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The role of δ-opioid receptor subtypes in neuropathic pain

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Abstract

A large body of evidence suggests an important role of δ-opioid receptor agonists in antinociception at the level of the spinal cord. Our study was undertaken to analyse the spinal antinociceptive and antiallodynic effects of δ_1- and δ_2-opioid receptor agonists and antagonist after their acute and chronic intrathecal administration in a neuropathic pain model in the rat. In rats with a crushed sciatic nerve, the δ_1-opioid receptor agonist [D-Pen^2, D-Pen^5]enkephalin (DPDPE, 5–25 μg i.t.) and the δ_2-opioid receptor agonist deltorphin II (1.5–25 μg i.t.) dose dependently antagonized the cold-water allodynia which developed after sciatic nerve injury. These effects of DPDPE were antagonized by 7-benzylidenenaltrexon (BNTX, 1 μg i.t.) while the effects of deltorphin II were antagonized by 5′naltrindole izotiocyanate (5′NTII, 25 μg i.t.). Both agonists had a dose-dependent, statistically significant effect on the tail-flick latency in two tests, with focused light and cold water. Chronic administration of DPDPE (25 μg i.t.) and deltorphin II (15 μg i.t.) resulted in significant prolongation of the reaction time determined on days 2, 4 and 6 post-injury. In conclusion, our results show an antiallodynic and antinociceptive action of DPDPE and deltorphin II at the spinal cord level, which suggests that both δ-opioid receptor subtypes play a similar role in neuropathic pain. This indicates that not only δ_1- but also δ_2-opioid receptor agonists can be regarded as potential drugs for the therapy of neuropathic pain.

Keywords: Neuropathic pain; δ-Opioid receptor subtypes; Allodynia; Hyperalgesia

1. Introduction

A large body of evidence suggests an important role of δ-opioid receptor agonists in antinociception at the level of the spinal cord. (Stewart and Hammond, 1993; Misicka et al., 1991; Mattia et al., 1992). Agonists of this receptor are very promising in pain therapy due to their lower potential for being abused and fewer undesired effects in comparison with μ-opioid receptor agonists. The administration of δ-opioid receptor agonists in combination with μ-opioid receptor agonists enhances their action on one hand and can delay the development of morphine tolerance and dependence, without loss of their antinociceptive properties, on the other (Jiang et al., 1990). Therefore, an intensive search for new analgesics has been carried out among the compounds belonging to this group (Mayfield et al., 1996).

Pharmacological studies have indicated the existence of δ-opioid receptor subtypes which can participate in several physiological functions. The δ_1-opioid receptor is selectively activated by [D-Pen^2, D-Pen^5]enkephalin (DPDPE) and blocked by 7-benzylidenenaltrexon (BNTX), while the δ_2-opioid receptor is selectively stimulated by deltorphin II and inhibited by naltriben methanesulfonate and 5′naltrindole izothiocyanate (NTII) (Vanderah et al., 1994; Shaw et al., 1982; Cowan et al., 1985; Lai et al., 1994). The results of experiments with the application of antisense oligonucleotides suggest that the cloned δ-opioid receptor is the δ_2-opioid receptor, according to the pharmacological classification (Lai et al., 1994), since the administration of antisense oligonucleotide for the δ-opioid receptor to the lateral brain ventricle inhibited the antinociceptive action of deltorphin II but did not influence the effects of DPDPE (Lai et al., 1994; Pasternak and Standifer, 1995). The existence of δ-opioid receptor subtypes is substantiated further by the fact that the agonists DPDPE and deltorphin II do not evoke cross-tolerance. Furthermore, the selective δ-opioid receptor antagonist NTII antagonizes DPDPE- and deltorphin II-induced analgesic effects in different ways (Mattia et al., 1992). Both δ-opioid receptor subtypes can also be activated by endogenous opioids, i.e. enkephalins and β-endorphin, and it is known that both δ-opioid

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receptor subtypes participate in antinociception (Mattia et al., 1992; Vanderah et al., 1994; Bhargava et al., 1996). Pharmacological data have revealed that activation of δ-opioid receptor subtypes differently influence nociception in some cases. For example, stimulation of δ_2-opioid receptors potentiates opioid analgesia in the hot-plate test in mice, while activation of δ_1-opioid receptors decreases it (Noble et al., 1996) and cold-water swim stress-induced antinociception in non-diabetic mice is mediated by δ_2-opioid receptors, whereas this antinociception in diabetic mice is mediated by both δ_1- and δ_2-opioid receptors (Kamei et al., 1994).

