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Editorial

Electroacupuncture on Visceral Hyperalgesia - What Is Its Mechanism?

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Article: Effect of electroacupuncture on visceral hyperalgesia, serotonin and Fos expression in an animal model of irritable bowel syndrome
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Acupuncture is widely used to induce analgesia. Electroacupuncture (EA) is a modification of traditional acupuncture that stimulates acupoints with electrical current instead of manual manipulations. Most studies use EA because EA can be standardized by frequency, voltage, wave form, length, etc and therefore appears to presented with more consistently reproducible results in both the clinical and research settings.[1] The analgesic effects induced by EA may be mediated through different mechanisms depending on the specific conditions which include opioid and non-opioid mechanisms. In EA, frequency is a basic determinant for different endogenous opiates secretion.[2] The analgesia by lower frequency (2 Hz) EA is mediated through μ- and δ-opioid receptors and analgesia by higher frequency (100 Hz) is mediated through the κ-opioid receptor. Two Hz EA stimulates the release of β-endophin, enkephalin and endomorphin within the CNS network and 100 Hz EA releases dynorphin.[3-5] One of non-opioid mechanisms involves serotonin (5-HT) and the descending pain inhibitory pathway. EA analgesia is blocked by 5-HT_{1A} and 5-HT_3 antagonists at both low (2 Hz) and high frequencies (100 Hz); whereas, EA analgesia is enhanced by 5-HT_2 antagonist at high frequency.[6] There are many serotonin releasing nuclei (serotoninergic neurons) in the CNS. The central parts of the descending pain inhibitory pathway are the periaqueductal gray in the upper brainstem (midbrain) and the nucleus raphe magnus (NRM) in the lower brainstem (from lower pons to medulla). The axons of these serotoninergic neurons terminate at the level of spinal cord.[7,8] The 5-HT_1 and 5-HT_3 subtypes are located in the dorsal horn of the spinal cord. The 5-HT_2 receptor is located in the cortex and hippocampus.[9] The NRM descends and projects its serotoninergic axons to the spinal cord. Enkephalinergic interneurons, especially in laminae I and II with responsiveness to nociception, are activated by 5-HT from the NRM. These interneurons then release enkephalin and presynaptically inhibit primary sensory neurons in the spinal cord. Therefore, the arcuate nucleus-periaqueductal gray-NRM-spinal cord axis is activated by lower frequency EA.[10]

In this study, Wu et al used a central rat model for visceral hyperalgesia with neonatal maternal separation stress and found that 10 Hz EA significantly reduced the visceromotor responses to colorectal balloon distension compared to sham acupuncture. They

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observed that the pain reduction was associated with significant reduction in serotonergic activities. The reduction in 5-HT expression was primarily seen at the spinal cord and brainstem and, not at the colonic mucosa. The previous studies reported that EA decreased 5-HT concentration in colonic tissue of the rats with chronic visceral hypersensitivity (CVH).[11,12] This discrepancy may be due to the different animal models and different electrical currents employed. In a recent report, EA reduced the 5-HT concentration and increased the serotonin 4 receptor ($5\text{-HT}_4\text{R}$) concentration, but had no effect on the $5\text{-HT}_3\text{R}$ concentration in the colonic tissue of CVH rats. It has demonstrated that EA could reduce the concentration of 5-HT by activating $5\text{-HT}_4\text{R}$, whereas $5\text{-HT}_3\text{R}$ may not be involved in the regulation of the visceral pain threshold in CVH rats.[11] However the study did not used sham control group. Further studies should be needed to identify 5-HT expression in the colonic tissue and 5-HT receptors involved in the regulation of the visceral pain threshold in CVH rats.

In this issue of the journal, Wu et al reported that the Fos positive cells increased in the colonic mucosa of the maternal separation rats treated with sham acupuncture which was reduced by EA. This result showed that EA might involve the peripheral anti-inflammatory and immune functions. Lao et al[13] found increased glucocorticoid level and a longer analgesic effect when 10 Hz EA was applied compared to 100 Hz EA. These results suggested that lower frequency EA elicited a stronger anti-inflammatory effect (through hypothalamic-pituitary-adrenal axis) and a longer-lasting analgesic effect than the higher frequency dose. Further studies are required to evaluate the effect of EA on peripheral inflammatory function and network of serotonergic pathways and inflammatory reflexes.

Wu et al studied the effects of EA in a sham-controlled manner which was distinct from previous stidies. The use of invasive sham had 2 advantages than without sham acupuncture. First, it enabled better blinding of investigators. Second, it demonstrated the genuine effects of EA which might be caused by transcutaneous electric nerve stimulations mostly than the probable non-specific analgesic effects through diffuse noxious inhibitory controls.

In summary, the study by Wu et al demonstrated that EA attenuates visceral hyperalgesia in a central rat model of irritable bowel syndrome and the anti-hyperalgesic effect is probably mediated through the down-regulation of serotonergic activities in CNS. This study also found that EA could involve the peripheral anti-inflammatory and immune functions. Although this study did not found a change of serotonergic activity in peripheral nervous system, these findings provided the possibility of close network of central serotonergic pathways and inflammatory reflexes in irritable bowel syndrome and EA to be a strategy for the treatment of visceral pain in irritable bowel syndrome by modulation of central serotonergic system. Further investigations on the efficacy of EA and its complex mechanisms are definitely warranted.

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