Sleep Medicine Reviews 65 (2022) 101691

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

The microbiota-gut-brain axis in sleep disorders

Zhe Wang [a], Zhong Wang [a], Tangsheng Lu [b], Wenhao Chen [c], Wei Yan [a], Kai Yuan [a], Le Shi [a], Xiaoxing Liu [a], Xinyu Zhou [d], Jie Shi [b], Michael V. Vitiello [e], Ying Han [b, **], Lin Lu [a, b, f, *]

[a] Peking University Sixth Hospital, Peking University Institute of Mental Health, NHC Key Laboratory of Mental Health (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing, 100191, China
[b] National Institute on Drug Dependence and Beijing Key Laboratory of Drug Dependence, Peking University, Beijing, 100191, China
[c] Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China
[d] Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[e] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, 98195-6560, USA
[f] Peking-Tsinghua Center for Life Sciences and PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing, 100871, China

ARTICLE INFO

Article history:
Received 10 May 2022
Received in revised form
4 August 2022
Accepted 19 August 2022
Available online 31 August 2022

Keywords:
Sleep
Sleep disorders
Sleep disturbances
Sleep-microbiome interaction
Microbiota-gut-brain axis
Interventions

ABSTRACT

Sleep is a complex physiological process and is a critical determinant of physical and mental health. In the past decades, significant progress has been made in understanding the neural mechanisms of sleep and awakening. However, the initiation and maintenance of the sleep-wake cycle is regulated not only by the central system but is also affected by signals from peripheral tissues. Growing evidence shows that the microbiota-gut-brain axis contributes to the regulation of sleep behavior both directly and indirectly and may play a critical role in the etiology and pathogenesis of sleep disorders. Sleep deprivation leads to dysfunction of gut microbiota and sleep disorders are accompanied by altered gut microbiota composition. In this review, we describe the bidirectional relationships between sleep and gut microbiota and summarize the abnormal characteristics of gut bacteria in distinct conditions including sleep disturbances, sleep disorders and sleep disorders comorbid with neuropsychiatric disorders. We also examine the potential routes of microbiota-gut-brain axis in sleep and gut microbiome interactions, including metabolic, immune, and neural pathways, and propose microbiota-targeted interventions for improving sleep. Manipulating gut microbiota may be a promising avenue for the development of novel interventions for sleep disorders.

1. Introduction

Sleep is an essential and complex physiological process of the body [1], which plays a vital role in maintaining physical and mental health. Recent studies have shown that with advancing age the time we spend sleeping declines, meanwhile, the incidence of sleep disorders increases [2]. Insufficient sleep caused by both willful sleep deprivation and as a result of sleep disorders have become increasingly prominent [3]. Insufficient sleep affects our physical and mental health and contributes to health problems such as cardiovascular and endocrine diseases [4,5]. Our earlier studies focused on negative effects of sleep disturbances on brain function, especially cognitive impairments [6,7]. Growing evidence indicates that sleep dysfunction may also contribute to the pathogenesis of various neuropsychiatric disorders [8]. Therefore, exploring the role of sleep in these disorders is important for their optimal diagnosis and treatment. The bulk of earlier research into sleep regulatory mechanisms has focused on the role of the central nervous system (CNS) in sleep-wake regulation [9]. The mechanisms by which peripheral tissues, such as the gut, contribute to sleep regulation and dysregulation remain unknown.

With the development of sequencing and multi-omics analysis technology, recent years have seen a revolution in our understanding of microbiota biology, revealing their major role in the pathophysiology of brain diseases. As the second genome of the

* Corresponding author. Institute of Mental Health/Peking University Sixth Hospital, 51 Huayuanbei Road, Haidian District, Beijing 100191, China.
** Corresponding author. National Institute on Drug Dependence and Beijing Key Laboratory on Drug Dependence, Peking University, 38 Xueyuan Road, Haidian District, Beijing, 100191, China.
E-mail addresses: yinghan@bjmu.edu.cn (Y. Han), linlu@bjmu.edu.cn (L. Lu).

https://doi.org/10.1016/j.smrv.2022.101691
1087-0792/

Abbreviations

AD	Alzheimer's disease
AIMD	antibiotic-induced microbiome depletion
ASD	autism spectrum disorder
CNS	central nervous system
EEG	electroencephalogram
FMT	fecal microbiota transplantation
GABA	gamma-aminobutyric acid
GF	germ-free
5-HT	5-hydroxytryptamine
HPA	hypothalamic-pituitary-adrenal axis
IBD	inflammatory bowel disease
IL-6	interleukin-6
iRBD	idiopathic rapid movement sleep behavior disorder
MT	melatonin
MDD	major depressive disorder
NREM	non-rapid eye movement
OSA	obstructive sleep apnea
PD	Parkinson's disease
REM	rapid eye movement
SCFAs	short-chain fatty acids
SPF	specific-pathogen-free
SWA	slow-wave activity
TNF	tumor necrosis factor
VNS	vagus nerve stimulation

human body, about 3.8×10^{13} microorganisms colonize the intestine [10]. Various factors can disrupt the abundance of microbiota and affect its diversity and function, including the environment and various external factors, such as drug intake, lifestyle, and stress [11]. Studies have shown that the gut microbiota is involved in the development of depression, Alzheimer's disease (AD), Parkinson's disease (PD) and other neuropsychiatric disorders [12]. Various factors can also interact with the gut microbiota to influence sleep, and the communication between gut microbiota and sleep-wake regulation may be bidirectional. Human studies have demonstrated that short sleepers have differential microbial composition such as increased abundance of *Pseudomonas* in feces compared to normal length sleepers [13]. On the other hand, when the gut microbiota was depleted by chronic treatment with broad-spectrum antibiotics, mice presented with abnormal sleep patterns [14]. However, the mechanisms by which the gut microbiota signal the brain to influence sleep-wake regulation need to be elucidated.

The relationship between circadian rhythms and the gut microbiome has been previously reviewed [15]. Others are exploring the possible factors or molecular mechanisms that involved in the interplay between sleep and gut microbiota [16,17]. However, with the development of sequencing technology and multi-omics analysis methods, there is a paradigm shift in our understanding of the brain-gut axis during the past decade [18]. Gut microbiota-targeted interventions have been shown to exert a therapeutic effect on sleep disturbances and recent studies demonstrate bidirectional microbiota-gut-brain axis activity may underlie sleep and gut microbiome interactions. Therefore, this review focuses on the current state of knowledge of the characteristics of gut microbiota alterations in various conditions including sleep disturbances, sleep disorders and comorbid sleep disorders in neuropsychiatric disorders. The current review further elucidates the possible mechanisms of how gut microbiota influence sleep regulation along the brain-gut axis. Last, we summarize microbiota-targeted interventions for improvement of sleep and treatment of sleep disorders.

2. Sleep and its regulation

Sleep is a dynamic biological process that affects virtually all physiological processes [19]. The sleep-wake cycle is achieved by the interplay of endogenous oscillatory processes and external factors, such as the light-dark cycle and feeding [20]. The suprachiasmatic nucleus of the hypothalamus controls the daily rhythms of nearly all physiological processes [21]. Aligned circadian rhythms in brain and periphery are vital for homeostasis. Normal sleep architecture comprises two distinct states, rapid eye movement (REM) sleep and non-REM (NREM) sleep [22]. NREMS can be further subdivided into N1, N2 and N3 stages. By detecting both the amplitude and synchronization of cortical neural activity, the electroencephalogram (EEG) is able to evaluate wakefulness and sleep stages objectively, and its coordination with other technologies such as functional magnetic resonance imaging and magnetoencephalography provides insights into the neuronal underpinnings of different phases of sleep [23]. Furthermore, multiple brain areas and several neural circuits have been shown to work together to control sleep-wake cycle. For example, wake-promoting brain regions include histamine neurons in the tuberomammillary nucleus [24] and orexin neurons in the lateral hypothalamus [25]. GABAergic neurons located in the ventrolateral preoptic area and the parafacial zone, contribute to NREM sleep [26,27]. REM sleep—promoting neurons include cholinergic neurons in the laterodorsal tegmental nucleus and pedunculopontine nucleus, which are crucial for REM sleep initiation but not maintenance [28]. The wake/sleep flip-flop switch theory proposes that these brain regions work together to maintain periods of sleep and wake and their transitions [29].

In addition to the direct regulation of sleep by the brain, the signals of peripheral organs can also affect sleep. The hypothalamic-pituitary-adrenal (HPA) axis is an endocrine pathway that plays a critical role in sleep regulation [30]. Studies using norepinephrine-deficient mice show that norepinephrine plays a critical role in the maintenance of wakefulness after stress [31]. Moreover, the neurotransmitters of sleep/wake promoting neurons are not only produced by the central nervous system, but most of them are produced peripherally. The microbiota located in the gut can produce metabolites such as gamma-aminobutyric acid (GABA), dopamine, serotonin (5-HT) and other substances, which are able to affect sleep regulation [32]. The influence of peripheral organs on the sleep-wake regulation cannot be ignored. Such peripheral signals can be transmitted to the brain through the circulatory and peripheral nervous systems to regulate sleep.

3. Gut microbiota influence on sleep physiology

Sleep has a complex interaction with microbial communities. The early phase of life is crucial for the establishment of the microbiome, and this period is also a critical phase for the development of cognition and physiological function [33]. Perinatal antibiotic exposure was related to higher EEG delta power at term age and this may contribute to increased attention problems in antibiotic-exposed infants [34]. Liu et al. found that gut microbial alteration during early-life induced behavioral impairment in adulthood [35]. Schoch et al. reported that daytime sleep was negatively correlated with α diversity of gut microbiota in infants

[36]. Evidence in preschool aged children showed that sleep duration was related to β diversity of gut microbiota, and children with high total nighttime sleep showed a higher relative abundance of *Bifidobacterium* [37]. A recent study in adult subjects also reported that microbiome diversity was positively correlated with total sleep time [38]. However, sleep extension did not alter gut microbiota in chronically sleep-deprived individuals [39]. Furthermore, a large-scale functional network study in healthy young adults found that some internetwork functional connectivity mediated the associations of microbial diversity with sleep quality, working memory, and attention [40]. The complex relationship between microflora and sleep at different ages needs to be fully investigated.

Recent evidence has shown that the deletion of gut microbiota could alter sleep architecture. Silva et al. revealed that no changes in circadian rhythmicity of locomotor activity in axenic flies, but axenic flies spent more time in sleep during the dark phase [41]. Antibiotic-induced microbiome depletion (AIMD) mice exhibited increased NREM sleep during the dark phase and decreased NREM sleep during light phase, and theta power density during REM sleep was significantly lower in AIMD mice by analyzing EEG power spectra [14]. The shortcoming of the AIMD mice model is that it could not exclude the direct effect of antibiotics on brain functions, thus the sleep architecture of germ-free (GF) mice needs to be evaluated to confirm that the observed sleep changes are the results of compromised microbiota.

4. Sleep disturbances and gut microbiota reciprocal relationship

Intestinal microbes have rhythmic activities [42]. Zeitgebers such as light, social interaction and diet, have important effects on the sleep-wake cycle [43]. Intervention with zeitgebers will simultaneously alter sleep rhythm and intestinal microbial components. In addition, sleep deprivation, sleep restriction, and sleep fragmentation can also lead to changes in the composition of gut microbiota (Fig. 1, Table 1), showing that sleep plays a critical role in the maintenance of microbial homeostasis.

