The Relationship Between Insomnia and Gut Microbiota

Yuqi Nie [1,*,†], Zouyang Tian [2,†]

[1] D School of Food Science, Southwest University, Chongqing, China

[2.]School of Life Science and Technology, Huazhong Agricultural University, Wuhan, China

* Corresponding Author Email: 631607010324@mails.cqjtu.edu.cn

[†]These authors contributed equally.

Abstract. The microbiota in the gut is a big and complicated biological community， which can not only affect the integrity of the intestinal barrier through metabolism and regulate the function, but also have an impact on the nervous system's development and emotional health through the microbe-brain-gut axis network. In modern life, overtime work and day and night reversal have brought about sleep deprivation and circadian rhythm disorders, which have become a common phenomenon and continue to affect human health. This article systematically describes the relationship connecting the intestinal flora and insomnia, investigate the gut microbiota's role in insomnia, summarize the current research status on how to treat insomnia by regulating gut microflora, and finally summarize and outlook the research on the interrelationship between insomnia and gut microflora.

Keywords: Gut Microbiota, Insomnia, Brain-gut-microbe Axis.

1. Introduction

With the accelerated pace of life and increased work pressure, problems such as insufficient sleep and poor sleep quality have become commonplace, affecting people's work and life. Good sleep quality and sufficient sleep time are the basis for maintaining good health, and abnormal sleep is often associated with poor health outcomes. Studies have shown that the normal amount of sleep for adults is 7-9 hours, while children and adolescents need 8-11 hours of sleep to ensure healthy physical and mental development [1]. In addition to this, sleep quality is an important factor to be assessed. There are two main factors affecting sleep quality: difficulty falling asleep and the inability to fall asleep consistently is the first factor.Another factor is various illnesses leading to poor sleep quality [2].Insomnia is a sleep condition defined by persistent difficulties getting asleep or staying asleep, resulting in a poor quality of sleep. It is linked to stress and emotions. There has recently been considerable evidence that intestinal flora populations play a critical part in the management of sleep and that sleep quality influences microbial community composition.

Microbial flora are bacteria that live in symbiotic relationships inside the body or on its surface and can cause disease under specific circumstances. The wide variety of microorganisms in the gastrointestinal tract of a healthy person is known as the gut flora. The human gut is the equivalent of a reservoir containing a collective genome, and these microbial populations have co-evolved and together with their metabolites have a major impact on the health. By tampering with the bacteria's equilibrium and metabolites in the intestinal microbiota, it has an effect on organisms, which can cause metabolic alterations and the onset of numerous diseases. Intestinal flora changes have been linked to sleeplessness in several studies. Some studies have shown that intestinal flora can influence host behavior through immune, neuroendocrine and vagal pathways in the entire-brain axis. In contrast, dysbiosis of the gut flora has been demonstrated in certain studies to aggravate peripheral and central neuroinflammatory responses, as well as impact sleep quality. [3, 4]. At the same time, animal and human experiments have shown that insomnia will lead to disruption of the host gut microflora, again demonstrating the interrelationship between the two [5]. The goal of this research is to study the links between insomnia and gut flora, to analyze the mechanism, and to summarise and prospect for relevant modalities of regulation and treatment.

2. Gut microbiota, insomnia and brain-gut-microbe axis

2.1. Gut microbiota characteristics

The human intestine is settled with a large number of microorganisms and is a complex ecosystem that is in a symbiotic relationship with the organism. Healthy gut microbiota and the human intestinal environment are in a state of mutual constraint and balance and have a bidirectional regulation of the state of the organism. The gut microbiota can self-repair and assist in host immune regulation in response to external stimuli. At the same time, intestinal flora is involved in nutrient metabolism of the organism as well as maintaining the stability of the gastrointestinal mucosal barrier.

