CHAPTER EIGHT

Acupuncture Therapy for Stroke Patients

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Contents

Abstract

Acupuncture is one of the most important parts of Traditional Chinese Medicine, has been used for more than 3000 years as prevention and treatment for various diseases in China as well as in adjacent regions, and is widely accepted in western countries in recent years. More and more clinical trials revealed that acupuncture shows positive

International Review of Neurobiology, Volume 111
ISSN 0074-7742
http://dx.doi.org/10.1016/B978-0-12-411545-3.00008-0

effect in stroke, not only as a complementary and alternative medicine for poststroke rehabilitation but also as a preventive strategy which could induce cerebral ischemic tolerance, especially when combined with modern electrotherapy. Acupuncture has some unique characteristics, which include acupoint specificity and parameter-dependent effect. It also involves complicated mechanism to exert the beneficial effect on stroke. Series of clinical trials have shown that acupuncture primarily regulates the release of neurochemicals, hemorheology, cerebral microcirculation, metabolism, neuronal activity, and the function of specific brain region. Animal studies showed that the effects of acupuncture therapy on stroke were possibly via inhibition of postischemic inflammatory reaction, stimulation of neurogenesis and angiogenesis, and influence on neural plasticity. Mechanisms for its preconditioning effect include activity enhancement of antioxidant, regulation of the endocannabinoid system, and inhibition of apoptosis. Although being controversial, acupuncture is a promising preventive and treatment strategy for stroke, but further high-quality clinical trials would be needed to provide more confirmative evidence.

1. INTRODUCTION

In recent years, the morbidity and mortality of stroke are dramatically increasing as a result of aging population, diet changes, and stress. Now, stroke is the second most common cause of death and the main cause of disability worldwide, which imposes a heavy burden on both family and community (Donnan, Fisher, Macleod, & Davis, 2008; Liu et al., 2007). Although many strategies have been used in clinical situations, such as angioplasty, stenting, thrombolysis, and many neuroprotective agents, their safety and efficacy remain controversial after a systematic review and meta-analysis of the clinical trials (Lansberg, Bluhmki, & Thijs, 2009; Toyoda et al., 2004). Moreover, researchers developed plenty of new methods either to prevent or to treat stroke in recent years, and most of them have been proved to reduce infarction volume and improve neurological recovery with animal models, but few of them show certain effects in clinical trials (Lees et al., 2006). Therefore, it is still a huge and urgent medical challenge to develop novel and rational ways aimed at preventing the occurrence of stroke or reducing impairments caused by stroke.

Acupuncture is a kind of traditional Chinese medicine, which has been used for more than 3000 years as prevention and treatment for many diseases. It is a procedure in which a fine needle is inserted into the skin at discrete acupoints and is manipulated manually, electrically, by heat or some drug injections. Although it was first developed in China, it has spread worldwide and is popularly used. In 2007, there were approximately 3 millions of adults who received acupuncture in the United States, 1 million more than that in 2002 (Barnes, Bloom, & Nahin, 2008). Since the acupuncture stimulation is supposed to be tightly associated with the nervous system, acupuncture is expected to improve the neurological function after stroke. So, acupuncture is most commonly used in the rehabilitation of stroke patients (Rabinstein & Shulman, 2003). Actually, 46% of the stroke survivors in the United States were engaged in some form of complementary and alternative medicine (CAM) therapy, in which acupuncture was the most frequently used CAM therapy among stroke survivors (Shah, Engelhardt, & Ovbiagele, 2008). A survey for stroke patients in Australia showed that almost all respondents (98%) wanted to know more about acupuncture in stroke rehabilitation and 87% were willing to consider acupuncture as a treatment option (Yam & Wilkinson, 2010). Although several systematic reviews indicated no strong evidence to support the positive effect of acupuncture on functional recovery after stroke (Kong, Lee, Shin, Song, & Ernst, 2010; Long & Wu, 2012; Park, Hopwood, White, & Ernst, 2001; Sze, Wong, Or, Lau, & Woo, 2002; Wu et al., 2006; Zhang, Liu, Asplund, & Li, 2005; Zhao, Du, Liu, & Wang, 2012), an increasing number of high-quality randomized controlled trials (RCTs) are in process, which might shed lights on the application of acupuncture therapy on stroke patients.

2. EFFICACY OF ACUPUNCTURE THERAPY FOR STROKE

Acupuncture is commonly used in rehabilitation of poststroke patients. A number of clinical trials have proved that acupuncture stimulation improved the balance function (Liu et al., 2009) and spastic states (Zhao et al., 2009), increased the muscle strength (Yan & Hui-Chan, 2009), reduced the muscle spasticity, and improved the motor function for chronic stroke survivors with moderate or severe muscle spasticity (Liu, Mukherjee, Sun, Liu, & McPeak, 2008). Acupuncture also improved the function of the affected upper limb in chronic hemiparetic stroke patients by increasing activity in the ipsilesional motor cortex (Schaechter et al., 2007). It can also improve insomnia in stroke patients by reducing the sympathetic nervous activity (Lee et al., 2009). The results of one clinical trial showed a clinically relevant decrease of relapse in the patients treated with resuscitating acupuncture intervention by the end of 6 months. The resuscitating acupuncture intervention could also improve self-care ability and quality of life (Shen, Kong, et al., 2012). A systematic review for seven RCTs concluded that acupuncture combined with exercise was effective for shoulder pain after stroke (Lee et al., 2012). With bee venom acupoint injection, acupuncture could significantly relieve the central poststroke pain (Cho, Park, et al., 2013). It is also an effective therapy on aphasia after stroke (Sun, Xue, & Zuo, 2012). Acupuncture plus conventional care was similar in effectiveness to physiotherapy treatment plus conventional care for poststroke rehabilitation without any obvious adverse events, which suggested that it might represent an additional treatment option for the stroke patients (Zhuangl et al., 2012).

3. ELECTROACUPUNCTURE THERAPY FOR STROKE

Integrated with electrotherapy, electroacupuncture (EA) is traditional acupuncture connected with electric stimulation apparatus, which is conducted by inserting acupuncture needles into the acupoints and then changing electric stimulation parameters, including the stimulation frequency, current intensity, pulse width, and pulse interval. Except for a small current passing through a pair of needles, EA is similar to the regular acupuncture. Therefore, EA not only inherits the benefits of the traditional acupuncture but also integrates with the physiological effects of electric stimulation (Napadow et al., 2005).

Compared with regular acupuncture, there are two advantages for EA. On the one hand, the acupoint of EA is not as precise as regular acupuncture, since current delivered by needles stimulates a larger area than that of the needle itself. On the other hand, there is an alternative technique for EA, which is called transcutaneous electrical nerve stimulation (TENS). TENS uses electrodes that are taped to the surface of the skin other than needles being inserted, so it can be applied in condition that patients deny insertion of needle or cannot be needled. Based on these two advantages, a growing number of basic researches and clinical trials are preceded in investigating the neuroprotective effect of EA and mechanism of this effect. A large number of animal studies have shown that EA could reduce neural apoptosis, promote cell proliferation, increase cerebral blood flow (CBF), and improve neurological function after stroke (Du et al., 2011; Liu, Zou, Du, & Wong, 2010; Tao et al., 2010; Wang et al., 2002). These results provide some evidence for further translational studies. So far, some clinical trials have focused on the effects of EA in stroke patients, but the results are ambiguous. Although many investigations with small enrollments support that EA treatment has positive effects on the motor function and quality of life (Chou, Chu, & Lin, 2009; Hsieh, Wang, & Lee, 2007), two RCTs including more patients find that there is no significant difference between EA and control groups in the improvement of functional outcome and life satisfaction (Gosman-Hedstrom et al., 1998; Johansson et al., 2001). In respect of this contradiction, the new method of EA treatment is required for further clinical application.