4.1. Sleep–wake cycle alterations

A recent study reported that relatively short sleep-wake time shifts influence the functional-profile gut microbes but found no significant overall alteration of the intestinal flora composition among recruited subjects, possibly due to the relative brief shift times of only 2–4 h [44]. Longer shift times were not investigated. In another study, continuous light exposure induced a reduction of *Bacteroidetes* and an increase of *Firmicutes* [45]. Additionally, after mice experienced an 8-h advance of the light/dark cycle for 4 months, the bacterium abundant of *Turicibacter* was significantly higher than controls, and fecal tryptophan metabolism levels were decreased [46]. These studies demonstrate that variations of light exposure times can affect the composition of gut microbes.

Chronotypes describe the body's circadian typology or the physiologic preference to sleep and wake at specific times. Carasso et al. reported that early chronotypes exhibited an increase in abundance of *Alistipes*, while *Lachnospira* was enriched in late chronotypes [47]. Differences in microbiological composition can alter metabolic profiles and affect health. Experimental manipulation of *Cyclocarya paliurus* flavonoids in a circadian rhythm disorder mouse model found significantly altered gut microbiome composition [48]. Alterations of the sleep-wake cycle can lead to abnormal time of eating [49], which are related to alterations of gut microbiome composition. In mice, irregular eating patterns cause a decrease in beneficial butyrate-producing bacteria and barrier dysfunction [50]. The diurnal rhythmicity of the intestinal microbiota is driven by nutritional factors and host physiology [51]. Additionally, the host circadian clock is able to affect microbial rhythmicity. The diurnal rhythmicity of the microbial community works together with the host circadian system to maintain the normal rhythmicity of the host physiology [52]. These studies suggest that variations in circadian rhythms can affect intestinal microecological balance.

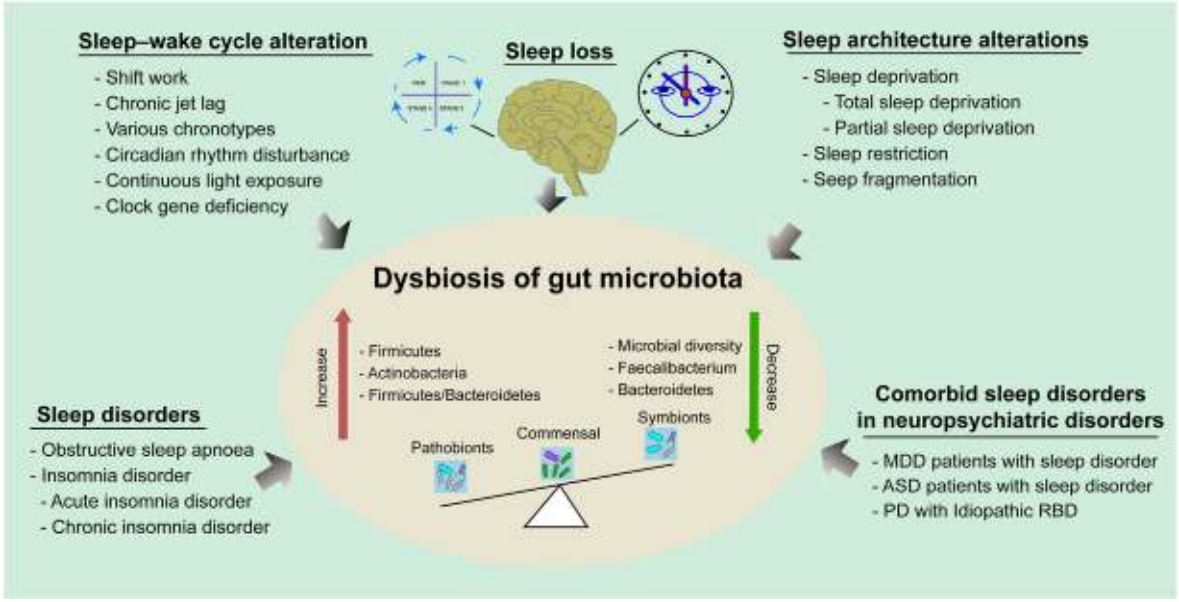

Fig. 1. Changes of gut microbiota compositions in sleep disturbances and sleep disorders. Sleep disturbances induced the dysbiosis of gut microbiota. Sleep loss caused the gut bacteria out of balance, which increases pathobionts in the gut. The Firmicutes/Bacteroidetes (F/B) ratio was increased in sleep disorders, which could influence normal intestinal homeostasis. *Faecalibacterium* was decreased in sleep disorders, which has been reported as one of the main butyrate producers found in the intestine. MDD, major depressive disorder; ASD, autism spectrum disorder; PD, Parkinson's Disease; RBD, REM sleep behavior disorder.

Table 1
Summary of studies investigating alterations of gut microbiota in sleep disturbances and sleep disorders.

Author and year of Publication	Models	Species	Sample size	Dysbiosis of microbiota	Other outcomes
Sleep–wake cycle alterations					
Liu et al., 2020 [44]	Sleep-wake cycle shift	Humans	22	Increase of the F/B ratio Increase of the phyla Fusobacteria, Tenericutes, classes Fusobacteriia and Mollicutes	Acetyl-CoA fermentation to butanoate II was significantly increased after the night of the sleep time shift
Li et al., 2021 [46]	Chronic jet lag	Male C57BL/6J mice	N = 3 −6/ group	Decrease of α-diversity Decrease of Bacteroidetes phylum Increase of Actinobacteria Increase of the F/B ratio	The abundance of amino acids indoles, peptides and phenylpropanoids in fecal metabolites were decreased
Sleep architecture alterations					
Wang et al., 2020 [7]	40 h sleep deprivation	Humans	25	Decrease of α-diversity The weighted analysis revealed an obvious difference of β-diversity Decrease of *g_Prevotella*, *g_Sutterella*, *g_Parasutterella*, *g_Alloprevotella*, *g_Anaeroplasma* and *g_Elusimicrobium*	The concentrations of acetate, propionate, and butyrate were significantly decreased The serum S100β levels were significantly increased
Wang et al., 2021 [53]	48 h sleep deprivation	Sprague −Dawley rats	N = 8/ group	Decrease of α-diversity Alteration of β-diversity Decrease of Shannon and Simpson indexes Decrease of the relative abundance of *g_Butyricicoccus*, *g_Butyricimonas*, *g_Alistipes*, *g_Intestinimonas*, and *g_Lactobacillus* Increase of the relative abundance of *g_Streptococcus*	Most of the different microbial species recovered after 1 week of sleep recovery Butyrate was decreased after 48 h SD
Triplett et al., 2020 [54]	Sleep fragmentation	Sprague Dawley rats	N = 9 −12/ group	Significant alterations to α-diversity more dramatically in the distal ileum Chronic SF result in altered β-diversity **Acute SF:** decrease in the Lactobacillaceae, Lachnospiraceae, F16, and Alcaligenaceae families; increased in S24-7 and Porphyromonadaceae families in the distal ileum **Chronic SF:** decrease in Enterobacteriaceae and Lactobacillaceae Families; increase in Turicibacteraceae and Clostridiaceae families	KC/GRO was increased after chronic SF in serum ACTH level was significantly decreased after chronic SF
Maki et al., 2020 [55]	Sleep fragmentation	Male Wistar-Kyoto rats	N = 7 −8/ group	**Middle-SF:** Decrease of α-diversity Decrease of the F/B ratio Increase of the relative abundance of *Proteobacteria* Decrease of the relative abundance of *Eubacterium*, *Oscillospira*, and *Butyrivibrio* **Late SF:** The F/B ratio was not significantly altered Increase of the relative abundance of *Dorea* Decrease of the relative abundance of *Parabacteroides*	Poor sleep was associated with increased mean arterial pressure
Sleep disorders					
Valentini et al., 2020 [57]	OSA	Children	15	Increase of *Bacteroides fragilis* Decrease of Chao1	F/B ratio was directly correlated to sleep clinical record Bacteria applied in the gut barrier integrity (*Desulfovibrionaceae*, *Bacteroides fragilis* and *Faecalibacterium prausnitzii*) were correlated with sleep parameters
Ko et al., 2019 [58]	OSA	Humans	113	Decrease of *Megamonas*, Ruminococcaceae, *Alistipes*, *Dialister*, *Oscillibacter*	IL-6 level was increased Short-chain fatty acid (SCFA)-producing bacteria were decreased and pathogens *Lactobacillus* was increased
Khalyfa et al., 2021 [60]	OSA	Male C57BL/6 J Mice	N = 5/ group	Increase of *Lachnospiraceae*, *Prevotella* and *Muribacululaceae* Decrease of *Alistipes*	
Liu et al., 2019 [62]	Insomnia	Humans	20	Decrease of α- and β-diversity Decrease of the F/B ratio Increase of *Bacteroides*	Vitamin B6 catabolism was increased Arachidonic acid biosynthesis was decreased
Li et al., 2020 [63]	Insomnia	Humans	96	**In the CID group:** Decrease of α-diversity (estimated using the Chao1 Index) Increase of Actinobacteria at the phylum level, *Blautia* and *Eubacterium hallii* at the genus level Decrease of *Faecalibacterium*, *Prevotella 9*, and *Roseburia* **In the AID group:** Decrease of *Firmicutes*, *Lachnospira* Increase of *Bacteroides*	In the CID group, the combination of two signature bacteria *Faecalibacterium* and *Blautia* was significantly correlated with PSQI In the AID group, the combination of two signature bacteria *Lachnospira* and *Bacteroides* was positively correlated with PSQI There was higher plasma level of IL-1β in CID and AID groups compared to healthy controls
Comorbid sleep disorders in neuropsychiatric disorders					
Zhang et al., 2021 [74]	MDD patients with sleep disorder	Humans	81	At the genus level, *Blautia, Coprococcus, Dorea,* and *Intestinibacter* were negatively correlated with PSQI *Intestinibacter* was negatively correlated with PSQI and ISI	*Acidaminococcus* was associated with better sleep quality
Hua et al., 2020 [76]	ASD patients with sleep disorder	Children	120	Increase of the ACE, Chao and Sobs diversity indices for the sleep disorder group Decrease of *Faecalibacterium* and *Agathobacter*	3-hydroxybutyric acid and melatonin levels were decreased and serotonin levels were increased There was a significantly negative correlation between CSHQ scores and the abundances of

Table 1 (*continued*)

Author and year of Publication	Models	Species	Sample size	Dysbiosis of microbiota	Other outcomes
					Faecalibacterium Hydroxybutyric acid and melatonin levels were positively correlated with Faecalibacterium abundance
Heintz et al., 2018 [78]	PD with Idiopathic RBD	Humans	175	Increase of *Akkermansia* sp.*and Prevotella* sp.	

F/B, Firmicutes/Bacteroidetes; OMA-IR, homeostatic assessment model of insulin resistance; SD, sleep deprivation; OTU, operational taxonomic unit; MT, melatonin; SF, sleep fragmentation; KC/GRO, keratinocyte chemoattractant/growth regulated oncogene; ACTH, adrenocorticotropic hormone; OSA, obstructive sleep apnoea; AID, acute insomnia disorder; CID, chronic insomnia disorder; PSQI, Pittsburgh Sleep Quality Index; MDD, major depressive disorder; ISI, Insomnia Severity Index; ASD, autism spectrum disorder; CSHQ, Children Sleep Habits Questionnaire; PD, Parkinson's Disease; RBD, REM sleep behavior disorder.

4.2. Sleep architecture alterations

The loss of gut microbiota may affect the sleep homeostasis, and axenic flies spent less time on recovery sleep after sleep deprivation [41]. Recently, we demonstrated that dysbiosis of gut microbiota mediated cognitive impairment caused by sleep deprivation in humans and mice. We found that 40 h of sleep deprivation in adult humans resulted in a decrease in α diversity and β diversity of gut microbiota [7]. We also found that 24 h of sleep deprivation did not change gut microbial composition, while 48 h of sleep deprivation significantly altered gut microbial composition in rats [53]. Surprisingly, the alterations in gut microbiota were reversible after 1 week of sleep recovery [53]. These studies demonstrate that the diversity of the gut microbiota is influenced by the duration of sleep deprivation.

