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Advances in the mechanism of action of acupuncture in regulating synaptic plasticity

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Abstract: *This paper illustrates the effects of acupuncture on synaptic plasticity through three aspects: plasticity of synaptic structures, function and expression of synaptic plasticity-related proteins, and summarizes the relevant mechanisms of acupuncture on synaptic plasticity, aiming to improve the mechanisms of acupuncture on neurological diseases in the field of neuroplasticity, and provide a more accurate, scientific and better basis for clinical treatment.*

Keywords: *Acupuncture; Synaptic plasticity; The ability to learn*

1. Introduction

Acupuncture and moxibustion has obvious clinical effects on nervous system diseases, and synaptic plasticity is an important aspect of neural plasticity (brain plasticity). Through the study of acupuncture and moxibustion on synaptic plasticity, this paper aims to explore the mechanism of acupuncture and moxibustion on nervous system diseases from the perspective of synaptic plasticity. The changes of brain plasticity caused by nervous system diseases include the abnormality of synaptic number, function, morphology and structure, neurotransmitter and synaptic plasticity related protein expression disorders. Brain plasticity is the ability of the damaged central nervous system to modify its structure and function in order to adapt to the environment. Brain plasticity is closely related to learning and memory. Learning and memory are thought to be encoded by changes in synaptic strength, and synaptic plasticity refers to changes in the strength of connections between neurons. So, acupuncture improves synaptic plasticity, which in turn improves overall learning and memory. Synaptic plasticity can be divided into three aspects: the plasticity of acupuncture structure from the perspective of morphology, the plasticity of synaptic function from the perspective of transmission efficiency, and the expression of synaptic related proteins at the molecular level. This article will discuss the effect of acupuncture and moxibustion on synaptic plasticity and related mechanism from these three aspects.

Acupuncture has benign bidirectional regulation effect. The reason why acupuncture can treat diseases and keep fit is to stimulate acupoints and meridians, stimulate meridians and qi, and regulate the functions of viscera to achieve the balance of Yin and Yang in the human body. The effect of moxibustion is closely related to the characteristics of meridians and acupoints. And the brain is closely related to most meridian connections. The "mark" and "knot" of the Three Yangjing of hands and feet are on the head and face, and the twelve meridians are on the head. The following six meridians enter the brain: Du veins enter the brain; Bladder meridian, from the top into the collaterals; The liver meridian, on the forehead, and the Du vein will and the summit; The stomach meridian also enters the brain; The Yin and Yang stilt veins of the eight meridians are all inserted into the back of the brain. "The essence of the five Zang and six FU organs is connected to the brain with the eyes." The essence of Qi, blood and body fluid mainly nourishes the brain and nourishes the emptiness. The gas is on the brain, the brain for the pulp of the sea, the brain for the meeting of all yang, "the blood and gas are on the face and walk empty" so "head gas street", the brain for the Yuan God's house, for the air of the place. Therefore, acupuncture is an important means of treating encephalopathy. Over the years acupuncture has been studied not only for learning and memory disorders, but also for psychiatric disorders such as depression.

2. Plasticity of synaptic structure

The changes of synaptic structure are the basis of physiological plasticity. According to different animal models, the changes of synaptic structure plasticity of acupuncture and moxibustion were

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observed from the perspective of multiple nervous system diseases, among which the changes were compared between the acupuncture group and the model group. See table 1.

Table 1: Changes of synaptic structural plasticity in the acupuncture group compared with the model group

Animal model	Changes in synaptic structural plasticity	Disease	Literature
AD model mouse	Postsynaptic dense material thickness (PSD)↑ Curvature of synaptic interface↑ Synaptic cleft↓	Alzheimer's disease	[1]
CUMS rats	Synaptic number density (Nv) ↑ Postsynaptic dense material thickness (PSD) ↑	Depressive disorder	[3]
MCAO rats	Number of synapses↑ Synaptic vesicles↑ Synaptic cleft fusion↓ Synaptic structural clarity↑	Stroke	[5]
PD model mouse	Number of synapses↑ Synaptic number density↑ Synaptic surface density↑ Average area of synaptic connection↑	Parkinson's disease	[6]

