Research advances in treatment of cerebral ischemic injury by acupuncture of conception and governor vessels to promote nerve regeneration

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ABSTRACT: Cerebral ischemia is one of the most common diseases treated by acupuncture therapeutics. Recent studies indicated that acupuncture treatment by needling the conception and governor vessels had positive effects in promoting neural regeneration in patients after cerebral ischemia injury. Acupuncture intervention could continuously promote the proliferation and differentiation of the neural stem cells in the brain, obviously up-regulate expression of growth factors, accelerate angiogenesis and inhibit apoptosis. Hence, it is necessary to present an exhaustive review on the mechanisms. The present review gives a detailed description of pathological changes of cerebral ischemia and acupuncture intervention applied to the conception and governor vessels, and proposes research prospects in the future.

KEYWORDS: brain ischemia; acupuncture; points; governor vessel; points; conception vessel; review

Cerebral ischemia results from a transient or permanent reduction in the cerebral blood flow that is restricted to the territory of a major brain artery. It is a pathological condition in which neuronal cell death occurs via apoptosis. In clinical practice, it is characterized by a partial neurological deficit, which is often irreversible and represents one of the leading causes of death, resulting in high rates of morbidity, mortality and disability. Hence, how to effectively prevent and treat neural injuries following cerebral ischemia and promote neural regeneration becomes a key issue. Recently, increasing experimental studies have demonstrated that acupuncture on the conception and governor vessels has positive effects of neural regeneration after cerebral ischemic...
injury, which has shown a certain advantage and has been proved to be effective in clinical practice[3,4]. This paper reviews the literature on the mechanism research of conception and governor vessel acupuncture in the treatment of cerebral ischemia.

1 Influence of acupuncture on neural stem cells and astrocytes

Many studies have indicated that there are neural stem cells (NSCs) in the pallium, subependymal region, hippocampus and corpus striatum, in the brain of human adults, which have the ability of self-duplication, self-regeneration and continuous differentiation into neurons and neuroglial cells. During the process of cerebral ischemia reperfusion (CIR), epoxidecystatrienoic acids derived from activated proliferous astrocytes have the function of enlarging cerebral vessels, and the responsive astrocytes could improve inactivation to glutamate, increase release of nerve growth factors (NGFs) to make nerve cells survive and axons grow, synthesize neurotransmitters, metabolize toxic substances and act directly on the neurons, among others[5]. What’s more, astrocytes are the source of NSCs in the human adult’s brain, which indicates that the astrocytes in the brain have the potentiality of becoming NSCs[6].

Glia1 fibrillar acidic protein (GFAP) is one of the markers of the activation and proliferation of the astrocytes, and neuron-specific enolase (NSE) is one of the markers of the neurons. Previous studies[7,8] indicated that acupuncture on the conception and governor vessels could continuously promote proliferation and differentiation of the NSCs in the ischemic brain. Needling acupuncture Baihui (GV20) and Shuigou (GV26) could down-regulate the number of GFAP-positive cells in hippocampal dentate gyrus and increase the number of GFAP/NSE double-labeled cells. After needling the acupoints Chengjiang (CV4), Guanyuan (CV4), Shuigou (GV26) and Baihui (GV20), proliferation of the GFAP-positive cells was reduced but that of the GFAP/NSE double-labeled cells increased more than that of the control group, suggesting that acupuncture on the conception and governor vessels could inhibit excessive proliferation of the hippocampal astrocytes and promote cellular differentiation. In the 14-day and 28-day sub-groups, the numbers of 5-bromodeoxyuridine (Brdu)/nestin and Brdu/NSE double-labeled cells in the conception vessel electro-acupuncture group (EA group) were significantly different from those in the 14-day control group (C-14 group) and the 28-day control group (C-28 group), respectively. The Brdu/GFAP double-labeled cells in the EA group were obviously greater in number than that in the C-28 group, indicating that acupuncture on the conception vessel could promote proliferation and differentiation of the NSCs in the sub-ventricular zone (SVZ) in cerebral ischemia rats and properly promote differentiation of the proliferative NSCs into astrocytes.

