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Research Progress on Mechanism of Acupuncture Treatment for Insomnia

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Abstract: ***Insomnia is one of the sleep disorders that seriously affect the quality of life of people all over the world. Several studies have shown that acupuncture and moxibustion have the advantages of significant curative effect and high total effective rate in the treatment of insomnia. Traditional Chinese medicine believes that insomnia is in the heart, closely related to liver, spleen and kidney, and its pathogenesis is Yang flourishing Yin failing, Yin and Yang disconnecting. Western medicine believes that insomnia is closely related to changes in neurotransmitter content, endocrine dysfunction, immune inflammatory response, and activation of antioxidant defense system. Based on the results of clinical trials and animal experiments at home and abroad in the past 10 years, this study discusses the latest research status of acupuncture treatment mechanism of insomnia and summarizes, providing help and reference for the mechanism research of acupuncture treatment of insomnia, and providing new ideas for clinical acupuncture treatment of insomnia.***

Keywords: Acupuncture, Insomnia, Machine made**.**

1. Introduction

Insomnia refers to long-term poor sleep quality, and its clinical manifestations are characterized by long-term difficulty to fall asleep, not deep sleep, easy to wake up after sleep, many dreams, and early wake up [1]. The light is only manifested as difficulty falling asleep, can not sleep after waking up, or wake up when sleeping, and the heavy is manifested as being unable to sleep all night, which seriously affects the daily life of patients, and reduces the quality of life of patients. In recent years, domestic and foreign studies have found that the incidence of insomnia is increasing year by year [2-6], and the prevalence of insomnia in the general population is as high as 29.2% [7], among which the prevalence of insomnia in medical staff is 38.9% [8], which reminds us to pay more attention to the prevention of insomnia and seek better intervention measures. Nowadays, Western medicine mostly uses sedative drugs for insomnia, but such drugs are prone to dependence and drug resistance, and withdrawal symptoms are easy to occur after drug withdrawal, and with the increase in the frequency and quantity of drug use, the risk of adverse reactions will continue to increase. Chinese medicine in the treatment of insomnia in the clinical effect of prominent features, acupuncture and moxibustion with non-toxic side effects, no dependence and addiction characteristics, for the majority of insomnia patients recognized.

At present, the mechanism of acupuncture treatment of insomnia in China is not perfect, and the animal based experimental research is still the main research. At present, acupuncture and moxibustion treatment of sleep disorders are mainly related to central neurotransmitters, endocrine hormones, immune cytokines, antioxidant defense system and other factors. Through reading the literature in recent years, the author made the following summary and induction of the mechanism of acupuncture treatment of insomnia by many doctors.

2. Regulation of Central Neurotransmitters

The occurrence of sleep is affected by different central neurotransmitters in the brain, and the change of neurotransmitter level may be an important cause of insomnia. Many studies have shown that acupuncture can affect sleep structure by regulating the content of three important central neurotransmitters, amines, amino acids and peptides.

2.1 Amine Neurotransmitters

2.1.1 Catecholamines

Catecholamine is a kind of neurotransmitter containing catecholamine and amine group. The content of catecholamine neurotransmitter in the body is increased, which can excite the sympathetic nerve and keep the body awake. Norepinephrine (NE) and dopamine (DA) are the main catecholamine neurotransmitters in the brain. Guo Xin et al. [9] found that insomnia rats with peritoneal injection of chlorophenylalanine suspension (PCPA) would show insomnia symptoms such as loss of circadian rhythm, constant day and night activity, abnormal sensitivity to external stimuli, irritability, and significantly increased serum NE and DA contents ($P<0.01$); After acupuncture treatment, the insomnia symptoms of rats were improved, and the serum NE and DA contents were significantly decreased ($P<0.01$). Wang Yan et al. [10] deprived rats of sleep by combined stimulation and detected that NE and DA contents in the brain stem of rats were significantly increased ($P<0.01$); The contents of NE and DA in the brain stem of insomnia rats were significantly reduced after 7 days of warm acupuncture treatment at corresponding acupoints. Chengcisong et al. [11] found that NE and DA contents in plasma, thalamus and brainstem of insomnia rats were significantly increased ($P<0.05$); After 20 days of electroacupuncture stimulation of "Shenmen" and "Sanyinjiao", the nocturnal activity of insomnia rats was not significantly different from that of normal rats, and the contents of NE and DA in plasma, thalamus and brainstem were significantly decreased ($P<0.05$). All the above studies