The effects of agonists and antagonists of δ-opioid receptor subtypes have not been studied in a neuropathic pain model, yet in this model there is a 40–60% loss of spinal δ-opioid receptors (Besse et al., 1990). Therefore, we decided to determine to what extent δ-opioid receptor subtypes are relevant to antiallodynic and antinociceptive reactions in a neuropathic pain model. For this purpose, we investigated the effects of specific δ_1- and δ_2-opioid receptor agonists and antagonists in a neuropathic pain model after their acute and chronic administration.

2. Materials and methods

2.1. Animals

Male Wistar rats (200–350 g) were housed in individual cages with sawdust bedding, under a standard 12-h/12-h light/dark cycle (lights on at 08:00 h) with food and water available ad libitum. The experiments were approved by the Institute's Animal Research Committee and were carried out according to the National Institute of Health Guide for the Care and Use of Laboratory Animals.

2.2. Surgical preparation

The rats were chronically implanted with intrathecal (i.t.) catheters under pentobarbital anaesthesia. They were placed on the David Kopf stereotaxic table, and an incision was made in the atlanto-occipital membrane. A catheter (PE 10, Clay Adams, Sparks, MD) was carefully introduced into the subarachnoid space at the rostral level of the spinal cord lumbar enlargement according to Yaksh and Rudy (1976). Intrathecal injection studies were carried out 7–12 days after surgery. Drugs were dissolved in sterile water and were injected in a volume of 5 μl, followed by an injection of 10 μl of sterile water (aqua pro-injectione) to flush the catheter. Control animals were injected i.t. with sterile water and tested according to the same time schedule as described below for the experimental groups. After completion of the experiment, the animals were killed with an overdose of pentobarbital.

2.3. Sciatic nerve injury

Sciatic nerve injury was performed under pentobarbital anaesthesia (i.p.) 5–10 days after intrathecal catheter implantation. The right sciatic nerve was crushed for 30 s using haemostatic forceps at a position 27 mm distal to the sciatic notch. The lesioning procedure has been described in detail by De Koning et al. (1986). All animals with injury to the sciatic nerve developed cold allodynia 2 days after surgery.

2.4. Drugs

DPDPE [D-Pen^2, D-Pen^5]enkephalin (δ_1-opioid receptor agonist; Research Biochemicals International, RBI, Nattic, MA, USA) and [D-Ala^2]deltorphin II, (H-Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH_2, δ_2-opioid receptor agonist; Geza Toth-Hungary) were used. BNTX 7-benzylidenenaltrexon, δ_1-opioid receptor antagonist was purchased from TOCRIS COOKSON (Northpoint, UK), and 5′NTII, 5′naltrindole izotiocyanate δ_2-opioid receptor antagonist was supplied by RBI.

2.5. Administration

2.5.1. Acute

The drugs were administered i.t. 2 days after injury to the sciatic nerve. The antagonists were injected i.t. 10 min

