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EXPERIMENTAL STUDY

Electroacupuncture alters pain-related behaviors and expression of spinal prostaglandin E_2 in a rat model of neuropathic pain

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Abstract

OBJECTIVE: To investigate the role of spinal prostaglandin E_2 (PGE_2) in electroacupuncture (EA) analgesia and assess the theoretical basis for selection of acupoints in the treatment of neuropathic pain.

METHODS: A rat model of neuropathic pain was established. Rats were randomly divided into normal, model, sham, EA 1, EA 2, and EA 3 groups. In EA 1 group, the rats were needled at bilateral L5 Jiaji (EX-B2), Dachangshu (BL 25), Weizhong (BL 40) and Kunlun (BL 60). In EA 2 group, the rats were needled at bilateral Weizhong (BL 40) and Kunlun (BL 60). In EA 3 group, the rats were needled at bilateral L5 Jiaji (EX-B2) and Dachangshu (BL 25). EA stimulation was administered once daily over 7 days. Motor function and thermal withdrawal latencies were evaluated at 1 day preoperatively and at 3, 5, and 7 days postoperatively. After 7 days of intervention, enzyme-linked immunosorbnent assay (ELISA) was used to quantify the expression of the spinal PGE_2.

RESULTS: Rats in the model group exhibited evident hyperalgesia in responses to thermal withdrawal latencies compared with those in the control group ($P < 0.01$), and EA reversed thermal withdrawal latencies ($P < 0.01$). The expression level of the spinal PGE_2 was significantly higher in the model group than that in the control group and was reversed by EA ($P < 0.01$; $P < 0.05$).

CONCLUSION: The effect of EA on neuropathic pain might alleviate the hyperalgesia state by an inhibition of local prostaglandin E_2 secretion.

Key words: Electroacupuncture; Neuralgia; Dinoprostone; Acupuncture analgesia; Spinal cord; Hyperalgesia

INTRODUCTION

Neuropathic pain induced by injuries of the nervous system is a severely clinical problem, which affects millions of people worldwide. Various studies investigate the pathological mechanisms of neuropathic pain.[1,2] Studies have shown that the inflammatory effects is possibly related to neuropathic pain. The local production of these inflammatory effects appears to account for many of the pathologic and clinical manifestations of neuropathic pain. It has been indicated that inflammatory reactions can demyelinate the nerve root and lead to neural hypersensitivity and neuropathic pain.[3,4] It has been widely accepted that prostanoids are involved in pain, fever, edema and various aspects of inflammation. Among them, prostaglandin E_2 (PGE_2) is

considered the principal proinflammatory prostanoid and plays an important role in nociceptive processing and sensitization in the spinal cord as well as in the periphery.[5] It has been suggested that PGE_2 is involved in the induction and maintenance of neuropathic pain as well as inflammatory pain.[6]

Generally, neuropathic pain in the clinics is mainly managed by physical, surgical, or pharmacological interventions. However, neuropathic pain is often poorly relieved by currently available treatments such as non-steroidal anti-inflammatory drugs and opioids.[7,8] The places for acupuncture, also known as acupoints, are the specific sites where the *Qi* of *Zang-Fu* organs and channels is transported to the body surface. The outcomes of the treatment are directly attributed to the validity of selecting appropriate acupoints. Selecting perfect acupoint module is the main aspect of an acupuncture prescription, which is known as compatibility of acupoints and is widely considered to be one of the key factors influencing the effects of acupuncture. The stimulation of the specific acupoints module by acupuncture may dredge channels and regulate the flow of *Qi* and blood.

Electroacupuncture is a combination of acupuncture and electrical stimulation techniques. It has been shown that electrical stimulation can promote motoneuron regeneration.[9,10] It has been indicated that EA produces anti-hyperalgesia in animal models of inflammatory pain. It has been investigated that EA can mitigate pain-related behaviors induced by nucleus pulposus in rat model and promote motor recovery by assessing muscle electrical activity elicited under peripheral nerve stimulation.[11,12] Animal studies have also shown that EA inhibits hyperalgesia in traumatic nerve injury-induced neuropathic pain. However, whether the roles of different acupoints compatibility for PGE_2 are involved in acupuncture analgesia remains unknown. What's more, there is no accepted study concerning the theoretical basis for selection of acupoints in the treatment of neuropathic pain. In this study, we aimed to investigate whether EA at different acupoint combinations could modulate the expression of spinal PGE_2 in the rat model of neuropathic pain, which in return would alleviate the hyperalgesia state.

MATERIALS AND METHODS

Animals

Fifty-four healthy male four-month-old Sprague Dawley rats of specific pathogen free grade, weighing (300 ± 20) g, were obtained from the Experimental Animal Center of Academy of Medical Science of Chinese People's Liberation Army [Beijing, China, Animal certificate: SCXK - (Army) 2007-004]. The rats were housed in standard polypropylene cages containing 2.5 cm of wood chip bedding material, and cages were maintained in an animal room with a 12-h light / 12-h dark cycle, at room temperature of (22 ± 1) ℃, and 50% ± 10% humidity. All rats had free access to food and water. Animals were habituated to the behavioral testing paradigms for 3-5 days before the experiment. All experimental procedures were in accordance with the Guidelines of International Association for the Study of Pain (IASP) and were approved by the Animal Care and Use Committee of Beijing University of Chinese Medicine. The behavioral experiments remained double blind. Rats were randomly divided into six groups by random number table method, 9 rats in each group: (a) control group (untreated); (b) sham group (a sham surgery without NP); (c) model group (normal NP); (d) EA 1 group (EA at "distant acupoints + local acupoints"); (e) EA 2 group (EA at distant acupoints); (f) EA 3 group (EA at local acupoints). In the model, EA 1, EA 2 and EA 3 groups, the neuropathic pain model was established by autologous nucleus pulposus. The rats in EA 1 group, EA 2 group and EA 3 group received EA treatment once per day, for 7 days. This study was approved by the Animal Ethics Committee, Beijing University of Chinese Medicine in China.

Establishment of neuropathic pain model induced by autologous nucleus pulposus (NP)

All surgical procedures were performed with the rats anesthetized with an intraperitoneal injection of 10% chloral hydrate (0.35 mL/100 g). The tail of rat was amputated 1 cm distal to the anus. Following amputation of the tail, the left L_5 nerve roots were exposed after partial hemilaminectomies and left L_5 facetectomy. Autologous nucleus pulposus (4 mg) obtained from the coccygeal intervertebral discs of the amputated tail in the same rat was relocated at the juncture of the L_5 nerve root and the dural sac. The nerve roots treated only by application of autologous nucleus pulposus were not mechanically compressed at the time of surgery. While rats of the sham surgery group underwent the sham procedure, the left L_5 nerve roots were exposed after partial hemilaminectomies and left L_5 facetectomy. After surgery, the wounds were irrigated and washed with preservative-free sterile saline solution. The operatic fields were closed in layers with 4-0 nylon sutures. Then all rats were sent to a relatively warm room for better recovery from anesthesia. Pain-related behaviors of the rats were evaluated.[13]

EA stimulation

For the animals that received EA treatment, EA administration started on day 1 post-surgery, twenty minutes each time, once a day for 7 days. After the surface of acupoints sterilized with 75% ethyl alcohol, the needles were vertically inserted into bilateral points to a relative depth (Location of the acupoints: L_5 Jiaji (EX-B 2), level with the lower border of the spinal process of the fifth lumbar vertebra, nearby to the posterior midline; Dachangshu (BL 25), level with the lower border