

THE NEUROPROTECTIVE EFFECT OF ELECTRO-ACUPUNCTURE AGAINST ISCHEMIC STROKE IN ANIMAL MODEL: A REVIEW

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Abstract**Background:** It is well established that electro-acupuncture can exert neuroprotection in animal experiments. However, the exact mechanism of electro-acupuncture against ischemic stroke is not very clear.**Materials and methods:** Literature retrieval was performed in four databases (OVID, PUBMED, EMBASE, and ISI Web of Science), from respective inception to July 2013.**Results:** Series of studies have demonstrated that electro-acupuncture might be a promising method in reducing brain damage after stroke and induce brain ischemic tolerance before stroke through the promotion of angiogenesis, alleviation of the inflammatory response, regulation of the blood brain barrier (BBB), inhibition of apoptosis, and so on. Through these mechanisms, electro-acupuncture may reduce the neural damages associated with stroke.**Conclusion:** An awareness of the benefits of acupuncture might lead more patients into accepting acupuncture therapy for the management of patients with ischemic stroke and patients with high risk of ischemic stroke.**Key words:** acupuncture, cerebral ischemia, brain ischemic tolerance, brain damage**Introduction**

In recent years, although the protective role of acupuncture for stroke patients has not been fully proved in clinics, a large number of animal experiments reveal its neuroprotective effect on ischemic stroke animals. The electro-acupuncture (EA), is the combination of acupuncture and electric stimulation, which is the integration of Traditional Chinese Medicine and modern medicine. The neuroprotective effect of EA before and after ischemic stroke is summarized as follows:

Search methods for identification of studies

Literature retrieval was performed through four databases (OVID, PUBMED, EMBASE, and ISI Web of Science), from their respective inceptions, to July 2013. After that, a total of 29 related papers were included in this review. The search strategy consisted of a combination of title and text words relating to the use of electro-acupuncture on ischemic stroke. The search terms used in databases were electro-acupuncture [Title/Abstract], OR electric acupuncture [Title/Abstract] OR electro-acupuncture [Title/Abstract]; ischemic stroke [Title/Abstract] OR cerebral ischemia [Title/Abstract] OR brain ischemia [Title/Abstract].

Electro-acupuncture and Brain Ischemic Tolerance

Different cannabinoid (CB), receptors involved in different types of ischemic tolerance. CB2 receptor involved in the delayed neuroprotective effect and CB1 receptor contributed to the rapid ischemic tolerance induced by EA pre-treatment against cerebral ischemic damage in rats (Ma et al., 2011). EA pre-treatment increases the expression of endocannabinoid 2 - arachidonylglycerol and N - arach -

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idonoyl ethanolamine - anandamide, inducing neuroprotection against transient cerebral ischemia through CB1 receptors (Wang et al., 2009). A recent study indicated that canonical Notch pathway also involved in the ischemic tolerance against focal cerebral ischemia (Zhao et al., 2012)

The single session of EA pre-treatment induced rapid tolerance to cerebral ischemia. The protective effect appeared at 2 hours after EA pre-treatment, other than 0.5, 1, 3 hours after preconditioning. The adenosine A1 receptor might be involved in the mechanism of rapid tolerance to focal cerebral ischemia. (Wang et al., 2005), EA pre-treatment increased the Bcl-2/Bax ratio after cerebral ischemia reperfusion, attenuating neuronal apoptosis. Furthermore, the inhibition of CB receptor type 1, could decrease the epsilon protein kinase C (ϵ PKC), over-activation. But the inhibition of CB receptor type 2 could not reverse the ϵ PKC over-activation and protective effect. Therefore, preconditioning with EA might attenuate the neuronal apoptosis by activating ϵ PKC via CB receptor type 1 in order to induce rapid tolerance on the subsequent ischemic damage. (Wang et al., 2011) These studies indicated that the EA might induce rapid cerebral ischemic tolerance.

EA pre-treatment could alleviate brain edema and blood brain barrier (BBB), dysfunction caused by cerebral ischemia via decreasing matrix metalloproteinase-9 (MMP-9), expression and activity, inducing delayed cerebral ischemic tolerance (Dong et al., 2009). Repeated preconditioning with EA promoted the release of enkephalins, which might inhibit delta- and micro-opioid receptors so as to induce the cerebral ischemia tolerance against subsequent ischemic damage (Xiong et al., 2007). EA at a single acupoint (Baihui), 30 minutes per day for 5 days markedly alleviate ischemic damage induced by transient cerebral ischemia (Xiong et al., 2003).

Preconditioning with EA could reduce infarct volumes and alleviate neurological outcome after cerebral ischemia, and the protective effects were reversed by the inhibitor of extracellular regulated protein kinases (ERK)1/2 (U0126). In addition, the promotion of phosphorylation-ERK1/2 (p-ERK1/2) expression after preconditioning with EA was abolished by the inhibitor of CB1R (AM251). Such results indicated that the delayed brain ischemic tolerance induced by EA pre-treatment might involved in the activation of p-ERK1/2 through CB1 receptor. (Du et al., 2010). What is more, MCP-1-induced protein 1 also was involved in the delayed brain ischemia tolerance against ischemic stroke. (Jin et al., 2013) These studies indicated that the EA might induce delayed cerebral ischemic tolerance.

The neuroprotective effect of electro-acupuncture after ischemic stroke

Influence of electro-acupuncture on the blood brain barrier after ischemic stroke

The function of blood brain barrier (BBB), was disrupted after cerebral ischemia. The Evans Blue (EB), was an indicator for assessing the integrity of BBB. EA could alleviate the extravasation of EB and decrease the concentration of extravasation of EB after ischemic damage. This demonstrated that EA might improve the function of BBB after cerebral ischemia. (Wu et al., 2001) EA might activate AST near the infarct area and alleviate excess reactive gliosis so as to promote the recovery after cerebral ischemic damage (Han et al., 2010). Cerebral ischemic might promote proliferation of neural stem cells (NSCs), and some of them could differentiate into astroglia or neurons. EA could enhance cells proliferation and differentiation into mature neurons, which might be one of the key reasons why EA could improve neurological dysfunction (Tao et al., 2010).

