Research Progress of Acupuncture Intervention on Depression Model Rats in recent five years

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Abstract. Depression is a mental disorder caused by multiple factors, characterized by changes in behavior, cognition and emotion. This disease not only severely affects the daily life of the affected people, but also interferes with their families and the whole society. In recent five years, through the research on acupuncture intervention in depression model rats, it was found that acupuncture intervention can effectively improve the behavioral indicators and symptoms of depression model rats. Therefore, many researchers began to study the mechanism of acupuncture intervention in depression. This paper reviews the research progress of acupuncture intervention in depression model rats. Taken together, by sorting out and summarizing, this paper has organized the research on the research progress of acupuncture intervention in depression model rats in the past five years (), and found that acupuncture is an important alternative treatment for depression. The possible mechanisms of acupuncture's antidepressant effects mainly include neurotransmitters, neural cell signal transduction pathways, neurons, gene expression, neuroendocrine and its metabolites, and neuroimmunity, which also provides a glimpse into the clinical treatment of depression.

Keywords: Depression model rats; Acupuncture; Traditional Chinese Medicine (TCM)

1 Introduction

Depression (MDD), also known as depressive disorder, is a common mental mental disease. Its clinical features include behavior, cognition and emotion [1]. Patients often show low mood, loss of interest, guilt or inferiority, insomnia or loss of appetite, fatigue or poor concentration [2]. Depression has become an important public health problem. According to the statistics of the World Health Organization (WHO), about 340 million people worldwide suffer from depression, and the cumulative suicide rate is 26.3%. By 2017, the Global Burden of Disease study identified depression as the third leading cause of disability [3]. The traditional treatment of depression includes antidepressant drugs and psychotherapy. Long-term use of antidepressants often leads to many side

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effects, such as sexual dysfunction, metabolic syndrome [4], and even suicide tendency in severe cases. Furthermore, the effect of psychotherapy is to some extent unsustainable. Therefore, it is necessary to seek a lasting green therapy of non-drug treatment.

Acupuncture is considered an alternative treatment for depression. Research [5-7] shows that acupuncture can improve the behavioral indicators of depression model rats, such as increasing the activity time in the Open Field Test (OFT) and increasing the sucrose preference of the Sucrose Preference Test (SPT), but its effects need to be further elaborated. Therefore, in the past five years, many scholars have explored its mechanism, mainly including neurotransmitters, signal transduction pathways of neural cells, neurons, gene expression, neuroendocrine and its metabolites, and neuroimmunity.

2 Research Overview

2.1 Regulating effect of acupuncture on neurotransmitters

In recent years, an increasing number of researchers have focused on the pathogenesis of depression, with the "biological mechanism hypothesis" being the most popular. Based on the theoretical basis of neurotransmitter mechanism, the "biological mechanism hypothesis" considers that the course and prognosis of depression are related to low levels of 5-hydroxytryptophan (5-HT) and norepinephrine (NE) in the brain, and therefore, the deficiency and systemic imbalance of various neurotransmitters such as 5-hydroxytryptophan and NE are the neurobiological basis of depression[8].

Sun et al. [9] established a model of post-stroke depression rats and applied the "Tongxiang Tiao Shen needle method" and found increased levels of NE, 5-HT and DA in the hippocampus. The experimental results showed that "Tongdu Tiaoshen" acupuncture significantly improved the behavior of post-stroke depressed rats because of the up-regulation of NE, 5-HT and DA in the hippocampus. To observe the effect of acupuncture on the expression of monoamine neurotransmitter-related genes and neurotransmitters, genes related to monoamine neurotransmitters, XU et al. [10] established a depression model and found that acupuncture treatment could reverse the genes of CAMP response element binding protein 1 (Creb1), glycogen synthase kinase 3α (Gsk3a), phospholipase A2 group V (Pla2g5), the voltage－dependent N － type α1B subunit of calcium channels (Cacna1b) and nuclear receptor subfamily 4 group A member 1 (Nr4a1) in the depressed rats, which confirmed that acupuncture can effectively reverse the behavior of depressed rats and regulate the expression of monoamine neurotransmitter－related genes.

