ELSEVIER

European Journal of Pharmacology 383 (1999) 241–247

ejp

www.elsevier.nl/locate/ejphar

The modulatory effect of (+)-TAN-67 on the antinociceptive effects of the nociceptin/orphanin FQ in mice

Junzo Kamei [a,*], Masahiro Ohsawa [a], Tomohiko Suzuki [b], Akiyoshi Saitoh [b], Takashi Endoh [b], Minoru Narita [c], Leon F. Tseng [c], Hiroshi Nagase [b]

[a] *Department of Pathophysiology and Therapeutics, Faculty of Pharmaceutical Sciences, Hoshi University, 4-41, Ebara 2-chome, Shinagawa-ku, Tokyo 142-8501, Japan*

[b] *Basic Research Laboratories, Toray Industries, Kamakura, Japan*

[c] *Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA*

Received 3 May 1999; received in revised form 31 August 1999; accepted 7 September 1999

Abstract

To clarify the pharmacological properties of (+)2-Methyl-4*a*α-(3-hydroxyphenyl)-1, 2, 3, 4, 4*a*, 5, 12, 12*a*α-octahydro-quinolino[2, 3, 3-*g*]isoquinoline ((+)-TAN-67), the effect of (+)-TAN-67 on the antinociception induced by the intrathecal (i.t.) administration of nociceptin/orphanin FQ was studied in mice using the tail-flick test and the formalin test. I.t. administration of (+)-TAN-67, at doses of 1 to 10 ng, facilitated the tail-flick response in a dose-dependent manner in mice. In addition, i.t. administration of (+)-TAN-67 (1 to 10 ng) in mice produced a marked pain-like aversive responses. I.t. pretreatment with D-Pro^{9}-[spiro-γ-lactam]-Leu^{10}-Trp^{11}-physalaemin(1–11) (GR82334, 0.1–1.0 nmol), a potent and selective tachykinin NK_1 receptor antagonist, dose-dependently blocked the reduction of the tail-flick response induced by (+)-TAN-67. Furthermore, (+)-TAN-67-induced facilitation of the tail-flick response was abolished in capsaicin-treated mice. On the other hand, (+)-TAN-67-induced flinching responses were dose-dependently and significantly reduced by i.t. pretreatment with GR82334 (0.1–1.0 nmol). The duration of i.t. (+)-TAN-67-induced flinching responses was significantly reduced in capsaicin-treated mice as compared with naive mice. I.t. administration of nociceptin/orphanin FQ (1–10 nmol) dose-dependently increased the tail-flick latency. I.t. administration of nociceptin/orphanin FQ (0.1–1.0 nmol) significantly and dose-dependently reduced the first-phase nociceptive response, but not the second-phase nociceptive response. I.t. pretreatment with (+)-TAN-67 (0.3–3.0 μg) for 30 min dose-dependently attenuated the antinociception induced by i.t. nociceptin (10 nmol) in the tail-flick test. Furthermore, the antinociceptive effect of nociceptin/orphanin FQ (1 nmol, i.t.) on the first-phase response in the formalin test was dose-dependently attenuated by s.c. pretreatment with (+)-TAN-67 (0.3–3.0 μg). (+)-TAN-67 (0.3–3.0 μg, i.t.), by itself, did not facilitate the tail-flick response or produce apparent behavioral changes. It is possible that (+)-TAN-67 has an antagonistic effect on nociceptin/orphanin FQ-induced antinociception.

Keywords: Nociceptin/orphanin FQ; (+)-TAN-67; Antinociception; Hyperalgesia; Substance P

1. Introduction

(±)2-Methyl-4*a*α-(3-hydroxyphenyl)-1, 2, 3, 4, 4*a*, 5, 12, 12*a*α-octahydro-quinolino[2, 3, 3-*g*]isoquinoline ((±)-TAN-67) is a non-peptidic δ-opioid receptor ligand (Nagase et al., 1994; Knapp et al., 1995). However, the high potency and selectivity of this racemic mixture of TAN-67 on δ-opioid receptors observed in in vitro studies is not consistent with findings in vivo that (±)-TAN-67 produced weak antinociceptive responses, if any (Kamei et al., 1995; Suzuki et al., 1995). The enantiomeric forms of (±)-TAN-67 have recently been resolved. (−)-TAN-67 given i.c.v. produced marked antinociception in the tail-flick test, whereas (+)-TAN-67, an enantiomer of (−)-TAN-67, did not produce the antinociception in mice (Kamei et al., 1996; Tseng et al., 1997). Recently, we demonstrated that unlike (−)-TAN-67, which produces antinociception, (+)-TAN-67 given intrathecal (i.t.) produces hyperalgesia (Tseng et al., 1997). This conclusion is based on the finding that (+)-TAN-67 given i.t. decreased the latencies of the tail-flick response at low doses (1.8–8.9 nmol) and produced scratching and biting at higher doses

* Corresponding author. Tel.: +81-3-5498-5030; fax: +81-3-5498-5029.