4. ACUPUNCTURE PRECONDITION FOR STROKE

The phenomenon of precondition-induced ischemic tolerance provides a new idea for the prevention of stroke injury. The preconditioning effect is that a brief exposure to sublethal or noninjurious stimuli can increase resistance to the subsequent, prolonged and lethal damage (Murry, Jennings, & Reimer, 1986). There are various kinds of precondition measures, such as ischemia (regional or remote), hypoxia, endotoxin, cytokines, and anesthetics. Accumulating preclinical evidences have demonstrated that these pretreatment methods, especially ischemia pretreatment, could induce neuroprotection and myocardial protection against ischemia and reperfusion (I/R) injury (Perez-Pinzon, Xu, Dietrich, Rosenthal, & Sick, 1997; Przyklenk, Bauer, Ovize, Kloner, & Whittaker, 1993). But from the clinical point of view, all the mentioned pretreatment ways have limitations and adverse effects to be applied in patients, especially the patients with severe illness.

As an indispensable part of traditional Chinese medicine, acupuncture has played an important role in prevention and treatment of diseases throughout the history. "Treating before sickness" is the plain idea of preventive medicine in traditional Chinese medicine. "Preventive acupuncture" is an approach using acupuncture to "treat before sick," namely, applying acupuncture in healthy or mildly sick patients, to stimulate the meridians of the body and enhance the body's resistance to disease, in order to prevent disease or to reduce the extent of damage following disease (Wang & Liang, 2008). In general, most of preclinical studies and clinical trials on acupuncture have been focused on its therapeutic role after stroke. However, prevention is definitely superior to treatment. Since acupuncture is economical, easily operated and has fewer negative side effects than the other preventative methods (e.g., pharmacological, ischemic, etc.), it should be more valuable and advantageous in preventing ischemic cerebral vascular disease, especially on patients with high risk of ischemic injury.

In 2003, Xiong and colleagues first defined the concept of EA pretreatment. They reported that repeated EA stimulation at the Baihui acupoint (GV20) before cerebral ischemia in rats could significantly reduce the infarct volume caused by transient middle cerebral artery occlusion (MCAO) as well as improve the neurological outcomes (Xiong et al., 2003). The results of previously published studies have shown that EA stimulation before ischemia could produce an effect similar to that of the ischemia pretreatment and could also induce ischemic tolerance. Later, this group showed that pretreatment with a single EA session could also induce tolerance to focal cerebral ischemia in rats (Wang, Xiong, Chen, Liu, & Zhu, 2005). At the same time, another group found that EA pretreatment at Hegu (LI4), a well-known acupoint commonly used in Oriental medicine for the treatment of neuronal injury resulting from hypoxia-ischemia, could induce neuroprotective effect in neonatal hypoxic–ischemic rat brains (Jiang, Zhang, & Shui, 2003).

Just like ischemia pretreatment, EA pretreatment has potential protective effects on the mammalian brain. Furthermore, both ischemia pretreatment and EA pretreatment can produce the acute and delayed neuroprotection. A single EA stimulation at Baihui acupoint for 30 min could induce biphasic tolerance against focal cerebral ischemia: the acute phase occurred 2 h after EA pretreatment, while the delayed ischemic tolerance was observed 24 h after the stimulus (Wang et al., 2005).

In addition, EA pretreatment was also observed in the heart. Researchers applied EA to bilateral Neiguan (PC6) before or during myocardial I/R induced by ligating and reperfusing the left anterior descending coronary artery. The results showed that there were significant reductions in cardiac enzymes, the duration of arrhythmia, and mortality rate in rats that were either preconditioned or treated with EA on PC6, as compared with those that did not underwent EA (Tsou, Huang, & Chiu, 2004).

The research for the EA precondition does not just stay in the labs. Two latest clinical trials provided some evidence for the effectiveness of EA pretreatment in the patients. Lu et al. enrolled 32 patients, requiring selective craniocerebral tumor resection to study the neuroprotection after EA pretreatment. The results showed that the serum levels of S100 calcium-binding protein β (S-100β) and neuron-specific enolase (NSE) in the EA group were significantly lower than that of the control group at the end of the surgery and 24 h postsurgery (Lu et al., 2010). In the same year, Yang and colleagues also designed an RCT, enrolling 60 patients to investigate the cardioprotective effect of EA pretreatment in patients undergoing heart valve replacement surgery. EA or sham stimuli were applied at bilateral Neiguan (PC6), Lieque (LU7), and Yunmen (LU2) for 30 min each day for 5 consecutive days before surgery. The level of serum cardiac troponin I was significantly decreased in the EA group at 6, 12, and 24 h after aortic cross-clamp removal. Meanwhile, EA pretreatment also reduced the inotrope use at 12, 24, and 48 h after the intensive care unit arrival and shortened intensive care unit stay time (Yang et al., 2010). These two clinical trials have indicated that EA pretreatment might have beneficial effects on patients undergoing surgery. But, this evidence was limited since the number of enrolled patients was small and both of these trials were conducted in a single center. Thus, multicenter RCTs would be needed to provide further evidence on EA pretreatment.

5. ACUPOINT OPTION OF ACUPUNCTURE THERAPY FOR STROKE

Based on meridian theory, an acupoint is relatively specific to certain functions or certain organs, and different effects occur when different acupoints are stimulated. The neuronal specificity of acupoints has been tested by functional magnetic resonance imaging (fMRI), providing neurobiological evidence for the existence of acupoint specific (Na et al., 2009; Wu et al., 2002). Lu et al. found that EA pretreatment of the Baihui acupoint could induce more robust neuroprotection against cerebral I/R injury as compared to stimulation 1 cm lateral to the Baihui acupoint or nonmeridian points of the distal limbs (Lu, Xiong, Zhu, Wang, & Cheng, 2002). The Baihui acupoint was chosen because the theory of meridians in the traditional Chinese medicine indicated that the Du meridian was closely related to the brain and spinal cord and Baihui is one of the acupoints of the Du meridian. At the same time, according to the neuroanatomy of western medicine, Baihui acupoint (GV20) is in the projection area of the motor and sensory cortex, as well as in the projection area of the anterior cerebral artery. Therefore, Baihui is probably an important acupoint in preventing and treating cerebral diseases, and this is why Baihui seems to be the mostly used acupoint in lab to study acupuncture effect for stroke. Similarly, EA pretreatment at Weizhong acupoint (BL40) was more beneficial for the spinal cord I/R injury in rabbits as compared to that of the Zusanli acupoint (ST36) (Lei et al., 2003). Hegu (LI4) was chosen for the treatment of neuronal injury resulting from hypoxia–ischemia (Jiang et al., 2003), and Neiguan (PC6) was preferred in EA pretreatment-induced cardioprotection for its effect on heart disease (Tsou et al., 2004).

