



Electro-acupuncture could be an effective pretreatment for cerebral ischemia

Feng Zhang¹, Yi Wu¹, Jie Jia¹, Qing-Chuan Guo² and Yong-Shan Hu¹

¹Department of Rehabilitation, Huashan Hospital, Fudan University, Shanghai, China

²Department of Rehabilitation, Third Hospital, Xinxiang Medical College, Xinxiang, Henan, China

Corresponding author:

Wu Yi, Department of Rehabilitation, Huashan Hospital, Fudan University, Shanghai, China.

Tel: + 86 21 52887820

Fax: + 86 21 52887820

E-mail: doctorwuyi@126.com

Received: 31 Jan 2010

Accepted: 19 Apr 2010

Published: 22 Apr 2010

Iran J Med Hypotheses Ideas, 2010, 4:8

© 2010 Feng Zhang et al. ; licensee Tehran Univ. Med. Sci.

Abstract

Electroacupuncture, the integration of traditional Chinese acupuncture and modern electrotherapy, has been used for clinical treatment of cerebral ischemic disease in both eastern and western countries; however, the mechanism underlying its effects is still unknown. It is well known that excessive glutamate results in neuronal excitotoxicity after ischemic stroke. Previous studies have indicated that electro-acupuncture may downregulate the overactivation of glutamate after ischemia, and a recent study implied that electro-acupuncture prior to ischemia could induce brain ischemic tolerance. Based on the present information, we hypothesize that electro-acupuncture could be an effective pretreatment for cerebral ischemia by regulating the glutamatergic system.

Keywords

Electroacupuncture, Glutamatergic system, Brain ischemic tolerance, Pretreatment

Introduction

Brain ischemic tolerance is a phenomenon whereby harmful stimuli that are near to but below the threshold of cell damage can promote the tolerance of the brain to subsequent ischemic injury(1). Several stimuli that can induce tolerance to cerebral ischemia have been studied, including hypoxia (2), ischemia (1), anoxia (3), oxidative stress (4), and inhibitors of oxidative phosphorylation (5); however, these stimuli lack the potential for clinical application. Consequently, safe, clinically applicable pretreatments have been sought. Recently, analog-

ous protection has been found to be induced by normobaric hyperoxia (6), electroacupuncture (EA) (7), and pre-ischemic treadmill training (8).

Generally speaking, the glutamatergic system includes the most abundant neurotransmitter in the mammalian central nervous system, glutamate, and both ionotropic and metabotropic glutamate receptors, and it is essential for normal brain functions (9). As a previous study illustrated, after a 10-min period of transient, complete cerebral ischemia, glutamate increases eightfold during the ischemic period (10). Subsequently, a series of studies also confirmed this phenomenon of excessive glutamate

release in the infarct area after cerebral ischemia, which results in neuronal excitotoxicity (11-13). Meanwhile, NMDA-receptor antagonists and calcium-channel blockers alleviate ischemic brain damage and cytotoxic brain edema, reduce cerebral infarct volume, and promote nerve function recovery (14).

Acupuncture, an integral part of traditional Oriental medicine, has been used for treating clinical disorders, including cerebral ischemia, for thousands of years. EA is the integration of traditional Oriental acupuncture and modern electric techniques. Clinically, EA has been used for treatment of cerebral ischemic diseases (15,16), and in animal studies, there is strong evidence suggesting that EA alleviates cerebral ischemia damage (17,18). These studies indicate that EA can be an effective treatment for stroke; however, the mechanism by which EA induces neuroprotection in the brain is unknown.

Hypothesis

We hypothesize that EA could be an effective pretreatment for cerebral ischemia by regulating the glutamatergic system. In detail, we plan to compare the difference in glutamate concentration between the group with EA and the group without EA prior to ischemic stroke.

Evaluation of the Hypothesis

The whole experimental plan is demonstrated in Figure 1.

