ELSEVIER

European Journal of Pharmacology 391 (2000) 91–96

ejp

www.elsevier.nl/locate/ejphar

The antinociceptive effects of endomorphin-1 and endomorphin-2 in diabetic mice

Junzo Kamei [a,*], Ko Zushida [a], Masahiro Ohsawa [a], 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 248-8555, Japan*

Received 23 September 1999; received in revised form 10 January 2000; accepted 14 January 2000

Abstract

The antinociceptive effects of endomorphin-1 and endomorphin-2, endogenous μ-opioid receptor agonists, were examined using the tail-flick test in non-diabetic and diabetic mice. Endomorphin-1, at doses of 1 to 10 μg, i.c.v., and endomorphin-2, at doses of 3 to 30 μg, i.c.v., each dose dependently inhibited the tail-flick response in both non-diabetic and diabetic mice. There was no significant difference between the antinociceptive effects of endomorphin-1 in non-diabetic mice and diabetic mice. The antinociceptive effect of endomorphin-2 was greater in non-diabetic mice than in diabetic mice. In non-diabetic mice, the antinociceptive effects of endomorphin-1 and endomorphin-2 were significantly reduced by β-funaltrexamine, a μ-opioid receptor antagonist, and naloxonazine, a selective μ_1-opioid receptor antagonist, but not by naltrindole, a δ-opioid receptor antagonist, or nor-binaltorphimine, a κ-opioid receptor antagonist. In diabetic mice, the antinociceptive effect of endomorphin-2 was significantly reduced by β-funaltrexamine and naloxonazine. However, these μ-opioid receptor antagonists had no significant effect on the antinociceptive effect of endomorphin-1 in diabetic mice. The antinociception induced by endomorphin-1 in diabetic mice was significantly reduced by naltrindole and 7-benzylidenenaltrexon, a selective δ_1-opioid receptor antagonist, administered i.c.v. However, nor-binaltorphimine had no significant effect on the antinociceptive effects of endomorphin-1 and endomorphin-2 in diabetic mice. These results indicate that the antinociceptive effects of endomorphin-1 and endomorphin-2 in non-diabetic mice are mediated through the activation of μ_1-opioid receptors, whereas in diabetic mice, endomorphin-1 and endomorphin-2 may produce antinociception through different actions at δ_1- and μ_1-opioid receptors, respectively.

Keywords: Endomorphin-1; Endomorphin-2; Diabetes; Antinociception; δ-Opioid receptor; μ-Opioid receptor

1. Introduction

Endomorphin-1 (Tyr–Pro–Trp–Phe–NH_2) and endomorphin-2 (Tyr–Pro–Phe–Phe–NH_2) are tetrapeptide amides isolated from bovine brain. They have high affinity and selectivity for the μ-opioid receptor, and have been shown to produce potent antinociceptive activity that is reversible by naloxone, β-funaltrexamine and naloxonazine (Zadina et al., 1997; Goldberg et al., 1998).

We previously reported that the antinociceptive effects of i.c.v. administration of μ-opioid receptor agonists, such as morphine and [D-Ala^2, *N*-MePhe^4, Gly-ol^5]enkephalin (DAMGO), were markedly less in diabetic mice than in non-diabetic mice (Kamei et al., 1992a,c). We also demonstrated that the δ-opioid receptor-mediated endogenous antinociceptive system is enhanced in diabetic mice as compared to non-diabetic mice (Kamei et al., 1992b). Furthermore, the antinociceptive potency of i.c.v. or i.t. administration of [D-Pen^{2,5}]enkephalin (DPDPE) was significantly greater in diabetic mice than in non-diabetic mice (Kamei et al., 1993, 1994b). Based on these results, we suggested that diabetic mice are selectively hyporesponsive to μ-opioid receptor-mediated antinociception, and that the blockade of μ-opioid receptor-mediated functions by diabetes may account for the up-regulation of supraspinal δ-opioid receptor-mediated functions.

Thus, functional abnormalities in the opioidergic system of diabetic animals may alter the antinociceptive activities of endomorphin-1 and endomorphin-2. To test this hypoth-

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

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

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00049-2

esis, we examined the effect of diabetes on the antinociceptive effects of endomorphin-1 or endomorphin-2.