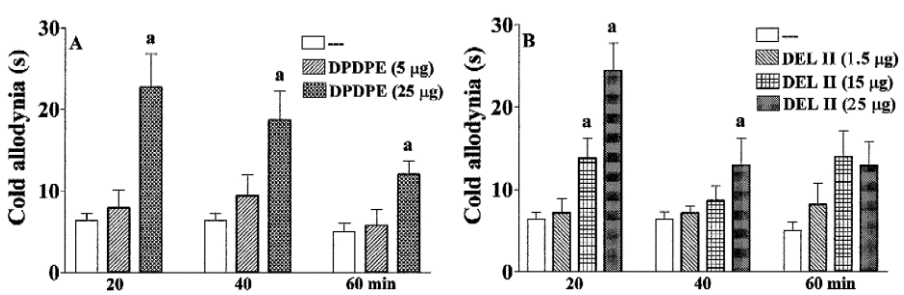

Fig. 1. The effect of (A) DPDPE (5, 25 μg i.t.) and (B) deltorphin II (DEL II; 1.5, 15, 25 μg i.t.) administration on day 2 after injury (sciatic nerve crush) on allodynia. The data denote the latency (s) in paw withdrawal and are shown as means ± S.E.M. for 12 animals per group. [a] $P < 0.05$ as compared with the group of animals subjected to sciatic nerve crush and injected with sterile water (ANOVA, Bonferroni test).

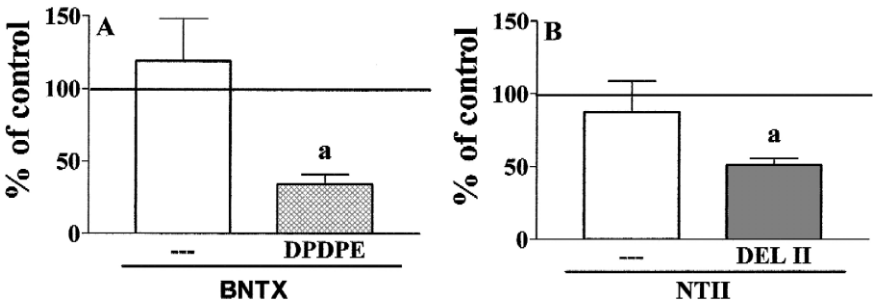

Fig. 2. (A) The influence of BNTX (1 μg i.t.) on the effects of DPDPE, administered on day 2 after injury (sciatic nerve crush), on allodynia. The reaction in the control group, i.e. the animals injected with sterile water and subjected to sciatic nerve injury (6.4 ± 0.94 s), and the reaction of the group administered an agonist, DPDPE at 25 μg (22.66 ± 4.18 s), were considered 100%. (B) The influence of NTII (25 μg i.t.) on the effect of DEL II, administered on day 2 post-injury (sciatic nerve crush), on allodynia. Reaction in the control group, i.e. the animals subjected to the sciatic nerve injury (6.4 ± 0.94 s), and the reaction of the group administered an agonist DEL II at 25 μg (24.42 ± 3.33 s) were considered 100%. The data denote the latency (s) in paw withdrawal and are presented as percent changes observed after antagonist administration. Each group comprised 12 animals. [a] $P < 0.05$ as compared with control group injected with the agonist (ANOVA, Bonferroni test).

after an agonist or saline, and the effects were measured 20 min after i.t. administration of the antagonist.

2.5.2. Chronic

The drugs were administered i.t., and the first injection was given 24 h before crush of the sciatic nerve and then the drugs were given every day for 10 days.

2.6. Behavioural tests

Three behavioural tests were used to evaluate antinociceptive and antiallodynic effects.

2.6.1. The tail-flick test

The tail-flick test was carried out using an Analgesia Meter (mod 33, IITC, Landing, NJ). A rat was gently restrained by hand, and radiant heat was directed to the animal's tail. The cut-off time was 9 s. Tail-flick measurements were taken 35 min (acute) and 15 min (chronic) after i.t. injection. Three measurements were taken at 15-s intervals and their mean was used for calculations.

