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REVIEW

Progress of Animal Research on Electro-acupuncture Treatment for Depression[△]

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Abstract This paper summarized the Chinese literatures in the previous 5 years about the pre-clinical animal researches on the application of electro-acupuncture (EA) treatment for depression, searched in China National Knowledge Infrastructure (CNKI). The efficiency of EA treatment for depression and the mechanism of it were discussed, to shed light on new ideas and new fronts for the further research on depression in clinical or pre-clinical fields.

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DEPRESSION is one of the common diseases of emotional disorder, referring to enduring low mood as the main feature, which could be induced by many factors. The incidence of depression is on the rise, and its great harm to health and life is more and more obvious.¹ Therefore, the researches of prevention of and treatment for depression have attracted attention. Drug therapy is the principal method for depression at present. Even though depression involves lesions in multiple systems, medication regimens for depression usually aim at a single target, hence the curative effect would reduce over long-time application, and the toxicity and side effects of antidepressants are inevitable.² Since acupuncture was introduced into the treatment for depression, it has produced curative effect.

Electro-acupuncture (EA) is based on the traditional acupuncture treatment in traditional Chinese medicine, adopting a small electric current to replace twisting needle manoeuvred by hand. Long stimulation time, controllable stimulating quantity, few side effects, easy operation are the strong points of EA, which show some advantages during the treatment for depression, but the mechanism underlying the therapeutic effect is not clarified yet. This paper reviewed the literature about the pre-clinical animal researches on EA treatment for depression in the latest 5 years, aiming to better understand the efficacy of EA treatment and its possible mechanism in treating depression.

EFFICACY OF EA TREATMENT FOR DEPRESSION

Effects on body weight, consumption of syrup, and behavior

Monotherapy with EA

Chen et al³ reported the effects of EA and catgut embedding at "Baihui" (GV 20) on the behaviors in a rat

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model of chronic stress induced-depression, the result showed that after receiving the EA treatment, the weight, the consumption of syrup, and the score for the behavior of the rats in the EA group all increased significantly.

Duan et al⁴ compared the effects and the mechanism of EA in different acupoint groups of depression rats. The body acupoint group was given EA at "Taichong" (LR 3), "Neiguan" (PC 6), and "Zusanli" (ST 36), while the scalp acupoint group received EA at "Baihui" (GV 20), "Yintang" (EX-HN3), and "Sishenchong" (EX-HN1). The results showed that the two groups of depression rats both got good anti-depressing effects and improved behaviors. The frequencies of horizontal movement and vertical motion in the scalp acupoint group are higher compared with the body acupoint group. Zhu et al⁵ also reported that applying EA treatment at "Baihui" (GV 20) and "Sanyinjiao" (SP 6) increased the frequency of horizontal and vertical movements compared with the normal control group, thus concluding that EA treatment can improve the behavior of depression rats. You et al⁶ performed EA treatment at "Baihui" (GV 20) and "Taichong" (LR 3) in rat model of depression, also observed changes in the abnormal behaviors of the rats.

Shi et al⁷ selected "Baihui" (GV 20) and "Yintang" (EX-HN3) for EA treatment, observed that the movement frequency in the open-field test increased significantly in the rats in EA group, and the resting time in forced swimming test decreased. Jiang et al⁸ selected the same acupoints, and observed, besides horizontal and vertical movements, the consumption of 1% sucrose solution before and after modeling and 1 week after receiving EA treatment. The results showed that there was a tendency in behavior improvement in depression rats after EA, and statistically significant increase in the consumption of 1% sucrose solution. Liu et al⁹ selected "Baihui" (GV 20), "Yintang" (EX-HN3), "Zusanli" (ST 36) (unilateral), and "Sanyinjiao" (SP 6) (unilateral) to perform EA, resulting in increased frequency of horizontal and vertical movements, the consumption of sugar solution, and body weight compared with the model group.

Combination therapy

Li et al¹⁰ compared the effects of EA treatment and fluoxetine on the behaviors of depression rats. The results showed that the numbers of horizontal movement, the frequency of vertical motion, the weight and the increment all improved compared with the model group, indicating that EA and fluoxetine can improve the behavior of depression rats. Yu et al¹¹ reported the behavioral improvement of depression rats after receiving the

combination treatment of EA and low-dose tricyclic antidepressant (TCA)-clomipramine, and discussed the effects between single-EA treatment and the combination treatment. The results showed that EA and high-dose antidepressant both can increase the rats' horizontal and vertical movements and reduce the resting time in the forced swimming test, while the combination treatment of EA and low-dose antidepressant can reduce the resting time and increase the horizontal and vertical movements to a greater extent, indicating that combining EA with antidepressant can reduce the dose of the drug on the one hand, and enhance the effects of EA on the other hand.