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science, Tokyo, Japan), weighing about 25–35 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. The 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 the injection of streptozotocin or vehicle. Mice with serum glucose levels above 4000 mg/l 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. Antinociceptive assay

The antinociceptive response was determined by recording the latency in the tail-flick test using radiant heat. The intensity of the thermal stimulus for the tail-flick test was adjusted so that the animal flicked its tail in 2–4 s. A cut-off latency of 15 s was used to prevent injury to the tail. The percent antinociception was calculated for each animal as % Antinociception = 100 × (post drug latency − pre drug latency)/(15 − pre drug latency).

2.3. Drugs

Streptozotocin was purchased from Sigma (St. Louis, MO, USA). Endomorphin-1, endomorphin-2, β-funaltrexamine, a μ-opioid receptor antagonist, naloxonazine, a selective μ_1-opioid receptor antagonist, nor-binaltorphimine, a selective κ-opioid receptor antagonist, naltrindole, δ-opioid receptor antagonist, 7-benzylidenenaltrexon, a selective δ_1-opioid receptor antagonist, and naltriben, a selective δ_2-opioid receptor antagonist were synthesized by Dr. Nagase (Toray Industries, Kamakura, Japan). All of the opioid agonists and antagonists were dissolved in saline. Endomorphin-1 and endomorphin-2 were injected i.c.v. 10 min before the antinociceptive assay. β-Funaltrexamine (20 mg/kg, s.c.) and naloxonazine (35 mg/kg, s.c.) were injected 24 h before testing. Nor-binaltorphimine (20 mg/kg, s.c.) was injected 3 h before testing. Naltrindole (1 mg/kg, s.c.) was injected 15 min before testing. 7-Benzylidenenaltrexone (0.3 mg/kg, s.c.) and naltriben (0.3 mg/kg, s.c.) were injected 10 min before testing. The i.c.v. injection was performed according to the method of Haley and McCormick (1957). I.t. injection was performed according to the method of Hylden and Wilcox (1980).

2.4. Data analysis

The data are expressed as means ± S.E. The statistical significance of differences between groups was assessed with an analysis of variance (ANOVA) followed by the Bonferroni/Dunn test. The ED_{50} values, the ED_{50} ratio and their 95% confidence intervals for the antinociceptive effect of endomorphin-1 and endomorphin-2 were determined using linear regression techniques. The potency ratios and their 95% confidence intervals for the antinociceptive effect of endomorphin-1 and endomorphin-2 were computed using Program 11 of the Pharmacological Calcu-

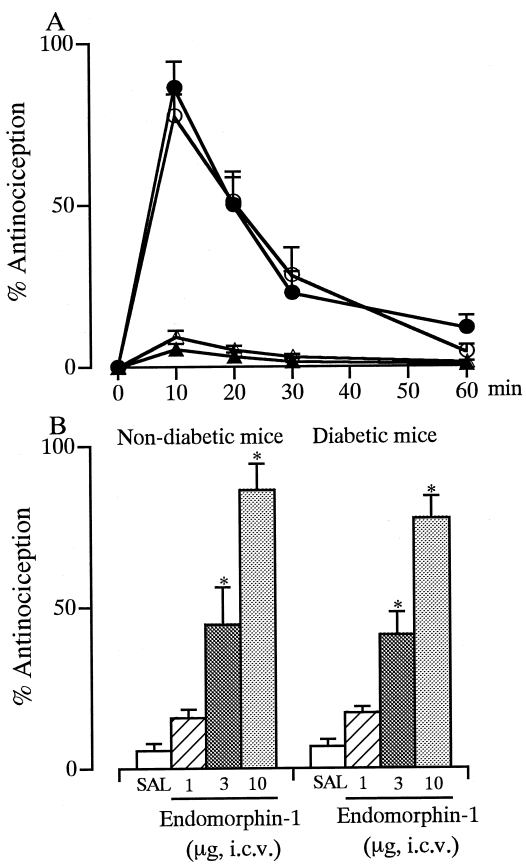

Fig. 1. Time course (A) and dose–response (B) curves for the antinociception induced by endomorphin-1 in non-diabetic and diabetic mice. In (A), the antinociceptive effect of endomorphin-1 (10 μg, diabetic mice: open circle; non-diabetic mice: closed circle) was measured in the tail-flick test 10, 20, 30 and 60 min after i.c.v. injection. In (B), the antinociceptive effects of endomorphin-1, at doses 1, 3 and 10 μg, were assessed in the tail-flick test 10 min after i.c.v. injection. Each point or column represents the mean with S.E. for 10–15 mice in each group. * $P < 0.05$ vs. the value for respective saline (SAL)-treated group (open column).

lations system of Tallarida and Murray (1987). A potency ratio value greater than one, with the lower 95% confidence limit greater than one, was considered a significant difference in potency.

