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SHORT COMMUNICATION

Effects of electroacupuncture on oxaliplatin-induced neuropathic cold hypersensitivity in rats

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Abstract This study investigated whether and how electroacupuncture (EA) attenuates cold hypersensitivity (allodynia) in a rat model of oxaliplatin-induced neuropathic pain. Cold allodynia [evaluated by immersing the tail into cold water (4 °C) and measuring the withdrawal latency] was induced 3 days after an oxaliplatin administration (6 mg/kg, i.p.). EA stimulation (2/100 Hz, 0.3-ms pulse duration, 0.2–0.3 mA) was delivered to ST36 acupoint or non-acupoint for 20 min. Low-frequency (2 Hz) EA at ST36 relieved cold allodynia more effectively than high-frequency EA at ST36 or low-frequency EA at non-acupoint. Naloxone (opioid antagonist, 2 mg/kg, i.p.) completely blocked such EA-induced anti-allodynia, whereas phentolamine (α-adrenergic antagonist, 2 mg/kg, i.p.) did not. Moreover, plasma β-endorphin levels significantly increased right after the end of EA and subsequently decreased. These results indicate that low-frequency EA at ST36 in rats has a marked relieving effect on oxaliplatin-induced cold allodynia that is mediated by the endogenous opioid, but not noradrenergic, system.

Keywords Oxaliplatin · Cold allodynia · Electroacupuncture · Endogenous opioid · Noradrenergic

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Introduction

Although advances in cancer detection and therapy have significantly enhanced life expectancy in cancer patients, quality of life may be severely compromised due to the development of painful neuropathy [1, 2]. Oxaliplatin is a third-generation platinum-based chemotherapy drug important in the treatment of colorectal cancer [3]. Unlike the other platinum compounds, oxaliplatin often induces a very acute painful neuropathy soon after an administration. About 85 to 95 % of oxaliplatin-treated patients rapidly develop significant pain without motor dysfunction during the oxaliplatin infusion period, peaking at the first 24–48 h [4, 5]. This acute neurotoxicity is characterized by the rapid onset of cold-induced distal dysesthesia, paresthesia, hypoesthesia, or dysesthesia of the hands, feet, peri-oral area or throat [4, 6].

Previous studies using rodents have shown that a single administration of 5–6 mg/kg oxaliplatin reproduces the neurotoxic profile, especially hypersensitivity to cold with allodynia and hyperalgesia, and also reproduces mechanical allodynia, but not heat thermal hyperalgesia and allodynia, or mechanical hyperalgesia [7–9]. However, there are a relatively small number of clinical reports showing the effective treatment or prevention of such neuropathic pain symptoms, since the mechanism of oxaliplatin-induced peripheral neuropathy is still unclear. Thus, it is of

high importance to find potential therapeutic options for the management of oxaliplatin-induced neuropathic pain.

Acupuncture has been used for thousands of years in East Asia, including China, Korea and Japan, to treat various diseases, especially pain, while generating few side effects. It is now viewed as an alternative method of medicine in Western countries [10, 11]. Electroacupuncture (EA) is a modified acupuncture technique that utilizes electrical stimulation to enhance the acupuncture effect. The acupuncture or EA-induced analgesic effects on neuropathic pain have been reported in several clinical studies [12–14], and many previous studies by us and others have shown that EA relieves the behavioral signs of hyperalgesia and allodynia in rat models of peripheral nerve injury-induced neuropathic pain [15–18]. However, it has not been studied whether or how EA relieves cold allodynia in oxaliplatin-induced neuropathic pain subjects.

It is well known that the analgesic effects of EA are mediated by endogenous opioid and/or non-opioid, noradrenergic system, even though whether either or both of the two endogenous analgesic systems are involved in the EA effects on specific pain types is still unclear [19–21]. In the present study, we examined whether EA can relieve cold allodynia produced by a single injection of oxaliplatin in rats, and if so, which endogenous analgesic system mediates the anti-allodynic action of EA.