The option for acupoint is much more important in clinical trials. A recent fMRI study found that acupuncture on Quchi (LI11) and Zusanli (ST36) induced activity of different brain regions, and the responses were also different between the healthy and stroke patients (Cho, Kim, et al., 2013). Sanjiao (SJ8) is a language-implicated acupoint. Acupuncture on SJ8 of the poststroke aphasia patients could induce a significant activation in opercular, triangular, and insula via fMRI, which demonstrated that language-deficit-implicated acupoint stimulation could selectively activate the language-associated brain region on the lesion side in the poststroke aphasia patients (Chau, Fai Cheung, Jiang, Au-Yeung, & Li, 2010; Li & Yang, 2011). Acupuncture stimulation at somatosensory-implicated acupoints (LI4, LI11, GB34) could induce a greater activation in the somatosensory cortex in stroke patients as compared to controls (Jeun et al., 2005; Li, Jack, & Yang, 2006). Qian et al. compared the effects of acupuncture at "Shuigou" (GV26), "Neiguan" (PC6), "Chize" (LU5), "Sanyinjiao" (SP6), and "Weizhong" (BL40) on MCAO rats. The results showed that "Shuigou" (GV26) and "Neiguan" (PC6) had a more obvious effect in the improvement of CBF (Qian et al., 2009). Wu and colleagues used the data mining technology to explore the characteristics of meridian points in the treatment of poststroke disorder with acupuncture. They found that the acupoints of the Yang meridians were the first option, which mainly distributed on the limbs, and the combination of Yangming and Shaoyang meridians was the most common (Wu, Li, & Ren, 2013).

6. PARAMETERS OF ACUPUNCTURE THERAPY FOR STROKE

Since the acupuncture needs to be manually manipulated after the needle was inserted into the skin of acupoints, different manipulation methods and time could significantly influence the effect of the acupuncture. He et al. observed the effect of different needle-retaining duration on hemorheology in stroke patients. The results showed that the effective rate of the 60-min group was significantly higher than those of the 20- and 40-min groups, and the improvement of the hemorheology parameters in the 60-min group was also remarkably higher than that of the 20- and 40-min groups (He et al., 2007).

The parameters are especially important in EA. Studies have shown that electric stimulation of different parameters might have different effects on these functions. Nested study design (Yang et al., 2004) was adopted to identify the influence of different parameters and their combination on EA preconditioning induced cerebral ischemic tolerance in rats. This study confirmed the optimal electrical stimulation parameters of the EA preconditioning to induce cerebral ischemic tolerance in rats. The results showed that varying frequency and waveform of the stimulus could produce different protective effects, but the current did not matter much. The density-sparse wave had the most obvious neuroprotective effect, followed by the intermittent wave, and the continuous wave's neuroprotective effect was relatively poor. The reason for this observation could be that the continuous wave tended to induce the tolerance of the electric stimulus, whereas the density-sparse wave could stimulate the release of different types of neurochemicals by transformation between low-, medium-, and high-frequency stimuli. Therefore, the density-sparse wave EA stimulation could generate neuroprotective effect at different targets via the activation of different signaling pathways. Two other groups did similar work and figured out the optimal parameters of EA of their labs to treat stroke (Wei, Fan, Wang, Yang, & Shi, 2010; Zhou, Guo, Cheng, Wu, & Xia, 2011).

7. MECHANISMS OF ACUPUNCTURE THERAPY FOR STROKE

Acupuncture is pleiotropic and could have multiple complicated influences on the physiology of brain and on the pathophysiology of stroke. Although effective mechanisms of acupuncture for stroke are largely unknown, a series of clinical trials have shown that acupuncture primarily regulates the release of neurochemicals, hemorheology, cerebral microcirculation, metabolism, neuronal activity, and the function of specific brain region. Animal studies showed that the effects of acupuncture therapy on stroke were possibly the inhibition of postischemic inflammatory reaction, cell apoptosis, stimulation of neurogenesis, angiogenesis, and influence on neural plasticity.

8. MECHANISMS OF ACUPUNCTURE THERAPY FOR POSTSTROKE PATIENTS

8.1. Acupuncture regulated the release of neurochemicals

The motor functions of the limbs and the activities of daily living in hemiplegic patients caused by acute stroke were significantly improved after the treatment with EA. This improvement was associated with reduced serum levels of NSE, S-100B, and endothelin (Zhang, Kang, Li, & Zhang, 2013). Proteomic analysis showed that serpin G1 protein expression in serum was downregulated, while the expression of gelsolin, complement component I, C3, C4B, and beta-2-glycoprotein I proteins were upregulated in the post-stroke patients after the EA stimulation, which indicated that EA appears to be effective in regulating the differential expression of multiple serum proteins involved in stroke (Pan et al., 2011).

8.2. Acupuncture-regulated hemorheology and cerebral microcirculation

Acupuncture could induce changes in the cerebral microvascular blood flow perfusion, that cause cardiovascular regulatory activities and changes of blood pressure, which in turn affect the cerebral circulation (Hsiu, Hsu, Chen, Hsu, & Lin, 2013). Using laser Doppler flowmetry, Hsiu et al. noted significant bilateral differences in patients' parameters following the acupuncture stimulation, with an increased pulsatile component of the microcirculatory blood flow (MBF), decreased blood flow resistance, and decreased MBF variability in the vascular beds on the stroke-affected side. Spectral analysis revealed that the vasodilation on the stroke-affected side could be partly attributed to decreased sympathetic neural activity (Hsiu, Huang, Chen, Hsu, & Hsu, 2011).

8.3. Acupuncture influenced the metabolism and activity of neurons

Acupuncture regulates the glucose metabolism and activates the cerebral structures and plasticity in the cerebral functional regions in chronic stage ischemic stroke patients (Fang, Ning, Xiong, & Shulin, 2012; Huang et al., 2012). It is effective for protecting neurons and facilitating the recovery proved by higher apparent diffusion coefficient and fractional anisotropy as compared to the control group, which correlates with the patient recovery and reveals the progress of secondary degeneration (Shen, Li, Wei, & Lou, 2012).

8.4. Acupuncture influenced the local function of brain and muscles

Manual acupuncture provides sufficient neuromuscular stimuli to promote immediate changes in the motor unit gross recruitment without repercussion in maximal force output in the healthy subjects. However, poststroke patients did not exhibit a significant reduction on the myoelectric activity and maximal force output (Fragoso & Ferreira, 2012). Enduring motor cortex functional changes were observed after acupuncture treatment, in terms of cortical excitability and output mapping using transcranial magnetic stimulation (Lo, Cui, & Fook-Chong, 2005).

