

Mechanism of acupuncture in the treatment of post-stroke depression

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Abstract: Post-stroke depression is depression secondary to stroke, which is mainly characterized by mood disorders such as pessimism and depression. Its bad mood seriously affects the patients' daily life, social activities and neurological function recovery, and brings trouble and pain to the patients and their families. A large number of clinical literature studies have shown that acupuncture treatment can effectively improve limb function and depression symptoms of stroke patients, but the mechanism of acupuncture treatment is still unclear. The author through the retrospective analysis in recent five years the mechanism of the relevant literature found that acupuncture play to the role of the antidepressant mechanism mainly with acupuncture dysregulation of neurotransmitter content, inhibiting inflammatory cytokines secretion, increase neurotrophic growth factor protein content, lower hippocampal neuron apoptosis, regulate signaling pathways related protein expression, inhibition of the hypothalamus-pituitary-adrenal axis hypersecretion, so as to provide guidance for clinical treatment.

1. Introduction

Post-stroke depression is depressive symptoms with varying degrees of symptoms lasting for more than 2 weeks under the combined action of multiple pathological factors after stroke [1], which is depressed. A variety of mental and physical symptoms such as loss of interest, insomnia, anxiety, and neurological deficits are the main clinical manifestations. Studies have shown that [2] about one-third of stroke patients can develop depressive symptoms after stroke, and the prevalence within 1 year after the onset of the disease is the highest, about 30%-35%. At present, the pathogenesis of PSD is relatively complicated and unclear. Studies at home and abroad have shown that the occurrence of PSD is mainly related to abnormal neurotransmitter content after stroke, reduction of brain-derived neurotrophic factor, damage to hippocampal neurons, and pro-inflammatory in the injured site. Increased cytokines, rupture of the forehead subcutaneous circuit, and post-stroke patients' physical disabilities lead to psychological inferiority, excessive stress, introverted neuroticism and other neurophysiological and psychosocial factors [3-5]. At present, the treatment of post-stroke depression mainly includes oral antidepressants, traditional Chinese medicine, acupuncture, and psychotherapy.

It has been clinically shown that acupuncture has a positive effect on post-stroke depression, is safe and effective, has fewer side effects, and is superior to Western antidepressant treatment [6]. However, the mechanism of acupuncture treatment of the disease is not clear. The author retrieved the relevant literature on the basic research of acupuncture treatment of post-stroke depression in the past 5 years, and reviewed it from the following aspects.

2. Research progress

2.1 Increase the content of monoamine neurotransmitters

Monoamine neurotransmitters mainly include 5-Hydroxytryptamine (5-HT), norepinephrine (NE), dopamine (DA) and so on. 5-HT and NE neuron cell bodies mainly exist in the brainstem, and neuronal axons from the brainstem pass through the hypothalamus, basal ganglia, corpus callosum, and radiation crown to reach the left frontal cortex to regulate emotions and psychological functions. When a stroke is caused when the above-mentioned parts and nerve pathways are damaged, the synthesis and secretion of 5-HT and NE in significant parts are reduced, which in turn induces PSD [7]. Kronenberg found that the delayed degeneration of dopaminergic neurons in the left ventral tegmental area of stroke rats led to a decrease in the concentration of DA in the striatum. Insufficient function of DA receptors caused excessive excitement of the amygdala, anxiety and fear, and induced PSD [8]. The possible mechanism of acupuncture treatment of PSD is to activate the "limbic system-midbrain functional loop" to up-regulate the content of monoamine neurotransmitters such as 5-HT, NE and DA in the amygdala, hypothalamus, hippocampus and other emotional-related parts, and then prevent and treat PSD. Sun Peiyang [9] used the method of "Tongdu Tiaoshen" to continuously acupuncture PSD model rats for 4 weeks. The results showed that acupuncture can significantly improve the depression-like behavior of rats and increase the content of neurotransmitters in the hippocampus of rats, such as NE, 5-HT and DA. Mei Cheng [10] observed the effect on PSD rats by puncturing the temples with Baihui acupoint and connecting with music electroacupuncture treatment. The results of music electroacupuncture treatment caused the ascending fibers of 5-HTergic neurons in the brain of PSD rats to continue to excite. In turn, it activates the "limbic system-midbrain functional loop", which leads to a sustained increase in the 5-HT content of emotion-related parts, thereby alleviating and improving the state of depression. Xiao Wei [11] found that acupuncture at the "Baihui", "Fengfu" and bilateral "Shenmen" and "Taichong" points in PSD rats can enhance the expression of 5-HT, NE and DA in brain tissue and improve Rat behavior and depression state.

