Brain Research Bulletin 86 (2011) 412–421

Contents lists available at SciVerse ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Chemical stimulation of the ST36 acupoint reduces both formalin-induced nociceptive behaviors and spinal astrocyte activation via spinal alpha-2 adrenoceptors

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ARTICLE INFO

Article history:
Received 27 January 2011
Received in revised form 27 July 2011
Accepted 19 August 2011
Available online 26 August 2011

Keywords:
Bee venom
Acupuncture
Astrocyte
Anti-nociceptive effect
Alpha-2 adrenoceptor

ABSTRACT

Spinal astrocytes have emerged as important mechanistic contributors to pathological and chronic pain. Recently, we have demonstrated that injection of diluted bee venom (DBV) into the Zusanli (ST36) acupoint produces a potent anti-nociceptive effect via the activation of spinal alpha-2 adrenoceptors. However, it is unclear if this anti-nociceptive effect is associated with alterations in spinal astrocytes. Thus, the present study was designed to determine: (1) whether DBV's anti-nociceptive effect in the formalin test involves suppression of spinal astrocyte activation; (2) whether DBV-induced astrocyte inhibition is mediated by spinal alpha-2 adrenoceptors; and (3) whether this glial modulation is potentiated by intrathecal administration of the glial metabolic inhibitor, fluorocitrate (FC) in combination with DBV injection. DBV was injected directly into the ST36 acupoint, and spinal expression of the astrocytic marker, glial fibrillary acidic protein (GFAP), was assessed together with effects on formalin-induced nociception. DBV treatment reduced pain responses in the late phase of the formalin test and significantly blocked the formalin-evoked increase in spinal GFAP expression. These effects of DBV were prevented by intrathecal pretreatment with selective alpha-2A and alpha-2C adrenoceptor antagonists. Moreover, low dose intrathecal injection of FC in conjunction with low dose DBV injection into the ST36 acupoint synergistically suppressed pain responses and GFAP expression. These results demonstrate that DBV stimulation of the ST36 acupoint inhibits the formalin-induced activation of spinal astrocytes and nociceptive behaviors in this inflammatory pain model and this inhibition is associated with the activation of spinal alpha-2 adrenoceptors.

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1. Introduction

Traditionally pain sensation was thought to be mediated exclusively by neurons with no involvement of glial cells. In this regard astrocytes and microglia were considered to play mainly a supporting role, providing nutritional and protective benefits to neurons, while having no substantial effect on neuronal signaling [40]. Over the past decade a large number of studies have demonstrated that glial cells play a much more active role in nervous system function and indeed astrocytes are now thought to be involved in processing synaptic information. With respect to nociception it has become clear that spinal cord glia play an important role in the development and maintenance of pathologic pain [10,44]. In particular, astrocytic activation is a common phenomenon following peripheral nerve injury [1,4]. Astrocytes can respond rapidly to various physiological, pathological or noxious stimuli and this response is often associated with an increase in glial fibrillary acidic protein (GFAP). Because of this association, GFAP is routinely used as a marker of astrocyte activation. With respect to the involvement of astrocytes in nociception, the staining density of GFAP has been analyzed in a large number of studies using animal models of acute or chronic pain. Based on studies of spinal cord astrocytes in a model of neuropathic pain, Colburn et al. hypothesized that following chronic constriction injury of the sciatic nerve, the activation of astrocytes contributed to the development of mechanical hypersensitivity associated with this model [3]. Moreover, mounting evidence from studies of animal models of chronic pain indicates that the

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doi:10.1016/j.brainresbull.2011.08.012

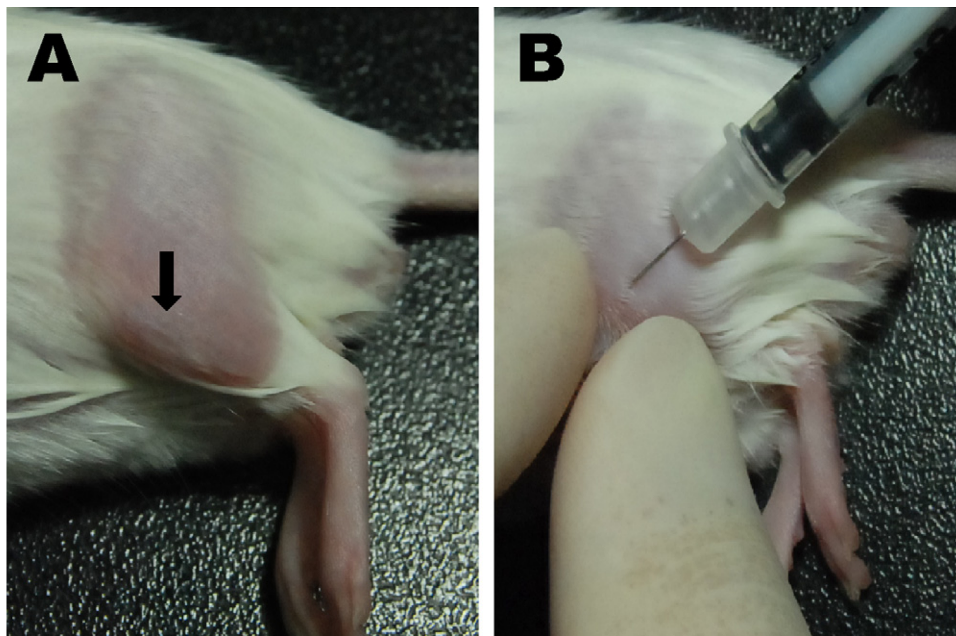

Fig. 1. (A) Photograph showing the location of the Zusanli (ST36) acupoint, which is located 5 mm below and lateral to the anterior tubercle of the tibia. Black arrow indicates the potential site of injection of DBV into ST36. (B) Photograph demonstrating an actual injection of DBV into the ST36 acupoint of the left hind limb in a representative mouse.