9. MECHANISMS OF ACUPUNCTURE FOR ANIMAL STROKE MODELS

9.1. Acupuncture regulated oxidative stress and inhibited inflammation and neuronal apoptosis

In animal stroke models, acupuncture exerts anti-inflammatory effects via suppression of the TLR4/NF-kB pathway, which could ameliorate the cognitive impairment induced by stroke (Feng et al., 2013; Lan et al., 2013). Furthermore, it promotes neurological functional recovery via the retinoic acid signaling pathway (Hong, Wu, Zou, Tao, & Chen, 2013). Acute EA stimulation after a moderate focal cerebral ischemia improves the tissue and functional recovery. The Ach/eNOS-mediated perfusion augmentation might be related to these beneficial effects (Kim et al., 2013). Liu et al. acquired 3-D fluorodeoxyglucose-microPET images after using acupuncture in stroke mice, which demonstrated that acupuncture reduced the injury volume by improving the metabolic recovery after the stroke (Liu et al., 2013). EA can alleviate the cerebral edema after ischemic stroke (Zhang, Wu, & Jia, 2011), attenuate the extracellular glutamate level in the ischemic cerebral tissues (Lee et al., 2010), and repair the cells under stress undergoing apoptosis via activation of heat-shock proteins (Cakmak, 2009). It could activate PI3K/Akt signaling in the ischemic cerebral tissue, which resulted in the inhibition of cerebral cell apoptosis, and increased the serum secretion levels of the PI3K activators, brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), as well as upregulated the antiapoptotic *Bcl-2/Bax* ratio in the ischemic cerebrum (Chen et al., 2012). Acupuncture stimulation is responsible for the potential protection of neurons through suppression of CBF response in the increased plasma osmolarity and extracellular glutamine release in diabetic rats under ischemic conditions (Choi et al., 2010).

9.2. Acupuncture stimulates neurogenesis and angiogenesis, facilitates plasticity

Acupuncture has been reported to improve the neuronal regeneration at the edge of the ischemic lesions (Wu et al., 2012) and to increase cell proliferation in dentate gyrus (Kim et al., 2001). Angiogenesis and improved CBF in the ischemic boundary area were detected after the EA treatment in the rats with ischemic stroke (Du et al., 2011). The acupuncture prevented the impairments of the spike encoding and synaptic transmission at the GABAergic neurons from ischemia. This prevention was associated with the resistance of these cells to ischemia-induced changes in the spike threshold potentials and refractory period (Zhang, Li, et al., 2011).

10. MECHANISMS OF ACUPUNCTURE PRECONDITIONING FOR STROKE

10.1. EA pretreatment regulates oxidative stress, maintains the integrity of BBB, and inhibits apoptosis

Abrupt reperfusion after ischemia results in an overproduction of reactive oxygen species (ROS), which can lead to the brain injury (Chan, 1996). EA pretreatment enhances the activity of mitochondrial respiratory enzymes, attenuates the lipid peroxidation, and reduces the production of ROS, which consequently improves the function of the respiratory chain and antioxidant capacity in the ischemic penumbra (Siu, Lo, & Leung, 2004; Zhong, Li, Huan, & Chen, 2009). In addition, it increases the levels of antiapoptotic genes like *Bcl-2* while decreasing the levels of proapoptotic genes such as *c-Jun* and *c-Fos*, which inhibits the subsequent apoptotic cascades (Jiang et al., 2003; Jiang, Zhao, Shui, & Xia, 2004). Jiang et al. also found that the antagonizing effect of EA pretreatment on the cerebral hypoxic/ischemic injury might be related to its activation of K_{ATP}, which inhibits the neuronal apoptosis induced by the immediate genes, *c-Fos* and *c-Jun*, at the early injury stages (Jiang et al., 2004).

Moreover, the blood-brain barrier (BBB) integration and stress reactions are involved in the neuroprotection after EA pretreatment. The BBB integration is disrupted by cerebral ischemia, resulting in the brain edema. Matrix metalloproteinases (MMPs) are neutral proteases that disrupt the BBB and are associated with subcortical ischemic vascular disease (Candelario-Jalil et al., 2011). The expression and activity of the matrix metalloproteinases-9 (MMP-9), one of MMPs, are decreased after the EA pretreatment, and subsequently the brain edema and BBB damage are significantly alleviated (Dong et al., 2009). This phenomenon has also been observed in another experiment, which indicates that extracellular signal-regulated kinases (ERK) pathway is involved in this process (Chaudhry et al., 2010).

10.2. Endocannabinoid system contributes to the neuroprotective effects of the EA pretreatment

Recent investigations have shown that the endocannabinoid system might be a new mechanism of EA pretreatment-induced neuroprotection. EA pretreatment increases the release of 2-arachidonylglycerol (2-AG) as well as *N*-arach-idonoylethanolamine-anandamide (AEA), two endocannabinoids, and upregulates the expression of cannabinod CB1 receptor in the brain. Selective CB1 antagonist AM251 or CB1 short-interfering RNA (siRNA) blocked the neuroprotective effects of the EA pretreatment. Meanwhile, pretreatment with 2-AG and AEA also reduced the infarct size and improved the neurological outcomes (Wang et al., 2009). Moreover, further studies (Ma et al., 2011) showed that both acute and delayed ischemic tolerance were associated with endocannabinoid system: the acute phase, which occurred in 2 h after the EA pretreatment, was mediated by CB1, whereas the delayed phase occurred in 24 h after the EA pretreatment via CB2 (Ma et al., 2011). These findings indicated that the endocannabinoid system might play an important role in the neuroprotective effect of EA pretreatment.

Activation of the CB1 receptor triggers the signaling transduction events that can influence the ischemic compensatory responses. The cellular responses that elicit neuroprotection might involve the CB1 receptors and their link to a variety of signaling elements, including the Gi/Go family of G-proteins, mitogen-activated protein kinase, MAP Kinase kinase (MEK1/2), and its substrate, ERK1/2. Further studies have demonstrated that the neuroprotection of EA pretreatment could be abolished by U0126 (a specific inhibitor of the MEK1/2) or TAT-εV1–2 (an εPKC-selective peptide inhibitor). The blockade of the CB1 receptor by a CB1 receptor antagonist, AM251, reversed the activation of the ERK1/2 and εPKC as a result of EA pretreatment. These findings suggested that the ERK1/2 and εPKC pathways might be involved in the EA pretreatment-induced cerebral ischemic tolerance via the cannabinoid CB1 receptor (Du et al., 2010; Wang et al., 2011).

10.3. EA pretreatment attenuates glutamate excitotoxicity via NMDAR

Cerebral ischemia has been reported to induce excessive glutamate release and excitotoxicity (Lei, Berthet, Hirt, & Gruetter, 2009). Transient increase of CBF during reperfusion (hyperemia) would aggravate the brain injury induced by excitotoxicity. Pre-, intra-, or posttreatment of EA could rescue hippocampal neurons from the ischemic insults via decreasing the production of glutamate and reducing hyperemia (Meng, Sun, Liu, & Yan, 2008; Pang, Itano, Sumitani, Negi, & Miyamoto, 2003). Previous studies indicated that NMDARs were responsible for the glutamate-induced excitotoxicity in the postischemic brain (Briz, Galofre, & Sunol, 2010; Lei et al., 2009). EA pretreatment suppressed the expression of NR1, a subunit of the NMDARs, which might contribute to its effect in reducing apoptosis and protecting the cerebral neurons (Meng et al., 2008). Further study suggested that the reduced NR1 expression could be reverted by specific inhibitors of the PI3K pathway, but the inhibition of the ERK pathway did not show the same effects (Sun et al., 2005). Therefore, EA pretreatment attenuated glutamate excitotoxicity by modulating the PI3K pathway.

