



Review Article

Effects of Acupuncture on Neuropathic Pain: Mechanisms in Animal Models

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Received: August 01, 2022 Revised: August 11, 2022 Accepted: August 17, 2022

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<https://doi.org/10.56986/pim.2022.09.004>

ABSTRACT

Neuropathic pain is a chronic condition/disease characterized by mechanical and thermal pain. Neuropathic pain can have various comorbidities such as depression, anxiety disorders and cognitive impairment, and as a result, can have a detrimental effect on quality of life. Pain and comorbid symptoms are often complicated, intertwined, affect each other, and present difficulties in treatment. Therefore, it is necessary to improve both pain and comorbid symptoms to treat neuropathic pain. Acupuncture is effective in treating not only pain but other conditions/diseases such as depression, anxiety, and cognitive impairment. Recently, acupuncture was reported to be effective in improving comorbid symptoms in patients with chronic pain. This review aimed to describe the mechanisms of action of acupuncture on the brain with respect to the improvement of comorbid symptoms that appeared in animal models of chronic neuropathic pain. Comorbidity-pain studies were comprehensively reviewed. Both manual acupuncture and electroacupuncture improved not only mechanical and thermal pain but also comorbid symptoms such as depression, anxiety, and cognitive impairment in patients with chronic neuropathic pain. The results of this review suggest that comorbid symptoms can be improved through various mechanisms, including the dopamine system in the brain, glutamate system, inflammation, epigenetic modulation, and mitochondrial function.

Keywords: acupuncture, cognitive impairment, comorbidity, neuropathic pain

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Introduction

Neuropathic pain is characterized by mechanical and thermal pain caused by nerve injury and compression, and may be accompanied by other symptoms, such as depression, anxiety disorders, and cognitive impairment [1-4]. Neuropathic pain is difficult to treat because the mechanism is complex with varying sites of onset, causes, and symptoms. In fact, antidepressants such as tricyclic antidepressants, are prescribed together with analgesics such as opioids, to patients with neuropathic pain [5,6]. This suggests the importance of simultaneously improving comorbid symptoms to treat complex neuropathic pain.

Neuropathic pain has a significant impact on various aspects of the peripheral nervous system, as well as the central nervous system. Accordingly, the descending pain pathway involving mostly the periaqueductal gray matter, rostral ventromedial medulla, and spinal cord has drawn much attention [7,8]. However, as comorbid symptoms are complexly intertwined with neuropathic pain and increasingly difficult to treat, the need to observe various regions of the brain, including the prefrontal cortex (PFC),

anterior cingulate cortex (ACC), hippocampus, amygdala, nucleus accumbens, and hypothalamus, has also increased, and human studies and animal models of pain have developed [9-14]. Nonetheless, observing various regions of the brain with respect to neuropathic pain is in its infancy, and thus the mechanism has not been clearly identified.

Manual acupuncture (MA) is a traditional Korean medicine procedure that has been used for thousands of years for pain relief, as well as for treating various conditions/diseases, including depression, sleep disorders, anxiety disorders, and cognitive impairment. Recently, the use of electroacupuncture (EA) with electricity has also been increasing and has been reviewed [15,16]. EA can be used in various treatments by adjusting the frequency and intensity used to pass through the needles. With the importance of improving comorbid symptoms in patients with neuropathic pain, the efficacy of acupuncture is focused not only on improvement of the level of pain but also on improving comorbid symptoms as we have previously discussed when using a murine model of neuropathic pain [17,18]. This review aimed to describe the mechanisms and effects of acupuncture on various regions of the brain with

respect to the improvement of comorbid symptoms that appeared in animal models of chronic neuropathic pain.

1. Emotional dysfunction

The limbic system includes the hippocampus, amygdala, hypothalamus, and thalamus, which are the regions typically responsible for controlling emotions [19]. These regions interact with each other to control emotions, however, defects in the limbic system can result in emotional disorders, such as depression and anxiety as shown in an animal model of chronic neuropathic pain [20].

