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Ketamine enhances the efficacy to and delays the development of tolerance to electroacupuncture-induced antinociception in rats

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Abstract

Our previous studies have shown that 100 Hz electroacupuncture (EA) produced antinociception through the release of endogenous opioids (mainly dynorphin) and the activated κ-opioid receptors in normal rats. Acupuncture is an effective treatment in relieving pain, but it develops tolerance after repeated administration. It has been reported that *N*-methyl-D-aspartate (NMDA) receptor antagonists could increase the antinociceptive effects induced by morphine and delay the development of tolerance to morphine but nothing has yet been described to reduce EA tolerance. Here we test whether ketamine, a non-competitive NMDA receptor antagonist, would enhance 100 Hz EA antinociception as well as prevent or delay the development of chronic tolerance to 100 Hz EA in normal rats. The results are as follows: (1) ketamine injected intraperitoneally (i.p.) 15 min prior to EA enhanced the antinociceptive effects of 100 Hz EA at a dose of 5.0 mg/kg, but not 0.2 or 1.0 mg/kg. However, ketamine at either dose did not affect the basal nociceptive threshold (represented by tail-flick latency). (2) Ketamine at a dose of 5.0 mg/kg delayed the development of chronic tolerance to 100 Hz EA antinociception. We conclude that ketamine can enhance antinociception of 100 Hz EA and delay the tolerance to 100 Hz EA in rats. These results suggest that the development of 100 Hz EA tolerance to antinociception was mediated, at least in part, through peripheral NMDA receptors, which may be useful in improving the therapeutic effects of EA in the treatment of pain when EA tolerance occurs.

Keywords: Electroacupuncture; Analgesia; Tolerance; Ketamine; NMDA receptor

Acupuncture has been used to relieve pain for more than two thousand years in Asian countries. Electroacupuncture (EA), which refers to the peripheral electrical stimulation, is a modern version of the traditional hand acupuncture. EA-induced antinociception has been proven to accelerate the release of endogenous opioid peptides, which further activates opioid receptors in rats and mice as well as in human beings [14]. EA analgesia is safe, but in most cases is moderate; furthermore, its antinociceptive effects decrease after prolonged administration, which is called "EA tolerance" [14,27].

Interactions exist between *N*-methyl-D-aspartate (NMDA) receptors and opioid receptors in nociception and antinociception [3,11,13,23]. Both are distributed in the dorsal horn particularly within Lamina II. NMDA receptor antagonists could increase opioid antinociception and prevent the development of tolerance to opioids in rodents [13,25,28]. Ketamine is a non-competitive antagonist of the NMDA receptor. It has been used as an anesthetic rather than an antinociceptive in clinical practice in past years, but recently began to be used as an antinociceptive agent in the management of chronic pain [12,16,29], including neuropathic and cancer pain [1,4]. However, the clinical application of ketamine is hindered because of its severe side effects at high doses [30].

Much effort has been put forth to improve the analgesic effects of EA. As stated above, NMDA antagonists interact with opioid receptor. Thus, in the present study, we aim to explore whether ketamine has any influence on EA antinociception and the development of chronic tolerance to EA antinociception in rats.

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Female Sprague–Dawley rats weighing 200–250 g were provided by the Department of Experimental Animal Sciences, Peking University Health Science Center. They were housed four to five per cage with food pellets and water ad libitum. All experimental procedures were approved by the Animal Use and Protection Committee, Peking University and in accordance with the NIH Guide for the Care and Use of Lab Animals revised in 1996. Ketamine hydrochloride (Sigma-Aldrich Chemical Co., USA) was dissolved in normal saline (NS). Ketamine (0.2, 1.0, 5.0 mg/kg) or NS was injected intraperitoneally (i.p.) 15 min prior to EA. Injection volume was 1.0 ml/kg.

Room temperature for experiments was controlled at $22 \pm 1\,^{\circ}C$. EA stimulation was conducted according to our routine procedure [24]. Briefly, each rat was gently placed into a specially designed polyethylene holder, with the hind legs and tail exposed. The skin of the hind legs of rats and acupuncture needles were sterilized with 75% alcohol. Stainless-steel needles (0.4 mm in diameter, 5 mm in length) were inserted into the 'acupoints' in each hind leg. One acupoint was "Zusanli" (ST 36, 4 mm lateral to the anterior tubercle of the tibia, which is marked by a notch) and the other was "Sanyinjiao" (SP 6, 3 mm proximal to the medial melleolus, at the posterior border of the tibia). During EA application, rats were kept in the holder without giving any anesthetic. The stimuli were generated from an electric device named Han's Acupoint Nerve Stimulator (HANS, LH series, manufactured in our university) and applied to both legs simultaneously. These electric stimuli were set as square waves, 0.2 ms in pulse width, and 100 Hz in frequency. Their intensities were increased in a stepwise manner at 1–2–3 mA, each lasting for 10 min.