3. Results

3.1. Effects of i.c.v. administration of endomorphin-1 and endomorphin-2 on the tail-flick response

Figs. 1A and 2A show the time course of the antinociception produced by endomorphin-1 (10 μg, i.c.v.) and endomorphin-2 (30 μg, i.c.v.) in both non-diabetic and diabetic mice. These effects reached their peak 10-min after administration and then decreased. Thus, a time interval of 10 min after i.c.v. administration was chosen for experiments designed to quantify the antinociceptive effects of endomorphin-1 and endomorphin-2.

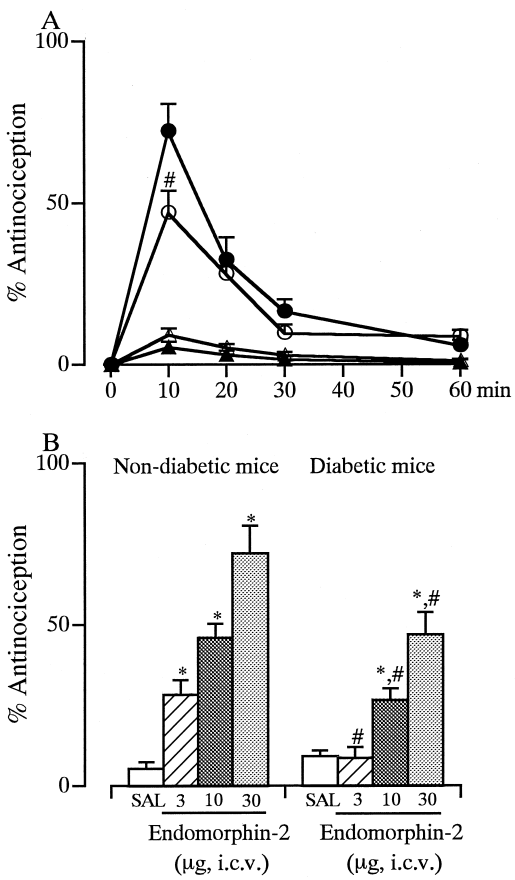

Fig. 2. Time course (A) and dose–response (B) curves for the antinociception induced by endomorphin-2 in non-diabetic and diabetic mice. In (A), the antinociceptive effect of endomorphin-2 (30 μg, diabetic mice: open circle; non-diabetic mice: closed circle) was measured in the tail-flick test 10, 20, 30 and 60 min after i.c.v. injection. In (B), the antinociceptive effects of endomorphin-2, at doses 3, 10 and 30 μg, were assessed in the tail-flick test 10 min after i.c.v. injection. Each point or column represents the mean with S.E. for 10–15 mice in each group. $^{*}P < 0.05$ vs. the value for respective SAL-treated group (open column). $^{\#}P < 0.05$ vs. the value for respective non-diabetic mice.

