Antinociceptive effects of the ORL1 receptor agonist nociceptin/orphanin FQ in diabetic mice

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Received 27 August 1998; received in revised form 13 January 1999; accepted 12 February 1999

Abstract

The antinociceptive potency of nociceptin/orphanin FQ, an opioid-like orphan receptor agonist, was examined using the tail-flick test and the formalin-induced nociception test in diabetic mice. Nociceptin/orphanin FQ, at doses of 0.1 to 10 nmol, intrathecally (i.t.), produced a marked and dose-dependent inhibition of the tail-flick response in both non-diabetic and diabetic mice. The antinociceptive effect of nociceptin/orphanin FQ in the tail-flick test in diabetic mice was greater than that in non-diabetic mice. The antinociceptive effect of nociceptin/orphanin FQ was not antagonized by pretreatment with either β-funaltrexamine, a selective μ-opioid receptor antagonist, naltrindole, a selective δ-opioid receptor antagonist, or nor-binaltorphimine, a selective κ-opioid receptor antagonist. The antinociceptive effects of nociceptin/orphanin FQ in diabetic, but not in non-diabetic mice, were abolished when mice were pretreated with capsaicin i.t. 24 h before testing. 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. Furthermore, nociceptin/orphanin FQ significantly and dose-dependently reduced the flinching responses to i.t.-administered substance P in diabetic mice, but not in non-diabetic mice. The results of the present experiments clearly indicate that the antinociceptive potency of nociceptin/orphanin FQ is significantly greater in diabetic mice than in non-diabetic mice. Furthermore, the results of this study suggest that the reduction of substance P-mediated nociceptive transmission in the spinal cord may be responsible for the antinociceptive effect of nociceptin/orphanin FQ. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Antinociception; Nociceptin/orphanin FQ; Substance P; Capsaicin; Diabetes

1. Introduction

Nociceptin/orphanin FQ was recently identified as a putative endogenous ligand of an opioid receptor-like receptor (ORL1) that has negligible affinity for μ-, δ- and κ-opioids (Meunier et al., 1995; Reinscheid et al., 1995). Nociceptin/orphanin FQ induced hyperalgesia in the tail-flick test when it was administered intracerebroventricularly (Reinscheid et al., 1995; Nishi et al., 1997). In contrast, by direct examination at the spinal cord level in the rat, nociceptin/orphanin FQ 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/orphanin FQ inhibits excitatory synaptic transmission in the superficial layers of the rat dorsal horn by acting on presynaptic ORL1 receptors. Furthermore, Xu et al. (1996) and Yamamoto et al. (1997) demonstrated that intrathecal (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 enhance the 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. Giuliani and Maggi (1996) reported that nociceptin/orphanin FQ decreased the release of tachykinin from the peripheral ends of capsaicin-sensitive primary afferent

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PFI: S0014-2999(99)00112-0
fibers in the renal pelvis. It is possible that the same mechanisms are involved in the inhibition of tachykinin release from the central endings of primary afferent fibers within the spinal cord. If the inhibition of tachykinin release, like substance P and neurokinin A release, in the spinal cord plays a role in the antinociceptive effect of nociceptin/orphanin FQ, the diabetic state may modulate the antinociceptive effect of nociceptin/orphanin FQ. Thus, in the present study, we investigated the influence of diabetes on the antinociceptive effect of nociceptin/orphanin FQ administered i.t.

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science, Tokyo, Japan), weighing about 20 g at the beginning of the experiments, were used. They had free access to food and water in an animal room that was maintained at 22 ± 1°C with a 12-h light-dark cycle. Animals were rendered diabetic by an injection of streptozotocin (200 mg/kg, i.v.) prepared in 0.1 N citrate buffer at pH 4.5. Age-matched non-diabetic mice were injected with the vehicle alone. The experiments were conducted 2 weeks after injection of streptozotocin or vehicle. Mice with serum glucose levels above 400 mg/dl were considered diabetic. This study was carried out in accordance with the Declaration of Helsinki and 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 50 (low heating rate) or 65 V (high heating rate). When withdrawal occurred, the stimulus was terminated and the response latency was measured electronically. Changes in tail flick latency [\(\Delta t (s)\)] was calculated for each animal according to the formula: \(\Delta t (s) = \text{post-drug latency} - \text{pre-drug latency}\).

