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Effects of electroacupuncture on cold allodynia in a rat model of neuropathic pain: Mediation by spinal adrenergic and serotonergic receptors

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Abstract

The present study was performed to examine the effects of electroacupuncture (EA) on cold allodynia and its mechanisms related to the spinal adrenergic and serotonergic systems in a rat model of neuropathic pain. For the neuropathic surgery, the right superior caudal trunk was resected at the level between S1 and S2 spinal nerves innervating the tail. Two weeks after the nerve injury, EA stimulation (2 or 100 Hz) was delivered to Zusanli (ST36) for 30 min. The behavioral signs of cold allodynia were evaluated by the tail immersion test [i.e., immersing the tail in cold water (4°C) and measuring the latency to an abrupt tail movement] before and after the stimulation. And then, we examined the effects of intrathecal injection of prazosin (α_1-adrenoceptor antagonist, 30 μg), yohimbine (α_2-adrenoceptor antagonist, 30 μg), NAN-190 (5-HT_{1A} antagonist, 15 μg), ketanserin (5-HT_{2A} antagonist, 30 μg), and MDL-72222 (5-HT_3 antagonist, 12 μg) on the action of EA stimulation. Although both 2 Hz and 100 Hz EA significantly relieved the cold allodynia signs, 2 Hz EA induced more robust effects than 100 Hz EA. In addition, intrathecal injection of yohimbine, NAN-190, and MDL-72222, but not prazosin and ketanserin, significantly blocked the relieving effects of 2 Hz EA on cold allodynia. These results suggest that low-frequency (2 Hz) EA is more suitable for the treatment of cold allodynia than high-frequency (100 Hz) EA, and spinal α_2-adrenergic, 5-HT_{1A} and 5-HT_3, but not α_1-adrenergic and 5-HT_{2A}, receptors play important roles in mediating the relieving effects of 2 Hz EA on cold allodynia in neuropathic rats.

Keywords: Neuropathic pain; Cold allodynia; Electroacupuncture; Adrenergic; Serotonin; Spinal cord

Introduction

Peripheral nerve injury often leads to neuropathic pain, which is characterized by spontaneous burning pain, allodynia, and hyperalgesia. The mechanisms underlying this pain are complex and appear to involve peripheral and central components of the nervous system (Bridges et al., 2001). Numerous studies have recently attempted to elucidate pathophysiological mechanisms or drug effects for neuropathic pain in patients and experimental animal models (Fields et al., 1999; Millan, 2002; Namaka et al., 2004). Many drugs or methods for pain control such as systemic local anesthetics, tricyclic antidepressants, morphine, and sympathectomy have been examined. Unfortunately, these therapeutic outcomes have been reported variable and several side effects have been observed (Kim

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et al., 1997c; Martin and Eisenach, 2001; Namaka et al., 2004).

Acupuncture has long been used in Eastern countries for the treatment of various diseases including pain, with few side effects, and recently considered a new alternative method of medicine in Western countries (Cherkin et al., 2003; Kaptchuk, 2002). Electroacupuncture (EA) is a modified technique using electrical stimulation and its analgesic effects have been shown in rodents by acute pain-related behavior tests (Chang et al., 2004; Han, 1987; Kim et al., 2000). Since chronic pain, especially neuropathic pain, is difficult to treat and is more complicated than acute pain, it is of interest to investigate the analgesic effect of EA on neuropathic pain. Clinical evidence that acupuncture or acupuncture-like stimulation, such as transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation, and EA, is effective for the neuropathic pain of malignancy (Filshie, 1988) and diabetic neuropathy (Abuaisha et al., 1998; Goodnick et al., 2000), and phantom limb pain (Carabelli and Kellerman, 1985; Finsen et al., 1988) has been reported. Furthermore, several recent studies have reported that EA significantly relieved neuropathic pain behaviors; mechanical and heat hyperalgesia in the chronic constriction injury model (Dai et al., 2001), and mechanical allodynia in the rat tail (Hwang et al., 2002) and spinal nerve ligation models (Huang et al., 2004). However, it is still unclear whether EA relieves cold allodynia.

It is well known that the analgesic effects of EA are mediated by descending inhibitory systems (Filshie and White, 1998; Han, 1987; Takeshige et al., 1992). Descending inhibition is translated into antinociception in the spinal cord mainly by activation of adrenergic, serotonergic, and opioidergic receptors (Millan, 2002; Stamford, 1995). Recently, the involvement of opioidergic system in the analgesic effects of EA on neuropathic pain has been elucidated (Huang et al., 2004; Hwang et al., 2002; Kim et al., 2004; Ma et al., 2004) and the results are consistent with previous studies using other types of pain model (Filshie and White, 1998; Han, 1987, 2003). However, the conflicting results have been reported regarding the adrenergic or serotonergic receptor mechanism of EA-induced analgesia, possibly due to the differences in the type of pain model (Chang et al., 2004; Radhakrishnan et al., 2003; Takagi and Yonehara, 1998). Furthermore, the mechanisms of EA-induced analgesic effects on neuropathic pain related to descending adrenergic and serotonergic systems have not yet been studied.

The present study, using the rat tail model (Kim et al., 1997a; Na et al., 1994), was performed to examine whether low (2 Hz)- or high (100 Hz)-frequency EA relieved the behavioral signs of cold allodynia. If so, we further examined whether spinal adrenergic and serotonergic receptors played a role in mediating the relieving effects of EA on cold allodynia.

Materials and methods

Experimental animals

Young adult, male Sprague–Dawley rats [Sam:TacN (SD)BR, 200–220 g] were housed in groups of four, with water and food available ad libitum. The room was maintained with a 12-h light/dark cycle (08:00–20:00 light, 20:00–08:00 dark) and kept at 23 ± 2°C. All experiments were conducted in accordance with the guidelines of the International Association for the Study of Pain (Zimmerman, 1983).

Neuropathic surgery

The rats were subjected to the neuropathic surgery as previously described by Na and his coworkers (Kim et al., 1997a; Na et al., 1994). Briefly, under sodium pentobarbital anesthesia (40 mg/kg, i.p.), the right superior caudal trunk was exposed, freed from the surrounding tissues and transected at the level between the S1 and S2 spinal nerves that innervate the rat tail. To prevent the possible rejoining of the proximal and distal ends of the severed trunk, an approximately 2-mm piece of the trunk was removed from the proximal end. This surgery eliminated the S1 spinal nerve innervation to the tail via the superior caudal trunk. Control rats underwent sham surgery, i.e., the same surgical procedures except for transection of the nerve. The present rat tail model, similar to the three widely used models produced by a partial injury of the nerves innervating the hind paw (Bennett and Xie, 1988; Kim and Chung, 1992; Seltzer et al., 1990), displays clear chronic neuropathic symptoms like mechanical, cold, and warm allodynia. In addition, this model is very easy to apply thermal stimulation to the tail. Blind behavioral tests are also possible due to the lack of deformity in the tail following the nerve injury (Na et al., 1994).

Behavioral test for cold allodynia signs

The behavioral signs of cold allodynia were sought by immersing the tail in cold water (4°C). As described previously (Kim et al., 1997a; Na et al., 1994), each animal was restrained in a plastic holder and its tail was drooped for proper application of cold water stimuli. Following the tail immersion, 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 the normal responses. The average latency was taken as a measure for the severity of cold allodynia; a shorter latency was interpreted as more severe cold allodynia.

EA stimulation

Two stainless-steel needles 0.25 mm in diameter and 4 cm in length were inserted into Zusanli (ST36) which is