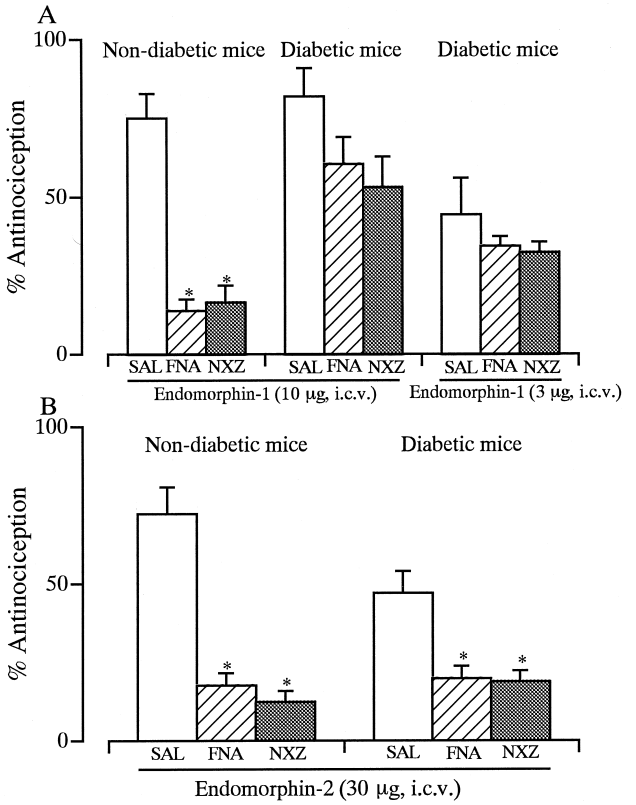

Fig. 3. Effects of β-funaltrexamine and naloxonazine on the antinociceptive effects of endomorphin-1 (A) and endomorphin-2 (B) in non-diabetic and diabetic mice. β-Funaltrexamine (FNA, 20 mg/kg) and naloxonazine (NXZ, 35 mg/kg) were injected s.c. 24 h before testing. The mice were tested 10 min after i.c.v. injection of endomorphins (endomorphin-1, 10 μg; endomorphin-2, 30 μg), using the tail-flick test. Each column represents the mean with S.E. for 15 mice in each group. $^{*}P < 0.05$ vs. respective SAL-treated group (open column).

As shown in Fig. 1B, endomorphin-1, at doses of 1–10 μg, i.c.v., produced a dose-dependent inhibition of the tail-flick response in both non-diabetic and diabetic mice. The ED_{50} values (μg with 95% confidence limits) were 3.2 (1.2–8.3) and 3.7 (1.2–11.1) for non-diabetic and diabetic mice, respectively. The potency ratio (95% confidence limits) of the antinociceptive effect of endomorphin-1 in non-diabetic mice vs. that in diabetic mice was 0.9 (0.6–1.3). There was no significant difference between the antinociceptive potencies induced by endomorphin-1 in non-diabetic and diabetic mice.

Although endomorphin-2, at doses of 3–30 μg, i.c.v. produced a dose-dependent inhibition of the tail-flick response in both non-diabetic and diabetic mice, the peak antinociceptive effect of endomorphin-2 (3, 10 and 30 μg, i.c.v.) was significantly less in diabetic mice than in non-diabetic mice. The ED_{50} values (μg with 95% confidence limits) were 10.2 (2.0–52.2) and 37.1 (10.0–137.2) for non-diabetic and diabetic mice, respectively. The po-

tency ratio (95% confidence limits) of the antinociceptive effect of endomorphin-2 in non-diabetic mice vs. that in diabetic mice was 3.5 (2.1–7.3). Thus, the antinociceptive potency of endomorphin-2 was significantly less in diabetic mice than in non-diabetic mice.

3.2. Effects of μ-opioid receptor antagonists on the antinociception induced by endomorphin-1 and endomorphin-2

The effects of β-funaltrexamine (20 mg/kg, s.c.), a μ-opioid receptor antagonist, and naloxonazine (35 mg/kg, s.c.), a selective μ_1-opioid receptor antagonist, on the antinociceptive effects of endomorphin-1 (3 and 10 μg, i.c.v.) and endomorphin-2 (30 μg, i.c.v.) in non-diabetic and diabetic mice are shown in Fig. 3. In non-diabetic mice, the antinociceptive effects of endomorphin-1 and endomorphin-2 were significantly reduced by β-funaltrexamine and naloxonazine (Fig. 3A). As shown in Fig. 3B, the antinociceptive effect of endomorphin-2 in diabetic mice was significantly reduced by β-funaltrexamine and naloxonazine, whereas the antinociceptive effect of endomorphin-1 in diabetic mice was not antagonized by either β-funaltrexamine or naloxonazine.

