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Functional interactions between δ- and μ-opioid receptors in rat thermoregulation

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Abstract

The selective δ-opioid receptor agonist deltorphin II (25.0–100.0 μg, i.c.v.) produced biphasic effects on core temperature in rats, in which hypothermia was followed by hyperthermia. Pretreatment with the selective δ-opioid receptor antagonist, naltrindole (25.0 μg, i.c.v.), blocked hypothermia produced by deltorphin II and had a tendency to potentiate the hyperthermic effect of deltorphin II. The non-selective opioid receptor antagonist naloxone (1.5 mg kg^{-1}, s.c.) potentiated hypothermia, and blocked hyperthermia, produced by deltorphin II (100.0 μg). Also, naloxone potentiated hypothermia produced by a lower dose of deltorphin II (25.0 μg), which did not produce hyperthermia. A similar pattern was found for the selective μ-opioid receptor antagonist, β-funaltrexamine (5.0 μg, i.c.v.), which potentiated and blocked deltorphin II-induced hypo- and hyperthermia, respectively. The selective κ-opioid receptor antagonist nor-binaltorphimine (20.0 μg, i.c.v.) had no effects on deltorphin II-induced temperature changes. The present results suggest that deltorphin II produces hypothermia through activation of δ-opioid receptors, whereas the hyperthermic effect of deltorphin II involves activation of μ-opioid receptors. This μ-opioid receptor stimulatory effect of deltorphin II is furthermore more pronounced than was anticipated based on the reported in vitro properties of this compound. The biphasic effect of deltorphin II implies a negative interaction between δ- and μ-opioid receptors in thermoregulation in rats.

Keywords: Deltorphin II; Body temperature; Hypothermia; Hyperthermia

1. Introduction

Endogenous opioids likely are involved in body temperature regulation in mammals. In rodents, systemic and central injections of opiates and opioid peptides produce profound body temperature changes (Geller et al., 1983, 1986; Adler and Geller, 1988), presumably through activation of opioid receptors within the preoptic area of the anterior hypothalamus, the primary temperature-control center in mammals (e.g., Xin et al., 1997). Three opioid receptors (δ, μ and κ) have been cloned (Evans et al., 1992; Kieffer et al., 1992; Chen et al., 1993; Thompson et al., 1993; Meng et al., 1993; Yasuda et al., 1993) and all are localized within the preoptic area of the anterior hypothalamus (Mansour et al., 1987). This suggests that all three opioid receptors may mediate temperature effects of opiates and opioid peptides.

Evidence from work with selective opioid receptor agonists and antagonists in rats indicates that all three opioid receptors indeed are involved in thermoregulation. Activation of μ-opioid receptors produces hyperthermia (Spencer et al., 1988; Handler et al., 1992) while activation of κ-opioid receptors induces hypothermia (Cavicchini et al., 1988; Spencer et al., 1988). In support of a specific role of δ-opioid receptors in thermoregulation, electrophysiological experiments have demonstrated specific effects by δ-opioid receptor agonists and antagonists on thermosensitive neurons expressing δ-opioid receptors within the preoptic area of the anterior hypothalamus (Yakimova et al., 1998). However, there are conflicting reports of δ-opioid receptor agonists that produce hypothermia, hypothermia followed by hyperthermia, or have no effects in vivo (Spencer et al., 1988; Broccardo and Improta, 1992; Handler et al., 1992). The reasons for these conflicting reports are not clear, but may be related to for example agonists used. Generally, these studies have used the δ-opioid receptor agonists [D-Pen^2, D-Pen^5]enkephalin (DPDPE) and deltorphin II, of which deltorphin II is

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believed to better in terms of selectivity and efficacy at δ-opioid receptors.

In this laboratory, preliminary studies with the selective δ-opioid receptor agonist deltorphin II indicated robust biphasic effects of deltorphin II on rat core temperature, in which hypothermia was followed by hyperthermia. The mechanisms behind the dual effects of deltorphin II were not addressed in these preliminary experiments, but the most obvious explanation is that deltorphin II interacts with another opioid receptor, apart from δ-opioid receptors. For example, functional interactions between μ- and δ-opioid receptors are well documented and are proposed to account for biphasic effects of deltorphins, for example, on locomotor activity (see Traynor and Elliott, 1993; Negri et al., 1996).

