



## Review Article

# Research advances in treatment of neurological and psychological diseases by acupuncture at the Acupuncture Meridian Science Research Center

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## ARTICLE INFO

## Article history:

Received 14 January 2014

Received in revised form

28 February 2014

Accepted 25 March 2014

Available online 1 April 2014

## Keywords:

acupuncture therapy

depression

multidisciplinary research

neurological diseases

Parkinson's disease

## ABSTRACT

Acupuncture is an ancient therapeutic intervention that can be traced back at least 2100 years and is emerging worldwide as one of the most widely used therapies in the field of complementary and alternative medicine. Due to limitations associated with Western medicine's focus on the treatment of diseases rather than on their causes, interests are shifting to complementary and alternative medicines. The Acupuncture and Meridian Science Research Center (AMSRC) was established in 2005 to elucidate the neurophysiological mechanisms of acupuncture for neurological diseases based on multidisciplinary research supported by the Korean Ministry of Science and Technology. In the AMSRC, resultant research articles have shown that acupuncture can improve neurological and psychological problems, including Parkinson's disease, pain, and depression, in animal models. Basic research studies suggest its effectiveness in treating various problems such as depression, drug addiction, epilepsy, ischemia, dementia, Parkinson's disease, and pain. We strongly believe that these effects, evident from the AMSRC research results, can play leading roles in the use of acupuncture for treating neurological diseases, based on collaboration among various academic fields such as neurophysiology, molecular genetics, and traditional Korean medicine.

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## 1. Introduction

Acupuncture has been practiced in China for more than 2100 years, and is a natural healing therapy that has gained increasing popularity and acceptance by the public and health care

professionals worldwide. Acupuncture had been used in Korea long before it was introduced to Japan in the 6th century AD, and spread to Europe and North America during the 16th–19th centuries AD.<sup>1</sup> In 1971, a report by James Reston in the New York Times about his experience of acupuncture treatment in

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<http://dx.doi.org/10.1016/j.imr.2014.03.003>

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China exposed countless Americans to acupuncture for the first time. Since then, research on acupuncture has been conducted extensively worldwide.

Acupuncture is claimed to be an effective treatment against diseases, with wide applications. It has advantages of low cost and minimal side effects. Acupuncture has been used for hwa-byung or depression, as well as for treating chronic illnesses and injuries such as back pain, knee osteoarthritis, tension headache, migraine, nausea, and vomiting.<sup>2,3</sup> There is a current trend to expand the therapeutic scope of acupuncture to cosmetic treatment, diet, and plastic surgery.

However, basic research on the efficacy of acupuncture and its mechanisms of action is insufficient to systematize and objectify acupuncture therapy due to a lack of experimental approaches. Therefore, the efficacy of acupuncture is being investigated intensively in huge research programs to identify its various uses in Western countries.

Acupuncture needling can affect multiple systems in the body including the nervous system, immune system, and cardiovascular system, so more than one research method is necessary. The necessity for multidisciplinary research also arises due to the merits of both Western and Oriental medicines.

The Acupuncture and Meridian Science Research Center (AMSRC) at Kyung Hee University, Seoul, Korea, was opened in 2005, with support from the Korean Ministry of Science and Technology with the aim of conducting multidisciplinary research. The primary goal of the AMSRC is to establish a scientific basis for understanding the functional mechanisms of acupuncture and to investigate the therapeutic effectiveness of acupuncture for neurological diseases. According to the article “Global trends and performances of acupuncture research,” Kyung Hee University has been ranked, by the articles listed in Science Citation Index-Expanded, as a leader in the field of complementary and alternative medicine<sup>4</sup> for the past 20 years, with contributions from the AMSRC. These research outcomes are a result of intensive efforts by Kyung Hee University to develop Korean medicine by identifying the value of traditional Korean medicine. The AMSRC brings scientific expertise and ancient traditional knowledge together in a comprehensive, translational, and integrated approach to identify the value of traditional Korean medicine.