indicated that acupuncture and moxibustion could reduce the content of NE and DA in plasma, thalamus and brainstem of rats, thus reducing brain excitability and achieving the purpose of treating insomnia. Liu Erjun et al. [12] divided 120 elderly patients with insomnia into the observation group and the control group by random number table method, with 60 cases in each group. The control group received conventional drug treatment, and the observation group received acupuncture and moxibustion based on the control group. The clinical efficacy of the two groups was compared, the TCM syndrome score and Pittsburgh Sleep Quality index (PSQI) score were evaluated, and NE and DA levels were measured. Results: The total effective rate of the observation group was higher than that of the control group (P<0.05), PSQI score decreased more significantly (P=0.000), serum NE and DA levels decreased significantly (P<0.05), improve sleep quality better. The above studies have shown that acupuncture improves patients' sleep quality. It may be achieved by reducing the content of NE and DA.

2.1.2 Serotonin (5-HT)

Five-hydroxytryptamine (5-HT) has a dual regulating effect on sleep-wake cycle, which can not only promote awakening, but also a necessary condition for non-rapid eye movement sleep, so 5-HT is one of the hubs of sleep and awakening [13]. 5-hydroxyindoleacetic acid (5-HIAA) is a metabolite of 5-HT, and the increase of 5-HIAA content indirectly indicates the increase of 5-HT production and metabolism [14]. Luo Benhua et al. [15] found that the content of 5-HT and 5-HIAA in hippocampus of PCPA insomnia rats was significantly lower than that of normal rats (P< After acupuncture treatment, the insomnia symptoms of rats were significantly improved, and the contents of 5-HT and 5-HIAA in hippocampus were significantly increased, which were significantly different from those before treatment (P<0.05). Wang Zhuohui et al. [16] found that the content of 5-HT in serum of PCPA insomnia rats was significantly reduced. After treatment with Shenmai and Zhaohai point for 1 week, the insomnia symptoms of rats were significantly improved, and the content of 5-HT in serum was significantly increased (P<0.05). Li Hucheng et al. [17] randomly divided insomnia patients into the conventional group and gave oral Esazolam tablets for treatment. In the acupuncture group, Baihui, Shenting, Shandao and Lingtai points were needled on the basis of the conventional group, and Shenmen and Neiguan points were selected to treat insomnia patients. The total effective rate in the acupuncture group was 93.3%, which was significantly higher than 80.0% in the conventional group (P<0.05). The serum 5-HT level in acupuncture group after treatment was higher than that in conventional group (P<0.05). All of these studies suggest that acupuncture may improve insomnia symptoms by increasing the level of 5-HT in serum.

2.2 Amino Acid Neurotransmitters

Glutamic acid (Glu) and gamma-aminobutyric acid (GABA) are the most important excitatory/inhibitory neurotransmitters in mammalian in the mammalian central nervous system [18]. GABA plays an important role in promoting sleep occurrence and maintaining sleep state. Gaba is widely distributed in all brain structures and is an inhibitory neurotransmitter [19]. Glu acts on postsynaptic receptors and can induce cortical cell activity to maintain arousal. It is a excitatory neurotransmitter [20]. Multiple studies have found that the content of Glu in insomnia body is higher than normal, and the content of GABA is lower than normal. Cheng Chunrui et al. [21] established PCPA insomnia rats. After the rats showed typical symptoms of insomnia, acupuncture treatment was given to the rats. The content of Glu and GABA in the brain tissue of the rats was detected for 7 consecutive days, and it was found that the level of Glu in the hypothalamus of the rats decreased, the level of GABA increased, and the value of Glu/GABA decreased, and the symptoms of the insomnia rats were significantly improved. Wei et al. [22] also found that the content of Glu in the hypothalamus of PCPA insomnia rats was significantly increased, the content of GABA was significantly decreased, and the ratio of Glu/GABA was significantly increased (P<0.01). After the rats were treated with acupuncture at umbilical annular point and insomnia point for 6 days, the insomnia symptoms of the rats were improved, and the content of Glu in the hypothalamus was significantly reduced through testing. The content of GABA increased significantly, and the ratio of Glu/GABA decreased significantly (P<0.01). The above experiments indicate that acupuncture may regulate the dynamic balance of excitation and inhibition by reducing the content of Glu, increasing the content of GABA and decreasing the ratio of Glu/GABA.