To follow up on our preliminary results this study was designed to (1) more thoroughly characterize the effects of deltorphin II on core temperature in rats with respect to dose-effect relationships and time course of action and (2) explore the mechanisms behind the biphasic temperature effects of deltorphin II. The specificity of effects produced by deltorphin II on core temperature was examined by the use of various selective opioid receptor antagonists.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats (280–320 g) (B&K Universal, Sollentuna, Sweden) were used. The animals arrived in the laboratory at least 1 week before experiments and were housed 4 per cage (Makrolon IV) under controlled conditions of light–dark cycle (12 h:12 h, lights off 7:30 p.m.), relative humidity (≈ 55%) and temperature (21.0 ± 1.0 °C). Food (R36, Ewos, Södertälje, Sweden) and tap water were available ad libitium. All experiments were approved by the Local Committee on Ethics of Animal Experimentation, Stockholm, Sweden.

2.2. Drugs

Tyr-D-Ala-Phe-Glu-Val-Val-Gly-amide ([D-Ala^2]deltorphin II) (Sigma, St. Louis, MO), naloxone HCl (Sigma), nor-binaltorphimine dihydrochloride (Sigma), naltrindole HCl (Sigma), β-funaltrexamine hydrochloride (Sigma). Deltorphin II was dissolved in 100% dimethyl sulfoxide, and injected i.c.v. as detailed below. Naloxone, naltrindole, nor-binaltorphimine and β-funaltrexamine were dissolved in physiological saline. Naloxone (1.5 mg kg^{-1}, 2 ml kg^{-1}, s.c.) was injected immediately after the administration of deltorphin II. Naltrindole (25.0 μg, 4 μl, i.c.v.) nor-binaltorphimine (20.0 μg, 4 μl, i.c.v.) and β-funaltrexamine (5.0 μg, 4 μl, i.c.v.) were injected 10 min, 40 min, 16 h prior to deltorphin II injection, respectively.

2.3. Animal surgery and i.c.v. injections

For injections into the right lateral ventricle, a guide cannula was stereotaxically mounted in the skull bone under barbiturate anaesthesia (pentobarbital 60.0 mg kg^{-1}, i.p.). The guide cannula was placed against the dura with the coordinates anterior posterior −1.0 mm and lateral −1.3 mm relative bregma (Paxinos and Watson, 1998), and thereafter securely fastened to the skull by acrylic dental cement. The injection needle (31-gauge) penetrated 4.0 mm below the dura. The injections were performed in animals that were awake and gently hand-restrained. The compounds were infused in a volume of 4 μl over 90 s. The injection needle was left in situ for another 120 s. Upon termination of experiments, the injection site was verified with an injection of 0.1% Evan's blue (4 μl). In most cases, both lateral ventricles and the third ventricle were labeled with the dye within 10 min. If not, the injection was regarded as misplaced and rats were excluded from the analyses.

2.4. Body temperature

Rat body temperature was recorded in a temperature-controlled room (ambient temperature 21.0 ± 1.0 °C). The core temperature was recorded by means of a flexible probe (YSI-402, Yellow Springs Instruments, Yellow Springs, OH, USA) that was lubricated with mucilago etalosi and inserted rectally (≈ 90 mm) in the gently hand-restrained rat. The probe was connected to an automated tele-thermometer with a printer device (Metod & Produkt Svenska, Västra Frölunda, Sweden) that was activated when the temperature reading had stabilized (± 0.1 °C) for 10 s. After the temperature reading, the probe was removed and the animal was placed in its home cage. The animals were habituated to the experimental conditions the day before experiments by a temperature reading, and used only once in experiments. The experiments took place between 9.00 and 14.00. For further details on temperature measurements, see Salmi et al. (1994).

2.5. Statistics

Data are expressed as means ± S.E.M. A one-way independent analysis of variance (ANOVA) followed by Dunnett's *t*-test for comparisons with a control was used to determine statistical significance. Student's *t*-test was used to compare means for two groups of cases. Differences were considered statistically significant at $P < 0.05$, as indicated by the asterisk in the figures.

