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Deltorphin II enhances extracellular levels of dopamine in the nucleus accumbens via opioid receptor-independent mechanisms

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Abstract

The effects of the δ_2-opioid receptor agonist, deltorphin II, on extracellular levels of dopamine in the rat nucleus accumbens were investigated in awake animals by in vivo brain microdialysis. In agreement with previous studies, perfusion of deltorphin II (50.0 nmol) into the nucleus accumbens significantly increased the extracellular amount of accumbal dopamine. The effect of deltorphin II (50.0 nmol) was not altered by the selective δ_2-opioid receptor antagonist, naltriben (1.5 nmol), which alone did not significantly affect the basal levels of dopamine. Selective antagonists of neither the μ-opioid receptors, D-Phe–Cys–Tyr-D-Trp–Orn–Thr–Phe–Thr–NH_2 (0.15 nmol), nor the δ_1-opioid receptors, (*E*)-7-benzylidenenaltrexone tartrate (0.15 nmol), failed to significantly alter the effects of deltorphin II. The nonselective opioid receptor antagonist, naloxone (0.75 and 1.5 nmol), which alone did not significantly affect the basal levels of dopamine, also failed to affect the effects of deltorphin II. Moreover, under the condition that the sodium channel blocker, tetrodotoxin (0.1 nmol), was perfused continuously into the nucleus accumbens, the deltorphin II-induced increase in extracellular levels of dopamine was reduced by 72%. These results suggest that deltorphin II enhances extracellular dopamine in the nucleus accumbens via opioid receptor-independent, tetrodotoxin-sensitive mechanisms.

Keywords: Deltorphin II; Extracellular dopamine; Opioid receptor; Tetrodotoxin; Nucleus accumbens

1. Introduction

Opioid receptors (i.e., μ-, δ- and κ-opioid receptors) are reported to regulate mesolimbic dopaminergic neuronal activities. For example, activation of μ-opioid receptors (Broekkamp et al., 1979; Latimer et al., 1987; Di Chiara and Imperato, 1988a,b; Spanagel et al., 1990, 1992; Leone et al., 1991; Devine et al., 1993; Pontieri et al., 1995; Yoshida et al., 1999) and δ-opioid receptors (Longoni et al., 1991; Pentney and Gratton, 1991; Yoshida et al., 1999) respectively enhances extracellular dopamine concentration in the nucleus accumbens, whereas activation of κ-opioid receptors decreases dopamine concentration in the nucleus accumbens (Spanagel et al., 1992). Involved receptors are thought to be located in the ventral tegmental area (for μ-opioid receptors) and the nucleus accumbens (for μ-, δ- and κ-opioid receptors). Recently, we have provided evidence that local application into the nucleus accumbens of the δ_2-opioid receptor agonist, deltorphin II, enhances extracellular dopamine concentration in this nucleus (Longoni et al., 1991; Yoshida et al., 1999); however, the receptor selectivity and the nature of the response to deltorphin II were not established.

In the present study, we therefore investigated initially the receptor specificity of the neurochemical effects of deltorphin II in the nucleus accumbens by using selective antagonists of μ-, δ_1- and δ_2-opioid receptors, and the nonselective opioid receptor antagonist, naloxone. Next, we analysed the nature of deltorphin II-induced increase in extracellular

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concentration of dopamine, as far as it concerned the voltage dependency, by using the Na^+ channel blocker, tetrodotoxin.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (250–300 g body weight; NRC Haruna, Japan) were housed in cages (27 × 45 × 20 cm) that were kept at constant room temperature (23 ± 2 °C) and relative humidity (55 ± 5%) under a 12 h light–dark cycle (lights on at 07:00 h), with free access to food and water.

2.2. Surgery

The rats were anaesthetised with sodium pentobarbitone (50 mg/kg, i.p.). The animals were placed in a stereotactic apparatus, and a guide cannula was implanted just above the left nucleus accumbens [anteroposterior (AP) 10.6 mm, mediolateral (ML) 1.5 mm, dorsoventral (DV) 4.0 mm from interaural line; Paxinos and Watson, 1998]. To avoid the ventricular system, the cannulas directed at the nucleus accumbens were angled 18° from the midsagittal plane. Damage to the target site was minimised by implanting the tips of the guide cannulas 2.0 mm above the desired site. After completing surgery, the rats were allowed to recover for a minimum of 5 days before the experiments were carried out, the guide cannulas being kept patent by stainless steel inserts to prevent occlusion. The animals were used only once.

