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Research Progress on the Plasticity Mechanism of Synapses in the Treatment of Senile Cognitive Impairment with Electroacupuncture

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Abstract: ***Senile cognitive dysfunction is a common type of cognitive disorder. Electroacupuncture therapy can effectively improve the degree of senile cognitive dysfunction and delay the development of cognitive disorders from dementia. In recent years, with the deepening research on the mechanism of electroneedle cognitive disorder, synaptic plasticity, as a new entry point, has provided a new idea for the study of the mechanism of electroacupuncture. As an important part of brain plasticity, synaptic plasticity plays an important role in the activities of the nervous system and is of great significance to explore the mechanism of electroacupuncture. By consulting the relevant literature in recent years, the research progress of electroacupuncture regulation of synaptic plasticity in the treatment of senile cognitive disorder is analyzed from the aspects of synaptic structural plasticity, synaptic functional plasticity and expression of synaptic plasticity-related proteins.***

Keywords: Electroacupuncture, Senile cognitive impairment, Synaptic plasticity.

1. Introduction

In recent years, the number of elderly people in China has continued to increase, which is worrying. China is also entering a new stage of population aging and is about to become one of the fastest aging countries in the world. As one of the countries with the highest rate of aging global population, it is predicted that the proportion of the global elderly population will increase significantly to 22% by 2050 [1]. In the process of aging, the body is accompanied by a weakening of various functions, including learning, memory, cognition, etc. The elderly are potential patients with cognitive impairment and are very likely to develop Alzheimer's disease. Relevant data show that the number of dementia patients is expected to continue to increase in the next decade, which will have a serious negative impact on society and individuals [2]. In today's society, the demand for the prevention and treatment of cognitive dysfunction is increasing, and active intervention measures are particularly important for China, which is facing a serious aging population. The aging process of the body is often accompanied by a decline in cognitive ability, which eventually develops into mild cognitive impairment or dementia (Alzheimer's disease) [3]. The prevalence of mild cognitive impairment increases with age, and the prevalence rate of mild cognitive impairment in patients with mild cognitive impairment aged > 65 years old is 14.9% [4]. Since there are no exact drugs in clinic that can completely cure cognitive dysfunction, the prevention of senile cognitive dysfunction is particularly critical. Depending on the degree of cognitive impairment, geriatric cognitive degeneration disorder can generally be divided into two main categories: mild cognitive degeneration disorder, which represents a transition state between normal aging and dementia; and Alzheimer's disease, which is the primary cause of such diseases. According to relevant data, the incidence of mild cognitive dysfunction is about 15% to 20% in the elderly population aged 60 and above [5]. In recent years, traditional Chinese medicine has played a significant advantage in the prevention and treatment of senile cognitive disorders. The clinical use of traditional Chinese medicine under the guidance of the overall concept pays attention to overall regulation and has the advantage of regulating multiple targets, which is more in line with the idea of traditional Chinese medicine to treat diseases. In addition, compared with Western medicine, it also has higher safety, and the effect of electric acupuncture treatment is particularly obvious. Among them, the selection of acupuncture points pre-treated by the "double solidification and one-pass" electric needle is guided by the concept of "prevention before the disease, prevention of disease and change", which plays the purpose of preventing and treating senile cognitive disorders by stimulating the potential self-regulation ability of the human body. As a key point of neuron communication, synapses will undergo long-term adjustments to the connection force and information transmission rate of synapses under the action of internal and external factors. Such adjustments will act on the interaction effect between neurons, leading to the self-adjustment of nerve circuits, which is defined as the plasticity of synapses [6]. In view of this, this paper collects and analyzes the relevant research literature in recent years, aiming to summarize the research progress of electroacupuncture therapy on the mechanism of synaptic plasticity in the treatment of senile cognitive dysfunction, so as a reference theoretical basis for the follow-up traditional Chinese medicine in the prevention and treatment of this disease.