2.6.2. The cold-water tail-flick test

The latency to withdrawal of the tail from a water bath maintained at 0–2°C was determined. Cold-water tail-flick

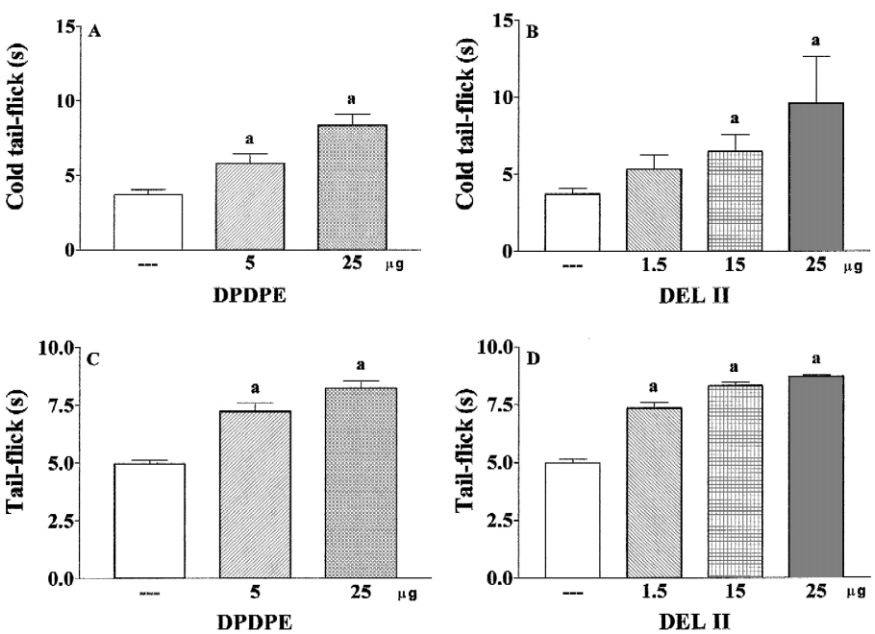

Fig. 3. The effect of (A and C) DPDPE (5; 25 μg i.t.) and (B and D) deltorphin II (DEL II; 1.5, 15, 25 μg i.t.), administered 2 days after sciatic nerve crush, on performance in the cold-water tail-flick and tail-flick tests. The data denote the latency (s) in tail flick and are presented as means ± S.E.M for 12 rats. [a] $P < 0.05$ as compared with the group of animals subjected to sciatic nerve crush and injected with sterile water (ANOVA, Bonferroni test).

