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Original Paper

An Overview of the Current State of Research on Immune Expression in Acupuncture for Insomnia Based on the Relationship between Sleep and Immunity

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Abstract

Sleep is a resting state under the action of the sleep-wake center, regulated by the nerve, endocrine and immune, and any change in the content of any of the substances involved in sleep may break the delicate balance between them, affecting the normal progression of sleep and thus insomnia. Cytokines are the common language signals of the three major systems of neuro-endocrine-immune, and play an important role in inflammation and immune response. Therefore, the relationship between insomnia and immune factors has also become a hot research topic in recent years. A large number of studies have shown that acupuncture has a clear regulatory effect on immune function, so based on the relationship between sleep and immunity to acupuncture treatment of insomnia as an entry point, to explore the current status of immune research on acupuncture treatment of insomnia, in order to provide certain thinking for the integration of in-depth research afterward.

Keywords

sleep, immune factor, acupuncture

1. Introduction

Insomnia is a sleep disorder [1] that has difficulty falling asleep for a long time, leading to insufficient sleep satisfaction. Epidemiological investigation found that about 10%~15% of adults in China suffer from insomnia, and about half of the patients have a course of more than 10 years [2]. Insomnia and depression and other mental illness close [3], sleep fragmentation can promote obesity, reduce leptin sensitivity, also can destroy the intestinal epithelial barrier cause bacteria and end product into the circulatory system, eventually run to the mesenteric lymph nodes, liver and brain [4], serious damage to

patients 'physical and mental health, affect the patient's quality of life. At present, the pathogenesis of insomnia mainly includes the imbalance of central neurotransmitter secretion, hypothalamic-pituitary-adrenal axis dysfunction, and the imbalance of immune inflammatory response factors. Studies have shown that acupuncture can regulate immune function, with clear anti-inflammatory effects [5-6], and clear efficacy in the treatment of insomnia. Therefore, this paper summarizes the relationship between immune factors and insomnia and the expression of immune factors in the treatment of insomnia.

2. Sleep and Immunity

REM sleep (REM) and rapid eye movement (REM) sleep alteralternating during sleep. NREM sleep is divided into four stages of sleep, among which N3 sleep is also known as slow wave sleep (slow wave sleep, SWS). Slow wave sleep is the key period for the repair of various body functions, and immune system repair is mainly concentrated in this stage [7]. The immune system (immune system) is composed of immune organs, immune cells and immune molecules, divided into innate immune system and adaptive immune system, which mediate innate immunity and adaptive immunity, respectively. Circadian rhythms coordinate the [8] through the immune responses of both innate and adaptive immune cells. All lymphoid organs and immune cells studied have a functional circadian clock. The circadian timing system has a hierarchical structure, with the central pacemaker located in the suprachiasmatic nucleus of the hypothalamus that synchronize the peripheral clock in body cells and organs. Circadian clock genes (including but not limited to BMAL) are known to regulate the circadian distribution of bone marrow and lymphocyte subsets in the circulation and, in some cases, the proinflammatory response [9] within activated immune cells (e. g., macrophages). In conclusion, more and more studies have shown that sleep and immunity are bidirectional links. Activation of the immune system changes sleep, which in turn affects our body's defense systems. A systematic genetic analysis of GWAS data by Bo Xiang et al revealed that the immune system and hippocampus may play a central role in neurodevelopment and insomnia risk [10]. In epidemiological investigations, people with short sleep had higher inflammation levels [11] than those with long sleep and normal sleep.

3. The Major Immune Factors Associated with Sleep

Cytokines are one of the important regulators of sleep, [12]. Cytokines (CK) are mainly small molecule peptides or glycoproteins synthesized and secreted by immune cells, and have various functions such as regulating innate immunity and adaptive immunity. According to the different sources of cytokines, they can be roughly divided into six types, namely interleukin (IL), interferon (IFN), tumor necrosis factor (RNF), hematopoietic factors, growth factors, chemokines, etc. In addition, there are two functional subtypes of cytokines: pro-inflammatory cytokines (IL-1, IL-1 β, IL-2, IL-6, IFN- γ, TNF- α, TNF- β, etc.) and anti-inflammatory cytokines (IL-1RA, IL-4, IL-5, IL-10, IL-13, etc.) [13]. A large number of clinical and experimental results show that cytokines involved in sleep activity, is one of the

important regulators of sleep, sleep regulation closely related to IL-1 β, TNF- α, IL- α, IL-2 and IL-6 [14-15], including interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF) promote sleep effect [16], such as TNF and IL-1 increase, can increase NREM sleep amount, regulate sleep [8]. It was also found that the serum levels of IL-1 β and TNF- α significantly in insomnia patients, that is, IL-1 β was significantly increased in insomnia patients, while TNF- α significantly decreased [17]. The anti-inflammatory cytokines IL-4, Il-10 and IL-13 were reported to reduce NREM sleep duration in rabbits, while the proinflammatory cytokines TNF- α, IL-2, IL-6, IL-15 and IL-18 have NREM sleep promotion in animal models. However, these cytokines received less attention [18] compared to IL-1 or TNF.

