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Modification of morphine-induced place preference by diabetes

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Abstract

The effects of diabetes on morphine-induced place preference in mice were examined. Morphine caused dose-related place preference in both diabetic and non-diabetic mice. This morphine-induced place preference in diabetic mice was greater than that in non-diabetic mice. The morphine (5 mg/kg)-induced place preference in both diabetic and non-diabetic mice was significantly antagonized by pretreatment with β-funaltrexamine, a selective μ-opioid receptor antagonist, but not with naloxonazine, a selective μ_1-opioid receptor antagonist. The morphine (5 mg/kg)-induced place preference in non-diabetic mice was attenuated by pretreatment with either naltriben, a selective δ_2-opioid receptor antagonist, or 7-benzylidenenaltrexone, a selective δ_1-opioid receptor antagonist. Moreover, the morphine (10 mg/kg)-induced place preference in non-diabetic mice was antagonized by pretreatment with 7-benzylidenenaltrexone (0.7 mg/kg). Although 7-benzylidenenaltrexone had no effect on the place preference induced by 5 mg/kg morphine in diabetic mice, it reduced the place preference induced by 3 mg/kg morphine. Furthermore, the morphine (5 mg/kg)-induced place preference in diabetic mice was significantly antagonized by co-pretreatment with β-funaltrexamine (10 mg/kg) and 7-benzylidenenaltrexone (0.7 mg/kg). 2-Methyl-4a α-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12a α-octahydroquinolino[2,3,3-g]isoquinoline (TAN-67), a non-peptide δ-opioid receptor agonist, produced place preference in diabetic, but not in non-diabetic mice. These results support the hypothesis that the morphine-induced place preference is mainly mediated through the activation of the μ_2-opioid receptor. Furthermore, the enhancement of the morphine-induced place preference in diabetic mice may be due to the up-regulation of δ-opioid receptor-mediated functions. © 1997 Elsevier Science B.V.

Keywords: Conditioned place preference; Diabetes; Opioid receptor; Morphine; Naloxonazine; Reinforcement

1. Introduction

The reinforcing effects of opioids, such as morphine and heroin, have been demonstrated by using self-administration and conditioned place preference procedures in rodents and other mammals. Place conditioning studies with rats and mice have provided evidence that the motivational effects of μ- and δ-opioid agonists result from the activation of μ- and δ-opioid receptors in central neuron systems, respectively (Shippenberg et al., 1987; Suzuki et al., 1991, 1993, 1994). These findings suggest that the activation of supraspinal μ- and/or δ-opioid receptors is required for the expression of the reinforcing effect of opioids. We previously demonstrated that systemically administered morphine produce place preference in μ_1-opioid receptor-deficient CXBK mice (Suzuki et al., 1993). Furthermore, the morphine-induced place preference in mice was not blocked by pretreatment with naloxonazine, a selective μ_1-opioid receptor antagonist. Based on these results, we suggested that morphine produces its motivational effects via naloxonazine-insensitive μ-opioid receptors, namely μ_2-opioid receptors (Suzuki et al., 1993). Furthermore, we suggested that δ_1- and δ_2-opioid receptors may be involved in the modulation of the reinforcing effect of morphine, since morphine-induced place preference was blocked by pretreatment with naltrindole, a selective δ-opioid receptor antagonist, 7-benzylidenenaltrexone, a selective δ_1-opioid receptor antagonist, and naltriben, a selective δ_2-opioid receptor antagonist (Suzuki et al., 1994).

It has been reported that the antinociceptive potency, but not maximal effect, of morphine is decreased in several rodent models of hyperglycemia, including a spontaneously diabetic strain of mice and streptozotocin-induced diabetes, a model of type I diabetes (Simon and Dewey, 1981). The induction of physical dependence on morphine

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was also significantly decreased in streptozotocin-induced diabetic mice and genetically diabetic mice (Shook and Dewey, 1986; Kamei et al., 1995a). In a clinical study, Morley et al. (1984) showed a significantly decreased pain tolerance in diabetic patients and in normal fasted subjects and suggested that the painful neuropathy experienced by some diabetic patients might involve an interaction of glucose with the action of endogenous opioid peptides.