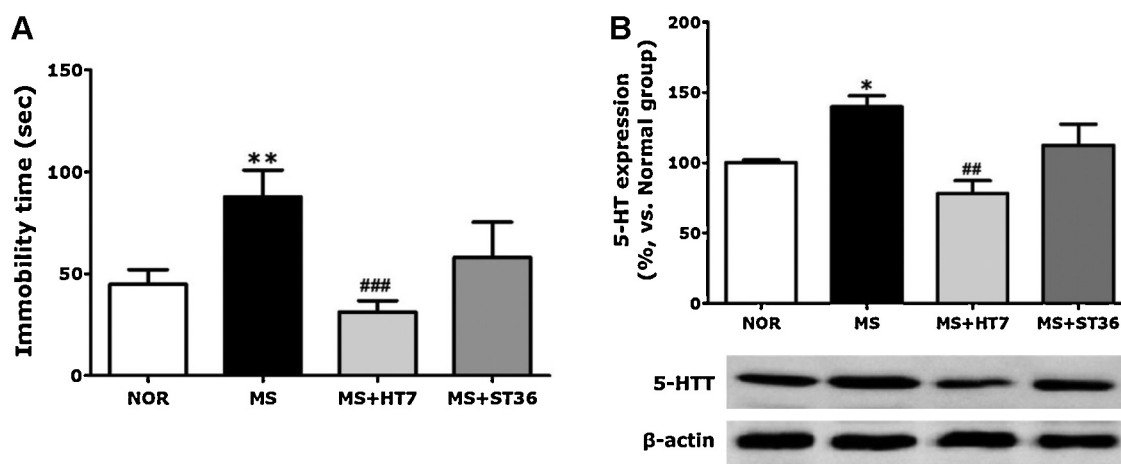
Despite the dramatic development of Western medicine along with considerable advances in modern medicine, neurological diseases increase considerably with aging. Neurological diseases are defined as hereditary and sporadic conditions characterized by progressive nervous system dysfunction. Neurological diseases such as dementia and Parkinson's disease (PD) are burdensome from individual and social perspectives due to their poor prognosis. Thus, it is possible that acupuncture, with its rapid and broad therapeutic effects when applied clinically, is the appropriate therapeutic method for treating neurological diseases. A number of AMSRC researchers are studying the efficacy and mechanism of acupuncture for neurological diseases. These researches are intended to both examine the efficacy of acupuncture for neurological diseases and establish improved clinical research models for acupuncture therapy through multidisciplinary research.

In this review article, we summarize the findings of 4 years of research at the AMSRC aimed at exploring the effectiveness of acupuncture for neurological and other diseases and expanding the understanding of its functional mechanisms and therapeutic effectiveness.