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 × 23 × 17 cm\(^3\)) for at least 5 min before the injection of formalin. Twenty five microliters 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 cumulative response time 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.

2.4. Substance P-induced flinching response

Each mouse was acclimated to an acrylic observation chamber (32 × 23 × 17 cm\(^3\)) for at least 5 min before the injection of substance P. A solution of substance P (0.1 nmol/5 μl) was administered i.t. Immediately after i.t. injection, each animal was returned to the observation chamber and its flinching response was recorded for 10 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. Intrathecal injection

Intrathecal 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 50-μl Hamilton syringe was inserted between vertebrae L5 and L6 of the mouse spinal column.

2.7. Drugs

Nociceptin/orphanin FQ was purchased from Research Biochemical International, Natick, MA, USA. β-Funaltrexamine, naltrindole and nor-binaltorphimine were synthesized by Dr. H. Nagase (Toray Industries, Kamakura, Japan). All of the drugs were dissolved in saline. Nociceptin/orphanin FQ was injected i.t. 10 min before antinociceptive assay. β-Funaltrexamine (20 mg/kg, s.c.) was injected 24 h before testing. Naltrindole (1.0 mg/kg, s.c.) was injected 15 min before the injection of nociceptin/orphanin FQ, as previously described (Kamei et al., 1994). Nor-binaltorphimine (20 mg/kg, s.c.) was injected 3 h before the injection of nociceptin/orphanin FQ (Endoh et al., 1992).

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2.8. Statistical analysis

called a one-way ANOVA, and the multiple comparisons were made by the Dunnett test. All data are expressed as mean ± S.E. *p < 0.05, **p < 0.01, ***p < 0.001, compared to the control group.

3. Results

3.1. Effect of diabetes on nociception

A solution of formalin (0.5% FQ) was injected into the dorsal surface of the right hindpaw. 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.

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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\textsubscript{50} values, the ED\textsubscript{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 nociceptin/orphanin FQ were computed using Program 11 of the Pharmacological Calculations system of Tallarida and Murray (1987).

3. Results

3.1. Effect of nociceptin/orphanin FQ on tail-flick latency

At the high heating rate, no significant difference in the nociceptive threshold, as determined by the tail-flick latency, was seen between diabetic (5.1 ± 0.2 s) and non-diabetic mice (6.0 ± 0.4 s).

Intrathecal administration of nociceptin/orphanin FQ, at doses of 1 to 10 nmol, resulted in a significant and dose-dependent prolongation of the tail-flick latency at the high heating rate in non-diabetic mice (Fig. 1A). On the other hand, nociceptin/orphanin FQ, at doses of 0.1 to 1 nmol, also produced a marked and dose-dependent prolongation of the tail-flick latency at the high heating rate in diabetic mice (Fig. 1B). The dose–response curve for nociceptin/orphanin FQ in diabetic mice was shifted to the left of that in non-diabetic mice (Fig. 2). The potency ratio (95% confidence limits) of the effect of nociceptin/orphanin FQ on the tail-flick latency in diabetic mice vs. that in non-diabetic mice was 8.9 (5.5–14.2). Thus, the antinociceptive potency of nociceptin/orphanin FQ in diabetic mice was significantly greater than that in non-diabetic mice.

3.2. Effects of selective opioid-receptor antagonists on the antinociceptive effect of nociceptin/orphanin FQ

The effects of \( \beta \)-funaltrexamine, a selective \( \mu \)-opioid receptor antagonist, naltrindole, a selective \( \delta \)-opioid receptor antagonist and nor-binaltorphimine, a selective \( \kappa \)-opioid receptor antagonist, on the antinociceptive effect of nociceptin/orphanin FQ are summarized in Fig. 3. The antinociceptive effect of nociceptin/orphanin FQ was not antagonized by pretreatment with either \( \beta \)-funaltrexamine, naltrindole or nor-binaltorphimine in either diabetic or non-diabetic mice.
3.3. Effect of pretreatment with capsaicin on the antinociceptive effect of nociceptin/orphanin FQ

At the low heating rate, diabetic mice had lower nociceptive threshold values than did non-diabetic mice, as evidenced by a significant ($P < 0.05$) difference in the tail-flick latency between the two groups (diabetic mice, $7.5 \pm 0.4$ s; non-diabetic mice, $13.1 \pm 0.8$ s) (Fig. 4). When capsaicin (0.56 nmol) was administered i.t. 24 h before testing, the tail-flick latency at the low heating rate in diabetic mice was significantly prolonged (Fig. 4). However, pretreatment with capsaicin had no significant effect on tail-flick latency at the high heating rate in diabetic mice, or at the low or high heating rates in non-diabetic mice (Fig. 4).