The experiments were performed in accordance with Institutional Guidelines in the Care and Use of Experimental Animals. All efforts were made to minimise animal suffering and to reduce the number of animals used.

2.3. Dialysis and neurochemical measurements

The commercially available I-shaped removable-type dialysis probe (2 mm length regenerate cellulose membrane, 0.25 mm O.D., 50,000 molecular weight "cutoff", EICOM A-I-8-02 type, Kyoto, Japan) was used. The experiment started with the removal of the stylet from the guide cannula and the insertion of the dialysis probe of which just the dialysis tubing protruded from the tip. The probe was secured to the guide cannula by a screw. The rat was then placed in a plexiglass box (30 × 30 cm), and the inlet and outlet tubes were connected to a swivel located on a counterbalanced beam to minimise discomfort to the rat. The probe was perfused at a rate of 2.0 μl/min with modified Ringer solution (NaCl 147 mM, KCl 4 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 1.1 mM; pH 7.4) and the outflow connected by Teflon tubing to a high-performance liquid chromatography system (EICOM).

Dopamine was separated on an Eicompak CA-5ODS column (particle size, 5 m, 4.6 × 150 mm, EICOM) using phosphate buffer (0.1 M) containing octane-sulfonic acid (3.2 mM), EDTA (1.5 mM) and methanol (20%, pH 6.0) as the mobile phase at a flow rate of 1.0 ml/min. The compounds were quantified by electrochemical detection using a glassy carbon working electrode set at +400 mV against a silver–silver chloride reference electrode (EICOM), giving a detection limit for dopamine of about 0.5 pg per sample. The probes had an in vitro recovery of approximately 12% for dopamine, but the reported concentrations were not adjusted for recovery in vivo because these estimations are inaccurate (Benveniste et al., 1989; Lindefors et al., 1989). Previous experiments in which we have used the same technique and procedure, have shown that the dopamine efflux is more or less stabilised 4 h after probe insertion, and that the release seen at that time is largely dependent on neuronal release as the release is tetrodotoxin-sensitive and Ca^{2+}-dependent (Takada et al., 1993; Tomiyama et al., 1993, 1995; Murai et al., 1994). Perfusate samples were taken every 25 min for quantification of dopamine. Drugs were administered intracerebrally through the dialysis probe, at least 4 h after the probe insertion; baseline levels of dopamine were the mean of the last three samples before the drug administration.

2.4. Drugs

The drugs used were the δ_2-opioid receptor agonist deltorphin II ([D-Ala^2,Glu^4]-deltorphin; Peninsula Laboratories, CA, USA) (Kreil et al., 1989; Erspamer et al., 1989), the δ_2-opioid receptor antagonist naltriben methanesulfonate hydrate (NTB; synthesised by H.N.) (Portoghese, 1991), the μ-opioid receptor antagonist CTOP (D-Phe–Cys–Tyr-D-Trp–Orn–Thr–Phe–Thr–NH_2; Research Biochemicals International, MA, USA) (Pelton et al., 1986; Kramer et al., 1989), the δ_1-opioid receptor antagonist (*E*)-7-benzylidenenaltrexone tartrate [BNTX; synthesised by H.N.] (Portoghese, 1991), the nonselective opioid receptor antagonist naloxone (naloxone HCl; Sankyo, Japan) (Kosterlitz, 1985) and the Na^+ channel blocker tetrodotoxin (Sigma, USA). All intracerebrally administered drugs were dissolved in the modified Ringer solution that was used for the perfusion. The agonists were infused via dialysis membrane for 25 min, whereas the antagonists were similarly infused for 50 min (starting 25 min before agonists infusion).

The doses administered via the microdialysis tube were based on the outcome of the study of Yoshida et al. (1999), who showed that all drugs selected were neurochemically effective. The reported doses were the amount (nmol) of opiates in 25-min perfusion liquid (50 μl).

