Editorial

Anti-nociceptive mechanisms of electroacupuncture in inflammatory pain

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Comment on: Liao HY, Hsieh CL, Huang CP, *et al*. Electroacupuncture Attenuates CFA-induced Inflammatory Pain by suppressing Nav1.8 through S100B, TRPV1, Opioid, and Adenosine Pathways in Mice. Sci Rep 2017;7:42531.

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Acupuncture and electroacupuncture (EA) are widely applied as non-invasive treatment for acute and chronic pain. In the last decade, mechanisms of EA analgesia in inflammatory pain have been extensively studied (1-4).

A recent study by Liao *et al.* (5) investigated mechanisms of EA in a rodent model of inflammatory pain. The authors showed that intraperitoneal injection of the opioid-specific agonist endomorphin reduced mechanical and thermal hyperalgesia in inflammatory pain. Meanwhile, intraperitoneal injection of naloxone into the acupoint ST36 blocked the analgesic effects of EA. It is known that in inflamed tissues, EA activates immune cells such as lymphocytes, monocytes/macrophages and granulocyte (6,7). Furthermore, EA promotes the release of different endogenous opiates in a frequency-dependent manner (8). In rats, low-frequency (2 Hz) EA at ST36 stimulated the release of β-endorphin, enkephalin and endomorphin, whereas high-frequency (100 Hz) EA stimulated dynorphin to inhibit nociception (9,10). These findings have also been verified in humans (11). In addition, pulse width of EA influences its analgesic effect as well (12). Consistent with these findings, low- and high-frequency EA are mediated by μ-/δ-receptors and k-receptors, respectively under physiological conditions (10,13). However, in pathological conditions such as CFA/carrageenan-induced inflammatory pain rats, μ- and δ-receptors but not κ-receptors seem to be involved in EA analgesia (14,15). Further studies showed that lesions of the arcuate nuclei abolished low-frequency EA induced analgesia but not high-frequency EA, whereas lesions of the parabrachial nuclei attenuated high-frequency EA induced analgesia but not low-frequency EA (16,17). It appears that low- and high-frequency EA-induced analgesia may be mediated by different brain areas expressing opioid receptors.

Besides opioid peptides, various other signal molecules are implicated in acupuncture analgesia, including cholecystokinin octapeptide, 5-hydroxytryptamine, noradrenalin, glutamate etc. (18). Recently, increasing evidence revealed that adenosine A1 receptors participate in anti-nociception in peripheral, spinal and supraspinal levels (19,20). In 2010, Goldman *et al.* (21) first demonstrated that adenosine acting on A1 receptors in sensory afferents of ascending nerves mediated the anti-nociceptive actions of acupuncture. In the study by Liao *et al.* (5), researchers showed that administration of adenosine A1 receptor agonist at ST36 attenuated inflammatory pain behaviors, while an intramuscular injection of rolofylline, an adenosine A1 receptor antagonist, blocked the analgesic effects of EA. The authors further revealed that expression of the astrocyte marker GFAP, the microglia marker Iba-1, and associated proteins S100B and RAGE dramatically increased in the dorsal root ganglion and spinal dorsal horn of CFA-treated mice, which were reversed by EA.

Spinal astrocytes and microglia are involved in the induction and development of inflammatory pain (22-24). Combinative application of minocycline, a microglial inhibitor, enhanced EA's analgesia effects in CFA-induced monoarthritic rat (25,26). EA stimulation at GB30 and GB34 markedly inhibited CFA-induced behavioral hypersensitivity, attenuated astrocyte and microglia activation, and upregulated TNF-α, IL-1β and IL-6 mRNA levels in the spinal cord (27,28). These findings

suggest that analgesic effects of EA at least partially result from inhibiting spinal glial activities and proinflammatory cytokine production.

In conclusion, the study by Liao *et al.* (5) reveals the roles of glia/neuropeptide/adenosine in the analgesic effects of EA, and provides insight on mechanisms underlying EA's therapeutic effects against inflammatory pain. Further investigation is required for elucidating detailed interactions between these molecular changes and EA stimulation.

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