Studies have shown that acupuncture can effectively improve synaptic structural plasticity and learning and memory ability in many neurological diseases. In the clinical symptoms of Alzheimer's disease (AD), cognitive decline is the main manifestation, and the decline of cognitive function is associated with synaptic changes. In the study of neural rehabilitation mechanism of AD, from the perspective of acupuncture, Feng Min [1] elaborated the action mechanism of acupuncture on synaptic structural plasticity from the aspect of AMPA receptor and believed that acupuncture can increase the proportion of GluR2 subunits in hippocampal neurons, which can not only improve synaptic plasticity but also protect neurons and reduce neurotoxicity. One of the mechanisms of acupuncture in the treatment of AD may be the regulation of AMPA receptor number and subunit composition in hippocampal neurons by acupuncture. From the perspective of moxibustion, Lin Yao [2], through moxibustion intervention at Guanyuan point in rapidly aging mice (SAMP8), observed the improvement of synaptic structural parameters including thickening of hippocampal PSD, narrowing of synaptic cleft and up-regulation of related proteins, which improved cognitive function. And its rehabilitation mechanism may be achieved by upregulating BDNF/TrkB signaling pathway. Depression is a mental disorder characterized by enhanced negative memory, decreased cognitive function and depressed mood. Zhang Hao [3] believed that the mechanism of Electric Acupuncture in the treatment of depression is closely related to the regulation of electrical regulation on synaptic plasticity of neurons. Electric Acupuncture can effectively improve the synaptic ultrastructure and behavioral characteristics of depression model (CUMS) rats and regulate the expression of proteins related to synaptic plasticity to improve synaptic plasticity. Hippocampus is not only a key brain region for memory formation and consolidation, but also a sensitive region for cerebral ischemia. Cognitive dysfunction is one of the main clinical manifestations of stroke patients. Acupuncture can improve limb spasm and cognitive dysfunction in stroke patients after the disease. Guo Bin [4] acupuncture SCA model rats with bilateral "Quchi and Yanglingquan points" improved synaptic ultrastructure (synaptic number, number of vesicles, concave new synapses, the PSD had increased significantly in the model group and narrow synaptic cleft) gives synaptic function repair, improve the synaptic plasticity, effectively relieve the limb spasm in mice model. Chang-Ming Song [5] found that Electroacupuncture (EA) in Baihui and Shenting points can effectively improve the learning and memory ability of cerebral ischemia-reperfusion rats, and its mechanism may be related to improving the ultrastructure of hippocampal CA1 synapses and improving synaptic plasticity. Tang Yong [6] elaborated the mechanism of acupuncture and moxibustion affecting the synaptic plasticity of dopamine neurons in Parkinson's disease mice from the cellular and molecular level. In terms of synaptic structural plasticity, it was believed that acupuncture and moxibustion enhanced the expression of endogenous BDNF, promoted synaptic reconstruction, and promoted the expression of nerve cell adhesion molecule (NCAM). The phenomenon of adhesion and the expression of nest in promoted by acupuncture indicate the proliferation, differentiation and metastasis of neural stem cells, and then promote synaptic reconstruction.

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3. Plasticity of synaptic function

Synaptic function plasticity is also equivalent to synaptic transmission plasticity, which mainly has two manifestations, namely, Long-term potentiation (LTP) and Long-term depression (LTD). LTP [7] is related to the formation and storage of memory, and LTD is related to the integration of memory, forgetting and the recovery of synaptic function to continue to generate LTP. Studies have shown that induction or enhancement of LTP improves overall learning and memory in animals. Zhang Xiaoshu [8] stimulated "Baihui" and "Yongquan" points in AD model mice by acupuncture, and the results showed that acupuncture could increase the LTP growth in hippocampus of model mice, and improve the synaptic ultrastructure (PSD↑, synaptic cleft width ↓, synaptic interface curvature ↑). Since the plasticity of synaptic morphology is the basis of functional plasticity, Therefore, the synaptic transmission function is improved, which further improves the learning and memory ability of the model mice, and reveals one of the neural rehabilitation mechanisms of acupuncture on AD. Zhang Yuhao [9] improved the LTP and basal transmission efficiency of hippocampal CA1-CA3 region by electroacupuncture intervention at "Baihui" and "Shenting" points in VD model rats, and then improved synaptic plasticity and cognitive function of rats. The rehabilitation mechanism was related to the up regulation of Nr2B, CluR1 and CaMKII protein expression. In pain perception and analgesia, the plasticity of synaptic transmission is closely related to pain perception. Acupuncture has obvious clinical effect on pain. Feng Kehui [10] by electroacupuncture sciatic nerve branch selective damage (SNI) model rats "Huantiao and Weizhong points", by looking at the mechanical pain threshold of rats and C fiber evoked field potentials change, according to the results will effectively improve the mechanical pain threshold and pain behavior also markedly improved, will also restrain the C fibers induce the formation of a potential LTP. Its analgesic mechanism may be achieved by inhibiting synaptic plasticity (LTP) of spinal dorsal horn neurons.