persistent activation of spinal astrocytes is a unique feature of various types of chronic pain including bone cancer [21], neuropathic pain [48,46], spinal cord injury-induced pain [27] and adjuvant-induced inflammatory pain [30]. Because astrocytes are activated in these pain models and interact robustly with neurons to create complex pain pathophysiologies, the role of these cells cannot be ignored when considering the neuronal involvement in the spectrum of pain conditions.

One of the treatments for pain is the use of acupuncture stimulation to produce an analgesic effect and reduce the severity of pain. In this regard subcutaneous injection of diluted bee venom (DBV) into an acupoint, termed *apipuncture*, has been used clinically in traditional oriental medicine to produce a potent anti-nociceptive effect in human patients. Previous experimental studies in our laboratory provide support for this alternative medicine approach by demonstrating that subcutaneous injection of DBV into the Zusanli (ST36) acupuncture point produces a robust anti-nociceptive and anti-hyperalgesic effect in a variety of animal models of pain including the formalin test [15], the writhing test [18] and a carrageenan-induced inflammatory pain model [19]. We have further shown that this apipuncture-induced anti-nociceptive effect is mediated by the activation of descending coeruleospinal noradrenergic pathways, which in turn activate spinal alpha-2 adrenoceptors [14,17,31]. In this regard administration of alpha-2 adrenoceptor agonists produce a dose-dependent attenuation of PSNL-induced mechanical and thermal hyperalgesia, but also markedly inhibit neuroimmune related glial activation [5]. In addition, it has been shown that the antidepressant-induced reduction of astrocytic activation can be blocked by alpha-2 adrenoceptor antagonists [47]. However, it is not clear whether acupuncture's anti-nociceptive effect is associated with the modulation of spinal cord glial cells.

Based on the above studies, we hypothesize that administration of DBV into the ST36 acupoint reduces nociceptive responses and that this is mediated in part through alpha-2 adrenoceptor suppression of spinal astrocyte activation. Thus, the present study was designed to determine: (1) whether DBV's anti-nociceptive effect involves the suppression of spinal astrocyte activation in a formalin-induced pain mode and (2) whether DBV-induced astrocyte modulation is mediated by the activation of spinal alpha-2 adrenoceptors and whether this is potentiated by intrathecal co-application of the glia cell metabolic inhibitor, fluorocitrate.

2. Materials and methods

2.1. Animals

Experiments were performed on male ICR mice weighing 20–25 g. All experimental animals were obtained from the Laboratory Animal Center of Seoul National University. They were housed in colony cages with free access to food and water and maintained in temperature and light controlled rooms (24 ± 2 °C, 12-h/12-h light/dark cycle with lights on at 07:00) for at least 1 week before the study. All of the methods used in the present study were approved by the Animal Care and Use Committee at Seoul National University and conform to NIH guidelines (NIH publication No. 86-23, revised 1985). All algesiometric assays were conducted under the ethical guidelines set forth by the International Association for the Study of Pain (IASP).

2.2. DBV treatment

Whole Bee Venom (Sigma, St. Louis, MO) was diluted and subsequently injected at doses of 0.8 or 0.08 mg/kg as previously described [31]. Briefly DBV was dissolved in a 20 μl volume of saline, and administered subcutaneously into the Zusanli (ST36) acupoint. The ST36 acupoint is located 5 mm below and lateral to the anterior tubercle of the tibia (Fig. 1A). Animals in the control group were injected into the ST36 acupoint with an equal volume of saline. DBV or saline was injected 10 min before intraplantar formalin injection (Fig. 1B).

2.3. Intrathecal treatment of drugs

Idazoxan (IDX, an alpha-2 adrenoceptor antagonist, 10 μg/mice), BRL44408 (BRL, a selective alpha-2A adrenoceptor antagonist, 0.3, 1 μg/mice), JP1302 (JP, a selective alpha-2C adrenoceptor antagonist, 1, 5 μg/mice) or fluorocitrate (FC, a glial metabolic inhibitor, 0.3, 0.1 and 0.03 nmol/mice) were administered by intrathecal injection, based on the technique developed by Hylden and Wilcox [13]. Briefly, for mouse intrathecal injections, a 30-gauge needle (length, 0.5 in.) connected to a 50-μl Hamilton syringe was inserted into the subarachnoidal space between lumbar vertebrae L5 and L6. A flick of the mouse's tail provided a reliable indicator that the needle had penetrated the dura. The syringe was held in position for a few seconds after the injection of a volume of 5 μl/mouse. IDX, BRL, JP and FC were purchased from Sigma (St. Louis, MO) and diluted in saline. These drugs were injected 5 min before DBV or saline administration into the ST36 acupoint.

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