2.3 Peptide Neurotransmitters

2.3.1 Orexin

Orexin is A pair of excitatory neuropeptides with about 50% sequence homology in the hypothalamus, which can be divided into Orexin A and Orexin B, and exerts physiological effects in the brain through the activation of two G-protein-coupled receptors [23-24]. Current studies have shown that the maintenance of wakefulness is closely related to the increase of Orexin A, and the plasma Orexin A level of patients with primary insomnia is significantly higher than that of normal sleepers [25]. Wang Yixin et al. [26] found that Shu Jin and Shen Shen method in the treatment of primary insomnia had A significant therapeutic effect on mild to moderate insomnia, with a total effective rate of more than 91.7%. After treatment, the total score of PSQI and each score were significantly decreased (P<0.05), and the plasma Orexin A level of patients was also significantly decreased (P<0.05). Wang Yanping et al. [27] used acupuncture and drug combination to treat patients with insomnia after cerebral infarction and randomly divided the patients into treatment group and control group. The control group was given dexzopiclone tablet for oral treatment before going to bed, and the treatment group was given acupuncture treatment on the basis of the control group. The changes of PSQI score, National Institutes of Health Neurological Deficit Scale (NIHSS) score, General Hospital Anxiety and Depression Scale (HADS) score, polysomnography (PSG) parameters and plasma Orexin-A level before and after treatment were observed in the two groups, and the clinical efficacy of the two groups was compared. The results showed that the scores of PSQI, NIHSS and HADS in the treatment group were significantly lower than those in the control group, the difference was statistically significant (P<0.05), and the serum Orexin-A level was lower than that in the control group (P<0.05). The results showed that the combination of

acupuncture and medicine can effectively improve the sleep quality of patients, improve their anxiety and depression state, and promote the recovery of nerve function, and the effect is better than that of drug therapy alone.

2.3.2 Neuropeptide Y (NPY)

Neuropeptide Y (NPY) is a bioactive polypeptide secreted by the hypothalamus, distributed in the central and peripheral nervous system, and is one of the most abundant neuropeptides in mammals. It has various functions such as anti-anxiety, anti-epilepsy, inhibition of sympathetic nerve excitation, and maintenance of homeostasis. It can play a role in regulating circadian rhythm by regulating the expression of various substances in brain tissue [28]. In recent years, many studies have shown that acupuncture treatment of insomnia may be related to the regulation of NPY content in the body. He Zhouhuan et al. [29] found that acupuncture combined with ear tip bleeding in the treatment of insomnia with difficulty falling asleep resulted in a decrease in PSQI scores and an increase in serum NPY content before and after treatment compared with that before treatment in the same group ($P<0.05$), with a total effective rate of 92.5% in the observation group, suggesting that the improvement of insomnia in patients may be related to the increase in serum NPY level. Liu Tingting [30] treated chronic insomnia by embedding suture in Sun's abdominal acupuncture area. After 2 courses of treatment, the patient's sleep condition, anxiety and depression were significantly improved, and the total effective rate was as high as 93.75%. The serum NPY level of the patient was detected to be increased ($P<0.01$). The mechanism of acupuncture in the treatment of insomnia may be to directly stimulate the neurons of the enteric nervous system, corresponding to the emotional, autonomic and endocrine regulation areas of the brain, thereby increasing the secretion of NPY and thereby improving sleep conditions.