2.2 Inhibit the content of amino acid neurotransmitters

Inflammatory cytokines are a type of cytokines involved in immune inflammatory response, and are involved in the occurrence and development of PSD, such as serum high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), serum interleukin, etc. After stroke, the release of inflammatory cytokines increases and is activated. After activation, the expression of indoleamine 2,3-dioxygenase gene is up-regulated. This enzyme metabolizes tryptophan to kynurenine, which makes it synthesize with 5-HT. The separation of pathways leads to the decrease of 5-HT content in the frontal cortex and basal ganglia, and then PSD occurs [17]. Acupuncture has a benign regulatory effect, which can regulate the synthesis, secretion and biological activity of inflammatory cytokines in the body, that is, inhibit the secretion of inflammatory factors, reduce the concentration of serum inflammatory factors, thereby reducing inflammation and improving post-stroke depression symptoms. Fu Wei [18] used "Xingnao Kaiqiao" acupuncture to treat patients with PSD. As a result, acupuncture can improve depressive symptoms by reducing serum IL-6 and TNF- α levels in patients with PSD. Feng Wan [19] found that acupuncture treatment can inhibit the secretion of inflammatory

factors on the basis of conventional treatment, reduce inflammation, restore nerve function, and improve depression.

2.3 Increase the content of neurotrophin growth factor

Neurotrophic factors are protein molecules necessary to promote the development and survival of neurons, including brain-derived nerve growth factor (BDNF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), etc. Studies have shown [20] that after acupuncture treatment, the content of serum neurotrophin growth factor in PSD patients can be increased, thereby promoting the neurotrophic function of PSD patients, reducing nerve damage, and preventing and treating PSD.

2.3.1 Up-regulation of BDNF expression

BDNF is mainly distributed in the hippocampus and cortex of the brain, and its combination with tyrosine can promote the repair and regeneration of damaged neurons. Studies have shown that a large number of neuronal cells are destroyed in the local lesion tissue after stroke, inhibiting the content of BDNF in the brain area, hindering the regeneration and repair of neurons, causing abnormal changes in the neural network related to emotion and cognition, and ultimately leading to the occurrence of PSD. Cai Li [21] found that the number and expression of BDNF positive cells in the hippocampal CA3 area of PSD model rats were significantly reduced. Acupuncture treatment can increase the content and expression of BDNF in rats, thereby improving depression symptoms. Li Xueyong [22] found that the BDNF level of the prefrontal cortex of PSD model rats was significantly decreased. Acupuncture at the Mengyi Dinghui acupoints and frontal lobe group points can increase the BDNF level of the frontal cortex and improve the depressive state of PSD rats.

2.3.2 Up-regulation of VEGF expression

Vascular endothelial growth factor (VEGF) plays an important role in promoting angiogenesis and neuron regeneration after stroke. Studies have found that the number of VEGF-positive cells in the limbic system such as hippocampus, hypothalamus and amygdala in rat models of stroke increased significantly in the first week, and then gradually decreased [23]. Acupuncture can stimulate the proliferation and migration of neural precursor cells in this area by up-regulating the expression of VEGF, thereby promoting the repair and regeneration of blood vessels and neurons to improve depression symptoms. Zhao Lifeng [24] used immunohistochemical staining to observe the expression of VEGF in the brain tissue of PSD model rats. Compared with the model group, the expression of VEGF in the electroacupuncture group was significantly increased ($P < 0.05$). It is suggested that electroacupuncture can improve the repair ability of neurons by promoting the high expression of VEGF in brain nerve cells to achieve the therapeutic effect of preventing and treating PSD.

