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Antinociceptive effect of oxycodone in diabetic mice

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Abstract

The effect of oxycodone on thermal hyperalgesia in streptozotocin-induced diabetic mice was examined. The antinociceptive response was assessed by recording the latency in the tail-flick test using the radiant heat from a 50-W projection bulb on the tail. The tail-flick latency in diabetic mice was significantly shorter than that in non-diabetic mice. When diabetic mice were treated with oxycodone (5 mg/kg, s.c.), the tail-flick latency in diabetic mice was prolonged to the level considerably longer than the baseline latencies of non-diabetic mice. However, s.c. administration of morphine (5 mg/kg) did not produce a significant inhibition of the tail-flick response in diabetic mice. Oxycodone, at doses of 1.25–5.0 mg/kg administered s.c., produced a dose-dependent increase in the tail-flick latencies in both diabetic and non-diabetic mice. The antinociceptive effect of oxycodone was antagonized by pretreatment with a selective δ-opioid receptor antagonist, β-funaltrexamine (20 mg/kg, s.c.), in both non-diabetic and diabetic mice. In non-diabetic mice, pretreatment with a selective κ-opioid receptor antagonist, nor-binaltorphimine (20 mg/kg, s.c.) had no effect on the peak antinociceptive effect of oxycodone observed 30 min after administration, however, it slightly but significantly reduced oxycodone-induced antinociception observed 60 and 90 min after administration. On the other hand, pretreatment with nor-binaltorphimine practically abolished the peak (30 min) and persistent (60 and 90 min) antinociceptive effects of oxycodone in diabetic mice. Naltrindole (35 mg/kg, s.c.), a selective δ-opioid receptor antagonist, had no effects on the antinociceptive effect of oxycodone in both non-diabetic and diabetic mice. These results suggest that the antinociceptive effects of oxycodone may be mediated by μ- and κ-opioid receptors in diabetic mice, whereas it may interact primarily with μ-opioid receptors in non-diabetic mice.

Keywords: Oxycodone; Diabetes; κ-Opioid receptor; Hyperalgesia; Antinociception

1. Introduction

Diabetic neuropathy is one of the most common long-term complications of diabetes mellitus. Painful diabetic neuropathy poses a major medical problem (Simon and Dewey, 1981; Brown and Asbury, 1984; Boulton et al., 1998). Diabetic neuropathic pain can occur either spontaneously or as a result of exposure to only mildly painful stimuli (hyperalgesia) or to stimuli not normally perceived as painful (allodynia). Although μ-opioids have been widely used to treat patients with acute and chronic pain, they are often ineffective in the treatment of diabetic neuropathic pain (Wright, 1994; Boulton et al., 1998; Adriaensen et al., 2005). In this regard, we previously reported that the antinociceptive effects of the i.c.v. administration of μ-opioid receptor agonists, such as morphine, [D-Ala^2,*N*-MePhe^4, Gly-ol^5]enkephalin (DAMGO) and endomorphin-2, in diabetic mice were less than those in non-diabetic mice (Kamei et al., 1992a,b, 1994a, 2000; Ohsawa and Kamei, 1997). On the other hand, we also reported that the antinociceptive effect of i.c.v. administration of μ-opioid receptor agonists, such as [D-Pen^2, D-Pen^5]enkephalin (DPDPE) and (±)TAN-67 in diabetic mice were markedly greater than those in non-diabetic mice (Kamei et al., 1994b, 1995, 1997). Furthermore, we reported that the antinociceptive potency of a s.c. administered κ-opioid receptor agonist, U-50,488H, was not significantly reduced in diabetic mice compared to its effects in non-diabetic mice (Kamei et al., 1992a), or was even enhanced in diabetic mice relative to non-diabetic mice (Suzuki et al., 2001). Based on these results, we concluded that diabetic mice were selectively hypo-responsive to an antinociceptive effect mediated by μ-opioid receptor, but were sufficiently sensitive to the antinociceptive effect mediated by δ- and/or κ-opioid receptors.

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Oxycodone is a semi-synthetic opioid analgesic derived from a naturally occurring alkaloid, thebaine. In humans, oxycodone has been shown to have an analgesic potency 0.7 times that of morphine after systemic administration (Beaver et al., 1978; Kalso et al., 1990). It has been used clinically for over 80 years, but its pharmacology has been studied only recently. While it is known as a μ-opioid receptor agonist, Ross and Smith (1997) reported that the antinociceptive effects of oxycodone are induced by putative κ-opioid receptors, in contrast to morphine, since oxycodone's antinociceptive effects were markedly attenuated by i.c.v. administration of nor-binaltorphimine, a selective κ-opioid receptor antagonist but not by the i.c.v. administration of naloxonazine, a μ_1-selective opioid receptor antagonist, or naltrindole, a δ-selective opioid receptor antagonist.