E-mail address: kamei@hoshi.ac.jp (J. Kamei)

0014-2999/99/$ - see front matter
PII: S0014-2999(99)00648-2

(17.9–89.4 nmol) (Tseng et al., 1997). We found that (+)-TAN-67 given i.c.v. had no significant effects on the tail-flick latencies in mice (Kamei et al., 1996). Furthermore, (+)-TAN-67 given i.c.v. did not produce abnormal behaviors, such as scratching or biting (Kamei et al., 1996). Although the exact mechanism is not yet clear, it is possible that the site of action of (+)-TAN-67 for producing hyperalgesia exists in the spinal cord, but not in a supraspinal site (Kamei et al., 1996). However, little is known about the mechanism of the hyperalgesic effect of (+)-TAN-67.

By direct examination at the spinal cord level in the rat, nociceptin/orphanin FQ, an opioid receptor-like1 (ORL1) receptor agonist, has been shown to inhibit sensory input (Faber et al., 1996). Nociceptin/orphanin FQ depressed both C-fiber- and A-fiber-mediated synaptic responses in a hemisected spinal cord preparation (Faber et al., 1996). Liebel et al. (1997) reported that nociceptin inhibits excitatory synaptic transmission in the superficial layers of the rat dorsal horn by acting on presynaptic opioid-like1 receptors. Furthermore, Xu et al. (1996) and Yamamoto et al. (1997) demonstrated that i.t. administration of nociceptin/orphanin FQ produced a pronounced antinociception in the tail-flick test and formalin test, respectively. These studies indicate that nociceptin/orphanin FQ likely produces antinociception at the spinal cord level.

We previously demonstrated that diabetes selectively and significantly enhances nociceptive transmission involving substance P in the spinal cord (Kamei et al., 1990, 1991a,b). Furthermore, the release of substance P from the dorsal horn of the spinal cord was significantly increased in diabetic rats, compared with that in non-diabetic rats (Kamei et al., 1991a). Recently, we observed that the antinociceptive effect of nociceptin/orphanin FQ in the tail-flick test in diabetic mice was greater than that in non-diabetic mice (Kamei et al., 1999). Furthermore, the antinociceptive effects of nociceptin/orphanin FQ in both diabetic and non-diabetic mice were abolished when mice were pretreated with capsaicin i.t. 24 h before testing (Kamei et al., 1999). In the formalin test, nociceptin/orphanin FQ also produced a marked and dose-dependent antinociceptive effect on the first-phase response, but not the second-phase response, in both diabetic and non-diabetic mice (Kamei et al., 1999). Nociceptin/orphanin FQ significantly and dose-dependently reduced the flinching in response to i.t.-administered substance P in diabetic mice, but not in non-diabetic mice (Kamei et al., 1999). Furthermore, Giuliani and Maggi (1996) reported that nociceptin/orphanin FQ decreased the release of tachykinin from the peripheral ends of capsaicin-sensitive primary afferent fibers in the renal pelvis. Based on these results, we suggested that the reduction of substance P-mediated nociceptive transmission in the spinal cord may be responsible for the antinociceptive effect of nociceptin/orphanin FQ (Kamei et al., 1999). Among the tachykinins, substance P is important in sensory processing in the dorsal horn of the spinal cord, where its activates tachykinin NK_1 receptors (Helke et al., 1990).

The purpose of this study was to examine whether tachykinin NK_1 receptors play an important role in the mechanism of (+)-TAN-67-induced hyperalgesia, and the effect of (+)-TAN-67 on the antinociceptive effect of nociceptin/orphanin FQ.

2. Materials and methods

2.1. Animals

Male ICR mice (6 weeks old, weighing about 25 g, Tokyo Laboratory Animals Science, Tokyo, Japan) were used. They had free access to food and water in an animal room that was maintained at 24°C ± 1°C with a 12-h light–dark cycle. This study was carried out in accordance with the Declaration of Helsinki and/or with the guide for the care and use of laboratory animals as adopted by the committee on the care and use of laboratory animals of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture.

2.2. Tail-flick test

The antinociceptive effect was evaluated by recording the latency in the tail-flick test using radiant heat as a stimulus. The tails of mice were blackened using India ink and exposed to the focused beam of light from a preheated 500 W projection bulb. The heat intensity was set to one of two values by adjusting the source voltage of the bulb to 65 V. When withdrawal occurred, the stimulus was terminated and the response latency was measured electronically.