2.4 Reduce hippocampal neuron apoptosis and repair damaged hippocampal neurons

The hippocampus is an important brain area closely related to emotional and behavioral functions. At the same time, the hippocampus is also the main target area that is vulnerable to stress response. Neurons in different brain regions have different sensitivity to ischemia. The hippocampus is the most sensitive. The social and psychological chronic stress stimulation after stroke can significantly inhibit the proliferation of hippocampal neurons on the side of the stroke injury by stimulating corticosteroid stress hormones. , Differentiation and neurogenesis, which induce PSD [25]. Acupuncture may play an antidepressant effect by reversing the damaged neurons caused by chronic stress after stroke. Zhang Xianbao [26] found that chronic stress after stroke caused hippocampal cell damage such as cytoplasmic edema, loss of organelles, and apoptosis of hippocampal neurons in rats. Acupuncture

can alleviate hippocampal neurons caused by post-stroke stress to a certain extent. Apoptosis, repair damaged nerve cells and improve depression symptoms in rats. Cai Wa [27] found that the number of neurons in the hippocampus of PSD rats was significantly reduced, the Bcl-2/Bax ratio, and the expression of Shh, Gli1, and genes were significantly reduced through histopathological examination and immunohistochemical examination. Reverse the apoptosis of hippocampal neurons, and increase the number of neurons in the hippocampus, the Bcl-2/Bax ratio Shh, Gli1, and gene expression, play a protective effect on hippocampal neurons in PSD rats and improve depressive symptoms.

2.5 Regulate the expression of related proteins in signaling pathways

In recent years, studies have found that neuronal regeneration dysfunction due to dysfunction of intracellular signal transduction pathways after stroke is one of the important reasons for the occurrence of PSD [28-29]. Acupuncture may play an antidepressant effect by up-regulating the expression of CREB signaling pathway-related proteins. Liang Fajun [30] found that CREB positive cells in the hippocampus of PSD model rats decreased. After 4 weeks of intervention by the "Tongdu Zhiyu" acupuncture method, the expression of CREB in the hippocampus increased, and the expression in the treatment group was significantly higher than that in the model group ($P < 0.01$). Zhang Yingjie [31] found that electroacupuncture can phosphorylate the relevant factors of the BDNF/ERK/CREB signaling pathway, thereby increasing the expression of CREB and BDNF to play the neuroprotective effect of electroacupuncture in PSD rats, and improve the motor function of the rats' limbs. Relieve symptoms of depression. Li Shaoyuan [32] observed that the expression of ERK and CREB protein and their genes in the model group was significantly reduced, and the protein expression was significantly increased after treatment with ear concha electroacupuncture, and the depressive behavior of rats was improved. It is suggested that acupuncture can regulate the activity of related proteins in the ERK/CREB signaling pathway, thereby protecting and promoting the regeneration of neurons in the body, and improving the depressive behavior of rats.

2.6 Inhibit hypersecretion of hypothalamic-pituitary-adrenal axis

Hypothalamic-Pituitary-Adrenal (HPA) axis is an important pathway that regulates the body's neuroendocrine network, and is closely related to the body's life activities such as food intake, psychology, and behavior. HPA axis misalignment can cause PSD to occur. Stroke increases the release of pro-inflammatory cytokines, which in turn stimulates the HPA axis to release glucocorticoids and increases the secretion of plasma cortisol [33]. Elevated cortisol damages brain nerve cells, resulting in a decrease in 5-HT and NE and eventually PSD [34]. Acupuncture can act on the hypothalamus through afferent nerves at acupoints, regulate the secretion and release of HPA axis hormones, improve the HPA axis dysfunction caused by chronic stress, maintain a balanced state of function, and improve depression. Shi Rongzheng [35] found that the ACTH level of the pituitary and the CORT level of the adrenal glands in the model group of depressed rats were significantly increased. The content of monoamine neurotransmitters in the brain can improve the neurological activity and depression of rats.