Human health may be influenced by the makeup and metabolism of the gut microbiota. Bifidobacterium spp. and Lactobacillus spp. can metabolize probiotics within the gastrointestinal tract and produce metabolites that benefit intestinal microorganisms, while inhibiting the proliferation of harmful bacteria and improving the intestinal environment [6, 7]. Prevotella and Bacillus spp. can use complex carbohydrates to produce acetic acid and propionic acid, which provide nutrients to the body to maintain normal intestinal function [8]. Acinetobacter can specifically utilize mucins in the intestine to improve intestinal barrier function as well as hypolipidemic and hypoglycemic functions and are considered as potential probiotics.

There is no unique optimal gut microbiota composition, which varies from person to person. When the microbial diversity of the gut ecosystem is high and the microbiota balance is not disrupted, the system is considered healthy [9]. When the intestinal flora is disturbed and the dynamic balance it maintains is disrupted, it can affect the normal physiologic functions of the host and lead to the development of multiple diseases.

2.2. Insomnia and its effects

Sleep disorders are becoming increasingly common in today's society, leading to a range of serious health issues. This disorder is a subjective experiment in the quality of sleep or quantity not meeting normal needs caused and developed by environment, behaviour, cognition, genetics, and medical factor. Whether or whether it is caused by a main medical ailment, it is referred to as insomnia. The frequency and length of the onset of insomnia are used to classify clinical diagnoses as short-term and other insomnia disorders. Insomnia increases the risk of depression and suicidal ideation in adolescents and also increases the population's likelihood of developing Alzheimer's disease [10, 11]. Usually, insomnia has a higher chance of co-morbidity with hypertension, heart disease, and respiratory diseases, so insomnia is usually used as an observational symptom of other diseases. Insomnia has become a serious threat to the health of individuals and has a high socioeconomic cost [12].

2.3. Brain-gut-microbe axis

The brain-gut-microbial axis of the flora is a bidirectional information regulating network that connects the brain, gastrointestinal tract, and microbiota. In related investigations, the gut microbiome was already discovered to play a key function in brain development and behavior coordination. Important neurogenic processes including blood-brain barriers and myelin development, microglia maturation is all influenced by the gut bacteria. Bacterial metabolites in the gastrointestinal system, such as short-chain fatty acids, can stimulate neuronal pathways and signaling mechanisms. The presence of regulatory bacteria in brain-gut-microbe axis that feed on the obligate neurotransmitter γ-aminobutyric acid (GABA) may be an essential part in the pathogenesis of insomnia [13, 14].

3. Mechanisms of the influence of intesitinal flora on insomnia

The brain-gut axis serves as a crucial linking brain and the intestinal microbiota. Insomnia and intestinal microbiota can interact via brain-gut axis pathways. Its relationship with insomnia is influenced by multiple pathways in the brain-gut axis, involving immune, neurosecretory and

metabolic factors. The relationship between intestinal flora and insomnia is affected by multiple pathways in the brain-gut axis, involving immune, neurosecretory and metabolic interactions.

3.1. Intestinal flora affect insomnia via neuroendocrine pathways

3.1.1 Regulation of the gamma-amino butyric acid (GABA) ergic system

GABA, the most significant central nervous system (CNS) inhibitory neurotransmitter of mammals, is considered strongly linked to sleep and is unique to the central nervous system and is less in tissues outside the brain and spinal cord, where it inhibits neurons in the nervous system and has neuroprotective properties. The sleep regulation mechanism of the GABA neurotransmitter system is complex and there are two main systems that regulate normal sleep and wakefulness. The GABA neurotransmitter system has two systems, the reticular upward activating system, which consists mainly of monoamine neurotransmitter systems, and the inhibitory system, which consists of inhibitory projection fibres from the ventral lateral nucleus of the optic chiasm, which consists mainly of GABAergic neurotransmitter systems that project to the hypothalamic and brainstem pro-wake nuclei, thereby inhibiting the activity of these nuclei and acting as a sleep aid [15].

