

The Effect of Circadian and Sleep Disruptions on Obesity Risk

Junghyun Noh*

Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea

The prevalence of obesity continues to increase worldwide. Multiple risk factors and complex mechanisms are involved in the development and maintenance of obesity. Recently, emerging evidence has indicated that the circadian rhythm is important for regulating metabolism because the circadian system modulates energy metabolism and enhances certain energetic activities during day and night. Lifestyle also has a great impact on the circadian system. In addition to traditional risk factors, sleep and circadian disruptions are known modifiable risk factors for obesity and other metabolic disorders. This paper reviews recent evidence of relationships between energy metabolism and the circadian system and discusses how sleep disruption and circadian misalignment influence the development of obesity.

Key words: Obesity, Circadian rhythm, Sleep wake disorders

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*Corresponding author
Junghyun Noh

 <https://orcid.org/0000-0002-7964-0515>

Department of Internal Medicine, Inje University Ilsan Paik Hospital, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea
Tel: +82-31-910-7930
Fax: +82-31-910-7217
E-mail: jhnoh@paik.ac.kr

INTRODUCTION

Obesity rates are increasing throughout the world, including Korea.¹ The latest estimates in Korea suggest that approximately 37.6% of men and 48.5% of women have diabetes, and 35.7% of Korean men and 45.2% of Korean women without diabetes are obese.¹ Obese people are at an increased risk for many comorbidities, including insulin resistance, type 2 diabetes mellitus (T2DM), high blood pressure, and cardiovascular disease, compared to those at a healthy weight. Genetics, an unhealthy diet, and inactivity are common causes of adverse metabolic health, including obesity and glucose intolerance.² However, these well-known factors do not fully explain the significant epidemic of obesity. Increasing evidence from both laboratory and epidemiological studies indicates

that sleep and circadian rhythm disturbances are novel risk factors for obesity and obesity-related comorbidities.³⁻⁵ Sleep is an important modulator of neuroendocrine function and glucose metabolism, and sleep loss has been shown to result in metabolic and endocrine alterations, including impaired glucose tolerance and modification of hormones that affect appetite regulation. These results suggest that improvement of sleep and circadian disruptions may promote metabolic health. This review is focused on the relationship between sleep and circadian disruption and obesity risk at the population and laboratory levels.

CIRCADIAN CLOCK SYSTEM

The circadian system consists of two parts: central and peripher-

al clocks. The central circadian clock is located at the hypothalamic suprachiasmatic nucleus (SCN). The central circadian clock, which is entrained by light, controls diurnal rhythm and thereby synchronizes metabolic functions during the daytime. Diffusible factors, such as cortisol and melatonin, and synaptic projections are considered to be the main pathways of the central clock.^{6,7} A series of peripheral clocks is located in almost every cell throughout the body, including the liver, gastrointestinal tract, pancreas, skeletal muscle, and adipose tissue.⁸ Peripheral clocks receive signals from central clocks through hormones and synaptic projections, including the autonomic nervous system, and external factors, such as light, sleep, physical activity, and feeding. Peripheral clocks have their own autonomous rhythms consist of a transcriptional-translational feedback loop (TTFL) made up by a set of clock genes involving, circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) activators and their target genes named *Period* (*Per1*, *Per2*, *Per3*), *cryptochrome* (*Cry1*, *Cry2*) and *Rev-erba*, whose gene products form a negative feedback repressor complex (Fig. 1).⁹ The TTFL operates on a 24-hour cycle. The individual cellular clocks have to be synchronized to produce a physiologic circadian clock system. A disturbance of any stage in this mechanism initiates misalignment of the circadian clock system and induces multiple metabolic effects.

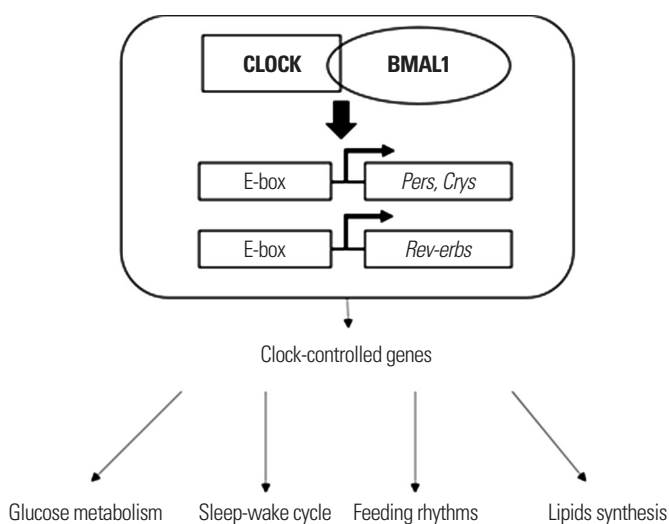


Figure 1. A schematic diagram of the regulatory role of the cellular circadian CLOCK system in the metabolic pathway. CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1.