2.2 Regulating effect of acupuncture on cell signal transduction pathway

Depression is associated with the activation of the body's inflammatory response system. Acupuncture can down-regulate the serum and encephalitis cytokines of rats with chronic stress depression [11]. Pu et al. [12] established a CUMS rat model to and found

that the expression levels of NF-κB, iNOS and NO in the prefrontal cortex of rats are significantly lower than those in the model group, suggesting that acupuncture may play an antidepressant role by down-regulating the levels of NF-κB, iNOS and NO in the prefrontal cortex. Through CUMS rat model, Li et al. [13] found that P-ERK1/2 protein expression level and BDNF protein expression level were significantly up-regulated in the acupuncture group, which suggests that acupuncture may improve the depression of rats by upregulating the phosphorylation of p-ERK1/2 and increasing BDNF protein in the prefrontal lobe.

Li et al. [14] established another CUMS rat model, and found that compared with the model group, the hippocampal Raf, P-Raf, ERK, P-ERK, RSK, CREB and PCREB of rats in EA group were significantly increased, which indicates that ear acupuncture may play an antidepressant role by regulating the Raf/ERK/RSK/CREB signaling pathway in the hippocampus. To investigate whether EA can improve the state of depressed rats by regulating p38MAPK signal pathway, LIU et al. [15] established a model for post-stroke depression rats, and conducted EA stimulation in Baihui, Dazhui, Neiguan and Taichong respectively. It was found that the levels of serum TNF-α, IL-1β,TRAF6 and IL-1βR, the protein expressions of TRAF6, IL-1βR and p38MAPK in the hippocampus of the rats in the model group were significantly higher than those in the blank group. On the contrary, the above indexes of rats in the acupuncture group were significantly lower than those in the model group. These results suggest that acupuncture may improve the state of post-stroke depression rats by regulating p38MAPK signal pathway.

2.3 Regulating effect of acupuncture on neurons

Synapses.

Chronic stress and depression lead to region specific changes in synaptic form and function. Changes in synaptic plasticity during stress and depression may be related to signal transduction pathways (such as NOS-NO, camp-PKA, RAS-ERK, PI3K-Akt, GSK-3, mTOR and CREB) and upstream receptors (such as NMDAR, TrkB) and P75NTR [16]. Shen et al. [17] used CUMS rat model and acupuncture of “Yintang” and “Baihui”, and found that all indexes in the open field test of rats in the EA group were significantly increased, synaptic ultrastructure was improved, and the expression of nNOS and nNOS mRNA in hippocampus was decreased. In a word, acupuncture intervention may play an antidepressant role by reducing the expression of nNOS in hippocampus and affecting synaptic plasticity.

Regulating effect of acupuncture on hippocampal nerve.

Research shows reducing hippocampal nerve can lead to depression, and acupuncture treatment can effectively reduce hippocampal neuronal apoptosis thus protecting neurons [18]. BDNF is a neurotrophic protein that participates in the regulation of nerve cell function by activating TrkB. Xu et al. [19] established a CUMS rat model and found that acupuncture of “Baihui” and “Yintang” can improve TGF- β 3 (fold change =1.61, 1.61), reduce the protein level of bFGF (fold change =0.61, 0.45). It can be seen that

acupuncture intervention can increase TGF by- β 3 protein expression level and benign regulatory neuroprotective factor bFGF can improve the behavioral symptoms of chronic stress depression model rats. Sun et al. [20] used CUMS rat model and found that acupuncture of "Baihui", "Yintang" and bilateral "Sanyi sexual intercourse" can significantly reduce the levels of ROS, cytochrome C, caspase-3 and apoptosis-inducing factor (AIF) in hippocampus. The experimental results showed that the depressive state of rats was significantly improved. Therefore, acupuncture intervention may play an antidepressant role by decreasing the mitochondrial ROS content rat hippocampus mitochondria and the expression levels of key factors of apoptosis pathway (cytochrome C, caspase-3, AIF).