Based on these reports, we hypothesized that the diabetic state may influence the antinociceptive effects of oxycodone. In the present study, we examined the antinociceptive effects of oxycodone in diabetic mice.

2. Materials and methods

2.1. Animals

Male ICR 4-week-old mice (Tokyo Animal Laboratories Inc., 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 24±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 carried out 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/or with the guide for the committee on the care and use of laboratory animals of Hoshi University, which is accredited by the Ministry of Education, Sports and Culture.

2.2. Antinociceptive assessment

The nociceptive response was evaluated by recording the latency in the tail-flick test (D'Amour and Smith, 1941) using radiant heat as a stimulus. Briefly, the tails of mice were exposed to the focused beam of light from a 50-W projection bulb. We previously reported that diabetic mice exhibit thermal hyperalgesia in the tail-flick test after heating the tail at 50 V (Ohsawa and Kamei, 1997, 1999; Kamei et al., 2001). Thus, the heat intensity was set by adjusting the source of voltage for the bulb to 50 V. When a withdrawal response occurred, the stimulus was terminated and the response latency was measured electronically. The heat intensity at 50 V produced surface skin heating rates of 0.9 °C/s. A cut-off latency of 30 s was used to prevent injury to the tail. Tail-flick latency times were determined following injection of opioid agonist or saline at the following times: 30, 60 and 90 min.

2.3. Drugs

Streptozotocin and naltrindole hydrochloride, a selective δ-opioid receptor antagonist, were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Oxycodone hydrochloride was purchased from Mallinckrodt Pharmaceuticals Inc. (St. Louis, MO, USA). Morphine hydrochloride was purchased from Sankyo Inc. (Tokyo, Japan). β-Funaltrexamine hydrochloride, a selective μ-opioid receptor antagonist, and nor-binaltorphimine dihydrochloride, a selective κ-opioid receptor antagonist, were kind gifts from Toray Industries, Inc. All drugs were dissolved in saline (0.9% NaCl) and injected subcutaneously. Oxycodone (1.25–5.0 mg/kg, s.c.) and morphine (5.0 mg/kg, s.c.) was administered 30 min before the antinociceptive assay. β-funaltrexamine (20 mg/kg, s.c.) and nor-binaltorphimine (20 mg/kg, s.c.) were administered 24 h before testing (Kamei et al., 1995a,b, 2000; Endoh et al., 1992). Naltrindole (3 mg/kg, s.c.) was administered 30 min before testing (Saitoh et al., 2004).

2.4. Data analysis

The antinociceptive effect was expressed as the area under the time–response curve (AUC) calculated by plotting the increase in threshold (Δs) from the pre-value and the time interval (min) on the abscissa. The results are expressed as means±S.E. The statistical significance of differences between groups was assessed with Student's *t*-test (comparison of two groups) or an analysis of variance (ANOVA) followed by the Bonferroni-Dunn test (comparison among multiple groups). In all cases, differences of $P<0.05$ were considered significant.

3. Results

3.1. Antinociceptive effects of oxycodone on the tail-flick latency in diabetic and non-diabetic mice

Diabetic mice had lower nociceptive threshold values than non-diabetic mice, as evidenced by a significant difference ($P<0.05$) in the tail-flick latency (diabetic mice, 6.5±0.4 s; non-diabetic mice, 11.4±0.3 s). The s.c. administration of morphine (5.0 mg/kg) produced a significant inhibition of the tail-flick response in non-diabetic mice, but not in diabetic mice (Fig. 1). On the other hand, s.c. administration of oxycodone (5.0 mg/kg) resulted in a significant prolongation of the tail-flick latency in both non-diabetic and diabetic mice.

The antinociceptive effects of oxycodone in non-diabetic and diabetic mice were also determined by the AUC calculated from the time–response curve of the tail-flick latency (Fig. 2). Oxycodone produced a dose-dependent inhibition of the tail-flick response in both non-diabetic and diabetic mice at doses of 1.25–5.0 mg/kg. The antinociceptive effect induced by a high dose of oxycodone (5.0 mg/kg) in diabetic mice was significantly less than that in non-diabetic mice. However, there was no significant difference between the antinociceptive potencies induced by lower doses of oxycodone (1.25–2.5 mg/kg) in non-diabetic and diabetic mice (Fig. 2).