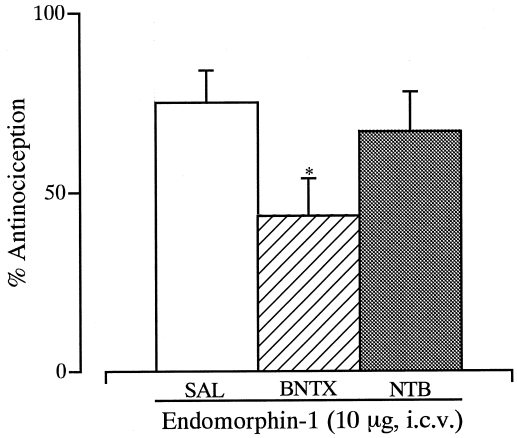

Fig. 5. Effects of 7-benzylidenenaltrexone and naltriben on the antinociceptive effects of endomorphin-1 in diabetic mice. 7-Benzylidenenaltrexone (0.3 mg/kg, s.c.) and naltriben (0.3 mg/kg, s.c.) were injected 10 min before the injection of endomorphin-1. The mice were tested 10 min after i.c.v. injection of endomorphin-1 (10 μg) in the tail-flick test. Each column represents the mean with S.E. for 15 mice in each group. $^{*}P < 0.05$ vs. respective SAL-treated group (open column).

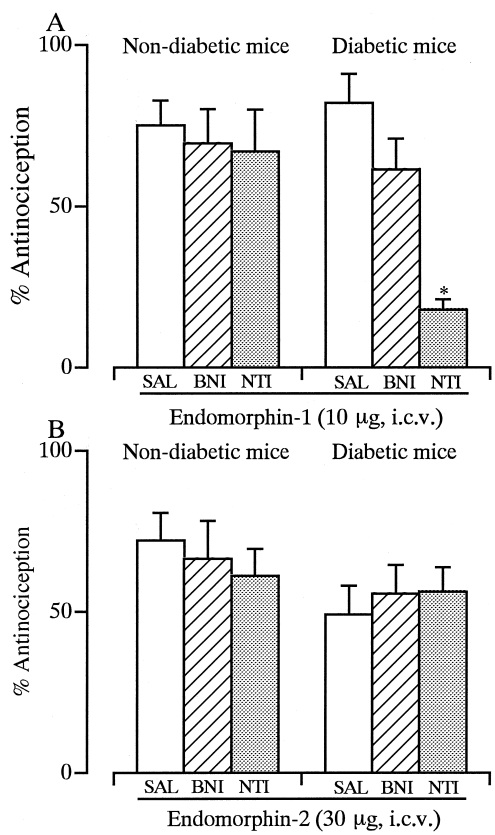

Fig. 4. Effects of nor-binaltorphimine and naltrindole on the antinociceptive effects of endomorphin-1 (A) and endomorphin-2 (B) in non-diabetic and diabetic mice. Nor-binaltorphimine (BNI, 20 mg/kg) was injected s.c. 3 h before testing. Naltrindole (NTI, 1 mg/kg) was injected s.c. 15 min before the injection of endomorphins. The mice were tested 10 min after i.c.v. injection of endomorphins (endomorphin-1, 10 μg; endomorphin-2, 30 μg) in the tail-flick test. Each column represents the mean with S.E. for 15 mice in each group. $^{*}P < 0.05$ vs. respective SAL-treated group (open column).

3.3. Effects of κ-opioid receptor antagonist on the antinociception induced by endomorphin-1 and endomorphin-2

Nor-binaltorphimine, a selective κ-opioid receptor antagonist, had no significant effect on the antinociceptive effect of either endomorphin-1 or endomorphin-2 in either non-diabetic or diabetic mice (Fig. 4A,B).

3.4. Effects of δ-opioid receptor antagonists on the antinociception induced by endomorphin-1 and endomorphin-2

In non-diabetic mice, naltrindole (1 mg/kg, s.c.), a δ-opioid receptor antagonist did not antagonize the antinociceptive effects of endomorphin-1 (10 μg, i.c.v.) or endomorphin-2 (30 μg, i.c.v.) (Fig. 4A,B). In diabetic mice, naltrindole significantly reduced the antinociceptive effect of endomorphin-1 (10 μg, i.c.v.), but not of endomorphin-2 (30 μg, i.c.v.) (Fig. 4A,B). In diabetic mice, the antinociceptive effect of endomorphin-1 (10 μg, i.c.v.) was significantly reduced by 7-benzylidenenaltrexone (0.3 mg/kg, s.c.), a selective δ_1-opioid receptor antagonist, but not by naltriben (0.3 mg/kg, s.c.), a selective δ_2-opioid receptor antagonist (Fig. 5). Furthermore, in diabetic mice the antinociceptive effect of endomorphin-1 (10 μg, i.c.v.) was significantly reduced by i.c.v. administration of 7-benzylidenenaltrexone (1 μg) (Fig. 6). However, i.t.-adminis-

