Epigenetic Regulation of Chronic Pain
Review

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The analgesic effect of acupuncture in neuropathic pain: regulatory mechanisms of DNA methylation in the brain

Jae-Hwan Jang[a], Yoon Jae Lee[a], In-Hyuk Ha[a], Hi-Joon Park[b,*]

Abstract

Recent research has demonstrated that chronic pain, resulting from peripheral nerve injury, leads to various symptoms, including not only allodynia and hyperalgesia but also anxiety, depression, and cognitive impairment. These symptoms are believed to arise due to alterations in gene expression and neural function, mediated by epigenetic changes in chromatin structure. Emerging evidence suggests that acupuncture can modulate DNA methylation within the central nervous system, contributing to pain relief and the mitigation of comorbidities. Specifically, acupuncture has been shown to adjust the DNA methylation of genes related to mitochondrial dysfunction, oxidative phosphorylation, and inflammation pathways within cortical regions, such as the prefrontal cortex, anterior cingulate cortex, and primary somatosensory cortex. In addition, it influences the DNA methylation of genes associated with neurogenesis in hippocampal neurons. This evidence indicates that acupuncture, a treatment with fewer side effects compared with conventional medications, could offer an effective strategy for pain management.

Keywords: Acupuncture, Neuropathic pain, Comorbidity, Epigenetic mechanisms, DNA methylation

1. Introduction

Chronic pain, enduring or recurring over a period exceeding 3 to 6 months, presents significant socioeconomic challenges, incurring annual costs ranging $560 to $635 billion because of medical visits, medications, and reduced productivity.[33,41] Notably, neuropathic pain, a subset of chronic pain experienced by up to 10% of individuals,[43] involves increased sensitivity to pain stimuli.[53] This condition is characterized by allodynia, where nonpainful stimuli cause pain, and hyperalgesia, where the response to painful stimuli is amplified.[54] Beyond this physical discomfort, neuropathic pain is associated with diminished quality of life, contributing to depression, anxiety, and sleep disorders.[3,4,8,13] Given these complex etiology and symptoms, understanding the role of central nervous system (CNS), including epigenetic mechanisms like DNA methylation, histone modification, noncoding RNA, is crucial for developing effective treatments.[10,12,15,31,45]

For more than 2 millennia, acupuncture has been a corner stone in treating chronic conditions in East Asian Medicine, including various types of pain, depression, and sleep disorder.[30,56] Recent research, including studies by Wang et al., suggests the acupuncture's potential to modulate epigenetic mechanisms, such as hypertensive rats,[50,51] indicating broader therapeutic applications, like enhancing reproductive functions and alleviating depression through epigenetic regulation in animal models.[9] The influence of acupuncture on DNA methylation, particularly regarding neuropathic pain, has garnered increasing interest, although the underlying mechanisms remain to be fully elucidated.[24,28,39] This review aims to consolidate existing research on the relationship between DNA methylation and the analgesic effects of acupuncture, underscoring the importance of epigenetic processes in acupuncture's therapeutic potential.

2. DNA methylation in neuropathic pain

Neuropathic pain is difficult to treat because the peripheral and central mechanisms are complexly intertwined.[43] The

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[a] Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, Seoul, Republic of Korea, [b] Acupuncture and Meridian Science Research Center (AMSRC), College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

**Corresponding author. Address: Acupuncture and Meridian Science Research Center (AMSRC), College of Korean Medicine, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea. Tel.: +82 2 961 9435. E-mail address: acufind@khu.ac.kr (H.-J. Park).*

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development and maintenance of neuropathic pain following peripheral nerve injury is characterized by long-term structural and physiological changes in various regions of the CNS, such as prefrontal cortex (PFC), anterior cingulate cortex (ACC), primary somatosensory cortex (S1), periaqueductal gray matter (PAG), hippocampus, amygdala, and spinal cord.[4,32,54] Recently, there has been an increase in studies suggesting that DNA methylation is involved in multiple mechanisms induced by peripheral nerve injury.[10,15]