2.4 Regulating effect of acupuncture on gene expression

MiRNA may be involved in the pathophysiological process of depression, especially in regulating the gene expression of key elements in synaptic plasticity, neurogenesis and signal transduction pathways. MiRNA can play an important role in regulating synaptic plasticity by influencing the translation process of mRNA or its stability [21]. Zhao et al. [22] established a CUMS rat model and stimulated "Yintang" and "Baihui" with EA. They found that the levels of mirNA-16 and SERT in the hippocampus and raphe nucleus decreased in EA group, suggesting that the changes of mirNA-16 in the brain regions are related to the occurrence of depression, and acupuncture intervention may play an antidepressant role by inhibiting the expression of SERT in the brain regions. Huang et al. [23] established a CUMS rat model and acupuncture the "Shisan Ghost Points", and found that the overexpression of βcamKii protein and mRNA in the lateral habenula of rats was inhibited. This result indicates that acupuncture may play an antidepressant role by down-regulating the overexpression of βcamKii protein and mRNA in the lateral sellar nucleus of rats. In order to explore the therapeutic effect and mechanism of the three-acupoints balance acupuncture of Mongolian medicine on depression, Saiyin et al.[24] used the three-acupoints balance needling on rats of Mongolian medicine to conduct acupuncture intervention on CUMS rats, and found that the expression of p11/tPA/BDNF pathway and miRNA-16 in hippocampus and middle raphe nucleus (MRN) of chronic stress depression model rats changed after acupuncture intervention. This results may be related to the up-regulated expression of p11 and tPA proteins and BDNF mRNA in hippocampus and MRN and the down-regulation of miRNA-16 in hippocampus, indicating that the p11/tPA/BDNF signal pathway controlled by miRNA-16 is involved in the antidepressant effect of acupuncture.

2.5 Regulating effect of acupuncture on neuroendocrine and its metabolites

Hypothalamic-pituitary-adrenal (HPA) axis hyperfunction is closely related to the onset of depression [25]. The brain is stimulated under pressure and sends signals to the hypothalamus to release adrenocorticotropic hormone (CRH), the adrenal gland releases adrenocorticotropic hormone (ACTH), and the adrenal gland releases cortisol (CORT)

and glucocorticoid (GC).If CRH is excessive, the pituitary gland will increase the secretion of ACTH and GC, leading to HPA axis hyperfunction and depression. At present, the specific mechanism of HPA axis dysfunction in patients with depression is still unclear, which is also one of the research directions of the pathogenesis of depression in the future.

Le et al. [26] constructed a CUMS rat model and found that EA can significantly down-regulate CRH mRNA expression, reduce ACTH and CORT concentrations, indicating that EA may play an antidepressant role by inhibiting the excessive activity of HPA axis in rats. Based on CUMS rat model, Shi et al. [27] found that after acupuncture intervention, the levels of 5-HT in the hippocampus and BDNF in the serum increased significantly, and the levels of adrenocortical hormone decreased significantly, indicating that acupuncture may play an antidepressant role by increasing the levels of 5-HT in the hippocampus and BDNF in the serum, and downregulating the levels of adrenocortical hormone. Jiang et al. [28] established a perimenopausal depression model of rats, and found that acupuncture of "Baihui", bilateral "Shenshu" and bilateral "three-yin moxibustion" can increase the sucrose consumption rate of rats, compared with the model group, the content of CRH, ACTH and CORT in serum of rats in the EA group decreased. The content of β-EP was increased, suggesting that acupuncture intervention may improve the depression state of the perimenopausal depression rats by regulating HPA axis and β-EP content.