Recently, we demonstrated that the potency of the naloxonazine-sensitive pharmacological actions of μ-opioid receptor agonists, i.e., supraspinal antinociception, Straub tail reaction and locomotor-enhancing effect, in diabetic mice were markedly reduced as compared with those in non-diabetic mice (Kamei et al., 1994a,c, 1995a). Furthermore, we reported that μ_1-opioid receptor-mediated naloxone-precipitated signs of withdrawal from physical dependence on morphine in diabetic mice are significantly less than those in non-diabetic mice (Kamei et al., 1995a). In contrast, there was no significant difference in the naloxonazine-insensitive pharmacological actions of an μ-opioid receptor agonist, i.e., spinal antinociception, antitussive effect and gastrointestinal antitransit effect, between diabetic mice and non-diabetic mice (Kamei et al., 1993a,b, 1994a, 1995b). Therefore, we proposed that mice with diabetes are selectively hyporesponsive to activation of μ_1-opioid receptors, but are normally responsive to μ_2-opioid receptors. However, we previously reported that the 7-benzylidenenaltrexone-sensitive antinociceptive effect of [D-Pen^{2,5}]enkephalin (DPDPE) was significantly greater in diabetic mice than in non-diabetic mice, whereas there was no significant difference in the naltriben-sensitive antinociceptive effect of [D-Ala^2]deltorphineII between diabetic and non-diabetic mice (Kamei et al., 1994b). These findings suggested that mice with diabetes are selectively hyperresponsive to activation of δ_1-opioid receptors, but are normally responsive to δ_2-opioid receptors. Therefore, functional abnormalities in μ- and δ-opioid receptor functions of diabetic animals may alter the reinforcing effect of morphine.

Thus, the primary aim of our study was to compare morphine-induced place preference in diabetic and non-diabetic mice to clarify our hypothesis that functional abnormalities in μ- and δ-opioid receptor functions of diabetic animals may alter the reinforcing effect of morphine.

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 which 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 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 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. Place conditioning

Place conditioning was conducted as previously described, using a minor modification of the biased procedure (Suzuki et al., 1991) according to the method of Bardo et al. (1984). The apparatus used was a shuttle box ($15 \times 30 \times 15$ cm) which was divided into two compartments of equal size. One compartment was white with a textured floor and the other was black with a smooth floor. For conditioning, mice were immediately confined to the white compartment after drug injections and to the black compartment after saline injections. Saline conditioning was conducted before confinement to either compartment. In another set of experiments, diabetic and non-diabetic mice were immediately confined to the black compartment after morphine injection and to the white compartment after saline injections. Conditioning sessions (3 for drug: 3 for vehicle) were carried out over a 60-min period once a day. The 6 conditioning sessions were carried out alternately. On day 7, tests of conditioning were performed as follows: the partition separating the two compartments was raised 7 cm above the floor and a neutral platform was inserted along the junction separating the compartments. Mice were not given any injections before the test session. The time spent in each compartment during a 900 s session was then measured by a infrared beam sensor (KN-80, Natume, Tokyo) in a blinded fashion. The position of the mouse was defined by the position of its body. All sessions were conducted under conditions of dim illumination (40 lx) and white masking noise. Mice exhibited no preference for either of the compartments under these conditions.

2.3. Drugs

Streptozotocin was purchased from Sigma (St. Louis, MO, USA). Morphine hydrochloride was purchased from Sankyo (Tokyo, Japan). β-Funaltrexamine, naloxonazine, 7-benzylidenenaltrexone, naltriben and 2-methyl-4a α-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12a α-octahydroquinolino-[2,3,3-g]isoquinoline (TAN-67) were synthesized by Dr. Nagase (Toray Industries, Kamakura, Japan). All drugs were dissolved in 0.9% saline solution. β-Funaltrexamine (10 and 20 mg/kg, s.c.) and naloxonazine (35 mg/kg, s.c.) were injected 24h before injection of morphine. 7-Benzylidenenaltrexone (0.3 and 0.7 mg/kg, s.c.) was in-

jected 30 min before injection of morphine. Naltriben (0.1 and 0.5 mg/kg, s.c.) was injected 30 min before injection of morphine. The dose and schedule for each opioid receptor antagonist in this study were determined as described previously (Suzuki et al., 1993, 1994). Each antagonist was injected before each morphine injection. Glucose was injected 30 min before injection of morphine.

2.4. Data analysis

The conditioning score represents the time spent in the drug-paired place minus the time spent in the vehicle-paired place is expressed as the mean ± S.E. Statistical analysis of differences between groups was assessed with Wilcoxon rank-sum test (comparison of two groups) or one-way analysis of variance (ANOVA) followed by the Kruskal–Wallis test (comparison between multiple groups). The potency ratio of morphine to induce place preference in non-diabetic mice and diabetic mice was calculated using Program 11 of the Pharmacological Calculations systems of Tallarida and Murray (1987).