The dose–response curve for the antinociceptive effect of nociceptin/orphanin FQ on the tail-flick latency at the low heating rate in capsaicin-treated diabetic mice was shifted to the right of that in vehicle-treated diabetic mice (Fig. 5). The potency ratio (95% confidence limits) of the effect of nociceptin/orphanin FQ on the tail-flick latency at the low heating rate in capsaicin-treated diabetic mice vs. that in vehicle-treated diabetic mice was 12.2 (6.6–23.4). The antinociceptive potency of nociceptin/orphanin FQ in capsaicin-treated diabetic mice was reduced to the level of vehicle-treated non-diabetic mice (Fig. 5). However, pretreatment with capsaicin had no effect on the antinociceptive potency of nociceptin/orphanin FQ in non-diabetic mice (Fig. 5).

3.4. Effects of nociceptin/orphanin FQ on the formalin-induced flinching response

In non-diabetic 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. In diabetic mice, s.c. injection of formalin into the hindpaw also produced biphasic flinching responses. The cumulative response time

![Fig. 3](image1.png)

Fig. 3. Blockade of the antinociceptive effects of nociceptin/orphanin FQ by opioid antagonists in non-diabetic (A) and diabetic (B) mice. Naltrindole (NTI, 1.0 mg/kg) was injected s.c. 15 min before the administration of nociceptin/orphanin FQ. β-Funaltrexamine (FNA, 20 mg/kg) was injected s.c. 24 h before the test. Nor-binaltorphimine (BNI, 20 mg/kg, s.c.) was injected 3 h before the administration of nociceptin/orphanin FQ. $\Delta t$ (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.

![Fig. 4](image2.png)

Fig. 4. Effect of i.t. pretreatment with capsaicin on the tail-flick latency at radiant low- (50 V) and high-rate (65 V) heating in non-diabetic and diabetic mice. Capsaicin (0.56 nmol, closed column) was injected 24 h before testing. Each column represents the mean with S.E. for 10 mice in each group. * $P < 0.05$ vs. the respective non-diabetic group. * $P < 0.05$ vs. the respective vehicle-treated group (open column).

![Fig. 5](image3.png)

Fig. 5. Effect of i.t. pretreatment with capsaicin on the dose–response curve of i.t. nociceptin/orphanin FQ on the tail-flick latency in non-diabetic and diabetic mice. Capsaicin (0.56 nmol) was injected 24 h before testing. The effects of nociceptin/orphanin FQ were measured 10 min after injection. (○) Vehicle-treated non-diabetic mice. (□) Capsaicin-treated non-diabetic mice. (●) Vehicle-treated diabetic mice. (●) Capsaicin-treated diabetic mice. $\Delta t$ (s) = post-drug latency – pre-drug latency. Each point represents the mean with S.E. for 10 mice in each group.
of the flinching response in the first phase was significantly longer in diabetic mice than in non-diabetic mice. However, the cumulative response time of the flinching response in the second phase was significantly shorter in diabetic mice than in non-diabetic mice (Fig. 6).

Intrathecal administration of nociceptin/orphanin FQ, at doses of 0.03 to 1 nmol, resulted in a marked and dose-dependent reduction in the cumulative response time of the first phase of the formalin-induced flinching responses in both non-diabetic (Fig. 6A) and diabetic mice (Fig. 6B).

The dose–response curve for nociceptin/orphanin FQ in diabetic mice was shifted to the left of that in non-diabetic mice. The ED50 values (nmol with 95% confidence limits) were 0.44 (0.27–0.73) and 0.02 (0.01–1.12) for non-diabetic and diabetic mice, respectively. The potency ratio (95% confidence limits) of the antinociceptive effect of nociceptin/orphanin FQ in diabetic mice vs. that in non-diabetic mice was 15.1 (8.9–31.6). Thus, the antinociceptive potency of nociceptin/orphanin FQ in diabetic mice was significantly greater than that in non-diabetic mice. However, nociceptin/orphanin FQ had no significant effect on the second phase of the formalin-induced flinching responses in both diabetic and non-diabetic mice (Fig. 6).

