, A. & Ueno, Y. (2005). κ-Opioid System in Uremic Pruritus: Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Studies, *J. Am. Soc. Nephrol.*, 16, 12, 3742-3747, ISSN 1046-6673.

Yamamizu, K.; Furuta, S.; Katayama, S.; Narita, M.; Kuzumaki, N.; Imai, S.; Nagase, H.; Suzuki, T.; Narita, M.; Yamashita, J. K. (2011). The κ opioid system regulates endothelial cell differentiation and pathfinding in vascular development, *Blood,* 118, 3, 775-785, ISSN 0006-4971.

Yoshikawa, S.; Hareyama, N.; Ikeda, K.; Kurokawa, T.; Nakajima, M.; Nakao, K.; Mochizuki, H.; Ichinose, H. (2009). Effects of TRK-820, a selective kappa opioid receptor agonist, on rat schizophrenia models, *Eur. J. Pharmacol.,* 606, 1-3, 102-108, ISSN 0014-2999.



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The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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