Materials and methods

Young adult male Sprague–Dawley rats [Sam:TacN(SD)BR, 7 weeks old, average 200 g] were housed in group cages with water and food available ad libitum. The room was maintained with a 12-h light/dark cycle (08:00–20:00 h light, 20:00–08:00 h dark) and kept at 23 ± 2 °C. All of the procedures involving animals were conducted in accordance with the National Institutes of Health (NIH) guidelines and were approved by the Institutional Animal Care and Use Committee of Kyung Hee University.

Oxaliplatin was obtained from Sigma Chemical Co. USA. It was dissolved in a 5 % glucose (Sigma, USA) solution at a concentration of 2 mg/ml and was intraperitoneally administered at 6 mg/kg. The same volume of 5 % glucose solution was injected in the control group [7, 8].

The behavioral signs of cold allodynia were determined by immersing the tail in cold (4 °C) water as previously described [16, 22]. Briefly, each animal was lightly immobilized in a plastic holder and its tail was drooped for a proper application of cold water stimuli. After 5 cm of tail was immersed, the latency to an abrupt tail movement was measured with a cutoff time of 15 s. The tail immersion test was repeated five times at 5-min intervals. When calculating the average latency, the cutoff time was assigned to normal responses. The average latency was taken as a measure of the severity of cold allodynia (i.e. a shorter latency was interpreted as more severe allodynia).

For EA stimulation at ST36, a pair of stainless steel acupuncture needles (0.2 mm in diameter and 3 cm length) was inserted (5 mm in depth); one into the right ST36 acupoint, which is located in the anterior tibial muscle, and 5 mm lateral and distal to the anterior tubercle of the tibia, and another into the point 5 mm distal from the first needle. EA stimulation at this acupoint is known to produce systemic analgesic effects in various pain types, including neuropathic pain, through the activation of the endogenous analgesic systems [16, 19, 23]. The output terminals of the electrical stimulator (Nihon Kohden, Japan) were connected to the two acupuncture needles and constant rectangular current pulses (2 or 100 Hz, 0.3-ms pulse duration) were applied for 20 min. To exclude the stress effect that might be induced by EA stimulation itself, we adjusted the intensity of the muscle twitch threshold (0.2–0.3 mA). For the control, rats were simply immobilized in the same plastic holder without acupuncture needle insertion and electrical stimulation. For EA stimulation at non-acupoint, the two needles were inserted (5 mm in depth and apart from each other) at non-acupoint, which is located midway between the right coccyx and hip joints [24], and electrical stimulation was applied the same as with EA stimulation at ST36.

Because EA stimulation is known to activate β-endorphin release from the hypothalamus and the pituitary that results in analgesia [19, 20, 29], we measured the levels of plasma β-endorphin in the control and EA groups. Cardiac blood was collected under CO_2 asphyxiation, and plasma was separated by centrifugation and stored at −70 °C until the day of analysis. The measurement of plasma β-endorphin levels was performed with a commercial rat β-endorphin ELISA kit (MyBioSource Inc., USA) following the manufacturer's protocol.

For pharmacological blockade experiments, naloxone (opioid receptor antagonist, 2 mg/kg, Sigma) or phentolamine [α-adrenoceptor (AR) antagonist, 2 mg/kg, Sigma] was injected intraperitoneally 20 min before the EA stimulation. Drugs were dissolved in sterile 0.9 % NaCl (normal saline, NS). For the control, the same volume of NS (i.p.) was injected 20 min before EA stimulation.

Data are presented as mean ± SEM. For the statistical analysis, paired t test, unpaired t-test, one-way ANOVA followed by Dunnett's multiple comparison test, or two-way ANOVA followed by Bonferroni post-test was used. In all cases, $P < 0.05$ was considered significant.

Results

The results of the tail immersion test before and after a single administration of oxaliplatin are shown in Fig. 1. The withdrawal latency was nearly cutoff value (15 s) before the oxaliplatin injection and significantly decreased from 3 days to at least 7 days after the injection, compared with that of the control group ($P < 0.001$). This indicates that the rats developed hypersensitivity to cold stimuli after the administration of oxaliplatin, and we interpreted this as a sign of cold allodynia. Our data are similar to the results of a previous study [8] showing the rapid development of cold allodynia from 2 days after a single administration of oxaliplatin (6 mg/kg, i.p.). The small discrepancy in the onset time of cold allodynia between our result and the previous result might be due to the difference in vender (Sam Tac vs. Charles River). Alternatively, it might be due to the difference in the age of rats used. The following experiments were performed between 3 and 7 days after an oxaliplatin injection, to see whether and how EA attenuates oxaliplatin-induced cold allodynia.