### 1.1. Effects of acupuncture on depression and anxiety disorders

To develop an animal model that perfectly reproduces the symptoms of depression in patients, researchers at the AMSRC choose maternal separation (MS), exposure to chronic stress, and depression with chronic inflammation response in the rats or mice. First, Kim et al<sup>5</sup> and Park et al<sup>6</sup> conducted animal model experiments using MS as representative of an event that might cause a depressive disorder. Early stressors such as MS or social isolation can influence the development of biological and neurological systems and increase vulnerability to neurodegenerative diseases and psychiatric conditions such as depression and anxiety. Long-term consequences of stress due to MS usually appear as neurodegenerative changes in the brain and depressive-like behavior in a stress-dependent manner.<sup>7</sup> A proteomic approach was used to express and identify new hypothalamic proteins in MS rats in an animal model to study early environmental insults.<sup>5</sup> In a group with MS given acupuncture at acupoint Sobu (HT8), five proteins were downregulated and nine were upregulated, compared with the untreated MS group. Among the nine proteins upregulated by acupuncture treatment, Kim et al<sup>5</sup> and Park et al<sup>6</sup> found four to be related to neurodevelopment. Therefore, acupuncture at HT8 may affect neurodevelopment and be a possible therapy for neurodevelopmental disorders. Additionally, acupuncture at acupoint Shenmen (HT7) significantly increased the frequency of entry and the amount of time spent in the open arms in the elevated plus maze test, reduced plasma corticosterone (CORT) levels, and reduced arginine vasopressin expression in the hypothalamus of MS rats, suggesting that it may reduce anxiety-related behaviors and modulate activation of the hypothalamic–pituitary–adrenal (HPA) axis.<sup>6</sup> In further studies, acupuncture at HT7 improved MS-induced depressive-like behaviors in the tail suspension test, normalized the 5-hydroxyindole-3-acetic acid (5-HIAA)/serotonin (5-HT) ratio, alleviated serotonin transporter (5-HTT), and increased brain-derived neurotrophic factor (BDNF) reduction in the prefrontal cortex (Fig. 1).<sup>8</sup> Although it remains elusive whether reduction of 5-HTT expression or restoration of the 5-HIAA/5-HT ratio by acupuncture stimulation is more crucial for improving these behaviors, it is obvious that acupuncture at HT7 alleviated MS-induced impairment of the 5-HT system in that study. The authors of these studies also suggested that the MS-induced changes in the 3,4-dihydroxyphenylacetic acid/dopamine (DA) ratio in the hippocampus and prefrontal cortex, and plasma CORT levels in MS rats were significantly alleviated after HT7 stimulation (Fig. 1).<sup>9</sup> Based on the results of these and previous studies, the authors suggested that functional recovery of the prefrontal–limbic system by acupuncture stimulation plays an important role in the treatment of depression-like symptoms in MS rats.

Second, chronic stress results in dysregulation of the HPA axis in the neuroendocrine system, as evidenced by



**Fig. 1 – Effect of acupuncture on immobility time and expression of serotonin transporter of maternally-separated rat pups. (A) Immobility times of rat pups in the tail suspension test. (B) Expression of serotonin transporter (5-HTT) in the prefrontal cortex of rat pups.**

\* $p < 0.05$ .

\*\* $p < 0.01$  versus NOR group.

## $p < 0.01$ .

### $p < 0.001$  versus MS group.

HT7, acupoint Shenmen; MS, maternally separated control group; MS + HT7, maternally separated group with acupuncture stimulation at HT7 acupoint; MS + ST36, maternally separated group with acupuncture stimulation at ST36; NOR, normal group; ST36, acupoint Zusanli.

observations that the elevation of circulating CORT levels disrupts the circadian regulation of CORT secretion as well as the glucocorticoid receptor-negative feedback circuit.<sup>10</sup> Activation of the HPA axis by high-dose CORT administration is associated with the development of psychic-related disorders, such as depression and anxiety, in rats.<sup>11</sup> Lee et al<sup>12</sup> reported that acupuncture stimulation at acupoint Neiguan (PC6) significantly reduced chronic CORT-induced depression and anxiety-like behaviors, and increased neuropeptide Y expression in the hypothalamus. That study suggested that acupuncture may be an effective treatment for stress-related disorders such as depression and anxiety, probably by modulating the HPA axis.

Third, gradual and continuous experimental inoculation of mice with *Bacillus Calmette–Guerin* (BCG) vaccine elicited chronic inflammation-associated depressive-like behavior.<sup>13</sup> Acupuncture stimulation at Sanyinjiao (SP6) had antidepressant-like effects in a murine depression-like behavior model following chronic systemic inflammation/immune response induced by BCG inoculation by modulating the aggravated tryptophan–kynurenine metabolism pathway and dopaminergic neurotransmission in the hippocampus.<sup>13</sup> These results support the possibility that acupuncture has antidepressant and anxiolytic effects.