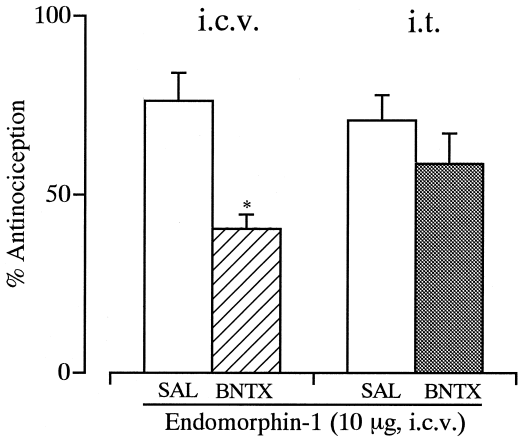

Fig. 6. Effect of either i.c.v. or i.t. pretreatment with 7-benzylidenenaltrexone on the antinociceptive effects of endomorphin-1 in diabetic mice. 7-Benzylidenenaltrexone (1 μg) was injected i.c.v. or i.t. 10 min before the injection of endomorphin-1. The mice were tested 10 min after the i.c.v. injection of endomorphin-1 (10 μg) in the tail-flick test. Each column represents the mean with S.E. for 15 mice in each group. * $P < 0.05$ vs. respective SAL-treated group (open column).

tered 7-benzylidenenaltrexone had no effect on the antinociceptive effect of endomorphin-1 (10 μg, i.c.v.) in diabetic mice (Fig. 6).

4. Discussion

The present experiments demonstrate that i.c.v. administration of endomorphin-1 and endomorphin-2 produces dose-dependent antinociception in non-diabetic (normal) mice. Furthermore, the antinociceptive effect of endomorphin-1 was about threefold greater than that of endomorphin-2. This result is consistent with the observation of Zadina et al. (1997). In non-diabetic mice, the antinociceptive effects of endomorphin-1 and endomorphin-2 were significantly reduced by β-funaltrexamine, a μ-opioid receptor antagonist, and naloxonazine, a selective μ_1-opioid receptor antagonist. However, nor-binaltorphimine, a κ-opioid receptor antagonist, and naltrindole, a δ-opioid receptor antagonist, had no significant effect on the antinociceptive effects of endomorphin-1 and endomorphin-2 in non-diabetic mice. These results are consistent with the previous indication that endomorphins may produce antinociception through the activation of μ_1-opioid receptors at supraspinal sites (Goldberg et al., 1998).