2.3. Formalin-induced flinching response

The experiment was performed according to the method described by Shibata et al. (1989). Each mouse was acclimated to an acrylic observation chamber ($32 \times 23 \times 17$ cm^3) for at least 5 min before the injection of formalin. Twenty-five microliter of a 0.5% solution of formalin in 0.9% saline were administered into the dorsal surface of the right hindpaw. Immediately after the injection, each animal was returned to the observation chamber and its flinching response was recorded for 30 min. The mouse licked and bit the injected paw, and these responses were distinct and easily observed. The cumulative response time (s), i.e., the duration of licking and biting of the injected paw, was measured for each 5-min block. The cumulative response times during the initial two blocks and during and after the third block were regarded as the first-phase and second-phase responses, respectively.

The cumulative response time (s) in each phase was normalized to the mean response time shown by the

control group. Percent antinociception was expressed as: $100 \times (\text{mean control time} - \text{test time})/(\text{mean control time})$.

2.4. (+)-Tan-67-induced flinching response

Each mouse was acclimated to an acrylic observation chamber ($32 \times 23 \times 17$ cm^3) for at least 5 min before the injection of (+)-TAN-67. A solution of (+)-TAN-67 (1, 3 and 10 ng/5 μl) was administered intrathecally. Immediately after i.t. injection, each animal was returned to the observation chamber and its flinching response was recorded for 30 min. The cumulative response time (s) of biting, paw licking and scratching episodes was measured according to the method described by Hylden and Wilcox (1981).

2.5. Capsaicin pretreatment

To reduce substance P content or release from the spinal cord, capsaicin was injected i.t. 24 h before the experiments. Mice were anesthetized with ether before the i.t. administration of capsaicin at a dose of 0.56 nmol.

2.6. Experimental protocol

I.t. administration, in a volume of 5 μl, was performed according to the methods of Hylden and Wilcox (1980). The mouse was manually restrained and a 30-gauge 1/2-in. needle mated to a 50-μl Hamilton syringe was inserted between vertebrae L5 and L6 of the mouse spinal column. Various doses of (+)-TAN-67 were injected i.t., and the tail-flick response was measured 30 and 60 min after injection. GR82334 was injected i.t. 10 min before the i.t. administration of (+)-TAN-67. The antinociceptive effect of nociceptin/orphanin FQ was tested 10, 20, 30 and 60 min after i.t. injection. (+)-TAN-67 was injected i.t. 10 min before the i.t. administration of nociceptin/orphanin FQ.

2.7. Drugs

Nociceptin/orphanin FQ and D-Pro^9-[spiro-γ-lactam]-Leu^{10}-Trp^{11}-physalaemin(1–11) (GR82334) were purchased from Research Biochemical International, Natick, MA, USA. (+)-TAN-67 was synthesized by Dr. H. Nagase (Toray Industries, Kamakura, Japan). Capsaicin was dissolved in a 10% ethanol and Tween 80 in saline (0.9% NaCl). The solution was diluted with saline. All other drugs were dissolved in saline.

2.8. Statistics

The data are expressed as the mean ± S.E. The statistical significance of differences was assessed with the Newman–Keuls test. A level of probability of 0.05 or less was accepted as significant. The ED_{50} values, the ED_{50} ratio and their 95% confidence intervals for the antinociceptive effect of nociceptin/orphanin FQ were determined using linear regression techniques. The potency ratios and their 95% confidence intervals for the antinociceptive effect of nociceptin/orphanin FQ were computed using Program 11 of the Pharmacological Calculations system of Tallarida and Murray (1987).

3. Results

3.1. Hyperalgesic effects of (+)-TAN-67 on tail-flick latency and behavior

I.t. administration of (+)-TAN-67, at doses of 1 to 10 ng, resulted in a dose-dependent reduction of the tail-flick latency in mice (Fig. 1A). Indeed, (+)-TAN-67, at a dose of 10 ng, significantly reduced the tail-flick latency when mice were tested 60 min after i.t. administration of (+)-