3. Results

3.1. Effects of deltorphin II on core body temperature

Deltorphin II (25.0–100.0 μg, i.c.v.) produced a biphasic change on body temperature, in which hypothermia was

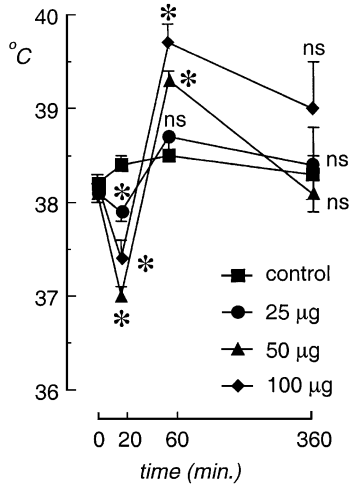

Fig. 1. Effects of deltorphin II on body core temperature in rats: dose–effect relationships and time course of action. Deltorphin II (25.0–100.0 µg, i.c.v.) was injected 20 min before first temperature measurements. Results are shown as mean ± S.E.M. based on six to eight animals per group. One-way independent ANOVA, followed by Dunnet's *t*-test for comparisons with vehicle-treated control group, was used to determine statistical significance. Differences were considered statistically significant at $P < 0.05$, as indicated by the asterisks in the figure.

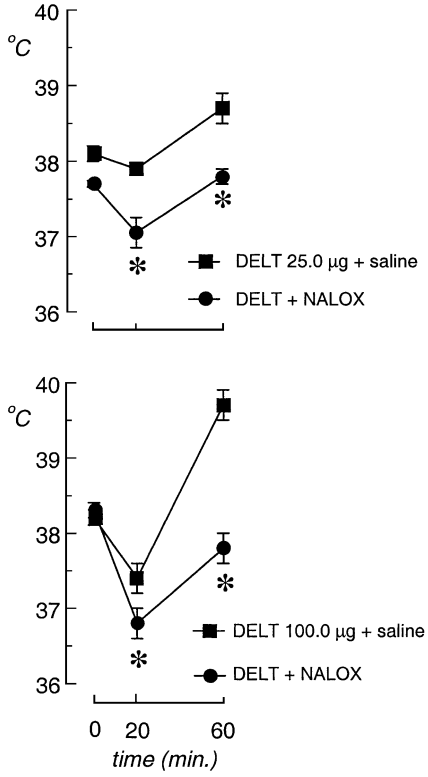

Fig. 2. Effects of naloxone on deltorphin II-induced temperature changes in rats. Naloxone (NALOX) (1.5 mg kg^{-1}, s.c.) was injected immediately after the administration of deltorphin II (DELT) (25.0 and 100.0 µg, i.c.v.) (top and bottom, respectively), and temperature was measured 20 and 60 min after the injections. Results are shown as mean ± S.E.M. based on four to six animals per group. Student's *t*-test was used to determine statistical significance and differences were considered statistically significant at $P < 0.05$, as indicated by the asterisks in the figure.

followed by hyperthermia (Fig. 1). Throughout the dose range deltorphin II induced a statistically significant hypothermia 20 min after the injection [$F(3,22) = 26.2$, $P < 0.01$], followed by hyperthermia 60 min after the injection [$F(3,22) = 10.1$, $P < 0.01$] , in which the 50.0 and 100.0 µg doses reached statistical significance (Fig. 1). The 50.0 µg dose of deltorphin II appeared to be somewhat more efficacious than the 100.0 µg dose in producing hypothermia, while the opposite was true for the hyperthermic effects. Six hours after the injection of deltorphin II, the temperatures of the rats returned to normal.

3.2. Effects of the non-selective opioid receptor antagonist naloxone on deltorphin II-induced body temperature changes

The administration of naloxone (1.5 mg kg^{-1}, s.c.) resulted in a potentiation of deltorphin II-induced (100.0 µg) hypothermia, whereas the hyperthermia was antagonized (Fig. 2). Also, by the use of a threshold dose of deltorphin II (25.0 µg), which produced slight hypothermia but no hyperthermia, it was observed that the hypothermic effect of deltorphin II was statistically significantly potentiated by the pretreatment with naloxone (Fig. 2). Naloxone by itself had no effects on body temperature (Table 1).

3.3. Effects of naltrindole and β-funaltrexamine on deltorphin II-induced body temperature changes

Pretreatment with the selective δ-opioid receptor antagonist naltrindole (25.0 µg, i.c.v) blocked the hypothermia produced by deltorphin II (Fig. 3, top). On the other hand, hyperthermia produced by deltorphin II was not statistically significantly affected by naltrindole pretreatment, even though there was a slight tendency to a potentiation of hyperthermia (Fig. 3, top).