Sleep fragmentation could alter the composition of gut microbiota. Rats were exposed to sleep fragmentation, with disrupted sleep every 3 min during a 12/12-h light/dark cycle for 6 consecutive days and exhibited significant alteration of α diversity in the distal ileum. It is worth noting that α diversity showed different changes in different intestine segments in rats, with disrupted sleep every 3 min for 21 h/day for the 6 consecutive weeks [54]. Short chain fatty acid (SCFA)-producing bacteria exhibited differentially abundant during different periods of sleep fragmentation. Maki et al. analyzed fecal samples of rats and found that rats had lower abundance in butyrate-producing bacteria on day 13, while rats had higher relative abundance in acetate-producing genera on day 27 [55]. These results suggest that the effects of sleep fragmentation on SCFA-producing bacteria are particularly noticeable.

5. Sleep disorders and gut microbiota

Recently, many studies have reported changes in gut microbiota composition in both patients with sleep disorders and animal models. Changes in gut microbes are also increasingly being reported in patients with comorbid sleep disorders and neuropsychiatric disorders.

5.1. Sleep-related breathing disorders

Obstructive sleep apnea (OSA) is characterized by episodes of obstruction of the upper airway, leading to fragmentation of night sleep and daytime sleepiness [56] (Fig. 2A). Children with OSA syndrome (OSAS) are characterized by decreased microbiota diversity and increased inflammation levels compared to children without OSAS [57]. Ko et al. found that SCFA-producing bacteria was decreased, and the level of interleukin-6 (IL-6) was increased in OSA-hypopnea syndrome patients [58]. These findings suggest increased levels of intestinal inflammation in OSA. Additionally, it is worth noting that fecal microbiota transplantation (FMT) from OSA model mice increased sleep during dark phase in naïve mice [59]. It suggested that the sleep-wake cycle is affected by the changes of gut microbiota in OSA. In addition, after FMT of intermittent hypoxia exposed mice into naïve lean mice, FMT-recipients displayed insulin resistance, and plasma exosomes of FMT-recipients undermined p-AKT/AKT responses to exogenous insulin. These results suggest that the effect of intermittent hypoxia on insulin resistance is mediated by the gut microbiota [60]. Taken together, these findings suggest that the alterations of gut microbiota may play an important role in the pathogenesis of OSA.

5.2. Insomnia

Insomnia is the most common sleep disorder affecting the health of an increasing number of individuals [61]. Liu et al. found marked changes in gut microbiota diversity and composition in 10 chronic insomnia patients compared with 10 healthy controls [62]. Li et al. observed a decrease in microbiome diversity in acute and chronic insomnia patients, with greater effects on bacterial diversity found in chronic insomnia patients [63]. Both studies noted that an increase of *Bacteroidetes* phylum could be a biomarker to identify insomnia. It may be possible to distinguish acute or chronic insomnia patients based on microbial differences [63]. Moreover, there is evidence that gut microorganisms are capable of influencing brain function. A regional homogeneity study found a negative association between the relative abundance of *Lactobacilli* and regional homogeneity values in the left fusiform gyrus of chronic insomnia patients [64]. An experimental work using a pharmacologic mouse model of insomnia reported that P-chlorophenylalanine treatment altered the diversity and composition of gut microbiota [65]. Additionally, some beneficial bacteria such as *Akkermansia* and *Lactobacillus* were reserved after Bailemian (a proprietary Chinese medicine to treat insomnia) administration in this insomnia mice model [65]. Moreover, a recent study using the same pharmacologic mouse model of insomnia suggested that acupuncture improved both the sleep loss and disruption of gut microbiota [66]. It is possible that the gut microbiome might be a new target for the treatment of insomnia. Insomnia may be caused by a relative decrease in sleep-promoting neurochemical factors and increase in wake-promoting neurochemical factors in the gut (Fig. 2B). Microorganisms which can produce the sleep and wakefulness related neurotransmitters should be paid more attention to the field of insomnia. Strandwitz et al. isolated a variety of GABA-producing bacteria in human gut microbiota and found that *Bacteroides* ssp. could produce lots of GABA [67]. It is reported that the *E. coli, M. morganii* and *L. vaginalis species* from human feces were able to product the histamine [68].

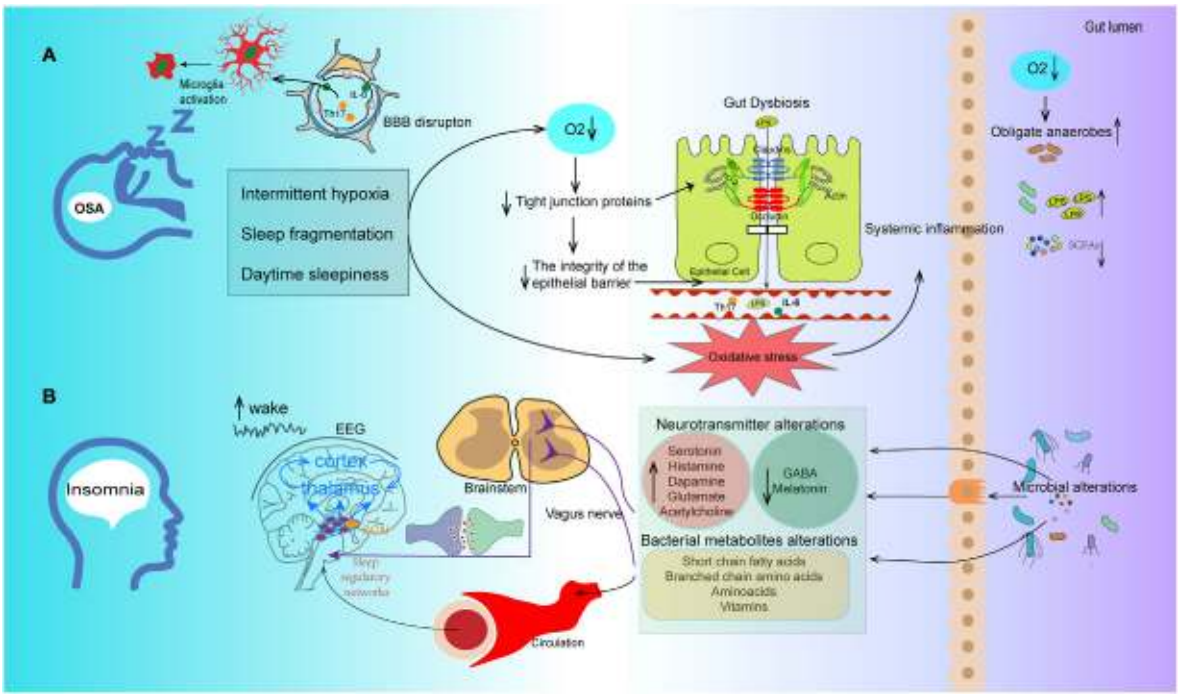

Fig. 2. A diagram showing how gut microbiota dysbiosis contributes to the pathogenesis of sleep disorders. (A) Common symptoms of obstructive sleep apnea (OSA) include intermittent hypoxia, daytime sleepiness, and sleep fragmentation. Exposure of the body to chronic hypoxia-reoxygenation will cause gut dysbiosis and damage to the gut-vascular barrier and blood-brain barrier (BBB), and disrupt metabolites derived from gut microbiota. Lipopolysaccharide (LPS)-producing bacteria will increase, and short-chain fatty acids (SCFAs)-producing bacteria will reduce in gut. Under the condition of intermittent hypoxia, gut tight junction proteins are lower so that microbial interactions with immune cells of the intestinal could facilitate inflammation compounds crossing the gut and brain barrier. This could expose of the host to LPS and other inflammatory mediators, which then lead to systemic inflammation. **(B)** The microbiota composition and metabolites in patients with insomnia were changed, which decreased sleep-promoting neurotransmitters and increased wake-promoting neurotransmitters. Meanwhile, the alterations of gut metabolites could travel through blood circulation and neural pathways to interact with the sleep regulatory networks in the brain, which then triggers a state of hyperarousal. EEG, electroencephalogram; SCN, suprachiasmatic nucleus; GABA, γ-aminobutyric acid.

5.3. Circadian rhythm disorders

Circadian rhythm disorders are a group of sleep disorders that the sleep-wake cycle is out of sync with the day-night cycle [69]. Numerous studies have indicated that circadian rhythm disruption causes alterations of the gut microbiota. Circadian disruption decreased the relative abundance of *Bacteroidetes* in night shift individuals [70]. Voigt et al. found that disrupted circadian rhythmicity in the host can decrease microbiota diversity in mice [71]. There are a number of strategies to treat circadian rhythm sleep disorders and foster circadian rhythm. One of the effective treatments is lifestyle and behavior therapy, which encourages the development of good sleep habits and a regular routine of exercise [72]. In addition, timed light exposure and melatonin may be used to adjust and maintain the sleep-wake cycle [73]. Finally, it is promising and worthy to develop targeted microbiota interventions for the treatment of circadian rhythm disorders.

5.4. Sleep disorders comorbid with neuropsychiatric disorders

Many studies demonstrate that the comorbidity of sleep disorders with neuropsychiatric disorders showed distinctive microbial characteristics in patients. Whether gut microbiota is a co-pathogenic factor of comorbidity deserves further investigation. Zhang et al. found that the composition of the gut microbiota is related to sleep abnormalities in major depressive disorder (MDD), of which four microbiota targets at the genus level are related to sleep quality, and *Intestinibacter* is related to sleep severity [74]. Long time sleep deprivation can lead to depression and changes in gut flora [75]. The relationships between sleep changes and specific types of flora in depression deserves further exploration.

Patients with autism spectrum disorder (ASD) often have sleep problems. Studies have found that *Faecalibacterium* and *Agathobacter* abundance is reduced in patients with ASD [76]. At the same time, tests on the metabolites of ASD patient fecal samples have found that melatonin levels were decreased and tryptophan levels were increased in ASD patients with sleep disorders, and the changes in neurotransmitter levels may be related to sleep problems [76]. Melatonin supplementation can treat sleep disturbances in ASD animal model. Animal experiments showed that melatonin relieved sleep disturbances aggravated by light in the Cntnap2 mouse model of ASD [77]. Future studies could explore whether supplementation with melatonin precursor-producing strains could achieve therapeutic effects in ASD patients with sleep disorders.

Secondary idiopathic rapid eye movement sleep behavior disorder (iRBD) often occurs in Parkinson's disease. A recent study suggested that 41 abundant operational taxonomic units (OTUs) differed in iRBD subjects versus healthy individuals, and *Akkermansia* sp. and *Prevotella* sp. exhibited increased abundance in PD patients with iRBD versus without iRBD [78]. Both human and animal studies have reported that sleep problems in AD may be closely related to the deposition of Aβ [79]. At the same time, alteration of bacterial flora can also occur in AD [80]. Further investigations are needed to better define the relationships between gut microbiota and sleep problems in AD.

To date, only a few studies have explored the gut microbiota alterations in sleep disorders comorbid with neuropsychiatric disorders. More studies are needed to further clarify the specific microbiota alterations at strain level and elucidate the possible mechanisms linking them to the comorbid sleep and neuropsychiatric disorders.

