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Research report

Brain opioid-receptors are involved in mediating peripheral electric stimulation-induced inhibition of morphine conditioned place preference in rats

Xiang-Dang Shi, Wei Ren, Gui-Bin Wang, Fei Luo, Ji-Sheng Han, Cai-Lian Cui*

Neuroscience Research Institute, Peking University, 38 Xueyuan Road, Beijing 100083, China

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Abstract

Conditioned place preference (CPP) paradigm has been suggested as one of the animal models for drug craving. The present study was performed to examine the effect of 100 Hz peripheral electric stimulation (PES) on the expression of morphine-induced CPP. Rats were trained with morphine for 4 days to establish the CPP paradigm in a three-chamber 'unbiased' apparatus. Morphine-induced CPP was maintained up to 4 weeks when tests were given once a week. PES of 100 Hz administered 30 min a day for 3 days significantly attenuated morphine-induced CPP ($P<0.01$). I.c.v. injection of the δ-opioid receptor antagonist naltrindole (NTI) or the κ-antagonist norbinaltorphimine (nor-BNI) but not the μ-antagonist cyclic D-Phe–Cys–Tyr–D-Trp–Arg–Thr–Pen–Thr–NH_2 (CTAP), completely blocked the inhibitory effect of 100 Hz PES on the expression of morphine-induced CPP ($P<0.05$–0.01). These results indicate that the anti-craving effects induced by repeated PES of 100 Hz is mediated by the activation of supra-segmental δ- and κ-opioid receptors in the central nervous system.

Theme: Neural basis of behavior

Topic: Drugs of abuse: opioids and others

Keywords: Conditioned place preference; Craving; Peripheral electric stimulation; Opioid receptor

1. Introduction

Opioid drugs such as morphine and heroin can elicit intense euphoric effects, which may cause psychic dependence or craving for drugs, and contribute to the vulnerability to relapse [18,29]. The conditioned place preference (CPP) paradigm has been used widely to study the rewarding effects of various drugs of abuse [25], since it involves a drug-associated conditioned cue, which may be responsible for relapse in drug-free former addicts. This property makes the CPP paradigm a useful tool for testing medication or other approaches for its anti-craving activity [25,1].

Peripheral electric stimulation (PES) is an effective treatment that developed on the basis of acupuncture. It has been proved to be clinically effective in the induction of analgesia as well as the suppression of withdrawal syndrome and relapse to drug in heroin addicts [10,28]. Wang et al. have shown that a single session of 2 Hz PES but not 100 Hz PES could inhibit the expression of morphine-induced CPP in rats in a two-compartment apparatus. This effect could be blocked by a small dose of naloxone, indicating the involvement of endogenous opioid peptides interacting with μ- and δ-opioid receptors [27]. Luo et al. have reported that repeated electrical stimulation of 100 Hz could produce a cumulative therapeutic effect on chronic pain [15]. Guo et al. [8] demonstrated that PES of 100 Hz accelerated the biosynthesis of preproenkephalin and predproynorphin mRNA in rat brain, which might account for the cumulative therapeutic effect observed in

*Corresponding author. Tel.: +86-10-6209-1150; fax: +86-10-8207-2207.
E-mail address: clcui@bjmu.edu.cn (C.L. Cui).

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the treatment of clinical disorders with PES. We hypothesized that repeated 100 Hz PES may produce similar cumulative therapeutic effect to combat opiate craving in humans and morphine CPP in the rat.

2. Materials and methods

2.1. Animals

All experiments were performed on male Sprague–Dawley rats, obtained from the center of Peking experimental animals, weighing 180–220 g at the beginning of the experiment. Animals were housed four per cage in a 12-h light–12-h dark normal cycle (lights on at 07:00 h) with food and water available at all times. The room temperature was maintained at 24±1 °C, and relative humidity at 50%. Animals were conditioned and tested during the light phase of the cycle. They were handled daily for approximately 10 min during the first week after arrival. All experimental procedures were approved by the Animal use Committee of Peking University Health Science Center.