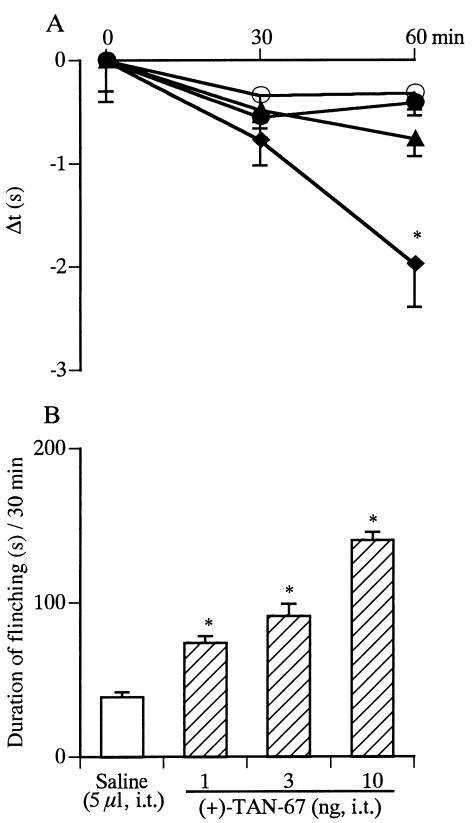

Fig. 1. The dose–effect curves for (+)-TAN-67 on the tail-flick latency (Δt(s)) within 60 min after i.t. administration (A) and the cumulative response time (s) in flinching during the 30 min after i.t. administration (B) of (+)-TAN-67. Mice were injected i.t. with 1 ng (●), 3 ng (▲) or 10 ng (♦) of (+)-TAN-67. Δt(s) = post-drug latency–pre-drug latency. Each point or column represents the mean with S.E. for 10 mice in each group. $^*P < 0.05$ vs. the saline-treated group (open circle or open column).

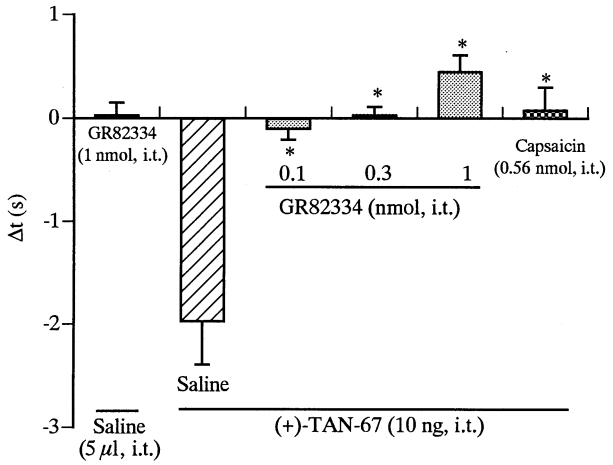

Fig. 2. Effect of i.t. pretreatment with GR82334 or capsaicin on the hyperalgesic effect of i.t. (+)-TAN-67 on the tail-flick latency in mice. GR82334 was injected i.t. 10 min before the i.t. administration of (+)TAN-67. Capsaicin (0.56 nmol) was injected 24 h before testing. The effects of (+)-TAN-67 were measured 60 min after injection. Δt(s) = post-drug latency–pre-drug latency. Each column represents the mean with S.E. for 10 mice in each group. $^{*}P < 0.05$ vs. the saline-treated group (hatched column).

TAN-67 (Fig. 1A). I.t. injection of (+)-TAN-67, by itself, dose-dependently produced pain-like aversive responses. Mice developed flinching responses, i.e., licking and biting, immediately after i.t. injection of (+)-TAN-67 (1–10 ng), which lasted about 30 min (Fig. 1B).

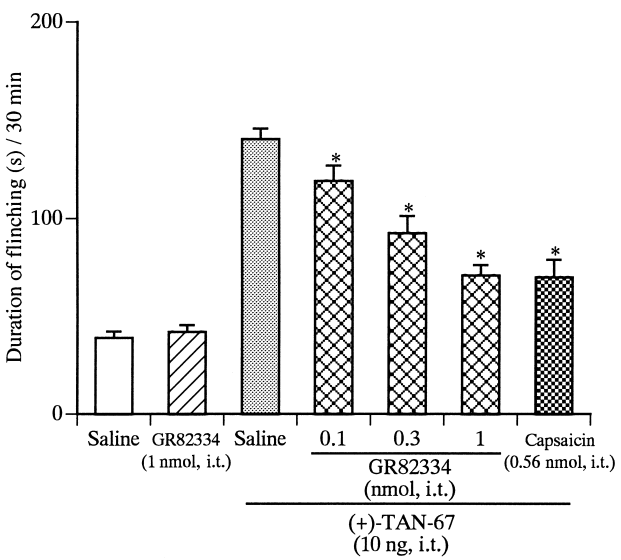

Fig. 3. Effect of i.t. pretreatment with GR82334 or capsaicin on the cumulative response time (s) in flinching during the 30 min after i.t. administration of (+)-TAN-67 in mice. GR82334 was injected i.t. 10 min before the i.t. administration of (+)-TAN-67. Capsaicin (0.56 nmol) was injected 24 h before testing. The effects of (+)-TAN-67 were measured 60 min after injection. Each column represents the mean with S.E. for 10 mice in each group. $^{*}P < 0.05$ vs. the saline-treated group (dotted column).