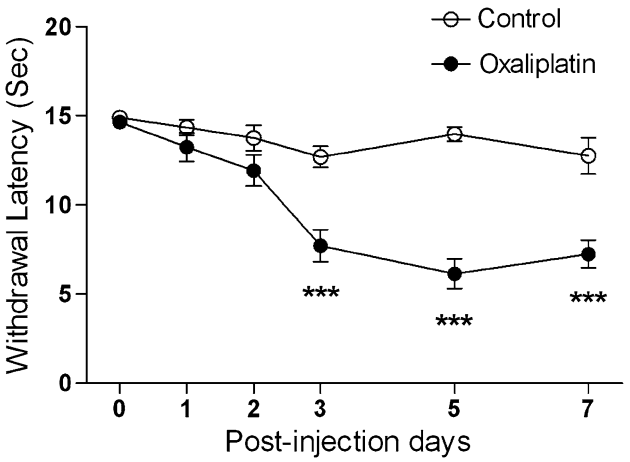

Fig. 1 Time course of cold allodynia induced by a single injection of oxaliplatin. Tail withdrawal latencies to cold (4 °C) water stimuli in the control (vehicle, $n = 8$) and oxaliplatin (6 mg/kg, i.p., $n = 10$) groups are plotted against post-injection days. Data are expressed as mean ± SEM. ***$P < 0.001$, by Bonferroni post-test after two-way ANOVA

The relieving effects of EA with different stimulation parameters (2 and 100 Hz, ST36 acupoint and non-acupoint) on oxaliplatin-induced cold allodynia are shown in Fig. 2. Behavioral tests were done before the start of EA and immediately after the end of EA stimulation. In the control group, no significant difference in withdrawal latency was observed before and after a light immobilization without EA (Fig. 2a). The low-frequency (2 Hz) EA stimulation at ST36 acupoint markedly relieved cold allodynia ($P < 0.001$, Fig. 2b), while high-frequency (100 Hz) EA stimulation at ST36 showed a slight, but not significant, increase in withdrawal latency ($P > 0.05$, Fig. 2c). Interestingly, low-frequency EA at non-acupoint produced a significant anti-allodynic effect ($P < 0.05$, Fig. 2d). However, the potency of anti-allodynic action was significantly higher in the ST36 low-frequency EA group than in the

