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Research Progress on the Mechanism of Acupuncture in Treating Menopausal Syndrome in Women

Jiaxin Yuan [1], Shuai Jiang [2]

[1] School of Acupuncture Moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, Tianjin, 301617, China

[2] Second Clinical Medical College, Anhui Medical University, Clinical Medicine, Hefei, 230601, China

ABSTRACT

Menopausal syndrome is a common clinical disease. In recent years, its incidence has shown a high growth rate and a younger trend, seriously threatening the physical and mental health of women. Acupuncture therapy starts from the whole body, regulates the functions of the zang-fu organs and Chong and Ren meridians, and can thus alleviate the clinical symptoms of patients. By retrieving relevant literature on acupuncture treatment of menopausal syndrome in recent years, this paper aims to explore the mechanism of acupuncture in treating this disease. Through analysis, it is found that acupuncture can intervene in the treatment of menopausal syndrome from multiple targets, multiple levels and multiple systems, mainly involving the neuro-endocrine system, immune system, vasomotor factors, monoamine neurotransmitters, oxidative stress levels and cell signaling pathways. By summarizing the relevant mechanisms of acupuncture in treating menopausal syndrome, this paper points out the existing deficiencies and development directions in current research, thereby deepening the understanding of acupuncture in treating menopausal syndrome and providing theoretical basis and new ideas for clinical practice.

KEYWORDS

Menopausal syndrome; Mechanism of action; Acupuncture; Review

1. INTRODUCTION

Premenopausal syndrome, also known as perimenopausal syndrome, refers to a group of symptoms that occur in women before and after menopause due to the gradual decline of ovarian function, resulting in fluctuations or reductions in sex hormone levels, and leading to a series of symptoms mainly characterized by autonomic nervous system dysfunction, accompanied by neuro-psychological symptoms. It is a special physiological stage from the reproductive period to the elderly period. During this period, women often face irregular menstrual cycles, increased or decreased menstrual flow, hot flashes, sweating, palpitations, insomnia, mood swings, back and waist pain, and memory decline. According to epidemiological surveys, almost every woman has perimenopausal symptoms, with 50% to 75% having obvious symptoms, and 10% to 15% having severe symptoms that require drug treatment, which has a significant impact on women's quality of life [1]. Modern medical research shows that menopause is caused by the decline of ovarian function, irreversible reduction in the number of follicles, and continuous exhaustion of follicular reserve function, leading to unstable changes in estrogen levels, causing functional disorders of the hypothalamus-pituitary-ovarian axis or adrenal glands [2]. Currently, hormone replacement therapy is the preferred method for treating menopausal syndrome in clinical practice. It can improve the estrogen levels of women, alleviate physical and mental disorders, and relieve menopausal symptoms. However, hormone

replacement therapy requires strict mastery of relevant indications and contraindications, and it may bring certain side effects. Long-term use may increase the risk of cancer and reduce patient compliance [3-4].

Perimenopause in traditional Chinese medicine is called "before and after menopause syndromes", and it belongs to "dampness-heat syndrome", "yin-yang depression syndrome", and "butterfly disease". In the "Synopsis of the Golden Chamber - Gynecological Diseases" section, it is recorded: "When women have yin-yang depression, they are sad and sorrowful, wanting to cry, like being controlled by a deity. They often stretch their limbs frequently." This disease has kidney yin deficiency as the basic pathogenesis, with the main pathogenesis evolution characteristics of kidney yin deficiency - kidney yang insufficiency - kidney yin-yang deficiency. It often involves the heart, liver, and spleen, and often combines water dampness, phlegm turbidity, blood stasis, qi stagnation, and blood deficiency syndromes. Clinically, menopausal syndrome is mainly divided into five types of syndromes: kidney yang deficiency, kidney yin deficiency, kidney yin-yang deficiency, heart-kidney disharmony, and heart-lung qi deficiency. The treatment mainly focuses on tonifying the kidney, combined with regulating the liver, strengthening the spleen, eliminating dampness, transforming phlegm, removing blood stasis, nourishing blood, and other syndrome differentiation and treatment methods [4]. In recent years, traditional Chinese medicine therapy has gradually gained popularity in treating menopausal syndrome through various intervention methods, and certain progress has been made in clinical practice. Acupuncture, as a characteristic technique of traditional Chinese medicine clinical practice, has the functions of regulating qi and blood, regulating the organs and the Chong and Ren meridians, improving the body's state, and thus alleviating the related symptoms of menopausal syndrome patients. The following is a review of the related mechanisms of acupuncture treatment for menopausal syndrome, aiming to provide a reference for the clinical treatment of this disease.