2.5. Histology

At the end of the experiment, the rat was deeply anaesthetised with sodium pentobarbitone (80 mg/kg, i.p.) and perfused transcardially with 10% formaldehyde solu-

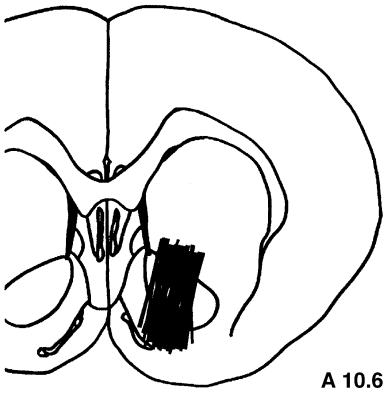

Fig. 1. Schematic illustration showing location of the probe in the nucleus accumbens. The plane is taken from the atlas of Paxinos and Watson (1998); an approximate coordinate indicated is in millimeters anterior to the interaural line.

tion. The brain was removed, sectioned (50 μm) and stained with Cresyl violet to permit probe location.

2.6. Statistical analysis

All values were expressed as a percentage of baseline levels. The comparison was performed using two-way analysis of variance (ANOVA) for repeated measures, followed by a post hoc Newman–Keuls test where appropriate. In addition, a Student's *t*-test was used to analyse effects of tetrodotoxin on deltorphin II-induced dopamine levels. Statistical significance was considered when $P<0.05$.

3. Results

3.1. Histology

Placements of the dialysis probes in the nucleus accumbens are given in Fig. 1.

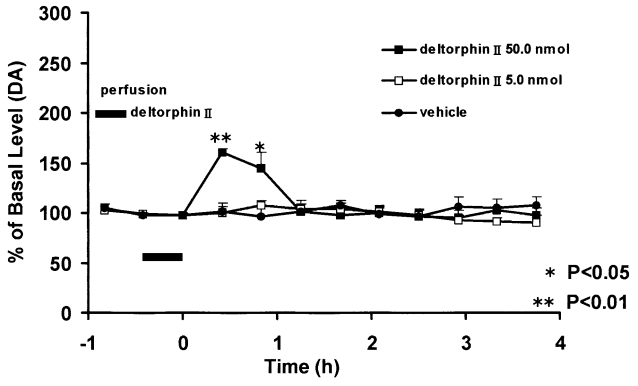

Fig. 2. Effects of infusion of vehicle (●), 5.0 nmol deltorphin II (□) and 50.0 nmol deltorphin II (■) into the nucleus accumbens on the concentrations of dopamine (DA) in dialysates of the nucleus accumbens. The data are expressed as the mean of change in 25-min observation periods after treatment ($n=6$ in each group). Vertical bars indicate S.E.M. *$P<0.05$, **$P<0.01$ vs. vehicle control group (Newman–Keuls test).

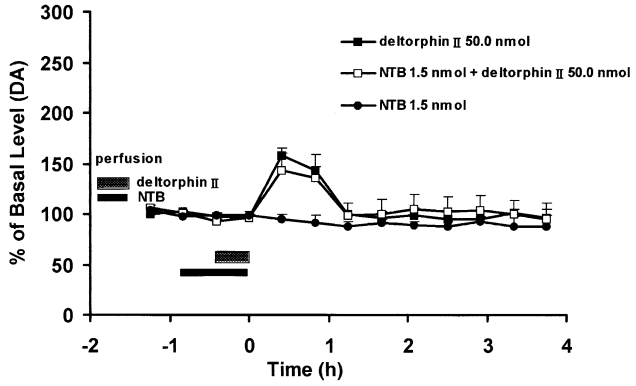

Fig. 3. Effects of NTB (1.5 nmol) on deltorphin II (50.0 nmol)-induced increase in dopamine (DA) concentration in the nucleus accumbens. Deltorphin II alone (■); NTB with deltorphin II (□); NTB alone (●). The data are expressed as the mean of change in 25-min observation periods after treatment ($n=6$–9). Vertical bars indicate S.E.M. Control responses to deltorphin II alone were the same as that shown in Fig. 2.

