The Relationship between Intestinal Flora and Sleep Disorders and Research Progress

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Abstract: Insomnia is one of the most common sleep disorders, which is closely related to mood and stress. Long-term insomnia can not only lead to fatigue, poor concentration and other problems, but more serious cases can lead to memory loss, mood disorders and even neurodegenerative diseases. The current chemotherapeutics have many defects, such as high side effects and insufficient efficacy, so it is urgent to develop new prevention and treatment strategies. In recent years, with the deepening understanding of the 'microbiome-gut-brain' axis in the scientific community, gut microbes have been shown to regulate sleep function by communicating with the brain through several mechanisms: regulating the serotonin system; Regulating the blood-brain barrier; Produce functional metabolites. Breakthroughs have been made in theory to regulate the host's biological rhythm and improve the nervous system problems caused by sleep disorders. It has great practical significance. Starting from the pathological mechanism of insomnia (including neurotransmitter system disorders and disorder of the Hypothalamic-Pituitary Aadrenal Axis (HPA) system), this paper will explain the pathogenesis of intestinal flora in sleep disorders and the interaction and internal relationship between the two.

Keywords: Insomnia; Gut-Brain Axis; Intestinal Flora; Sleep Disorder

1. Introduction

Insomnia is one of the most common sleep disorders and is closely related to stress and mood. As the "second largest gene" of human, intestinal flora has something to do with the development of diseases. Studies have found that intestinal flora and insomnia can interact through multiple pathways (neuroendocrine, immune, metabolic, etc.) on the gut-brain axis[1-5]. This article will explore the relationship between gut microbiota and sleep disorders, and review the research progress of intestinal flora in the pathogenesis of insomnia.

2. Pathological Mechanism of Insomnia

Clinical insomnia falls into the category of primary insomnia and secondary insomnia. Secondary insomnia is caused by physical diseases, mental disorders, drug abuse, sleep-disordered breathing, etc. The diagnosis of primary insomnia lacks specific indicators and is mainly an exclusionary diagnosis. At present, the pathogenesis of insomnia is not clear, but scientists generally believe that it is a chronic disease affected by multiple factors.

2.1 Neurotransmitter System Disorders

Dysfunction of neurotransmitter synthesis and secretion is an important cause of insomnia, including 5-hydroxytryptamine (5-HT), norepinephrine (NE), gamma-aminobutyric acid (GABA), melatonin (MT), etc.[6] 5-HT is closely related to human circadian rhythm and sleep disorders, and is an important precursor to the formation of melatonin. It can deepen sleep by interacting with 5-HT2 receptor and 5-HT1A receptor in brain, antagonizing 5-HT2 receptor or mildly activating 5-HT1A receptor, and the two have a synergistic effect[7]. GABA is an important inhibitory neurotransmitter in the human brain, which mainly maintains the balance between excitation and inhibition in the brain. If the amount of GABA synthesized in the brain is insufficient, it will cause insufficient inhibitory function in the brain, resulting in continuous brain excitation, which will lead to insomnia [8].

2.2 Disorder of the Hypothalamic-Pituitary Aadrenal Axis (HPA) System

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in regulating emotions, human immune system and biological rhythm[9]. Sleep exerts an restraining impact on the activity of the HPA axis, and the activated of the HPA axis will lead to wakefulness and insomnia[10]. In addition, chronic disease, overexpression of inflammatory factors in the body due to sleepiness and sleep disordered breathing can also lead to dysfunction of the HPA axis, which in turn responds to inflammation-related sleep disorders. Therefore, the interaction between the HPA axis and inflammatory factors in the body is also an important cause of insomnia[11].

3. Brain-Gut Axis and Intestinal Flora

3.1 Brain-Gut Axis

Currently, it is believed that the brain-gut axis is a bidirectional response system connecting cognitive and emotional centers with multiple systems, including the interaction of nervous, immune and endocrine systems, such as enteric nervous system, HPA axis, etc.[12] The brain can regulate intestinal digestion through the brain-gut axis, while the enteric nervous system of the gastrointestinal tract can transmit signals to the central nervous system through the vagus nerve, thus affecting the central nervous system, and the gastrointestinal tract is also known as the "second brain" of the organism. According to the theory of traditional Chinese medicine, "stomach disharmony leads to sleeping restlessness" and "soothing stomach" is the classic treatment principle of traditional Chinese medicine in the clinical treatment of insomnia. Attention is paid to improving sleep deprivation by regulating gastrointestinal tract, which is in the same direction as the concept of brain-gut axis proposed by modern medicine[13].

3.2 Intestinal Flora

The gut microbiota is a group of microorganisms that are designated to live in the digestive system, and its composition is complex, mainly including sclericutes and Bacteroidetes. Intestinal flora is involved in regulating intestinal peristalsis, intestinal barrier homeostasis, and nutrient digestion and absorption. In addition, intestinal flora can regulate the central nervous system through various neural pathways, thereby affecting the sleep and mental state of the host, which is closely related to the host's emotions, physiological stress and circadian rhythm[14], and also participates in the occurrence of various neuropsychiatric diseases[15]. Intestinal flora and sleep disorders can interact through a variety of pathways along the brain-gut axis, including immune regulation, neuroendocrine, vagal and metabolic pathways[16].