2.2. Drugs

Morphine hydrochloride was purchased from the First Pharmaceutical Factory of Shenyang (China). The μ-opioid antagonist cyclic D-Phe–Cys–Tyr–D-Trp–Arg–Thr–Pen–Thr–NH_2 (CTAP), the δ-opioid antagonist naltrindole (NTI) and the κ-opioid antagonist norbinaltorphimine (nor-BNI) were purchased from Sigma (USA). All drugs were dissolved in 0.9% saline to their final concentrations. Cannulation for i.c.v. injection was performed stereotaxically under 10% chlorohydrate anesthesia (0.3 ml/100 g body weight). Stainless steel tubing (0.8 mm O.D.) was fixed on the skull at coordinates A 5.4, LR 1.5, H 3.5 mm according to Pellegrino et al. [21]. Experiments began 5 days postoperatively. The i.c.v. injection volume was 5 μl followed by a 5-μl saline flush, to be completed in 30 s.

2.3. Apparatus

Conditioning was conducted in black rectangular PVC boxes (71.5×36.5×30 cm), containing three chambers separated by guillotine doors. The two large black colored conditioning chambers (A and C, 24×35 cm) were separated by a small gray colored center choice chamber B (15.5×19.5 cm). Chamber A had four light-emitting diodes (LEDs) formed a square on the walls and a stainless steel mesh floor (1.3×1.3 cm^2), chamber C had four LEDs forming a triangle on the wall and a stainless-steel rod floor (1.3 cm apart), whereas chamber B has a plain floor. Fifteen photobeams are placed across chambers 4.75 cm apart. Through a computer interface, the time spent by the rat in each chamber was recorded by means of infrared beam crossings.

2.4. Place preference procedure

The place conditioning procedure consisted of three phases: preconditioning, conditioning and postconditioning test (CPP test). All animals were allowed to habituate to the colony room and to handling for 5 days before the start of the experiment.

Following habituation, animals received a single preconditioning test in which they were placed in the center choice chamber with the guillotine doors removed to allow access to the entire apparatus for 15 min. The amount of time spent in each chamber was monitored and used to assess unconditioned preferences. During the following conditioning phase (4 days), rats were assigned to receive drug pairings with one of the two end chambers (A or C) in a counterbalanced fashion (the 'unbiased' procedure). All to-be conditioned rats were injected with either saline or morphine (4 mg/kg, i.p.) in the morning and afternoon. Half of each group began the experiment on the drug-paired side and half on the saline-paired side. Morphine and saline treatments were alternated in morning and afternoon sessions for every conditioned animal, so that rats given morphine in the morning were given saline in the opposite compartment in the afternoon, and vice versa on subsequent days. Morning and afternoon injections were at least 6 h apart. One day after the last conditioning trial, a test for CPP was given. Animals were placed in the center choice chamber with the guillotine doors raised and allowed free access to the entire apparatus for 15 min. The amount of time spent in each chamber was recorded to assess individual preferences. No injections were given during the CPP test, with the same procedure maintained as that used during the preconditioning test.

2.5. Peripheral electric stimulation

Rats were kept in special holders, with their hind legs and tails exposed [11]. Two stainless steel needles of 0.3 mm diameter were inserted into each hind leg, one in the acupoint ST36 (5 mm lateral to the anterior tubercle of the tibia), and the other in SP6 (3 mm proximal to the medial malleolus, at the posterior border of the tibia). Constant current square-wave electric stimulation produced by a HANS LH-800 programmed pulse generator (produced by Peking University of Astronautics and Aeronautics Aviation) was given via the two needles for a total of 30 min. The frequency of stimulation used was 100 Hz (0.2 ms pulse width). The intensity of the stimulation was increased stepwise from 0.5 to 1 mA and 1.5 mA, with each step lasting for 10 min. The PES was given 24 h after the postconditioning test.