6. Potential mechanisms underlying the bidirectional relationship between sleep and gut microbiota

Intestinal signals communicate with the sleep-related nuclei through the microbiota-gut-brain axis (Fig. 3). The microbiota-gut-brain axis is an important pathway for central/peripheral interactions. Bidirectional communication between the brain and the gut is achieved through metabolic, immune, and neuronal pathways. The afferent vagus nerve can sense and recognize metabolic and immune activity through peripheral transmitters, hormones, fatty acids, and inflammatory factors. Physiological and pathological products in the gut can be transmitted to the brain through the intestinal and blood-brain barriers, providing another pathway of communication from gut to brain. Here, we describe the potential routes of communication of the microbiota-gut-brain axis in the context of sleep and gut microbiome interactions.

6.1. Metabolic and endocrine signals from the gut involved in sleep regulation

6.1.1. Melatonin

Melatonin (MT) is a hormone that plays a critical role in regulating the sleep-wake cycle. MT1 and MT2 are receptors of melatonin which belong to G-protein coupled receptors [81]. Melatonin is secreted by the pineal gland but also by gut, skin, bone marrow and other organs [81]. After a meal, melatonin produced in the gut can be up to 400-fold higher than that secreted by the pineal gland [82]. Recent studies reported that sleep deprivation disrupts composition of the microbiota and decreases melatonin level in plasma [83]. Interestingly, supplementation with melatonin in sleep deprived mice improved dysbiosis of the jejunal microbiota [84]. Furthermore, Jiffin et al. showed that *Enterobacter aerogenes* was sensitive to melatonin and respond to its regulatory function [85]. The relationship between gut-derived melatonin and the pineal-released melatonin and their differences in regulating sleep-wake rhythm needs further investigation. Melatonin produced by the gut microbiota may influence sleep by acting on MT1 or MT2 receptor signaling in the brain.

6.1.2. GABA

GABA is an amino acid well-known for promoting sleep [86], and it is also helpful for preventing anxiety, stress and balance mood [87]. Many drugs that target the GABAergic system are used for treatment of insomnia [88]. The gut microbiota can influence GABA metabolism. Compared with GF mice, higher fecal levels of GABA were found in specific-pathogen-free (SPF) mice [89]. Duranti

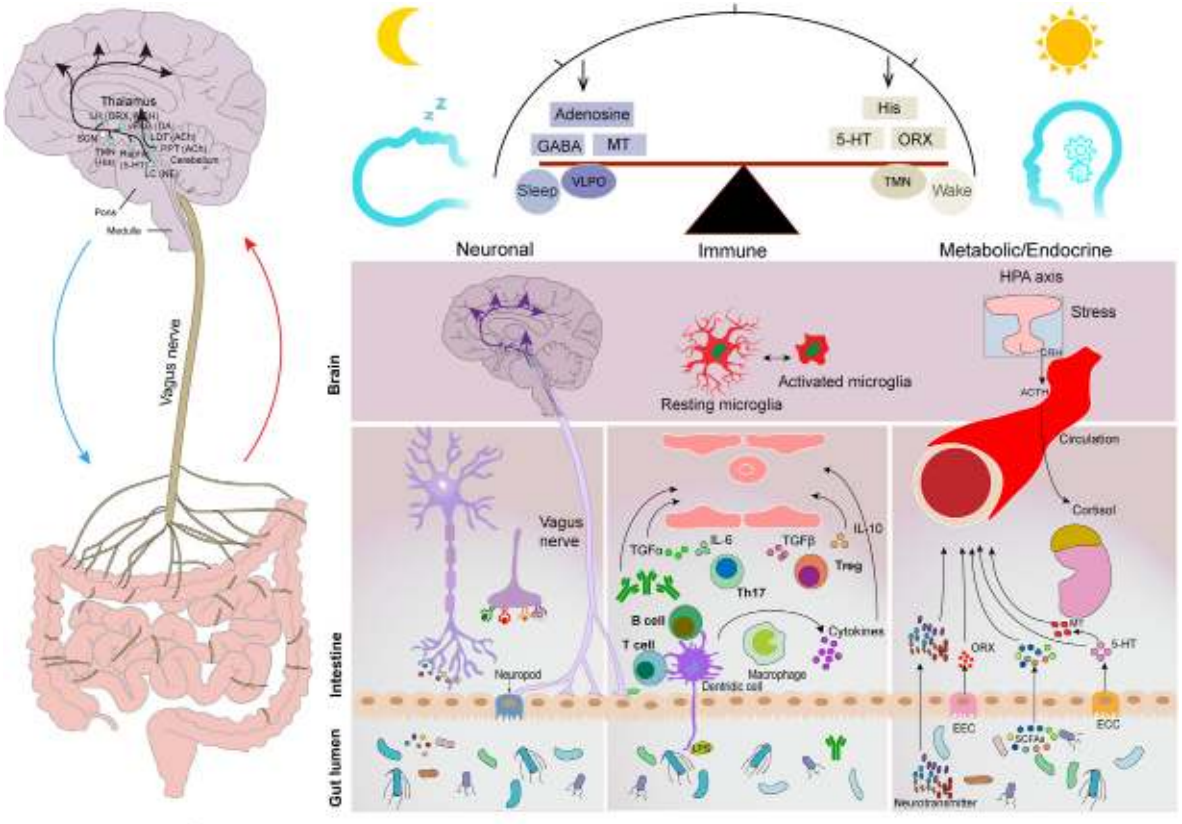

Fig. 3. Schematic diagram of the routes of sleep-microbiome interactions via the microbiota—gut—brain axis. The signals produced by the gut microbiome can be received by the flip-flop switch and regulate the state of sleep and wakefulness. Sleep molecular signals (such as melatonin, GABA, and adenosine) from gut microbiome could be received by the ventrolateral preoptic nucleus (VLPO), and wakefulness molecular signals (such as 5-HT, ORX and His) from gut microbiome could be received by tuberomammillary nucleus (TMN). The gut microbiome and sleep-wake regulation are achieved through three pathways. **Neuronal pathways**. Gut microbes and their metabolites can affect neurons of the enteric nervous system (ENS) and interact with afferent pathways of the vagal nerve that affects neural circuits involved in sleep-wake regulation. **Immune pathways**. Gut-derived immune mediators can be transmitted to the brain through the blood circulation system and afferent vagal pathways to affect sleep. For example, lipopolysaccharide (LPS) and short-chain fatty acids (SCFAs) can affect immune cells responses and interact with inflammatory homeostasis that triggers the activation of microglia to affect sleep-wake regulation. **Metabolic and endocrine pathways**. Neurotransmitters and metabolites produced by gut microbes and enteroendocrine cells or enterochromaffin cells of intestinal tissue can affect sleep-wake regulation through the blood circulation system. What is more, the activation of the hypothalamic—pituitary—adrenal axis (HPA) axis under stress affects sleep and the microbiota composition. The interactive regulation of sleep by central signals and peripheral intestinal signals is a dynamic balance, the regulation of sleep and the gut microbiome is bidirectional, and the interaction between sleep homeostasis and the stability of the gut microbiome supports a normal state. PPT, pedunculopontine nucleus; LH, lateral hypothalamus; LDT, laterodorsal tegmental nucleus; LC, locus coeruleus; vPAG, ventral periaqueductal gray; SCN, suprachiasmatic nucleus; Ach, acetyl choline; DA, dopamine; His, histamine; NE, noradrenaline; MT, melatonin; 5-HT, 5-hydroxytryptamine; ORX, orexin; GABA, γ-aminobutyric acid; ACTH, adrenocorticotrophic hormone; CRH, corticotropin receptor hormone.

et al. showed that *Bifdobacterium adolescentis* isolated from the human gut could produce GABA [90]. Nobile et al. discovered that *Limosilactobacillus reuteri PBS072* and *Bifidobacterium breve BB077* are able to improve sleep quality in stressed students [91]. More direct evidence is needed to confirm the effect of GABA-producing bacteria on improving sleep and treating sleep disorders.

6.1.3. Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that plays a critical role in regulating mood, sleep, feeding, learning and memory [92]. Serotonin is synthesized by enterochromaffin cells in the gut, and more than 90% of the body's 5-HT is gastrointestinal [93]. Several bacterial strains can secrete 5-HT, such as the *Clostridiaceae* and *Turicibacteraceae* families [94]. Recent work has shown that *L. rhamnosus* significantly increased the level of 5-HT in the frontal cortex and hippocampus in the chronic unpredictable mild stress rat model [95]. These studies suggest that the gut microbiota plays an important role in the secretion of 5-HT. Yao et al. found that *Ganoderma lucidum* was able to promote sleep and improve the 5-HT level in the hypothalamus in mice [96]. Of note was that the gut microbiota was necessary for the *Ganoderma lucidum* mycelia-mediated improvement of sleep [96]. Controlling the 5-HT secretion in the gut could be a novel approach to improve sleep and mood that bears further examination.

6.1.4. Orexin

Orexin A is a neuropeptide, is found not only in the CNS, but also in various tissues of the periphery in humans, such as the gut [97]. Immunoreactive orexin A probes have shown that orexin A can be produced in enteroendocrine cells of the mucosa in the small intestine and the colon [97,98] (Fig. 3). Enteroendocrine cells are widely dispersed throughout the epithelial cells of the intestinal wall and are sensitive to bacteria in the gastrointestinal tract [99]. Neuroreceptors for orexin A, OX1R and OX2R (G protein-coupled receptors), are widely dispersed throughout the digestive system including all regions of the human bowel and islets of Langerhans of the pancreas [98]. Orexin A plays a critical role in the regulation of the sleep-wake cycle and food intake [100]. Clinical studies have shown that the orexin receptor antagonist daridorexant can be used to treat insomnia disorder [101]. It is possible that peripheral orexin could influence sleep via the gut-brain axis.

6.1.5. Histamine

Histamine is a biogenic amine that secreted by many types of cells. Histamine regulates immune function and the sleep-wake cycle via central and peripheral pathways [102]. It has been reported that bacteria from gut microbiota secrete histamine [68] (Fig. 3). When compared with controls, nonobese patients with asthma showed higher levels of histamine-secreting bacteria including *M morganii* and *L. vaginalis* species in the gut microbiota with levels of *M. morganii* positively related to the severity of asthma symptoms [68]. Histamine H1 receptor antagonist LY2624803 has been used to treat insomnia in clinic trials [103]. Targeted knockout of histamine-producing strains in gut may be useful for improving sleep.

6.1.6. Short chain fatty acids

Short-chain fatty acids (SCFAs, primarily acetic, propionic, and butyric acids) are involved in several physiological processes [104,105]. Dietary fiber was fermented by microbiota and produced SCFAs in the gut [106]. The concentration of SCFAs among cecal feces in AIMD mice showed significant changes when compared to vehicle-treated mice [107]. SCFAs may affect sleep behavior (Fig. 3). For example, higher concentration of propionate in feces was related to longer uninterrupted sleep in infants [108] and higher levels of propionate were related to lower sleep efficiency in older adults with insomnia symptoms [109]. Furthermore, Wang et al. found that the concentration of propionate was negatively correlated with wake-time after sleep onset in children [37]. The relationship between propionate and sleep in different age groups is still to be fully explored. Tributyrin, as a butyrate pro-drug, improved NREM sleep in rats, an effect mediated through the vagus in the hepatoportal region [110]. A recent study in young subjects showed that sleep quality was positively associated with higher relative abundance of butyrate-producing genera [111]. These experiments suggest that microbiota plays an important role in SCFAs metabolism, potentially regulating sleep behavior. Further work is needed to identify the mechanisms underlying the effects of SCFAs on sleep architecture.

