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Circadian Clock, Sleep, and Diet

Junichiro Irie

Abstract

Circadian rhythm is a fundamental process of sustaining metabolic homeostasis by predicting changes in the environment. This is driven by biological clocks, which operate within a 24-h period to orchestrate daily variation of metabolism and sleep. The central clock in the hypothalamus is the master keeper of the circadian rhythm and is primarily reset by light, while the feeding-fasting rhythm, that is, nutritional stimulus, entrains peripheral clocks in peripheral organs such as the intestine and liver. Nutritional stimuli are important modulators of peripheral circadian rhythms and may affect the central clock and sleep homeostasis through metabolic alterations. In this chapter, I will summarize the significance of circadian rhythm and sleep in metabolic regulation as well as discuss the impact that diet has on circadian rhythm and sleep.

Keywords: circadian rhythm, sleep, clock gene, intestinal microbiota, jet lag

1. Introduction

The term circadian rhythm refers to the natural and internal process that regulates the sleep-wake cycle in all mammals, and repeats about every 24 h, which is almost the same as the rotation of the earth. Circadian rhythm is not only an important mechanism for the sleep-wake cycle, but also for the homeostasis of endocrine and metabolic systems that rely on the body to predict and adapt to changing environments during daytime and nighttime. Since the circadian rhythm is maintained even in the absence of light stimulation, this rhythm is called the “circadian clock” and determines diurnal fluctuations such as blood pressure and body temperature [1]. In mammals, the suprachiasmatic nucleus (SCN) in the hypothalamus of the brain is the master keeper of circadian rhythms, and it also controls the circadian rhythms of other organs. Animals in which the SCN has been damaged are unable to perform circadian activities, and the transplantation of the SCN restores their circadian rhythm. SCN neurons form a network and transmit circadian rhythms by transcription factors CLOCK, BMAL1, and Period (Per) and Cryptochrome (CRY), which suppress their activities.

Although the circadian clock is best known for producing 24-h cycle rhythms in movements, metabolism, and hormones, a circadian rhythm also exists in peripheral organs, including the liver and digestive tract. These rhythms are called peripheral clocks. In addition to the rhythms of clock genes in peripheral organs, nutritional stimuli, such as diet, have also been shown to modulate circadian rhythms in peripheral organs. Furthermore, the circadian rhythms in peripheral organs likely affect the central clocks and *vice versa*.

In this chapter, we will focus on the role that circadian rhythms play in systemic metabolism as well as the role that nutritional stimuli play in circadian rhythm and sleep.

2. The circadian rhythms and metabolic regulation

Circadian rhythms can be found in humans, including a sleep-wake rhythm, an eating-hunger rhythm, and hormonal fluctuations that occur on a roughly 24-h cycle that is synchronized with the light-dark cycle [2]. This rhythm is mainly driven by the biological clock, which in mammals consists of a central clock located in the hypothalamus and a peripheral clock in other organs. Light is the main environmental synchronizer of the central clock, while eating and motion synchronize the peripheral clock. Optical signals are transmitted from the central clock to peripheral organs, such as the skin and muscles, and regulate the circadian rhythm of the cell cycle and insulin sensitivity [3].

In mammals, the circadian clock is mainly tuned by transcription factors called Circadian Locomotor Output Cycles Kaput (CLOCK) and brain and muscle ARNT-like protein-1 (BMAL1), which form a heterodimer and activate transcription of target genes in the light phase [4, 5]. They target genes that suppress biological clocks such as *Per* (Period) and *Cry* (Cryptochrome), which suppress the transcription of CLOCK-BMAL1 in the dark phase [5]. The clock gene circuit is also regulated by the nuclear receptors retinoic acid receptor-related orphan receptor (ROR) and REV-ERB, which regulate *Bmal1* gene expression positively and negatively, respectively. In addition to the transcriptional feedback loop of clock genes, various oscillations of gene expression are modulated by the regulation of transcription factors other than clock genes [6].