11. PROSPECTS OF ACUPUNCTURE THERAPY FOR STROKE

Available data indicate that acupuncture might have a positive effect on the stroke prevention and rehabilitation, but the evidence is not strong enough. Although large numbers of clinical trials were conducted, most of them were small-sampled, single-centered, and with low quality. There are some difficult to conduct acupuncture studies in relation to stroke. First, unlike other treatments, acupuncture has acupoints specificity and optimal parameters. Therefore, it needs a lot of practice and training before application. But there are identified differences in practice and training between acupuncture practitioners in different countries (Robinson et al., 2012). This is probably the main reason for the different results among these clinical trials. Second, most of the trials were conducted in China and were published in Chinese. Doctors and scientists in the field of traditional Chinese medicine usually lack the experience to communicate with foreign peers and have less knowledge for the standards of RCT, which is designed for modern western medicine. Similarly, researchers interested in acupuncture but from different cultures might be confronted with the language obstacle to acquire enough information. Finally, acupuncture is a procedure from which the patients could have strong feelings. So it is very hard to use placebo procedures as control. Researchers often give sham acupuncture at nonacupoint area or do not give electric stimulation when conducted with EA. But the patients can easily tell whether they receive the treatment in this situation, and the emotion of happiness or disappointment will seriously influence the results of the study.

However, current studies intend to confirm whether the acupuncture has a positive effect on stroke and just provide limited information about the mechanisms of acupuncture therapy for stroke. More studies need to be conducted to explain how the acupuncture works, which would provide further reasoning as to advocate for its effects among general public in order for them to accept it as a method of treatment.

In conclusion, there have been some proof for the efficiency of acupuncture therapy for stroke, but more large, collaborative, innovative, and high-quality trials are still needed to provide more confirmative and conceivable evidence.

REFERENCES

Barnes, P. M., Bloom, B., & Nahin, R. L. (2008). Complementary and alternative medicine use among adults and children: United States, 2007. *National Health Statistics Reports*, *12*, 1–23.

Briz, V., Galofre, M., & Sunol, C. (2010). Reduction of glutamatergic neurotransmission by prolonged exposure to dieldrin involves NMDA receptor internalization and metabotropic glutamate receptor 5 downregulation. *Toxicological Sciences*, *113*, 138–149.

Cakmak, Y. O. (2009). A review of the potential effect of electroacupuncture and moxibustion on cell repair and survival: The role of heat shock proteins. *Acupuncture in Medicine*, *27*, 183–186.

Candelario-Jalil, E., Thompson, J., Taheri, S., Grossetete, M., Adair, J. C., Edmonds, E., et al. (2011). Matrix metalloproteinases are associated with increased blood-brain barrier opening in vascular cognitive impairment. *Stroke*, *42*, 1345–1350.

Chan, P. H. (1996). Role of oxidants in ischemic brain damage. *Stroke*, *27*, 1124–1129.

Chau, A. C., Fai Cheung, R. T., Jiang, X., Au-Yeung, P. K., & Li, L. S. (2010). An fMRI study showing the effect of acupuncture in chronic stage stroke patients with aphasia. *Journal of Acupuncture and Meridian Studies*, *3*, 53–57.

Chaudhry, K., Rogers, R., Guo, M., Lai, Q., Goel, G., Liebelt, B., et al. (2010). Matrix metalloproteinase-9 (MMP-9) expression and extracellular signal-regulated kinase 1 and 2 (ERK1/2) activation in exercise-reduced neuronal apoptosis after stroke. *Neuroscience Letters*, *474*, 109–114.

Chen, A., Lin, Z., Lan, L., Xie, G., Huang, J., Lin, J., et al. (2012). Electroacupuncture at the Quchi and Zusanli acupoints exerts neuroprotective role in cerebral ischemia-reperfusion injured rats via activation of the PI3K/Akt pathway. *International Journal of Molecular Medicine*, *30*, 791–796.

Cho, S. Y., Kim, M., Sun, J. J., Jahng, G. H., Kim, H. J., Park, S. U., et al. (2013). A comparison of brain activity between healthy subjects and stroke patients on fMRI by acupuncture stimulation. *Chinese Journal of Integrative Medicine*, *19*, 269–276.

Cho, S. Y., Park, J. Y., Jung, W. S., Moon, S. K., Park, J. M., Ko, C. N., et al. (2013). Bee venom acupuncture point injection for central post stroke pain: A preliminary single-blind randomized controlled trial. *Complementary Therapies in Medicine*, *21*, 155–157.

Choi, S., Lee, G. J., Chae, S. J., Kang, S. W., Yin, C. S., Lee, S. H., et al. (2010). Potential neuroprotective effects of acupuncture stimulation on diabetes mellitus in a global ischemic rat model. *Physiological Measurement*, *31*, 633–647.

Chou, P., Chu, H., & Lin, J. G. (2009). Effects of electroacupuncture treatment on impaired cognition and quality of life in Taiwanese stroke patients. *Journal of Alternative and Complementary Medicine*, *15*, 1067–1073.

Dong, H., Fan, Y. H., Zhang, W., Wang, Q., Yang, Q. Z., & Xiong, L. Z. (2009). Repeated electroacupuncture preconditioning attenuates matrix metalloproteinase-9 expression and activity after focal cerebral ischemia in rats. *Neurological Research*, *31*, 853–858.

Donnan, G. A., Fisher, M., Macleod, M., & Davis, S. M. (2008). Stroke. *Lancet*, *371*, 1612–1623.

Du, Y., Shi, L., Li, J., Xiong, J., Li, B., & Fan, X. (2011). Angiogenesis and improved cerebral blood flow in the ischemic boundary area were detected after electroacupuncture treatment to rats with ischemic stroke. *Neurological Research*, *33*, 101–107.

Du, J., Wang, Q., Hu, B., Peng, Z., Zhao, Y., Ma, L., et al. (2010). Involvement of ERK 1/2 activation in electroacupuncture pretreatment via cannabinoid CB1 receptor in rats. *Brain Research*, *1360*, 1–7.

Fang, Z., Ning, J., Xiong, C., & Shulin, Y. (2012). Effects of electroacupuncture at head points on the function of cerebral motor areas in stroke patients: A PET study. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 902413.

Feng, X., Yang, S., Liu, J., Huang, J., Peng, J., Lin, J., et al. (2013). Electroacupuncture ameliorates cognitive impairment through inhibition of NF-kappaB-mediated neuronal cell apoptosis in cerebral ischemia-reperfusion injured rats. *Molecular Medicine Reports*, *7*, 1516–1522.