3.2. Effects of deltorphin II infusion into the nucleus accumbens on dopamine release in the nucleus accumbens

The concentration of dopamine in dialysates of the nucleus accumbens reached a stable baseline value of 3.94 ± 0.55 pg/25 min (mean S.E.M., $n=18$) approximately 4 h after probe insertion, and was not affected over the ensuing 4 h (vehicle; $n=6$). A 25-min infusion of deltorphin II (50.0 nmol, $n=6$) into the nucleus accumbens significantly increased extracellular amount of accumbal dopamine [$F(2,180)=5.33$, $P<0.01$], while a smaller concentration (5.0 nmol, $n=6$) did not affect the amount of dopamine. The peak effect of deltorphin II (50.0 nmol) occurred 25 min after administration being 160% of control ($P<0.01$ vs. vehicle, Newman–Keuls test; Fig. 2). Under the chosen measurement conditions, we found that the obtained dopamine peak was not interfered with deltorphin II itself.

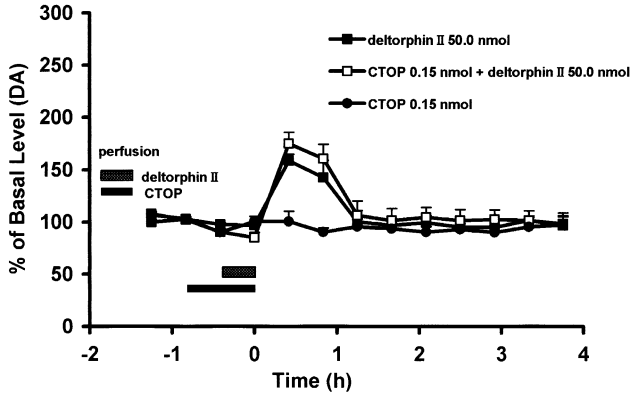

Fig. 4. Effects of CTOP (0.15 nmol) on deltorphin II (50.0 nmol)-induced increase in dopamine (DA) concentration in the nucleus accumbens. Deltorphin II alone (■); CTOP with deltorphin II (□); CTOP alone (●). The data are expressed as the mean of change in 25-min observation periods after treatment ($n=6$ in each group). Vertical bars indicate S.E.M. Control responses to deltorphin II alone were the same as that shown in Fig. 2.

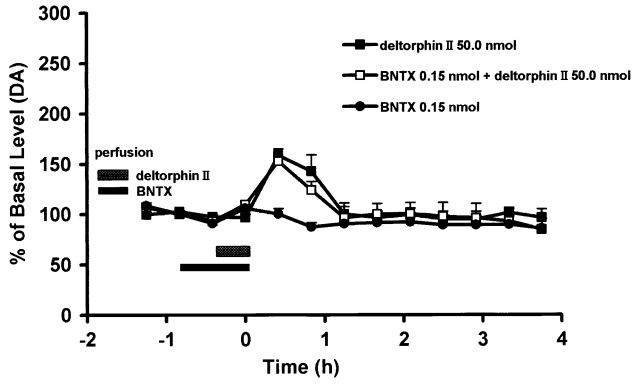

Fig. 5. Effects of BNTX (1.5 nmol) on deltorphin II (50.0 nmol)-induced increase in dopamine (DA) concentration in the nucleus accumbens. Deltorphin II alone (■); BNTX with deltorphin II (□); BNTX alone (●). The data are expressed as the mean of change in 25-min observation periods after treatment ($n=6$ in each group). Vertical bars indicate S.E.M. Control responses to deltorphin II alone were the same as that shown in Fig. 2.

3.3. Effects of NTB, CTOP, BNTX and naloxone on the deltorphin II-induced dopamine increase in the nucleus accumbens

Perfusion of the nucleus accumbens with the δ_2-opioid receptor antagonist, NTB (1.5 nmol; $n=6$), which alone did not significantly affect the basal levels of dopamine, did not alter the effect of accumbal deltorphin II (50.0 nmol; $n=6$) on the extracellular amount of accumbal dopamine [$F(1,130)=0.00$, $P=0.967$; Fig. 3]. Similarly, neither the selective antagonist of the μ-opioid receptors, CTOP (0.15 nmol; $n=6$) nor the selective antagonist of the δ_1-opioid receptors, BNTX (0.15 nmol; $n=6$), significantly changed the effects of deltorphin II [CTOP: $F(1,130)=0.90$, $P=0.344$; BNTX: $F(1,130)=0.34$, $P=0.561$; Figs. 4 and 5]. The nonselective opioid receptor antagonist, naloxone [0.75 nmol ($n=6$) and 1.5 nmol ($n=6$)], which alone did not significantly affect the basal levels of dopamine, also failed to alter the effects of deltorphin II [0.75 nmol: $F(1,130)=0.03$, $P=0.872$; 1.5 nmol: $F(1,130)=0.00$, $P=0.968$; Fig. 6].