Insomnia is caused by an imbalance in the equilibrium of neurotransmitters of excitatory amino acids and inhibitors in the central nervous system. The sleep-related CNS contains a large number of GABAergic neurons, an important inhibitory amino acid-like transmitter in brain tissue that inhibits neuronal activity. The mechanism of action is shown in Figure 1. Glutamate (Glu) is an important excitatory amino acid-like transmitter in brain tissue that excites neuronal activity, and if it is released in excess, it can produce excitatory neurotoxicity thereby inducing insomnia. Therefore, the level of GABA or the ratio of Glu/GABA can be used to determine whether the body is insomniac, suggesting that abnormalities in GABA can lead to insomnia [16]. Strandwitz et al. isolated KLE1738 using co-culture and found that GABA was the only nutrient supporting its growth, suggesting that the amount of GABA in the brain is most likely influenced by the ratio of GABA-consuming KLE1738 to GABA-producing intestinal bacteria [13]. The above suggests that certain specific intestinal flora may be involved in the process of GABA regulation, reducing GABA levels and thereby helping to develop insomnia.

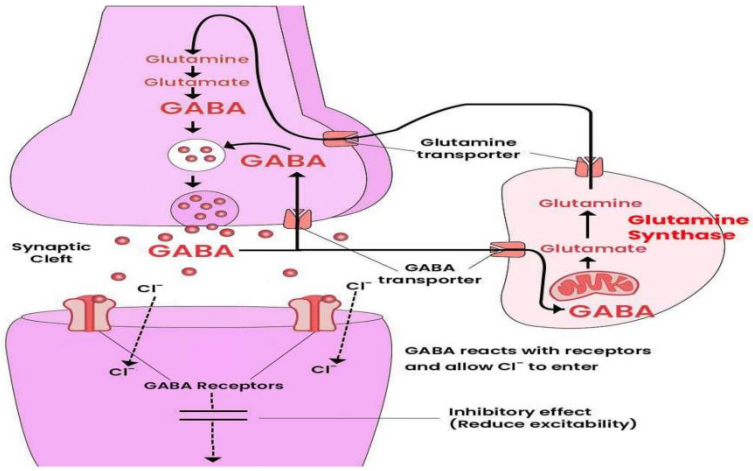

Figure 1. The mechanism of action of GABA [17]

3.1.2 Adjusting the HPA axis

The hypothalamic-pituitaryadrenal (HPA) axis is an important neuroendocrine axis of the body, involved in controlling the stress response, which alters the distribution and structure of the intestinal flora by affecting gastrointestinal motility, intestinal mucosal permeability and the release of related neurotransmitters and hormones, resulting in dysbiosis [18]. Studies have shown that stress factors lead to intestinal gut barrier failure and inflammation, and increased endotoxin, IL-8 and AGP in the serum of broiler chickens subjected to chronic stress stimuli [19]. Alexandros et al. measured ACTH and cortisol serially in the plasma of insomniacs and healthy controls by sleep experiments and found

significantly higher levels of both in insomnia patients than in controls, indicating chronic activation of the HPA axis. This demonstrates a link between insomnia and activation of the HPA axis. Sleep impairment leads to deregulation of hormone levels associated with the HPA axis, and activating the HPA axis plays a significant role in sleep disorders.

Intestinal flora may contribute to insomnia by mediating the activation of the HPA axis. Intestinal flora can regulate endocrine cells, and sleep architecture is associated with neuroendocrine functions such as glucose metabolism [20]. Intestinal flora can activate the HPA axis and promote the secretion of adrenocorticotropin-releasing hormone (CRH) and corticotropin-releasing hormone (CRH), thus increasing the susceptibility of the body to exogenous stressors and increasing arousal leading to insomnia.

3.1.3 Regulation of endocrine cells

In addition to the indirect regulation of sleep structure by endocrine cells as described above, gut flora can also directly regulate the secretory function of endocrine cells, acting centrally by secreting related hormones, thus establishing a link between the brain and the gut. 5-hydroxytryptamine (5-HT), an indole derivative with wide distribution and biological activity in the body, is an important neurotransmitter. 5-HT neurons have an irreplaceable role in maintaining and improving sleep, being the first factor thought to be a true sleep regulator [21]. It is the first factor considered to be a true sleep regulator. Because 95 percent of 5-HT in the body is dispersed in the intestine and produced by intestinal chromophores, the intestinal flora can control brain emotional activity by modulating 5-HT release from chromophores. Therefore, intestinal flora can regulate sleep indirectlythrough controlling the chromophores' release of 5-HT.