3. Results

3.1. Effects of diabetes on morphine-induced place preference

As shown in Fig. 1, none of the mice receiving saline in conditioning sessions exhibited a significant preference for either compartment of the test box. Testing of saline-treated mice in the test session revealed that neither non-diabetic nor diabetic mice showed a significant preference for one side of the test box over the other. The place conditioning produced by morphine is shown in Fig. 1. In non-diabetic mice, morphine, over a dose range from 3 to 30 mg/kg, s.c., caused a dose-related preference for the drug-associated place, and significant conditioning was observed at doses of 5, 10 and 30 mg/kg. In diabetic mice, morphine (1 mg/kg) induced a slight place preference, although this effect was not statistically significant. Significant conditioning was observed at doses of 3, 5 and 10 mg/kg in diabetic mice. At these doses, all diabetic mice exhibited preference for the drug-associated place. When morphine (5 mg/kg, s.c.) was paired with the black compartment, morphine also caused a significant place preference in both diabetic (mean conditioning score of 178.9 ± 67.9 s, $n = 7$) and non-diabetic mice (mean conditioning score of 117.2 ± 34.6 s, $n = 8$). Pretreatment with glucose (30 mmol/kg, i.p.) increased the serum glucose levels of non-diabetic mice (432.3 ± 11.3 mg/dl, $n = 8$) to the level of diabetic mice. However, morphine-induced place preference in non-diabetic mice was not affected by pretreatment with glucose. There was no significant difference in the morphine-induced place preference between glucose-treated non-diabetic (139.6 ± 38.1 s, $n = 8$) and glucose-untreated non-diabetic mice (112.9 ± 36.4 s, $n = 10$).

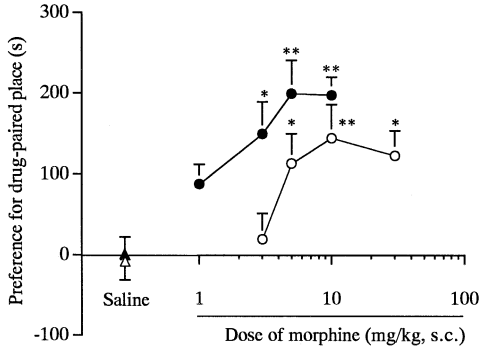

Fig. 1. Place conditioning produced by morphine (circle) in non-diabetic (open symbol) and diabetic (closed symbol) mice. Ordinate: mean difference (s) between times spent on drug- and saline-paired sides of test box. Each point represents the mean ± S.E. for 10–16 mice. The asterisk denotes significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$, $^{**}P < 0.01$ versus respective saline alone (triangle)).

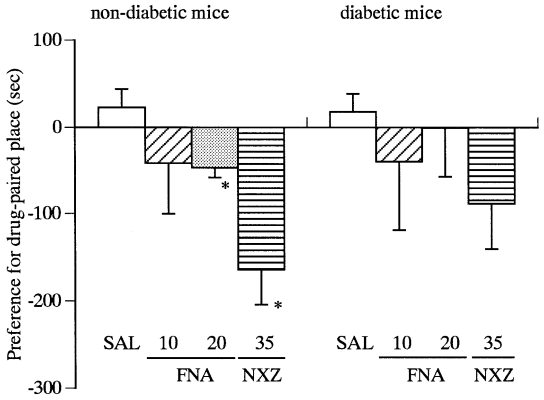

Fig. 2. Place conditioning produced by β-funaltrexamine (FNA, 10 and 20 mg/kg, s.c.) and naloxonazine (NXZ, 35 mg/kg, s.c.) in non-diabetic and diabetic mice. Each column represents the mean ± S.E. for 7–12 mice. The asterisk denotes significant place aversion conditioning (Wilcoxon test: $^{*}P < 0.05$ versus saline (SAL) alone).

3.2. Influence of μ-opioid receptor antagonists pretreatment upon the morphine-induced place preference

β-Funaltrexamine (10 and 20 mg/kg, s.c.), a selective μ-opioid receptor antagonist, caused aversion for the drug-associated place and significant conditioning aversion was observed at a dose of 20 mg/kg in non-diabetic mice (Fig. 2). However, β-funaltrexamine did not cause either place aversion or place preference in diabetic mice. Moreover, naloxonazine (35 mg/kg, s.c.), a selective μ_1-opioid receptor antagonist, caused significant ($P < 0.05$) place aversion in non-diabetic mice, but not in diabetic mice (Fig. 2).