Circadian rhythms in the expression of genes and proteins have also been observed in peripheral organs such as the liver and intestine. In fact, approximately 30% of gene expression in the intestinal tract shows a circadian rhythm, and this is also observed in the proliferation of intestinal epithelium and intestinal permeability. A circadian rhythm can also be observed in the blood concentration of triglyceride-rich lipoproteins synthesized in the intestinal tract [7, 8]. Furthermore, clock genes such as *Clock* and *Bmal1* are expressed in the gastrointestinal tract, and their expression is particularly high in the lower gastrointestinal tract and large intestine, with the expression site found mainly in the epithelial layer rather than the mucosal layer [8].

These clock genes affect the functions of the intestine by altering the expression of target genes, such as sodium-glucose cotransporter (SGLT) 1, which is involved in glucose absorption and peptide transporter (PEPT) 1, which is involved in peptide absorption. In mice, the transporter involved in glucose uptake increases in the dark phase, while the peptide transporter increases during the light phase. Similarly, a diurnal variation was observed in lipid absorption, and the number of genes involved in lipid absorption increased in the dark phase. Additionally, it has been reported that in mice with a clock gene mutation, the absorption of sugar, triglyceride, and cholesterol from intestinal contents was higher and the absorption of peptides was lower. In addition to intestinal epithelial cells, enteroendocrine cells, such as ghrelin-producing cells, are also regulated by clock genes such as *Bmal1* and *Per1/2*. For example, in *Bmal1*-deficient mice, no diurnal variation in ghrelin nor diurnal variation in feeding was observed [9, 10]. It has also been reported that a circadian rhythm is observed in the expression of toll-like receptors in the small intestine, which is involved in intestinal immunity [11]. Since diurnal rhythms in the function of the intestine were first observed, it was assumed that they may affect the intestinal microbiota in the intestinal lumen. Recent findings

have revealed that the intestinal microbiota plays a pivotal role in the regulation of host homeostasis [12–16]. Importantly, several groups have reported diurnal oscillations of intestinal microbiota [17–19]. The bacteria belonging to Clostridiales and Lactobacillaceae showed diurnal variation, and at the species level, *Lactobacillus reuteri* decreased and *Dehalobacterium* increased in the dark phase. Along with the diurnal changes in the composition of intestinal bacteria, diurnal fluctuations are also observed in the functions of the microbiota, such as vitamin and nucleic acid metabolism by the bacteria. The functions of DNA repair, cell proliferation, and mucin degradation were dominant in the dark phase, whereas bacterial motility and sensing pathways were dominant in the light phase. The diurnal rhythm in intestinal microbiota was also examined in humans, and it was found that *Parabacteroides* and *Bulleidia* were increased in the daytime and decreased at night, while *Lachnospira* decreased in the daytime and increased in the nighttime. This is consistent with the findings in mice and suggests that there are diurnal rhythms in protein synthesis as it primarily occurs in the daytime.

These findings demonstrate that peripheral organs, including intestinal microbiota, have circadian rhythms and systemically modulate energy homeostasis and metabolism.

3. The nutritional stimuli and circadian rhythms

Metabolic homeostasis is modulated by circadian rhythms, as mentioned above, but nutritional stimuli affect circadian rhythms and vice versa.

Importantly, the circadian rhythm found in gene expression is tissue-specific, and the type and number of oscillating genes differ depending on the type of tissue or cell [20]. Transcriptional factors can define tissue specificities and result in the diversity of chromatin structures, but an oscillation has been reported to be reconstructed by various nutritional stimuli [6, 21–23]. Notably, the molecular mechanism by which metabolic alterations affect circadian rhythms has been investigated intensively. For example, the transcriptional factors SREBP1 and PPARs, which are related to lipid metabolism, are activated periodically by the intake of a high-fat diet, thereby driving the specific oscillation of gene expression [24, 25]. It has also been shown that fluctuations in energy metabolites are deeply involved in transcriptional regulation. Acetyl-CoA is used as an acetylating substrate for histones and clock genes, and NAD modulates the oscillation of gene expression by acting as a coenzyme for sirtuins that deacetylate proteins [26, 27]. The acetylation of histones is also conducted by S-adenosylmethionine (SAM) by the transfer of a methyl donor from SAM. S-adenosylhomocysteine (SAH) is produced from SAM by methyltransferases. Interestingly, the SAH hydrolyzing enzyme binds to clock genes and contributes to the interaction among methionine metabolism, clock gene expression, and chromatin remodeling [28]. These findings indicate the adaptability and plasticity of transcriptional regulation of clock genes, which flexibly respond to metabolic changes, and imply the existence of a circuit in which transcriptional and metabolic rhythms regulate each other.