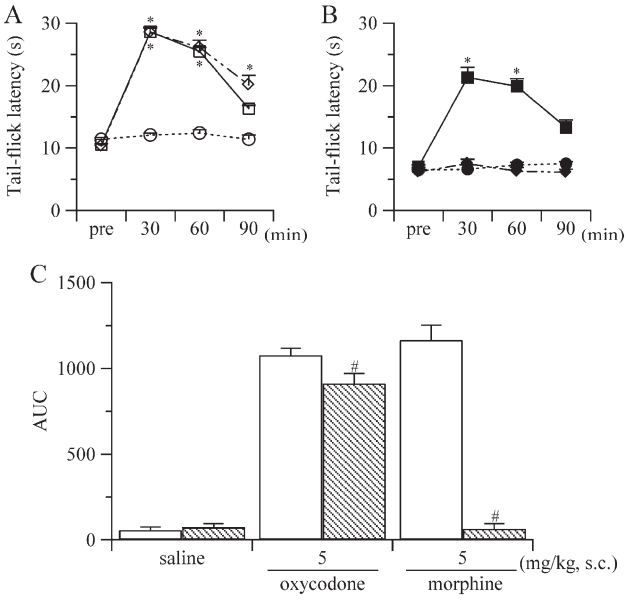

Fig. 1. Upper panel (A, B): Time-course of the antinociceptive effects of oxycodone and morphine in non-diabetic (A) and diabetic (B) mice. The nociceptive threshold was determined by the tail-flick test. The antinociceptive effect was determined 30, 60 and 90 min after the administration of vehicle (saline, circle), oxycodone (5 mg/kg, s.c., square) and morphine (5 mg/kg, s.c., diamond). Each point represents the mean with S.E.M. ($n=10$). *$P<0.05$ vs. respective saline-treated mice (Bonferroni-Dunn test). Lower panel (C): Antinociceptive effects of oxycodone and morphine in non-diabetic (open column) and diabetic (hatched column) mice. The results are shown as the area under the time–response curve (AUC). Each column represents the mean with S.E.M. ($n=10$). $^{\#}P<0.05$ vs. respective non-diabetic mice (Student's *t*-test).

3.2. Effects of opioid receptor antagonists on the antinociceptive effect of oxycodone

Fig. 3 shows the effects of various opioid receptor antagonists on the time-courses of oxycodone-induced antinociception in both non-diabetic and diabetic mice. The antinociceptive effect was determined at 30, 60 and 90 min after the s.c. administration

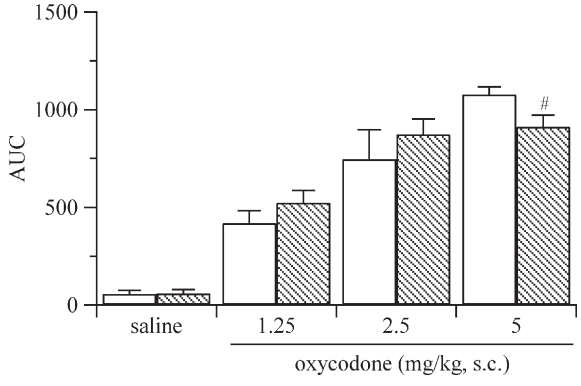

Fig. 2. Dose–response relationship of the antinociceptive effects of oxycodone in non-diabetic (open column) and diabetic (hatched column) mice. Tail-flick responses were determined 30, 60 and 90 min after the administration of vehicle or oxycodone (1.25, 2.5 and 5 mg/kg, s.c.). The antinociceptive effect was evaluated by the AUC calculated from the time–response curve of tail-flick latency. Each column represents the mean with S.E.M. ($n=10$). $^{\#}P<0.05$ vs. respective non-diabetic mice (Student's *t*-test).