3.2. Effects of GR82334 and capsaicin on hyperalgesic effects of (+)-TAN-67 on tail-flick latency and behavior

As shown in Fig. 2, the hyperalgesic effect of (+)-TAN-67 on the tail-flick latency was attenuated by pretreatment with GR82334, a potent and selective tachykinin NK_1 receptor antagonist (Maggi et al., 1994). Indeed, i.t. pretreatment with GR82334, at doses of 0.1 to 1.0 nmol, dose-dependently blocked the reduction in the tail-flick response induced by (+)-TAN-67. Furthermore, (+)-TAN-67-induced facilitation of tail-flick response was abolished in capsaicin-treated mice (Fig. 2). The effect of GR82334 on (+)-TAN-67-induced pain-like aversive responses is shown in Fig. 3. (+)-TAN-67-induced flinching responses were dose-dependently and significantly reduced by i.t. pretreatment with GR82334 (0.1–1.0 nmol). Capsaicin-treated mice had higher nociceptive threshold values for (+)-TAN-67 than did naive mice, as evidenced by a significant ($P < 0.05$) decrease in the duration of i.t. (+)-TAN-67-induced flinching responses (Fig. 3).

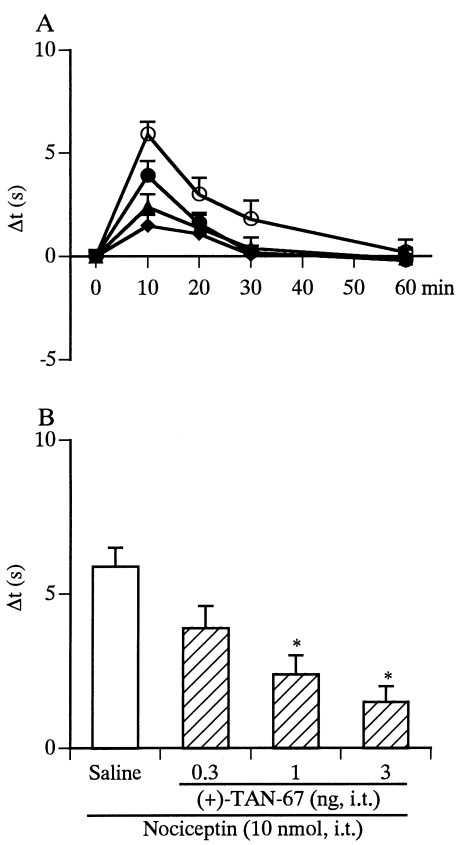

Fig. 4. The time course (A) and dose–response effects (B) for i.t. (+)-TAN-67 on the antinociceptive effect of nociceptin/orphanin FQ on tail-flick latency. (+)-TAN-67 (0.3 ng (●), 1 ng (▲) or 3 ng (◆)) was injected i.t. 10 min before the administration of nociceptin/orphanin FQ (10 nmol, i.t.) Each point or column represents the mean with S.E. for 10 mice in each group. Δt(s) = post-drug latency–pre-drug latency. $^{*}P < 0.05$ vs. the saline-treated group.

3.3. Effect of (+)-TAN-67 on the antinociceptive effect of nociceptin / orphanin FQ in the tail-flick test

I.t. administration of nociceptin/orphanin FQ, at a dose of 10 nmol, significantly inhibited the tail-flick response (Fig. 4A). This tail-flick inhibition reached its peak 10 min after injection, gradually declined and returned to the preinjection level 60 min after injection. The effect of (+)-TAN-67 on the antinociceptive effect of nociceptin/orphanin FQ on the tail-flick response is summarized in Fig. 4B. The antinociceptive effect of nociceptin/orphanin FQ was significantly and dose-dependently antagonized by pretreatment with (+)-TAN-67 (0.3–3.0 μg, i.t.). However, (+)-TAN-67 (0.3–3.0 μg, i.t.), by itself, had no significant effect on the tail-flick latency.

3.4. Effect of (+)-TAN-67 on the antinociceptive effect of nociceptin / orphanin FQ on the formalin-induced flinching response

In mice, s.c. injection of 0.5% formalin into the hindpaw caused an acute, immediate flinching response, i.e., licking and biting, which lasted about 5 min (first-phase response). The second-phase response then began and lasted about 20 min. I.t. administration of nociceptin/orphanin FQ, at a dose of 1.0 nmol, resulted in a marked reduction in the duration of the first phase, but not of the second phase of formalin-induced flinching (Fig. 5). The antinociceptive effect of nociceptin/orphanin FQ on the first-phase response of formalin-induced flinching