2 Effects of acupuncture on expressions of growth factors

Due to the stress of cerebral ischemia, expressions of some growth factors in the brain such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), NGF, among others, are responsively up-regulated to repair the nerves. Among them, EGF is closely related to the proliferation, growth and differentiation of the cells and tissues in the central nervous system (CNS)[9], which could nourish numerous neurons and glial cells in the CNS via activation to EGF receptors and mitogen-activated protein kinase (MAPK) pathway[10]. Polypeptide growth factors have diverse biological activities. For example, bFGF could protect the neurons, promote growth of nerves and check cerebral injuries following ischemia[11], which could also improve production of antioxidant and free radical scavengers and prevent the nerve cells from apoptosis following CIR[12]. NGF is also of significance. Diverse studies indicated that the neuronal precursors could continuously proliferate with the NGF, and the NGF could terminate natural death of specific neurons, maintain survival of neurons and
increase synthesis of neurotransmitters\(^{[11]}\). Once the cerebral ischemia occurs, the NGF expression could be responsively up-regulated and protect the neurons\(^{[12]}\).

Previous animal experiments\(^{[15,16]}\) indicated that electro-acupuncture on the conception vessel had great impacts on expressions of some growth factors in the brain. After focal CIR, the expressions of bFGF, EGF and NGF mRNAs were all increased in both the SVZ and the hippocampal dentate gyrus. However, with the prolonging of the reperfusion period, the responsive up-regulation was time-limited, and the positive expression had the tendency of decreasing. The positive expression was the highest in the 7-day reperfusion group (R-7 group), lower in the R-14 group compared with that in the R-7 group and was the lowest in the R-28 group. Acupuncture on the conception vessel could prolong the time. By needling acupoints Chengjiang (CV24), Guanyuan (CV4) and Qihai (CV3), the expressions of bFGF and EGF after 14 d of reperfusion and the expression of NGF after 28 d of reperfusion obviously up-regulated. The up-regulation of the growth factors could activate nerve repair in the brain.

3 Intervention of acupuncture to local angiogenesis

Angiogenesis is the structural basis for neural repair following ischemia, which could promote the regeneration of nerves\(^{[17]}\). The vascular endothelial growth factor (VEGF) and its receptor (VEGFR) and the angiopoietin (Ang-1 and Ang-2) and its receptor system (Ang/Tie) are the major angiogenic modulators being concerned most, which play essential roles in the regulation of angiogenesis in the early phase of post-ischemia. VEGF is a kind of mitogen and chemokine of endothelial cells with specificity, which could promote endothelialization in vitro and induce angiogenesis in vivo, and it could synthesize the endothelial cells to proteolytic enzyme, degrade the basement membrane of blood vessels and improve vasopermeability. VEGFR is mainly expressed in the endothelial cells, which have a high affinity with the VEGF. Ang-1 could improve interreaction between the endothelial cells and the cellular matrix surrounding them, accelerate vessel branching and reconstruction, and promote maturation and stabilization of blood vessels. Actions of Ang-2 depend on the VEGF, which could promote angiogenesis.

Previous studies indicated that electro-acupuncture on the governor vessel had impact on the expressions of VEGF, Ang-1 and Ang-2 and angiogenesis in cerebral ischemia-reperfusion rats. Fourteen days after needling Baihui (GV20) and Dazhui (GV14), expressions of VEGF and Ang-1 and the microvessel density were obviously increased around the ischemic focus\(^{[18]}\). After needling Baihui (GV20) and Shuigou (GV26), expressions of VEGF, VEGFR and Ang-2 around the ischemic focus of rats were up-regulated, indicating that acupuncture on the governor vessel could up-regulate expressions of VEGF and angiopoietin, which could promote proliferation and migration of the endothelial cells and accelerate angiogenesis, hence recover blood supply, improve tissue perfusion around the ischemic focus and promote neurological recovery following ischemia\(^{[19,20]}\). Acupuncture intervention could up-regulate the expression of VEGF mRNA, which may be the mechanism of angiogenesis\(^{[21]}\).