CIRCADIAN SYSTEM AND ENERGY METABOLISM

There is clear evidence that the circadian system and energy metabolism are intimately conjugated at both the central and peripheral levels. In studies with single-celled cyanobacteria or red blood cells, the production of adenosine triphosphate (ATP) induces a clear 24-hour circadian rhythm. In cyanobacteria, ATP production by the oxidative phosphorylation of adenosine diphosphate (ADP) follows a circadian rhythm that is synchronized to a 24-hour light-dark cycle.¹⁰ When cyanobacteria are subjected to an abnormal light-dark cycle with an 8-hour dark period in the daytime, which causes a circadian misalignment, the ATP to ADP ratio and enzymatic reactions for ATP metabolism are reduced.¹⁰ In an animal study, transcript levels of *Niemann-Pick disease, type C1* and other enzymes involved in cholesterol synthesis and degradation in liver exhibited a circadian rhythm.¹¹ This result supports that the gene expressions coding for metabolically important enzymes are regulated by a circadian clock mechanism.

Direct regulation of the circadian system on energy metabolism occurs via binding of CLOCK and BMAL1 to E-box elements in the promoters of a gene.^{12,13} Mice with a mutation of the CLOCK gene not only show an altered and blunted circadian rhythm for wheel running in comparison with heterozygous mice but also exhibit a decrease in energy expenditure along with an increase in caloric intake and body mass.¹⁴ Dysregulation of BMAL1 in mice leads to changes in energy and lipid homeostasis similar to those of the metabolic syndrome. BMAL1 knockout (KO) mice exhibited suppression of the diurnal variation in glucose and triglyceride levels.¹⁵ Furthermore, *Rev-erb* KO mice showed circadian arrhythmicity in wheel-running activity.¹⁶ Several transcription factors regulated by the CLOCK system are also known to control metabolic genes, including the D site of albumin promoter binding protein (DBP), thyrotroph embryonic factor (TEF), hepatic leukemia factor (HLF), and nuclear receptors.¹⁷ Peroxisome proliferator-activated receptor gamma coactivator1- α , a nuclear receptor involved in lipid metabolism, has been suggested to be the key integrator of CLOCK.¹⁸ Its activity is impaired in mice lacking the three circadian proline and acidic amino acid-rich basic leucine zipper factors DBP, TEF, and HLF.¹⁹ Less is known about the relationship be-

tween energy metabolism and the circadian system in humans. Cross-sectional studies in humans have reported associations between the CLOCK locus and the prevalence of obesity, plasma glucose levels hypertension and T2DM²⁰, which suggests the integration between energy metabolism and the circadian system.

DISRUPTED SLEEP AND OBESITY

Insufficient and disrupted sleep is common in modern society. The American Academy of Sleep Medicine and Sleep Research Society recommends that 7 or more hours of sleep are necessary each day to maintain optimal health and functioning.²¹ However, it is unclear that more than 9 hours of sleep or less than 7 hours are inappropriate. A short sleep period has been demonstrated to have a relationship with obesity in numerous studies. A meta-analysis of 36 cross-sectional studies showed that a short sleep duration was independently associated with weight gain, particularly in younger age groups.²² Theoretically, the increased energy expenditure that results from longer periods of wakefulness should cause weight loss, but short sleep generally produces weight gain instead. It has been suggested that the paradoxical relationship between short sleep and obesity in humans is mediated by increased dietary intake and altered physical activity. The increase in food intake that resulted when sleep was restricted in healthy men in several studies might induce weight gain.²³⁻²⁵ Epidemiologic studies that have examined sleep duration in relation to diet have indicated that a higher fat intake, lower quality diets and irregular eating behavior occur during sleep restriction.²⁶ Disrupted sleep is now regarded as a new and important risk factor for abnormal lifestyle behavior, especially unhealthy eating.