The effects of pretreatment with β-funaltrexamine on the place preference produced by morphine in both dia-

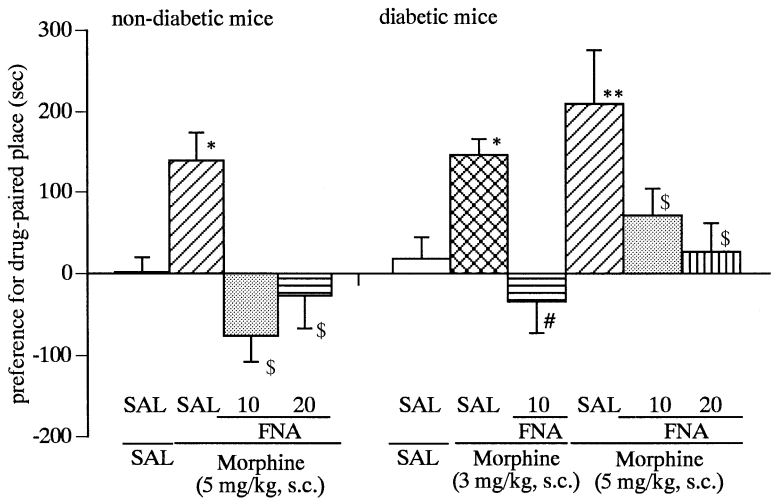

Fig. 3. Effect of β-funaltrexamine (FNA, 10 and 20 mg/kg, s.c.) on morphine (3 or 5 mg/kg, s.c.)-induced conditioned place preference in non-diabetic and diabetic mice. Each column represents the mean ± S.E. for 7–13 mice. The asterisk denotes significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$, $^{**}P < 0.01$ versus saline (SAL) alone). The sharp denotes significant difference from morphine alone (Wilcoxon test: $\#P < 0.05$). Significant difference from respective morphine (5 mg/kg) alone (Kruskal–Wallis test followed by Wilcoxon test: $\$P < 0.05$).

betic and non-diabetic mice are shown in Fig. 3. After pretreatment with saline, morphine (5 mg/kg) produced a significant preference for the drug-paired compartment in both non-diabetic mice and diabetic mice. Thus, pretreatment with saline did not alter this effect of morphine. However, the morphine-induced place preference was significantly antagonized by pretreatment with β-funaltrexamine in both non-diabetic and diabetic mice. The mean conditioning scores for morphine (5 mg/kg) in both non-diabetic and diabetic mice pretreated with β-funaltrexamine at doses of 10 mg/kg and 20 mg/kg were significantly ($P < 0.01$) lower than those in saline-pretreated non-diabetic and diabetic mice, respectively. Furthermore, morphine (3 mg/kg)-induced place preference in diabetic mice was also antagonized by pretreatment with β-funaltrexamine. However, as shown in Fig. 4, pretreatment with naloxonazine did not modify the morphine (5 mg/kg)-induced place preference in non-diabetic mice. The mean conditioning score did not significantly differ from that in mice that had been pretreated with saline. Furthermore, naloxonazine also had no effect on morphine-induced place preference in diabetic mice. Indeed, there was no significant difference in the mean conditioning score for morphine (3 and 5 mg/kg) between saline-pretreated diabetic mice and naloxonazine-treated diabetic mice. Thus, pretreatment with naloxonazine did not modify the appetitive effect of morphine in either diabetic or non-diabetic mice.

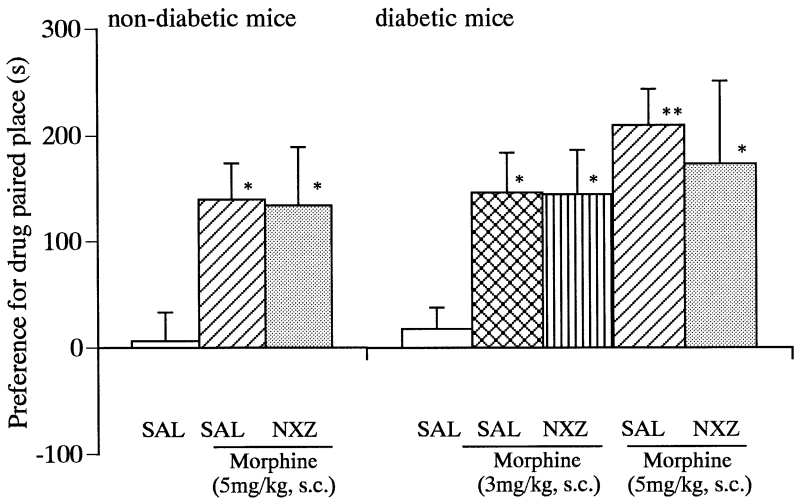

Fig. 4. Effect of naloxonazine (NXZ, 35 mg/kg, s.c.) on morphine (3 or 5 mg/kg, s.c.)-induced conditioned place preference in non-diabetic and diabetic mice. Each column represents the mean ± S.E. for 7–12 mice. The asterisk denotes significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$, $^{**}P < 0.01$ versus saline (SAL) alone).