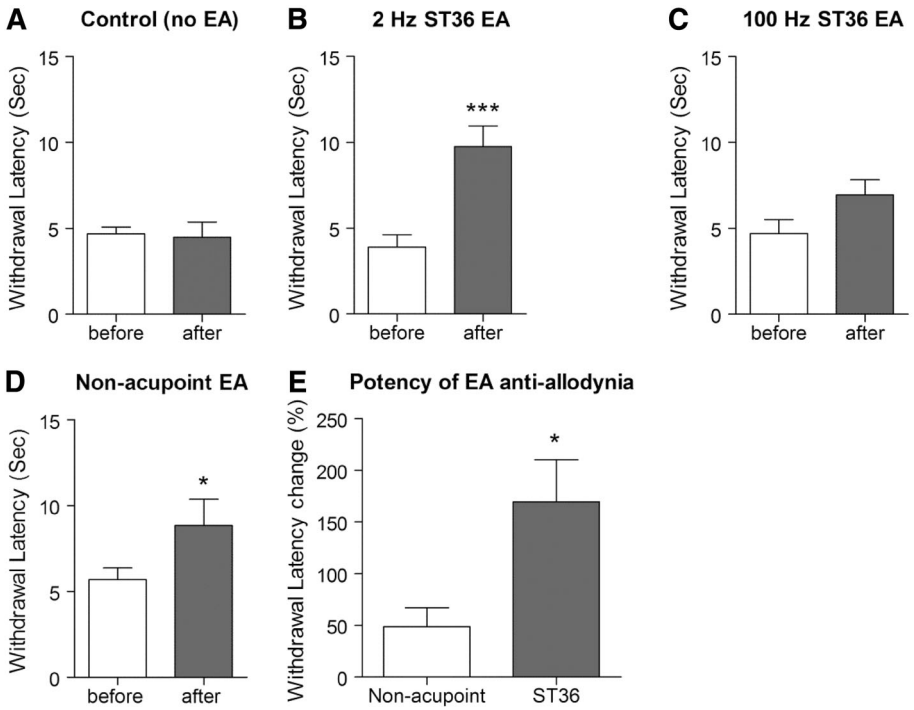

Fig. 2 Effects of EA with different stimulation parameters on oxaliplatin-induced cold allodynia. The behavioral tests for cold allodynia were performed before and after the EA (2 or 100 Hz, ST36 acupoint or non-acupoint, 0.3-ms pulse width, 0.2–0.3 mA, for 20 min). **a** Control (light immobilization without EA, $n = 8$). **b** 2 Hz ST36 EA (low-frequency EA stimulation at ST36 acupoint, $n = 13$). **c** 100 Hz ST36 EA (high-frequency EA stimulation at ST36 acupoint, $n = 10$). **d** Non-acupoint EA (low-frequency EA stimulation at non-acupoint, $n = 9$). **e** Comparison of increase rate in withdrawal latency between ST36 EA (**b**) and non-acupoint EA (**d**) groups. Data are expressed as mean ± SEM. *$P < 0.05$, ***$P < 0.001$, by paired (**a**–**d**) or unpaired (**e**) t test

non-acupoint EA group ($P < 0.05$, Fig. 2e). The relieving effects of low-frequency EA at ST36 on oxaliplatin-induced cold allodynia was maximal immediately after the end of EA, and then gradually decreased and finally diminished at 1.5 h after the end of EA stimulation (Fig. 3e).

To determine whether the anti-allodynic effect of EA in oxaliplatin-injected rats is mediated by the endogenous opioid or noradrenergic system, we pre-treated either an opioid or adrenergic receptor antagonist and evaluated the effects of low-frequency EA stimulation at ST36 on cold allodynia signs (Fig. 3). Each drugs without EA stimulation had no significant effect on cold allodynia signs. In the control group (normal saline pre-treatment), there was a significant increase in withdrawal latency after EA ($P < 0.05$, Fig. 3a). Pre-administration of the opioid receptor antagonist naloxone (2 mg/kg, i.p.) completely blocked the anti-allodynic effect of EA ($P > 0.05$, Fig. 3b), whereas the α-adrenergic receptor antagonist phentolamine (2 mg/kg, i.p.) did not block the EA effect ($P < 0.05$, Fig. 3c). In addition, plasma β-endorphin levels significantly increased 10 min after the end of EA stimulation and subsequently decreased (Fig. 3d), correlating with the time course of EA-induced anti-allodynic effect (Fig. 3e). Morphine hydrochloride (2 mg/kg, i.p., Myungmoon Pharm., Korea) showed a stronger, but similarly lasting, anti-allodynic action with EA stimulation, whereas increased duration of EA stimulation (i.e. 30-min EA) showed more prolonged analgesic action than morphine (Fig. 3e).

Discussion

Oxaliplatin is a third-generation platinum-based chemotherapy drug that has gained importance in the treatment of advanced metastatic colorectal cancer [3, 25]. Because oxaliplatin is a platinum-based drug, it is structurally similar to cisplatin and carboplatin, and has a neurotoxic side effect. However, no nephrotoxicity as with cisplatin,