DNA methylation, which partly silences gene expression without affecting the primary DNA sequence, plays a significant role in oncology, neurological diseases, pathological gene expression states, and abnormal activity in the CNS. It is associated with synaptic plasticity and memory formation, as well as in neuropsychiatric disorders, such as depression.[35,44,48] DNA methylation is the covalent addition of methyl residues to cytosine-phosphoguanine (CpG) dinucleotides, enzymatically catalyzed by methylated DNA methyltransferases (DNMTs), forming 5-methylcytosine (5-mC) on CpG islands.[7,19,34] CpG islands are clusters of CpG dinucleotides found in the promoters of many genes and are highly conserved in rodents and humans.[2,25] It has been reported that 6 months after peripheral nerve injury, mice develop depression and anxiety, and global DNA methylation is reduced in the PFC.[18,24,46] In addition, methyl donor S-adenosylmethionine (SAM) attenuated spared nerve injury (SNI)–induced mechanical hypersensitivity and reduced active avoidance of mechanical stimuli.[18] These results show that normalization of DNA methylation changes induced by neuropathic pain is important for analgesic effects.

DNMT families, including DNMT1, DNMT3a, and DNMT3b, are responsible for the transferring a methyl group from the universal methyl donor SAM to the carbon-5 position of cytosine residues in the nucleic acid sequence and are essential for the development.[42] Zhao et al.[58] suggest that DNMT3a may contribute to the development of neuropathic pain by repressing *Kcna2* expression in the dorsal root ganglion. In addition, 6 months after partial sciatic nerve ligation (PSNL), the mRNA and protein expression levels of DNMT3a were suppressed by increasing DNA methylation in the *Dnmt3a* promoter in the PFC.[24]

DNA methylation is mediated by separate protein families, namely, methyl-CpG-binding domain (MBD), ubiquitin-like, containing PHD and ring finger domain (UHRF), and zinc finger proteins.[34] The methylation of CpG islands represses gene expression by recruiting DNMT-mediated MBD proteins. Methyl-CpG binding protein 2 (MeCP2) is a MBD family protein that primarily functions as a transcriptional repressor. In preclinical studies, MeCP2 mRNA expression levels were decreased in the ipsilaterally superficial dorsal horn following SNI surgery.[47] Furthermore, DNA methylation in the *Mecp2* promoter was increased in the PFC following PSNL, whereas MeCP2 mRNA and protein expression levels were decreased.[24]

In neurons, there is a balance of DNA methylation and demethylation. DNA demethylation refers to the removal or modification of a methyl group at 5-mC during specific enzymatic processes, occurring both actively and passively.[36] 5-Hydroxymethyl cytosine (5-hmC) is an intermediate form of DNA demethylation and is enriched within the promoters and bodies of genes.[26] The continuous reaction of ten-eleven translocation (TET) enzymes initiates DNA demethylation, converting 5-mC to 5-hmC.[40] The TET family is divided into 3 proteins: TET1, TET2, and TET3. TET1 and TET3 primarily regulate the level of 5-hmC in gene promoters and transcription start sites, and TET2 mainly regulates the level of 5-hmC in the gene body.[1] It was reported that overexpression of TET1 through microinjection into the dorsal root ganglion can alleviate neuropathic pain by restoring the expression of μ-opioid receptor (MOR) and Kv1.2, which were reduced by peripheral nerve injury.[55] In addition, TET2 and TET3 are associated with neuropathic pain, and it was recently indicated that *Tet3* demethylase plays a major role in active DNA demethylation for axon regeneration and regional hypomethylation of genes linked to nerve regeneration after peripheral nerve injury.[6,52]

Therefore, DNA methylation and demethylation play important roles in the development and maintenance of neuropathic pain, suggesting that DNMT3a, MeCP2, and TET family may be important therapeutic targets.