The impact of the timing of the nutritional stimuli has also been investigated. The exposure of the intestine to the nutrients is fundamental, but bile acids in the intestine secreted from the liver are also reported to be important regulators to elicit circadian rhythms [29]. Importantly, time-restricted feeding (TRF), which limits feeding time, has been reported to be a good method for restoring circadian rhythms by modulating nutritional stimuli. Even when the food had the same amount of energy in this model, if the feeding time was limited to less than nine hours a day (TRF) in comparison with the mice fed ad libitum for 24 h, the suppression of body fat accumulation and

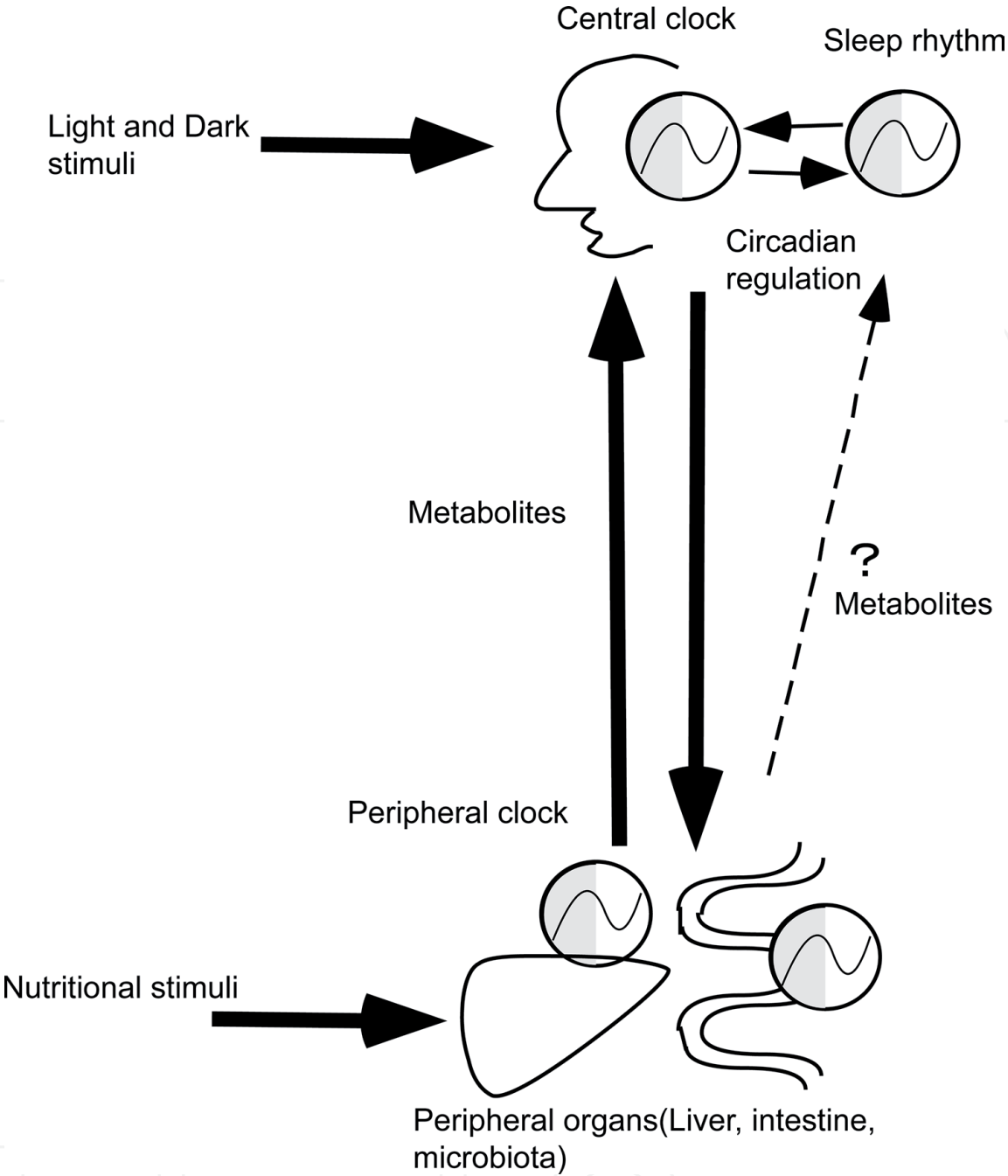


Figure 1. The interaction between the circadian rhythm in the central nervous system (CNS), peripheral organs, and sleep. The central clock in the hypothalamus is the master keeper of circadian rhythm and is primarily entrained by light and dark stimuli, while feeding-fasting rhythm, that is, nutritional stimuli, entrains peripheral clocks in peripheral organs such as the liver and intestine. Sleep rhythm is evoked mainly by the central clock, and disturbed sleep affects the circadian rhythm in the CNS. The rhythm in peripheral organs that is regulated by nutritional stimuli may modulate sleep rhythm.

the improvement of glucose intolerance were observed [30, 31]. In addition, TRF improved the metabolic disarrangement found in various organs, and the circadian rhythm of intestinal bacteria and functions recovered. These findings indicate that nutritional stimuli. That is, diet is an important regulator of circadian rhythm and systemic metabolism (**Figure 1**).

4. The sleep, circadian rhythm, and the intestine

The sleep-wake cycle is a good example of the circadian rhythms found in living organisms that are regulated by many biological and environmental factors.