When the forced swimming test and elevated plus maze tests were conducted after applying EA to “Bai-Hui” (GV20) and unilateral “Yang-Ling-Quan” (GB34) acupoints, EA was determined to have antidepressant and anxiolytic effects. In addition, phosphorylation of NMDA receptor Type 1 in the hippocampus was reduced in a chronic constrictive injury (CCI) model of neuropathic pain, which was restored by EA. EA improved not only mechanical hyperalgesia but also depressive and anxiety-like behaviors in the CCI model of neuropathic pain. Examination of neuroinflammation in the amygdala of rats showed that EA could inhibit astrocyte activity, and the increase the expression of TNF α and IL-1 β proteins due to CCI [21]. In addition, EA could restore the dopamine system, such as tyrosine hydroxylase, dopamine D1 receptor, and dopamine D2 receptor, the levels of which were reduced by CCI [21]. These findings suggest that the improvement in neuropathic pain by EA may be associated with the dopamine system for inhibiting neuroinflammation in the amygdala [21].

The ACC and PFC are typical primary cortices, which are regions that receive signals from other regions of the brain and relay commands [22-24]. They also contribute to controlling emotions by receiving signals from regions in the limbic system [24].

EA can not only reduce mechanical hyperalgesia and thermal allodynia caused by CCI, but also improve depressive and anxiety disorders, as observed in the open field test and the tail suspension test. In CCI in mice, the levels of brain-derived neurotrophic factor and 5-hydroxytryptamine in the ACC and spinal cord were increased, as were the protein expression levels of cAMP-response element-binding protein and brain-derived neurotrophic factor in the ACC [25].

In a partial sciatic nerve ligation (PSNL) model of neuropathic pain, long-term application of MA to “Yang-Ling-Quan” (GB34) and “Huan-tiao” (GB30) acupoints resulted in not only recovery from mechanical hypersensitivity and cold allodynia, but also an improvement in anxiety. Following acupuncture treatment, changes in DNA methylation, an epigenetic modulation in the PFC, hippocampus, amygdala, and periaqueductal gray matter were observed. In particular, acupuncture reduced

DNA methylation in the PFC. The expression of RNA and proteins in the DNA methyltransferase family and methyl-cytosine-phospho-guanine binding protein 2, which contribute to DNA methylation, was reduced by PSNL. However, recovery was achieved following acupuncture treatment. In addition, acupuncture normalized genes associated with cell death and mitochondrial function regulated by methyl-cytosine-phospho-guanine binding protein 2. These findings suggest that acupuncture may be suitable for the long-term treatment and management of pain, as well as depressive and anxiety disorders as we have previously discussed [17].

2. Cognitive impairment

The hippocampus is a typical region of the brain that controls memory and has been studied in humans in association with various cognitive dysfunctions, such as dementia, Alzheimer’s disease [24,26], and in mice to study neuropathic pain [27]. Memory circuits that connect the dentate gyrus to CA3 and CA1 induce long-term potential to form and generate short-term memory. However, problems with these circuits can cause problems in learning and memory, which could affect short-term memory loss [24,28]. Cognitive impairment is a common comorbid symptom in patients with neuropathic pain, the outcome of which can have a significant impact on their quality of life. Therefore, instead of treating pain, comorbid symptoms must be treated to improve the quality of life of the patient.

In a cobra venom-induced trigeminal neuralgia model of neuropathic pain, EA applied to “Shou-san-li” (LI10) and “Qu-chi” (LI11) acupoints improved spatial learning and memory as observed in the Morris water maze test. In addition, the

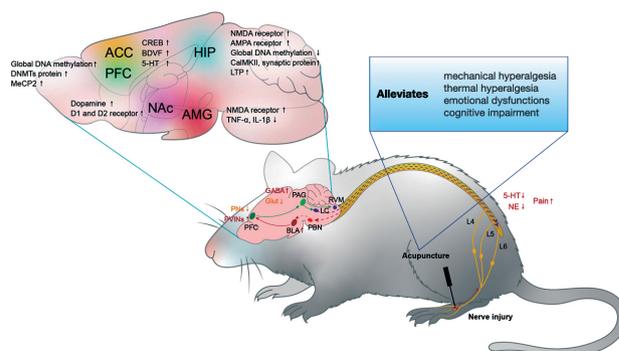


Fig. 1. The effects of acupuncture on neuropathic pain: Brain mechanisms. PAG-RVM and PAG-LC, which arrive at the signals from various regions of the brain such as ACC, PFC, HIP, NAC, and AMG, transmit signals to the spinal cord as a descending pain pathway, and loss of descending modulation increases pain. Acupuncture may induce normalization of the descending pain pathway by restoring the functions of various brain regions such as ACC, PFC, HIP, NAC, and AMG.