Table 1
Effects of naloxone, naltrindole and β-funaltrexamine on core temperature in rats

Treatment	Pretest (°C)	20 min (°C)	60 min (°C)
Control	38.8 ± 0.1	38.3 ± 0.1	38.0 ± 0.1
Naloxone 1.5 mg kg^{-1}	38.7 ± 0.2[a]	38.0 ± 0.2[a]	37.8 ± 0.1[a]
Control	38.7 ± 0.1	38.3 ± 0.2	38.4 ± 0.2
Naltrindole 25.0 µg	38.4 ± 0.2[a]	38.6 ± 0.1[a]	38.4 ± 0.05[a]
Control	38.2 ± 0.2	38.4 ± 0.2	38.4 ± 0.2
β-Funaltrexamine 5.0 µg	38.3 ± 0.1[a]	38.3 ± 0.1[a]	38.4 ± 0.2[a]

Naloxone (1.5 mg kg^{-1}, s.c.) and naltrindole (25.0 µg, i.c.v.) were administered 20 and 30 min before the temperature measurements, respectively, whereas β-funaltrexamine was administered 16 h before the measurements. Results are shown as mean ± S.E.M. based on four to five animals per group.

[a] $P > 0.05$, Student's *t*-test.

Pretreatment with the selective μ-opioid receptor antagonist, β-funaltrexamine (5.0 μg, i.c.v.) resulted in effects similar to naloxone. Thus, deltorphin II-produced hypothemia was potentiated and hyperthermia antagonized (Fig. 3, bottom). Naltrindole or β-funaltrexamine by themselves had no effects on body temperature (Table 1).

3.4. Effects of the selective κ-opioid receptor antagonist nor-binaltorphimine on deltorphin II-induced body temperature changes

Pretreatment with the selective κ-opioid receptor antagonist nor-binaltorphimine (20.0 μg, i.c.v.) had no effects on the temperature changes produced by deltorphin II (Table 2).

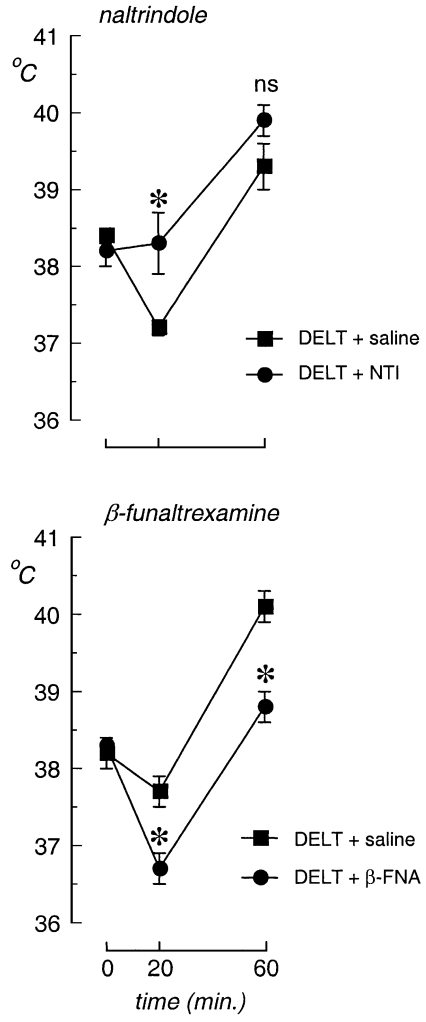

Fig. 3. Effects of naltrindole and β-funaltrexamine on deltorphin II-induced temperature changes in rats. Naltrindole (NTI) (25.0 μg, i.c.v.) (top) and β-funaltrexamine (β-FNA) (5.0 μg, i.c.v.) (bottom) were injected 10 min and 16 h prior to administration of deltorphin II (DELT) (100.0 μg, i.c.v), respectively, and body temperature was recorded 20 and 60 min after the deltorphin II injections. Results are shown as mean ± S.E.M. based on four to six animals per group. Student's *t*-test was used to determine statistical significance and differences were considered statistically significant at $P < 0.05$, as indicated by the asterisks in the figure.

Table 2
Effects of nor-binaltorphimine on deltorphin II-induced core temperature changes in rats

Treatment	Pretest (°C)	20 min (°C)	60 min (°C)
Deltorphin II 100.0 μg	38.2 ± 0.1	37.3 ± 0.3	39.3 ± 0.3
Nor-binaltorphimine 20.0 μg + deltorphin II 100.0 μg	38.6 ± 0.1[a]	37.6 ± 0.4[a]	39.2 ± 0.2[a]

Nor-binaltorphimine (20.0 μg, i.c.v.) was injected 40 min before deltorphin II (100.0 μg, i.c.v.) injection. The core temperature was measured 20 and 60 min after deltorphin II injection. Results are shown as mean ± S.E.M. based on four to six animals per group.

