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Disturbances of sleep and circadian rhythms: Novel risk factors for obesity

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Abstract

Purpose of review—To summarize recent developments linking disturbances of sleep and circadian rhythms to an increased risk for obesity, and to review novel research on potential countermeasures.

Recent findings—Effective treatments for obesity are limited, with long-term adherence to life style changes proving difficult. Identifying new preventive strategies based on modifiable risk factors is therefore imperative in the fight against obesity. Disturbances of sleep and circadian rhythms have an adverse impact on food choices, hunger and appetite and have lifelong deleterious metabolic effects when present during childhood and early adulthood. The upregulation of the endocannabinoid system and abnormalities in the temporal distribution of caloric intake have been recently implicated in the link between sleep loss and obesity risk. Lastly, alterations in the circadian variation in the composition and functionality of the gut microbiome have been identified as potential contributors to metabolic dysfunction in conditions of jet lag and shift work. Insufficient sleep and circadian misalignment are thus new modifiable risk factors for obesity. Emerging evidence suggests that novel countermeasures, such as manipulations of the timing of food intake, may be effective strategies in the prevention of obesity.

Summary—Four important findings are briefly reviewed: 1. disturbances of sleep and circadian rhythms in children and young adults are risk factors for the development of lifelong obesity; 2. circadian misalignment, as occurs in shift work, has an adverse impact on energy balance and increases the risk of weight gain; 3. the endocannabinoid system, an important regulator of hedonic feeding, could be a potential link between sleep, circadian rhythms and feeding behavior; 4. disturbances of the circadian variation in composition of the gut microbiome could be involved in the increased risk of obesity associated with insufficient sleep and circadian misalignment.

Keywords

Insufficient sleep; circadian disruption; chrononutrition; time-restricted feeding; hedonic food intake; weight gain; gut microbiome; obesity

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Introduction

Obesity is a highly prevalent condition in industrialized societies and is associated with an increased risk for adverse health consequences including diabetes, cardiovascular disease, arthritis, depression and cancer (as reviewed by [1]). The resultant comorbidities make obesity the leading cause of preventable death in the United States, and are associated with large socioeconomic burdens, including a steep increase in healthcare costs attributed to obesity-related diseases [2]. Effective behavioral treatments for obesity are limited, with research in humans focused primarily on reducing food intake and increasing physical activity. Long-term adherence to these lifestyle changes has proven difficult, however, and the development of preventive strategies based on new, modifiable risk factors is therefore imperative moving forward in the fight against obesity.

A meta-analysis of cross-sectional epidemiologic studies comprising over 600,000 people have demonstrated a clear association between short sleep duration and elevated body mass index (BMI) in both adult and pediatric populations [3]. A systematic review of both cross-sectional and longitudinal studies also supports a consistent association between short sleep duration and concurrent as well as future obesity [4]. During the current review period, another meta-analysis on a total of 56,259 participants reported a significant negative association between sleep duration and waist circumference, indicating shorter sleep durations co-vary with central adiposity [5]*. This relationship appears stronger in children and young adults than in older adults.

Experimental studies in healthy adults have revealed that sleep restriction stimulates hunger and appetite, leading to excessive food intake when food is available *ad libitum*. In addition, sleep restriction increases the hedonic drive for food and an elevation in food-related reward signals. The extended wakefulness resulting from sleep restriction is associated with an increase in basal energy expenditure and subsequent over-compensation in energy intake, leading to positive energy balance and weight gain. Moreover, there is evidence that sleep-restricted individuals tend to reduce their levels of physical activity [6]. In addition to the accumulating evidence for adverse effects of insufficient sleep on the risk of obesity, non-human models of obesity suggest an important role for the integrity of the circadian system in metabolic health.

In the following review, we present findings that have been recently published that examine: 1. disturbances of sleep and circadian rhythms in children and young adults as novel risk factors for the development of long-term obesity; 2. the impact of circadian misalignment, as occurs in shift work, on energy balance and the risk of weight gain; 3. the role of the endocannabinoid system as a potential link between sleep, circadian rhythms and feeding; 4. the role of disturbances in the circadian structure of the gut microbiome as a putative mediating mechanism linking abnormal eating pattern and the risk of weight gain. We conclude with a brief discussion on the emerging field of “chrononutrition” as a potential countermeasure.