3.2. Intestinal flora affect insomnia via immune pathways

The gastrointestinal tract is the body's largest immune system, and the intestinal mucosa is home to over 70% of the body's lymphoid tissue. The lymphatic system contains a large number of immune cells that isolate external pathogens from the body's internal environment and act as a mucosal immune system. The vagus nerve, short-chain fatty acids (SCFA) with some soluble mediators link the gut and the brain that communicates in both directions, which allows the intestinal bacteria to directly regulate the immune system. Figure 2 depicts the interaction of the microflora, immune system, and CNS. The intestinal flora produces various cytokines and chemokines that alter the peripheral inflammatory markers and immune environment, interacting with brain immune cells and affecting the host brain immune system. The immune system of the host brain is affected. Disturbed intestinal flora can lead to an imbalance in the intestinal microecological environment and stimulate an immune response [22]. The intestinal flora can lead to an imbalance in the intestinal micro-ecological environment and stimulate an immune response, thus releasing substances such as IL-1 and IL-6, which were first identified as sleep-promoting cytokines IL-1 is the first cytokine found to promote sleep, thus regulating sleep [23].

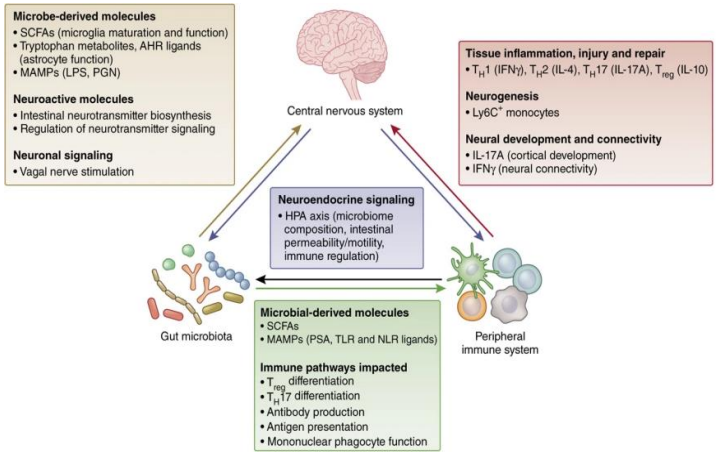

Figure 2. The interaction of the microflora, immune system, and CNS [22]

3.3. Intestinal flora affect insomnia via metabolic pathways

The gut microbiota is influenced by diet, stress, circadian rhythms, and thus sleep. Wang et al. based on metabolomics platform found that ginsenoside glycoprotein (GPr) may be involved in purine metabolism, nicotinic acid and nicotinamide metabolism, amino acid metabolism such as glycine and serine, and steroid hormone biosynthesis and other brain metabolic pathways to exert sedative-hypnotic effects. Christopher et al. experimentally verified that the intestinal epithelial barrier's permeability has been enhanced when the circadian rhythm is disrupted, mainly due to increased circulating lipopolysaccharide (LSP) and bacterial translocation, resulting in low-level chronic inflammation that is an important feature of dysfunctional metabolism [24].

4. Effects of insomnia on gut microbiota

The conclusion that sleep and the nature of the gut microbiota are in two-way communication has been confirmed. A comprehensive understanding of such physiological functions is beneficial to generate novel approaches to the treatment of sleep disorders. This paper focuses on analyzing insomnia's impact on the gut microbiota through three mainstream design ideas represented by the sleep disruption experiment, the sleep fragmentation experiment, and the circadian rhythm disruption experiment.