### 1.2. Effects of acupuncture on drug addiction

The AMSRC researchers have explored repeated administration of three kinds of psychostimulant drugs, including cocaine, nicotine, and morphine, to establish drug addiction in the animal model. Abuse of drugs such as cocaine, nicotine, amphetamine, and morphine and their subsequent

withdrawal cause a negative emotional state and psychiatric side effects, including depression and anxiety.<sup>14</sup> Many studies have demonstrated that drug withdrawal causes depressive- and anxiety-related symptoms in humans and corresponding behavioral responses in animals.<sup>15</sup> Chae et al<sup>16</sup> reported that increases in the corticotrophin-releasing factor may be involved in the negative emotional state associated with nicotine withdrawal, and acupuncture at HT7 may attenuate anxiety-like behavior following nicotine withdrawal by modulating corticotrophin-releasing factor in the amygdala. Repeated administration of various psychoactive substances, including cocaine and morphine, can produce a more robust effect than the first dose alone, even after an abstinence period.<sup>17</sup> This phenomenon, called behavioral sensitization, may play an important role in the development of drug addiction and drug-induced psychosis, as evidenced by an enhanced locomotor response to a subsequent injection of the drug.<sup>18</sup> Many studies suggest that the development and expression of behavioral sensitization due to repeated cocaine or morphine exposure are related to an elevation in DA neurotransmission.<sup>19</sup> The authors clearly showed that treatment with acupuncture at the HT7 point significantly suppressed repeated cocaine-induced behavioral sensitization and increased tyrosine hydroxylase expression in the ventral tegmental area of the central dopaminergic pathways.<sup>20</sup> Repeated morphine-induced behavioral sensitization is closely associated with the overexpression of DA biosynthesis and its activity in the postsynaptic neurons in the nucleus accumbens of the central DA pathway.<sup>21</sup> Acupuncture stimulation has an acupoint-specific property that may be useful as a therapeutic alternative with few side effects for treating addiction to drugs such as nicotine, cocaine, and morphine.

### 1.3. Effects of acupuncture on chronic intractable epilepsy

Epilepsy is one of the most common and devastating neurological diseases characterized by seizures, and its prognosis is not good among the grave symptoms of a serious brain disease.<sup>22</sup> The AMSRC researchers have suggested that intracerebral injection of kainic acid (KA) in the hippocampus or amygdala in rats could represent a model of temporal lobe epilepsy, because it reproduced the typical histopathological changes seen in epileptic patients.<sup>22</sup> Kim et al<sup>23</sup> reported that acupuncture inhibits KA-induced epileptic seizures and hippocampal cell death by increasing glutamate decarboxylase-67 expression. Acupuncture at HT8 reduced the severity of KA-induced epileptic seizures and the rate of neural cell death; it also decreased expression of c-Fos and c-Jun induced by KA in the hippocampus, as shown by immunohistochemistry and Western blotting. In further research, acupuncture stimulation at HT8 suppressed KA-induced microglia activation and expression of proinflammatory cytokine, such as interleukin (IL)-1 $\beta$ , in the hippocampus.<sup>24</sup> These results suggest that acupuncture exhibits a variety of neuromodulatory functions in patients with epileptic seizures, such as regulating neuronal gene expression and proinflammatory cytokines.

### 1.4. Effect of acupuncture on cerebral ischemia

Cell proliferation and apoptosis from ischemia in the hippocampus can effectively be improved by acupuncture. Increased cell proliferation in the dentate gyrus of the hippocampus following cerebral ischemia is a compensatory response to ischemia-induced increased apoptosis in gerbils via 5-bromo-2'-deoxyuridine immunohistochemistry, and it is possible that acupuncture at the Zusanli (ST36) and Ho-Ku (LI4) acupoints plays an important role in the regulation of cell proliferation and apoptosis following ischemic injury.<sup>25</sup> Intracerebral hemorrhage-induced Fos expression and cell proliferation in the dentate gyrus of rats following acupuncture treatment at the ST36 acupoint has also been investigated.<sup>26</sup> Thus, acupuncture treatment alleviates ischemia-induced apoptosis and cell proliferation, and holds possible therapeutic potential for recovery following stroke.