3. DNA methylation on the analgesic effect of acupuncture

Acupuncture has been established as a viable pain management strategy, with a wealth of clinical and preclinical research supporting its efficacy in pain relief.[11,22] It operates, in part, by desensitizing peripheral nociceptors and mitigating inflammation, achieved through the upregulation of endogenous opioids.[56] Beyond these effects, acupuncture prompts significant structural and physiological modifications within the CNS, affecting regions including the PFC, ACC, S1, PAG, hippocampus, amygdala, and spinal cord.[24,37,56,59] Acupuncture stimulation promotes the release of adenosine and histamine from the skin and muscle layers, thereby increasing the expression of phosphorylated ERK and the transient receptor potential vanilloid 1, activating signal transduction to the central nervous system.[16,20,38,49] A recent study reported that acupuncture applied to acupoints in the legs transmits signals to the central nervous system by activating prokineticin receptor 2 expressing neurons, thereby having an antiinflammatory effect.[29] However, although substantial, these findings do not fully elucidate the complex analgesic mechanisms underpinning acupuncture's effects. Recently, with emerging importance of DNA methylation changes in neuropathic pain,[25] and new studies have begun to explore a novel perspective, suggesting that acupuncture may exert its therapeutic effects not only through neural and physiological pathways but also at the genomic level, by modulating DNA methylation patterns (**Tables 1 and 2**).

Cortical regions play a crucial role in neuropathic pain, with several areas, including the PFC, ACC, and S1, pivotal in the modulation of nociception. This modulation occurs through the

Table 1

Acupuncture protocols and sham controls in neuropathic pain: a focus on DNA methylation.

Author (y)	Acupuncture modality	Acupoints	Frequency (Hz)	Current (mA)	Time (min)	Tx sessions	Sham control procedures
Jang (2021)	MA	GB30, GB34	2	N/A	0.5	Thrice/wk for 6 mo	Nonacupoints with the same MS
Li (2023)	EA	ST36, SP6	100	0.3	30	Once daily for 5 or 7 d	Same insertion without ES
Ping (2023)	EA	GB34	2/100	0.1	15	Once daily for 7 d	N/A

EA, electroacupuncture; ES, electrical stimulation; MA, manual acupuncture; mo, month; MS, manual stimulation; N/A, not applicable; Tx, treatment; wk, week.

Table 2

Effects of acupuncture on neuropathic pain: behavioral and DNA methylation outcomes.

Author (y)	NP model	Behavioral outcomes			DNA methylation analysis			
		Pain	Emotion	Cognition	DNA methylation vs NP	Brain areas	Genes	Function
Jang (2021)	Partial sciatic nerve ligation	Mechanical hyperalgesia↓, cold allodynia↓	Anxiety↓, depression↓	Short-term memory↑	PFC↑ HIP↓ AMG↓ HT↓ PAG↑	PFC	*Mecp2, Dnmt3a, Nr4a1, Rasgrp1, Rassf1, Chkb*	Mitochondrial dysfunction
Li (2023)	Spared nerve injury	Mechanical allodynia↓	Anxiety↓, depression↓, anhedonia↓	None	DG↓	DG	*Tet1, Prox1*	Hippocampal neurogenesis
Ping (2023)	Tibial nerve injury	Mechanical allodynia↓	None	None	ACC (ipsi)↑ S1 (contra)↓	ACC, S1	*Gphn*	Mitochondrial dysfunction

ACC, anterior cingulate cortex; AMG, amygdala; contra, contralateral; DG, dentate gyrus; HIP, hippocampus; HT, hypothalamus; ipsi, ipsilateral; NP, neuropathic pain; PAG, periaqueductal gray matter; PFC, prefrontal cortex; S1, primary somatosensory cortex.

activation of the descending pain pathway by corticospinal projections or activation of brainstem structures, such as PAG.[14] In the S1 and ACC regions, electroacupuncture (EA) treatment has been shown to partially restore the increased levels of 5-mC in the contralateral S1 in a tibial nerve injury mouse model, while simultaneously increasing the levels of 5-hmC in the contralateral S1 and ipsilateral ACC.[39] It is well understood that 5-mC nucleotides mediate gene suppression, particularly at CpG dinucleotides, whereas 5-hmC generally has the opposite effect,[10] facilitating gene expression. Furthermore, research indicates that acupuncture can reduce the activity of the S1 cortex in rats with peripheral nerve injury, with varying responses observed in the ipsilateral and contralateral S1 areas.[5] Specifically, EA regulated inflammation-related pathways predominantly in the contralateral S1, modulating interleukin-15 production and signal transducer and activator of transcription 3 pathway in the ipsilateral S1. In addition, EA influenced pathways related to mitochondrial dysfunction, oxidative phosphorylation, GP6, HOTAIR, and HIF1a in ACC.[39]