4.1. Sleep interruption effect on gut microbiota

Chronic sleep interruption has been shown to worsen symptoms of various gastrointestinal disorders, but the impact of various types of sleep disruption on the human gut flora varies significantly. Several normal-weight men were subjected to two nights of sporadic sleep disturbance, results showed that short-term sleep interruptions had a minimal effect on gut microbiota [25]. In addition, no significant improvements in gut microbiota were discovered after sleep extension in subjects with prolonged sleep interruption [26]. In contrast, a significant decrease in gut microbiota diversity was observed after a full night of sleep interruption experiment in 25 healthy individuals [3].

Several animal experiments have shown that sleep disruption leads to considerable changes in gut microbial diversity, and these flora are significantly linked to metabolic and mental problems. The results of a 7-day paradoxical sleep disruption experiment in rats showed significant alterations in the gut microbiota which had been linked to inflammatory cytokine abnormalities and the risk of depression [27]. In another study of mice subjected to repeated sleep interruptions for five days, lasting until four days following the conclusion of the experiment, the number of probiotics in the gut microbiome decreased significantly [28].

4.2. Effects of sleep debris exposure on gut microbiota

It's commonly assumed that SF causes changes in GM composition, which worsens insomnia symptoms. It mainly leads to an increase in the thick-walled phylum, along with a decrease in a large number of probiotic bacteria such as lactobacilli, actinomycetes, and bifidobacteria, resulting in elevated inflammatory factors. A four-week sleep debris exposure study in mice showed that sleep debris induced a 20% rise in the thick-walled phylum's abundance, and a 20% and 50% decrease in the abundance of Bacillus spp. and Actinobacter spp., respectively, predisposing the systemic tissue to inflammatory responses and metabolic disorders [29]. Furthermore, it was shown that chronic rat sleep debris significantly reduces microbial adhesion and permeability in the small intestine and cecum, implying that SF induces a greater susceptibility to disturbance of gut microbiota ecology [30].

4.3. Effects of circadian rhythm disturbance on gut microbiota

Circadian rhythm disorders, one of the common types of insomnia, have an effect on both gut microbiota dysregulation and the onset of inflammatory reactions. On the makeup of the gut microbiota of people who sleep for various lengths of time, one type of bacterium Alistipes,

commonly found in the gut of older individuals, is enriched in the early sleep time type, while another type of Lachnospira, is enriched in the late sleep time type, implying that energy expenditure in late sleeping individuals will be delayed [31]. The phylum Anaplasma has a lower relative abundance at night, while Actinomycetes and Thick-walled bacteria have a higher relative abundance. Also, on the study of jet lag changes in mice, a simultaneous decrease in the number of probiotics such as Lactobacillus and Lactococcus with concomitant effects of increased body fat was observed [32].

5. Gut microbiota regulation for insomnia

The gut microbiota therapies that have been carried out for insomnia symptoms include acupuncture treatment and probiotic supplementation. In addition, probiotics, synbiotics and faecal microbiota transplantation have all shown potential value in the treatment of insomnia, however there is currently no study evidence evaluating the effectiveness of the aforementioned strategies on insomnia.

5.1. Acupuncture therapy

In China classical acupuncture therapy to alleviate insomnia and improve sleep symptoms has been practiced for thousands of years [33]. Lactobacilli abundance was significantly enhanced in mice treated with acupuncture for p-chlorophenylalanine-induced sleeplessness as compared to the control group, suggesting that acupuncture treatment may treat insomnia by modulating host immune pathways through the regulation of intestinal flora [34].

Mongolian medical warm acupuncture therapy (MMWA) stimulates certain parts of the body with special silver needles, and current clinical investigations have demonstrated that Mongolian warm acupuncture is beneficial in treating insomnia with no negative side effects. The regulation mechanism of MMWA is shown in Figure 3. By interfering with the regulation of a variety of lactic acid bacteria genera linked to insomnia, MMWA treatment has been shown to reverse butyrate-mediated abnormalities in the cAMP signaling pathway and GAT-1 expression, allowing for a greater knowledge of the molecular principles underpinning insomnia treatment with warm acupuncture.