2. Traditional Chinese Medicine's Understanding of Senile Cognitive Impairment

In the process of aging, the body's cognitive function gradually declines, and there is a potential cognitive dysfunction, which is very likely to develop into senile

cognitive disorder. Among them, what needs special attention is Alzheimer's disease. Western medicine mostly calls it Alzheimer's disease, which is a neurodegenerative disease. Clinically, there are no drugs to fundamentally treat neurodegenerative diseases, and some existing treatments can only alleviate or suppress such diseases. In the theoretical system of traditional Chinese medicine, the insight into cognitive decline in old age has a long history. The symptom is summarized into the categories of "foolishness", "depression", "forgetfulness", "mental loss" and so on, which are mainly manifested as dullness, intellectual decline, memory decline and other symptoms. After thousands of years of medical exploration, traditional Chinese medicine has accumulated a lot of theoretical and clinical knowledge about the cause, pathological mechanism and treatment methods of this disease. According to the modern Department of Traditional Chinese Medicine [7], it is believed that the occurrence of dementia is related to the brain and is closely related to the functional imbalance of the liver, spleen and kidney. The pathological characteristics of dementia are the empirical evidence of original weakness and standard symptoms, and the clinical symptoms are common. Therefore, under the guidance of the concept of "prevention before the disease" of traditional Chinese medicine, acupuncture and moxibustion treatment pays attention to the principle of "preventing diseases without diseases and preventing diseases". During treatment, acupuncture points of Renmai, Dumai and stomach meridians are usually selected to recuperate the acquired foundation, enhance the body's righteousness and fight against diseases and evil. On this basis, combined with syndrome differentiation and treatment, acupuncture points such as "large vertebrae" with the effect of activating blood circulation, removing blood stasis and exorcism will also be selected to relieve the evil spirit of stasis in the body.

The discussion of this disease in traditional Chinese medicine is scattered in ancient books and literature, and has been gradually developed and improved. Lingshu · Tiannian, "Eighty years old, lung qi failure, soul separation, so words are good and wrong", put forward the theory of "qi decline and soul separation", which is based on nourishing qi, focuses on regulating the mind, is in line with the clinic, and discusses the treatment of dementia. Wang Shu of the Jin Dynasty and the Jing Mai· Volume II records that "if the ulnar of the left hand shows yin empirical evidence after closing the pulse, it is an empirical image of the kidneys." Patients often manifest themselves as trance, memory loss, blurred vision, hearing loss, and frequent sound. During treatment, it is necessary to stimulate the yin meridian to recuperate yin qi." In Chao Yuanfang's Theory of the "Zhu Bing Yuan Hou Lun" in the Sui Dynasty, the discussion on "forgetfulness" mentioned that it was caused by weak mental qi. The heart supervises the bloodline and stores the spirit. Once the wind and qi invades the blood qi, it leads to the imbalance between yin and yang, the interaction between qi and blood is disordered, sometimes weak and sometimes full, and finally makes the heart and blood confused and the mind is damaged, thus causing frequent forgetfulness. "Hua Tuo Shen Yi Mi Zhuan" mentioned the concept of "dementia" for the first time, and believed that the drastic changes in mood and the chaos of the qi machine were the causes of dementia [8]. In the Ming Dynasty, Zhang Jingyue first clearly regarded "dementia" as an independent disease in the "Jingyue Quan Book · Za Zheng Mo", and described that this disease usually occurs without phlegm, and may gradually develop due to emotional depression, attempted wishes, excessive thinking, doubts or panic.

3. Modern Medicine's Understanding of Senile Cognitive Impairment

Cognitive impairment is mainly manifested in the symptoms of cognitive dysfunction of the body, which is most common in memory loss. Rare manifestations include language, visual space, execution, calculation, understanding and judgment. The degree of cognitive decline can be divided into two states: mild cognitive impairment and Alzheimer's disease, where mild cognitive impairment refers to a certain degree of memory or other cognitive dysfunction of an individual, but does not meet the diagnostic criteria for dementia, which is located in the critical area of normal aging and early Alzheimer's disease. In recent years, people have studied cognitive disorders and made some progress. Cognitive disorders mainly include senile cognitive disorders, vascular cognitive disorders, and diabetes cognitive dysfunction. Senile cognitive dysfunction is closely related to neurodegenerative diseases. Aging is an inevitable process of human cells and the main cause of most neurodegenerative diseases [9]. During the development of aging and neuroregressive diseases, damaged cells accumulate in the nervous system, further exacerbating aging and neuroregressive diseases [10]. The development of aging and neurodesic diseases is generally accompanied by a decline in learning and memory ability, while the hippocampus, as a core part of the brain limbic system, plays a key role in maintaining and improving an individual's learning and memory [11]. According to the guidelines [12] issued by the American Academy of Neurology in 2018 for mild to moderate cognitive dysfunction, it is pointed out that such dysfunction is often a concurrent manifestation of other diseases, such as neurodegenerative diseases or mental illness. Patients affected by these disorders may maintain their current state or restore neurological function to a certain extent, but there is no exact drug or treatment to effectively slow down its transformation to Alzheimer's disease. Drugs currently approved for the treatment of Alzheimer's disease, such as cholinesterase inhibitors and n-methyl-D-aspartic acid receptor antagonists, can only relieve symptoms, not cure the disease. As an extremely complex and worsening cause of neurodegenerative lesions such as Alzheimer's disease, Alzheimer's disease includes the abnormal deposition of amyloid substances, the imbalance of nerve signal transmission substances, the weakening of mitochondrial autophagy, the activation of inflammatory reactions, and the damage caused by oxidative stress.