2.6 Regulating effect of acupuncture on neuroimmunity

At the beginning of the 20th century, the relationship between the immune system and major mental illnesses was proposed. Stress can induce the activation of immune responses, lead to abnormal inflammatory level and persistent proinflammatory state, and affect homeostasis and a series of depressive symptoms [29]. Sha et al. [30] established a depressed rat model and conducted acupuncture intervention. They found that compared with the model group, the GFAP content in the hippocampus was significantly increased, and the GFAP content in the prefrontal cortex was significantly reduced. Meanwhile, compared with the model group, the serum IL-10 of the rats was significantly increased. Acupuncture can regulate the expression of GFAP in astrocytes (AST) in hippocampus and prefrontal cortex of rats, improve the AST function in hippocampus and prefrontal cortex, and increase the content of serum anti-inflammatory cytokine IL-10, which is beneficial to play an antidepressant role. Lu et al. [31] found that the levels of nitric oxide (NO), prostaglandin E2 (PGE2), nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) in hippocampus and prefrontal cortex of CUMS rats significantly decreased after acupuncture intervention. Therefore, acupuncture can significantly inhibit the activation of NF-κB in the rat brain, suggesting that the antidepressant effect of acupuncture may be mediated by regulating the inflammatory mediators of NF-κB in the brain. In addition, Lu [32] in another acupuncture intervention experiment that in the hippocampus, prefrontal cortex and serum proinflammatory cytokines, interleukin 1 beta ([beta] IL - 1), the mRNA expression levels of interleukin-6 ([IL-6])

and tumor necrosis factor-α ([TNF-α]) significantly decreased, suggesting that acupuncture intervention may play an antidepressant role by inhibiting the expression of proinflammatory cytokines.

3 Discussion

Although the name of depression is not clearly recorded in traditional Chinese medicine (TCM), the depression referred to in western medicine may be included in the "constraint syndrome" and "globus hyertericus" of TCM. "Lingshu" is one of the earliest references for acupuncture treatment of diseases similar to depression. Through continuous accumulation and development, TCM has formed a relatively complete system of treatment based on syndrome differentiation. The clinical treatment of depression with western medicine has achieved certain effects, but there are also some side effects, complications and drug dependence. In the course of clinical experiments, acupuncture intervention, such as acupuncture at "Baihui" and "Yintang", has been widely recognized for the treatment of depression. Different from western antidepressant drugs, acupuncture intervention therapy can regulate the systemic mechanism of anti-depression, with multiple ways and targets, good efficacy, small side effects, high safety and low price. Therefore, the exploration of TCM based treatment may be one of the breakthroughs in clinical treatment.

As the basis of basic medical research, animal experiment is an important springboard for the combination of TCM and modern medicine. The innovation of this paper consists in the search and summary of the research progress of acupuncture intervention in depression model rats in the past five years, mainly from six aspects: neurotransmitters, nerve cell signal transduction pathways, neurons, gene expression, neuroendocrine and its metabolites, and neuroimmunity to further explore the internal mechanism of acupuncture treatment of depression from multiple levels, mechanisms, and targets. These successes also tell us that we can also explore the underlying causes of depression mechanism from the perspective of acupuncture points, methods and classical theories of TCM, and combine the progress of modern medicine with TCM.

At the same time, we can also carry out more abundant animal experiments in the future[33] and develop depression into the leading disease of TCM clinical treatment by combining different treatment methods of TCM. In addition, future research can establish different animal models to simulate different incidence and clinical manifestations of the same disease based on different TCM evidence symptoms of the same disease. Moreover, the model can then be combined with TCM treatment, thus opening the door for TCM acupuncture to treat depression.

4 Conclusion

To sum up, by sorting out and studying the research progress of acupuncture intervention in depression model rats in the past five years, it is found that acupuncture n is an important alternative therapy for depression. The possible mechanisms of acupuncture antidepressant effects mainly include neurotransmitters, neural cell signal transduction

pathways, neurons, gene expression, neuroendocrine and its metabolites, and neuroimmunity, which sheds a light on the clinical treatment of depression.