In humans, sleep regulation is governed by homeostatic mechanisms and circadian rhythms, that is, a two-process model [32, 33]. In this model, sleep is regulated by sleep homeostasis (process S) and circadian rhythm (process C; circadian rhythm) (**Figure 2**). Sleep controlled through homeostasis means that sleep debt increases during wakefulness and decreases with sleep; thus, when the sleep debt reaches the sleep threshold, humans fall asleep and when it reaches the lower limit, humans awaken. It is believed that this threshold is dominated by the circadian rhythm, and diurnal variation is observed (process C). This idea is that daytime awakening and nighttime sleep are determined by the sleep debt that accumulates by continuing to stay awake and drowsiness that is induced by the biological clock. It is understood to be a system that compensates for sleep time in response to changes in the environment while physiologically promoting sleep *via* circadian rhythm.

When mammals sleep, rapid eye movement (REM) sleep and non-rapid eye movement sleep (non-REM sleep) occur in a cycle of about 90 min. When you fall asleep, non-REM sleep appears first. Subsequently, light REM sleep appears. REM sleep is accompanied by rapid eye movements, and the body is in a resting state with relaxed skeletal muscles, but the brain is active and awake. The cerebral cortex is more active than during wakefulness, and electroencephalography (EEG) shows mainly theta waves from 4 to 7 Hz and exhibits an amplitude close to that during awakening. Sleep without REM is called non-REM sleep, and the brain is in the so-called state of deep sleep. Low-frequency, high-amplitude brain waves called delta waves ranging from 1-4 Hz are observed in brain waves, and non-REM sleep is characterized as slow-wave sleep based on EEG findings. However, the molecular mechanism(s) underlying the cyclical changes that occur in non-REM sleep and REM sleep are not yet clear.