4. Electroacupuncture Regulates the Plasticity of Synaptic Structure

The promotion of electrotherapy on the plasticity of synaptic structures is particularly evident in the ultrastructural changes of synapses. This change is mainly reflected in the number and structural changes of synapses, the growth of axons, and the adjustment of post-synaptic dense matter. Relevant studies

pointed out that [13] electrotherapy can enhance the efficiency of synaptic transmission and optimize the cognitive ability of rats by increasing the number of synapses and vesicles and restoring the ultrastructure of synapses. The plasticity of synaptics is a key element of the learning and memory process [14] and plays an extremely critical role in alleviating cognitive impairment in the elderly. Researchers Ji et al. [15] observed that acupuncture therapy can improve the intensity of synaptic connections and effectively improve learning and memory disorders in Alzheimer's disease model mice. Similarly, the research results of Wu Jianli and her team members [16] also show that electrical acupuncture can significantly enhance synaptic plasticity in the hippocampus area. The morphological change of dendritic spines on the surface of neuron dendritic is closely related to synaptic plasticity and has a direct impact on cognitive function. Early studies have proved that the plasticity of dendritic spines is crucial to the development of synapses and the remodeling of neural networks, and constitutes the structural basis of learning and memory. Other studies have pointed out that the rapid reversible changes in the structure of dendritic spines are related to the severity of cerebral ischemia. The research team led by Chen Lidian found that electric needles to stimulate Baihui acupoints and Shenting acupoints can not only alleviate the widespread atrophy and fall off of dendritic spines, increase the density of dendritic spines, and optimize the neural network synaptic plasticity in the CA3-CA1 area of the hippocampus [19], but also adjust the expression level of miR-134 in the CA1 area of the hippocampus, improve the phosphorylation degree of LIM kinase 1, and improve the morphology of dendritic spines, so as to further regulate synaptic plasticity and promote the recovery of cognitive function in rats [20].

5. Electroneedle Regulates the Plasticity of Synaptic Function

As the core feature of synaptic function, its plasticity is mainly manifested in long-term Potentiation (LTP) and long-term Depression (LTD), both of which involve the adjustment of synaptic transmission efficiency [21]. Under the action of high-frequency stimulation, the LTP phenomenon increases the excitatory potential after the synaptic and maintains an extended state. In contrast, the LTD phenomenon is triggered by low-frequency stimulation, and the potential is significantly reduced after the synapse, revealing the weakening of synaptic efficiency. Extensive research results point out that the molecular mechanism of LTP and LTD to the learning and memory process [22] is closely related to learning and memory, especially the relationship between LTP and cognitive function is more extensive. In addition, the study points out that [23] LTD plays a key role in the formation of long-term memory. It can selectively suppress the overactivity of LTP, maintain the stability of synaptic intensity, avoid excessive saturation, and thus maintain the sensitivity of LTP excitation. In the study of Xiao et al. [24], DA-β-hydroxygenase in the hippocampal region of rats with chronic cerebral perfusion was regulated by electrical stimulation and Zusanli acupoints. The results showed that the upregulated DA-β-hydroxygenase may then convert dopamine, including dopamine, into norepinephrine, further affecting the cognitive function and synaptic plasticity of the hippocampus, and significantly improving the plasticity of synaptic function. However, after reviewing the literature, it is found that at present, most of the synaptic functional plasticity is mainly studied by LTP, and there are few studies on the effects of LTD.