First, Sprague-Dawley rats will be anesthetized with 12% (v/v) chloral hydrate (0.345 mg/kg, intraperitoneally). We will keep the animals under anesthesia for at least 8 h by gradually supplementing chloral hydrate. Then, the rats in the group with EA will be stimulated using an EA instrument (1 mA intensity, 15 Hz frequency) for 30 min in the acupoint "Baihui (GV20)". The "Baihui" acupoint is targeted because this point is commonly used for stroke patients in clinics. In addition, the rats in the group without EA will also be anesthetized but without stimulation by EA.

Second, two hours after the end of EA, cerebral ischemia will be induced by middle cerebral artery occlusion for 120 min, followed by reperfusion. The left middle cerebral artery of every rat will be occluded by the intraluminal suture technique in the sham group, and the external and internal carotid arteries will be isolated but without ligation.

Finally, the rats will be placed in the prone position in a stereotaxic apparatus. Dialytic samples will be taken while the rats are unconscious. Microdialysis will be used to collect dialysates from the striatum immediately before ischemia and at 40, 80, and 120 min after ischemia, as well as at 40, 80, 120, 160, 200, and 240 min after reperfusion. A high performance liquid chromatography (HPLC) system, consisting of an Agilent 1100 LC system (Palo

Alto, CA, USA) equipped with a column incubator (G1316A), online degasser device (G1322A), four pumps (G1311A), a fluorescence detector (FD, G1321A), hand sampling system, and an HPLC workstation (Hewlett Packard, Palo Alto, CA, USA), will be used for the separation of amino acid neurotransmitters.

Discussion and conclusion

Recent studies have found that cannabinoids and the CB1 receptor underlie the endogenous neuroprotective effects of cerebral ischemic preconditioning (19,20); however, whether the glutamatergic system is involved in EA pretreatment in the brain is still unknown.

A series of studies indicate that EA pretreatment could induce tolerance to focal cerebral ischemia. First, it has been reported that the induction of brain ischemic tolerance by EA could be regulated by the adenosine A1 receptor (21). Second, pretreatment with EA increases the production of endocannabinoid 2-arachidonylglycerol and N-arachidonylethanolamine (anandamide), which elicits protective effects against transient cerebral ischemia through CB1 receptors (7). Moreover, pre-ischemia EA can partly regulate lipid peroxidation in cerebral ischemia (22). Taken together, we suggest that EA, as a cerebral ischemic pretreatment, could induce brain ischemic tolerance.

Additionally, our previous study implies that electric treadmill training prior to ischemia can downregulate the excessive release of glutamate, reducing brain damage after ischemia (23). Furthermore, voluntary exercise for one month increased glutamatergic-related proteins, including GluR1 (129%), SAP-97 (179%), GRIP-1 (129%), and GluR2/3 (118%) (24). In summary, cerebral ischemic pretreatment could influence the glutamatergic system after ischemic stroke; thus, EA, as an ischemic pretreatment, may ameliorate the abnormal activation of the glutamatergic system after ischemia.

A recent study found that, after global cerebral ischemia, acupuncture attenuates extracellular glutamate levels in rats (25). Similarly, after focal ischemic stroke, EA downregulates the abnormal increase of glutamate, thus preventing serious excitotoxicity (26). Therefore, after cerebral ischemia, EA could alleviate the excitotoxicity caused by excessive release of glutamate. However, whether EA pretreatment is able to regulate the glutamatergic system after ischemic stroke is still unknown.

On the whole, whether the glutamatergic system is involved in EA preconditioning of cerebral ischemia is still unknown. Therefore, based on the above evidence, we hypothesized that EA pretreatment may affect the glutamatergic system after ischemic stroke, preventing subsequent excitotoxicity.

Acknowledgement

The present study was supported by the National High Technology Research and Development Program of China (No. 2007AA02Z482).

Overview Box

First Question: What do we already know about the subject?

Electroacupuncture (EA) is the integration of traditional Chinese acupuncture and modern electric techniques. Clinically, EA has been used for treatment of cerebral ischemic diseases, and in animal studies, there is strong evidence suggesting that EA alleviates cerebral ischemia damage. These studies indicate that EA can be an effective treatment for stroke.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

Previous studies indicated that application of acupuncture after stroke could influence the glutamatergic system and thus alleviate the damage caused by cerebral ischemia. Furthermore, we hypothesize that pretreatment with EA could reduce the injury after ischemic stroke by regulating glutamatergic system. Provided we can clarify the mechanism underlying the effects of EA, more patients with high-risk factors may be willing to accept EA as a preventive intervention.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

In a further study, we plan to explore whether glutamate transporters, especially GLT-1, are involved in the reduction of glutamate excitotoxicity.