In diabetic mice, the antinociceptive effect of endomorphin-1 was not antagonized by either β-funaltrexamine, naloxonazine, or nor-binaltorphimine. However, naltrindole significantly reduced the antinociceptive effect of endomorphin-1 in diabetic mice. Furthermore, the antinociceptive effect of endomorphin-1 in diabetic mice was significantly reduced by i.c.v. but not i.t. administration of 7-benzylidenenaltrexone, a selective δ_1-opioid receptor antagonist. However, naltriben, a selective δ_2-opioid receptor antagonist, had no effect on the antinociceptive effect of endomorphin-1 in diabetic mice. Zadina et al. (1997) reported that endomorphin-1 showed a high affinity for μ-opioid receptors ($K_i = 0.36$ nM) and a low affinity for δ-opioid receptors ($K_i = 1506$ nM) and κ-opioid receptors ($K_i = 5428$ nM) in mice brain. Thus, the reasons for the involvement of δ_1-opioid receptors in the endomorphin-1-induced antinociception in diabetic mice remain unclear. Since several opioids show competitive binding with shallow Hill slopes and endomorphins produce antinociception in μ-opioid receptor knockout mouse, Goldberg et al. (1998) suggested that the actions of endomorphins may involve more than just traditional μ-opioid receptors. We previously reported that the antinociceptive effects of μ-opioid receptor agonists, such as morphine and DAMGO, administered i.c.v. were markedly less in diabetic mice than in non-diabetic mice (Kamei et al., 1992a,c). Therefore, we suggested that diabetic mice are selectively hyporesponsive to supraspinal μ-opioid receptor-mediated antinociception. We previously demonstrated that the antinociceptive effects of δ-opioid receptor agonists, such as [D-Pen^{2,5}]enkephalin (DPDPE) and (−)2-methyl-4aα-(3-hydroxyphenyl)-1, 2, 3, 4, 4a, 5, 12, 12aα-octahydro-quinolino[2, 3, 3-g]isoquinoline ((−)-TAN-67), administered i.c.v. were significantly greater in diabetic mice than in non-diabetic mice (Kamei et al., 1995, 1997). The antinociceptive effects of DPDPE and (−)-TAN-67 were antagonized in both diabetic and non-diabetic mice following pretreatment with 7-benzylidenenaltrexone, but not naltriben. (Kamei et al., 1992b, 1994b, 1995, 1997). Based on these results, we concluded that mice with diabetes are selectively hyperresponsive to supraspinal δ_1-opioid receptor-mediated antinociception. Thus, although endomorphin-1 has a low affinity for δ-opioid receptors, it is possible that δ_1-opioid receptors may be the predominant receptors for supraspinal endomorphin-1-induced antinociception in diabetic mice. Holmes et al. (1998) and Rady et al. (1998) have reported similar observations. They demonstrated that the μ-opioid receptor-mediated antinociceptive effect of heroin in non-diabetic mice switched to δ-opioid receptor antagonist sensitivity in mice made diabetes with streptozotocin. Furthermore, several studies have shown that strain differences in mice in the sensitivity to opioid agonists and in the mediation of effects by different opioid receptor subtypes (Porreca et al., 1992; Rady et al., 1994a,b, 1997). Based on these previous and present findings, it is possible that a given opioid receptor agonist can switch its receptor mediation in response to manipulation, such as induced pathosis and strain differences.

In diabetic mice, the antinociceptive effect of endomorphin-2 was significantly reduced by β-funaltrexamine and naloxonazine. In contrast, nor-binaltorphimine and naltrindole had no significant effect on the antinociceptive effect of endomorphin-2 in diabetic mice. These results suggest that endomorphin-2 may produce antinociception

through the activation of μ_1-opioid receptors in diabetic mice. Wolozin and Pasternak (1981) and Goodman and Pasternak (1985) have suggested that different μ-opioid receptor subtypes are responsible for spinal and supraspinal morphine-induced antinociception. μ_1-Opioid receptors mediate supraspinal morphine-induced antinociception, while μ_2-opioid receptors are responsible for spinal antinociception. Previously, we reported that the naloxonazine-sensitive antinociceptive effect of i.c.v. morphine in diabetic mice was significantly less than that in non-diabetic mice (Kamei et al., 1994a). However, there were no significant differences in the naloxonazine-insensitive antinociceptive effect of i.t. morphine in non-diabetic and diabetic mice. Therefore, we suggested that mice with diabetes are selectively hyporesponsive to μ_1-opioid receptor-mediated antinociception, but are normally responsive to activation of μ_2-opioid receptors (Kamei et al., 1994a). Thus, the lower antinociceptive activity of endomorphin-2 in diabetic mice supports its μ_1-opioid receptor selectivity.

In conclusion, the present results suggest that, in non-diabetic mice, i.c.v. endomorphin-1 and endomorphin-2 may produce antinociception through the activation of μ_1-opioid receptors. In contrast, in diabetic mice, i.c.v. endomorphin-1 may produce antinociception mainly through δ_1-opioid receptors, while i.c.v. endomorphin-2 may induce antinociception through μ_1-opioid receptors.

Acknowledgements

We thank Ms. K. Yoshida for her excellent technical assistance.

References

Goldberg, I.E., Rossi, G.C., Letchworth, S.R., Mathis, J.P., Ryan-Moro, J., Leventhal, L., Su, W., Emmel, D., Bolan, E.A., Pasternak, G.W., 1998. Pharmacological characterization of Endomorphin-1 and Endomorphin-2 in mouse brain. J. Pharmacol. Exp. Ther. 286, 1007–1013.