EA chronic tolerance was developed according to our previous report [19]. EA was applied to rats once daily, 30 min for each time for six days consecutively. The thermal latency was examined (see the following for method) immediately following EA to evaluate the EA-induced antinociceptive effect. The antinociceptive effect decreased over the course of EA administration, which indicated the development of chronic tolerance to EA [27].

Thermal latency was assessed using radiant heat tail-flick as described previously [24]. Focused light (3 mm diameter) from a 12.5 W projection bulb was applied to the tail skin 3–4 cm from the tip and the tail-flick latency (TFL) was measured to the nearest 0.1 s. The intensity of the thermal stimulus was adjusted by changing the voltage of electricity to obtain a basal latency within the range of 4–6 s. To avoid tissue damage, a cut-off limit of 15 s was used. After rats were placed in the holder and inserted with acupuncture needles for 30 min, the basal TFL was examined. The mean of three consecutive measures at 5 min intervals was taken as the basal TFL. TFL was measured every 10 min during the 30 min of EA application. The percent increase of TFL for the three assessments was taken as the EA-induced antinociception and was calculated as follows: TFL (%) = (latency after EA − basal latency)/basal latency × 100.

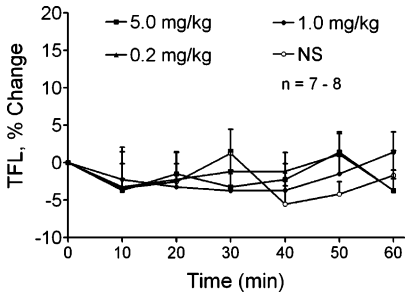

Fig. 1. Effect of i.p. ketamine on basal tail-flick latency (TFL) in rat with tail-flick test. TFL was transformed to the percent change according to the basal TFL. The area under the curve of the entire 60-min testing period was calculated with ANOVA analysis. No significant difference was found among groups ($P > 0.05$); $n = 7$–8.

The experimental data were expressed as mean ± S.E.M. Difference between groups was analyzed with two-way or one-way analyses of variance (ANOVA) where appropriate, followed by Newman–Keuls post hoc test. Statistical significance was determined as $P < 0.05$.

The effect of i.p. ketamine on basal pain threshold in the rat tail-flick test is shown in Fig. 1. Rats were randomly divided into four groups with seven to eight in each group. TFL was measured at 10 min interval for a total of 60 min after the i.p. injection of ketamine or NS. There was no significant difference in basal TFLs among all groups ($P > 0.05$), suggesting that ketamine produced neither antinociception nor hyperalgesia in the rats.

The time course of the effects of ketamine on 100 Hz EA is shown in Fig. 2. Rats were randomly divided into four groups with 9–10 in each group, and the animals received i.p. injection of ketamine at different doses (0.2, 1.0 and 5.0 mg/kg) or NS 15 min prior to EA. It can be seen that ketamine at the dose of 5.0 mg/kg significantly increased TFL compared with NS ($P < 0.05$). These results suggested that ketamine can dose-dependently enhance the antinociceptive effect of 100 Hz EA in normal rats.

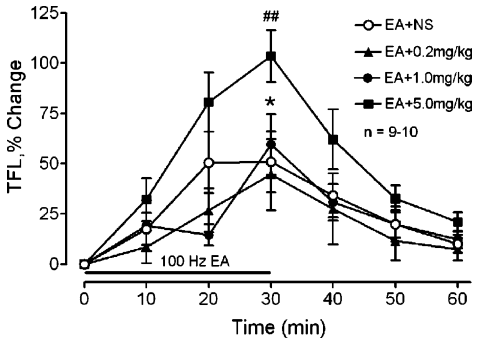

Fig. 2. Potentiation of ketamine to EA-induced antinociception. Ketamine at doses of 0.2, 1.0, and 5.0 mg/kg or NS was injected i.p. before EA application. Tail-flick latency (TFL) increased significantly in animals receiving ketamine at 5.0 mg/kg. Statistical analysis was carried out by two-way ANOVA followed by Newman–Keuls post hoc tests. $^{*}P < 0.05$ compared with NS group; $^{\#\#}P < 0.01$ compared with NS group at the corresponding points.