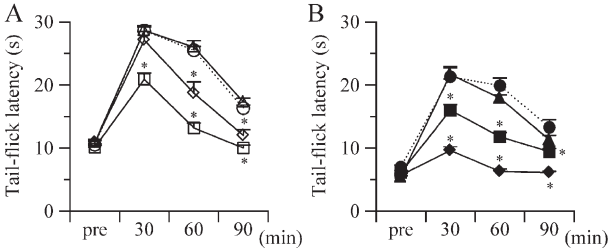

Fig. 3. Effects of various opioid receptor antagonists on the antinociceptive effects of oxycodone in non-diabetic (A) and diabetic mice (B). The nociceptive threshold was determined by the tail-flick test. The antinociceptive effect was determined 30, 60 and 90 min after the administration of oxycodone (5 mg/kg, s.c.). β-Funaltrexamine (square) and nor-binaltorphimine (diamond) were injected s.c. 24 h before testing. Naltrindole (triangle) was injected s.c. 30 min before the injection of oxycodone. Each point represents the mean with S.E.M. ($n=10$). *$P<0.05$ vs. respective vehicle (saline, circle)-treated mice (Bonferroni-Dunn test).

of oxycodone (5 mg/kg). The effects of various opioid receptor antagonists were also determined by the AUC calculated from the time–response curve of the tail-flick latency (Fig. 4). As shown in Figs. 3A and 4, the antinociceptive effect of oxycodone in non-diabetic was significantly antagonized by pretreatment with β-funaltrexamine (20 mg/kg, s.c.). Furthermore, pretreatment with β-funaltrexamine (20 mg/kg, s.c.) also partially, but significantly, antagonized the antinociceptive effect of oxycodone in diabetic mice (Figs. 3B and 4). In non-diabetic mice, pretreatment with nor-binaltorphimine (20 mg/kg, s.c.) had no effect on the peak antinociceptive effect of oxycodone observed 30 min after administration, however, it slightly but significantly reduced oxycodone-induced antinociception observed 60 and 90 min after administration (Fig. 3A). On the other hand, pretreatment with nor-binaltorphimine practically abolished the peak (30 min) and persistent (60 and 90 min) antinociceptive effects of oxycodone in diabetic mice (Fig. 3B). Indeed, the AUC calculated from the time–response curve of the tail-flick latency shows that the antagonism of

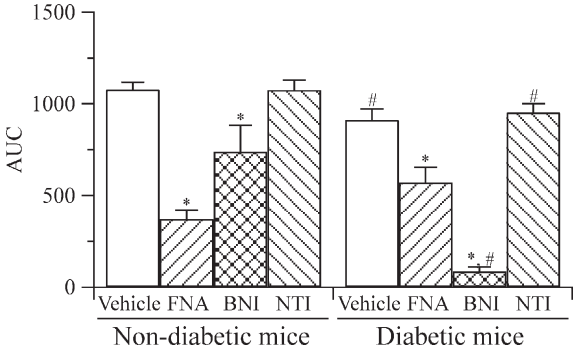

Fig. 4. Effects of various opioid receptor antagonists on the antinociceptive effect of oxycodone in non-diabetic and diabetic mice. Tail-flick responses were determined 30, 60 and 90 min after the administration of oxycodone (5 mg/kg, s.c.). The antinociceptive effect was evaluated by the AUC calculated from the time-response curve of the tail-flick latency. β-Funaltrexamine (FNA) and nor-binaltorphimine (BNI) were injected s.c. 24 h before testing. Naltrindole (NTI) was injected s.c. 30 min before the injection of oxycodone. Each column represents the mean with S.E.M. ($n=10$). *$P<0.05$ vs. respective vehicle (saline)-pretreated mice (Bonferroni-Dunn test). $^{\#}P<0.05$ vs. respective non-diabetic mice (Student's *t*-test).

nor-binaltorphimine in diabetic mice was significantly greater than that in non-diabetic mice (Fig. 4). Furthermore, naltrindole had no effects on the antinociceptive effect of oxycodone in both non-diabetic and diabetic mice (Figs. 3A, B and 4).

4. Discussion

The present experiments demonstrated that s.c. administration of oxycodone produced marked antinociception in both diabetic and non-diabetic mice. In the present study, diabetic mice showed thermal hyperalgesia in the tail-flick test. We previously reported that heat intensity at voltages of 65 and 80 V evoked a rapid tail-flick response (3 and 2.2 s), whereas that at 50 V evoked an intermediate tail-flick latency (12.1 s) in non-diabetic mice (Ohsawa and Kamei, 1997, 1999). We also reported that the tail-flick latency after heating the tail at 50 V in diabetic mice was significantly shorter than that in non-diabetic mice, indicating that diabetic mice exhibit thermal hyperalgesia (Ohsawa and Kamei, 1997, 1999; Kamei et al., 2001). Although morphine (5 mg/kg, s.c.) had no effect on the reduction of the nociceptive threshold observed in diabetic mice, the same dose of oxycodone produced a significant prolongation of the tail-flick latency. The antinociceptive effects of s.c. oxycodone in both diabetic and non-diabetic mice were significantly antagonized by pretreatment with β-funaltrexamine (20 mg/kg, s.c.), a selective μ-opioid receptor antagonist. Furthermore, we also observed that antinociception induced by oxycodone was antagonized by nor-binaltorphimine, a selective κ-opioid receptor antagonist, in both non-diabetic and diabetic mice. Interestingly, this antagonism was significantly greater in diabetic mice than in non-diabetic mice.