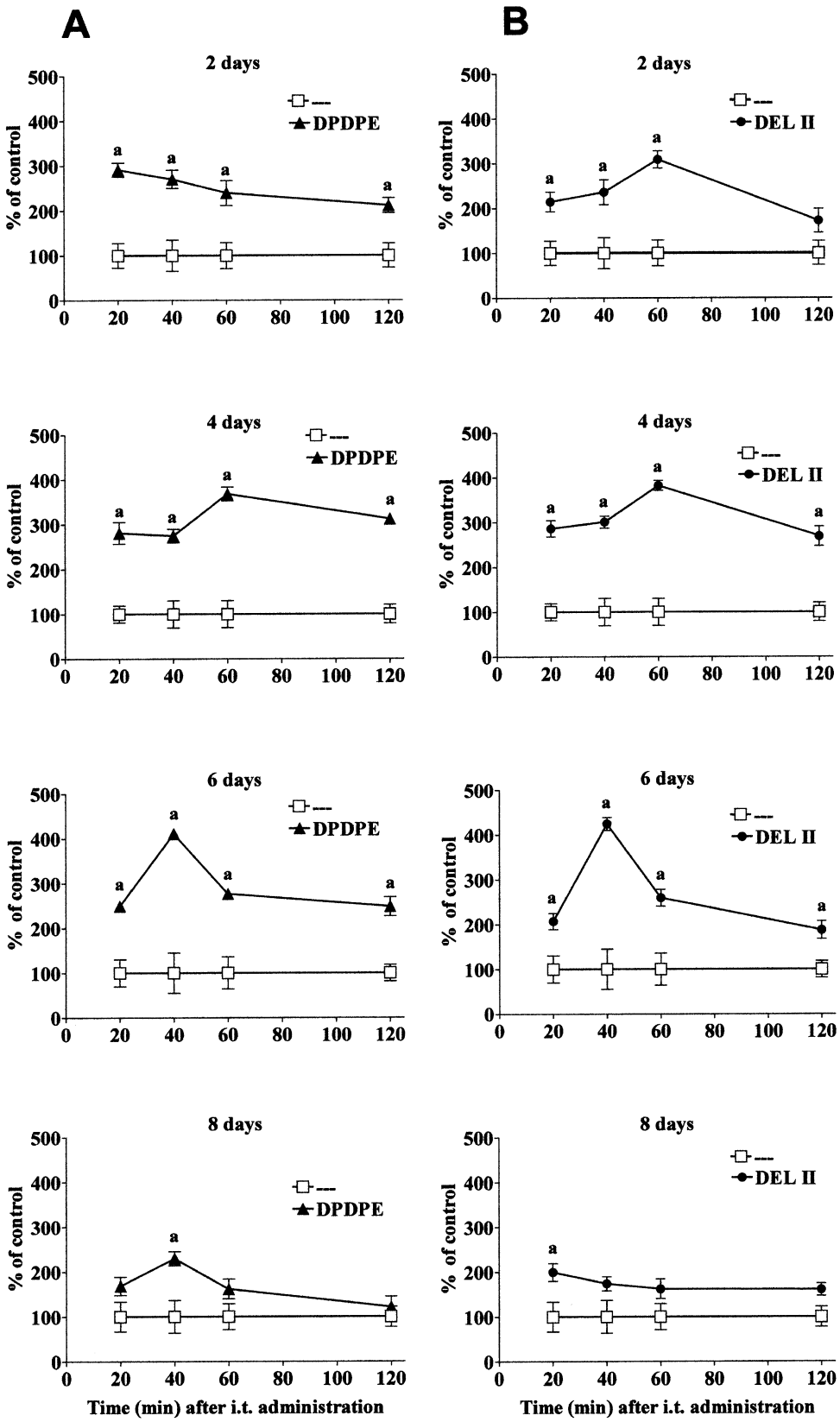

Fig. 4. The effect of (A) DPDPE (25 μg i.t.) and (B) deltorphin II (DEL II; 15 μg i.t.) administered 24 h before and every day after sciatic nerve crush on allodynia measured on 2, 4, 6, 8 days after injury. The data denote the latency (s) in paw withdrawal and are shown as percentages of the control. The control values on the first test day, i.e. day 2 post-injury, and on days 4, 6 and 8 were 6.9 ± 1.87, 6.2 ± 0.78, 7.7 ± 2.3 and 9.3 s ± 3.1 s, respectively. Each group comprised 12 animals. [a] $P < 0.05$ as compared with the group of animals subjected to the sciatic nerve crush and injected with sterile water (ANOVA, Bonferroni test).

test measurements were taken 55 min after i.t. injection of the substances. The cut-off latency was 60 s.

2.6.3. The cold-water allodynia test

The cold-water allodynia test has been previously described in detail (Hunter et al., 1997). Each animal was placed on a metal stage submerged to a depth of 1.5 cm in ice-cold water (0°C). An animal responds by lifting the paw out of the water. The measurements were taken 20, 40 and 60 min after i.t. injection. The cut-off latency was 40 s.

2.7. Statistics

The results of the experiments were evaluated by analysis of variance (ANOVA), followed by Bonferroni test, and presented as means ± S.E.M.

3. Results

3.1. Effects of δ-opioid receptor agonists and antagonists after a single injection

DPDPE administration at a dose of 25 μg on day 2 after injury of the sciatic nerve caused a statistically significant attenuation of allodynia. The strongest effect was observed 20 min after drug administration, and the reaction persisted for 60 min. The lower dose of 5 μg did not evoke such an effect (Fig. 1A). Deltorphin II administration at doses of 1.5, 15 and 25 μg on day 2 after injury dose dependently attenuated allodynia. The strongest, statistically significant effects were noted 20 min after the injection of two higher doses (Fig. 1B).

BNTX administration at a dose of 1 μg significantly decreased the DPDPE-induced antiallodynic effect measured 10 min after the administration of the δ_1-opioid receptor antagonist (Fig. 2A). NTII injection at a dose of 25 μg significantly reduced the deltorphin II-evoked antiallodynic action measured 10 min after the administration of the δ_2-opioid receptor antagonist (Fig. 2B).