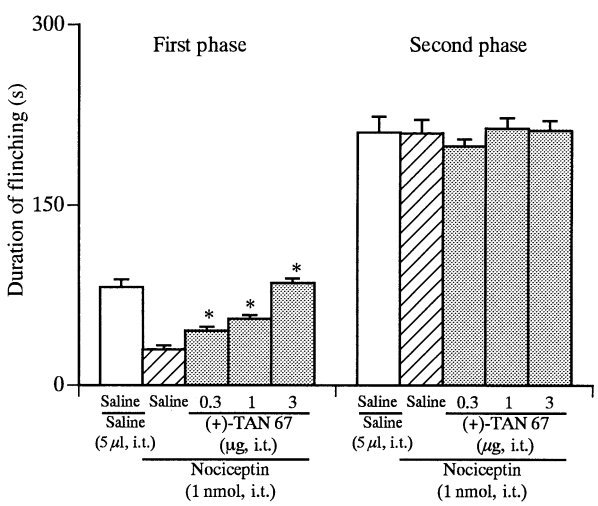

Fig. 5. Effect of (+)-TAN-67 on the antinociceptive effect of nociceptin/orphanin FQ on the formalin-induced biphasic nociceptive response in mice. (+)-TAN-67 (0.3, 1 or 3 ng) was injected i.t. 10 min before the administration of nociceptin/orphanin FQ (1 nmol, i.t.). Data are expressed as the cumulative flinching time during the first (0–10 min) and second (10–30 min) phases. Each column represents the mean with S.E. for 10 mice in each group. $^{*}P < 0.05$ vs. the saline-treated group (hatched column).

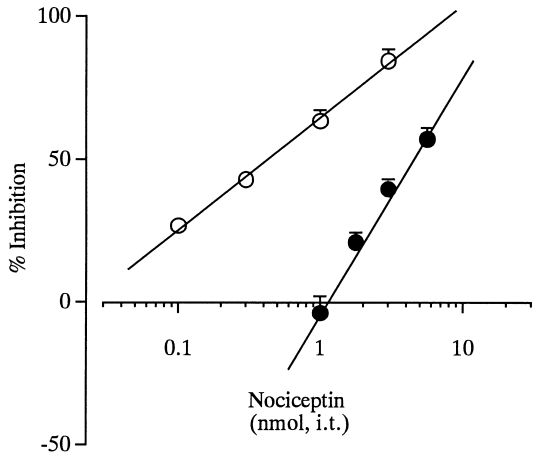

Fig. 6. Effect of (+)-TAN-67 (●) on the dose–response curve for i.t. nociceptin/orphanin FQ on the first phase of the formalin-induced nociceptive response in mice. (+)-TAN-67 (3 ng) was injected i.t. 10 min before the i.t. administration of various doses of nociceptin/orphanin FQ. The cumulative response time (s) in each phase was normalized to the mean response time shown by the control group. Percent antinociception was expressed as: 100×(mean control time−test time)/(mean control time). Each point represents the mean with S.E. for 10 mice in each group.

was significant and dose-dependently antagonized by pretreatment with (+)-TAN-67, at doses of 1–10 μg/kg, s.c. Furthermore, when mice were pretreated with (+)-TAN-67 (10 μg/kg, s.c.), the dose-response curve for nociceptin/orphanin FQ was shifted to the left (Fig. 6). The ED_{50} values (nmol with 95% confidence limits) were 0.44 (0.27–0.73) and 0.02 (0.01–1.12) for naive and (+)-TAN-67-treated mice, respectively. The ED_{50} ratio (95% confidence limits) of the antinociceptive effect of nociceptin/orphanin FQ in naive mice vs. that in (+)-TAN-67-treated mice was 15.1 (8.9–31.6). However, (+)-TAN-67 (1–10 μg/kg, s.c.), by itself, did not produce apparent behavioral changes.

4. Discussion

In the present study, i.t. administration of (+)-TAN-67 facilitated the tail-flick response in a dose-dependent manner in mice. In addition, i.t. administration of (+)-TAN-67 in mice produced a marked pain-like aversive responses. These results are consistent with our previous findings (Tseng et al., 1997). In the present study, we observed that i.t. pretreatment with GR82334, a potent and selective tachykinin NK_1 receptor antagonist (Maggi et al., 1994), dose-dependently blocked the reduction of the tail-flick response induced by (+)-TAN-67. Furthermore, (+)-TAN-67-induced facilitation of the tail-flick response was abolished in capsaicin-treated mice. On the other hand, (+)-TAN-67-induced flinching responses were dose-dependently and significantly reduced by i.t. pretreatment with GR82334 (0.1–1.0 nmol). The duration of i.t. (+)-

TAN-67-induced flinching responses was significantly reduced in capsaicin-treated mice as compared with naive mice. It has been demonstrated that pretreatment with capsaicin decreases the content and release of substance P from primary afferent fibers (Gamse, 1982; Goettl et al., 1997). It is possible that the reduction in the hyperalgesic effect of (+)-TAN-67 in capsaicin-treated mice may be associated with a decrease in the content and release of substance P from primary afferent fibers in the spinal cord. Thus, these results suggest that the enhancement of substance P-mediated nociceptive transmission, and particularly the increase in the release of substance P in the spinal cord, may be, at least in part, responsible for the hyperalgesic effect of (+)-TAN-67.