Fragoso, A. P., & Ferreira, A. S. (2012). Immediate effects of acupuncture on biceps brachii muscle function in healthy and post-stroke subjects. *Chinese Medicine*, *7*, 7.

Gosman-Hedstrom, G., Claesson, L., Klingenstierna, U., Carlsson, J., Olausson, B., Frizell, M., et al. (1998). Effects of acupuncture treatment on daily life activities and quality of life: A controlled, prospective, and randomized study of acute stroke patients. *Stroke*, *29*, 2100–2108.

He, Y. Z., Han, B., Zheng, S. F., Wang, L. N., Chen, Z. M., Hu, J., et al. (2007). Effect of different acupuncture needle-retaining time on hemorheology in ischemic stroke patients. *Zhen Ci Yan Jiu*, *32*, 338–341.

Hong, J., Wu, G., Zou, Y., Tao, J., & Chen, L. (2013). Electroacupuncture promotes neurological functional recovery via the retinoic acid signaling pathway in rats following cerebral ischemia-reperfusion injury. *International Journal of Molecular Medicine*, *31*, 225–231.

Hsieh, R. L., Wang, L. Y., & Lee, W. C. (2007). Additional therapeutic effects of electroacupuncture in conjunction with conventional rehabilitation for patients with first-ever ischaemic stroke. *Journal of Rehabilitation Medicine*, *39*, 205–211.

Hsiu, H., Hsu, C. L., Chen, C. T., Hsu, W. C., & Lin, F. C. (2013). Effects of acupuncture on the harmonic components of the radial arterial blood-pressure waveform in stroke patients. *Biorheology*, *50*, 69–81.

Hsiu, H., Huang, S. M., Chen, C. T., Hsu, C. L., & Hsu, W. C. (2011). Acupuncture stimulation causes bilaterally different microcirculatory effects in stroke patients. *Microvascular Research*, *81*, 289–294.

Huang, Y., Tang, C., Wang, S., Lu, Y., Shen, W., Yang, J., et al. (2012). Acupuncture regulates the glucose metabolism in cerebral functional regions in chronic stage ischemic stroke patients—A PET-CT cerebral functional imaging study. *BMC Neuroscience*, *13*, 75.

Jeun, S. S., Kim, J. S., Kim, B. S., Park, S. D., Lim, E. C., Choi, G. S., et al. (2005). Acupuncture stimulation for motor cortex activities: A 3T fMRI study. *The American Journal of Chinese Medicine*, *33*, 573–578.

Jiang, K. W., Zhang, Y., & Shui, Q. X. (2003). Possible mechanism of electroacupuncture preconditioning for hypoxia/ischemic brain injury protection effect in neonatal rats. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, *23*, 914–917.

Jiang, K., Zhao, Z., Shui, Q., & Xia, Z. (2004). Electro-acupuncture preconditioning abrogates the elevation of c-Fos and c-Jun expression in neonatal hypoxic-ischemic rat brains induced by glibenclamide, an ATP-sensitive potassium channel blocker. *Brain Research*, *998*, 13–19.

Johansson, B. B., Haker, E., von Arbin, M., Britton, M., Langstrom, G., & Terent, A. (2001). Acupuncture and transcutaneous nerve stimulation in stroke rehabilitation: A randomized, controlled trial. *Stroke*, *32*, 707–713.

Kim, J. H., Choi, K. H., Jang, Y. J., Bae, S. S., Shin, B. C., Choi, B. T., et al. (2013). Electroacupuncture acutely improves cerebral blood flow and attenuates moderate ischemic injury via an endothelial mechanism in mice. *PLoS One*, *8*, e56736.

Kim, E. H., Kim, Y. J., Lee, H. J., Huh, Y., Chung, J. H., Seo, J. C., et al. (2001). Acupuncture increases cell proliferation in dentate gyrus after transient global ischemia in gerbils. *Neuroscience Letters*, *297*, 21–24.

Kong, J. C., Lee, M. S., Shin, B. C., Song, Y. S., & Ernst, E. (2010). Acupuncture for functional recovery after stroke: A systematic review of sham-controlled randomized clinical trials. *CMAJ*, *182*, 1723–1729.

Lan, L., Tao, J., Chen, A., Xie, G., Huang, J., Lin, J., et al. (2013). Electroacupuncture exerts anti-inflammatory effects in cerebral ischemia-reperfusion injured rats via suppression of the TLR4/NF-kappaB pathway. *International Journal of Molecular Medicine*, *31*, 75–80.

Lansberg, M. G., Bluhmki, E., & Thijs, V. N. (2009). Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: A metaanalysis. *Stroke*, *40*, 2438–2441.

Lee, S. Y., Baek, Y. H., Park, S. U., Moon, S. K., Park, J. M., Kim, Y. S., et al. (2009). Intradermal acupuncture on shen-men and nei-kuan acupoints improves insomnia in stroke patients by reducing the sympathetic nervous activity: A randomized clinical trial. *The American Journal of Chinese Medicine*, *37*, 1013–1021.

Lee, J. A., Park, S. W., Hwang, P. W., Lim, S. M., Kook, S., Choi, K. I., et al. (2012). Acupuncture for shoulder pain after stroke: A systematic review. *Journal of Alternative and Complementary Medicine*, *18*, 818–823.

Lee, G. J., Yin, C. S., Choi, S. K., Choi, S., Yang, J. S., Lee, H., et al. (2010). Acupuncture attenuates extracellular glutamate level in global ischemia model of rat. *Neurological Research*, *32*(Suppl 1), 79–83.

Lees, K. R., Zivin, J. A., Ashwood, T., Davalos, A., Davis, S. M., Diener, H. C., et al. (2006). NXY-059 for the treatment of acute ischemic stroke. *The New England Journal of Medicine*, *354*, 588–600.

Lei, H., Berthet, C., Hirt, L., & Gruetter, R. (2009). Evolution of the neurochemical profile after transient focal cerebral ischemia in the mouse brain. *Journal of Cerebral Blood Flow and Metabolism*, *29*, 811–819.

Lei, Y., Xiong, L., Zeng, Y., Sun, Y., Chen, S., Wang, Q., et al. (2003). The compare of preconditioning with repeated electroacupuncture on different acupoints to induce neuroprotection against spinal cord ischemia-reperfusion injury in rabbits. *Chinese Journal of Clinical Rehabilitation*, *7*, 3.

Li, G., Jack, C. R., Jr., & Yang, E. S. (2006). An fMRI study of somatosensory-implicated acupuncture points in stable somatosensory stroke patients. *Journal of Magnetic Resonance Imaging*, *24*, 1018–1024.

Li, G., & Yang, E. S. (2011). An fMRI study of acupuncture-induced brain activation of aphasia stroke patients. *Complementary Therapies in Medicine*, *19*(Suppl. 1), S49–S59.

Liu, S. Y., Hsieh, C. L., Wei, T. S., Liu, P. T., Chang, Y. J., & Li, T. C. (2009). Acupuncture stimulation improves balance function in stroke patients: A single-blinded controlled, randomized study. *The American Journal of Chinese Medicine*, *37*, 483–494.