4. Expression of synaptic related proteins

At the molecular level, and the study of a protein involved in synaptic plasticity is increasing, acupuncture can regulate what related proteins, as well as to what the protein expression related to the regulation and control mechanism, further research can be more comprehensive understanding of the reconstruction of the synapses, axon regeneration of nerve repair process, designed to acupuncture and moxibustion for diseases prevention and treatment of neural plasticity.

4.1 Growth associated protein-43, GAP-43

GAP-43 is an axon membrane protein rich in growth cones, neuron specific phosphoprotein, it is composed of 226-243 amino acids, of which the acid amino acid content is the most, hydrophobic amino acid is less. It is involved in the formation of new synaptic connections and nerve cell regeneration, and can extend axons, which is an important symbol of axon regeneration. During the development and growth of neurons, axons grow and extend along specific routes, and eventually reach the target cells with which it has synaptic relationship, so that axons can grow along appropriate growth routes. GAP-43 is highly expressed during neuronal development and regeneration. And widely distributed in the spinal cord, spinal root ganglia, cerebellum and autonomic neurons. Zheng Mengyu [11] used electroacupuncture at "Baihui", "Yintang" and "Zusanli" points in MCAO model rats to expound the neural mechanism of acupuncture on cerebral ischemic stroke from the perspective of observing the expression level of GAP-43. Compared with the model group, the content of GAP-43 in the EA group was significantly increased ($P<0.05$). The results showed that acupuncture improved the sensorimotor ability and repaired the plasticity of brain. Li Ying [12] To investigate the mechanism of electroacupuncture on cerebral infarction in MCAO model rats by using different frequencies of electroacupuncture at "Qiansanli" and "Waiguan" points. Compared with the model group, the content of GAP-43 in the EA group increased and maintained at a higher level, and the effect of 50Hz frequency was the best, indicating that EA promoted synaptic plasticity and improved neural function.

4.2 Brain-derived neurotrophic factor, BDNF

BDNF is the most abundant nutrient factor in the human body, which is widely distributed and closely related to synaptic plasticity. BDNF is involved in synaptic reconstruction and promotes neuronal development and regeneration. By binding to receptors, BDNF activates multiple neural signaling pathways to cause changes in synaptic plasticity, among which BDNF and TrkB (tyrosine

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kinase B) have high affinity. The combination of BDNF and TRKB (tyrosine kinase B) activates Ras-MAPK pathway and finally activates CREB, which can regulate transcription through its own phosphorylation. CREB can stimulate genes involved in long-term memory, and CREB can increase synaptic plasticity by increasing the expression of BDNF gene and anti-apoptotic protein gene BCL-2. BDNF especially promotes the development of hippocampal nerve and promotes the growth, development, differentiation and regeneration of neuronal cells. Both NMDA and AMPA isoforms can participate in the production of LTP, and BDNF can increase the opening rate of NMDA receptor, and then induce the production of LTP. Wang Xiaolan [13] used moxibustion to intervene "Baihui" and "Shenshu" points in AD model rats. Compared with the model group, the number of BDNF positive cells in the moxibustion group was significantly increased, and the brain plasticity and cognitive function of rats were improved. Lin Yao [14] Using moxibustion to intervene Guanyuan point in SAMP8 mice, compared with the model group, the content of BDNF in the moxibustion group was significantly increased ($P<0.05$), and the cognitive function was also improved. One of the mechanisms of rehabilitation is through upregulation of BDNF/TrkB pathway.