2. THE INFLUENCE ON THE NEURO-REPRODUCTIVE ENDOCRINE SYSTEM

2.1. Regulating the Function of the Hypothalamus-Pituitary-Ovarian (HPO) Axis

Modern medicine believes that the normal reproductive endocrine function of women depends on the balance and coordination of the hypothalamus-pituitary-ovarian three elements. The hypothalamic neurons secrete gonadotropin-releasing hormone (GnRH), which acts on the pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which promote follicle development and maturation. Follicles secrete estrogen, progesterone, and small amounts of androgens to regulate women's physiological functions. Among them, estrogen mainly includes estradiol (E2), estriol, and estrone, with E2 being the main component and having the highest activity. With the arrival of perimenopause, women's ovarian function declines, estrogen levels decrease, ovulation decreases or stops, and follicles also decrease accordingly, and this process is irreversible. The ovary cannot effectively exert negative feedback on the hypothalamus-pituitary, causing an increase in the secretion of FSH, LH, etc., and thereby breaking the original physiological balance between the HPO axis, resulting in a series of endocrine metabolic disorders, hormone secretion disorders, and autonomic nerve disorders [5]. Acupuncture can further regulate the HPO axis by modulating the secretion of E2, thereby achieving a relatively balanced and stable state of endocrine secretion in the human body. JING et al. [6] demonstrated that electroacupuncture (EA) can improve the E2 level and reduce the levels of LH and GnRH to varying degrees. Some experimental studies have also found that electroacupuncture at the "Guanyuan", "Zhongji", "Sanyinjiao", and "Uterus" acupoints can increase the protein expression of estrogen receptor (ER) α and ERβ in the uterus of PMS rats, increase the serum E2 level, thereby inhibiting the secretion of FSH and LH by the pituitary gland, reconstructing part of the negative feedback of estrogen, and reducing the degree of uterine atrophy [7]. Wang Hongzhen et al. [8] found that the "Qiadian Shuweichong" acupuncture method

used to treat perimenopausal syndrome can not only improve the symptoms of perimenopausal syndrome patients, but also has certain persistence of efficacy. During the follow-up after the treatment, the MRS score, MENQOL score, and hot flush score of the patients continued to decrease, suggesting that the mechanism lies in that the local acupoint stimulation acts on the disease site, improving the local blood supply of the ovary and the regulatory effects of sympathetic and parasympathetic nerves; on the other hand, this therapy can activate the function of the HPO axis in the patient's body, thereby exerting a bidirectional adjustment effect, regulating the levels of E2, FSH, and LH hormones in the body, and restoring the normal physiological dynamics of reproductive endocrinology.

2.2. Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis Function

The HPA axis is an important component of the neuroendocrine system. It is secreted by the hypothalamus with corticotropin-releasing hormone (CRH), which acts on the pituitary to stimulate its secretion of adrenocorticotropic hormone (ACTH). ACTH enters the bloodstream and acts on the adrenal cortex to stimulate its secretion of cortisol. Cortisol plays an important role in responding to stress, regulating blood sugar levels, and inhibiting inflammatory responses. Under normal circumstances, the HPA axis maintains the balance of cortisol levels through a negative feedback mechanism, and participates in regulating stress responses, playing an indispensable role in emotional regulation and sleep. Perimenopausal women are exposed to multiple stressors from society, physiology, family, etc., and the body remains in a state of stress for a long time, leading to hyperactivity of the HPA axis.