3. Conclusions and Discussion

Compared with the treatment of PSD with antidepressant drugs in western medicine, acupuncture has more extensive effects in the treatment of PSD, and its regulation has the characteristics of multi-system, multi-step, multi-level, and multi-target overall regulation. Acupuncture points can affect the functions of multiple organs and multiple systems at different levels at the same time. On the other hand, in pathological conditions, acupuncture can improve the quality of the system, improve the

state of the body, enhance the ability to regulate, stimulate and induce brain protection, improve brain tissue disease resistance, and thereby improve stroke and post-stroke depression symptoms.

At present, there are still some shortcomings and problems in the basic research of acupuncture and moxibustion for PSD: the selection and treatment of acupuncture and moxibustion for PSD lack objective and standardized standards and guidance. In animal experiments, the angle, depth, technique and amount of stimulation of acupuncture lack quantification. Indexes affect the objectivity and reproducibility of experimental results, making it difficult to promote and apply on a large scale. At present, a large number of studies focus on the observation of the efficacy of acupuncture and moxibustion in the treatment of PSD, and there are few studies and discussions on related mechanisms; although animal experimental studies can make up for the deficiencies of human experimental research and copy the PSD model for research and analysis, but there are certain differences between humans and animals. Therefore, in future research, it is necessary to further standardize the quantitative indicators of acupuncture in animal experiments and study the mechanism of acupuncture treatment of PSD; the conclusions of basic research need to be explored, revised, and verified in the process of guiding clinical practice. In the clinical transition phase, it is hoped that the theory and methods will be better guided and applied in practice.

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References

- [1] Drevets W C, Price J L, Furey M L. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression [J]. *Brain Structure and Function*, 2008, 213(1-2): 93-118.
- [2] Wei N, Yong W, Li X, et al. Post-stroke depression and lesion location: a systematic review [J]. *JOURNAL OF NEUROLOGY*, 2015, 262(1): 81-90.
- [3] Huang Jingjing, Chen Ningyong. Research progress on the pathogenesis of post-stroke depression [J]. *Journal of Shanghai University of Traditional Chinese Medicine*, 2014(3): 104-107.
- [4] Kronenberg, Endres. Stroke and Depression [J]. *Aktuelle neurologie*, 2013, 40(10):553-556.
- [5] Yu Zheng, Zhang Meiyong, Li Mengqian, et al. The influence of psychosocial factors on the onset of post-stroke depression [J]. *Journal of Nanchang University (Medical Edition)*, 2012, 52(2): 48-51.
- [6] Zhou Xin, Ren Lu, Gao Yuanyuan, et al. Meta-analysis of acupuncture on the improvement of depression in patients with post-stroke depression [J]. *Chinese Journal of Traditional Chinese Medicine*, 2018, 36(12): 2875-2879.
- [7] Wang Fang. Research progress on biomarkers of post-stroke depression [J]. *Journal of International Neurology and Neurosurgery*, 2019, 46(3): 325-329.
- [8] Kronenberg G, Balkaya M, Prinz V, et al. Exofocal Dopaminergic Degeneration as Antidepressant Target in Mouse Model of Poststroke Depression[J]. *Biological Psychiatry*, 2012, 72(4):273---281.
- [9] Sun Chongqing, Cai Ronglin, Li Peifang, et al. Acupuncture with "Tongdu Tiaoshen" on the protective effect of hippocampal neurons and the effect of monoamine neurotransmitters in post-stroke depression rats[J]. *Chinese Acupuncture and Moxibustion*, 2019, 39(7):741-747.
- [10] Mei Cheng, Zhao Jingyuan, Duan Guoxiang, et al. The effect of scalp acupuncture with music electro-acupuncture on the behavior and brain tissue NE and 5-HT content in rats with post-ischemic stroke depression [J]. *Journal of Acupuncture and Moxibustion*, 2016, 32(12): 64-66.
- [11] Xiao Wei, Zhang Xianbao, Wang Zhen, et al. Effects of acupuncture on neurotransmitters, serotonin transporter, serotonin 1A receptor, and norepinephrine α_2 receptor in brain tissue of rats with post-stroke depression [J]. *Acupuncture Research*, 2016, 41(6): 528-534.
- [12] Dhawan J , Benveniste H , Nawrocky M , et al. Transient focal ischemia results in persistent and widespread neuroinflammation and loss of glutamate NMDA receptors [J]. *Neuroimage*, 2010, 51(2): 599-605.
- [13] Li Shulan, Liu Fenglian, Wang Xuebin, et al. The existence of glutamate and its receptors in the brain and the neurotoxicity of glutamate [J]. *Chinese Tissue Engineering Research*, 2004, 8(22): 4553-4555.