ACC, anterior cingulate cortex; PFC, prefrontal cortex; HIP, hippocampus; NAC, nucleus accumbens; AMG, amygdala.

field excitatory postsynaptic potential in CA1, reduced by cobra venom, could be improved by EA [29]. In the PSNL model of neuropathic pain, MA applied to “Yang-Ling-Quan” (GB34) and “Huan-tiao” (GB30) acupoints increased the levels of NMDA and AMPA receptors NR1 and GluR1 in CA1, CA3, and the dentate gyrus, while also restoring long-term potential in the hippocampus and increasing the levels of CaMKII protein and synaptic proteins Syn-1 and PSD-95. These findings suggest that acupuncture can help to restore the overall function of the hippocampus damaged by neuropathic pain as we have previously discussed [18].

In addition to the hippocampus, the PFC is a region that receives memory-related signals and relays various commands. Thus, it is responsible for an important role in memory function. In the cobra venom-induced trigeminal neuralgia model of neuropathic pain in rats, genomic and proteomics analyses on the PFC and hippocampus showed changes in functions associated with cognition, regulation of behavior, and the glutamatergic system after EA was applied to “Yang-Ling-Quan” (GB34) and “Huan-tiao” (GB30) acupoints [30]. Similarly, when cognitive function was assessed using a novel object recognition test using a spared nerve injury model of neuropathic pain in rats, the results showed that EA could improve not only pain due to spared nerve injury but also cognitive impairment. Moreover, TMEM126A increased by EA as per the proteomics analysis in the hippocampus, is a protein that acts on the TLR4 signaling pathway in macrophages, which plays an important role in inflammatory immune regulation. In other words, the results suggest the possibility of EA regulating the immune system of the hippocampus [31].

In the PSNL model of neuropathic pain, an improvement in cognitive function by the long-term application of MA to the “Yang-Ling-Quan” (GB34) and “Huan-tiao”(GB30) acupoints was confirmed by the Y-maze and novel object recognition tests. Moreover, the increase in global DNA methylation in the hippocampus caused by PSNL was reduced by treatment with MA. In other words, an improvement in cognitive function by long-term MA treatment could start with changes in DNA methylation as we have previously discussed [17]. However, additional studies are needed, as the mechanism for the genes undergoing DNA methylation has not yet been elucidated.

Conclusion

This review included various animal studies that examined the role of the brain in relation to comorbid symptoms in various neuropathic models of pain. These findings showed that acupuncture may help improve neuropathic pain, depression, anxiety, and cognitive impairment. In addition, the findings could also be interpreted as the capacity of acupuncture regulation of

various mechanisms such as mitochondrial function, as well as the dopamine system, glutamate system, inflammation, and epigenetic modulation in regions in the brain, including the PFC, ACC, hippocampus, and amygdala (Fig. 1). However, animal, and human studies on acupuncture in this field are lacking compared with pharmacological studies. Therefore, more studies are needed to identify the mechanisms underlying the effects of acupuncture.

Acknowledgments

This research was supported by grants from the National Research Foundation of Korea funded by the Korean government (no.: NRF-2020R111A1A01072607). All other authors declare no competing financial interests.

Author Contributions

Writing the original draft: JHJ. Writing - review and editing: JHJ, and HJP.

Conflicts of Interests

The authors have no conflicts of interest to declare.

Ethical Statement

This research did not involve any human or animal experiments.

Data Availability

Not applicable.

References

- [1] Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci* 2013;14(7):502-11.
- [2] Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, et al. Genome-wide meta-analysis of 158,000 individuals of European ancestry identifies three loci associated with chronic back pain. *PLoS Genet* 2018;14(9):e1007601.
- [3] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. *Pain* 2015;156(6):1003-7.
- [4] Woo AK. Depression and Anxiety in Pain. *Rev Pain* 2010;4(1):8-12.
- [5] Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17(9):1113-e88.
- [6] Kane CM, Mulvey MR, Wright S, Craigs C, Wright JM, Bennett MI. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. *Palliat Med* 2018;32(1):276-86.
- [7] Millan MJ. Descending control of pain. *Prog Neurobiol* 2002;66(6):355-474.
- [8] Fields H. State-dependent opioid control of pain. *Nat Rev Neurosci* 2004;5(7):565-75.
- [9] Bilbao A, Falfan-Melgoza C, Leixner S, Becker R, Singaravelu SK, Sack M, et al. Longitudinal Structural and Functional Brain Network Alterations in a Mouse Model of Neuropathic Pain. *Neuroscience* 2018;387:104-15.
- [10] Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, et al. Effective treatment of chronic low back pain in