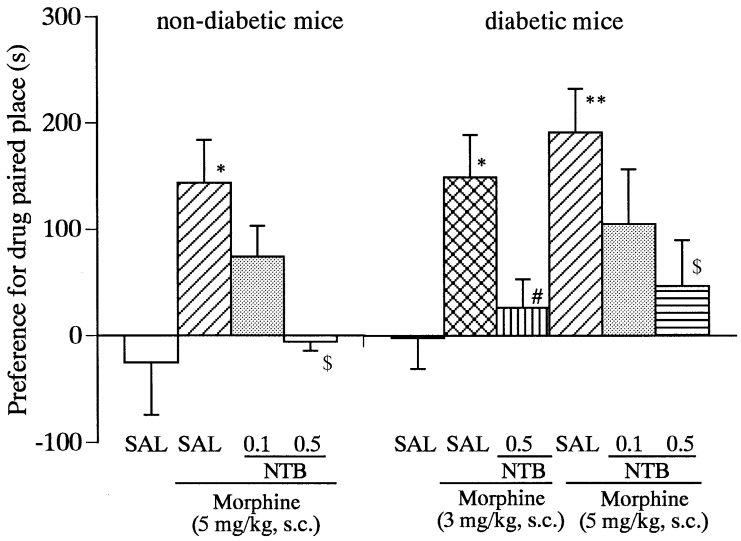

Fig. 5. Effects of naltriben (NTB, 0.1 and 0.5 mg/kg, s.c.) on morphine (3 or 5 mg/kg, s.c.)-induced conditioned place preference in non-diabetic and diabetic mice. Each column represents the mean ± S.E. for 7–14 mice. The asterisk denotes significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$, $^{**}P < 0.01$ versus saline (SAL) alone). The sharp denotes significant difference from morphine alone (Wilcoxon test: $\#P < 0.05$). Significant difference from respective morphine (5 mg/kg) alone (Kruskal–Wallis test followed by Wilcoxon test: $\$P < 0.05$).

3.3. Influence of δ_1- and δ_2-opioid receptor antagonist pretreatment upon morphine-induced place preference

7-Benzylidenenaltrexone (0.3 and 0.7 mg/kg, s.c.), a selective δ_1-opioid receptor antagonist, alone caused neither place preference nor place aversion in non-diabetic and diabetic mice. Furthermore, naltriben (0.1 and 0.5 mg/kg, s.c.), a selective δ_2-opioid receptor antagonist, alone also did not cause place preference or place aversion. The effects of 7-benzylidenenaltrexone and naltriben on the morphine-induced place preference are shown in Figs. 5 and 6. Morphine-induced place preference was antagonized by pretreatment with naltriben in a dose-related manner in both diabetic and non-diabetic mice. Indeed, naltriben, at a dose of 0.5 mg/kg, significantly ($P < 0.01$) abolished morphine (5 mg/kg)-induced place preference. In diabetic mice, naltriben, at a dose of 0.5 mg/kg, significantly antagonized the place preference induced by morphine (3 and 5 mg/kg). 7-Benzylidenenaltrexone, at a dose of 0.7 mg/kg, significantly ($P < 0.01$) abolished the