2.6. Statistical analysis

Data from the CPP test were expressed as a preference ratio scores [3]. A preference ratio for each rat was calculated by dividing the time spent in the drug-paired compartment by the time spent in both conditioning compartments. Data were processed using commercially available software GraphPad PRISM 3.0. Results are presented as mean±S.E.M. Comparisons between means of groups were analyzed with one-way analysis of variance (ANOVA) followed by Student–Newman–Keul's test. The accepted level of statistical significance is $P<0.05$.

3. Results

3.1. Morphine induced conditioned place preference

The preconditioning test showed that animals spent an equal amount of time (mean±S.E.M.) in the two end chambers (A: 317±7.39 s, C: 318±6.52 s) and less time in the small center choice chamber (B: 264±8.72 s). There were no significant differences in the time spent in the end chambers ($P>0.05$). Thus, the test boxes were truly unbiased in terms of chamber preferences of untreated rats.

On the basis of the conditions mentioned above, forty-eight rats were evenly and randomly distributed into four groups. Three of the four groups were trained with morphine doses of 1, 4 and 8 mg/kg for CPP; one group was given same volume of saline as a control. As shown in Fig. 1, all groups trained with morphine presented significantly higher CPP scores ($P<0.01$) than the control group, with no apparent dose–effect relationship. A 4-mg/kg dose was thus used in subsequent studies.

3.2. Maintenance of the CPP

Twelve rats were trained with 4 mg/kg of morphine for 4 days. CPP maintenance was tested weekly after the postconditioning test. The results (Fig. 2) showed that CPP scores decreased significantly at the fifth and sixth week ($P<0.05$), which indicates that morphine-induced CPP can endure for 4 weeks.

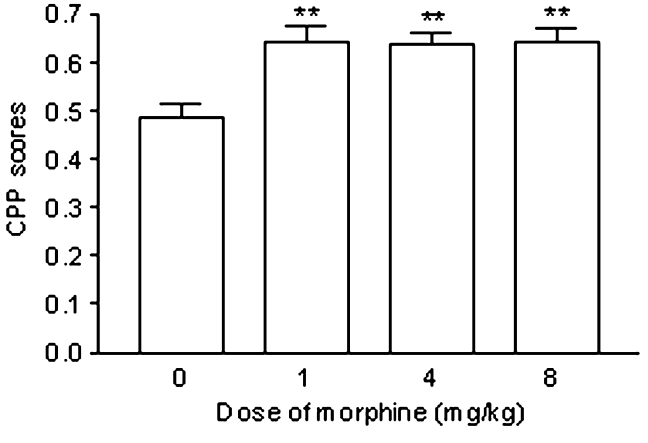

Fig. 1. Effect of the dose of morphine on the acquisition of morphine-induced CPP. **, $P<0.01$ compared with saline control group; $n=12$.

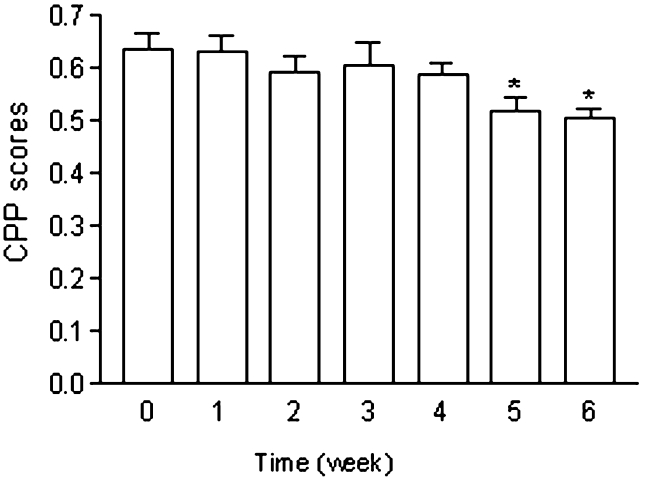

Fig. 2. Maintenance of morphine-induced CPP. CPP scores was tested once a week postconditioning. *, $P<0.05$ compared with the initial CPP group; $n=12$.