6. Effect of Electricity on Synaptic Plasticity-related Proteins

These two proteins, synaptin and growth-associated protein 43, are located in the presynaptic membrane. They play a key role in regulating the efficiency of synaptic transmission and reshaping synaptic structures, and are regarded as key indicators of synaptic remodeling. According to literature research [25], growth-associated protein 43 is recognized as a molecular signal for neuronal axon repair. They are usually used as specific presynaptic markers to assess the plasticity of synapses. Research literature points out [26] that the content of synaptin is directly positively related to the number of synapses and has a significant impact on cognitive ability. In addition, according to the research of the literature [27], the combination of brain-derived neurotrophic factors and their receptors can be enhanced by electrical stimulation of the curve pool and the three-mile acupoints, thus improving the expression of synapsin and optimizing synaptic function. In the study of postsynaptic plasticity-related proteins, postsynaptic dense substances are a uniform dense structure on the postsynaptic membrane. Actin fibrin filaments and regulatory proteins in post-synaptic dense substances are essential to maintain the normal morphology of dendritic spines. The impairment of the integrity of the dense material after the synapse will lead to the loss of plastic-related proteins, which will affect the stability of the dendritic spine structure, and thus affect the plasticity of the synapse. The literature shows that [28] dense protein-95 is located in the post-synaptic dense zone, which plays a vital role in synaptic remodeling and function. The research in the literature found that [29], the expression of dense protein-95 can alleviate the morphological changes and memory loss of hippocampus neurons caused by hypoxia. Calcium ion/calcin-dependent protein kinase II, as a key component of post-synaptic density, exists in large quantities in the hippocampus region. It plays an indispensable role in long-term enhancement and memory formation. When the function of calcium ion/calcin-dependent protein kinase II is impaired, it will lead to the damage of hippocampus neurons, which may lead to cognitive dysfunction [30]. Relevant studies pointed out that [31] The level of dense protein-95 can be improved by electrically stimulating Baihui acupoints and Shenting acupoints, which helps to maintain the integrity of synaptic structures and enhance the plasticity of synapses, thus improving the cognitive function of rats.

7. The Influence of Electricity on Neurotransmitters and Receptors

Acetylcholine (ACh) is a key neurotransmitter substance that promotes learning and memory processes. Its generation and decomposition are controlled by choline acetyl transferase and acetylcholinesterase, which correspond to the generation and decomposition rates of ACh respectively. According to the study, electroacupuncture can significantly reduce the activity of acetylcholinesterase, and then adjust the release of

choline neurotransmitters, thus helping to improve learning and memory. As an excitatory neurotransmitter, glutamate can activate neurons and enhance cognitive ability. However, its overexpression may lead to intracellular calcium ions overloading, thus damaging neurons. As an inhibitory neurotransmitter, gamma-aminobutyric acid can resist excessive activity of glutamate. The imbalance between glutamate and gamma-aminobutyric acid may cause synaptic dysfunction [33]. Zhai Lijing [34] used enzyme-linked immunohistochemical technology to detect acetylcholine and enzyme activity in the hippocampus of Alzheimer's disease mice, and detected the content of monoamine neurotransmitters in the cerebral cortex by high performance liquid chromatography. The study found that electroacupuncture stimulation of Sanyin Jiao acupoints can improve the cognitive disorders of these mice, which may be related to the regulation of acetylcholine production in the hippocampus and the content of monoamine neurotransmitters in the cortical region. In summary, a neurotransmitter is a chemical messenger of information transmission between neurons or between neurons and effectors. Its abnormal expression may have a negative impact on physiological processes such as learning memory, cognitive function and emotional regulation.

8. Summary

At present, clinical medicine has not developed a drug that can completely cure cognitive deterioration in old age, so the prevention of this disease is particularly important. Although some progress has been made in the research on the mechanism of electroacupuncture therapy in improving cognitive degradation in old age, its research is still limited, and there is a close interaction between the studies. In view of this, making full use of the therapeutic potential of electroacupuncture, formulating a comprehensive and scientific electroacupuncture intervention programs, taking into account all potential mechanisms of action, clarifying the primary and secondary relationship, and building a systematic mechanism framework of action have become a key direction for future research. In addition, the study of synaptic plasticity has become a new focus on the treatment of cognitive dysfunction, which plays a key role in explaining the therapeutic mechanism of electricity against cognitive decline in the elderly. By studying how electroacles regulate the plasticity and functional structure of synapses, as well as the activity of related proteins, it has been proved that electroacles can effectively promote synaptic plasticity, thus improving learning and memory. However, in the field of research that uses electric needles to regulate synaptic plasticity to overcome cognitive impairment, although scientific research progress has been made in recent years, many aspects still need to be further explored. Topics such as the impact of specific parameters of electroacupuncture on synaptic plasticity and the interaction mode of neurotransmitters need to be further studied. Therefore, accurately grasping the regulatory mechanism of electrical synaptic plasticity and its specific ways and goals in improving senile cognitive impairment is of decisive significance for building an electroacupuncture treatment and rehabilitation plan for cognitive decline in the future.

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