Table 1
Ketamine delayed the development of chronic tolerance to EA antinociception. EA (100 Hz in frequency, 1–2–3 mA in intensity, 10 min for each intensity) was given for 30 min once daily for 6 days

Group	*n*	Tail-flick latency (%)					
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
EA + NS	8	68.8 ± 11.5	59.6 ± 8.8	35.9 ± 6.2*	20.6 ± 8.2*	18.3 ± 5.4*	11.9 ± 7.4*
EA + ketamine	8	72.8 ± 9.7	81.6 ± 9.0	58.0 ± 7.8	62.6 ± 9.5#	40.0 ± 9.5*,#	40.2 ± 7.8*,#

Ketamine at 5.0 mg/kg or NS was injected i.p. beginning two days before EA application. Statistical analysis was carried out by two-way or one-way analyses of variance (ANOVA) where appropriate.

* $P < 0.01$ compared with that at day 1 in the same group by one-way ANOVA.

# $P < 0.05$ compared with that at the same day in EA plus NS group by two-way ANOVA.

Ketamine delayed the development of chronic tolerance to 100 Hz EA as shown in Table 1. As stated above, all rats were given EA for 6 days. From day 2, half of rats received i.p. injections of NS, the other half received ketamine (5.0 mg/kg). In the group of EA plus NS, the antinociceptive effects of EA from day 3 on also decreased significantly, indicating the development of tolerance to EA. For example, the antinociceptive effects decreased from 68.8 ± 11.5% at day 1 to 11.9 ± 7.4% at day 6 ($P < 0.05$). In the group of EA plus ketamine, the EA antinociceptive effects at day 6 also decreased from 72.8 ± 9.6% to 40.2 ± 7.8% at day 1 ($P < 0.05$). At days 5 and 6, the EA antinociceptive effects decreased significantly compared with that in day 1, indicating that EA tolerance also develops. Interestingly, EA tolerance developed much slower in the group of EA plus ketamine. At days 4–6, the antinociceptive effects of EA in the group of EA plus ketamine were significantly higher than those in the group of EA plus NS ($P < 0.05$). These results indicate that ketamine could delay the development of chronic tolerance to 100 Hz EA.

In the present study, we observed that ketamine (5.0 mg/kg) increased the antinociceptive effects of 100 Hz EA (Fig. 2), whereas the basal pain threshold was not affected (Fig. 1) in normal rats. Furthermore, ketamine could delay the development of chronic tolerance to EA antinociception (Table 1).

The interaction between NMDA and opioid receptors is of great interest [2,7,13,23]. A growing body of evidence indicates that NMDA receptor antagonists could affect the function of opioids. For example, Mao et al. [22] reported that i.p. injection of dextromethorphan (3.0 mg/kg), an NMDA receptor antagonist, greatly enhanced peak antinociception and duration of antinociception produced by s.c. injection of 5.0 mg/kg morphine. LY235959, a competitive NMDA receptor antagonist, was reported to enhance the antinociceptive effect of U-50,488H (a κ-receptor agonist) in rat tail-flick test [5,7]. However, there are reports in which NMDA receptor antagonists increased the analgesia induced by κ-receptor agonists. For example, ketamine and dextromethorphan, an NMDA receptor antagonist, could potentiate the antinociceptive effects of μ-, but not δ- or κ-opioid agonists in mouse with hot plate test [2]. MK-801 (0.03–0.30 mg/kg, i.p.) was ineffective in enhancing the antinociception of U-50,488H (25.0 mg/kg, i.p.) in the mouse tail-flick test [6]. In contrast, intracerebroventricular (i.c.v.) injection of MK-801 (0.001–0.10 μg) dose-dependently attenuated antinociception induced by U-50,488H (60 μg, i.c.v.) in mouse tail-flick and hot plate tests [26]. The mechanisms for this discrepancy in whether NMDA receptor antagonists potentiate or decrease κ-opioid agonist-induced antinociception remain largely unclear. The differences in drug doses, administration routes, behavioral test methods and animal species may be partially accountable.

Ketamine is a weak antagonist of NMDA receptors. It often causes severe side effects when used at high doses in clinic [30]. It is well-known that EA produces reliable analgesic effects, but mostly moderate. Our previous results showed that 100 Hz EA produced antinociception via stimulating the release of endogenous dynorphin and the subsequent interaction of dynorphin with κ receptor in rats as well as human beings [14]. Intrathecal injection of dynorphin elicited antinociception in rabbits [15]. In the present study, we did not conduct opioid receptor antagonist experiments, for example, naloxone blockade experiment since many of our previous studies have repeatedly demonstrated that 100 Hz EA produced antinociception through the release of endogenous opioids (mainly dynorphin), which then activated κ-opioid receptors in animals as well as human beings [14]. Recently, we observed that the effects of ketamine and EA combination on mechanical allodynia could be partially blocked by the opioid receptor antagonist naloxone [18]. Thus, in the present study, we did not repeat the experiment to prove the opioid mechanism for 100 Hz EA-induced antinociception with opioid receptor antagonist in normal rats again. The present results indicate that ketamine (5.0 mg/kg) could enhance 100 Hz EA-induced antinociception in rats (Fig. 2). Although we did not produce direct evidence in the present experiment that the mechanism of action of ketamine is through NMDA antagonism, but many other reports [11,25] convincingly support this assumption. Based on this evidence, we speculate that the potentiation of ketamine on EA antinociception might be through the inhibition of NMDA antagonism of dynorphin released by 100 Hz EA in rats.