4 Mediation of acupuncture on signal transducers and transcription activators

After ischemia, necrocytosis and apoptosis occur in and around the focus. Signal transducers and activators of transcription (STATs) are important molecules for Janus kinase (JAK)/STAT in the intracellular data-transmission system, which is closely related to the expression regulation of genes such as caspase, Bcl-2, Bcl-xL, among others, and participates in the process of cellular proliferation, differentiation, apoptosis and immune regulation, etc\(^{[22]}\). Among the STATs, STAT-1, STAT-3 and STAT-5 participate in the pathological process of cerebral ischemia. The apoptosis is related to the activation of STAT-1, and the cell survival and repair are related to the activations of STAT-3 and STAT-5. According to the literature referred, STAT-1 activation following the cerebral ischemia may participate in the induction of the neural cell death in the cortex, hippocampus and corpus striatum\(^{[23]}\). STAT-3 activation may function in nerve protection, which could check the apoptosis\(^{[24]}\). STAT-5 participates in the cellular signal transmission of the erythropoietin and its receptors, which could enhance the ability of focal neurons in tolerating anoxia\(^{[25]}\).

Previous studies indicated that electro-acupuncture on the governor vessel could remarkably intervene the contents and expressions of STAT-1, STAT-3 and STAT-5\(^{[26,28]}\). By needling Baihui (GV20) and Dazhui (GV14), the STAT-1 content and its mRNA expression were obviously increased in the focal cortex and hippocampus on the third day after ischemia. After 2 h of ischemia, the expression of STAT-3 mRNA and the content of STAT-5 started increasing. At the 24th hour of ischemia, the expression of STAT-3 mRNA was the highest and the content of STAT-5 started decreasing, and after 3 d of ischemia, the expression of STAT-3 mRNA started decreasing. Acupuncture intervention could inhibit increase of STAT-1 content and the expression of STAT1 mRNA and increase the expression of STAT3 mRNA and the content of STAT-5. Compared with those in the modeling group, it had the advantage in the 24-hour and 3-day acupuncture groups, which indicated that acupuncture at the
initial phase could inhibit the content of STAT-1 and its mRNA expression and up-regulate the expression of STAT-3 mRNA and the content of STAT-5, hence activate self-protection of the body and reduce apoptosis of the nerve cells in and around the ischemic focus.

5 Conclusion
In conclusion, acupuncture of the conception and governor vessels could protect and intervene cerebral injuries after ischemia. According to traditional Chinese medicine theories, the conception vessel governs embryonic pregnancy, which controls growth and development of the fetus and is “the sea of yin vessels”; the governor vessel manages yang qi, thereby governing and activating yang qi and is “the sea of yang vessels”. The conception and governor vessels are closely related to the brain. Currently, one of the forward studies in the cerebral ischemia treatments is the stem cell transplantation. Hence, on the basis of traditional Chinese medical theories and previous experimental and clinical research, studies may focus on the effects of acupuncture on the proliferation and differentiation of the exogenous stem cells.

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7 Competing interests
The authors declare that they have no competing interests.

REFERENCES


On the topic of extracellular calcium in rats with cerebral ischemia, the study by Zhongguo Kang Fu (2003) found significant changes in the expression of bFGF, Ang-2, and Tie-2. Electroacupuncture was found to influence these markers, as reported by Han XH, Huang XL, Guo TC, and Yu L in 2006. These findings were supported by Darnell JE Jr.'s work on STATs and gene regulation in 1997, highlighting their role in neurological response.

Further studies by Li HC and Zheng L in 2008 showed STAT-1 induction following focal cerebral ischemia in rats. The role of aspirin in anti-oxidative effects was explored by Sheng and colleagues, underscoring its neuroprotective function. Hematopoietic factors and electroacupuncture were also linked to neuroprotection, as demonstrated by Chong ZZ, Kang JQ, and Maiese K in 2002, and Yu T et al. in 2010.
针刺任督脉穴位促进脑缺血后神经再生的研究近况

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摘要：脑缺血是针灸治疗的常见病症之一，近年来相关研究表明针刺任督脉经穴对脑缺血损伤后神经修复具有积极作用。针刺具有促进脑内神经干细胞增殖与分化，明显上调脑内生长因子的表达，促进血管新生及抗细胞凋亡等效应，值得进行深入的实验与临床研究。本文就脑缺血损伤后病理机制及针刺任督脉干预后效应等进行系统的整理，并对进一步的针刺研究提出展望。

关键词：脑缺血，针刺，穴位，督脉，任脉，综述