Sleep disturbances deteriorate the circadian rhythms across various organs. For example, when mice were subjected to sleep disturbances in which the light and dark phases were changed weekly, the circadian rhythm of *Per2* expression in the large intestine disappeared, and the intestinal microbiota was altered, with increased Firmicutes and decreased Bacteroidetes at the phylum level [34]. Other sleep disorders have been reported to increase intestinal permeability and blood LPS levels [35]. In addition, the effects of interventions that cause sleep disorders using tactile stimulation without changing the cycle of light and dark phases have also been investigated, in which the cycle of light stimulation is

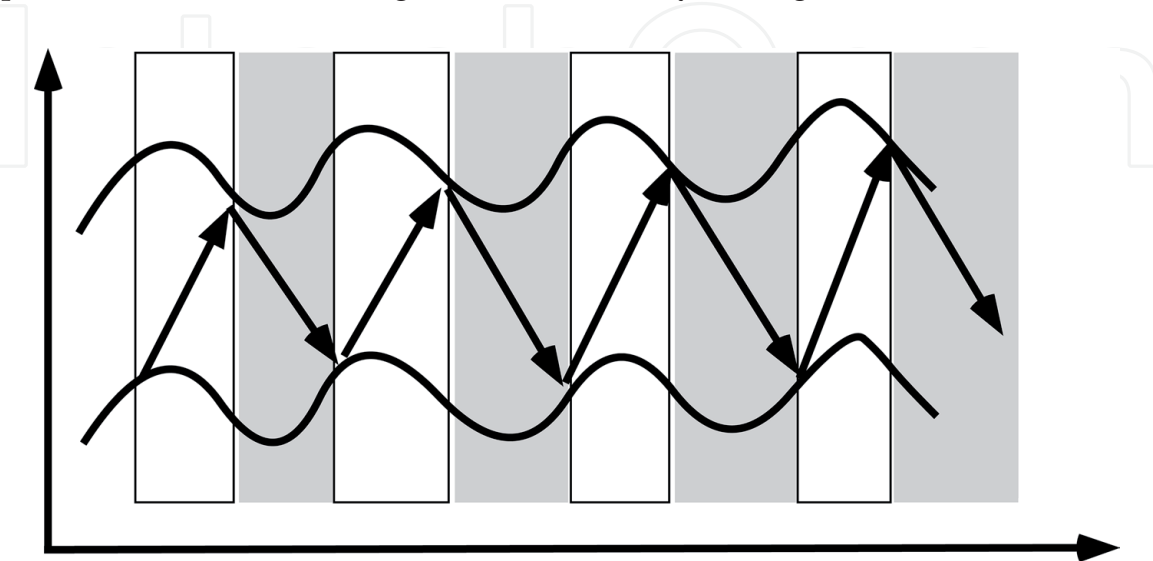


Figure 2.
A two-process model of sleep. Sleep debt accumulates during awakening, and sleep is encouraged when the sleep threshold is reached. Sleep reduces sleep debt and awakens when the wake threshold is reached. Sleep debt increases during awakening and decreases during sleep (process S). The sleep-wake threshold fluctuates diurnal (process C).

periodic. An increase in Lachnospiraceae and Ruminococcaceae and a decrease in Lactobacillaceae and Bifidobacteriaceae were observed after a 4-week sleep disturbance [36]. Furthermore, the intestinal contents, such as propionate and citrate, changed after the intervention, indicating functional changes in the intestinal microbiota. When intestinal bacteria from sleep-disturbed mice were transplanted into germ-free mice, the blood levels of inflammatory cytokines, such as IL-6, increased and insulin resistance was exacerbated in the recipient mice. The blood concentration of lipopolysaccharide-binding protein (LBP), which transports LPS to the CD14-TLR4-MD2 complex on the cell membrane of macrophages, was also increased in sleep-disordered mice. The effects of sleep disturbance without alteration of meals and motions in life were also examined in humans. A randomized crossover study was conducted in which nine healthy subjects slept for about 4 h for two days and about 8 h for two days with equal daily activities other than sleep. A short sleep for two days increased Firmicutes, and decreased Bacteroidetes in the intestine as well as worsened insulin resistance and glucose tolerance [37]. These findings demonstrate that sleep disturbances deteriorate the central and peripheral circadian rhythms, leading to metabolic disorders.

5. The stimuli from the intestine, circadian rhythm, and sleep

From the abovementioned examination of sleep disturbances in animals and humans, it was shown that sleep disturbances distort circadian rhythms in the central nervous system and peripheral organs. As mentioned above, the circadian rhythm in the intestine is regulated by the central and peripheral clocks as well as nutritional stimuli, that is, dietary intake. Therefore, the possibility of recovery of the host's circadian rhythm and the control of sleep *via* the intestine is being investigated. In fact, even in *Per1/2*-deficient mice, diurnal oscillation in the intestinal microbiota was observed by feeding them in a timely fashion.