A recent study employing the clinically relevant PSNL model of neuropathic pain investigated DNA methylation changes in the PFC of mice. This study found that 6 months of acupuncture

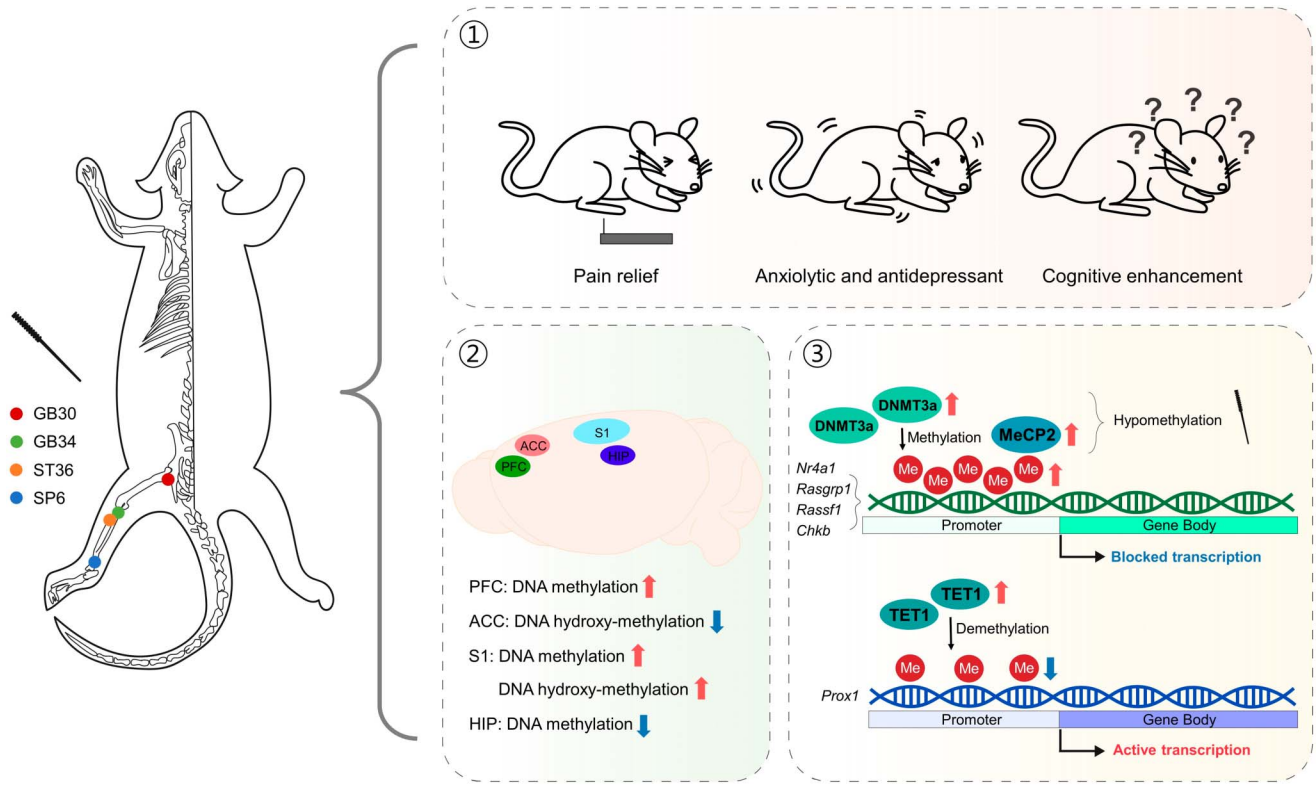

Figure 1. Summary of acupuncture's effect on chronic pain through DNA methylation. Peripheral nerve injury may cause changes in DNA methylation in the brain and, thus, may have a crucial role in chronic pain mechanisms. Acupuncture affects various brain areas by transmitting signals to the central nervous system through peripheral nerve stimulation. Acupuncture improves not only pain but also comorbidity, such as anxiety, depression, and cognitive impairments and induces changes in DNA methylation in ACC, S1, PFC, and HIP. Acupuncture modulates the expression of various genes by regulating the DNA methylation process–related proteins, such as DNMT3a, MeCP2, and TET1. ACC, anterior cingulate cortex; DNMT3a, DNA methyltransferase 3a; HIP, hippocampus; MeCP2, methyl-CpG-binding protein 2; PFC, prefrontal cortex; S1, primary somatosensory cortex; TET1, ten-eleven translocation 1.