### 1.5. Effect of acupuncture on dementia

Acupuncture stimulation at the PC6 point is effective in restoring chronic mild stress-induced behavioral impairments, such as impaired learning and memory, in the Morris water maze test, and increased acetylcholinesterase reactivity in the hippocampus.<sup>27</sup> Acupuncture significantly alleviated memory-associated decreases in cholinergic immunoreactivity and BDNF and cyclic adenosine monophosphate-response element-binding protein (CREB) mRNA expression in the hippocampus of rats following repeated exposure to exogenous CORT in the Morris water maze test.<sup>28</sup> Attenuation of memory and cognitive impairments by acupuncture stimulation may be due to restoration of cholinergic neurochemical abnormalities and regulation of BDNF and CREB expression. It is likely that acupuncture as an alternative therapy can improve chronic stress-induced memory deficit symptoms by

modulating the HPA axis and can retard the progression of memory deficits in patients with neurodegenerative disease.

### 1.6. Effect of acupuncture on PD

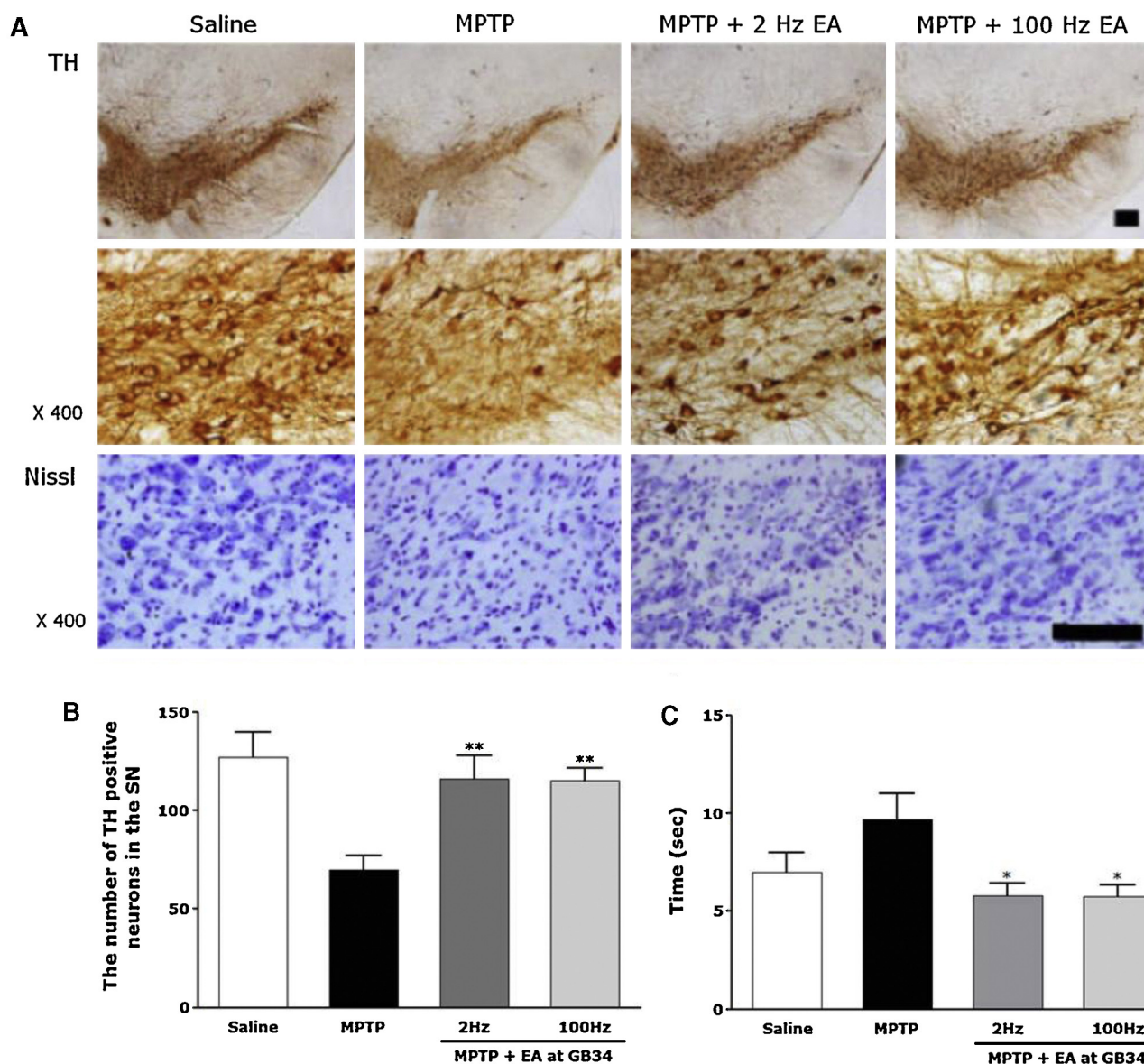
Park's research group reported that acupuncture improves patients with PD by increasing the generation of cranial nerve protective protein. This was reported in the international protein research journal *Proteomics* in November 2008 as an Oriental medicine article (Fig. 2).<sup>29</sup> This study demonstrated that electroacupuncture (EA) at acupoint Yanglingquan (GB34) protected against DA neuronal damage in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse PD model and altered expression of proteins in the substantia nigra that are implicated in cell death mechanisms following MPTP treatment. In further studies, 100-Hz EA at GB34 and GB39 points significantly protected DA neuronal fiber, and restored the decrease in COX5b and increases in cytosolic malate dehydrogenase (cMDH), Munc18-1, and Hydroxyacylglutathione hydrolase (HAGH) in the substantia nigra in the MPTP-induced PD mouse model, suggesting that these striatal proteins are associated with the neuroprotective actions of EA.<sup>30</sup> These authors also found that bee venom acupuncture at the GB34 point protected DA neurons effectively against MPTP toxicity, possibly by inhibition of phospho-Jun activation.<sup>31</sup> Acupuncture also facilitated motor function improvement against MPTP significantly, suggesting modulation of the phosphatidylinositol 3-kinase/Akt signaling pathway in a PD mouse model.<sup>32</sup> These results suggest that increased DA release after acupuncture treatment at GB34 may lead to enhanced DA availability in the synaptic cleft, which, in turn, may play an essential role in motor function improvement against MPTP.<sup>33</sup> Taken together, the findings suggest that acupuncture may be an effective therapy for patients with PD.<sup>34</sup> Park's<sup>35</sup> research group have continued to study the efficacy and mechanism of acupuncture therapy in patients with PD in recent years.

