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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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 constriction 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-1β 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 neuropathic 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 neuropathic 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
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.

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Conflicts of Interests

The authors have no conflicts of interest to declare.

Ethical Statement

This research did not involve any human or animal
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Data Availability

Not applicable.

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