3.3. Effect of multiple treatment with 100 Hz PES on the CPP

To test the effect of 100 Hz PES on the expression of morphine-induced CPP, three groups of rats were conditioned with 4 mg/kg of morphine. At 24 h after the CPP expression, group 1 received no treatment as control, group 2 was merely restrained in the holder for 30 min, serving as control for restraint stress, and 100 Hz PES was given to group 3. All groups were tested again for their CPP expression 24 h after the treatment. Fig. 3 shows that 100

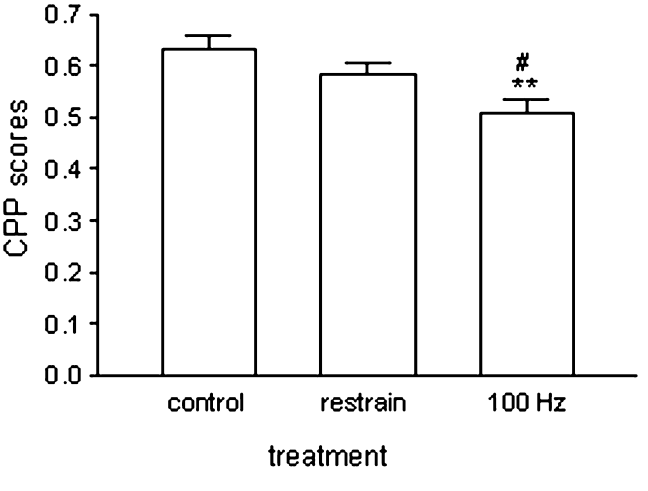

Fig. 3. Morphine-induced CPP in rats was suppressed by 100 Hz PES, but not by restraint. **, $P<0.01$, compared with control group. #, $P<0.05$ compared with restraint group; $n=9$–11.

Hz PES significantly decreased the expression of the morphine-induced CPP ($P<0.01$ compared with the control group, and $P<0.05$ compared with the restraint control group).

3.4. Effect of i.c.v. injection of CTAP on 100 Hz PES suppression of CPP expression

Firstly we tested the effect of CTAP treatment alone on CPP maintenance in the expression of morphine-induced CPP. Four groups of rats conditioned with 4 mg/kg of morphine, with eight in each group, were treated as described above. After the post-conditioning test, the rats received different doses of CTAP (0.25, 0.5, 1 μg/10 μl or 10 μl saline, i.c.v.) for three consecutive days (once a day). All groups were tested for their CPP expression 24 h after the last session of treatment. The results are shown in Fig. 4A. The rats receiving different doses of CTAP did not show significant difference from that of the NS control group ($p>0.05$).

Second, five groups of rats with ten to twelve in each group were conditioned with 4 mg/kg of morphine. After the postconditioning test, group 1 received no treatment as control. Groups 2–5 received a consecutive 3-day treatment (once a day) of normal saline (10 μl, i.c.v.) or 0.25, 0.5, 1.0 μg of CTAP (i.c.v.) respectively. A 100 Hz PES was started 15 min after the termination of the injection. All groups were tested for their CPP expression 24 h after the last session of treatment. As shown in Fig. 4B CTAP did not reverse the effect of PES at doses ranging from 0.25 to 1.0 μg ($P<0.05$–0.01) compared with the control group. The CPP of the rats receiving different doses of CTAP did not show significant difference from that of the NS control group ($P>0.05$).