Lü Xin et al. [9] found that hyperfunction of the HPA axis can lead to increased levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol (CORT), and the increase in the expression of ACTH and CORT can cause arousal effects. Xi Hanqing et al. [10] found that acupuncture at Baihui, Shenting, Yinhang, bilateral Shenmen, and bilateral Sanyinjiao can regulate the HPA axis, significantly reducing the levels of CRH, ACTH, and CORT related to the HPA axis. For example, Jiang Xirong [11] found that in the intervention measures of electroacupuncture at Baihui, Shentu, and Sanyinjiao acupoints for perimenopausal depressed rats, compared with the model group, the sugar water consumption rate increased, and the immobility time in the tail suspension test and forced swimming test decreased. Electroacupuncture treatment could reduce the overexpression of adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and corticosterone (CORT), increase the content of β-endorphin (β-EP) to a certain extent, thereby improving the imbalance state of the HPA axis. A large number of studies have shown that electroacupuncture stimulation at different acupoints or auricular regions can significantly reduce the level of CRH in the paraventricular nucleus of the hypothalamus, reduce the serum hormone levels related to the HPA axis, and alleviate anxiety and depression in unpredictable chronic mild stress animal models [12, 13].

3. EFFECTS ON THE IMMUNE SYSTEM

Abnormal immune function is closely related to the occurrence of perimenopausal syndrome. Estrogen plays a key role in regulating the growth and development of immune cells, which can promote the proliferation and differentiation of immune cells, thereby enhancing the function of the immune system. During the perimenopausal period, the immune system of women ages, with the most obvious impairment of T cell function. The interaction between Th1 cells and Th2 cells regulates each other, and the balance between them affects the occurrence and development of gynecological diseases [14]. Studies have shown that when the body is under psychological stress or physical stress, the immune system is activated, and a series of cytokines are secreted, resulting in an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines, leading to the occurrence of depression disorders [15]. At the same time, due to the decline in immune function, repeated

infections occur or the immune system mistakenly attacks the body's own tissues, causing tissue damage and functional disorders, resulting in autoimmune diseases. With the decline of immune system function, the number of CD8+ subgroups increases in perimenopausal women, while the number of CD3+ and CD4+ subgroups decreases, and the total T lymphocytes decrease, resulting in an unbalanced composition of immune cells.

Acupuncture therapy can regulate the levels of immune cells, inflammatory cytokines and autoantibodies in perimenopausal patients, thereby improving immune disorders and stabilizing a series of symptoms during perimenopause. Wu Yinghui et al. [16] showed that stimulating the Zusanli acupoint can increase the levels of CD3+, CD4+, IgG and IgA in the human body, indicating that acupuncture can improve the imbalance of lymphocyte subgroups in patients and participate in regulating the disorder of the immune system and regulating immune levels. In addition, the increase in IL-2 levels in the body by acupuncture may be an important mechanism for improving cell immune function [17].

4. EFFECTS ON VASOMOTOR FACTOR

Vasomotor factors mainly include calcitonin gene-related peptide (CGRP), endothelin (ET), and nitric oxide (NO). Among them, CGRP has a direct and crucial role in the hot flush symptoms of perimenopausal women. CGRP may directly mediate the occurrence of hot flushes [18]. CGRP and ET-1 are the most common endogenous vasomotor factors in the human body. Under physiological conditions, they work together to maintain a relatively balanced vascular morphology, and the imbalance of the ratio of CGRP and ET-1 is one of the causes of hot flushes during perimenopause. Studies have found that the level of CGRP increases and the level of ET-1 decreases during hot flushes, and the imbalance of the ratio leads to vasodilation [19]. Acupuncture can reduce CGRP and restore the normal ratio, improving hot flushes [20].