The effects on the intestine and digestive function

Digestive dysfunction is the main somatization during depression, impairing the quality of life of the patients. In clinical practice, EA treatment for depression and digestive dysfunction has a good effect, but the mechanism is not clear, hence exploring the effects of EA on digestive disorders during depression is important. Huang et al¹² had researched the effects of EA at "Hegu" (LI 4) and "Taichong" (LR 3) on the content of nitric oxide (NO) and the activity of nitric oxide synthase (NOS) and glutathione peroxidase (GSH-Px) in the colon tissue of depression rats, to investigate the mechanism of EA in protecting the colon tissue. The study of Qin et al¹³ at "Baihui" (GV 20), "Yintang" (EX-HN3), and "Tianshu" (ST 25) showed that the content of colonic inducible NOS and NO in the rats of chronic stress both increased, and the expression of cyclooxygenase-2 was up-regulated significantly compared with the control group, which were all reduced by EA treatment. The results indicated that the regulatory effects of EA on the enteric nervous system might be an important way to improve the digestive function of the rats under depression. Qin et al¹⁴ reported that the chronic stress rats' somatostatin in hypothalamus decreased and gastrin in serum increased significantly, which could be reversed by EA treatment, demonstrating that regulation of the release of brain-gut peptides might be involved in the improvement of digestive function by EA.

The effects on sexual activity and sex hormone

Hypo-sexuality is one of the symptoms of depression, affecting patients' quality of life. Anti-depressants also have adverse effects on sexual activity. Seeking a therapy to not only control depression but improve sexual activity has become a hot topic in the field of depression research. EA treatment for depression and sexual dysfunction has showed some effects. Shi et al¹⁵ had studied the regulatory effect of EA treatment on sexual activity in the rats of

depression and its mechanism. After performing EA at "Baihui" (GV 20) and "Yintang" (EX-HN3), the times of licking and straddling increased, the content of testosterone in serum increased, but the serum level of luteinizing hormone was not changed significantly, indicating that EA could improve the sexual activity of rats under depression through regulating the level of testosterone. Lu et al¹⁶ observed the effects of EA at "Baihui" (GV 20) and "Yintang" (EX-HN3) on NO and cyclic guanosine monophosphate (cGMP) in the penile tissue of depressive rats, noticed that EA improved the sexual activity of the rats, increased the concentration of cGMP in the penile tissue significantly with no obvious change in NO concentration. The effect on cGMP might be one of the mechanisms of improving sexual activity in depression.

MECHANISMS UNDERLYING EA TREATMENT FOR DEPRESSION

Neurotransmitters and their receptors in the central nervous system

The development of depression is connected with the content of neurotransmitters and the neurobiological mechanisms of depression associated with the metabolism of the neurotransmitters. The neurotransmitters include acetylcholine, monoamines, amino acids, peptides, etc. The imbalance among different neurotransmitters is also one of the mechanisms of depression. In addition, researches upon the neurotransmitter-related mechanism of depression observed not only the decrease of the content of neurotransmitters, but also the disorder of the postsynaptic receptor functions. In the study of Liu et al,⁹ they also noticed that EA could elevate the level of monoamines in the brain. Zhou et al¹⁷ studied the regulatory effects of EA treatment for the imbalance of monoamines and γ -GABA in rats with chronic emotional stress-induced anxiety. EA performed at "Baihui" (GV 20) and "Sanyinjiao" (SP 6) reduced the content of monoamines in the brain of the model rats, and up-regulated the expression of γ -GABA. The results indicated that the anti-anxiety effects could be connected with regulating the balance between the two types of neurotransmitters. Zhu et al¹⁸ performed EA at the same two acupoints, and found that the activity of 5-serotonin and acetylcholinesterase in the hippocampus of depression rats decreased, while EA increased the integrated optical density values of these two substances significantly compared with the model rats. Kang et al¹⁹ employed 3H radioactive ligand-receptor binding to measure the binding of 5-HT1A specific receptors in the

hippocampus of depression rats, in order to explore the mechanism of anti-depression effects of EA. The binding sites of 5-HT1A in depression rats' hippocampus decreased markedly, while EA at "Baihui" (GV 20) and "Taichong" (LR 3) resulted in a significant increase in the 5-HT1A receptor binding compared with depression rats. Qin et al²⁰ had reported that EA at "Baihui" (GV 20), "Yintang" (EX-HN3), and "Tianshu" (ST 25) could up-regulate the release of neurotensin (a brain-gut peptide hormone) in chronic stress rats, showing better effect than fluoxetine. Shi et al²¹ reported that EA could improve the rewarding effect of the chronic stress model rats, and up-regulate the content of dopamine in different brain regions to recover the rewarding effect under depression.