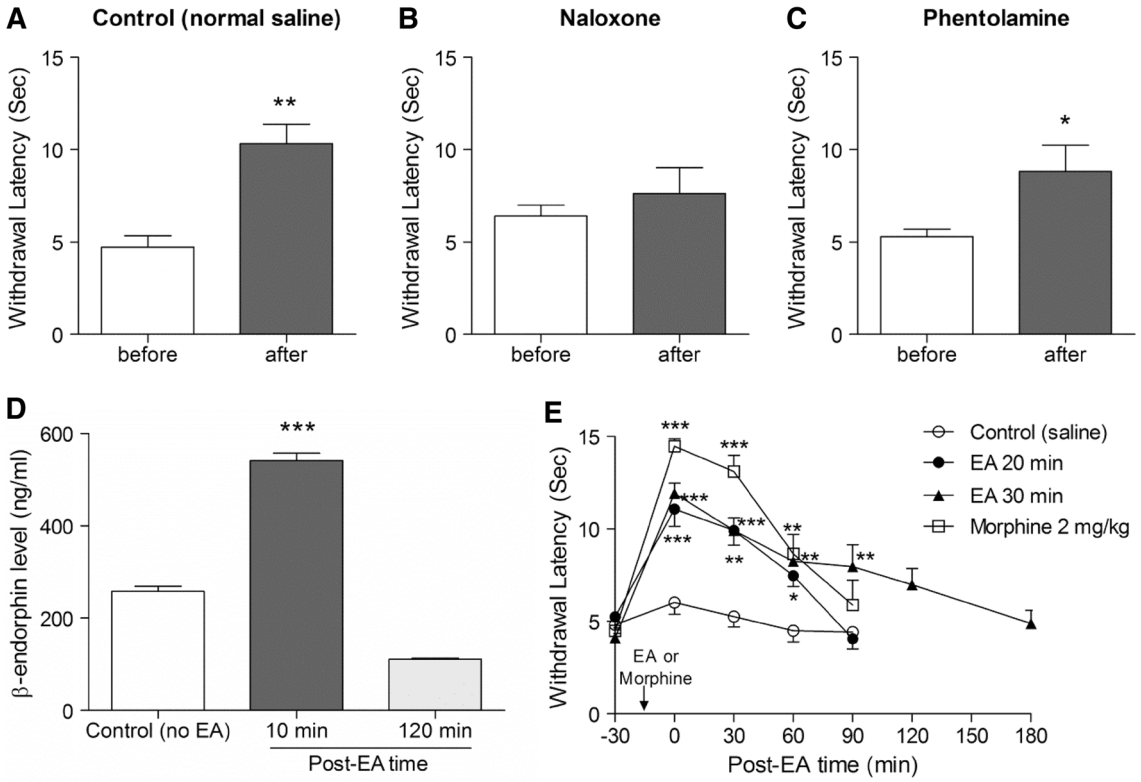

Fig. 3 Effects of opioid and adrenergic receptor antagonists on EA-induced anti-allodynic action in oxaliplatin-injected rats. The behavioral tests for cold allodynia were performed before the i.p. injection of the drugs [**a** Normal Saline control ($n = 8$), **b**; Naloxone ($n = 8$), **c**; Phentolamine ($n = 8$)] and after the EA stimulation (2 Hz, ST36 acupoint, 0.3-ms pulse duration, 0.2–0.3 mA, for 20 min). Each drugs without EA stimulation had no significant effect on cold allodynia signs. **d** Plasma β-endorphin levels were significantly increased at 10 min after the end of EA stimulation as compared to the control (no EA) condition, and subsequently decreased at 120 min post-EA ($n = 4$/group). **e** Time course of anti-allodynic actions of morphine (2 mg/kg, i.p., $n = 8$), 20 min ($n = 8$) or 30 min ($n = 8$) EA stimulation, and saline control ($n = 9$) in oxaliplatin-injected rats. Data are presented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ by paired t test (**a**–**c**) or one-way ANOVA followed by Dunnet's test (**d**, **e**)

and no hematotoxicity as with carboplatin, has been observed [5, 26]. Therefore, if the neurotoxic effects of oxalipaltin are attenuated, patients who receive oxaliplatin treatment might overcome cancer without suffering neuropathic pain.