6.2. The vagal pathways involved in sleep regulation

The vagus nerve is the high-speed pathway of brain-gut bidirectional communication between the CNS and enteric nervous system in the body (Fig. 3). As the essential sensory nerve, the vagus nerve can regulate and receive information from the digestive system. On the one hand, gut bacteria can transmit signals directly to the brain via vagus nerve. Tanida et al. reported that gastric vagus nerve activity could be improved by the administration of *Lactobacillus johnsonii* [112]. *Lactobacillus rhamnosus* JB1 has been reported to improve depression and anxiety and modulate GABA receptor expression in the brain via a vagus nerve-dependent pathway [113]. GABAergic neurons can regulate NREM and REM sleep [114]. Benzodiazepines such as zolpidem which target GABA receptor are used to treat insomnia [115]. *Lactobacillus (L.) reuteri* was able to improve social deficits in ASD mice in the vagus nerve-dependent manner, mediated by oxytocinergic and dopaminergic signaling in ventral tegmental area [116]. Recent research has also reported that optogenetic stimulation of ventral tegmental area dopaminergic neurons induced wakefulness [117]. More work remains to be done on the details of how specific bacteria communicate with the brain through the vagus nerve.

Neurotransmitters produced in the gut can also send signals to the brain via the vagus nerve. 5-HT receptors on vagus nerve fibers may facilitate specific pathways in the CNS, and treatment with selective serotonin reuptake inhibitors produced anti-depressive-like effects which depend on vagal fiber activity [118]. A study in patients with refractory epilepsy showed that vagus nerve stimulation was able to prolong alertness [119]. Furthermore, cats exposed to chronic vagus nerve stimulation (VNS) showed increased REM sleep [120]. VNS is able to induce the alteration of neurotransmitter levels such as GABA, 5-HT and norepinephrine [121], which are closely related to sleep-wake behavior. Inflammatory signals in the gut can also travel to the brain via the vagus nerve. Rao et al. showed that the gut microbiota can improve anorexia by preventing IL-1β mediated signaling in the hypothalamus via the vagus nerve [122]. Altogether, these studies indicate that a wide variety of signals from the gut pass through the vagal pathway to impact sleep.

6.3. Immune pathways for gut microbiota and sleep interactions

As the body's largest immunological organ**,** the gastrointestinal tract is vital for maintaining health [123] and the gut-vascular barrier prevents harmful substances in the gut lumen from entering the blood circulation [124]. Intestinal tissue holds a large number of immune cells (such as macrophages, dendritic cells, and natural killer cells). Moreover, $CD4^+$ effector cells (Th17 cells) and regulatory T cells can migrate to extraintestinal organs in the

adaptive immune system (Fig. 3). All these processes work together to support intestinal immune balance [125].

Sleep and immune system activity are bidirectionally linked [126]. Recently, abnormal diversity of the microbiota and IL-6 levels in the nasal cavity was found in patients with OSA, and high IL-6 levels in nasal lavage were associated with increased abundance of *Moraxella* [127]. Moreover, patients with primary insomnia showed an increase of IL-6 levels compared with healthy individuals [128]. Our earlier study showed that transplantation of gut bacteria from sleep deprived humans into GF recipient mice induced an increase of serum IL-6 levels [7]. Growing evidence shows that cytokines can influence sleep architecture. Administration of IL-6 can prolong NREM sleep in rats [129]. In humans, total microbiome diversity was positively related to IL-6 and total sleep time [38]. Lipopolysaccharide, a class of heterogeneous glycolipids, is rich in the cell envelope of Gram-negative bacteria [130]. Lipopolysaccharide administration increased NREM sleep in mice, which is partly mediated by IL-6 [131]. These findings suggest that the bidirectional relationship between the microbiome and sleep may be mediated by immune system. Further experiments are needed to explore causal links between microbiota-dependent inflammatory response and sleep.

Gut microbiota can affect the permeability of the blood-brain barrier and intestinal barrier permeability [132], which may result in intestinal immune cells and pathogens of the gut lumen entering the CNS. An earlier study demonstrated that the decrease of mRNA expression levels of tight junction proteins in a rat OSA model [133], which result in disruption of gut barrier function. Khalyfa et al. found that plasma extracellular vesicles can disrupt BBB in children with OSA [134] (Fig. 2A). Sleep deprivation also can result in disruption of BBB permeability and increase saliva cortisol level, which may be linked to HPA axis activation [7,135]. Stress is one of the main factors causing insomnia [136], Xu et al. reported that stress could influence intestinal barrier permeability and activate T helper-17 (Th17) cells of the intestinal [137]. Together, these studies suggest that the increase of intestinal barrier permeability can result in proliferation of inflammation. However, further work is needed to show whether the disruption of brain barrier and intestinal barrier can affect sleep architecture.

7. Microbiota-targeted interventions for improving sleep

Gut microbes play an important role in maintaining the mental health of the body through the brain-gut axis. Gut microbiota-targeted interventions through different strategies have been shown to exert a therapeutic effect in different conditions. Traditional sleep medications usually have a series of side effects. There is an urgent need to develop a new strategy to treat sleep disorders. Microbiota-targeted interventions (probiotics/prebiotics/synbiotics/postbiotics/FMT) may be promising novel strategies for the management of sleep disorders (Fig. 4, Supplemental Table 1).

7.1. Probiotics

In recent years, probiotics, types of live bacteria that help keep you healthy, have received extensive attention from scientific researchers and biological companies. Lin et al. sifted out a specific *Lactobacillus fermentum* strain (named PS150^{TM}), which was able to improve sleep in the caffeine-induced sleep disturbance in mice [138]. Moreover, PS150^{TM} increased NREM sleep length during a first night effect in mice [139]. Matsuda et al. reported that oral administration of ergothioneine, a metabolite of *Lactobacillus reuteri*, increased REM sleep duration in a rat depression model [140]. Dietary prebiotics improved sleep quality in a rat stress-induced depression model [141]. Administration of probiotics, either *Lactobacillus acidophilus* (DDS-1) or *Bifidobacterium animalis* subsp. *Lactis* (UABla-12), protect against stress caused by night shifts, which may be probably via regulating inflammation [142]. Production of *Lactobacillus brevis* ProGA28 increased the EEG power density of delta percentages and attenuated stress-related sleep disturbance in cage exchange paradigms [143]. Future studies should investigate the efficacy of microbial-based therapies in insomnia, circadian clock misalignment, shift experience, jet lag and other sleep disorders.

7.2. Prebiotics

Prebiotics are nondigestible compounds the metabolism of which can regulate the composition and activity of microorganisms and produce beneficial physiological effects on the host [144]. Dietary prebiotics improved NREM sleep by modulating specific metabolites of gut microbiota in rats [145]. They also increased the relative abundances of *Parabacteroides distasonis* and *Ruminiclostridium 5*, moreover, *Ruminiclostridium 5* and cholic acid were linked to core body temperature realignment rhythms after light/dark reversal in rats [146]. Bowers et al. found that a prebiotic diet was able to prolong NREM and REM sleep in rats, and the relative abundance of *P. distasonis* may play an important role in mediating the sleep-promoting effects of the prebiotic diet [147]. A double-blind randomized study showed that early-life supplementation of a prebiotic blend prolonged latency to nap and maintained daytime waking state in infants; an effect mediated by alterations in gut microbiota [148]. Taken together, these studies suggest the potential of prebiotics for the treatment of sleep disorders.

7.3. Synbiotics

Synbiotics are mixtures of probiotics and prebiotics [149]. Sleep loss is common in military field training, and soldiers typically experience sleep loss and sleepiness during and after field training. Valle et al. found that synbiotic ice cream helped resistance to sleepiness during field training, which may be associated with alteration of melatonin metabolism in gut microbiota [150]. Further work is needed to assess the therapeutic effect of synbiotics on sleep and sleep disorders.

7.4. Postbiotics

Postbiotics are preparations of inanimate microorganisms and/or their components that confer a health benefit on the host [151]. Nishida et al. found that administration of heat-inactivated *Lactobacillus gasseri* CP2305 for 24 weeks significantly improved sleep disturbance in chronically stressed students. Compared with other strategies targeting microorganisms, postbiotics are safer as they have no biological activity [152]. As with synbiotics, there is lack of sufficient evidence to evaluate the effects of postbiotics on sleep.

7.5. FMT

FMT is an approach that transfers an entire microbial consortium into the intestinal tract of a recipient to treat a disease [153]. A recent systematic review reported that FMT improved autism-related symptoms including irritability, hyperactivity, and lethargy in patients with ASD [154]. Kurokawa et al. found that sleep related symptoms may be improved by FMT in patients with irritable bowel syndrome [155]. Nevertheless, how to screen a proper recipient-donor match, and how to develop the time and frequency of FMT need to be fully explored, standardized, and optimized to ensure its efficacy and the safety.

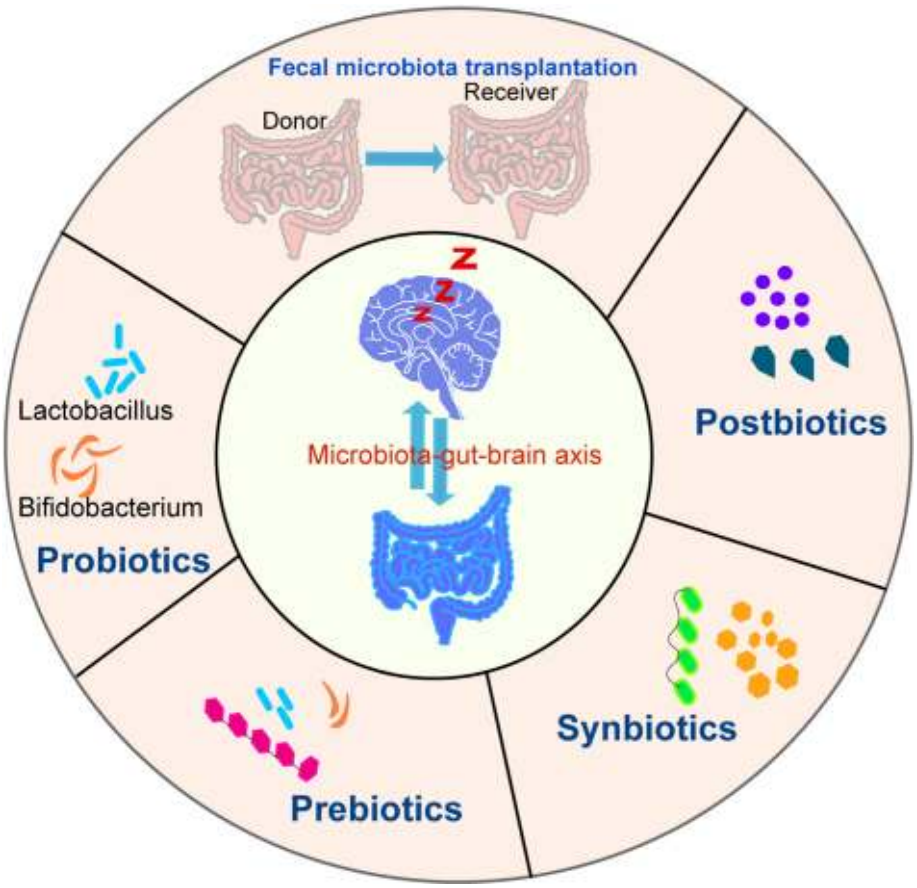

Fig. 4. Proposed microbiota-targeted interventions for improving sleep. Five treatments that intervene gut microbiota directly are depicted. These microbiota-targeted interventions including probiotics, prebiotics, postbiotics, synbiotics, as well as fecal microbiota transplantation. Microbiota-targeted interventions can improve sleep though regulating the microbiota-gut-brain axis and could be promising treatments for sleep disorders.