Liu, W., Mukherjee, M., Sun, C., Liu, H., & McPeak, L. K. (2008). Electroacupuncture may help motor recovery in chronic stroke survivors: A pilot study. *Journal of Rehabilitation Research and Development*, *45*, 587–595.

Liu, H., Shen, X., Tang, H., Li, J., Xiang, T., & Yu, W. (2013). Using microPET imaging in quantitative verification of the acupuncture effect in ischemia stroke treatment. *Scientific Reports*, *3*, 1070.
Liu, M., Wu, B., Wang, W. Z., Lee, L. M., Zhang, S. H., & Kong, L. Z. (2007). Stroke in China: Epidemiology, prevention, and management strategies. *Lancet Neurology*, *6*, 456–464.
Liu, Y., Zou, L. P., Du, J. B., & Wong, V. (2010). Electro-acupuncture protects against hypoxic-ischemic brain-damaged immature rat via hydrogen sulfide as a possible mediator. *Neuroscience Letters*, *485*, 74–78.
Lo, Y. L., Cui, S. L., & Fook-Chong, S. (2005). The effect of acupuncture on motor cortex excitability and plasticity. *Neuroscience Letters*, *384*, 145–149.
Long, Y. B., & Wu, X. P. (2012). A meta-analysis of the efficacy of acupuncture in treating dysphagia in patients with a stroke. *Acupuncture in Medicine*, *30*, 291–297.
Lu, Z. H., Bai, X. G., Xiong, L. Z., Wang, Y. H., Wang, Y., & Wang, Q. (2010). Effect of electroacupuncture preconditioning on serum S100beta and NSE in patients undergoing craniocerebral tumor resection. *Chinese Journal of Integrative Medicine*, *16*, 229–233.
Lu, Z. H., Xiong, L. Z., Zhu, Z. H., Wang, Q., & Cheng, M. (2002). Acupoint specificity of electroacupuncture preconditioning effect on cerebral ischemia injury in rats. *Zhongguo Zhen Jiu*, *22*, 3.
Ma, L., Zhu, Z., Zhao, Y., Hou, L., Wang, Q., Xiong, L., et al. (2011). Cannabinoid receptor type 2 activation yields delayed tolerance to focal cerebral ischemia. *Current Neurovascular Research*, *8*, 145–152.
Meng, P. Y., Sun, G. J., Liu, S. H., & Yan, H. M. (2008). Effect of electroacupuncture pretreatment on glutamate-NMDAR signal pathway in hippocampal neurons of vascular dementia rats. *Zhen Ci Yan Jiu*, *33*, 103–106.
Murry, C. E., Jennings, R. B., & Reimer, K. A. (1986). Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. *Circulation*, *74*, 1124–1136.
Na, B. J., Jahng, G. H., Park, S. U., Jung, W. S., Moon, S. K., Park, J. M., et al. (2009). An fMRI study of neuronal specificity of an acupoint: Electroacupuncture stimulation of Yanglingquan (GB34) and its sham point. *Neuroscience Letters*, *464*, 1–5.
Napadow, V., Makris, N., Liu, J., Kettner, N. W., Kwong, K. K., & Hui, K. K. (2005). Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. *Human Brain Mapping*, *24*, 193–205.
Pan, S., Zhan, X., Su, X., Guo, L., Lv, L., & Su, B. (2011). Proteomic analysis of serum proteins in acute ischemic stroke patients treated with acupuncture. *Experimental Biology and Medicine (Maywood)*, *236*, 325–333.
Pang, J., Itano, T., Sumitani, K., Negi, T., & Miyamoto, O. (2003). Electroacupuncture attenuates both glutamate release and hyperemia after transient ischemia in gerbils. *The American Journal of Chinese Medicine*, *31*, 295–303.
Park, J., Hopwood, V., White, A. R., & Ernst, E. (2001). Effectiveness of acupuncture for stroke: A systematic review. *Journal of Neurology*, *248*, 558–563.
Perez-Pinzon, M. A., Xu, G. P., Dietrich, W. D., Rosenthal, M., & Sick, T. J. (1997). Rapid preconditioning protects rats against ischemic neuronal damage after 3 but not 7 days of reperfusion following global cerebral ischemia. *Journal of Cerebral Blood Flow and Metabolism*, *17*, 175–182.
Przyklenk, K., Bauer, B., Ovize, M., Kloner, R. A., & Whittaker, P. (1993). Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*, *87*, 893–899.
Qian, Y. F., Fan, X. N., Li, Y. J., Zhang, Y. N., Wei, Y. Y., Zhang, X., et al. (2009). Effects of acupuncture at different acupoints on cerebral blood flow in cerebral ischemia model rats. *Zhongguo Zhen Jiu*, *29*, 213–216.

Rabinstein, A. A., & Shulman, L. M. (2003). Acupuncture in clinical neurology. *The Neurologist*, *9*, 137–148.
Robinson, N., Lorenc, A., Ding, W., Jia, J., Bovey, M., & Wang, X. M. (2012). Exploring practice characteristics and research priorities of practitioners of traditional acupuncture in China and the EU—A survey. *Journal of Ethnopharmacology*, *140*, 604–613.
Schaechter, J. D., Connell, B. D., Stason, W. B., Kaptchuk, T. J., Krebs, D. E., Macklin, E. A., et al. (2007). Correlated change in upper limb function and motor cortex activation after verum and sham acupuncture in patients with chronic stroke. *Journal of Alternative and Complementary Medicine*, *13*, 527–532.
Shah, S. H., Engelhardt, R., & Ovbiagele, B. (2008). Patterns of complementary and alternative medicine use among United States stroke survivors. *Journal of Neurological Sciences*, *271*, 180–185.
Shen, P. F., Kong, L., Ni, L. W., Guo, H. L., Yang, S., Zhang, L. L., et al. (2012). Acupuncture intervention in ischemic stroke: A randomized controlled prospective study. *The American Journal of Chinese Medicine*, *40*, 685–693.
Shen, Y., Li, M., Wei, R., & Lou, M. (2012). Effect of acupuncture therapy for postponing Wallerian degeneration of cerebral infarction as shown by diffusion tensor imaging. *Journal of Alternative and Complementary Medicine*, *18*, 1154–1160.
Siu, F. K., Lo, S. C., & Leung, M. C. (2004). Effectiveness of multiple pre-ischemia electro-acupuncture on attenuating lipid peroxidation induced by cerebral ischemia in adult rats. *Life Sciences*, *75*, 1323–1332.
Sun, Y., Xue, S. A., & Zuo, Z. (2012). Acupuncture therapy on apoplectic aphasia rehabilitation. *Journal of Traditional Chinese Medicine*, *32*, 314–321.
Sun, N., Zou, X., Shi, J., Liu, X., Li, L., & Zhao, L. (2005). Electroacupuncture regulates NMDA receptor NR1 subunit expression via PI3-K pathway in a rat model of cerebral ischemia-reperfusion. *Brain Research*, *1064*, 98–107.
Sze, F. K., Wong, E., Or, K. K., Lau, J., & Woo, J. (2002). Does acupuncture improve motor recovery after stroke? A meta-analysis of randomized controlled trials. *Stroke*, *33*, 2604–2619.
Tao, J., Xue, X. H., Chen, L. D., Yang, S. L., Jiang, M., Gao, Y. L., et al. (2010). Electroacupuncture improves neurological deficits and enhances proliferation and differentiation of endogenous nerve stem cells in rats with focal cerebral ischemia. *Neurological Research*, *32*, 198–204.
Toyoda, K., Fujii, K., Kamouchi, M., Nakane, H., Arihiro, S., Okada, Y., et al. (2004). Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. *Journal of Neurological Sciences*, *221*, 11–17.
Tsou, M. T., Huang, C. H., & Chiu, J. H. (2004). Electroacupuncture on PC6 (Neiguan) attenuates ischemia/reperfusion injury in rat hearts. *The American Journal of Chinese Medicine*, *32*, 951–965.
Wang, Q., Li, X., Chen, Y., Wang, F., Yang, Q., Chen, S., et al. (2011). Activation of epsilon protein kinase C-mediated anti-apoptosis is involved in rapid tolerance induced by electroacupuncture pretreatment through cannabinoid receptor type 1. *Stroke*, *42*, 389–396.
Wang, H., & Liang, F. X. (2008). Analysis on the features of preventive treatment with acupuncture and moxibustion. *Journal of Traditional Chinese Medicine*, *28*, 281–285.
Wang, S. J., Omori, N., Li, F., Jin, G., Zhang, W. R., Hamakawa, Y., et al. (2002). Potentiation of Akt and suppression of caspase-9 activations by electroacupuncture after transient middle cerebral artery occlusion in rats. *Neuroscience Letters*, *331*, 115–118.
Wang, Q., Peng, Y., Chen, S., Gou, X., Hu, B., Du, J., et al. (2009). Pretreatment with electroacupuncture induces rapid tolerance to focal cerebral ischemia through regulation of endocannabinoid system. *Stroke*, *40*, 2157–2164.