[a] $P > 0.05$, Student's *t*-test.

4. Discussion

The present study provides further support for a role of δ-opioid receptors in thermoregulation in rats. Thus, even though some research groups ascribe a minor, or no, role of δ-opioid receptors in thermoregulation, the present results are in agreement with previous results that indeed indicate a role of this opioid receptors in thermoregulation (see Introduction). Such conflicting results between research groups may reflect differences in binding-site specificity and efficacy among δ-opioid receptor agonists used. In this context, deltorphin II is believed to be among the most efficacious and selective δ-opioid receptor agonists available. Thus, deltorphin II displays low nanomolar affinity for δ-opioid receptors, whereas the affinity for μ- or κ-opioid receptors is at micromolar concentrations (e.g., Nevin et al., 1994; Fowler and Fraser, 1994). Altogether, this favors deltorphin II over for example [D-Pen^2, D-Pen^5]enkephalin (DPDPE) in functional studies.

In this study we initially found that deltorphin II produced biphasic effects on core temperature, in which hypothermia was followed by hyperthermia. The treatment with the selective δ-opioid receptor antagonist naltrindole blocked the hypothermia, whereas the hyperthermia was unaffected, or slightly potentiated. The non-selective opioid receptor antagonist naloxone, on the other hand, potentiated hypothermia, and antagonized hyperthermia, produced by a high dose (100.0 μg) of deltorphin II. Also, hypothermia produced by the low dose (25.0 μg) of deltorphin II, which lacked hyperthermic effects, was potentiated by naloxone. These effects are in agreement with a negative interaction between δ-opioid receptors and an additional opioid receptor. In support of a specific role of μ-opioid receptors in such effects, the selective μ-opioid receptor antagonist β-funaltrexamine potentiated hypothermia and blocked hyperthermia of deltorphin II in a similar fashion as naloxone. Altogether, these effects strongly support the notion of a functional antagonism between δ- and μ-opioid receptors underlying the biphasic temperature effects of deltorphin II.

κ-Opioid receptors are not likely relevant here, as activation of this opioid receptor results in hypothermia (Spencer et al., 1988; Chen et al., 1995), and, as shown here, hypothermia produced by deltorphin II is related to the activation of δ-opioid receptors. However, to exclude a possible contribution of κ-opioid receptors in the biphasic effects observed here, we examined the effects of the selective κ-opioid receptor antagonist nor-binaltorphimine in a dose that previously has shown to effectively block hypothermia caused by κ-opioid receptor agonists (Handler et al., 1992), on deltorphin II-induced temperature changes. As expected, this experiment found no evidence for an involvement of this opioid receptor type in the temperature effects observed here.

There is considerable interest in developing agonists for clinical uses at opioid receptors other than μ-opioid receptors. This is because undesirable effects, including respiratory depression and physical dependence, are associated with the use of agonists at μ-opioid receptors (e.g., Shook et al., 1990; van Ree et al., 1999). Deltorphins, including deltorphin II, are interesting in this contex, as animal experiments have supported beneficial properties, like stimulatory effects on respiration, minimal abuse liability and analgesia, of these compounds (Cheng et al., 1993; Cowan et al., 1988; Rapaka and Porreca, 1991; Lazarus et al., 1999). Generally, such effects of deltorphin analogs are attributed to the activation of δ-opioid receptors. However, by using temperature measurements, results from this study suggest that deltorphin II interacts with μ-opioid receptors, in addition to its actions at δ-opioid receptors. Thus, it cannot be excluded that the potential analgesic effects of deltorphin II are, at least in part, attributed to the activation of μ-opioid receptors. Furthermore, the activation of δ-opioid receptors by compounds such as deltorphin II may contribute to the improvement of the side effect profile by counteracting the adverse effects of μ-opioid receptor activation on, for example, respiration.

In conclusion, the present study demonstrates biphasic effects of deltorphin II on core temperature in rats, with hypothermia followed by hyperthermia. These effects of deltorphin II were most readily explained by a negative functional interaction between μ- and δ-opioid receptors.

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