Goodman, R.R., Pasternak, G.W., 1985. Pharmacological effects produced by intracerebral injections of drugs in the conscious mouse. Br. J. Pharmacol. 12, 12–15.

Haley, M.J., McCormick, W.G., 1957. Pharmacological effects produced by intracerebral injection of drug in the conscious mice. Br. J. Pharmacol. 12, 12–15.

Holmes, B.B., Rady, J.J., Fujimoto, J.M., 1998. Heroin acts on delta opioid receptors in the brain of streptozotocin-induced diabetic rats. Proc. Soc. Exp. Biol. Med. 218, 334–340.

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

Kamei, J., Iwamoto, Y., Hitosgi, H., Misawa, M., Nagase, H., Kasuya, Y., 1994a. Streptozotocin-induced diabetes selectively reduces the antinociceptive effect which mediated by μ_1-opioid receptors, but not that mediated by μ_2-opioid receptors. Neurosci. Lett. 165, 141–143.

Kamei, J., Iwamoto, Y., Misawa, M., Nagase, H., Kasuya, Y., 1994b. Streptozotocin-induced diabetes selectively enhances antinociception mediated by δ_1- but not δ_2-opioid receptors. Life Sci. 55, L121–PL126.

Kamei, J., Kawai, K., Mizusuna, A., Saito, A., Morita, K., Narita, M., Tseng, L.F., Nagase, H., 1997. Supraspinal δ_1-opioid receptor-mediated antinociceptive properties of (−)-TAN-67 in diabetic mice. Eur. J. Pharmacol. 322, 27–30.

Kamei, J., Kawashima, N., Hitosugi, H., Misawa, M., Nagase, H., Kasuya, Y., 1993. Effect of diabetes on the antinociceptive effect of β-endorphin. Brain Res. 619, 76–80.

Kamei, J., Kawashima, N., Kasuya, Y., 1992a. Role of spleen or spleen products in the deficiency in morphine-induced analgesia in diabetic mice. Brain Res. 576, 139–142.

Kamei, J., Kawashima, N., Kasuya, Y., 1992b. Paradoxical analgesia produced by naloxone in diabetic mice is attributable to supersensitivity of δ opioid receptor. Brain Res. 592, 101–105.

Kamei, J., Ohhashi, Y., Aoki, T., Kawashima, N., Kasuya, Y., 1992c. Streptozotocin-induced diabetes selectively alters the potency of analgesia produced by δ opioid agonists, but not by μ and κ opioid agonists. Brain Res. 571, 199–203.

Kamei, J., Saito, 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.

Porreca, F., Takemori, A.E., Sultana, M., Portoghese, P.S., Bowen, W.D., Mosberg, H.I., 1992. Modulation of μ-mediated antinociception in the mouse involves opioid delta-2 receptors. J. Pharmacol. Exp. Ther. 263, 147–152.

Rady, J.J., Aksu, F., Fujimoto, J.M., 1997. The heroin metabolite, 6-monoacetylmorphine, activates delta opioid receptor subtype activity of to produce antinociception in Swiss Webster mice. J. Pharmacol. Exp. Ther. 268, 1221–1231.

Rady, J.J., Baemmert, D., Takemori, A.E., Portoghese, P.S., Fujimoto, J.M., 1994a. Spinal delta opioid receptor subtype activity of 6-monoacetylmorphine in Swiss Webster mice. Pharmacol. Biochem. Behav. 56, 243–249.

Rady, J.J., Gorny, J.M., Fujimoto, J.M., 1998. Heroin antinociception changed from mu to delta receptor in streptozotocin-treated mice. Jpn. J. Pharmacol. 78, 443–454.

Rady, J.J., Takemori, A.E., Portoghese, P.S., Fujimoto, J.M., 1994b. Supraspinal delta receptor subtype activity of heroin and 6-monoacetylmorphine in Swiss Webster mice. Life Sci. 55, 603–609.

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

Wolozin, B.L., Pasternak, G.W., 1981. A classification of multiple morphine and enkephalin binding sites in the central nervous system. Proc. Natl. Acad. Sci. U.S.A. 78, 6181–6185.

Zadina, J.E., Hackler, L., Ge, L.-J., Kastin, A.J., 1997. A potent and selective endogenous agonist for the μ opiate receptor. Nature 386, 499–502.