5. EFFECTS ON MONOAMINE NEUROTRANSMITTERS

Under normal circumstances, the secretion of neurotransmitters in the central nervous system can maintain a relatively coordinated and stable state. With the increase of age, the content of neurotransmitters also changes accordingly, which may induce various symptoms of autonomic nerve dysfunction such as hot flushes, anxiety, insomnia, etc. One of the main manifestations of the decline of hypothalamic function is the disorder of monoamine neurotransmitters.

4.1. Effects on 5-HT

5-HT is an important central regulatory substance, and its function is related to various physiological mechanisms such as sleep, temperature regulation, emotion, cognition, and sensation. Studies have shown that the serum 5-HT level of postmenopausal women is lower than that of normal menstruating women. In studies on different acupuncture methods for PMI treatment, it was observed that while improving sleep structure and process and improving sleep quality, the level of 5-HT increased [21]. In the study of electroacupuncture at Zhongzhu for the anxiety behavior of perimenopausal rats, it was found that the content of 5-HT in the hippocampus of the model group increased, and the ratio of 5-HT/NE significantly increased, which had a good therapeutic effect on treating anxiety during perimenopause [22].

Effects on DA and NE DA is a precursor substance for NE synthesis, which can cause excitation of neurons and lead to the release of DA at the terminals. It plays a key role in regulating somatic movement, mental emotions, endocrine secretion of the pituitary gland, and cardiovascular activities. NE acts on α and β adrenergic receptors and participates in the regulation of various brain functions such as sleep, arousal, attention, learning, and memory. At the same time, it also participates in the

regulation of cardiovascular activities. Estrogen regulates cellular functions by binding to cell receptors, regulates synthetases, and regulates the synthesis of neurotransmitters and neuropeptides. Once the HPO axis is out of balance, the body will present a series of clinical symptoms of varying degrees. Peng Xiaotao [23] conducted research to prove the effect of electroacupuncture on monoamine neurotransmitters in natural perimenopausal rats. The experiment found that the content of NE significantly increased after acupuncture, thereby improving perimenopausal symptoms.

4.2. Effects on β-Endorphin (β-EP)

β-EP is an endogenous opioid neuropeptide and peptide hormone that plays an important role in regulating blood vessels and emotions. It is generally recognized that there is ER in β-EP neurons in the arcuate nucleus of the hypothalamus, and it has a significant inhibitory effect on the release of GnRH in the hypothalamus through negative feedback of the HPA. During perimenopause, the estrogen level of patients decreases. On the one hand, it can lead to a weakened tension inhibition effect on NE, thereby affecting the cardiovascular system and the thermoregulatory center in the anterior hypothalamic area, resulting in palpitations, restlessness, hot flashes, etc.; on the other hand, it may directly affect the thermoregulatory center in the hypothalamus, causing hot flashes and sweating. Jiang Xirong [24] et al. used electroacupuncture therapy to stimulate perimenopausal depression model rats with "Baihui", bilateral "Shenshu", and bilateral "Sanyingjiao", and found that the content of β-EP increased, and the contents of CRH, ACTH, and CORT decreased, and the symptoms improved.

6. EFFECTS ON OXIDATIVE STRESS LEVELS

Oxidative stress plays a key role in the physiological and pathological aspects of sleep disorders. Free radicals in the brain accumulate during wakefulness and are cleared during sleep [25]. The content of free radicals such as glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD) is positively correlated with age, while the content of scavengers is negatively correlated with age growth. Research [26] found that there is a significant imbalance between lipid peroxidation (LPO) and the antioxidant defense system in menopausal insomnia patients.

Tian Suling [27] experimentally found that electroacupuncture of "Guanyuan" and "Sanyingjiao" significantly increased LPO products such as serum malondialdehyde (MDA) in perimenopausal sleep disorder model rats, and significantly decreased blood SOD and GSH-Px, indicating an improvement in the ability to eliminate oxygen free radicals. Observational studies found that electroacupuncture of Shenmen, Touwei, Sishencong, Yin Tang, and Baihui can significantly reduce the levels of oxidative stress by-products - lipid peroxidation hydrogen peroxide in patients with insomnia [28]. The underlying antioxidant mechanism may be related to its influence on the enzyme cluster related to oxidative stress [29].