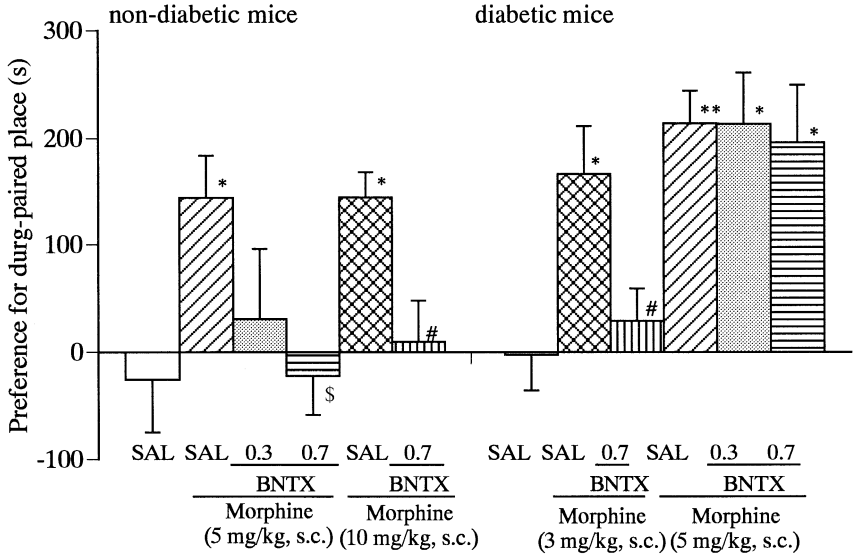

Fig. 6. Effect of 7-benzylidenenaltrexone (BNTX, 0.3 and 0.7 mg/kg, s.c.) on morphine (3 or 5 mg/kg, s.c.)-induced conditioned place preference in non-diabetic and diabetic mice. Each column represents the mean ± S.E. for 7–13 mice. The asterisk denotes significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$, $^{**}P < 0.01$ versus saline (SAL) alone). The sharp denotes significant difference from morphine alone (Wilcoxon test: $\#P < 0.05$). Significant difference from respective morphine (5 mg/kg) alone (Kruskal–Wallis test followed by Wilcoxon test: $\$P < 0.05$).

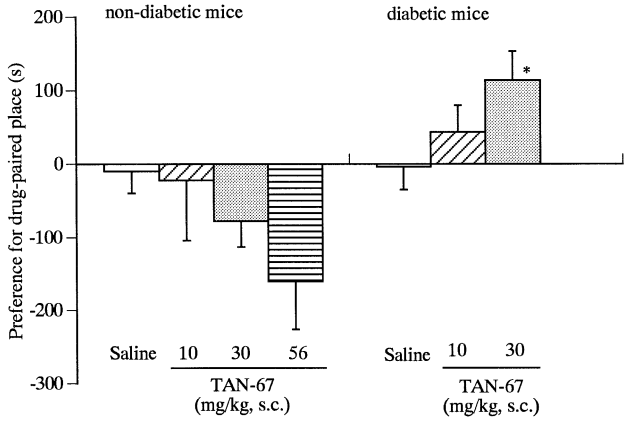

Fig. 7. Place conditioning produced by TAN-67 (10 and 30 mg/kg, s.c.) in non-diabetic and diabetic mice. Ordinate: mean difference (s) between times spent on drug- and saline-paired sides of the test box. Each column represents the mean ± S.E. for 7–16 mice. The asterisk denotes significant preference conditioning (Wilcoxon test: $^{**}P < 0.05$ versus saline alone).

place preference induced by morphine (5 and 10 mg/kg) in non-diabetic mice. In diabetic mice, the place preference induced by 3 mg/kg morphine was significantly suppressed by pretreatment with 7-benzylidenenaltrexone, at a dose of 0.7 mg/kg, whereas that induced by 5 mg/kg morphine was not.

As shown in Figs. 3 and 6, the morphine (5 mg/kg)-induced place preference in diabetic mice was significantly but not completely suppressed by pretreatment with β-funaltrexamine and was not affected by 7-benzylidenenaltrexone. However, when β-funaltrexamine (10 mg/kg) and 7-benzylidenenaltrexone (0.7 mg/kg) were co-applied with morphine, the morphine (5 mg/kg)-induced place preference in diabetic mice was completely abolished (morphine alone, 199.4 ± 42.0 s, $n = 8$; morphine with β-funaltrexamine, 71.2 ± 44.9 s, $n = 8$; morphine with β-funaltrexamine and 7-benzylidenenaltrexone, 19.1 ± 52.1 s, $n = 8$).

3.4. TAN-67-induced place preference in diabetic mice

The place conditioning produced by TAN-67, a non-peptide selective δ-opioid receptor agonist, is shown in Fig. 7. In non-diabetic mice, TAN-67, at doses of 10, 30 and 56 mg/kg, s.c., caused neither place preference nor place aversion for the drug-associated place. However, in diabetic mice, TAN-67 caused dose-dependent place preference. TAN-67, at a dose of 10 mg/kg, induced slight place preference, although this effect was not statistically significant. Significant conditioning was observed at a dose of 30 mg/kg.