In a previous study, we showed that the antinociceptive effect of U-50,488H, a selective κ-opioid receptor agonist, in streptozotocin-induced diabetic mice as assessed by the tail-pinch test was the same as that in non-diabetic mice (Kamei et al., 1992a). We also previously reported that the antinociceptive effect of U-50,488H in streptozotocin-induced diabetic mice as assessed by the tail-pressure test was greater than that in non-diabetic mice (Suzuki et al., 2001). Several investigators have also reported that the antinociceptive effect of pentazocine, another κ-opioid receptor agonist, was greater in diabetic mice than in non-diabetic mice (Kamei et al., 1994c; Tandon et al., 2000). Our previous study also showed that the antinociceptive effects of μ-opioid receptor agonists in diabetic mice are significantly lower than those in non-diabetic mice (Kamei et al., 1992a,b, 1994a, 2000; Ohsawa and Kamei, 1997). It has been suggested that this hyposensitivity in diabetic mice arises due to a functional change rather than a change in the number of μ-opioid receptors (Ohsawa et al., 2000; Chen et al., 2002; Chen and Pan, 2003). In the present study, morphine (5 mg/kg, s.c.) had no effect on the reduction of the nociceptive threshold observed in diabetic mice. This result supports our previous report. Oxycodone produced a significant prolongation of the tail-flick latency in diabetic mice and this antinociception was abolished by pretreatment with β-funaltrexamine. On the other hand, the antinociceptive effect induced by a high dose of oxycodone (5.0 mg/kg) in diabetic mice was significantly less than that in non-diabetic mice. These results suggest that although μ-opioid receptors are involved in s.c. oxycodone-induced antinociception in diabetic mice, the role of μ-opioid receptors in s.c. oxycodone-induced antinociception in diabetic mice might be weaker than in non-diabetic mice.

Previously, we hypothesized that the hypo-responsiveness of μ-opioid receptors may account for the enhanced κ-opioid receptor-mediated antinociceptive effect, since there was no significant difference in the antinociceptive effect of pentazocine between diabetic mice and β-funaltrexamine-treated non-diabetic mice (Kamei et al., 1994c). On the other hand, Ross and Smith (1997) showed that nor-binaltorphimine, at a dose that did not attenuate the antinociceptive effects of i.c.v. morphine, completely abolished the antinociceptive effects of i.c.v. oxycodone. They also reported that both i.c.v. and i.v. morphine showed incomplete antinociceptive cross-tolerance with i.v. oxycodone (Nielsen et al., 2000). Furthermore, radioligand studies using [^{3}H] DAMGO have shown that oxycodone's affinity for the μ-opioid receptor was relatively low compared to that of morphine (Chen et al., 1991). Thus, based on these results, Nielsen et al. (2000) concluded that the receptors that mediate the antinociceptive effects of oxycodone are distinctly different from those that mediate the pain-relieving effects of morphine. In the present study, the antinociceptive effect of oxycodone in diabetic mice was partially antagonized by pretreatment with the κ-opioid receptor antagonist nor-binaltorphimine, however, the antinociceptive effect of oxycodone in diabetic mice was almost completely antagonized by pretreatment with nor-binaltorphimine. Based on a previous report and the present study, we suggested that the antinociceptive effect of oxycodone is mediated through the activation of μ-opioid receptors in both non-diabetic and diabetic mice, whereas κ-opioid receptors also strongly mediate the antinociceptive effect of oxycodone in diabetic mice.

In summary, the antinociceptive effect induced by the s.c. administration of oxycodone was observed in both non-diabetic and diabetic mice. Although morphine had no effect on hyperalgesia in diabetic mice, the same dose of oxycodone produced marked antinociception. The present results suggest that the antinociceptive effects of oxycodone are mediated by κ-opioid receptors in diabetic mice, whereas it may interact primarily with μ-opioid receptors in non-diabetic mice. Furthermore, it is possible that oxycodone might be useful for the treatment of painful diabetic neuropathy.

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