- [14] Yan Jianing, Zhao Lifeng, Yu Tao, et al. Effects of electroacupuncture on the expression of glutamate neurotransmitters and their receptors in post-stroke depression rats [J]. *Journal of Ningbo University (Science and Technology Edition)*, 2018, 31(3): 72-75.
- [15] Zhao Lifeng, Fu Runxi, Yan Jianing, et al. Effect of electroacupuncture on the expression of γ -aminobutyric acid and vascular endothelial growth factor in brain nerve cells of rats with post-stroke depression [J]. *Chinese Journal of Gerontology*, 2018, 38(19): 4751-4753.
- [16] Wei Yanying. The effect of acupuncture and thread embedding on amino acid neurotransmitters in depression model rats [D]. Guangzhou: Guangzhou University of Traditional Chinese Medicine, 2018. Villa, Roberto, Federico, et al. Post-stroke depression: Mechanisms and pharmacological treatment [J]. *Pharmacology & Therapeutics*, 2018, 184(4): 131-144.
- [17] Fu Wei. The effect of combined acupuncture and medicine on EEG and serum NE, NSE, IL-6 and TNF- α levels in patients with post-stroke depression [J]. *Shanghai Journal of Acupuncture*, 2019, 38(11): 1214-1218.
- [18] Feng Wan, Yang Yaojun. Effect of acupuncture adjuvant treatment on serum cytokines and neurotransmitters in patients with post-stroke depression [J]. *Journal of Hainan Medical University*, 2017, 23(14): 2010-2013.
- [19] Sun Xiaodong, Yang Ning, Che Wensheng. The effect of acupuncture on patients with post-stroke depression and its influence on neurotrophic status and monoamine neurotransmitters [J]. *World Chinese Medicine*, 2018, 13(9): 2285-2287, 2291.
- [20] Cai Li, Liu Yi, Lu Xiaoqing. Effects of acupuncture on spatial learning and memory function and brain-derived neurotrophic factor in hippocampus CA3 area of rats with post-stroke depression [J]. *Shanghai Journal of Acupuncture and Moxibustion*, 2016, 35(4): 88-91.
- [21] Li Xueyong, Wulan, Miao Mei. Effects of acupuncture on monoamine transmitters and brain-derived growth factors in the frontal cortex of rats with post-stroke depression [J]. *Journal of Chinese Medicine*, 2018, 33(7): 153-156.
- [22] Li Dongmei, Tang Qisheng, Zhao Ruizhen, et al. Dynamic changes of vascular endothelial growth factor in the limbic system of rat models of stroke and the intervention of traditional Chinese medicine [J]. *Journal of Beijing University of Traditional Chinese Medicine*, 2014, 37(9): 606-610.
- [23] Zhao Lifeng, Fu Runxi, Yan Jianing, et al. Effects of electroacupuncture on the expression of γ -aminobutyric acid and vascular endothelial growth factor in brain nerve cells of rats with post-stroke depression [J]. *Chinese Journal of Gerontology*, 2018, 38(19): 4751-4753.
- [24] José Tomás Egaña, Zambrano C, Marco Tulio Nuñez, et al. Iron-induced oxidative stress modify tau phosphorylation patterns in hippocampal cell cultures [J]. *Biometals*, 2003, 16(1): 215-223.