4. Discussion

The present study demonstrated that morphine produced dose-related conditioned place preference in both diabetic and non-diabetic mice. Furthermore, the morphine-induced place preference was significantly antagonized by pretreatment with β-funaltrexamine, a selective μ-opioid receptor antagonist, but not naloxonazine, a selective μ_1-opioid receptor antagonist, in both diabetic and non-diabetic mice. Similarly, Suzuki et al. (1993) demonstrated that morphine-induced place preference was not suppressed by pretreatment with naloxonazine, but was completely suppressed with β-funaltrexamine. Furthermore, they reported that morphine produced β-funaltrexamine-sensitive place preference in μ_1-opioid receptor deficient CXBK mice. Therefore, the present results along with the findings of Suzuki et al. (1993) strongly support the hypothesis that morphine-induced place preference is mediated by naloxonazine-insensitive μ-opioid receptors (namely, μ_2-opioid receptors).

In the present study, place aversion was observed following s.c. administration of naloxonazine and β-funaltrexamine in non-diabetic mice, but not in diabetic mice. It has been shown that opioid receptor antagonists, such as naloxone and naltrexone, produce conditioned place aversion in rats (Mucha and Iversen, 1984; Bechara and Van der Kooy, 1985) and mice (Mucha and Walker, 1987). Recent evidence suggests that the aversive properties of naloxone primarily reflect antagonism of the activity of central β-endorphin-containing neurons in the mediobasal arcute hypothalamus (Mucha et al., 1985). In receptor binding studies, it has been reported that naloxonazine inhibits [^{3}H] β-endorphin binding, suggesting that [^{3}H] β-endorphin might label μ_1 sites (Houghten et al., 1984). Furthermore, it should be noted that a reasonable naloxonazine dose to obtain μ_1 selectivity in mice is 35 mg/kg, s.c. (Ling et al., 1986). In the present study, naloxonazine (35 mg/kg, s.c.) produced conditioned place aversion, suggesting that selective blockade of μ_1-opioid receptors results in aversive motivational states. Possibly, a β-endorphinergic pathway is involved in the aversive properties of naloxonazine. Nevertheless, the morphine-induced place preference was not blocked by pretreatment with naloxonazine in either non-diabetic or diabetic mice. These findings also strongly support the possibility that the motivational effect of morphine may be mediated by μ_2-opioid receptors. Recently, we proposed that mice with diabetes are selectively hyporesponsive to activation of μ_1-opioid receptors, but are normally responsive to μ_2-opioid receptors, since naloxonazine-sensitive, but not naloxonazine-insensitive, pharmacological actions of μ-opioid receptor agonists in diabetic mice were markedly reduced as compared with those in non-diabetic mice (Kamei et al., 1994a,c, 1995a). This possibility might be supported by the present findings that naloxonazine and β-funaltrexamine did not produce place aversion in diabetic mice.

The morphine (5 mg/kg)-induced place preference in non-diabetic mice was antagonized by pretreatment with either 7-benzylidenenaltrexone, a selective δ_1-opioid re-

ceptor, or naltriben, a selective δ_2-opioid receptor antagonist. These results are also consistent with our previous findings that δ_1- and δ_2-opioid receptors may be involved in the modulation of the reinforcing effect of morphine (Suzuki et al., 1994). The morphine-induced place preference in diabetic mice was suppressed by pretreatment with naltriben. Furthermore, the place preference induced by the lower dose (3 mg/kg) of morphine in diabetic mice was significantly antagonized by pretreatment with 7-benzylidenenaltrexone. These results indicate that the motivational effect of morphine in diabetic mice is also modulated by δ_1- and δ_2-opioid receptors. In the present study, the morphine (5 mg/kg)-induced place preference in diabetic mice was significantly but not completely antagonized by pretreatment with β-funaltrexamine. Moreover, 7-benzylidenenaltrexone had no effect on morphine (5 mg/kg, s.c.)-induced place preference in diabetic mice. However, when mice were pretreated with both β-funaltrexamine and 7-benzylidenenaltrexone, morphine (5 mg/kg)-induced place preference in diabetic mice was completely abolished. It is not clear whether the lack of the effect of 7-benzylidenenaltrexone on morphine-induced place preference in diabetic mice is caused by the increasing dose of morphine overcoming the 7-benzylidenenaltrexone antagonism or by the up-regulation of δ_1-opioid receptor-mediated functions. In this regard, we previously demonstrated that the antinociceptive effect of DPDPE was significantly greater in diabetic mice than in non-diabetic mice, whereas there was no significant difference in the antinociceptive effect of [D-Ala^2]deltorphin II between diabetic and non-diabetic mice (Kamei et al., 1994b). Furthermore, pretreatment with 7-benzylidenenaltrexone, but not naltriben, significantly antagonized the antinociceptive effect of DPDPE. In contrast, the antinociceptive effect of [D-Ala^2]deltorphin II was antagonized by naltriben, but not by 7-benzylidenenaltrexone (Kamei et al., 1994a).