Influence of electro-acupuncture on the reactive oxygen species after ischemic stroke

EA could obviously improve neurological dysfunction, increase the activities of respiratory enzymes and decrease the production of reactive oxygen species (ROS), improving the function of respiratory chain and anti-oxidative capability of infarct penumbra area, which was one of the reasons why EA could reduce brain damage post cerebral ischemia. (Zhong et al., 2009) EA treatment at the acupoint of Fengchi might alleviate the lipid peroxidation after cerebral ischemia/reperfusion via promoting the activities of SOD (superoxide Dismutase), and GPx (glutathione peroxidase). (Siu et al., 2004)

Influence of electro-acupuncture on growth factors after ischemic stroke

For the monkey subjected to cerebral ischemic injuries, EA treatment might increase the endogenous IGF-1 (insulin-like growth factor-1), expression after middle cerebral artery occlusion, which might be a key reason for the neuroprotection of EA. (Gao et al., 2006), EA could increase GDNF (glial cell line-derived neuro-trophic factor), expression and the lasting time of upregulated GDNF expression after transient focal cerebral ischemia, which might be an important mechanism of the neuroprotective effect of EA. (Wei et al., 2000) According to the result of cDNA (complementary DNA), microarray, EA could increase the IGF-1 mRNA expression in striatum of Macaca

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mulatta after cerebral ischemia. (Guo et al., 2004).

Influence of electro-acupuncture on cerebral blood flow after ischemic stroke

Based on the animal model of common carotid artery occlusion in Sprague-Dawley (SD), rats, 2 or 15 Hz EA at bilateral Zusanli acupoints could increase cerebral blood flow (CBF), of rats with and without cerebral ischemia. In addition, neither 2 nor 15 Hz EA influenced the expression of NO in peripheral blood and levels of CGRP (calcitonin gene-related peptide), in cerebral cortex and thalamus. The specific mechanism was still unknown, requiring further study (Hsieh et al., 2006). Both hyperemia and glutamate over-release after ischemia were vital factors for brain damage due to reperfusion injury. EA treatment (7 Hz, 6 mA), at Fengfu (GV16) and Shendao (GV11), for 30 minutes might inhibit the over-release of glutamate and CBF transient increase after cerebral ischemia so as to protect neurons against from ischemia-reperfusion injury. (Pang et al., 2003)

Influence of electro-acupuncture on other factors after ischemic stroke

A recent study indicated that EA seems to be effective in regulating multiple serum proteins which were closely related to stroke, and in promoting functional recovery in acute ischemic stroke patients. (Pan et al., 2011) EA might alleviate the neurological dysfunction in ischemic stroke patients and somatosensory evoked potential (SEP), on ischemic stroke rats. (Si et al., 1998), EA could obviously reduce the infarct volume and enhance the residual cells of ipsilateral striatum and cortex, indicating that EA treatment could alleviate cerebral ischemic damages after ischemic stroke in monkeys. (Gao et al., 2002)

After transient cerebral middle artery occlusion, EA treatment could promote the number of bromodeoxyuridine (BrdU, newly generated neuron marker), positive cells, activating cell proliferation. Furthermore, EA might increase collapsing response mediated protein-4 (immature neuron marker), and microtubule-associated protein 2 (mature neuron marker), indicating that EA treatment could promote neurogenesis and maturation of newborn neurons. Furthermore, EA increased the distribution of DiI-stained cells in striatum. (Yang et al., 2005)

EA treatment could increase the expression of Akt and decrease the activation of caspase-9, thus suppressing the apoptosis of neuronal cells. (Wang et al., 2002), EA obviously suppressed the promotion of extracellular aspartate level, and enhanced the increase of taurine after cerebral ischemia. Such results demonstrated that the therapeutic effect of EA might be due to the bidirectional regulation of extracellular aspartate (excitatory amino acid) and taurine (inhibitory amino acid), level. (Zhao et al., 1997)

The stimulation on the acupoint of Shuigou (GV26), could promote the proliferation of vascular endothelial cell (EC), via double-immuno-fluorescence labeling technique (Ki67 and vWF), and increase region cerebral blood flow through laser Doppler flowmeter. This study indicated that EA stimulating might promote angiogenesis and decrease neurological dysfunction in the cerebral ischemic condition. (Du et al., 2011) EA treatment might decrease the up-regulation of NMDA receptor N-methyl-d-aspartate receptor-1 (NR1), subunit and increase the expression of tropomyosin-related kinase A (TrkA). Furthermore, according to the results of inhibiting the key protein kinase in the specific signaling pathways, the neuroprotection of EA was regulated by activation of the PI3-K (phosphatidylinositol 3-kinase) pathway, nor extracellular regulated protein kinases (ERK), pathway. (Sun et al., 2005) Furthermore, The acupuncture treatment in the acupoint of Baihui alleviate the impairment of cortical GABAergic neurons. (Zhang et al. 2011)

Conclusion

The elucidation of the mechanisms underlying EA-induced neuroprotective effect may facilitate the development of new strategies to induce brain ischemic tolerance before stroke and reduce brain injury after stroke. The knowledge of the many mechanisms by which EA can promote brain ischemic tolerance and reduce brain damage after stroke may encourage stroke patients and patients with high stroke risk factors to accept EA for prevention and treatment method.

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