8. Conclusions and perspectives

This review provides an overview of human and animal studies describing gut microbiota alterations in distinct conditions, including sleep disturbances, sleep disorders and sleep disorders comorbid with neuropsychiatric disorders. Over the last few decades there has been considerable progress in understanding of the interaction between sleep and gut microbiota. Gut microbiota regulates sleep-wake behavior via modulating bacterial metabolites, endocrine signaling, neuronal signaling and immune responses. Sleep loss induces gut microbiota dysbiosis and sleep disorders both reliably correlate with alteration of gut microbiome composition. Experimental studies have explored new avenues to treat sleep disorders by targeting the gut microbiota. However, great challenges remain for this field to yield viable therapeutic approaches to improving sleep.

Current evidence regarding to the association between gut microbiota and sleep disorders is limited to small sample size studies. Larger sample-size studies are needed to draw more reliable conclusions. The biomedical research community now faces the challenge of the expense and complexity of good manufacturing practice facilities for the development of microbiota-targeted therapeutics. For FMTs in treating diseases, what constitutes a 'healthy' microbiome and the selection criteria need to be established. With the launching of nation-wide microbiome initiatives, multi-national cohort studies also necessitate common criteria. Building international and cross-cultural research teams to work in this space will accelerate the development of microbiome-based treatments. These endeavors will also expand our recognition of geographic variability in the microbiome. Using microbial sequencing and microbial cultivation technology, future studies will have the ability to screen and classify the microbiota as wake bacteria, NREM sleep bacteria and REM sleep bacteria. In addition, the mechanistic pathway of gut microbes involved in sleep regulation is unclear. One path may involve direct impact on sleep through the vagus nerve, while indirect impact on sleep may occur through endocrine, metabolic, and immune pathways.

New techniques that can realize real-time molecule marking and monitoring of gut-brain communication need to be developed. Additionally, pre-clinical studies cannot be limited to GF or AIMD mice, as sleep-wake characteristics in mice are different from humans. Thus, GF models in non-rodents such as dogs, pigs, or primates should be established, which will help shed light on the role of microbes in sleep, health, and disease. Although a few studies have advocated the use of gut microbes as an adjunct diagnostic reference for disease, clinical studies are also needed to develop evidence-based guidelines for the auxiliary diagnosis of sleep disorders. Additionally, there remains the need for developing new techniques that could edit the microbiome in a more precise way.

Notably, optogenetic methods have been used to accurately control the bacterial gene expression in microorganisms. Previous study demonstrated that optogenetics could achieve quantitative and temporal control of gut bacterial metabolism to promote longevity [156]. Optogenetic control of microbes could be beneficial to discover specific microbial species in sleep/wake regulation and

facilitate the clinical application of engineered microbial therapeutics to regulate host health. A further consideration is that genetic manipulation of bacteria residing in the gut is a novel strategy for microbial-based disease treatment. Construction of engineering symbiotic bacteria for producing desired metabolites or compounds might have promising implications for treating sleep disorders.

The fields of sleep medicine and microbiology, along with transcriptomics, metabolomics, and other disciplines, need multidisciplinary collaboration to elucidate the exact mechanism of the microbiota-gut-brain axis. Clinical studies that aim at ensuring the efficacy and safety of therapeutic strategies are a must. Development of new strategies that target the gut microbiota may well provide effective therapeutic options for sleep disorders and other neuropsychiatric disorders.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Practice points

1. Signals from the peripheral tissues can affect sleep-wake cycle, and depletion of gut microbiota induces marked changes in behaviors relevant to mood and sleep.
2. Sleep plays a critical role in the maintenance of microbial homeostasis, sleep loss disrupts gut microbiota diversity and function, and gut microbiota composition was altered in patients with sleep disorders.
3. The microbiota-gut-brain axis carries the bi-directional communications between the microbiota and the brain in the pathophysiology of sleep disorders. Sleep-microbiome interactions can be achieved through metabolic, endocrine, immune, and neural pathways.
4. Gut microbiota-targeted interventions may prove to be viable approaches to improve sleep and treat sleep disorders.

Research agenda

1. Methodology in both animal and human studies evaluating of the effects of sleep loss (sleep deprivation or sleep restriction) and sleep disorders on the composition of gut microbiota needs to be standardized and critically controlled.
2. Which metabolites of gut microbiota are involved in sleep regulation and how these metabolites cross the intestinal barrier and blood-brain barrier and enter the brain to regulate sleep should be explored.
3. Manipulating the gut microbiome could be a promising avenue for developing novel therapeutic strategies to improve sleep. More and better sleep psychobiotics needed to be developed.
4. Future investigations are needed to identify the specific microbiota that can promote wake, NREM sleep and REM sleep, respectively.

Acknowledgements

This work was supported in part by the Chinese National Programs for Brain Science and Brain-like Intelligence Technology (no. 2021ZD0200800), and PKU-Baidu Fund (no. 2020BD011).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.smrv.2022.101691.

References

[1] Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 2015;66:143–72.
[2] Ford ES, Cunningham TJ, Giles WH, Croft JB. Trends in insomnia and excessive daytime sleepiness among U.S. adults from 2002 to 2012. Sleep Med 2015;16:372–8.
[3] Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults–United States, 2014. MMWR Morb Mortal Wkly Rep 2016;65:137–41.
[4] Huang T, Mariani S, Redline S. Sleep irregularity and risk of cardiovascular events: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol 2020;75:991–9.
[5] Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. Metabolism 2018;84:56–66.
[6] Shi L, Chen SJ, Ma MY, Bao YP, Han Y, Wang YM, et al. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. Sleep Med Rev 2018;40:4–16.
[7] * Wang Z, Chen WH, Li SX, He ZM, Zhu WL, Ji YB, et al. Gut microbiota modulates the inflammatory response and cognitive impairment induced by sleep deprivation. Mol Psychiatr 2021;26:6277–92.
[8] Malhotra RK. Neurodegenerative disorders and sleep. Sleep Med Clin 2018;13:63–70.
[9] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257–63.
[10] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 2016;14:e1002533.
[11] Dong TS, Gupta A. Influence of early life, diet, and the environment on the microbiome. Clin Gastroenterol Hepatol 2019;17:231–42.
[12] Morais LH, Schreiber HLt, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. Nat Rev Microbiol 2021;19:241–55.
[13] Agrawal R, Ajami NJ, Malhotra S, Chen L, White DL, Sharafkhaneh A, et al. Habitual sleep duration and the colonic mucosa-associated gut microbiota in humans-a pilot study. Clocks Sleep 2021;3:387–97.
[14] Ogawa Y, Miyoshi C, Obana N, Yajima K, Hotta-Hirashima N, Ikkyu A, et al. Gut microbiota depletion by chronic antibiotic treatment alters the sleep/wake architecture and sleep EEG power spectra in mice. Sci Rep 2020;10:19554.
[15] * Matenchuk BA, Mandhane PJ, Kozyrskyj AL. Sleep, circadian rhythm, and gut microbiota. Sleep Med Rev 2020;53:101340.
[16] Sen P, Molinero-Perez A, O'Riordan KJ, McCafferty CP, O'Halloran KD, Cryan JF. Microbiota and sleep: awakening the gut feeling. Trends Mol Med 2021;27(10):935–45.
[17] Han M, Yuan S, Zhang J. The interplay between sleep and gut microbiota. Brain Res Bull 2022;180:131–46.
[18] Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. Cell Mol Gastroenterol Hepatol 2018;6:133–48.
[19] Cirelli C, Tononi G. Is sleep essential? PLoS Biol 2008;6:e216.
[20] Logan RW, McClung CA. Rhythms of life: circadian disruption and brain disorders across the lifespan. Nat Rev Neurosci 2019;20:49–65.
[21] Patton AP, Hastings MH. The suprachiasmatic nucleus. Curr Biol 2018;28:R816–22.
[22] Brancaccio A, Tabarelli D, Bigica M, Baldauf D. Cortical source localization of sleep-stage specific oscillatory activity. Sci Rep 2020;10:6976.
[23] Dang-Vu TT, Schabus M, Desseilles M, Albouy G, Boly M, Darsaud A, et al. Spontaneous neural activity during human slow wave sleep. Proc Natl Acad Sci U S A 2008;105:15160–5.
[24] Yoshikawa T, Nakamura T, Yanai K. Histaminergic neurons in the tuberomammillary nucleus as a control centre for wakefulness. Br J Pharmacol 2021;178:750–69.
[25] Yamashita T, Yamanaka A. Lateral hypothalamic circuits for sleep-wake control. Curr Opin Neurobiol 2017;44:94–100.
[26] Anaclet C, Ferrari L, Arrigoni E, Bass CE, Saper CB, Lu J, et al. The GABAergic parafacial zone is a medullary slow wave sleep-promoting center. Nat Neurosci 2014;17:1217–24.
[27] Saito YC, Maejima T, Nishitani M, Hasegawa E, Yanagawa Y, Mieda M, et al. Monoamines inhibit GABAergic neurons in ventrolateral preoptic area that make direct synaptic connections to hypothalamic arousal neurons. J Neurosci 2018;38:6366–78.