### 1.7. Effect of acupuncture analgesia on pain

Diluted bee venom acupuncture enhanced clonidine-induced analgesia significantly in both the mouse formalin test and the rat chronic constriction injury neuropathic pain model, suggesting that a combination of low-dose clonidine and acupuncture therapy decreases the side effects of clonidine. It also suggests a possible novel strategy for pain management (Fig. 3).<sup>36</sup> These findings indicate that pairing a lower dose of a  $\alpha_2$ -adrenoceptor agonist such as clonidine with acupuncture stimulation may be an improved strategy for pain management, by enhancing analgesia and decreasing  $\alpha_2$ -adrenoceptor agonist-induced side effects. A low-dose intrathecal injection of fluorocitrate in conjunction with low-dose diluted bee venom injection at ST36 synergistically suppressed pain responses in the late phase of the formalin test and significantly blocked the formalin-evoked increase in spinal expression of the astrocytic marker, glial fibrillary acidic protein.<sup>37</sup>

Warm-needle acupuncture (WNA) therapy combines the effects of acupuncture and heat produced by moxibustion. WNA pretreatment at acupoint Pungsi (GB31) alleviated





**Fig. 2 – Neuroprotective effects of EA at acupoint GB34 in MPTP-induced mice. (A)** TH-specific immunohistochemical staining (upper two rows) in the SN. Scale bar, 200  $\mu$ m. MPTP administration resulted in a considerable loss of Nissl-stained cells (bottom row) with a concomitant loss of TH-positive cells in the SN, while EA treatments increased the survival of Nissl-stained cells (bottom row) in the same areas. **(B)** The number of TH-positive neurons in the SN. MPTP destroys TH-positive neurons in the SN, whereas EA at GB34 prevents this destruction after MPTP injection. **(C)** Results of time spent in the pole tests. The time elapsed prior to mice arrived on the ground from the 50-cm-high pole was measured. Both MPTP + 2 Hz EA and MPTP + 100 Hz EA groups spent significantly shorter times on the pole, as compared to the MPTP group. Data are shown as means  $\pm$  SEM.