The administration of DPDPE at doses of 5 and 25 μg and deltorphin II at doses of 1.5, 15 and 25 μg caused dose-dependent prolongation of the reaction time, determined in the cold water (0°C) tail flick test performed 55 min after drug administration, but the effect of deltorphin II at 1.5 μg did not reach the level of statistical significance (Fig. 3A,B).

The injection of DPDPE at doses of 5 and 25 μg and deltorphin II at doses of 1.5, 15 and 25 μg evoked dose-dependent diminution of nociceptive sensitivity, measured in the tail-flick test. A strong effect was observed even at the lowest deltorphin II dose of 1.5 μg (Fig. 3C,D).

Table 1
The effect of the δ_1-opioid receptor antagonist BNTX and the δ_2-opioid receptor antagonist NTII on allodynia after injury of the sciatic nerve

Days (after injury)	Control	BNTX (1 μg)	Control	NTII (25 μg)
20 min after i.t. drug administration				
2	6.9 ± 1.9	15.9 ± 3.0[a]	10 ± 2.3	14.75 ± 2.6
4	6.2 ± 0.8	7.25 ± 2.5	9.5 ± 1.7	9.5 ± 3.2
6	7.7 ± 2.3	5.4 ± 1.7	9.5 ± 2.3	10.3 ± 3.1
8	9.3 ± 3.1	6.8 ± 1.4	6.6 ± 2	8.1 ± 3.3
40 min after i.t. drug administration				
2	6.2 ± 2.1	11.88 ± 3.4[a]	9.12 ± 2.88	19.14 ± 3.2[a]
4	6.6 ± 2.2	7.88 ± 3.3	9.7 ± 0.9	15.7 ± 4.4
6	6.3 ± 2.9	8.0 ± 2.9	10.5 ± 3.2	15.9 ± 3.5
8	10 ± 3.6	12.5 ± 3.1	9.8 ± 3.1	8.6 ± 4.6

The data denote the latency (s) in paw withdrawal and are shown as means ± S.E.M. for 12 animals per group.

[a] $P < 0.05$ as compared with the group of animals subjected to the sciatic nerve crush and injected with sterile water (ANOVA, Bonferroni test).

3.2. Effects of δ-opioid receptor agonists and antagonists after chronic injection

DPDPE administration at a dose of 25 μg 1 day before nerve injury and then every day for 10 days after the injury resulted in significant prolongation of the reaction time in the cold-water allodynia test on days 2, 4 and 6 post-injury, and the effect persisted for 2 h. However, on day 8 after injury, a weaker effect was observed, which was statistically significant only after 40 min (Fig. 4A).

Deltorphin II injection at 15 μg 1 day before nerve injury, and then every day for 10 days post-injury significantly prolonged the reaction time in the cold-water allodynia test on days 2, 4, 6 and 8 after injury, and it persisted for 2 h. However, the effect was less pronounced on day 8, and it was statistically significant only after 20 min (Fig. 4B).

The antagonists were administered chronically according to the same schedules and procedures as the agonists. Neither BNTX at doses of 1 and 5 μg nor an antagonist NTII (25 μg) statistically significantly influenced the reaction time on days 4, 6 and 8. The injection of 1 μg BNTX caused a significant prolongation of the reaction time measured on day 2, 20 and 40 min after drug administration (Table 1) and a statistically significant prolongation of the reaction time was noted on day 2, 40 min after NTII administration (Table 1). It was a short-lasting effect and it did not occur 60 and 120 min after administration (data not shown).

4. Discussion

Our experiments were designed to study the effects of δ_1- and δ_2-opioid receptor agonists and antagonists in a model of neuropathic pain. Both DPDPE, an δ_1-opioid

receptor agonist, and deltorphin II, a δ_2-opioid receptor agonist, inhibited allodynia and evoked antinociceptive effects in a tail-flick test conducted with the use of both cold and warm stimuli. Allodynia and hyperalgesia development were inhibited not only by single but also by chronic administration of agonists of δ-opioid receptor subtypes. No differences in the activity profile of the investigated agonists were observed.