[28] Van Dort CJ, Zachs DP, Kenny JD, Zheng S, Goldblum RR, Gelwan NA, et al. Optogenetic activation of cholinergic neurons in the PPT or LDT induces REM sleep. Proc Natl Acad Sci U S A 2015;112:584–9.
[29] Luthi A. Sleep: switching off the off-switch. Curr Biol 2016;26:R765–7.
[30] Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. J Clin Endocrinol Metab 2005;90:3106–14.
[31] Hunsley MS, Palmiter RD. Altered sleep latency and arousal regulation in mice lacking norepinephrine. Pharmacol Biochem Behav 2004;78:765–73.
[32] Strandwitz P. Neurotransmitter modulation by the gut microbiota. Brain Res 2018;1693:128–33.
[33] Kelsey CM, Prescott S, McCulloch JA, Trinchieri G, Valladares TL, Dreisbach C, et al. Gut microbiota composition is associated with newborn functional brain connectivity and behavioral temperament. Brain Behav Immun 2021;91:472–86.
[34] Firestein MR, Myers MM, Austin J, Stark RI, Barone JL, Ludwig RJ, et al. Perinatal antibiotics alter preterm infant EEG and neurobehavior in the Family Nurture Intervention trial. Dev Psychobiol 2019;61:661–9.
[35] Liu G, Yu Q, Tan B, Ke X, Zhang C, Li H, et al. Gut dysbiosis impairs hippocampal plasticity and behaviors by remodeling serum metabolome. Gut Microb 2022;14:2104089.
[36] * Schoch SF, Castro-Mejia JL, Krych L, Leng B, Kot W, Kohler M, et al. From alpha diversity to Zzz: interactions among sleep, the brain, and gut microbiota in the first year of life. Prog Neurobiol 2021:102208.
[37] Wang Y, van de Wouw M, Drogos L, Vaghef-Mehrabani E, Reimer RA, Tomfohr-Madsen L, et al. Sleep and the gut microbiota in preschool aged children. Sleep 2022.
[38] Smith RP, Easson C, Lyle SM, Kapoor R, Donnelly CP, Davidson EJ, et al. Gut microbiome diversity is associated with sleep physiology in humans. PLoS One 2019;14:e0222394.
[39] Reutrakul S, So-Ngern A, Chirakalwasan N, Saetung S, Chanprasertyothin S, Thakkinstian A, et al. No changes in gut microbiota after two-week sleep extension in chronically sleep-deprived individuals. Sleep Med 2020;68:27–30.
[40] Cai H, Wang C, Qian Y, Zhang S, Zhang C, Zhao W, et al. Large-scale functional network connectivity mediate the associations of gut microbiota with sleep quality and executive functions. Hum Brain Mapp 2021;42:3088–101.
[41] Silva V, Palacios-Munoz A, Okray Z, Adair KL, Waddell S, Douglas AE, et al. The impact of the gut microbiome on memory and sleep in Drosophila. J Exp Biol 2021:224.
[42] Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. Cell 2014;159:514–29.
[43] Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. J Sleep Res 2016;25:131–43.
[44] Liu Z, Wei ZY, Chen J, Chen K, Mao X, Liu Q, et al. Acute sleep-wake cycle shift results in community alteration of human gut microbiome. mSphere 2020;5.
[45] Hong F, Pan S, Xu P, Xue T, Wang J, Guo Y, et al. Melatonin orchestrates lipid homeostasis through the hepatointestinal circadian clock and microbiota during constant light exposure. Cells 2020;9.
[46] Li Q, Wang B, Qiu HY, Yan XJ, Cheng L, Wang QQ, et al. Chronic jet lag exacerbates jejunal and colonic microenvironment in mice. Front Cell Infect Microbiol 2021;11:648175.
[47] Carasso S, Fishman B, Lask LS, Shochat T, Geva-Zatorsky N, Tauber E. Metagenomic analysis reveals the signature of gut microbiota associated with human chronotypes. Faseb J 2021;35:e22011.
[48] Song D, Ho CT, Zhang X, Wu Z, Cao J. Modulatory effect of cyclocarya paliurus flavonoids on the intestinal microbiota and liver clock genes of circadian rhythm disorder mice model. Food Res Int 2020;138:109769.
[49] Northeast RC, Vyazovskiy VV, Bechtold DA. Eat, sleep, repeat: the role of the circadian system in balancing sleep-wake control with metabolic need. Curr Opin Physiol 2020;15:183–91.
[50] Bishehsari F, Engen PA, Adnan D, Sarrafi S, Wilber S, Shaikh M, et al. Abnormal food timing and predisposition to weight gain: role of barrier dysfunction and microbiota. Transl Res 2021;231:113–23.
[51] Nobs SP, Tuganbaev T, Elinav E. Microbiome diurnal rhythmicity and its impact on host physiology and disease risk. EMBO Rep 2019;20.
[52] Wang H, Zhang H, Su Y. New insights into the diurnal rhythmicity of gut microbiota and its crosstalk with host circadian rhythm. Animals 2022;12:1677.
[53] Wang Z, Yuan K, Ji Y-B, Li S-X, Shi L, Wang Z, et al. Alterations of the gut microbiota in response to total sleep deprivation and recovery sleep in rats. Nat Sci Sleep 2022;14:121–33.
[54] Triplett J, Ellis D, Braddock A, Roberts E, Ingram K, Perez E, et al. Temporal and region-specific effects of sleep fragmentation on gut microbiota and intestinal morphology in Sprague Dawley rats. Gut Microb 2020;11:706–20.
[55] * Maki KA, Burke LA, Calik MW, Watanabe-Chailland M, Sweeney D, Romick-Rosendale LE, et al. Sleep fragmentation increases blood pressure and is associated with alterations in the gut microbiome and fecal metabolome in rats. Physiol Genom 2020;52:280–92.
[56] Patel SR. Obstructive sleep apnea. Ann Intern Med 2019;171:ITC81–96.
[57] Valentini F, Evangelisti M, Arpinelli M, Di Nardo G, Borro M, Simmaco M, et al. Gut microbiota composition in children with obstructive sleep apnoea syndrome: a pilot study. Sleep Med 2020;76:140–7.
[58] Ko CY, Liu QQ, Su HZ, Zhang HP, Fan JM, Yang JH, et al. Gut microbiota in obstructive sleep apnea-hypopnea syndrome: disease-related dysbiosis and metabolic comorbidities. Clin Sci 2019;133:905–17.
[59] * Badran M, Khalyfa A, Ericsson A, Gozal D. Fecal microbiota transplantation from mice exposed to chronic intermittent hypoxia elicits sleep disturbances in naive mice. Exp Neurol 2020;334:113439.
[60] Khalyfa A, Ericsson A, Qiao Z, Almendros I, Farre R, Gozal D. Circulating exosomes and gut microbiome induced insulin resistance in mice exposed to intermittent hypoxia: effects of physical activity. EBioMedicine 2021;64:103208.
[61] Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol 2015;14:547–58.
[62] Liu B, Lin W, Chen S, Xiang T, Yang Y, Yin Y, et al. Gut Microbiota as an objective measurement for auxiliary diagnosis of insomnia disorder. Front Microbiol 2019;10:1770.
[63] Li Y, Zhang B, Zhou Y, Wang D, Liu X, Li L, et al. Gut microbiota changes and their relationship with inflammation in patients with acute and chronic insomnia. Nat Sci Sleep 2020;12:895–905.
[64] Feng Y, Fu S, Li C, Ma X, Wu Y, Chen F, et al. Interaction of gut microbiota and brain function in patients with chronic insomnia: a regional homogeneity study. Front Neurosci 2021;15:804843.
[65] Wang H, Qin X, Gui Z, Chu W. The effect of Bailemian on neurotransmitters and gut microbiota in p-chlorophenylalanine induced insomnia mice. Microb Pathog 2020;148:104474.
[66] Hong J, Chen J, Kan J, Liu M, Yang D. Effects of acupuncture treatment in reducing sleep disorder and gut microbiota alterations in PCPA-induced insomnia mice. Evid Based Complement Alternat Med 2020;2020:3626120.
[67] Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, et al. GABA-modulating bacteria of the human gut microbiota. Nat Microbiol 2019;4:396–403.
[68] Barcik W, Pugin B, Westermann P, Perez NR, Ferstl R, Wawrzyniak M, et al. Histamine-secreting microbes are increased in the gut of adult asthma patients. J Allergy Clin Immunol 2016;138:1491–1494 e7.
[69] Steele TA, St Louis EK, Videnovic A, Auger RR. Circadian rhythm sleep-wake disorders: a contemporary review of neurobiology, treatment, and dysregulation in neurodegenerative disease. Neurotherapeutics 2021;18:53–74.
[70] Mortas H, Bilici S, Karakan T. The circadian disruption of night work alters gut microbiota consistent with elevated risk for future metabolic and gastrointestinal pathology. Chronobiol Int 2020;37:1067–81.
[71] Voigt RM, Summa KC, Forsyth CB, Green SJ, Engen P, Naqib A, et al. The circadian clock mutation promotes intestinal dysbiosis. Alcohol Clin Exp Res 2016;40:335–47.
[72] Potter GD, Skene DJ, Arendt J, Cade JE, Grant PJ, Hardie LJ. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. Endocr Rev 2016;37:584–608.
[73] Pandi-Perumal SR, Trakht I, Spence DW, Srinivasan V, Dagan Y, Cardinali DP. The roles of melatonin and light in the pathophysiology and treatment of circadian rhythm sleep disorders. Nat Clin Pract Neurol 2008;4:436–47.
[74] Zhang Q, Yun Y, An H, Zhao W, Ma T, Wang Z, et al. Gut microbiome composition associated with major depressive disorder and sleep quality. Front Psychiatr 2021;12:645045.
[75] Ma W, Song J, Wang H, Shi F, Zhou N, Jiang J, et al. Chronic paradoxical sleep deprivation-induced depression-like behavior, energy metabolism and microbial changes in rats. Life Sci 2019;225:88–97.
[76] * Hua X, Zhu J, Yang T, Guo M, Li Q, Chen J, et al. The gut microbiota and associated metabolites are altered in sleep disorder of children with autism spectrum disorders. Front Psychiatr 2020;11:855.
[77] Wang HB, Tahara Y, Luk SHC, Kim YS, Hitchcock ON, MacDowell Kaswan ZA, et al. Melatonin treatment of repetitive behavioral deficits in the Cntnap2 mouse model of autism spectrum disorder. Neurobiol Dis 2020;145:105064.
[78] Heintz-Buschart A, Pandey U, Wicke T, Sixel-Doring F, Janzen A, Sittig-Wiegand E, et al. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. Mov Disord 2018;33:88–98.
[79] Wang C, Holtzman DM. Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. Neuropsychopharmacology 2020;45:104–20.
[80] Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. Sci China Life Sci 2016;59:1006–23.
[81] * Sugden D, Davidson K, Hough KA, Teh MT. Melatonin, melatonin receptors and melanophores: a moving story. Pigm Cell Res 2004;17:454–60.
[82] Ma N, Zhang J, Reiter RJ, Ma X. Melatonin mediates mucosal immune cells, microbial metabolism, and rhythm crosstalk: a therapeutic target to reduce intestinal inflammation. Med Res Rev 2020;40:606–32.
[83] Gao T, Wang Z, Cao J, Dong Y, Chen Y. Melatonin attenuates microbiota dysbiosis of jejunum in short-term sleep deprived mice. J Microbiol 2020;58:588–97.
[84] Gao T, Wang Z, Dong Y, Cao J, Lin R, Wang X, et al. Role of melatonin in sleep deprivation-induced intestinal barrier dysfunction in mice. J Pineal Res 2019;67:e12574.
[85] Paulose JK, Cassone VM. The melatonin-sensitive circadian clock of the enteric bacterium Enterobacter aerogenes. Gut Microb 2016;7:424–7.
[86] Luppi PH, Peyron C, Fort P. Not a single but multiple populations of GABAergic neurons control sleep. Sleep Med Rev 2017;32:85–94.