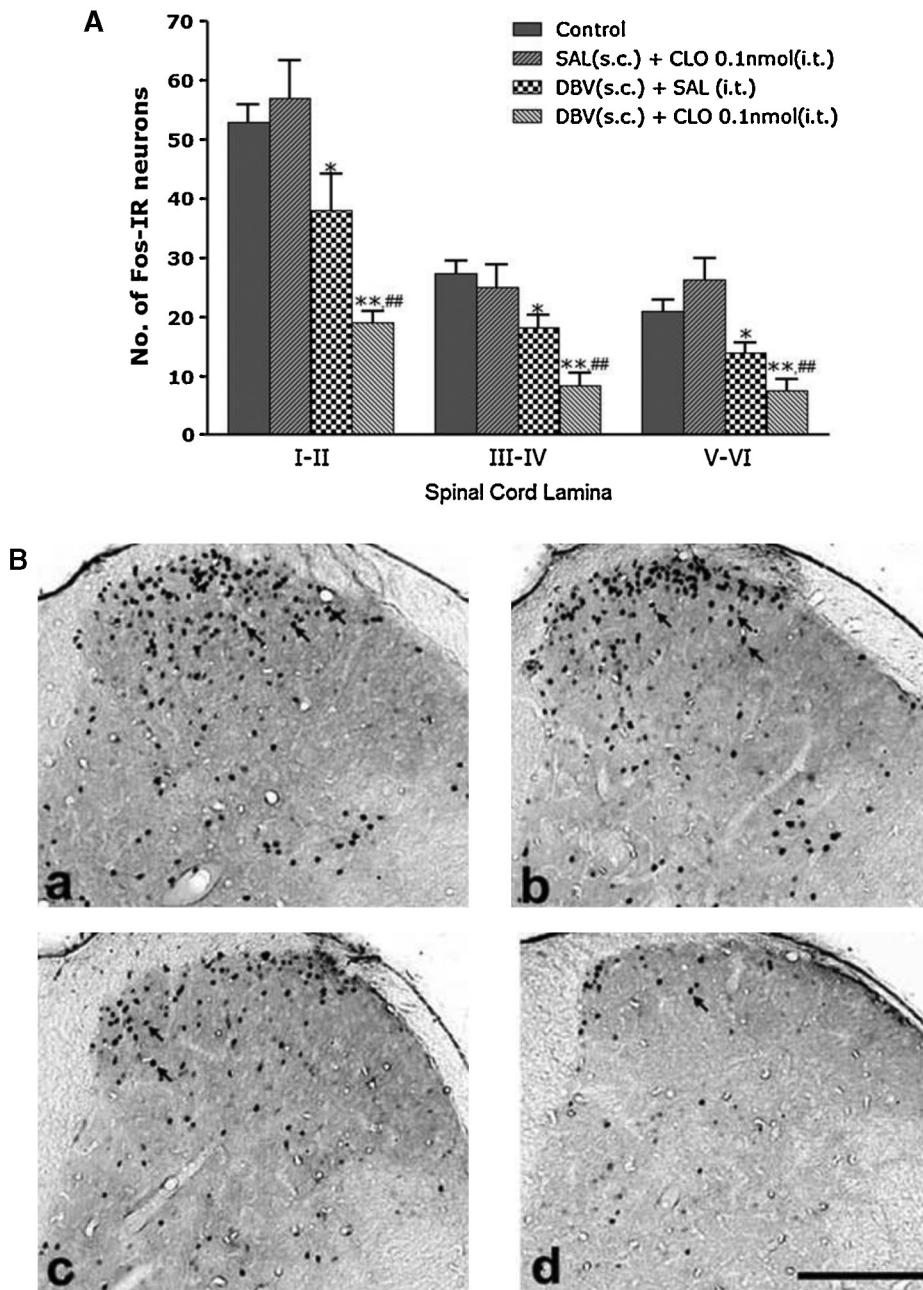
\* $p < 0.05$  and \*\* $p < 0.01$ , compared with the MPTP group.