Recently, Leone et al. compared the expression of clock genes *Bmal1* and *Clock* in the medial basal hypothalamus and liver of germ-free mice with that of control mice and found that circadian rhythms diminished in the germ-free mice [19]. The mechanism by which intestinal bacteria regulate the circadian rhythm of the liver and hypothalamus has also been investigated, and butyric acid, a metabolite of intestinal bacteria, was found to be a key molecule in tuning the circadian rhythm in the CNS and peripheral organs. In fact, when butyric acid was administered to hepatic organoids *in vitro*, an increase in the circadian rhythm of *Per2* and *Bmal1* expression was observed. Moreover, when butyric acid was injected into germ-free mice every 12 h, the circadian rhythm of the clock gene in the liver reappeared, and the amplitude of the clock gene tended to be enhanced in the medial basal hypothalamus. Consistent with this report, the circadian rhythm of *Bmal1* and *Cry1* in the intestinal epithelium disappears in mice in which intestinal bacteria are reduced by the administration of a set of antibiotics [38]. Bile acids deconjugated by intestinal bacteria are an important signal for tuning the clock genes in the intestine by dietary stimuli [12, 39]. Therefore, it is considered that changing the circadian rhythm of the intestine by nutritional stimuli could change the circadian rhythm in other organs, including the CNS, and may also affect sleep.

In terms of the stimuli from the intestine to modulate sleep, various modulations have been examined. The muramyl peptide derived from the cell wall of bacteria, LPS, and inflammatory cytokines such as IL-1b, TNF- α , and IL-18 have been reported to promote sleep [40, 41]. These microbial products prolonged and increased non-REM sleep and reduced REM sleep in model animals. In humans without infectious diseases, the levels of serum IL-1b and TNF- α showed

a circadian rhythm, which peaked at night and troughed at dawn, implying that these molecules may be a trigger for falling asleep [42]. Studies on sleep have also been conducted using antibiotic agents to modulate stimuli from the intestine. For example, one study administered a single dose of 200 mg of minocycline or 500 mg of ampicillin to 19 healthy men and found that administration of minocycline significantly reduced the proportion of non-REM sleep, an effect that lasted for two days. No effect was observed on REM sleep, and ampicillin did not affect either non-REM sleep or REM sleep [43]. These findings imply that changes in the gut microbiota may lead to improved sleep quantity and quality. Considering that long-term administration of antibiotics is not realistic in clinics, prebiotics and probiotics have been intensively investigated. It was reported that administration of *Lactobacillus brevis* to mice increased physical activity, prolonged waking hours, and reduced non-REM sleep [44]. Similarly, the administration of prebiotics containing lactoferrin to rats prevented the expected decrease in non-REM sleep due to electric shock [45]. In humans, many clinical trials have been conducted to evaluate the effects of prebiotics and probiotics on sleep. For example, the daily administration of *Lactobacillus gasseri* CP2305 for five weeks was reported to improve sleep quality in healthy volunteers, with a reduction in the amount of intestinal Enterobacteriaceae [46, 47]. Additionally, administration of a probiotic mixture of *Lactobacillus fermentum*, *L. rhamnosus*, *L. plantarum*, and *Bifidobacterium longum* for six weeks was reported to improve sleep quality [48]. Nevertheless, more studies are needed to conclude that modulation of nutritional stimuli from the intestine changes circadian rhythm and sleep quality.

6. Conclusions

The mechanisms by which circadian rhythm and sleep regulate systemic metabolism and nutritional stimuli from the intestine modulate circadian rhythm and sleep were summarized and discussed dietary therapies could be a novel treatment strategy for both metabolic and sleep disorders, although future studies are needed to validate these strategies.

Acknowledgements

This work was supported in part by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant-in-Aid (C) 16K09374 and the Japan Agency for Medical Research and Development (Grant JP21gm1010007s0505).

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