Thus, the obtained results showed that both δ-opioid receptor subtypes made a significant and similar contribution in neuropathic pain at doses similar to effective ones in acute pain (Łabuz et al., 1998). It has been reported that morphine, an exogenous ligand of μ-opioid receptor, is devoid of activity in neuropathic pain (Bian et al., 1995); however, a potent antiallodynic effect of endomorphins, endogenous ligands of the μ-opioid receptor, has been reported (Przewłocka et al., 1999). Interestingly, the effectiveness of agonists of δ-opioid receptor subtypes is similar to that of endomorphins, but much stronger than the morphine-induced response in the same animal model. Moreover, tolerance development is much slower after δ-opioid receptor agonists than that observed in the case of endomorphin-1 (Przewłocka et al., 1999).

An interesting effect was observed following single BNTX administration in the cold-water tail-flick test (data not shown). Single administration of this δ_1-opioid receptor antagonist aggravated hyperalgesia. Other authors also reported an increase in δ_1-opioid receptor antagonist-induced pain behaviour in an inflammatory pain model (Ossipov et al., 1996). Moreover, using the model of inflammatory pain, Bhargava et al. (1996) demonstrated that receptor blockade by BNTX or naltriben increased the biosynthesis of δ_1- and δ_2-opioid receptors, which could lead to an increase in the antinociceptive effects of their endogenous ligands.

In chronic experiments, an antiallodynic action of BNTX and NTII was observed, which can suggest a tonic role of δ-opioid receptor subtypes in the studied nociceptive process. Stapelfeld et al. (1992) obtained similar results using naltrindole, a non-selective antagonist of both δ-opioid receptor subtypes, which was shown to inhibit the antinociceptive effects of DPDPE and Tyr-D-Ser-Gly-Phe-Leu-Thr (DSLET), but it exerted an analgesic action itself. A dose-dependent analgesic activity of naltrindole was also shown in mice; however, the applied doses were higher than those used for the inhibition of agonist actions. These effects were observed in the tail-flick test and in the hot-plate test after intraventricular drug injections and were reversed by naloxone and N,N-Diallyl-Tyr-Aib-Aib-Phe-Leu (ICI-174,864), a peptide antagonist of the δ-opioid receptor, whereas βFunaltrexamine, a μ-opioid receptor antagonist and nor-binaltorphimine, a κ-opioid receptor antagonist were without effect. This suggests that antagonists of the δ-opioid receptor can play a double role in neuropathic pain by mediating opposing effects, dependent on the dose (Stapelfeld et al., 1992).

Consecutive injections of δ-opioid receptor agonists lead to diminution of the analgesic effects. Tolerance to the effects of everyday drug dosing appears at about day 8 post-injury. Beside tolerance, the effect may result from decreased δ-opioid receptor binding after injury, which is in agreement with the autoradiographic studies of Stevens et al. (1991). The results demonstrated changes in the binding of the highly selective opioid radioligand ^{3}H-DPDPE after unilateral chronic constriction injury of the sciatic nerve. δ_1-Opioid receptor binding displayed little change at 2 days post-injury but declined gradually thereafter. By day 10 post-injury, δ_1-opioid receptor binding was significantly decreased. These decreases were bilateral in all areas and approximately equal in laminae V and X but were significantly greater on the nerve-injured side in laminae I–II. In our experiments, the effectiveness of chronic DPDPE injection in a neuropathic pain model also decreased on day 8, which parallels the changes in receptor binding. There are no studies concerning changes in δ_2-opioid receptor binding in neuropathic pain.

The results obtained in the present study indicate a significant role of both δ-opioid receptor subtypes in neuropathic pain. Agonists of both δ_1- and δ_2-opioid receptors exert strong antiallodynic and analgesic actions. These results justify the use of DPDPE against pain and suggest that also δ_2-opioid receptor agonists evoke desired reactions thus encouraging the search for potential analgesics among these compounds.

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