4. The Pathogenesis of Intestinal Flora in Sleep Disorders

4.1 Circadian Rhythm and Metabolic Pathways

Sleep disorders, which mainly include insomnia and lethargy, are a sleep disorder caused by an imbalance between the sleep-awaken cycle and the biological rhythm. Intestinal flora has a day-night rhythm[17]. Sleep disorders mainly affect the diel rhythm of intestinal flora, thus disrupting the homeostasis of intestinal microbes, causing microbial imbalance, and then changing the abundance of intestinal flora[18]. In turn, changes in the microbial environment in the intestinal flora can drive the transcription of clock genes, affect the oscillation of metabolic level and epigenetic modification, and then trigger the change of clock genes, and eventually lead to the disturbance of circadian rhythm and exacerbate sleep disorders. In addition, the interaction between gut flora and the body's biological clock, the circadian rhythm, also has a significant impact on human metabolism. Studies have shown that microorganisms in the intestinal flora promote metabolism by promoting the expression of the transcription factor NFIL3[19]. People with long-term shift work may experience circadian dysregulation and increased permeability of the intestinal epithelial barrier[20], which may lead to low levels of chronic inflammation, one of the characteristics of metabolic dysfunction, and this chronic metabolic disease is a risk factor for insomnia[21].

4.2 Immune Regulatory Pathways

Gut flora influences the human immune system by providing a two-way communication pathway between the gut and the brain via the vagus nerve, short-chain fatty

acids (SCFA), and soluble mediators[22]. IL-1 is one of the earliest discovered sleep-promoting cytokines[23]. Animal experiments show that IL-1 receptor antagonists can adjust the composition of gut microbiota and keep the variety of intestinal flora in rats. If lacking, the abundance of gut flora is reduced, resulting in an increase in Helicobacter pylori and a decrease in ruminococcus and Prevotella. In addition, TNF-α has the function of regulating neuroendocrine and is secreted by macrophages and lymphocytes, thereby promoting the secretion of 5-HT and increasing slow wave sleep[24-25]. Gut microbiota may improve sleeping quality by boosting the ability of pro-inflammatory factors such as IL-1 and TNF-α[26].

4.3 Neuroendocrine Pathways

4.3.1 Brain-gut peptide

Studies have shown that insomnia has something to do with brain-gut peptides[27]. Gastrointestinal hormones are also known as brain-gut peptides. These hormones and neurotransmitters produced by intestinal flora enter the central nervous system through the vagus nerve pathway, excitating or inhibiting relevant neurons and participating in the sleep-arousal regulation[28]. They can also affect sleep structure by acting on the brain through the intestinal epithelial barrier or even the blood-brain barrier[29].

In addition, studies have shown that the decrease of GABA level may be a trait marker of objective sleep disorders, and the abnormality of GABA energy system may also cause insomnia[30]. Some intestinal bacteria can synthesize GABA,5-HT and other neurotransmitters, which transmit information to intestinal nerve cells through the HPA axis and affect brain function[31]. In addition, there is a kind of bacteria called KLE1738 that exclusively feeds on GABA in the human gut [32], therefore, the content of GABA in the brain is likely to be related to the ratio of KLE1738 bacteria and GABA-producing intestinal bacteria. Activation of GABA receptors is conducive to sleep, and the GABA energy system may lead to insomnia or wakefulness by activating the HPA axis and other neural pathways[33].

5-HT is a neurotransmitter closely related to sleep. Studies have revealed that gut microbiota can affect sleep by regulating the release of 5-HT by intestinal pheochromotropic cells[34].

4.3.2 HPA axis

The HPA axis is involved in regulating the secretion of various hormones, and then changes the structure and distribution of intestinal flora, resulting in flora imbalance. Studies have shown that insomnia is highly correlated with hyperactivity of HPA axis[35]. The function of host HPA axis interacts with the composition of intestinal flora. The intestinal flora overactivates the HPA function, resulting in changes in intestinal permeability, the release of pro-inflammatory factors, and the intestinal inflammatory response, thus changing the proliferation and toxicity of intestinal flora and forming the basis of intestinal pathogenesis of insomnia. In addition, adrenocorticotropin and corticosterone increase, and activated HPA axis can promote the synthesis and secretion of adrenocorticotropin and corticosterone, and then cause insomnia[36].

5. Conclusion

The regulation of sleep-arousal mechanism is the result of the comprehensive action of intestinal flora through the intestinal axis. Although previous studies have shown that gut microbiota and sleep disorders can interact, this research is still in its infancy, and large-scale clinical trials are lacking, and the mechanisms by which sleep disorders affect gut microbiota are still limited to animal studies. In addition, whether probiotics can improve insomnia symptoms by correcting specific intestinal flora disorders, and the mechanism of intestinal flora mediating insomnia needs to be confirmed by more experiments. In addition, some intestinal flora can produce neurotransmitters that regulate sleep, but relevant studies have not yet been perfected. If more such studies are carried out, the mapping of neurotransmitters secreted by intestinal flora can provide personalized treatment for patients, which will not only guide the relief of sleep disorders, but also guide the treatment of neuroendocrine and immune system diseases.

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