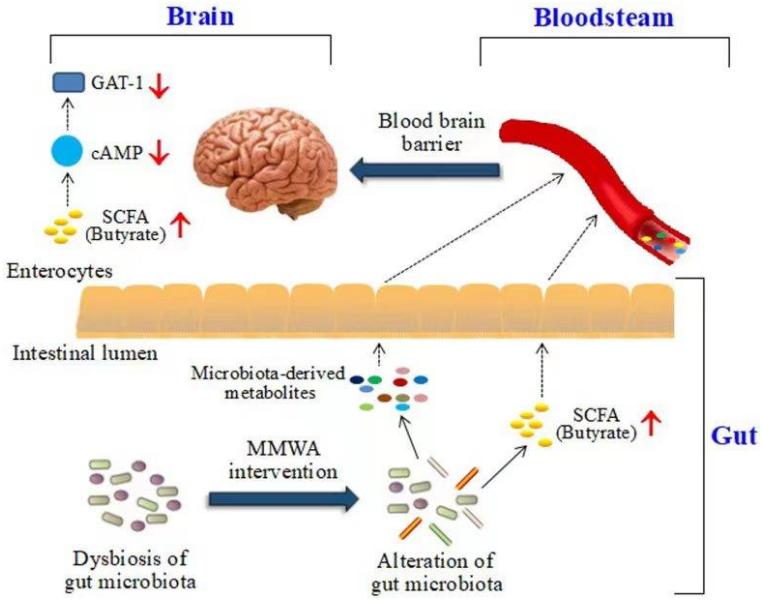

Figure 3. The regulation mechanism of MMWA [35]

5.2. Probiotic supplementation

Psychiatric problems can be prevented and treated with specific probiotics. Probiotic supplementation as a new treatment for insomnia has been initially demonstrated in clinical studies. When compared to a control group, treatment with the probiotic NVP-1704 resulted in significantly

reduced serum concentrations of the pro-inflammatory cytokine IL-6, as well as an increased proportion of Bifidobacterium family and Lactobacillus family abundance compared to Enterobacteriaceae in treated individuals, which may be associated with good mental health [36]. An oral dietary supplement containing Lactobacillus fermentum PS150 improved symptoms of caffeine-induced sleep disturbance in mice and increased sleep duration and recovery time in pentobarbital sodium-induced sleep mice when administered for more than 14 days, however, the exact mechanism remains to be further investigated [37].

6. Conclusion

As the body's 'second genome', the gut microbiota is involved in the body's numerous physiological and pathological processes and is involved in the regulation of insomnia through neurological, endocrine, immune and metabolic pathways. Insomnia, a clinical condition that poses a significant risk to human health, is now well documented to support that there can be a two-way communication and influence between gut flora and sleep. A comprehensive understanding of this physiological function could be beneficial in generating new strategies for the treatment of sleep. The majority of research has focused on the brain-gut axis and the link between gut bacteria and sleep regulation, and its relationship with insomnia is influenced by multiple pathways in the brain-gut axis involving immune, neurosecretory and metabolic factors and their interactions. Intestinal flora modulates the GABAergic system, regulates the HPA axis and the endocrine cell-dominated brain-gut-microbe axis through which insomnia occurs or is reduced. Gut flora can also act on immune and metabolic pathways to influence insomnia symptoms. Sleep disruption, circadian rhythm disorders and fragmented sleep can, to some extent, influence the gut microbiota's number and composition. The gut microbiota therapies that have been carried out for insomnia symptoms include acupuncture treatment and probiotic supplementation. In addition, probiotics, synbiotics and faecal microbiota transplantation have all shown potential value in the treatment of insomnia, but there is currently no research evidence to assess the effects of the above approaches on insomnia. This paper investigates the interrelationship between insomnia and intestinal microecology, which may modify the structure of intestinal microecology to give a source of information and a theoretical foundation for the treatment of insomnia.

References

[1] Singh Rasnik K, Chang Hsin-Wen, Yan DI, et al. Influence of diet on the gut microbiome and implications for human health [J]. Journal of translational medicine, 2017, 15(1): 1-17.

[2] Costa Shíntia Viana da,Ceolim Maria Filomena. Factors that affect inpatients' quality of sleep [J]. Revista da Escola de Enfermagem da USP, 2013, 47: 46-52.