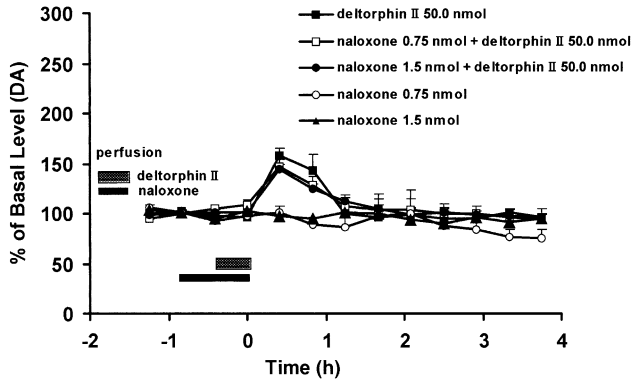

Fig. 6. Effects of naloxone on deltorphin II (50.0 nmol)-induced increase in dopamine (DA) concentration in the nucleus accumbens. Deltorphin II alone (■); 0.75 nmol naloxone with deltorphin II (□); 1.5 nmol naloxone with deltorphin II (●); 0.75 nmol naloxone alone (○); 1.5 nmol naloxone alone (▲). The data are expressed as the mean of change in 25-min observation periods after treatment ($n=6$ in each group). Vertical bars indicate S.E.M. Control responses to deltorphin II alone were the same as that shown in Fig. 2.

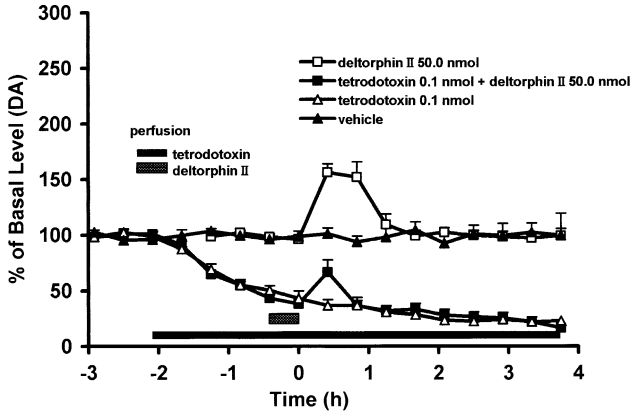

Fig. 7. Effects of tetrodotoxin (0.1 nmol) perfusion on dialysate dopamine levels and the deltorphin II-induced dopamine increase in the nucleus accumbens. Vehicle (▲); deltorphin II alone (□); tetrodotoxin alone (△); tetrodotoxin with deltorphin II (■). The data are expressed as the mean of change in 25-min observation periods after treatment ($n=6$ in each group). Vertical bars indicate S.E.M. Control responses to deltorphin II alone were the same as that shown in Fig. 2.

3.4. Effects of tetrodotoxin perfusion on dialysate dopamine levels and the deltorphin II-induced dopamine increase in the nucleus accumbens

Tetrodotoxin (0.1 nmol) perfused for 2 h via the dialysis probe significantly reduced extracellular levels of dopamine to 1.69 ± 0.15 pg/25 min (approximately 60% reduction) in the nucleus accumbens, after which the levels gradually decreased over the ensuing 4 h by approximately 80% [$F(1,202)=204.56$, $P<0.001$, $n=6$] (Fig. 7). Additional perfusion of deltorphin II (50.0 nmol; $n=6$) increased levels of dopamine at 25 min after the start of deltorphin II perfusion, although the effects were significantly smaller (approximately 72% reduction; $P<0.01$, Student's t-test) than those seen in the controls (Fig. 7).