I.t. administration of nociceptin/orphanin FQ resulted in a significant increase in the latency to the tail-flick in mice. Furthermore, i.t. administration of nociceptin/orphanin FQ resulted in a reduction in the cumulative response time in the first phase of the formalin-induced flinching responses in mice. However, nociceptin/orphanin FQ had no significant effect on the second phase of the formalin-induced flinching response in mice. These results are consistent with our previous findings that nociceptin/orphanin FQ produced a marked and dose-dependent antinociception in the tail-flick and formalin tests (Kamei et al., 1999). Interestingly, in the present study, the antinociceptive effects of nociceptin/orphanin FQ in both the tail-flick test and formalin test were significantly and dose-dependently antagonized by i.t. pretreatment with (+)-TAN-67. The mechanism of the antagonistic effect of (+)-TAN-67 on nociceptin/orphanin FQ-induced antinociception remains to be clarified. Several possibilities should be considered. We recently reported that the reduction of substance P-mediated nociceptive transmission, and particularly the inhibition of the release of substance P in the spinal cord, is responsible for the antinociceptive effect of nociceptin/orphanin FQ (Kamei et al., 1999). Giuliani and Maggi (1996) reported that nociceptin/orphanin FQ decreased the release of tachykinin from the peripheral ends of capsaicin-sensitive primary afferent fibers in the renal pelvis. Furthermore, as mentioned above, the hyperalgesic effect of i.t. (+)-TAN-67 may account for the enhancement of the release of substance P from the spinal cord. It is possible that these opposite effects on substance P-mediated nociceptive transmission by (+)-TAN-67 and nociceptin/orphanin FQ negate each other. Thus, this counteraction of the release of substance P from the spinal cord may be responsible for the antagonistic effect of (+)-TAN-67 on nociceptin/orphanin FQ-induced antinociception. However, doses of (+)-TAN-67 which antagonized the antinociceptive effect of nociceptin/orphanin FQ had no significant effect on the tail-flick latency, and did not produce apparent behavioral changes. Receptor binding studies have indicated that (+)-TAN-67 does not displace nociceptin/orphanin FQ binding in membranes of Chinese hamster ovary (CHO) cells transfected with ORL_1 receptor (our unpublished data). These results suggest that (+)-TAN-67 does not directly interact with nociceptin/orphanin FQ at ORL_1 receptors. On the other hand, the inhibitory activity of nociceptin/orphanin FQ on forskolin-stimulated cAMP accumulation was dose-dependently antagonized by (+)-TAN-67, at doses of 1 and 10 nM, in membranes of CHO cells transfected with ORL_1 receptor (our unpublished data). Although the binding sites for (+)-TAN-67 have not yet been identified, this result suggests that activation of (+)-TAN-67 receptor can modulate ORL_1 receptor signaling in a cellular system. This may explain why (+)-TAN-67 given i.t. produced a dose-dependent and significant inhibition of the antinociceptive effect of nociceptin/orphanin FQ. However, further studies are necessary before this issue can be resolved with greater certainty.

In conclusion, this study clearly indicates that the increase in the release of substance P in the spinal cord, may be, at least in part, responsible for the hyperalgesic effect of (+)-TAN-67. Furthermore, the results of this study suggest that modulation of ORL_1 receptor signaling in a cellular system by (+)-TAN-67 in the spinal cord may be responsible for its antagonistic effect on the antinociceptive effect of nociceptin/orphanin FQ. Moreover, it seems likely that not only nociceptin/orphanin FQ, but also (+)-TAN-67, may be a useful tool for further investigation of analgesic and counteranalgesic pathways modulate pain perception.

References

Faber, E.S.L., Chambers, J.P., Evans, R.H., Henderson, G., 1996. Depression of glutaminergic transmission by nociceptin in the neonatal rat hemisected spinal cord preparation in vitro. Br. J. Pharmacol. 119, 189–190.

Gamse, R., 1982. Capsaicin and nociception in the rat and mouse. Possible role of substance P. Naunyn-Schmiedeberg's Arch. Pharmacol. 320, 205–216.

Giuliani, S., Maggi, C.A., 1996. Inhibition of tachykinin release from peripheral nerve endings of sensory nerves by nociceptin, a novel opioid peptide. Br. J. Pharmacol. 118, 1567–1569.

Goettl, V.M., Larson, D.L., Portoghese, P.S., Larson, A.A., 1997. Inhibition of substance P release from spinal cord tissue after pretreatment with capsaicin in adult mice. Pain 71, 271–278.

Helke, C.J., Krause, J.E., Mantyh, P.W., Couture, R., Bannon, M.J., 1990. Diversity in mammalian tachykinin peptidergic neuron: multiple peptides, receptor, and regulatory mechanisms. FASEB J. 4, 1606–1615.