Wang, Q., Xiong, L., Chen, S., Liu, Y., & Zhu, X. (2005). Rapid tolerance to focal cerebral ischemia in rats is induced by preconditioning with electroacupuncture: Window of protection and the role of adenosine. *Neuroscience Letters*, *381*, 158–162.

Wei, Y. Y., Fan, X. N., Wang, S., Yang, S., & Shi, X. M. (2010). Specificity effect of acupuncture at "Shuigou" (GV 26) on brain infarction area in MCAO rats and the influence of acupuncture parameter. *Zhongguo Zhen Jiu*, *30*, 221–225.

Wu, Z., Hu, J., Du, F., Zhou, X., Xiang, Q., & Miao, F. (2012). Long-term changes of diffusion tensor imaging and behavioural status after acupuncture treatment in rats with transient focal cerebral ischaemia. *Acupuncture in Medicine*, *30*, 331–338.

Wu, L. T., Li, Y., & Ren, Y. L. (2013). Exploration on the characteristics of meridian points in the treatment of post-stroke disorder with acupuncture and moxibustion based on the data mining technology. *Zhongguo Zhen Jiu*, *33*, 125–130.

Wu, M. T., Sheen, J. M., Chuang, K. H., Yang, P., Chin, S. L., Tsai, C. Y., et al. (2002). Neuronal specificity of acupuncture response: A fMRI study with electroacupuncture. *NeuroImage*, *16*, 1028–1037.

Wu, H. M., Tang, J. L., Lin, X. P., Lau, J., Leung, P. C., Woo, J., et al. (2006). Acupuncture for stroke rehabilitation. *The Cochrane Database of Systematic Reviews*, CD004131.

Xiong, L., Lu, Z., Hou, L., Zheng, H., Zhu, Z., Wang, Q., et al. (2003). Pretreatment with repeated electroacupuncture attenuates transient focal cerebral ischemic injury in rats. *Chinese Medical Journal (English)*, *116*, 108–111.

Yam, W., & Wilkinson, J. M. (2010). Is acupuncture an acceptable option in stroke rehabilitation? A survey of stroke patients. *Complementary Therapies in Medicine*, *18*, 143–149.

Yan, T., & Hui-Chan, C. W. (2009). Transcutaneous electrical stimulation on acupuncture points improves muscle function in subjects after acute stroke: A randomized controlled trial. *Journal of Rehabilitation Medicine*, *41*, 312–316.

Yang, J., Xiong, L., Wang, Q., Liu, Y., Chen, S., & Xu, N. (2004). Effects of different stimulating parameters and their various combinations on electroacupuncture induced cerebral ischemic tolerance in rats. *Zhongguo Zhen Jiu*, *24*, 5.

Yang, L., Yang, J., Wang, Q., Chen, M., Lu, Z., Chen, S., et al. (2010). Cardioprotective effects of electroacupuncture pretreatment on patients undergoing heart valve replacement surgery: A randomized controlled trial. *The Annals of Thoracic Surgery*, *89*, 781–786.

Zhang, H., Kang, T., Li, L., & Zhang, J. (2013). Electroacupuncture reduces hemiplegia following acute middle cerebral artery infarction with alteration of serum NSE, S-100B and endothelin. *Current Neurovascular Research*, *10*, 216–221.

Zhang, S., Li, G., Xu, X., Chang, M., Zhang, C., & Sun, F. (2011). Acupuncture to point Baihui prevents ischemia-induced functional impairment of cortical GABAergic neurons. *Journal of Neurological Sciences*, *307*, 139–143.

Zhang, S. H., Liu, M., Asplund, K., & Li, L. (2005). Acupuncture for acute stroke. *The Cochrane Database of Systematic Reviews*, CD003317.

Zhang, F., Wu, Y., & Jia, J. (2011). Electro-acupuncture can alleviate the cerebral oedema of rat after ischemia. *Brain Injury*, *25*, 895–900.

Zhao, J. G., Cao, C. H., Liu, C. Z., Han, B. J., Zhang, J., Li, Z. G., et al. (2009). Effect of acupuncture treatment on spastic states of stroke patients. *Journal of Neurological Sciences*, *276*, 143–147.

Zhao, X. F., Du, Y., Liu, P. G., & Wang, S. (2012). Acupuncture for stroke: Evidence of effectiveness, safety, and cost from systematic reviews. *Topics in Stroke Rehabilitation*, *19*, 226–233.

Zhong, S., Li, Z., Huan, L., & Chen, B. Y. (2009). Neurochemical mechanism of electroacupuncture: Anti-injury effect on cerebral function after focal cerebral ischemia in rats. *Evidence-Based Complementary and Alternative Medicine*, *6*, 51–56.

Zhou, F., Guo, J., Cheng, J., Wu, G., & Xia, Y. (2011). Electroacupuncture increased cerebral blood flow and reduced ischemic brain injury: Dependence on stimulation intensity and frequency. *Journal of Applied Physiology*, *111*, 1877–1887.

Zhuangl, L. X., Xu, S. F., D'Adamo, C. R., Jia, C., He, J., Han, D. X., et al. (2012). An effectiveness study comparing acupuncture, physiotherapy, and their combination in poststroke rehabilitation: A multicentered, randomized, controlled clinical trial. *Alternative Therapies in Health and Medicine*, *18*, 8–14.