3.5. Effects of nociceptin/orphanin FQ on the substance P-induced flinching response

In non-diabetic mice, i.t. injection of substance P (0.1 nmol) caused an acute, immediate flinching response, i.e., licking and biting, which lasted about 10 min. In diabetic mice, i.t. injection of substance P (0.1 nmol) also produced flinching responses. The cumulative response time of the substance P-induced flinching response was significantly longer in diabetic mice than in non-diabetic mice (Fig. 7).

As shown in Fig. 7, nociceptin/orphanin FQ (0.3, 1 and 3 nmol), administered i.t. 10 min before the injection of substance P, had no significant effect on the cumulative response time of substance P-induced flinching responses in non-diabetic mice. In contrast, i.t. administration of nociceptin/orphanin FQ, at doses of 0.03, 0.1 and 0.3 nmol, dose-dependently and significantly reduced the cumulative response time of substance P-induced flinching
responses in diabetic mice (Fig. 7). Indeed, nociceptin/orphanin FQ, at a dose of 0.3 nmol, reduced the cumulative response time of substance P-induced flinching responses to the level observed in non-diabetic mice.

4. Discussion

In the present study, i.t. administration of nociceptin/orphanin FQ reduced the tail-flick response in a dose-dependent manner in non-diabetic mice. In addition, i.t. administration of nociceptin/orphanin FQ in diabetic mice produced a marked and dose-dependent antinociceptive effect in the tail-flick test. Furthermore, the results of the present experiments clearly indicate that the antinociceptive potency of nociceptin/orphanin FQ is significantly greater in diabetic mice than in non-diabetic mice. On the other hand, nociceptin/orphanin FQ-induced antinociception in both diabetic and non-diabetic mice was not antagonized by s.c. pretreatment with β-funaltrexamine, a selective μ-opioid receptor antagonist, nor-binaltorphimine, a selective κ-opioid receptor antagonist, or naltrindole, a selective δ-opioid receptor antagonist, indicating that the antinociceptive effect of nociceptin/orphanin FQ does not result from the activation of opioid receptors.

Interestingly, the antinociceptive effect of nociceptin/orphanin FQ in diabetic mice was markedly reduced when diabetic mice were pretreated with capsaicin, which prolonged the latency of the tail-flick response at a low heating rate to the level that observed in non-diabetic mice. However, the same procedures had no significant effect on the antinociceptive effect of nociceptin/orphanin FQ in non-diabetic mice. We previously demonstrated that diabetes selectively and significantly enhance nociceptive transmission involving substance P in the spinal cord (Kamei et al., 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. Zachariou et al. (1997) suggested that the release of substance P from primary afferent terminals may mediate nociception evoked by low rate heating but not high-rate heating. In the present study, i.t. pretreatment with capsaicin prolonged the tail-flick latencies in diabetic mice, but not in non-diabetic 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). Thus, it seems likely that the increase in the tail-flick latencies by pretreatment with capsaicin may be due to a decrease in the content and release of substance P from primary afferent fibers in the spinal cord. Therefore, it is possible that the reduction in the antinociceptive effect of nociceptin/orphanin FQ in capsaicin-treated diabetic mice may be associated with a decrease in the content and release of substance P from primary afferent fibers in the spinal cord. Along these lines, the present study also demonstrates that the first phase, but not the second phase of the formalin-induced flinching response, is significantly and dose-dependently reduced by i.t. treatment with nociceptin/orphanin FQ. It has been suggested that substance P is involved in nociceptive transmission during the first phase of the formalin-induced flinching response in mice (Ohkubo et al., 1990). Thus, it is likely that the inhibition of substance P-mediated neurotransmission in the spinal cord could involve the antinociceptive effect of nociceptin/orphanin FQ. Furthermore, since nociceptin/orphanin FQ given i.t. had no effect on the i.t. substance P-induced flinching responses in non-diabetic mice, the antinociceptive effect of i.t. nociceptin/orphanin FQ is not due to the blockade of substance P-mediated neurotransmission, which would inhibit postsynaptic substance P receptor activation. Although there is no direct evidence that nociceptin/orphanin FQ prevents the release of substance P in the spinal cord, Giuliani and Maggi (1996) demonstrated that nociceptin/orphanin FQ reduces tachykinin release from peripheral endings of sensory nerves. Thus, it is possible that the antinociceptive effect of nociceptin/orphanin FQ administered i.t. may account for the inhibition of the release of substance P from the spinal cord.