EA, electroacupuncture; GB34, acupoint Yanglingquan; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SEM, standard error of the mean; SN, substantia nigra; TH, tyrosine hydroxylase.

formalin-induced pain behavior significantly.<sup>38</sup> Pretreatment using WNA and stimulation without needle insertion decreased c-Fos expression in the superficial dorsal horn of the spinal cord, even though the WNA procedure itself resulted in elevated c-Fos levels.

EA at ST36 and SP9 induced a decrease in neuronal nitric oxide synthase immunoreactivity in the superficial layer of

the spinal cord, leading to an analgesic effect on the withdrawal response after nerve injury.<sup>39</sup> Low-frequency (1 Hz, 3 mA) EA stimulation at BL60 inhibited flinching behaviors and c-fos expression in the late phase after formalin injection in rats.<sup>40</sup> These studies show that cytokine expression in the dorsal root ganglia and injured peripheral nerves increased dramatically in neuropathic rats but declined significantly



**Fig. 3 – Improved pain management by a combination of clonidine and acupuncture. (A)** Graph illustrating the number of Fos-positive neurons in the ipsilateral spinal cord dorsal horn (L3–L5) induced by injection of formalin in the control and each of the three treatment groups ( $n = 5$  mice per groups). Mice were injected i.t. with saline or CLO (0.1 nmol) 5 minutes after s.c. injection of SAL or DBV into the Zusanli acupoint. **(B)** Representative photomicrographs of Fos protein immunostaining (black arrows) in spinal cord sections from each experimental and control group ( $n = 5$  mice per group) (a, control; b, SAL + CLO, 0.1 nmol; c, DBV + SAL; d, DBV + CLO, 0.1 nmol). Scale bar = 200  $\mu$ m.

\* $p < 0.01$  different from the number of Fos-labeled neurons in the control [SAL (s.c.) + SAL (i.t.)] group.

\*\* $p < 0.01$ , significantly different from DBV (s.c.) + SAL (i.t.) group value.

CLO, clonidine; DBV, diluted bee venom; i.t., intrathecally; NECK, neck of dorsal horn (laminae V–VI); NP, nucleus proprius (laminae III–IV); SAL, saline; s.c., subcutaneous; SDH, superficial dorsal horn (laminae I–II).

after EA stimulation.<sup>41</sup> They also indicate that increased levels of cytokines, such as IL-1, IL-6, and tumor necrosis factor- $\alpha$ , may be related to persistent pain that can be modulated by acupuncture stimulation including EA.

## 2. Conclusion

We have identified alterations in neuronal activity and neurotransmitters due to acupuncture therapy, and verified

acupuncture's functional mechanism of action in the central nervous systems for neurological and other diseases. Acupuncture has demonstrated efficacy for treating chronic problems such as pain and depression. The AMSRC has published around 200 Science Citation Index-grade articles in various complementary and alternative medicine fields over 9 years and a number of studies on neurological diseases. These results were achieved through multidisciplinary research involving acupuncture and meridian science, neuroscience, and molecular biology. However, because explaining or identifying the functional mechanisms of acupuncture therapy in scientific and objective terms inevitably requires the cooperative efforts in various fields of biomedical science, researchers at the AMSRC have to collaborate with more multidisciplinary groups to provide experimental and clinical evidence. We try to elucidate the neurophysiological mechanism of acupuncture and map the acupuncture point-specific brain function in neurological animal models for PD, dementia, and stress. Whether therapeutic effect of acupuncture can be applied to neurovascular and neurodegenerative diseases will also be investigated. We believe that this approach to research on acupuncture through multidisciplinary collaboration between various academic fields such as neurophysiology, molecular genetics, and traditional Korean medicine may provide support for the neurobiological bases of acupuncture and for the clinical rationale for treating several types of diseases with acupuncture.

### Conflicts of interest

All authors declare no conflicts of interest.

### Acknowledgments

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science and Technology (No. 2005-0049404).

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