7. EFFECTS ON CELL SIGNALING PATHWAYS

It was found that the ACT-INH-FS pathway is abnormally involved in the occurrence of perimenopausal syndrome. The ACT-INH-FS pathway can regulate the endocrine functions of the pituitary and ovary and play an important role in female reproductive physiology. It regulates the synthesis and secretion of FSH in the pituitary through the endocrine pathway. At the same time, in the local ovary, this system also regulates the responsiveness of follicular membrane cells and granulosa cells to gonadotropin through autocrine or paracrine pathways. Shen Jiewen [30] et al. found that the combination of acupuncture and medication can reduce serum levels of FSH, LH, FS, and ACTA, increase serum levels of E2 and INHB, and have a significant effect on the ACT-INH-FS pathway, exerting antidepressant and alleviating symptoms of perimenopausal women syndrome effects.

8. CONCLUSION

To sum up, the mechanism of acupuncture treatment for menopausal syndrome mainly lies in: regulating the release of neurotransmitters and the functions of the hypothalamus-pituitary-ovarian axis and adrenal axis, improving the levels of related hormones such as FSH, LH, E2 and CRH, thereby maintaining the reproductive endocrine environment of women; regulating the imbalance of lymphocyte subsets, reducing the expression of inflammatory cytokines and inhibiting abnormal autoantibodies, thereby regulating the disorder of the immune system and alleviating related symptoms during the perimenopausal period; regulating the expression of various signaling molecules in the ACT-INH-FS signaling pathway, affecting the physiological function of this pathway; regulating vasoconstrictor and vasodilator factors, regulating oxidative stress levels, and improving related symptoms. It can be seen that acupuncture treats menopausal syndrome from multiple targets, multiple levels and multiple systems, thereby improving the clinical symptoms of patients. Acupuncture therapy based on the theory of syndrome differentiation and treatment in traditional Chinese medicine for treating menopausal syndrome has stable efficacy, individualized advantages, low adverse reactions and high safety; at the same time, combined with the concept of preventing disease before it occurs in traditional Chinese medicine, it can regulate human functions at an early stage, so it has a good preventive and therapeutic effect on menopausal syndrome.

Through the review of acupuncture treatment literature, it is found that there are still some deficiencies in the current research on acupuncture treatment for menopausal syndrome. For example, clinical data are mostly small sample studies or prospective case cohort studies, lacking high-quality, multi-center, large-sample clinical randomized controlled double-blind trials; assessment methods are not unified, the selection of acupoints is relatively complicated, resulting in a lack of comparability between related studies; research results mostly focus on short-term efficacy and lack attention to long-term efficacy; mechanism research mostly focuses on the influence on hormone levels, involving studies on the nervous system are few, and research on signaling pathways, genomics and proteomics is relatively scarce, and the correlation research among different systems is also relatively rare.Therefore, in future research, we should follow evidence-based medicine, design more rigorous trial schemes, conduct large-sample, multi-center clinical randomized controlled studies, formulate standardized and standardized clinical efficacy evaluation criteria and acupuncture point selection indicators, optimize acupuncture intervention methods, enhance follow-up awareness; at the same time, establish diverse animal models, strengthen the connection between experimental research and clinical practice; deepen research directions, increase research on the mechanisms of the nervous system, cell signaling pathways and gene proteomics, and explore the correlations among various systems, thereby improving the basic research on related mechanisms and providing a strong basis for clinical treatment. In addition, in clinical practice, we should combine the modern biopsychosocial medical model, pay more attention to the psychological state of patients, emphasize "harmony between form and spirit", comprehensively regulate the body's state, in order to seek the most ideal therapeutic effect.

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