3.1 Proinflammatory Factor

3.1.1 Tumor Necrosis Factor (TNF)

TNF mainly includes TNF- α and TNF- β, the former is mainly produced by macrophages, while the latter is mainly produced by lymphocytes, both have different amino acid sequences, although the biological roles are similar, TNF- α is more extensive. TNF- α is a pro-inflammatory cytokine that can activate the hypothalamic-pituitary-adrenal cortex (HPA) axis, thus inhibiting the immune function [19]. Moreover, TNF- α is also one of the important sleep-promoting factors in the brain to increase slow-wave sleep. The clinical study of [20] and others found that serum TNF- α in insomnia patients increased significantly compared with the normal control group, and was negatively correlated with non-rapid eye movement sleep (NREM) sleep duration, but not significantly with REN sleep duration. Studies have shown that TNF- α is circadian rhythmic, low levels of TNF- α during the day favor arousal, and elevated TNF- α at night, especially at night, favor deep sleep. Huang Yan [21] et al. tested TNF- α levels in chronic insomnia patients around 8 am, and found that the TNF- α levels in chronic insomnia patients were significantly higher than that in healthy people, indicating that TNF- α has circadian disorder in insomnia patients [21]. Charan [22] et al found that serum TNF- α and TNF-RI decreased significantly in chronic insomnia disorder, suggesting that TNF- α promotes insomnia and TNF-RI protects sleep.

3.1.2 Interleukins-1 (IL-1)

Interleukins (IL-1) are mainly secreted by monocytic macrophages and function on a variety of cells. L-1 has two genes, IL-1 α and IL-1 β, among which IL-1 β is involved in a variety of brain functions, [23], including sleep regulation, which can effectively promote physiological sleep. Related studies have shown that IL-1 β cytokines are closely related to NREM, extending NREM sleep mainly by inhibiting pro-awakening nerve nuclei, especially increasing slow-wave sleep [24-25]. Another study reported that [26] can regulate sleep by enhancing the firing rate of hypothalamic sleep-activated neurons and inhibiting the activity of awake-activated neurons. Studies have shown that 1L-1 and TNF can participate in the sleep regulation of [27] by regulating the monoamine neurotransmitter 5-HT (which can stimulate the generation of slow-wave sleep).

3.1.3 Interleukins-2 (IL-2)

Interleukin 2 is mainly derived from T cells and has a wide range of biological activities, and its main physiological function is to activate inflammatory cell T cells to promote cytokine production and play an important role in inflammatory responses. IL-2 improves the depth of sleep and extends sleep duration. Animal experiments have shown that the input of cytokine IL-2 into the locus coeruleus structure in the subject rat brain can cause prolonged [28] of slow-wave sleep time related to sleep quality. Chronic insomnia can increase the expression of IL-2 and other cytokines. Some studies have shown that in [29], the degree of insomnia is positively correlated with the serum concentration of IL-2 and IL-6.

3.1.4 Interleukins-6 (IL-6)

IL-6 is a cytokine produced by lymphocytes and non-lymphocytes, with high biological activity, which can regulate the body's immune response, and has the function of acute stress response, and can also participate in the regulation of [30] in a variety of cells.

Under physiological conditions, IL-6 secretion showed a circadian rhythm with a biphasic pattern, with two nados at 8:00 am and 9:00 pm, two peaks from 5:00 PM to 7:00 pm and from 4 am to 5 am, including peaks at 5 am. One study found that insomnia patients had significantly higher mean IL-11 levels in the afternoon and evening (6 p. m. to 5 p. m.) than in the healthy group. Furthermore, the significant peak of IL-6 secretion changed significantly [31] from morning (5 am) to evening (8 pm) in insomnia patients compared to the healthy group. Some researchers injected an effective dose of synthetic IL-6 to the rat ventricle and found that it could significantly prolong NREM sleep [32] in rats. Zhang Naiwen [33] et al. deprived rats of sleep by a modified multi-platform water environment method. After successful mold making, they found that the level of TNF- α and REMS sleep time were significantly increased in model rats compared with model rats and normal rats.

3.2 Anti-inflammatory Factors

Anti-inflammatory factors are also involved in the regulation of sleep, such as IL-10 and IL-4 during slow-wave sleep (SWS)[34]. Zhao Chen [35] et al. used a modified multi-platform method (modified multiple platform method, MMPM) to perform chronic sleep deprivation in rats, and found that the expression of TGF- β 1 in the condylar cartilage also increased with the time of sleep deprivation, while the expression of TGF- β 1 decreased after sleep recovery in rats. Combing the data found that compared with the relationship between anti-inflammatory factors and sleep, the relationship between anti-inflammatory factors and sleep was rare.