[3] Wang Zhong, Chen Wen-Hao, Li Su-Xia, et al. Gut microbiota modulates the inflammatory response and cognitive impairment induced by sleep deprivation [J]. Molecular Psychiatry, 2021, 26(11): 6277-6292.

[4] Wagner-Skacel Jolana, Dalkner Nina, Moerkl Sabrina, et al. Sleep and microbiome in psychiatric diseases [J]. Nutrients, 2020, 12(8): 2198.

[5] Chen Xiao, D'Souza Roshan,Hong Seong-Tshool. The role of gut microbiota in the gut-brain axis: current challenges and perspectives [J]. Protein & cell, 2013, 4(6): 403-414.

[6] Zivkovic Milica, Hidalgo-Cantabrana Claudio, Kojic Milan, et al. Capability of exopolysaccharide-producing Lactobacillus paraplantarum BGCG11 and its non-producing isogenic strain NB1, to counteract the effect of enteropathogens upon the epithelial cell line HT29-MTX [J]. Food Research International, 2015, 74: 199-207.

[7] Azad Md, Kalam Abul, Sarker Manobendro, et al. Probiotic species in the modulation of gut microbiota: an overview [J]. BioMed research international, 2018, 2018.

[8] Wu Gary D, Chen Jun, Hoffmann Christian, et al. Linking long-term dietary patterns with gut microbial enterotypes [J]. Science, 2011, 334(6052): 105-108.

[9] Rinninella Emanuele, Raoul Pauline, Cintoni Marco, et al. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases [J]. Microorganisms, 2019, 7(1): 14.

[10] Chen Si-Jing, Zhang Ji-Hui, Li Shirley Xin, et al. The trajectories and associations of eveningness and insomnia with daytime sleepiness, depression and suicidal ideation in adolescents: A 3-year longitudinal study [J]. Journal of affective disorders, 2021, 294: 533-542.

[11] Sadeghmousavi Shaghayegh, Eskian Mahsa, Rahmani Farzaneh, et al. The effect of insomnia on development of Alzheimer's disease [J]. Journal of Neuroinflammation, 2020, 17(1): 1-20.

[12] Abad Vivien C,Guilleminault Christian. Diagnosis and treatment of sleep disorders: a brief review for clinicians [J]. Dialogues in clinical neuroscience, 2022.

[13] Strandwitz Philip, Kim Ki Hyun, Terekhova Darya, et al. GABA-modulating bacteria of the human gut microbiota [J]. Nature microbiology, 2019, 4(3): 396-403.

[14] Dalile Boushra, Van Oudenhove Lukas, Vervliet Bram, et al. The role of short-chain fatty acids in microbiota–gut–brain communication [J]. Nature reviews Gastroenterology & hepatology, 2019, 16(8): 461-478.

[15] Szymusiak Ronald, Alam Noor, Steininger Teresa L, et al. Sleep–waking discharge patterns of ventrolateral preoptic/anterior hypothalamic neurons in rats [J]. Brain research, 1998, 803(1-2): 178-188.

[16] Bravo Javier A, Forsythe Paul, Chew Marianne V, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve [J]. Proceedings of the National Academy of Sciences, 2011, 108(38): 16050-16055.

[17] Sarasa Sabna B, Mahendran Ramasamy, Muthusamy Gayathri, et al. A brief review on the non-protein amino acid, gamma-amino butyric acid (GABA): its production and role in microbes [J]. Current microbiology, 2020, 77(4): 534-544.

[18] Wells Jerry M, Brummer Robert J, Derrien Muriel, et al. Homeostasis of the gut barrier and potential biomarkers [J]. American Journal of Physiology-Gastrointestinal and Liver Physiology, 2017, 312(3): G171-G193.

[19] Chen Juxing, Tellez Guillermo, Richards James D, et al. Identification of potential biomarkers for gut barrier failure in broiler chickens [J]. Frontiers in veterinary science, 2015, 2: 14.