The mechanism of increased food intake during sleep disruption may be varied. Sleep restriction induces changes in appetitive hormones, such as ghrelin, as well as increased hunger and appetite in human studies. Short sleepers generally have reduced leptin, elevated ghrelin and increased weight compared to average sleepers.²⁷ A functional magnetic resonance imaging study also identified increased activation of brain regions that may be sensitive to food stimulation during sleep restriction.^{28,29} It has also been suggested that duration is not the only factor that plays an important role in obesity; sleep quality has been implicated as well. In a study that in-

cluded 522 patients with newly diagnosed T2DM, the average number of night awakenings was positively correlated with body mass index (BMI).³⁰ In a systemic review of 16 articles, six CLOCK single nucleotide polymorphisms were associated with sleep duration, and three variants were correlated with energy intake variables.³¹ These genetic variants may assist in identifying individuals more prone to overeating and gaining weight when experiencing sleep deprivation.

CIRCADIAN MISALIGNMENT AND OBESITY

As previously described, the circadian system and energy metabolism are tightly integrated with and synchronized to the environment. Circadian misalignment commonly occurs in shift workers and is defined as inappropriately timed sleep and wake cycles or the misalignment of sleep and wake with eating rhythms. Night-shift workers who suffer from circadian misalignment have a higher risk of obesity^{32,33}, cardiovascular disease and diabetes.³⁴ In a systemic review and meta-analysis of 28 studies, the overall odds ratio of night-shift workers was 1.23 (95% confidence interval, 1.17–1.29) for the risk of obesity and overweight. Shift workers were also at higher risk of abdominal obesity than other obesity types (odds ratio, 1.35).³⁵ Light at night (LAN) is a major precipitating factor of a disrupted circadian system. The retina senses light, and retinal ganglion cells project to the neurons of the SCN, evoking a signal that leads to changes in *Per1* and *Per2* CLOCK gene expression. As a consequence, a shift in the phase of the circadian oscillator in the SCN results in a shift of the circadian system in the body. Several studies have found that shift workers have a higher prevalence of obesity and support that artificial lighting may contribute to the increased prevalence of metabolic disorders.^{36,37} Exposing mice to constant bright light throughout a 24-hour period resulted in an increased body mass by shifting the time of food intake despite a lack of increased caloric intake and no variation in activity level.³⁸ In humans, increased levels of LAN exposure were associated with an increased obesity rate in 100,000 women.³⁹ Unusual meal timing is also an important factor in the development of obesity associated with circadian disruption. In rodent models, eating only during habitual sleep time increases body mass compared

with eating during habitual wake time even when the caloric intake and locomotor activity were similar.⁴⁰ A recent study uncovered an endogenous circadian rhythm for hunger; hunger senses are highest in the biological evening at about 8 PM and lowest around 8 AM. This observation supports a limited caloric intake after a long overnight fast.⁴¹ However, when food is easily accessible overnight, eating at night is associated with unwanted weight gain. Another study also showed that late sleepers consumed more calories at dinner and after 8:00 PM, had a higher fast food and full-calorie soda intake and lower fruit and vegetable consumption and had a higher BMI.⁴² Night eating syndrome, diagnosed as (1) no appetite for breakfast, (2) consumption of $\geq 50\%$ of daily energy after 7:00 PM, and (3) sleep difficulties ≥ 3 night/wk, is associated with a higher BMI and binge eating tendencies.⁴³ The decreased total energy expenditure in response to eating meals at inappropriate times may contribute to the mechanism of unwanted weight gain and obesity associated with circadian misalignment. In a study of 14 adults in a 6-day inpatient simulated shiftwork protocol, sleep duration during the biological day and wakefulness and eating during the biological night in a shift-work model decreased the participants' 24-hour energy expenditure.⁴⁴

CONCLUSION

There is strong evidence that disrupted sleep and circadian misalignment contribute to obesity and metabolic disorders. A short duration and poor quality of sleep are considered risk factors for the development of obesity. The inappropriate circadian timing of food intake is also regarded as a contributing factor for obesity. Greater weight gain and an altered glucose and energy metabolism occur when food intake during the biological night is increased in humans. Additional research will be needed to understand the mechanisms by which sleep and circadian disruption contribute to metabolic dysregulation and also to determine the potential for improving sleep and circadian rhythms to promote metabolic health.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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