It should be noted that the effect of dynorphin on acute or chronic pain has been controversial. Our and many other previous studies support the concept that dynorphin produces antinociception. As mentioned above, the release of dynorphin from EA stimulation and exogenously administrated

dynorphin to animal could induce antinociception. We recently observed that 100 Hz EA could attenuate mechanical hyperalgesia in a rat model of complete Freund's adjuvant (CFA)-induced inflammatory pain, and the effect was partially blocked by naloxone [17]. This result is similar with that observed in acute pain. Goldstein and Chavkin [9] demonstrated that dynorphin was an extremely potent opioid agonist in vitro and had a high degree of selectivity for κ-opioid receptors. When dynorphin expression was down-regulated by knockout of its enhancer called DREAM, the dream-deficient mice exhibited markedly attenuated pain responses across a battery of pain behavior tests [10]. However, other studies found that very low intrathecal doses of dynorphin in rodents resulted in prolonged tactile allodynia, which was attenuated by pre-treatment with NMDA receptor antagonists, but not opioid receptor antagonists [9]. Considering these data, it is possible that dynorphin may have differential physiological and pathological functions in nociception.

Many reports support NMDA receptor involvement in the tolerance to opioid antinociception [22,28]. For example, the NMDA receptor antagonist ketamine administrated systemically prevented the development of tolerance to morphine and reversed the pre-established tolerance to morphine [21,25]. Bell [4] reported that s.c. injection with low dose of ketamine appears to reduce morphine tolerance. Kolesnikov et al. [20] found that an NMDA receptor defect causes lack of morphine and enkephalin tolerance. In both mice and rats, MK-801 has been shown to prevent the development of antinociceptive tolerance induced by U-50,488H with tail-flick test [5,7]. In the present study, repeated co-administration of 100 Hz EA and normal saline daily produced tolerance to 100 Hz EA antinociception within three days. However, co-administration of 100 Hz EA and ketamine (5.0 mg/kg, i.p.) did not produce tolerance until the fifth day. This observation indicates that ketamine could delay the development of chronic tolerance to 100 Hz EA in rats (Table 1). It is well-known that 100 Hz EA stimulation produces antinociception mainly through releasing endogenous dynorphin in the spinal cord [4], thus we speculate that this delay of 100 Hz EA tolerance by ketamine might be due to the antagonism of ketamine to the endogenously released dynorphin. These data also suggest that the NMDA receptor might play a role in the development of chronic tolerance to 100 Hz EA antinociception.

It is worth noting the dose of ketamine used in our current study. It is known that the dose of ketamine required for antinociception or anesthesia is different. In the clinical practice for human beings, an intravenous injection of ketamine at 0.1 mg/kg or 2.0 mg/kg produces antinociception or anesthesia, respectively [11]. However, the doses of ketamine used in rats was much higher, 50.0 mg/kg for antinociception and 150.0 mg/kg for anesthesia [11]. In the present study, ketamine at a dose of 5.0 mg/kg did not produce either antinociception or hyperalgesia in the rat tail-flick test (Fig. 1). This is consistent with the fact that i.p. administration of ketamine (1.0, 5.0 or 10.0 mg/kg) produced dose-dependent antinociceptive effects in the acetic acid-induced writhing and formalin tests but not in tail-flick nor hot plate tests [8]. However, it was reported that systemic ketamine produces a small degree of antinociception with the tail-flick test [3], but at much higher doses (25.0–60.0 mg/kg). The reason for this difference is not clear. One of the side effects of ketamine is motor dysfunction, therefore, the motor impairment may have influenced the withdrawal of leg or tail to noxious stimulation. No abnormal locomotor behaviors were observed after administration of ketamine (5.0 mg/kg) in our present study (data not shown).

In summary, the present results indicate that ketamine could enhance antinociception of EA, and delay the development of chronic tolerance to EA antinociception in rats. From the perspective of reducing and/or abolishing the side effects of ketamine, combination of EA and low dose of ketamine may be an effective therapeutic in clinical pain management. In addition, such a strategy should be integrated into treatment not only for chronic pain management, but also for the prevention of evolving pain conditions such as neuropathic pain. This combination of EA and ketamine in the treatment of chronic pain is worthy of further study.

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