3. The Regulation of Endocrine Hormones

Endocrine system is an important system that regulates various physiological functions of human body. When the endocrine system is disturbed, the level of various hormones in the body will change, which may lead to decreased sleep quality, and then lead to insomnia.

3.1 Adrenotropin Releasing Hormone (CRH), Adrenocorticotropin (ACTH), Cortisol (CORT)

It has been proved [31] that there is a close relationship between the hypothalamic-pituitary-adrenal cortex (HPA) axis and sleep-wake regularity. The main physiological functions of the HPA axis are as follows [32]: hypothalamus releases CRH, CRH acts on the pituitary gland to release ACTH, and ACTH acts on the adrenal cortex to release CORT. These three hormones affect and correlate with each other on the HPA axis. The secretion and release of CRH will increase the number of wakefulness in the body and reduce slow wave sleep. At the same time, the body will be in a state of stress and the negative feedback ability of the HPA axis will be reduced. Then, the secretion and release of CRH will be continuously stimulated and the body will be continuously excited, resulting in insomnia [33]. ACTH is an important part of sleep and wake, which can improve the irritability of cerebral cortex. CORT is a recognized classic indicator of stress response and a target hormone for the study of sleep-wake cycle. Its level is positively correlated with arousal, that is, the higher the level, the stronger the function of arousal [34-35]. Studies have shown that the increased concentration of ACTH and CORT will cause chronic persistent insomnia [36]. Insomnia increases levels of all three hormones. After acupuncture of insomnia model rats, Wu Xuefen et al. [37] detected that the contents of these three hormones were all reduced to a certain extent compared with the model group, indicating that acupuncture has a definite effect on improving sleep disorders. The clinical study of Xi Hanqing et al. [38] showed that "Tongdu Tiaoshen" acupuncture could significantly reduce the levels of HPA axine-related hormones CRH, ACTH and CORT, and the total score of PSQI and the scores of each factor were also significantly decreased after treatment, indicating that acupuncture could significantly improve the sleep status of patients with chronic insomnia and had good clinical efficacy.

3.2 Melatonin (MT)

Melatonin (MT) is a substance secreted by the pineal gland to regulate sleep. Its secretion occurs more at night and less in the day, and its peak occurs at night. Its physiological effects are mainly mediated by MT1 and MT2 receptors, thus showing obvious circadian rhythm [39]. Recent studies have shown [40] that these two receptors have specific roles in sleep regulation, such as MT1 receptor activation is mainly related to the regulation of REM sleep, and MT2 receptor can selectively increase non-REM sleep. Zheng Xuena et al. [41] found that acupuncture could increase MT content and MT1 and MT2 mRNA expression levels in pineal gland of insomnia rats, thereby restoring circadian rhythm, prolonging sleep time and shortening sleep latency, and effectively improving insomnia. Song Xiaojun et al. [42] in the treatment of insomnia patients, clinical research results showed that acupuncture Shenmen and Sanyinjiao could significantly up-regulate the serum MT level of patients, and significantly improve the quality of sleep at night and the symptoms of daytime fatigue and sleepiness. Xie Lina et al. [43] found that acupuncture at Baihui point, Shenmen point and Sanyi Jiao point could increase MT content and MT1 and MT2 mrna expression in the ventral lateral preoptic area of hypothalamus in PCPA insomnia model rats ($P<0.05$ $P<0.01$), and the insomnia symptoms of rats were significantly improved.