An unexpected but important finding in the present study is that nociceptin/orphanin FQ given i.t. produced dose-dependent and significant inhibition of the flinching response to i.t. substance P in diabetic mice. The cumulative response time of the substance P-induced flinching response was significantly longer in diabetic mice than in non-diabetic mice. Furthermore, in diabetic mice, nociceptin/orphanin FQ reduced the cumulative response time of the substance P-induced flinching responses to the level observed in non-diabetic mice. The doses of nociceptin/orphanin FQ which reduced the substance P-induced flinching response are the same as those which significantly reduced the first phase of the formalin-induced flinching response in diabetic mice. Previously, we observed that mice diabetic for 2 weeks had higher levels of substance P in the spinal cord (Kamei et al., 1991b). Conversely, mice diabetic for 8 weeks demonstrated a significant decrease, as compared to non-diabetic mice, in the levels of substance P in the spinal cord (Kamei et al., 1991b). We also reported that, in rats diabetic for 8 weeks, specific binding by receptors of 3H-substance P was significantly elevated in the spinal cord, whereas the content of substance P in the spinal cord was significantly reduced (Kamei et al., 1990). Accordingly, we concluded that postjunctional supersensitivity to substance P develops in the spinal cord of diabetic animals and the development of such supersensitivity to substance P may be the cause of the reduction in the threshold for pain perception in mice, which had been diabetic for 8 weeks (Kamei et al., 1990, 1991b). It is difficult to ascertain whether the increase in substance P in the spinal cord of mice diabetic for 2 weeks is brought about by a decrease in the rate of release of substance P or by an...
increase in the rate of its synthesis. However, we have also observed that the potassium-evoked release of substance P from the spinal cord of diabetic rats was greater than that in control rats (Kamei et al., 1991a). It seems likely, therefore, that the increased levels of substance P in the spinal cord of mice diabetic for 2 weeks are attributable to an increase in the rate of synthesis of substance P. The increase in the rate of synthesis of substance P may lead to an increase in the rate of turnover of substance P, so that the rate of release of substance P is increased. Based on these results, we suggested that an increased rate of substance P release, rather than postsynaptic supersensitivity to substance P in the spinal cord, may cause the enhancement of the nociceptive transmission involving substance P in the spinal cord of mice diabetic for 2 weeks, as used in this study (Kamei et al., 1990, 1991a,b). Thus, it is possible that an increased rate of endogenous substance P release may account for the enhancement of the substance P-induced flinching response in diabetic mice. This may explain why nociceptin/orphanin FQ given i.t. produced a dose-dependent and significant inhibition of the flinching response to i.t. substance P in diabetic mice, but not non-diabetic mice.

In contradiction to the present study, Hara et al. (1997) reported that i.t. treatment with nociceptin/orphanin FQ evoked allodynia in response to innocuous tactile stimuli, and hyperalgesia in response to noxious thermal stimuli. This discrepancy may be due to the dose of nociceptin/orphanin FQ (10 nmol in our study; 0.5 fmol in Hara's study). A simplified diagram is given in Fig. 8 for a hypothetical neuronal circuitry that indicates how nociceptin/orphanin FQ-activated nociceptin/orphanin FQ receptors at nociceptin/orphanin FQ cell bodies ('b'), which act as autoreceptor, result in inhibition of nociceptin/orphanin FQ release, resulting in the disinhibition of the substance P-mediated nociceptive transmission. Although this hypothesis may be relevant to explain why low dose of nociceptin/orphanin FQ produced allodynia and hyperalgesia, and high dose of nociceptin/orphanin FQ produced antinociception at present time, further study is necessary to clarify this possibility.

5. Conclusion

This study clearly indicates that the antinociceptive potency of nociceptin/orphanin FQ is significantly greater in diabetic mice than in non-diabetic mice. Furthermore, the results of this study suggest that the reduction of substance P-mediated nociceptive transmission, and particularly the inhibition of the release of substance P in the spinal cord, may be responsible for the antinociceptive effect of nociceptin/orphanin FQ.

Acknowledgements

We thank Ms. S. Ochiai and Ms. H. Ohtsuka for their excellent technical assistance.

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Fig. 8. A simplified diagram of a hypothetical neuronal circuit of the substance P and nociceptin/orphanin FQ receptors in the spinal cord (see text for discussion).


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