- humans reverses abnormal brain anatomy and function. *J Neurosci* 2011;31(20):7540-50.
- [11] Tajerian M, Alvarado S, Millecamps M, Vachon P, Crosby C, Bushnell MC, et al. Peripheral nerve injury is associated with chronic, reversible changes in global DNA methylation in the mouse prefrontal cortex. *PLoS One* 2013;8(1):e55259.
- [12] Zhang Y, Mao Z, Pan L, Ling Z, Liu X, Zhang J, et al. Dysregulation of Pain- and Emotion-Related Networks in Trigeminal Neuralgia. *Front Hum Neurosci* 2018;12:107.
- [13] Cheriyan J, Sheets PL. Altered Excitability and Local Connectivity of mPFC-PAG Neurons in a Mouse Model of Neuropathic Pain. *J Neurosci* 2018;38(20):4829-39.
- [14] Gao Y, Chen S, Xu Q, Yu K, Wang J, Qiao L, et al. Proteomic analysis of differential proteins related to anti-nociceptive effect of electroacupuncture in the hypothalamus following neuropathic pain in rats. *Neurochem Res* 2013;38(7):1467-78.
- [15] Seo SY, Lee KB, Shin JS, Lee J, Kim MR, Ha IH, et al. Effectiveness of Acupuncture and Electroacupuncture for Chronic Neck Pain: A Systematic Review and Meta-Analysis. *Am J Chin Med* 2017;45(8):1573-95.
- [16] Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018;19(5):455-74.
- [17] Jang JH, Song EM, Do YH, Ahn S, Oh JY, Hwang TY, et al. Acupuncture alleviates chronic pain and comorbid conditions in a mouse model of neuropathic pain: the involvement of DNA methylation in the prefrontal cortex. *Pain* 2021;162(2):514-30.
- [18] Jang JH, Kim YK, Jung WM, Kim HK, Song EM, Kim HY, et al. Acupuncture Improves Comorbid Cognitive Impairments Induced by Neuropathic Pain in Mice. *Front Neurosci* 2019;13:995.
- [19] Catani M, Dell'acqua F, Thiebaut de Schotten M. A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev* 2013;37(8):1724-37.
- [20] Ulrich-Lai YM, Xie W, Meij JT, Dolgas CM, Yu L, Herman JP. Limbic and HPA axis function in an animal model of chronic neuropathic pain. *Physiol Behav* 2006;88(1-2):67-76.
- [21] Zhang XH, Feng CC, Pei LJ, Zhang YN, Chen L, Wei XQ, et al. Electroacupuncture Attenuates Neuropathic Pain and Comorbid Negative Behavior: The Involvement of the Dopamine System in the Amygdala. *Front Neurosci* 2021;15:657507.
- [22] Rolls ET. The cingulate cortex and limbic systems for emotion, action, and memory. *Brain Struct Funct* 2019;224(9):3001-18.
- [23] Barbas H. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Res Bull* 2000;52(5):319-30.
- [24] Rolls ET. Limbic systems for emotion and for memory, but no single limbic system. *Cortex* 2015;62:119-57.
- [25] Cong W, Peng Y, Meng B, Jia X, Jin Z. The effect of electroacupuncture on regulating pain and depression-like behaviors induced by chronic neuropathic pain. *Ann Palliat Med* 2021;10(1):104-13.
- [26] Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. *Eur Neurol* 1993;33(6):403-8.
- [27] Ignatowski TA, Covey WC, Knight PR, Severin CM, Nickola TJ, Spengler RN. Brain-derived TNF α mediates neuropathic pain. *Brain Res* 1999;841(1-2):70-7.
- [28] McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci* 2001;933:265-77.
- [29] Gao J, Zhao C, Jiang W, Zheng B, He Y. Effect of Acupuncture on Cognitive Function and Quality of Life in Patients With Idiopathic Trigeminal Neuralgia. *J Nerv Ment Dis* 2019;207(3):171-74.
- [30] Zhang JF, Williams JP, Shi WR, Qian XY, Zhao QN, Lu GF, et al. Potential Molecular Mechanisms of Electroacupuncture With Spatial Learning and Memory Impairment Induced by Chronic Pain on a Rat Model. *Pain Physician* 2022;25(2):E271-83.
- [31] Gong D, Yu X, Jiang M, Li C, Wang Z. Differential Proteomic Analysis of the Hippocampus in Rats with Neuropathic Pain to Investigate the Use of Electroacupuncture in Relieving Mechanical Allodynia and Cognitive Decline. *Neural Plast* 2021;2021:5597163.