5 References

1. Mike Armour，Caroline A Smith，Li-qiong Wang，et al. AcuPuncture for DePression: A Systematic Review and Meta-Analysis（13）. J Clin Med，2019，8(8)：1140.
2. Bing-cong Zhao，Zhi-gang Li，Yuan-zheng Wang，et al. Manual or electroacuPuncture as an add-on theraPy to SSRIs for dePression：A randomized controlled trial（15）. J Psychiatr Res，2019，114：24-33.
3. Shan-xia Luo，You-lin Long，Wen-zhe Xiao , et al. Risk of bias assessments and rePorting quality of systematic reviews and randomized controlled trials examiningacuPuncture for dePression: An overview and meta-ePidemiology study（12）. J Evid Based Med，2020，13(1)：25-33.
4. Zhu Jianfeng, Jin Weidong. Adverse effects of antidepressants. Medicine Herald,2018，37（10）：1198-1202.
5. Peng Li , Wenya Huang , Yi-Ning Yan , et al. Acupuncture Can Play an Antidepressant Role by Regulating the Intestinal Microbes and Neurotransmitters in a Rat Model of Depression. Med Sci Monit，2021，
6. Zhinan Zhang , Xiaowen Cai , Zengyu Yao , et al. EA Ameliorated Depressive Behaviors in CUMS Rats and Was Related to Its Suppressing Autophagy in the Hippocampus. Neural Plast，2020，
7. Kun Zhang , Ran Liu , Jingruo Zhang , et al. Electroacupuncture Ameliorates Depression-Like Behaviour in Rats by Enhancing Synaptic Plasticity via the GluN2B/CaMKII/CREB Signalling Pathway. Evid Based Complement Alternat Med， 2021，
8. Chen Ninggui, Liao Min. Efficacy of Jieyu Pill combined with citalopram in the treatment of refractory depression and its effect on serum norepinephrine and serotonin and brain-derived neurotrophic factor indexes. Chinese General Practice，2017，（S2）：338-340.
9. Pei-Yang Sun , Rong-Lin Cai , Pei-Fang Li , et al. Protective effects on hippocampal neurons and the influence on hippocampal monoamine neurotransmitters with acupuncture for promoting the circulation of the governor vessel and regulating the mental state in rats with post-stroke depression. Chinese acupuncture & moxibustion, 2019，39（7）：741-747.
10. Xu Xuejiao, Li Tianying, Li Xin, et al. Effects of acupuncture on the expression of monoamine neurotransmitter-related genes in depressed rats. Journal of Acupuncture and Moxibustion, 2022, 38(5): 42-47.
11. Shao Runhui, Jin Shuying, Lu Jun, et al. Effects of acupuncture on the kaPPaB signaling pathway of the hippocampal nuclear transcription factor in chronic stress-depressed rats. Acupuncture research，2015，40（5）：368-372.
12. Pu Rong, Shao Runhui, Lu Jun, et al. Effects of acupuncture on the expression of nuclear transcription factor κB, inducible nitric oxide synthase and nitric oxide in the prefrontal cortex of depressed rats. Acupuncture research，2018，43(4)：226-230.
13. Li Xiang, Xu Mingmin, Jiang Huili, et al. Effects of acupuncture intervention on depressive behavior and expression of ERK 1/2 and BDNF in frontal cortex in chronic unpredictable mild stress-induced depression in rats. Acupuncture study，2018, 43（11）：705-710.
14. Li Shaoyuan, Rong Peijing, Gao Guojian, et al. Effects of auricular electroacupuncture on Raf/ERK/RSK/CREB signaling pathway in hippocampus of depression model rats. Acupuncture Research，2019，44（8）：554-559.