4. Discussion

The present study shows that intraaccumbens administration of the δ_2-opioid receptor agonist, deltorphin II, via microdialysis tube significantly increased the extracellular level of dopamine in the nucleus accumbens (Fig. 2). This finding is fully consistent with previously published studies showing that opiates that activate δ_2-opioid receptors enhance the release of dopamine in the nucleus accumbens (Longoni et al., 1991; Pentney and Gratton, 1991; Yoshida et al., 1999). However, it was unknown whether the

deltorphin II enhanced dopamine release via stimulation of δ_2-opioid receptors located in the nucleus accumbens because receptor specificity was not examined in these studies. The present study analysed the receptor specificity by using the selective δ_2-opioid receptor antagonist NTB. However, the deltorphin II (50.0 nmol)-induced elevation of extracellular dopamine could not be antagonised by an otherwise effective dose of NTB (Thorat and Hammond, 1997; Fig. 3).

Evidence has been provided that there are functional interactions between δ- and μ-opioid receptors (Vaught and Takemori, 1979; Rothman and Westfall, 1982; Lee et al., 1993; O'Neill et al., 1997). Given the complex interactions between δ- and μ-opioid receptors, it might be possible that μ- and δ_1-opioid receptors are involved in the deltorphin II-induced elevation of extracellular dopamine in the nucleus accumbens. Therefore, we utilised CTOP and BNTX, selective antagonists of μ- and δ_1-opioid receptors, respectively, in order to examine this possibility. The results show that neither CTOP (0.15 nmol) nor BNTX (0.15 nmol) infused into the nucleus accumbens, which alone did not affect accumbal dopamine, altered the effects of deltorphin II (Figs. 4 and 5); the doses used have previously been found to be effective in antagonising the μ- and δ_1-opioid receptors (Yoshida et al., 1999).

Because Longoni et al. (1991) have reported that deltorphin II-induced dopamine increase in the nucleus accumbens is inhibited by naloxone that acts at all opioid receptor subtypes, we next examined the effects of naloxone on deltorphin II-induced dopamine increase in the nucleus accumbens. The results show that otherwise effective doses of naloxone (0.75 and 1.5 nmol; Kischka et al., 1993; Stiller et al., 1996) locally administered through dialysis membrane to the nucleus accumbens failed to antagonise the effects of deltorphin II (Fig. 7). Because a number of factors such as type of dialysis probe (transversal type), route of naloxone administration (s.c.) and postoperation time of the experiment (24 h) differed from those of the present study, it is difficult to compare that study with the present one. Given the present data, it appears that the deltorphin II-induced increase in accumbal extracellular dopamine is not mediated via activation of opioid receptors. Because this does not comply with the generally accepted notion that deltorphin II primarily act as a δ_2-opioid receptor preferring agonist (Kreil et al., 1989; Erspamer et al., 1989), one might suggest that the doses of the various opioid receptor antagonists were too low in order to antagonise the effects of deltorphin II. However, this possibility is highly unlikely, because the chosen doses have been found to be highly effective in antagonising effects of their corresponding opioid receptors in comparable studies (Yoshida et al., 1999). Alternately, it is theoretically possible that deltorphin II enhances extracellular levels of dopamine in a way that is independent of neural activity (cf. Fairbrother et al., 1990). For that purpose, we examined the sensitivity of the effects of deltorphin II to the Na^+ channel blocker, tetrodotoxin. The results show that a large amount (72%) of the deltorphin II-induced increase of accumbal extracellular dopamine was tetrodotoxin-sensitive, indicating that the latter possibility has to be excluded. Accordingly, the nature of the receptors that mediate the effects of deltorphin II remains to be elucidated. On the other hand, it becomes interesting to compare the noted effects of deltorphin II with those of other δ_2-opioid receptor preferring agonists such as [D-Ser^2]Leu-enkephalin-Thr^6 to see whether δ_2-opioid receptors play indeed no role at all in this respect.

In conclusion, the present study suggests that deltorphin II enhances extracellular dopamine level in the nucleus accumbens via opioid receptor-independent mechanisms. Moreover, it is shown that the elevated extracellular dopamine is largely dependent on neuronal release, because 72% of the dopamine is tetrodotoxin-sensitive.

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