In this study, we demonstrate that EA stimulation strongly relieves oxaliplatin-induced cold allodynia in rats. More specifically, low-frequency EA stimulation at ST36 acupoint produces a more potent anti-allodynic effect than either high-frequency EA at ST36 or low-frequency EA at non-acupoint. These results are consistent with our previous studies showing that low-frequency EA at ST36 produced more robust and longer-lasting anti-allodynic effects on mechanical and cold allodynia in a rat model of peripheral nerve injury-induced neuropathic pain than did high-frequency EA [16, 27]. Others also reported that low-frequency EA has longer inhibitory effects on neural activity of the dorsal horn in neuropathic rats than high-frequency EA [28]. One of the interesting findings in the present study is the moderate, but significant, anti-allodynic effect of low-frequency EA stimulation at non-acupoint. This may be due to the proximity of the non-acupoint used in this study (hip) to the tested area for the cold allodynia signs (tail). However, the potency of anti-allodynic action (% increase rate of withdrawal latency after EA) was significantly higher in the ST36 low-frequency EA group than in the non-acupoint low-frequency EA group. Thus, it is strongly suggested that low-frequency EA stimulation at ST36 acupoint is suitable for the treatment of cold allodynia in neuropathic pain subjects.

The analgesic effects of EA are known to be mediated by the endogenous analgesic systems, especially the opioid and noradrenergic systems. However, which system is mainly involved in EA analgesia remains controversial [19–21, 29, 30]. Our previous studies using a rat model of peripheral nerve injury suggested that both the opioid and the noradrenergic systems contribute equally to the anti-allodynic effects of EA [15, 16, 27]. In contrast, Chung and his colleagues have consistently reported that the α-adrenergic receptor antagonist, phentolamine, blocked the analgesic effects of EA on ankle sprain pain in rats, whereas the opioid receptor antagonists, naloxone and naltrexone, failed to block the EA effects [31–33]. Intriguingly, the same group reported the opposite mechanism in a different pain rat model; the opioid, but not noradrenergic, system mediates the suppressive effects of EA on capsaicin-induced secondary hyperalgesia [34]. In the present study, phentolamine did not prevent the relieving effects of EA on oxaliplatin-induced cold allodynia, while naloxone pretreatment completely blocked the anti-allodynic effects of EA. It has been well documented from decades ago that acupuncture or EA stimulation activates the hypothalamus and pituitary gland, which releases endogenous opioid peptides, especially β-endorphin, into the circulating system, producing potent analgesic effects in various types of pain [19, 20, 35]. This study further demonstrated that plasma levels of β-endorphin were significantly increased right after EA stimulation and subsequently reduced, correlating with the time course of the EA-induced anti-allodynic effect in oxaliplatin-injected rats. Taken together, it might be suggested that the endogenous analgesic system involved in EA analgesia depends on the type of pain, and our findings indicate that the major analgesic system mediating the anti-allodynic effect of EA in oxaliplatin-induced neuropathic pain rats is the endogenous opioid system.

Although this study and many other previous reports have shown that increased levels of plasma β-endorphin after EA are correlated with increased pain threshold, the analgesic effect of plasma β-endorphin alone might be limited to the periphery, or be smaller than the central action of opioids [19, 36, 37]. Thus, in addition to β-endorphin, the other endogenous peptides in the spinal cord, such as enkephalin and endomorphin, which are known to be released by low-frequency EA stimulation [29], might play a role in the anti-allodynic effect shown in this study. It is also noteworthy that there is a functional interrelationship between the opioid and noradrenergic system spinally and/or supraspinally [38, 39]. Our previous studies suggest that the other non-opioid analgesic systems, including serotonergic, cholinergic and GABAergic systems, at least partly mediate the relieving effects of EA on cold allodynia in a rat model of peripheral neuropathic pain [16, 40, 41]. Further studies on this issue may increase our understanding of the analgesic mechanisms of acupuncture analgesia.

In conclusion, the data from the present study clearly show that low-frequency EA at ST36 markedly relieves the cold allodynia signs produced by a single injection of oxaliplatin in rats. This anti-allodynic effect of EA is mediated by the endogenous opioid, but not the noradrenergic, system. Thus, our findings suggest that EA treatment can be a potential therapeutic option in oxaliplatin-induced neuropathic pain.

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Conflict of interest There are no conflicts of interest to declare.

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