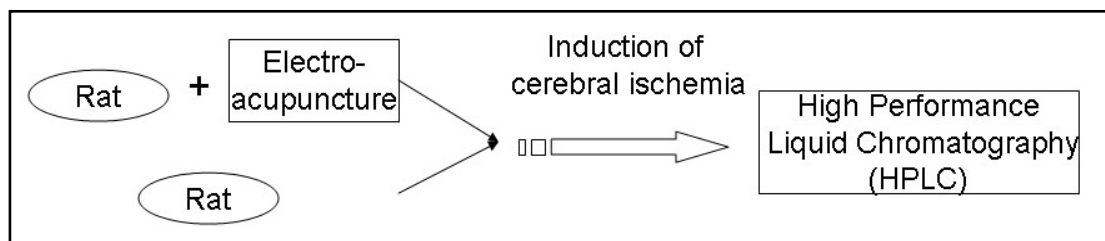


Figure 1. We plan to test the difference in glutamate levels between the group of rats with electro-acupuncture and the group of rats without electro-acupuncture prior to cerebral ischemia.

First, we divide the rats into two groups: one is treated with electroacupuncture; the other is not. Second, the middle cerebral artery of every rat will be occluded so as to induce cerebral ischemia. Finally, we will compare the difference in glutamate level between the two groups.