Hypothalamic-pituitary-adrenal (HPA) axis

HPA axis has many functions including regulating appetite, sleep, sexual desires and adapting stress. Dysfunction of HPA axis is closely connected with the symptoms of depression. Further research found that more than half of the depression patients expressed hyper-function of HPA axis. So the occurrence of depression might be related with the disturbance of HPA axis.²² Lu et al²³ reported that EA performed at "Baihui" (GV 20), "Yintang" (EX-HN3), "Zusanli" (ST 36), and "Fenglong" (ST 40) could regulate the function of HPA axis, possibly by regulating the relative enzymes (protein kinase A and protein kinase C in their experiment) in the signaling pathway in hippocampal cells. Chen et al²⁴ reported that EA at "Baihui" (GV 20) could antagonize the hyper-function of HPA axis. Shi et al²⁵ used radioimmunoassay to determine the content of corticotrophin releasing factor (CRF) in hypothalamus, adrenocorticotrophic hormone in pituitary, cortisol (CORT) in adrenal gland and plasma of depression rats. The results showed that EA could significantly reduce the content of CRF in hypothalamus, also reduce CORT in adrenal gland and plasma of depression rats. Their findings indicated that EA could regulate the related hormone of HPA axis in chronic stress rats.

Signaling pathways

The hypothesis of dysfunction of related signaling pathways also has drawn attention in the field of mechanism of depression. Han et al²⁶ reported that EA at "Baihui" (GV 20) and "Yintang" (EX-HN3) could increase the expression level of neuronal NOS and the content of cGMP in the hippocampus of depression rats, to maintain the information transmission function of NO-cGMP signaling pathway, exerting anti-depression effect. Fu et al²⁷ performed EA at "Hegu" (LI 4) and "Taichong" (LR 3), the

results indicated that CREB-BDNF post-receptor signaling pathway may be a target of EA in treating depression.

Neurons in the hippocampus

Researches have certified that the depression patients have the imbalance of HPA axis function, and that regeneration disorder of neurons in the hippocampus appears under persistent stress. Stress damaging the plasticity of hippocampus mainly results in: (1) atrophy of hippocampal neurons; (2) decreased regeneration of hippocampal neurons; and (3) apoptosis of hippocampal neurons.²⁸ Li et al¹⁰ detected the apoptotic rates of neurons and the expression of bcl-2 protein in the hippocampus, finding that EA lowered the apoptotic rates of hippocampal neurons and up-regulated the expression of bcl-2. Another study applying EA at Du and foot Yaiyang vessel found that EA activated extracellular signal-regulated kinase signaling pathway, which could alleviate the injury of hippocampal neurons, thus promoting the improvement of depression.²⁹

Neurotrophic factors

Nerve growth factor (NGF) is the nerve cell growth regulating factor which affects the development, differentiation, growth, regeneration, and expression for functional performance of neurons. Brain-derived neurotrophic factor (BDNF) is one of the most important members in the neurotrophic factor family, having important effects on the growth, differentiation, survival, plasticity, and repair after injury of neurons. BDNF can also enhance the effect of NGF. Tian et al³⁰ used immunohistochemistry to determine the concentration of NGF and BDNF in the hippocampal tissues of depression rats. The results showed that EA had some protective effects on NGF and BDNF in the hippocampus of depression rats, could reduce degeneration and death of neurons, suppress the speed of apoptosis, alleviate or prevent the occurrence of secondary pathological damage, then reaching the goal of treating depression.

Genome

Using gene-chip technology to research the mechanism of acupuncture can reflect the extensive way and therapeutic target of acupuncture. Jiang et al⁸ analyzed the whole-genome expression of the hippocampus of depression rats with gene-chips, finding that in depression rats, the expression of genes related to blood clotting, immunity, inflammation and apoptosis increased, while the expression of genes related to energy and substance metabolism, protein biosynthesis decreased, which resulted in damage, function disturbance, and apoptosis of

the hippocampus, followed by the appearance of a series of depression symptoms. The changed expressions of genes were turned to the normal levels in EA-treated rats. Their study has a significance in presenting the possible genetic mechanism of EA in treating depression.

Serum nitric oxide

High concentration of NO can influence the ultrastructure of neuron, which induces abnormal expression of many signal conducting molecules, then initiates a series of pathologic effects, damages the brain tissue, and possibly causes symptoms of depression.³¹ Tian et al³¹ reported that after EA at "Yintang" (EX-HN3) and "Zusanli" (ST 36), serum NO of depression rats was reduced, thus the toxic effects to neurons alleviated.

CONCLUSION

In conclusion, researches have supported the effectiveness of EA in treating depression. It involves multiple organs and possible targets, having multi-level therapeutic mechanisms while not imposing toxic and side effects as medications. However, the studies on depression have some shortages, which we summarized as follows after reviewing the literature: (1) EA was performed at multiple acupoints in the previous studies, it is necessary to prove that whether EA at one and single acupoint is equally effective for depression treatment; (2) depression requires a long therapeutic course and has high recurrence rate, the long-term efficacy of EA treatment and the recurrence rate of depression with EA treatment have not been investigated yet; (3) animal models of depression based on syndrome differentiation are needed for further research on the specific effect of EA in depression with different symptoms.

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