Recently, we demonstrated TAN-67, a novel non-peptide δ-opioid receptor agonist, produced a marked and dose-dependent 7-benzylidenenaltrexone-sensitive, but not naltriben-sensitive, antinociceptive effect in both non-diabetic and diabetic mice (Kamei et al., 1995c). Furthermore, the antinociceptive effect of TAN-67 is significantly greater in diabetic mice than in non-diabetic mice (Kamei et al., 1995c). Based on these results, we suggested that mice with diabetes are selectively hyperresponsive to δ_1-opioid receptor-mediated antinociception, but are normally responsive to activation of δ_2-opioid receptors. In the present study, we demonstrated that TAN-67 produced significant place preference in diabetic mice, but not in non-diabetic mice. This result suggests that the motivational effect mediated by δ_1-opioid receptors, which is silent in non-diabetic mice, occurs in diabetic mice. However, place preference induced by a higher dose of morphine (10 mg/kg) in non-diabetic mice was significantly antagonized by 7-benzylidenenaltrexone. Thus, it seems likely that the lack of effect of 7-benzylidenenaltrexone on place preference induced by a high dose of morphine (5 mg/kg) in diabetic mice is due to the up-regulation of δ-opioid receptor-mediated functions.

In the present study, we also demonstrated that the maximal conditioning effect of morphine in diabetic mice was relatively higher than that in non-diabetic mice. Furthermore, the mean conditioning score for morphine, at a dose of 3 mg/kg, was significantly greater in diabetic mice than that in non-diabetic mice. However, when glucose was administered to non-diabetic mice to raise their serum glucose levels, morphine-induced place preference in non-diabetic mice was not changed. This result suggests that the enhancement of morphine-induced place preference in diabetic mice was not due to their higher serum glucose levels. In this regard, a conditioned reinforcing effect of morphine has been observed following its injection into the nucleus accumbens (Olds, 1982; Koob and Goeders, 1989). Furthermore, it is reported that morphine binds with relatively high affinity to δ-opioid receptors (Magnan et al., 1982) and δ- rather than μ-opioid receptors are predominate in this region (Mansour et al., 1988). Therefore, the reinforcing effects of intra-nucleus accumbens morphine may reflect an interaction with δ- rather than μ-opioid receptors. Thus, it is possible that the enhancement of morphine-induced place preference in diabetic mice as compared to non-diabetic mice may be due to the up-regulation of δ_1-opioid receptor-mediated functions.

Many studies have indicated that morphine increases the activity of mesolimbic and nigrostriatal dopamine-containing neurons (Gysling and Wang, 1983; Matthews and German, 1984). Furthermore, it has been reported that acute morphine treatment increases the release and metabolism of dopamine in the caudate putamen and the nucleus accumbens (Wood and Richard, 1982; Di Chiara and Imperato, 1988). There is evidence that the motivational effect of morphine is mediated by dopamine neurons in these regions (Phillips and LePiane, 1980; Bozarth and Wise, 1981; Van der Kooy et al., 1982; Spyraki et al., 1983). Locomotor activity in experimental animals has been shown to be closely related to the activity of the mesolimbic dopaminergic system. We recently demonstrated that spontaneous locomotor activity in diabetic mice was significantly greater than that in non-diabetic mice. This enhanced spontaneous locomotor activity in diabetic mice was reduced by pretreatment with either *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390), a selective dopamine D_1 receptor antagonist, 7-benzylidenenaltrexone, or naltrindole (Kamei et al., 1994d). Furthermore, we also demonstrated that dopamine turnover in the limbic forebrain (including nucleus accumbens and olfactory tubercle) is increased in diabetic mice as compared to non-diabetic mice (Kamei et al., 1994d). However, the morphine-induced increase in dopamine turnover

in the mouse limbic forebrain was significantly suppressed by naltrindole (Narita et al., 1993). Based on these results, we previously suggested that the enhanced spontaneous locomotor activity in diabetic mice may result from increased dopamine release in mesolimbic dopamine systems, which might be due to the up-regulation of δ-opioid receptor-mediated functions (Kamei et al., 1994d). Therefore, the increased dopamine neurotransmission, which is related to the up-regulation of δ-opioid receptor-mediated functions, may account for the enhancement of morphine-induced appetitive effects in diabetic mice.

In conclusion, our results support the hypothesis that morphine-induced place preference is mainly mediated through the activation of the μ_2-opioid receptor, and suggest that enhancement of morphine-induced place preference in diabetic mice is due to the up-regulation of δ_1-opioid receptor-mediated functions.

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