4. Effect of Acupuncture Treatment on the Expression of Inflammatory Factors in Insomnia Patients

Both laboratory studies and clinical studies have confirmed that acupuncture treatment can modulate the expression of inflammatory factors in insomnia patients.Lunxin [36] et al. used the method of peritoneal chlorophylalanine (PCPA) to eliminate the sleep-awakening cycle of normal rats,

electroacupuncture insomnia rats shen Mai, Xinhai, Shenmu, Davertebral, Baihui point, once a day, after 5 days found that the content of sleep cytokines IL-1 β, IL-6, TNF- α increased. However, Ting Wei[37] et al. also used intraperitoneal injection of chlorophenzalanine (PCPA) suspension to establish the insomnia rat model. After iguan and Zusanli for 5 consecutive days, the sleep state was effectively improved in insomnia rats. However, the concentration of IL-1 β and TNF- α in the acupuncture group found that both were significantly reduced. It can be seen that acupuncture intervention can play a sleep-promoting effect on the insomnia model established by chlorophenylalanine (PCPA), which can regulate the concentration of TNF- α, IL-1 β, IL-6, but the concentration is increased or decreased, with different results.

Hua Haiyan [27] using acupuncture therapy and oral eszolam treatment in 90 patients with insomnia, comparing the two groups of cytokine expression, found that acupuncture group patients sleep time, and plasma inflammatory response factor IL-1 β, IL-6,5-HT and TNF- α levels than drug group, indicating that acupuncture can better inhibit inflammatory response, improve sleep. Huang Yinfeng [38] et al found that the levels of IL-1 β, TNF- α, 5-HT and 5-HIAA were higher than that of the warm acupuncture group, while IL-6 was lower than that of the warm acupuncture group. Zhang [39] et al. showed that acupuncture can significantly reduce the level of TNF- α and IL-6 levels in insomnia patients, and then lengthen the sleep time and improve the sleep quality. Ye Longlin [40] et al found that the level of inflammatory factors changed significantly before and after the treatment of insomnia, and the levels of IL-6 and TNF- α in insomnia patients after ischemic stroke. Wang Xinjing [41] et al used the eight method combined with fire needle to treat patients with insomnia, and 4 weeks later found that the serum levels of IL-1 β, TNF- α and IL-6 were decreased. Some studies have shown that cizao kernel soup combined with meridian flow injection treatment can significantly inhibit serum IL-1 β and TNF- α by regulating immune inflammatory state, inhibiting inflammatory response and improving [42] sleep quality of patients.

5. Discussion

Sleep is closely associated with the expression of immune factors. In the normal state, pro-inflammatory factors and anti-inflammatory factors are in a dynamic balance. When the body stress or contusion, this balance will be broken, and then cause a more severe inflammatory response. Studies have found that the imbalance between the two will affect the activity of enzymes that control tryptophan, affect the biological process of tryptophan to canine urinine, and then affect the synthesis of microglia cells, cause mitochondrial dysfunction, affect the metabolism of neurotransmitters, and induce or aggravate the development of sleep disorders [43]. Insomnia is directly related to the increase of pro-inflammatory factors and the decrease of anti-inflammatory factors. Pro-inflammatory factors mainly mediate cellular immunity to cause inflammatory response, while anti-inflammatory factors mainly mediate humoral immunity to protect tissues and organs from excessive inflammatory destruction. Sleep has a certain impact on the immune function of the human body. Sleep deficiency or

insomnia will induce the innate immune response, and it will also cause the expression of inflammatory factors in the peripheral blood and the brain. In the brain, the content of immunoregulatory factors shows rhythmic changes with the sleep process, and acts on specific central sites, affecting the state of sleep and awakening.

Chronic insomnia is closely related to cytokines, and the regulation of cytokines mainly depends on the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA). At present, it is believed that the increased secretion of proinflammatory cytokines in insomnia patients is due to the excessive activation of sympathetic nerves and the increase of neurohormones (such as arginine vasopressin) and neurotransmitters (such as neuropeptide Y and vasoactive intestinal peptide) in [44]. However, the relationship between cytokine levels and complex changes in the related nervous system and insomnia is not clear, and further research is needed.

In conclusion, we show that acupuncture regulates the pro-and anti-inflammatory factors associated with sleep. The analytical literature found that acupuncture regulates the concentration of inflammatory factors. After a certain period of acupuncture intervention, the level of inflammatory factors in insomnia patients showed a dynamic change, decreased and rising, which may be related to the measurement of inflammatory factors levels in insomnia patients in different periods; it may also be due to the effect of acupuncture in insomnia patients, that is, by adjusting the concentration of various immune factors in the body to achieve a relatively stable state, so as to improve the purpose of sleep quality. However, in the current study, the correlation of these cytokines in insomnia patients is unclear because of the different subjects and the different subjects with the same subjects, and will be studied in the future.

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