References

1. Kitagawa K, Matsumoto M, Tagaya M, Hata R, Ueda H, Niinobe M, et al. Ischemic tolerance phenomenon found in the brain. *Brain Res* 1990; 528: 21-24.
2. Gidday JM, Fitzgibbons JC, Shah AR, Park TS. Neuroprotection from ischemic brain injury by hypoxic preconditioning in the neonatal rat. *Neurosci Lett* 1994; 168: 221-224.
3. PerezPinzon MA, Mumford PL, Rosenthal M, Sick TJ. Anoxic preconditioning in hippocampal slices: Role of adenosine. *Neuroscience* 1996; 75: 687-694.
4. Ohtsuki T, Matsumoto M, Kuwabara K, Kitagawa K, Suzuki K, Taniguchi N, et al. Influence of oxidative stress on induced tolerance to ischemia in gerbil hippocampal-neurons. *Brain Res* 1992; 599: 246-252.
5. Riepe MW, Esclaire F, Kasischke K, Schreiber S, Nakase H, Kempinski O, et al. Increased hypoxic tolerance by chemical inhibition of oxidative phosphorylation: "chemical preconditioning". *J Cereb Blood Flow Metab* 1997; 17: 257-264.
6. Bigdeli MR, Hajizadeh S, Froozandeh M, Rasulian B, Heidarianpour A, Khoshbaten A. Prolonged and intermittent normobaric hyperoxia induce different degrees of ischemic tolerance in rat brain tissue. *Brain Res* 2007; 1152: 228-233.
7. Wang Q, Peng Y, Chen SY, Gou XC, Hu B, Du J, et al. Pretreatment with electroacupuncture induces rapid tolerance to focal cerebral ischemia through regulation of endocannabinoid system. *Stroke* 2009; 40: 2157-2164.
8. Guo M, Lin V, Davis W, Huang T, Carranza A, Sprague S, et al. Preischemic induction of tnfr-alpha by physical exercise reduces blood-brain barrier dysfunction in stroke. *J Cereb Blood Flow Metab* 2008; 28: 1422-1430.
9. Ozawa S, Kamiya H, Tsuzuki K. Glutamate receptors in the mammalian central nervous system. *Prog Neurobiol* 1998; 54: 581-618.
10. Benveniste H, Drejer J, Schousboe A, Diemer NH. Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral-ischemia monitored by intracerebral microdialysis. *J Neurochem* 1984; 43: 1369-1374.
11. Guyot LL, Diaz FG, O'Regan MH, McLeod S, Park H, Phillis JW. Real-time measurement of glutamate release from the ischemic penumbra of the rat cerebral cortex using a focal middle cerebral artery occlusion model. *Neurosci Lett* 2001; 299: 37-40.
12. Matsumoto K, Graf R, Rosner G, Taguchi J, Heiss WD. Elevation of neuroactive substances in the cortex of cats during prolonged focal ischemia. *J Cereb Blood Flow Metab* 1993; 13: 586-594.
13. Melani A, Pantoni L, Corsi C, Bianchi L, Monopoli A, Bertorelli R, et al. Striatal outflow of adenosine, excitatory amino acids, gamma-aminobutyric acid, and taurine in awake freely moving rats after middle cerebral artery occlusion - correlations with neurological deficit and histopathological damage. *Stroke* 1999; 30: 2448-2454.
14. Grasshoff C, Gillissen T. Effects of propofol on n-methyl-d-aspartate receptor-mediated calcium increase in cultured rat cerebrocortical neurons. *Eur J Anaesth* 2005; 22: 467-470.
15. Si QM, Wu GC, Cao XD. Effects of electroacupuncture on acute cerebral infarction. *Acupunct Electro-Ther Res* 1998; 23: 117-124.
16. Naeser MA, Alexander MP, Stiassnyeder D, Galler V, Hobbs J, Bachman D. Acupuncture in the treatment of paralysis in chronic and acute stroke patients improvement correlated with specific ct scan lesion sites. *Acupunct Electro-Ther Res* 1994; 19: 227-249.
17. Gao HM, Guo JC, Zhao P, Cheng JS. The neuroprotective effects of electroacupuncture on focal cerebral ischemia in monkey. *Acupunct Electro-Ther Res* 2002; 27: 45-57.
18. Siu FKW, Lo SCL, Leung MCP. Electroacupuncture reduces the extent of lipid peroxidation by increasing superoxide dismutase and glutathione peroxidase activities in ischemic-reperfused rat brains. *Neurosci Lett* 2004; 354: 158-162.
19. Hayakawa K, Mishima K, Nozako M, Ogata A, Hazekawa M, Liu AX, Fujioka M, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M. Repeated treatment with cannabidiol but not Delta9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance. *Neuropharmacology* 2007; 52: 1079 - 1087.
20. Schomacher M, Müller HD, Sommer C. Short-term ischemia usually used for ischemic preconditioning down-regulates central cannabinoid receptors in the gerbil hippocampus. *Acta Neuropathol* 2006; 111: 8-14.
21. Wang Q, Xiong LZ, Chen SY, Liu YH, Zhu XL. Rapid tolerance to focal cerebral ischemia in rats is induced by preconditioning with electroacupuncture: Window of protection and the role of adenosine. *Neurosci Lett* 2005; 381: 158-162.
22. Siu FKW, Lo SCL, Leung MCP. Effectiveness of multiple pre-ischemia electro-acupuncture on attenuating lipid peroxidation induced by cerebral ischemia in adult rats. *Life Sci* 2004; 75: 1323-1332.
23. Jia J, Hu YS, Wu Y, Liu G, Yu HX, Zheng QP, et al. Pre-ischemic treadmill training affects glutamate and gamma aminobutyric acid levels in the striatal dialysate of a rat model of cerebral ischemia. *Life Sci* 2009; 84: 505-511.
24. Dietrich MO, Mantese CE, Porciuncula LO, Ghisleni G, Vinade LC, Souza DO, et al. Exercise affects glutamate receptors in postsynaptic densities from cortical mice brain. *Brain Res* 2005; 1065: 20 -25.
25. Lee GJ, Yin CS, Choi SK, Choi S, Yang JS, Lee H, et al. Acupuncture attenuates extracellular glutamate level in global ischemia model of rat. *Neurol Res* 2010; 32: S79-S83.
26. Zhao P, Cheng JS. Effects of electroacupuncture on extracellular contents of amino acid neurotransmitters in rat striatum following transient focal cerebral ischemia. *Acupunct Electro-Ther Res* 1997; 22: 119-126.