3.3 Sex Hormones

According to statistics, more than half of menopausal women will suffer from circadian rhythm disturbance due to ovarian function degradation and sex hormone secretion disorder, resulting in varying degrees of sleep disorders [44]. There are also relevant studies [45-46] that the relative change of estrogen or progesterone levels in women often leads to an increase in sleep problems, such as low progesterone levels will prolong non-rapid eye movement sleep and night awake time. Decreased levels of estrogen such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) increase sleep latency, post-sleep awakenings and periodic spontaneous awakenings. Luo Junting et al. [47] treated perimenopausal insomnia patients with acupuncture at Shenmen, Sanyinjiao, and Guan Yuan points, and compared

PSQI scores and sex hormone levels before and after treatment, finding that all scores and sex hormone levels of patients after treatment were significantly lower than before, and the sleep quality of patients was improved. Luo Xiao et al. [48] treated perimenopausal insomnia by acupuncture Yintang, Baihui, Shenmen, Anmian, Shenmai, Datun, Taichong, Yingu and other acupoints combined with gua Sha, and the symptoms of insomnia were improved after treatment. The serum estradiol (E2) level of the two groups was higher than that before treatment ($P<0.05$), and the levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were lower than that before treatment ($P<0.05$).

4. Regulation of Immune Inflammatory Factors

Continuous sleep disturbance can cause the inflammatory response to be continuously activated, which can cause harm to the patient [49]. Experimental studies on sleep-related immune regulation have confirmed that the immune function of humans or animals can be changed during sleep, and sleep loss will affect the activity of interleukin (IL) [50]. Many studies have also found that tumor necrosis factor (TNF-α) and IL are involved in the regulation of sleep rhythm. Studies have shown that the severity of insomnia and changes in the levels of TNF-α and IL can cause cognitive impairment in elderly patients with chronic insomnia [51]. Lei Zhengquan et al. [52] treated insomnia patients with the acupuncture method of "invigorating the brain and calming the mind", and the total effective rate reached 91.67%, with statistically significant differences in TNF-α and IL-6 before and after treatment. Slenger [53] gave PCPA insomnia rats warm acupuncture treatment in Mongolian medicine. After treatment, the behavior status and sleep duration of the insomnia rats were improved, and the levels of interleukin IL-1, IL-2, IL-6 and TNF-α in the detected brain tissues were significantly increased compared with those before treatment (P< 0.05). It is suggested that the changes of serum TNF-α and IL content after acupuncture may be one of the mechanisms of acupuncture therapy for insomnia.

5. Regulation of Anti-oxidative Defense System

Patients with chronic insomnia disorder have abnormal levels of superoxide dismutase (SOD), serum propylene glycol (MDA), serum catalase (CAT), glutathione peroxidase (GSH-PX) and malondialdehyde (MDA), and oxidative stress may be one of the pathophysiological changes causing chronic insomnia disorder [54]. In the anima experimental study conducted by CAI Wa et al. [55], SOD and MDA contents in the brain stem of rats with insomnia caused by acupuncture and moxibustion were detected, and the results showed that SOD activity of rats in the observation group decreased, MDA content increased, sleep quality improved, and escape latency shortened, while rats in the control group still showed disappearance of circadian rhythm and extension of escape latency. The results suggest that the therapeutic effect of acupuncture on insomnia rats may be related to the regulation of SOD and MDA levels in the antioxidant defense system.

6. Summaries

Current studies have found that acupuncture can treat insomnia by regulating the levels of neurotransmitters, endocrine hormones, immune inflammatory factors, etc. However, the mechanism of acupuncture treatment for insomnia has not been thoroughly studied. Most of the current studies focus on the influence of neurotransmitters and hormones on insomnia, and few studies are involved in the study of neural pathways, and the involved neural nuclei are relatively limited, so further studies are needed. There are few studies on the mechanism of immune system and oxidative stress affecting sleep, and the specific mechanism needs further study. In addition, the animal models established in the previous studies on insomnia are various, but there is no internationally recognized animal model at present, and further exploration is still needed. However, on the whole, acupuncture and moxibustion is effective in the treatment of insomnia, so it is imperative to continue to deeply explore the mechanism of acupuncture and moxibustion on insomnia, in order to provide a more powerful experimental basis for acupuncture and moxibustion in the treatment of insomnia and better verify the effectiveness of acupuncture and moxibustion.

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