Hylden, J.K.L., Wilcox, G.L., 1980. Intrathecal morphine in mice; a new technique. Eur. J. Pharmacol. 67, 313–316.

Hylden, J.K.L., Wilcox, G.L., 1981. Intrathecal substance P elicits a caudally-directed biting and scratching behavior. Brain Res. 217, 212–215.

Kamei, J., Ogawa, M., Kasuya, Y., 1990. Development of supersensitivity to substance P in the spinal cord of the streptozotocin-induced diabetic mice. Pharmacol. Biochem. Behav. 35, 473–475.

Kamei, J., Ogawa, M., Ohhashi, Y., Kasuya, Y., 1991a. Alterations in the potassium-evoked release of substance P from the spinal cord of streptozotocin-induced diabetic rats in vitro. Gen. Pharmacol. 22, 1093–1096.

Kamei, J., Ohhashi, Y., Aoki, T., Kasuya, Y., 1991b. Streptozotocin-induced diabetes in mice reduces the nociceptive threshold, as recognized after application of noxious mechanical stimuli but not for thermal stimuli. Pharmacol. Biochem. Behav. 39, 541–544.

Kamei, J., Saitoh, A., Ohsawa, M., Suzuki, T., Misawa, M., Nagase, H., Kasuya, Y., 1995. Antinociceptive effects of the selective non-peptidic δ-opioid receptor agonist TAN-67 in diabetic mice. Eur. J. Pharmacol. 276, 131–135.

Kamei, J., Kawai, K., Mizusuna, A., Saitoh, A., Morita, K., Narita, M., Tseng, L.F., Nagase, H., 1996. Supraspinal δ_1-opioid receptor-mediated antinociceptive properties of (−)-TAN-67 in diabetic mice. Eur. J. Pharmacol. 322, 27–30.

Kamei, J., Ohsawa, M., Kashiwazaki, T., Nagase, H., 1999. Antinociceptive effects of the opioid receptor-like1 receptor agonist nociceptin/orphanin FQ in diabetic mice. Eur. J. Pharmacol. 370, 109–116.

Knapp, R.J., Landsman, R., Waite, S., Malatynska, E., Varga, E., Haq, W., Hruby, V.J., Roeske, W.R., Nagase, H., Yamamura, H.I., 1995. Properties of TAN-67, a nonpeptidic δ-opioid receptor agonist, at cloned human δ- and μ-opioid receptors. Eur. J. Pharmacol. Mol. Pharmacol. Sect. 291, 129–134.

Liebel, J.T., Swandulla, D., Zeilhofer, H.U., 1997. Modulation of excitatory synaptic transmission by nociceptin in superficial dorsal horn neurons of the neonatal rat spinal cord. Br. J. Pharmacol. 121, 425–432.

Maggi, C.A., Patacchini, R., Meini, S., Quartara, L., Sisto, A., Potier, E., Giuliani, S., Giachetti, A., 1994. Comparison of tachykinin NK1 and NK2 receptors in the circular muscle of the guinea pig ileum and proximal colon. Br. J. Pharmacol. 112, 150–160.

Nagase, H., Wakita, H., Kawai, K., Endoh, T., Matuura, H., Tanaka, T., Takezawa, Y., 1994. Syntheses of non-peptidic delta opioid agonists and their structure activity relationships. Jpn. J. Pharmacol. 64 (Suppl. I), 35.

Shibata, M., Ohkubo, T., Takahashi, H., Inoki, R., 1989. Modified formalin test: characteristic biphasic pain response. Pain 38, 347–352.

Suzuki, T., Tsuji, M., Mori, T., Misawa, M., Endoh, T., Nagase, H., 1995. Effects of highly selective nonpeptidic δ opioid receptor agonist, TAN-67, on morphine-induced antinociception in mice. Life Sci. 57, 155–168.

Tallarida, R.J., Murray, R.B., 1987. Manual of Pharmacologic Calculations with Computer Program. 2nd edn. Springer-Verlag, New York.

Tseng, L.F., Narita, M., Mizoguchi, H., Kawai, K., Mizusuna, A., Kamei, J., Suzuki, T., Nagase, H., 1997. δ_1-Opioid receptor-mediated antinociceptive properties of a nonpeptidic δ-opioid receptor agonist, (−)TAN-67, in the mouse spinal cord. J. Pharmacol. Exp. Ther. 280, 600–605.

Xu, X.-J., Hao, J.-X., Wiesenfeld-Hallin, Z., 1996. Nociception or antinociception: potent spinal antinociceptive effect of orphaninFQ/nociceptin in the rat. NeuroReport 7, 2092–2094.

Yamamoto, T., Nozaki-Taguchi, N., Kimura, S., 1997. Analgesic effect of intrathecally administered nociceptin, an opioid receptor-like1 receptor agonist, in the rat formalin test. Neuroscience 81, 249–254.