Links between sleep duration and weight in children and adolescents

The obesity epidemic does not spare children and it is crucial to study pediatric populations to identify behaviors that may lead to weight gain, as childhood obesity is a strong predictor of adult obesity. Insufficient sleep has also become an endemic condition in children and research conducted during this review period strongly confirmed the link between reduced sleep duration and obesity in children. In a recent prospective cohort with a sample size of 14,800, it was found that cumulative exposure to short sleep throughout adolescence and early adulthood exhibits a dose-response association with obesity outcomes. Specifically, relative to respondents with no instances of short sleep, participants who reported short sleep duration at all four waves of study follow-up (from 1994-2009) were nearly 1.5 times more likely to be obese and have an elevated waist circumference [7]**.

In another study of primary-school aged children, data from 39 schools were compiled to provide a sample of nearly 300 children. In this cross-sectional study, objective height and weight were collected, as well as self-reported sleep duration. Insufficient sleep, defined as less than 10 hours of time in bed each day, was found to be present in 33% of the children examined. Compared with those sleeping more than 10 hours, insufficient sleepers were significantly more likely to be overweight or obese [8]*.

One potential mechanism by which sleep loss may increase the risk of obesity in children is by altering food choices. Indeed, in a self-assessment survey study of nearly 2,000 4th and 7th graders, insufficient sleep, defined as less than 10 hours per day, was associated with more frequent soda consumption and less frequent vegetable consumption [9]*.

The impact of experimental sleep restriction on food choice was systematically addressed by a study involving adolescents aged 14-17 years who were examined using a 3-week in-home randomized crossover design. The protocol involved one baseline week followed by either 5 nights of sleep restriction to 6.5 hours or 5 nights of “healthy” sleep of 10 hours in bed, separated by a 2-day washout period. Sleep was measured by wrist actigraphy. On the final morning after 5 nights of sleep restriction or 5 nights of normal sleep, participants rated their hunger, provided a 24-hour diet recall and rated the appeal of different foods from photographs. Though the sleep restriction did not affect subjective hunger, the teens consistently and significantly rated sweet/dessert foods more appealing after sleep restriction than after sufficient sleep. When food intake itself was assessed by self-report, sleep restriction was associated with an 11% increase in overall food intake and a 52% increase in sweet/dessert servings [10]*. One of the strengths of this study is that it was conducted outside of the laboratory under free-living conditions.

Limitations of these studies include the subjective nature of recall data, however, the findings are consistent with nearly all previous studies in similar age groups, which have consistently found positive associations between insufficient sleep and weight gain or obesity.

The implications of sleep restriction in early life as a potential long-term contributor to future obesity risk and metabolic impairments are particularly worrisome. In a recent rodent study, sleep restriction during “adolescence” was shown to induce the expected reductions in

weight, fat mass and trigly cerides previously seen in adult rodent models. Sleep restriction was achieved using the disc-over-water method, and experimental animals were placed in the sleep restriction cage for 18 hours (16:00-10:00) each day for 21 days and returned to their home cages each day for 6 hours (10:00-16:00) where they could sleep freely. Control animals were placed in the same containers but the disk was rotating over sawdust rather than water. During the month of recovery following the intervention, rats who were previously sleep restricted showed greater body weight gain and energy stores and decreased energy expenditure as compared to controls, despite eating the same amount [11]**.

Given that in this rodent model, sleep loss is typically associated with drastic weight reductions and increased energy expenditure, the long-term effects of sleep loss on later weight gain suggests that sleep perturbations during development may have implications on the risk for obesity and metabolic complications later in life.

Links between circadian misalignment, sleep loss and energy balance

Insufficient sleep has been associated with an increase in the desire for high energy-dense food types [12]. However, less is known about the effects of circadian misalignment on hunger and appetite. In a recent study looking at food preferences during shiftwork, 16 participants (8 women) underwent one night of a simulated night work condition as compared today work condition in counter-balanced order after which high- and low-fat breakfast options were presented. The majority (81%) of participants in the night work condition chose the high-fat breakfast option, as compared to only one third of participants during the day work condition. However, there was no difference in total caloric intake between conditions [13]*.

In a longer study of simulated shiftwork, 14 healthy lean adults (7 women) were studied during a 6-day inpatient protocol under controlled caloric intake conditions [14]**. On the first day of transitioning to a simulated night work schedule, subjects were given an afternoon nap opportunity, but then remained awake overnight, resulting in reduced total sleep duration over a 24-hour period that resulted in a 4% increase in total daily energy expenditure due to extended wakefulness. However, during the following 2 days of simulated night work, total daily energy expenditure was reduced by approximately 3% per day when participants were sleeping during the day and awake at night. Additionally, on the 2 shiftwork days, energy expenditure during the daytime sleep opportunities was 12-16% lower than during the nighttime sleep opportunities prior to the initiation of shiftwork. In addition to exposing the complex nature of energy expenditure alterations during shiftwork, these findings suggest that reduced total daily energy expenditure, in combination with eating during the biological night, may be a mechanism by which nightshift schedules increase the risk of weight gain and obesity [14]**.