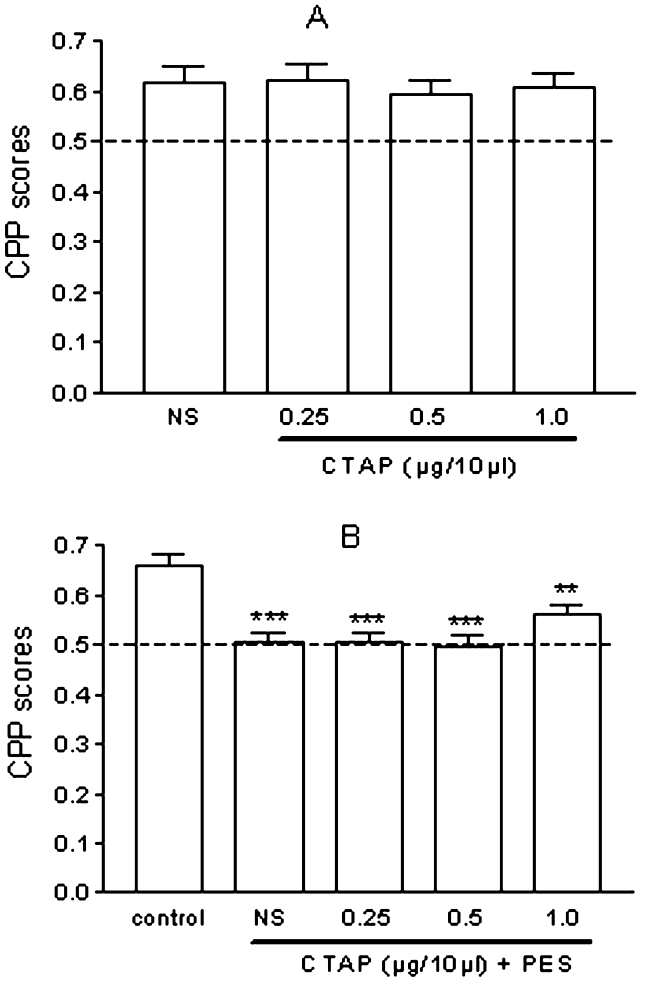

Fig. 4. I.c.v. injection of CTAP (0.25, 0.5, 1.0 μg/10 μl) showed no significant effect on morphine-induced CPP (A, $n=8$), nor did it affect the suppression of CPP expression by 100 Hz peripheral electrical stimulation (B, $n=10$–12). **, $P<0.01$, ***, $P<0.001$ compared with control group.