4.3 Synapsin

SYN is a phosphoprotein specific to the membrane of synaptic vesicles and has 307 amino acids. It regulates vesicle trafficking, number, and neurotransmitter release, meaning that a decrease in synaptophysin means a decrease in synaptic transmission and, consequently, an animal's overall ability to learn and remember. In addition, it is involved in the development of neurons, and plays a corresponding role in the formation and maintenance of extended neuronal processes and synaptic connections. Zhang Kangkang [15] used electroacupuncture at "Baihui" and "Shenshu" points in AD model rats and explored the neurological rehabilitation mechanism of AD under different frequency of electroacupuncture. The expression of SYN in EA group was directly proportional to the frequency of EA ($P<0.05$, $P<0.01$). High frequency EA at 50Hz had the best effect. Through studies, Li Ying [12] found that one of the rehabilitation mechanisms of cerebral infarction is the up-regulation of SYN expression in ischemic areas caused by electroacupuncture. However, in the study of Xiang Dulian [16], he used EA to prick the "Baihui" and "Yintang" points and then the "Shuigui" points of AD mice, but compared with the model group, the SYN expression in the acupuncture group did not change significantly, but the learning ability of mice was improved by acupuncture at the corresponding points.

4.4 Postsynaptic density protein-95, PSD —95

PSD-95 is a guanylate kinase (MAGUK) belonging to the postsynaptic dense region, which consists of three PDZ regions, a WW motif or a SH3 region and a homologous guanylate region. It contains abundant cytoskeleton, receptors and some signaling molecules. At synapses, PSD-95 can interact with membrane proteins by regulating their position, consolidating their stability, and modulating their functional properties, as demonstrated by changes in the inward integration of K+ channels and NMDA receptor-gated channels. In addition, PSD-95 also plays an important role in the transport of ionized glutamate receptors. Moreover, PSD-95 is closely related to cognitive function and is involved in the formation and maintenance of synapses, especially excitatory synapses. Zhang Kangkang [15] used EA to intervene AD model rats when discussing the rehabilitation mechanism of EA, and observed that compared with the normal group, the content of PSD-45 in the model group was significantly decreased, and the learning and cognitive ability was also decreased. However, compared with the EA group, the cognitive function of mice was improved after acupuncture. The escape latency was shortened ($P<0.01$), and the number of cross platforms was increased ($P<0.01$). The expression of PSD-95 was also up-regulated. One of the mechanisms of electroacupuncture in AD rehabilitation is related to the up-regulation of PSA-95 expression and the improvement of synaptic plasticity after acupuncture. Xie Zhengrong [17] et al used electroacupuncture to needle the pericardial meridian points and lung meridian points in MCAO model rats, and observed the changes of PSD-95 and synaptophysin contents in serum and brain tissue of rats. Compared with the model group, the expression of PSD-95 MRNA in both serum and brain tissues was up-regulated in the pericardial meridian group. The mechanism of cerebral ischemia after pericardial treatment may be related to the improvement of PSD-95 and brain plasticity by acupuncture.

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5. Conclusion

The above experiments effectively demonstrate that acupuncture and moxibustion has an obvious effect on the improvement of synaptic plasticity. Acupuncture and moxibustion effectively promotes the formation, development and repair of synapses through the regulation of synaptic ultrastructure, synaptic transmission efficiency and the expression of synapse-related proteins. Whether it is acupuncture or moxibustion, compared with medicine, acupuncture belongs to endogenous stimulation, by stimulating the human body "healthy qi" prevention and treatment of diseases, moxibustion is not a simple thermal stimulation, is through the use of moxa medicine, the warmth of the fire and the characteristics of meridians and acupoints to play a role in curing disease and self-defense. In terms of improving synaptic plasticity, acupuncture obviously has fewer or no side effects, and has more targets and more pathways. In the selection of acupuncture equipment, the frequency of use of EA is significantly higher than that of others, because compared with EA, there are too many uncontrollable factors of traditional hand acupuncture, such as acupuncture manipulation, frequency, amplitude and other influencing factors that interfere with the experimental results. Different frequencies of electricity have different effects on the body's nerves. In recent years, the study of acupuncture and moxibustion on synaptic plasticity is no longer limited to encephalopathy, and some psychiatric disorders, such as depression, have gradually attracted attention and research. However, the research on its mechanism is mostly at the molecular level. Acupuncture can respond to different signals, whether there is a relationship between different proteins should be further explored, and other mechanisms of acupuncture on synaptic plasticity should also be clearly studied.

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