[20] Kitamura Shingo, Katayose Yasuko, Nakazaki Kyoko, et al. Estimating individual optimal sleep duration and potential sleep debt [J]. Scientific reports, 2016, 6(1): 1-9.

[21] Jouvet Michel. Biogenic Amines and the States of Sleep: Pharmacological and neurophysiological studies suggest a relationship between brain serotonin and sleep [J]. Science, 1969, 163(3862): 32-41.

[22] Fung Thomas C, Olson Christine A,Hsiao Elaine Y. Interactions between the microbiota, immune and nervous systems in health and disease [J]. Nature neuroscience, 2017, 20(2): 145-155.

[23] Ballesteros-Zebadua Paola, Custodio Verónica, Franco-Perez Javier, et al. Whole-brain irradiation increases NREM sleep and hypothalamic expression of IL-1β in rats [J]. International Journal of Radiation Biology, 2014, 90(2): 142-148.

[24] Forsyth Christopher B, Voigt Robin M, Burgess Helen J, et al. Circadian rhythms, alcohol and gut interactions [J]. Alcohol, 2015, 49(4): 389-398.

[25] Benedict Christian, Vogel Heike, Jonas Wenke, et al. Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals [J]. Molecular metabolism, 2016, 5(12): 1175-1186.

[26] Reutrakul Sirimon, So-Ngern Apichart, Chirakalwasan Naricha, et al. No changes in gut microbiota after two-week sleep extension in chronically sleep-deprived individuals [J]. Sleep medicine, 2020, 68: 27-30.

[27] Ma Weini, Song Jing, Wang Heran, et al. Chronic paradoxical sleep deprivation-induced depressionlike behavior, energy metabolism and microbial changes in rats [J]. Life sciences, 2019, 225: 88-97.

[28] Bowers Samuel J, Vargas Fernando, González Antonio, et al. Repeated sleep disruption in mice leads to persistent shifts in the fecal microbiome and metabolome [J]. PloS one, 2020, 15(2): e0229001.

[29] Poroyko Valeriy A, Carreras Alba, Khalyfa Abdelnaby, et al. Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice [J]. Scientific reports, 2016, 6(1): 1-11.

[30] Triplett Judy, Ellis David, Braddock Amber, et al. Temporal and region-specific effects of sleep fragmentation on gut microbiota and intestinal morphology in Sprague Dawley rats [J]. Gut Microbes, 2020, 11(4): 706-720.

[31] Carasso Shaqed, Fishman Bettina, Lask Liel Stelmach, et al. Metagenomic analysis reveals the signature of gut microbiota associated with human chronotypes [J]. The FASEB Journal, 2021, 35(11): e22011.

[32] Thaiss Christoph A, Zeevi David, Levy Maayan, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis [J]. Cell, 2014, 159(3): 514-529.

[33] Huang Wei, Kutner Nancy,Bliwise Donald L. A systematic review of the effects of acupuncture in treating insomnia [J]. Sleep Medicine Reviews, 2009, 13(1): 73-104.

[34] Hong Jiajing, Chen Jian, Kan Junming, et al. Effects of acupuncture treatment in reducing sleep disorder and gut microbiota alterations in PCPA-induced insomnia mice [J]. Evidence-Based Complementary and Alternative Medicine, 2020, 2020.

[35] Yu Hong, Yu Hui, Si Lengge, et al. Influence of warm acupuncture on gut microbiota and metabolites in rats with insomnia induced by PCPA [J]. Plos one, 2022, 17(4): e0267843.

[36] Lee Hyuk Joo, Hong Jung Kyung, Kim Jeon-Kyung, et al. Effects of probiotic nvp-1704 on mental health and sleep in healthy adults: An 8-week randomized, double-blind, placebo-controlled trial [J]. Nutrients, 2021, 13(8): 2660.

[37] Lin Alexander, Shih Ching-Ting, Huang Chin-Lin, et al. Hypnotic effects of lactobacillus fermentum PS150TM on pentobarbital-induced sleep in mice [J]. Nutrients, 2019, 11(10): 2409.