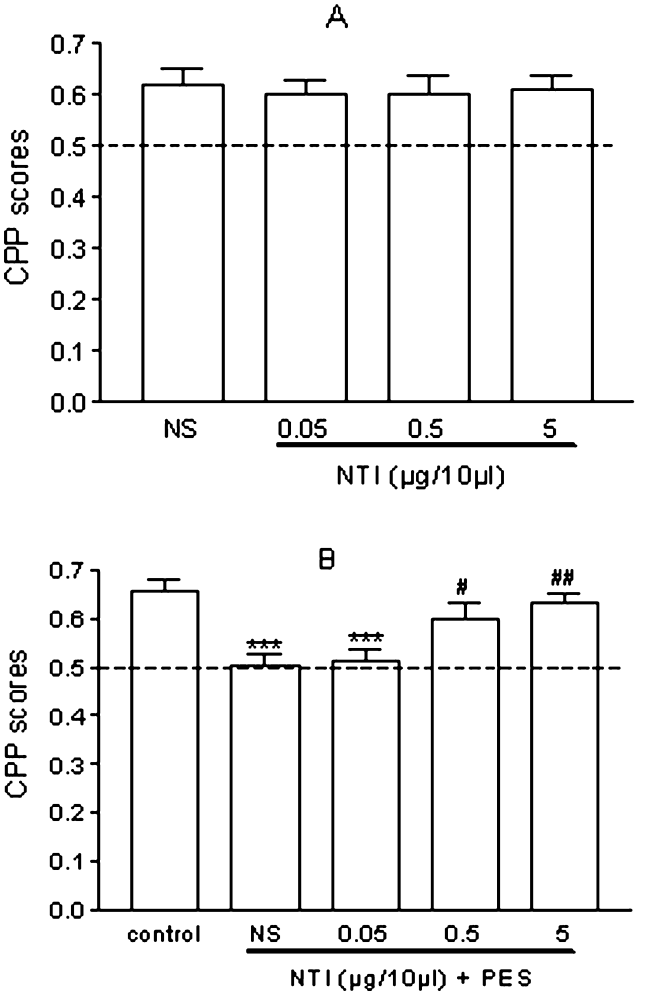

Fig. 5. I.c.v. injection of NTI (0.5 and 5 μg/10 μl) showed no significant effect on morphine-induced CPP (A, $n=8$), but reversed the blockade effect of PES on morphine-induced CPP (B, $n=10$–12). ***, $P<0.01$ compared with the control group. #, $P<0.05$, ##, $P<0.01$ compared with NS +100 Hz PES group.

3.5. Effect of i.c.v. injection of NTI on 100 Hz PES suppression of CPP expression

The protocol was the same as described above except that the CTAP was replaced by NTI. Fig. 5A shows that all groups receiving different doses of NTI (0.05, 0.5, 5 μg/10 μl; i.c.v) did not show significant differences compared with the NS control group ($P>0.05$), suggesting that NTI in the range of doses described above has no significant influences on the morphine-induced CPP expression in rats. The results in Fig. 5B showed that NTI (0.5 and 5 μg/10 μl, i.c.v) given 15 min prior to PES markedly antagonized the effect of 100 Hz on morphine-induced CPP expression.

3.6. Effect of i.c.v. injection of nor-BNI on 100 Hz PES suppression of CPP expression

The same protocol was followed as in the previous experiments except that CTAP was replaced by nor-BNI. Fig. 6A that nor-BNI (2.5, 5, 10 μg/10 μl, i.c.v) did not show a significant effect on the expression of morphine-induced CPP in rats ($P>0.05$, compared with the NS control group). The results shown in Fig. 6B indicate that the anti-craving effect induced by PES of 100 Hz was antagonized dose-dependently by 5 and 10 μg ($P<0.01$), but not by 2.5 μg of nor-BNI ($P>0.05$).