treatment reduced mechanical hyperalgesia and cold allodynia induced by PSNL and that global DNA methylation restored by acupuncture in the PFC negatively correlated with mechanical hyperalgesia. The reason why acupuncture was able to improve global DNA methylation in the PFC was because it restored DNA methylation in the promoters of *Mecp2* and *Dnmt3a*, which are involved in the DNA methylation process. Acupuncture also not only increased the protein expressions of 5-mC, which had been decreased in the PFC, but also upregulated mRNA and protein expressions of MeCP2, DNMT1, and DNMT3a. In addition, functional analysis revealed that acupuncture augmented DNA methylation in the promoters of genes associated with mitochondrial dysfunction, namely, *Nr4a1*, *Chkb*, *Rasgrp1*, and *Rassf1*, thereby suppressing mRNA expression.[24]

4. Effect of acupuncture on DNA methylation in pain-related comorbidity

The limbic system, comprising the amygdala, hippocampus, and cingulate cortex, is closely connected with the PFC in both structure and function. This network plays a crucial role in cognition, emotion, motivation, attention, memory, and planning.[27] Peripheral nerve injury can lead to pain-related comorbidities, such as depression, anxiety, and cognitive impairment by disrupting the structural and functional neural networks of the limbic system and PFC, highlighting the necessity of addressing these comorbidities in neuropathic pain treatments.[4,8]

Preclinical studies have demonstrated acupuncture's efficacy in alleviating depression, anxiety, and cognitive impairment associated with neuropathic pain.[17,21,23,24,28,57] Acupuncture enhanced hippocampal long-term action through synaptic plasticity[23] and inhibited neuroinflammation through recovery of the dopamine system in the amygdala.[57] Furthermore, acupuncture has been shown to restore the alteration of DNA methylation induced by PSNL in the amygdala, hippocampus, and PFC,[24,28] suggesting its role in neural network regulation. DNA methylation restored in the PFC by acupuncture was positively correlated with antianxiety and cognitive enhancement.[24]

Li et al. reported that EA stimulation could rejuvenate adult neurogenesis in the ventral dentate gyrus of mice with SNI. This was achieved by promoting neuronal differentiation and normalizing the morphology of newborn dendrites. The study proposed that the beneficial effects of EA on neurogenesis help maintain the normal methylation status of the *Prox1* promoter. This regulation is mediated by TET1, a key enzyme that demethylates the *Pro.x1* gene, a critical transcription factor in the differentiation of neural stem cells.[28]

5. Conclusion

This review underscores the intricate relationship between DNA methylation, neuropathic pain, and the modulatory effects of acupuncture. As neuropathic pain presents complex treatment challenges, understanding the role of epigenetic mechanisms like DNA methylation in its pathophysiology is crucial. Acupuncture has emerged as a significant modulator of these epigenetic processes, offering new insights into pain management strategies. The evidence points to acupuncture's ability to alter DNA methylation patterns within the central nervous system, suggesting a molecular basis for its therapeutic effects on pain and related comorbidities (**Fig. 1**).

Further research is necessary to elucidate the specific epigenetic changes induced by acupuncture and to integrate these findings into clinical practice effectively. Exploring acupuncture's potential in combination with conventional treatments could lead to improved management strategies for neuropathic pain, enhancing patient quality of life.

In sum, this review highlights the promising intersection of acupuncture and epigenetics in neuropathic pain management, advocating for a holistic approach that bridges traditional medicine and contemporary scientific research.

Disclosures

The authors have no conflict of interest to declare.

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