15. Liu Lili, Shi Ling, Leng Feng, et al. Effects of acupuncture on immune factors in post-stroke depression model rats based on p38MAPK signaling pathway. Modern Journal of Integrative Medicine. 2022, 31（7）：914-917，976.
16. W N Marsden. SynaPtic Plasticity in dePression: molecular, cellular and functional correlates. Prog NeuroPsychoPharmacol Biol Psychiatry，2013，43：168-84.
17. Shen Feier, Wang Xinjun, He Tizhen, et al. Effects of electroacupuncture on synaptic plasticity and neurogenic nitric oxide synthase in hippocampus of chronic stress-depressed rats. Chinese Journal of Basic Medicine of Traditional Chinese Medicine，2018，24（11）：1592-1596.
18. Lei Banglin, Xie Zhuoyu, Yuan Fengguo. Research on the progress of acupuncture in the treatment of depression. World Compound Medicine，2022，8（8）：192——198.
19. Xu Mingmin, Zhang Danmei, Shi Ronglong, et al. Effects of electroacupuncture on the expressions of transforming growth factor β3 and basic fibroblast growth factor in hippocampus of chronic stress-depressed rats[J]. Acupuncture Research，2016，41（2）：138-143.
20. Sun Yang, Tu Ya, Guo Yu, et al. Effects of acupuncture on apoptosis-related factors in hippocampus of chronic restraint stress-induced depression model rats. Acupuncture Research，2019，44（6）：412-418.
21. Zhang Yanhua, Shen Yifeng, Li Huafang. Research progress of microRNA in depression. Journal of Clinical Psychiatry，2013，23(2) : 135－137.
22. Zhao Jun, Tian Huiling, Li Yujie, et al. Effects of electroacupuncture on miRNA-16 and serotonin transporters in different brain regions of depression model rats. Journal of Clinical Acupuncture and Moxibustion，2019，35（11）：69-74.
23. Huang Wenya, Huang Yang, Zhu Anning, et al. Effects of acupuncture at thirteen ghost points on βCaMKII protein and mRNA expression in the lateral habenula of depressed rats. Chinese Journal of Traditional Chinese Medicine (formerly Chinese Journal of Medicine)，2020，35（3）：1417-1421.
24. Saiyin Chao Ketu, Song Meili, Ai Liya, et al. Effects of Mongolian medicine three-root balance acupuncture on miRNA expression profiles in hippocampus of chronic stress and depression model rats. Chinese Journal of Traditional Chinese Medicine，2021, 36（7）：3821-3827.
25. Mario F Juruena , Mariia Bocharova, Bruno Agustini , Allan H Young. Atypical depression and non-atypical depression: Is HPA axis function a biomarker? A systematic review. Affect Disord，2018，233：45-67.
26. Jing-jing Le，Tao Yi，Li Qi，et al. ElectroacuPuncture regulate hyPothalamic-Pituitary-adrenal axis and enhance hiPPocamPal serotonin system in a rat model of dePression .Neurosci Lett，2016，615：66-71.
27. Shi Ronglong, Ding Haitao, Li Hui, et al. Effects of acupuncture at different acupoint groups on hypothalamic-pituitary-adrenal axis-related factors and serum brain-derived neurotrophic factor in depressed rats [J]. Clinical Journal of Acupuncture and Moxibustion, 2015, 40(6): 444-448.
28. Jiang Xirong, Ren Lu. Effects of electroacupuncture on hypothalamic-pituitary-adrenal axis and β-endorphin in perimenopausal depression model rats. Chinese Journal of Traditional Chinese Medicine，2016，34（8）：1923-1925.
29. Angelos Halaris. Inflammation and depression but where does the inflammation come from? .Curr Opin Psychiatry，2019，32(5)：422-428.
30. Sha Dong , Hui-Li Jiang , Yu Wang ,et al.Effect of Acupuncture on Expression of Glial Fibrillary Acidic Protein in Hippocampus and Prefrontal Cortex and Serum Interleukin-10 in Chronic Restraint Stress Depression Rats.Acupuncture research, 2018，43(4)：209-214.

31. Jun Lu，Run-Hui Shao，Shu-Ying Jin，et al. AcuPuncture ameliorates inflammatory resPonse in a chronic unPredictable stress rat model of dePression.Brain Res Bull，2017，128：106-112.
32. Jun Lu，Run-Hui Shao，Li Hu，et al. Potential antiinflammatory effects of acuPuncture in a chronic stress model of dePression in rats.Neurosci Lett，2016，618：31-38.
33. Liu Zhiheng, Yuan Xiahong, Liu Lin. Advances in animal models of depression and its application in traditional Chinese medicine research. Chinese Journal of Comparative Medicine，2022.