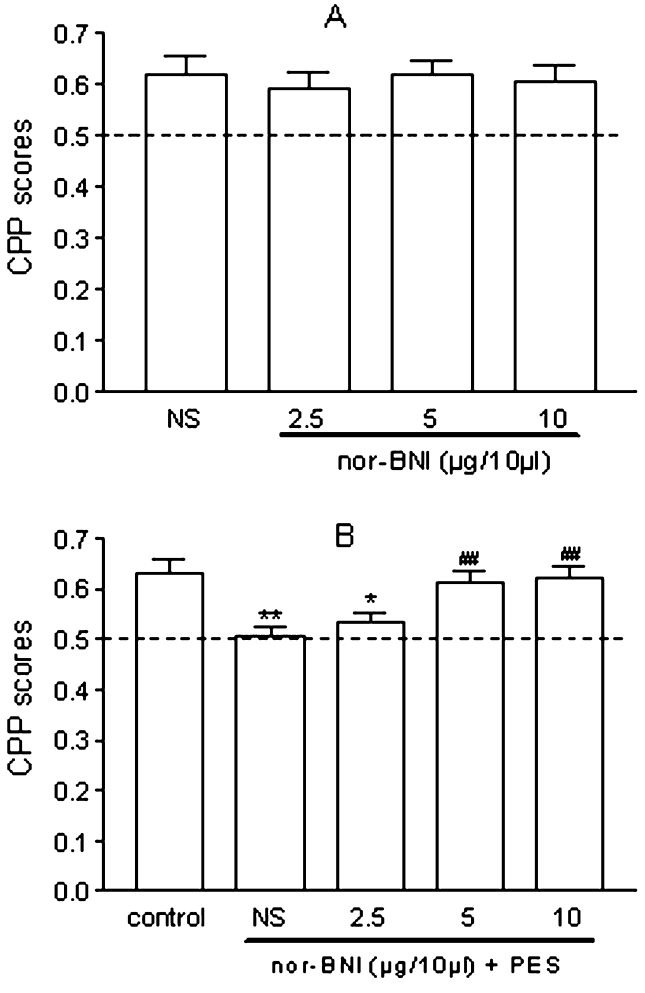

Fig. 6. I.c.v. injection of nor-BNI (5 and 10 μg/10 μl) showed no significant effect on morphine-induced CPP (A, $n=8$), but reversed the blockade effect of PES on morphine-induced CPP (B, $n=12$). *, $P<0.05$, **, $P<0.01$ compared with the control group. ###, $P<0.01$ compared with NS +100 Hz PES group.

4. Discussion

With regard to the CPP paradigm, there are some experimental variables that need to be taken into account. In the current study, we used different visual cues (LEDs forming different shapes) and tactile cues (different constructs of the floor) to make a difference in the environment, yet the animals showed no preference for one side of the apparatus over the other (unbiased design). Subsequent experimental settings were all arranged in a counterbalanced fashion.

Bardo et al. [2] have shown that the type of apparatus used may influence the size of CPP effect. With morphine, though no significant differences in effect size were reported between studies using either a 2- or 3-compartment apparatus, we still found that 3-compartment apparatus yielded a more stable and larger effect size than a 2-compartment device (data not shown). The absence or presence of a preconditioning preference test can also have a significant influence on the magnitude of the CPP effects [2], such that studies without preexposure usually produce larger effects. We chose to use a single preconditioning test prior to conditioning trials according to Mucha [20], whose study suggested that a single preconditioning test would not induce a latent inhibition. We have found that the CPP paradigm, once established, in the absence of any intervening test, remained stable for 4 weeks, and this is consistent with reports published previously [14,19].

Results in our laboratory clearly indicate that morphine-induced CPP can be suppressed not only by PES of 2 Hz [27] but also by PES of 100 Hz. It is noticeable that a variety of factors should be taken into consideration for the success of this manipulation. The intensity of electrical stimulation could be set in the range of 1–3 mA or 0.5–1.5 mA. Wang et al. [27] reported that one session of 2 Hz PES at an increasing intensity of 1–2–3 mA for a total of 30 min could effectively suppress morphine CPP in the rat. In the present study, we chose to use 100 Hz PES at a lower intensity of 0.5–1.0–1.5 mA in order to eliminate the possible stress. In the present setting the rats showed a mild trembling of the hind legs without any squeak or struggling as could be occasionally revealed in the previous study using 1–3 mA. In this experimental setting, one session of PES was not enough to reduce morphine CPP (data not shown). A significant reduction of CPP was obtained only after three consecutive daily sessions, sug-

gesting a cumulative therapeutic effect. It is clear that the effect of PES in suppressing CPP is not due to its possible interference on locomotor activity of the rat, since the computerized recording of the motor activities of the rat was not hindered by the electrical stimulation (data not shown). In fact, 100 Hz PES has been shown to increase the abundance of preprodynorphin mRNA in rat brain [7], suggesting an increased synthesis of dynorphin. In agreement with this, Uneklabh et al. have shown that intravenous injections of dynorphin at the dose of 180 or 60 μg/kg three times a day for 6 days produced a significant reduction of craving in heroin addicts after detoxification [26].