[87] Zhang X, Liu Y, Hong X, Li X, Meshul CK, Moore C, et al. NG2 glia-derived GABA release tunes inhibitory synapses and contributes to stress-induced anxiety. Nat Commun 2021;12:5740.
[88] Kay-Stacey M, Attarian H. Advances in the management of chronic insomnia. BMJ 2016;354:i2123.
[89] Lai Y, Liu CW, Yang Y, Hsiao YC, Ru H, Lu K. High-coverage metabolomics uncovers microbiota-driven biochemical landscape of interorgan transport and gut-brain communication in mice. Nat Commun 2021;12:6000.
[90] Duranti S, Ruiz L, Lugli GA, Tames H, Milani C, Mancabelli L, et al. Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Sci Rep 2020;10:14112.
[91] Nobile V, Giardina S, Puoci F. The Effect of a probiotic complex on the gut-brain axis: a translational study. Neuropsychobiology 2021:1–11.
[92] Bacqué-Cazenave J, Bharatiya R, Barrière G, Delbecque J-P, Bouguiyoud N, Di Giovanni G, et al. Serotonin in animal cognition and behavior. Int J Mol Sci 2020:21.
[93] Hata T, Asano Y, Yoshihara K, Kimura-Todani T, Miyata N, Zhang XT, et al. Regulation of gut luminal serotonin by commensal microbiota in mice. PLoS One 2017;12:e0180745.
[94] * Fung TC, Vuong HE, Luna CDG, Pronovost GN, Aleksandrova AA, Riley NG, et al. Intestinal serotonin and fluoxetine exposure modulate bacterial colonization in the gut. Nat Microbiol 2019;4:2064–73.
[95] Li H, Wang P, Huang L, Li P, Zhang D. Effects of regulating gut microbiota on the serotonin metabolism in the chronic unpredictable mild stress rat model. Neuro Gastroenterol Motil 2019;31:e13677.
[96] Yao C, Wang Z, Jiang H, Yan R, Huang Q, Wang Y, et al. Ganoderma lucidum promotes sleep through a gut microbiota-dependent and serotonin-involved pathway in mice. Sci Rep 2021;11:13660.
[97] Voisin T, Rouet-Benzineb P, Reuter N, Laburthe M. Orexins and their receptors: structural aspects and role in peripheral tissues. Cell Mol Life Sci 2003;60:72–87.
[98] Ehrstrom M, Gustafsson T, Finn A, Kirchgessner A, Gryback P, Jacobsson H, et al. Inhibitory effect of exogenous orexin a on gastric emptying, plasma leptin, and the distribution of orexin and orexin receptors in the gut and pancreas in man. J Clin Endocrinol Metab 2005;90:2370–7.
[99] Latorre R, Sternini C, De Giorgio R, Greenwood-Van Meerveld B. Enteroendocrine cells: a review of their role in brain-gut communication. Neuro Gastroenterol Motil 2016;28:620–30.
[100] Willie JT, Chemelli RM, Sinton CM, Yanagisawa M. To eat or to sleep? Orexin in the regulation of feeding and wakefulness. Annu Rev Neurosci 2001;24:429–58.
[101] Dauvilliers Y, Zammit G, Fietze I, Mayleben D, Seboek Kinter D, Pain S, et al. Daridorexant, a new dual orexin receptor antagonist to treat insomnia disorder. Ann Neurol 2020;87:347–56.
[102] Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev 2008;88:1183–241.
[103] Zisapel N. Current Phase II investigational therapies for insomnia. Expet Opin Invest Drugs 2015;24:401–11.
[104] Carley AN, Maurya SK, Fasano M, Wang Y, Selzman CH, Drakos SG, et al. Short-chain fatty acids outpace ketone oxidation in the failing heart. Circulation 2021;143:1797–808.
[105] Colombo AV, Sadler RK, Llovera G, Singh V, Roth S, Heindl S, et al. Microbiota-derived short chain fatty acids modulate microglia and promote Abeta plaque deposition. Elife 2021:10.
[106] * Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 1987;28:1221–7.
[107] Zarrinpar A, Chaix A, Xu ZZ, Chang MW, Marotz CA, Saghatelian A, et al. Antibiotic-induced microbiome depletion alters metabolic homeostasis by affecting gut signaling and colonic metabolism. Nat Commun 2018;9:2872.
[108] Heath AM, Haszard JJ, Galland BC, Lawley B, Rehrer NJ, Drummond LN, et al. Association between the faecal short-chain fatty acid propionate and infant sleep. Eur J Clin Nutr 2020;74:1362–5.
[109] Magzal F, Even C, Haimov I, Agmon M, Asraf K, Shochat T, et al. Associations between fecal short-chain fatty acids and sleep continuity in older adults with insomnia symptoms. Sci Rep 2021;11:4052.
[110] Szentirmai E, Millican NS, Massie AR, Kapas L. Butyrate, a metabolite of intestinal bacteria, enhances sleep. Sci Rep 2019;9:7035.
[111] Grosicki GJ, Riemann BL, Flatt AA, Valentino T, Lustgarten MS. Self-reported sleep quality is associated with gut microbiome composition in young, healthy individuals: a pilot study. Sleep Med 2020;73:76–81.
[112] Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Front Neurosci 2018;12:49.
[113] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A 2011;108:16050–5.
[114] Venner A, Todd WD, Fraigne J, Bowrey H, Eban-Rothschild A, Kaur S, et al. Newly identified sleep-wake and circadian circuits as potential therapeutic targets. Sleep 2019;42.
[115] Nutt DJ, Stahl SM. Searching for perfect sleep: the continuing evolution of GABAA receptor modulators as hypnotics. J Psychopharmacol 2010;24:1601–12.
[116] Sgritta M, Dooling SW, Buffington SA, Momin EN, Francis MB, Britton RA, et al. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. Neuron 2019;101:246–259 e6.
[117] Eban-Rothschild A, Rothschild G, Giardino WJ, Jones JR, de Lecea L. VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors. Nat Neurosci 2016;19:1356–66.
[118] McVey Neufeld KA, Bienenstock J, Bharwani A, Champagne-Jorgensen K, Mao Y, West C, et al. Oral selective serotonin reuptake inhibitors activate vagus nerve dependent gut-brain signalling. Sci Rep 2019;9:14290.
[119] Rizzo P, Beelke M, De Carli F, Canovaro P, Nobili L, Robert A, et al. Chronic vagus nerve stimulation improves alertness and reduces rapid eye movement sleep in patients affected by refractory epilepsy. Sleep 2003;26:607–11.
[120] Valdes-Cruz A, Magdaleno-Madrigal VM, Martinez-Vargas D, Fernandez-Mas R, Almazan-Alvarado S, Martinez A, et al. Chronic stimulation of the cat vagus nerve: effect on sleep and behavior. Prog Neuro-Psychopharmacol Biol Psychiatry 2002;26:113–8.
[121] Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci 2007;10:1116–24.
[122] Rao S, Schieber AMP, O'Connor CP, Leblanc M, Michel D, Ayres JS. Pathogen-mediated inhibition of anorexia promotes host survival and transmission. Cell 2017;168:503–516 e12.
[123] Zhou CB, Zhou YL, Fang JY. Gut microbiota in cancer immune response and immunotherapy. Trends Cancer 2021;7:647–60.
[124] Spadoni I, Zagato E, Bertocchi A, Paolinelli R, Hot E, Di Sabatino A, et al. A gut-vascular barrier controls the systemic dissemination of bacteria. Science 2015;350:830–4.
[125] Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res 2020;30:492–506.
[126] Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. Physiol Rev 2019;99:1325–80.
[127] Wu BG, Sulaiman I, Wang J, Shen N, Clemente JC, Li Y, et al. Severe obstructive sleep apnea is associated with alterations in the nasal microbiome and an Increase in inflammation. Am J Respir Crit Care Med 2019;199:99–109.
[128] Burgos I, Richter L, Klein T, Fiebich B, Feige B, Lieb K, et al. Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. Brain Behav Immun 2006;20:246–53.
[129] Hogan D. Interleukin-6 alters sleep of rats. J Neuroimmunol 2003;137:59–66.
[130] Kutschera A, Ranf S. The multifaceted functions of lipopolysaccharide in plant-bacteria interactions. Biochimie 2019;159:93–8.
[131] Morrow JD, Opp MR. Diurnal variation of lipopolysaccharide-induced alterations in sleep and body temperature of interleukin-6-deficient mice. Brain Behav Immun 2005;19:40–51.
[132] * Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med 2014;6:263ra158.
[133] Wu J, Sun X, Wu Q, Li H, Li L, Feng J, et al. Disrupted intestinal structure in a rat model of intermittent hypoxia. Mol Med Rep 2016;13:4407–13.
[134] Khalyfa A, Gozal D, Kheirandish-Gozal L. Plasma extracellular vesicles in children with OSA disrupt blood-brain barrier integrity and endothelial cell wound healing in vitro. Int J Mol Sci 2019;20.
[135] Sun J, Wu J, Hua F, Chen Y, Zhan F, Xu G. Sleep deprivation induces cognitive impairment by increasing blood-brain barrier permeability via CD44. Front Neurol 2020;11:563916.
[136] Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev 2021;101:995–1046.
[137] Xu C, Lee SK, Zhang D, Frenette PS. The gut microbiome regulates psychological-stress-induced inflammation. Immunity 2020;53:417–428 e4.
[138] Lin A, Shih CT, Huang CL, Wu CC, Lin CT, Tsai YC. Hypnotic effects of Lactobacillus fermentum PS150(TM) on pentobarbital-induced sleep in mice. Nutrients 2019;11.
[139] Lin A, Shih CT, Chu HF, Chen CW, Cheng YT, Wu CC, et al. Lactobacillus fermentum PS150 promotes non-rapid eye movement sleep in the first night effect of mice. Sci Rep 2021;11:16313.
[140] Matsuda Y, Ozawa N, Shinozaki T, Wakabayashi KI, Suzuki K, Kawano Y, et al. Ergothioneine, a metabolite of the gut bacterium Lactobacillus reuteri, protects against stress-induced sleep disturbances. Transl Psychiatry 2020;10:170.
[141] Thompson RS, Roller R, Mika A, Greenwood BN, Knight R, Chichlowski M, et al. Dietary prebiotics and bioactive milk fractions improve NREM sleep, enhance REM sleep rebound and attenuate the stress-induced decrease in diurnal temperature and gut microbial alpha diversity. Front Behav Neurosci 2016;10:240.
[142] West NP, Hughes L, Ramsey R, Zhang P, Martoni CJ, Leyer GJ, et al. Probiotics, anticipation stress, and the acute immune response to night shift. Front Immunol 2020;11:599547.
[143] Lai CT, Chen CY, She SC, Chen WJ, Kuo TBJ, Lin HC, et al. Production of Lactobacillus brevis ProGA28 attenuates stress-related sleep disturbance and modulates the autonomic nervous system and the motor response in anxiety/depression behavioral tests in Wistar-Kyoto rats. Life Sci 2022;288:120165.
[144] Bindels LB, Delzenne NM, Cani PD, Walter J. Towards a more comprehensive concept for prebiotics. Nat Rev Gastroenterol Hepatol 2015;12:303–10.

[145] Thompson RS, Vargas F, Dorrestein PC, Chichlowski M, Berg BM, Fleshner M. Dietary prebiotics alter novel microbial dependent fecal metabolites that improve sleep. Sci Rep 2020;10:3848.
[146] Thompson RS, Gaffney M, Hopkins S, Kelley T, Gonzalez A, Bowers SJ, et al. Ruminiclostridium 5, Parabacteroides distasonis, and bile acid profile are modulated by prebiotic diet and associate with facilitated sleep/clock realignment after chronic disruption of rhythms. Brain Behav Immun 2021.
[147] Bowers SJ, Summa KC, Thompson RS, Gonzalez A, Vargas F, Olker C, et al. A prebiotic diet alters the fecal microbiome and improves sleep in response to sleep disruption in rats. Front Neurosci 2022;16:889211.
[148] Colombo J, Carlson SE, Algarin C, Reyes S, Chichlowski M, Harris CL, et al. Developmental effects on sleep-wake patterns in infants receiving a cow's milk-based infant formula with an added prebiotic blend: a Randomized Controlled Trial. Pediatr Res 2021;89:1222–31.
[149] Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics- a review. J Food Sci Technol 2015;52:7577–87.
[150] Valle M, Vieira IA, Fino LC, Gallina DA, Esteves AM, da Cunha DT, et al. Immune status, well-being and gut microbiota in military supplemented with synbiotic ice cream and submitted to field training: a randomised clinical trial. Br J Nutr 2021;126:1794–808.
[151] Salminen S, Collado MC, Endo A, Hill C, Lebeer S, Quigley EMM, et al. Publisher correction: publisher correction: the international scientific association of probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nat Rev Gastroenterol Hepatol 2021;18:671.
[152] Nishida K, Sawada D, Kuwano Y, Tanaka H, Rokutan K. Health benefits of Lactobacillus gasseri CP2305 tablets in young adults exposed to chronic stress: a randomized, double-blind, placebo-controlled study. Nutrients 2019;11.
[153] Smits LP, Bouter KE, de Vos WM, Borody TJ, Nieuwdorp M. Therapeutic potential of fecal microbiota transplantation. Gastroenterology 2013;145:946–53.
[154] Tan Q, Orsso CE, Deehan EC, Kung JY, Tun HM, Wine E, et al. Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation in the treatment of behavioral symptoms of autism spectrum disorder: a systematic review. Autism Res 2021;14:1820–36.
[155] Kurokawa S, Kishimoto T, Mizuno S, Masaoka T, Naganuma M, Liang KC, et al. The effect of fecal microbiota transplantation on psychiatric symptoms among patients with irritable bowel syndrome, functional diarrhea and functional constipation: an open-label observational study. J Affect Disord 2018;235:506–12.
[156] Hartsough LA, Park M, Kotlajich MV, Lazar JT, Han B, Lin CJ, et al. Optogenetic control of gut bacterial metabolism to promote longevity. Elife 2020;9.