- [25] Zhang Xianbao, Wang Zhen, Wang Yan, et al. The effect of acupuncture on the ultrastructure of hippocampus in rats with post-stroke depression [J]. *Journal of Gansu University of Traditional Chinese Medicine*, 2017, 34(1): 1-5.
- [26] Cai Wa, Ma Wen, Wang Guantao, et al. Based on Shh-Gli1 signaling pathway to explore the protective effect of electroacupuncture on hippocampal neuronal apoptosis in rats with post-stroke depression [J]. *Chinese Journal of Traditional Chinese Medicine*, 2019, 34(09): 4282-4286.
- [27] Conway C R, Chibnall J T, Gebara M A, et al. Association of Cerebral Metabolic Activity Changes with Vagus Nerve Stimulation Antidepressant Response in Treatment-Resistant Depression [J]. *Brain Stimulation*, 2013, 6(5): 788-797.
- [28] Dai Wei, Li Weidong, Lu Jun, et al. Effect of electroacupuncture on hippocampal neuron apoptosis and JNK signal transduction pathway in chronic stress depression rats [J]. *Acupuncture Research*, 2010, 35(5): 12-16.
- [29] Liang Fajun, Kong Hongbing, Hu Huixing, et al. Effect of "Tongdu Zhiyu" acupuncture on body mass, behavior and hippocampal cyclic adenosine phosphate response element binding protein level in post-stroke depression model rats [J]. *Journal of Gansu University of Traditional Chinese Medicine*, 2017, 34(1): 5-9.
- [30] Zhang Yingjie, Zhang Wei, Xu Mingshu, Zhang Xinglin, Zhang Di, Cheng Aifang. Based on the BDNF/ERK/CREB signal transduction pathway to explore the regulation mechanism of electroacupuncture on the expression of BDNF in the hippocampus of PSD rats [J]. *Jiangsu Traditional Chinese Medicine*, 2020, 52(3): 81-85.
- [31] Li Shaoyuan. The effect of ear concha electroacupuncture on the Raf/ERK/RSK/CREB signaling pathway in the hippocampus of depression model rats [J]. *Acupuncture Research*, 2019, 44(8): 554-559.
- [32] Li Jingxue, Wang Tianjun. Research progress in the pathogenesis and treatment of post-stroke depression [J]. *Clinique Meta*, 2019, 34(6): 572-576.
- [33] Liu Yalu, Xu Shixin, Zhang Junping, et al. Based on HPA axis to explore the treatment of Chaihu plus Longgumuli Decoction for post-stroke depression [J]. *Chinese Journal of Traditional Chinese Medicine*, 2019, 34(4): 1629-1631.
- [34] Shi Rongying, Ding Haitao, Li Hui, et al. Effects of acupuncture in different acupoint groups on related factors of hypothalamus-pituitary-adrenal axis and serum brain-derived neurotrophic factor in depression rats [J]. *Acupuncture Research*, 2015, 40(6): 444-448.
- [35] Wu Yanfang, Zhang Wei. Research progress on the etiology, pathogenesis and acupuncture treatment of post-stroke depression [J]. *Yunnan Journal of Traditional Chinese Medicine and Materia Medica*, 2016, 37(10): 83-85.