Several reports have shown that δ- and κ-opioid receptors are involved in the analgesic effect induced by 100 Hz PES to a different extent in different animal models [13,5]. To evaluate the possible role played by opioid receptors in the mediation of the suppression of morphine-induced CPP by of 100 Hz PES, three types of opioid receptor antagonist were used. It was found that NTI (a selective δ-opioid receptor antagonist) nor-BNI (a selective κ-opioid receptor antagonist) but not CTAP (a selective μ-opioid receptor antagonist) significantly antagonized the inhibitory effect of 100 Hz PES on morphine-induced CPP. It suggests that δ- and κ-opioid receptors in the brain may play an essential role in the mediation of 100 Hz PES effect. Considerable evidence in our laboratory has been obtained to show that PES of known frequencies could mobilize different kinds of endogenous opioid peptides, acting on their corresponding receptors to induce analgesia [9]. For example, PES of 2 Hz could increase the release of enkephalin in brain to interact with μ- and δ-receptors, while PES of 100 Hz could increase the release of dynorphin to interact with κ-receptor. It was also demonstrated [8] that 100 Hz electrical stimulation could accelerate the expression of mRNA encoding preproenkephalin and preprodynorphin in brain. Taken together, we can infer that suprasegmental enkephalin and δ-receptor as well as dynorphin and κ-receptor are involved in mediating the PES inhibition of morphine-induced CPP.

Both δ- and κ-opioid receptors are densely distributed in the nucleus accumbens (NAc) and striatal regions, serving as the terminal projection sites of the midbrain dopamine (DA) neurons [16]. Evidence from animal experiments has shown that the activation of the mesolimbic DA system may be critically linked to the expression of the morphine-induced place preference in mice [6]. The release of DA from dopaminergic nerve terminals in nucleus accumbens (NAc) may be suppressed by the activation of presynaptic κ-opioid receptor [12]. Indeed, the activation of κ-opioid receptor could abolish both the place-preference and the increase in DA metabolites produced by morphine [6]. It implies that the inhibition of morphine-induced CPP produced by PES of 100 Hz is mediated by the activation of κ-opioid receptor, which in turn reduces the release of DA in NAc.

Although Suzuki et al. [23,24] reported that δ-receptor antagonists and antisense block the acquisition of morphine-induced CPP, we found in the present study that NTI did not affect the expression of morphine-induced CPP, suggesting that while δ-opioid mechanism is necessary for the acquisition of morphine-induced CPP, it may not be indispensable for the expression or maintenance of CPP (Fig. 5A). Interestingly, this mechanism is certainly important for the mediation of PES-induced modulation of morphine-induced CPP (Fig. 5B). The complex role played by enkephalin/δ-receptor in the acquisition and modulation of morphine-induced CPP remains to be elucidated.

Recently, Ren et al. [22] in our laboratory revealed that 100 Hz PES could abolish the expression of cocaine-induced CPP in the rat. This effect could be reversed only by a high dose of naloxone, suggesting the involvement of κ-opioid receptor. Together with the present study, it suggests that PES can be a promising therapeutic approach for the prevention of craving for both morphine and cocaine.

It is interesting to note that the parameters of the electrical stimulation (frequency and intensity) and the design of treatment protocols (single and multiple sessions) are very important in determining the effectiveness of the PES treatment. For example, 2 Hz is more effective than 100 Hz in suppressing morphine CPP [27], whereas 100 Hz is more effective than 2 Hz in suppressing cocaine CPP [22]. It is possible that the seemingly weak effect might be strengthened by multiple treatments.

The complex interactions between the electrical parameters, treatment sessions and experimental settings (e.g. two-compartment versus three-compartment CPP paradigm) need further exploration. This may have some implication on the situation that the outcomes of the clinical trials of acupuncture treatment for drug abuse today used ear acupuncture without electrical stimulation were not very satisfactory [17,4]. The principles unraveled from the studies using electrical stimulation in the animal experiment may shed some light on its possible clinical application in the future.

5. Conclusion

We demonstrate that three consecutive daily treatments of very mild 100 Hz PES for 30 min suppress morphine-induced CPP in the rat. Results obtained from intracranial administration of opioid receptor subtype antagonists suggest that the effect produced by 100 Hz PES may be mediated by δ- and κ-opioid receptors in brain.

Acknowledgements

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