Identifying potential mechanisms involved in the increase in food intake during insufficient sleep

Previous studies have reported an association between reduced sleep and an increase in hunger and appetite. Recently, our group reported the existence of a largediurnal rhythm in circulating levels of 2-arachidonoylglycerol (2-AG), the most abundant endogenous ligand

of the endocannabinoid receptor CB1 [15]*, which mediates the appetite-enhancing effects of endocannabinoids. In this study, all 14 participants exhibited a large circadian variation of 2-AG serum concentrations, with a nadir around mid sleep and a nearly threefold increase from early morning to peak levels around lunchtime, suggesting that activity of the endocannabinoid system, which has powerful influences on hedonic food intake, is profoundly modulated by circadian rhythmicity. The endocannabinoid receptors can be found in the brain as well as in peripheral organs involved in energy metabolism. The findings from this study suggest that the impact of the endocannabinoid system on the regulation of hedonic food intake is suppressed during sleep. When sleep was restricted in these same individuals, an activation of the endocannabinoid system occurred during daytime hours, with an elevation and a delay of the peak of 2-AG. When sleep was restricted, participants reported increases in hunger and appetite concomitant with the afternoon elevation of 2-AG concentrations, and were less able to inhibit intake of palatable snacks [16]*.

The ability of the endocannabinoid system to control appetite, feeding, and peripheral metabolism has been the target of pharmaceutical efforts to develop anti-obesity drugs, however the regulation of this system by circadian and sleep processes has not been examined previously. The results from these two studies suggest that activation of the endocannabinoid system may be involved in excessive food intake during insufficient sleep and may contribute to the associated increased risk of obesity and therefore requires further investigation.

Ghrelin is a hunger-promoting hormone that has also been implicated in hedonic feeding. Consistent with the findings of early studies of the neuroendocrine control of hunger and appetite in conditions of sleep restriction, a study published in 2016 explored the role of elevated ghrelin in the increase of food intake during sleep restriction. The 24-hour profiles of plasma ghrelin were examined after 3 nights of 8.5 hours in bed versus 4.5 hours in bed under controlled caloric conditions. When food intake was kept constant to a level designed to maintain energy balance, 24-hour mean, daytime, breakfast- and dinner-related peak ghrelin levels were all significantly elevated during sleep restriction as compared to normal sleep. There was also a positive correlation between the increase in evening ghrelin (i.e., dinner-related peak) and higher consumption of calories from sweets [17]*. The findings thus point at a role for an increase in ghrelin release in excessive food intake, particularly of sweets, in a state of sleep debt.

As described above, insufficient sleep alters physiological systems promoting appetite, as well as actual food intake, but whether overeating could affect sleep duration or quality remains an open question. To test whether altered dietary patterns can feedback to affect sleep parameters, 26 normal weight individuals were studied during habitual sleep for 5 days [18]**. During the first 4 days, caloric intake was strictly controlled but on the 5th day, participants were released into a buffet meal environment, followed by a 9h time in bed opportunity. Sleep on the night following *ad libitum* food intake from the buffet was of similar duration than sleep during controlled caloric intake but had less slow wave sleep (SWS) and a longer sleep-onset latency. A higher percent of total energy intake from saturated fat predicted less SWS while a higher energy intake from sugar and other

carbohydrates was associated with arousals. The timing of food intake was not reported in this study; however, it is conceivable that if the buffet was presented in the later part of the day, the misalignment of food intake relative to endogenous circadian timing may have played a role in the sleep disturbances.

Role of circadian variations in the gut microbiome in obesity risk

The gastro-intestinal tract is home to thousands of species of bacteria, collectively referred to as the gut microbiome, that together play an important role in the metabolic homeostasis of the host organism. Very recently it was reported that the intestinal microbiota exhibit diurnal oscillations, driven primarily by the food intake rhythms of the host organism, leading to rhythmic composition and functional profiles of intestinal bacteria [19, 20]**.

Closer examination of gut microbial rhythms indicates that variations in the community structure depend on the dietary composition of the host [21]*. Specifically, diet-induced obesity can dampen the rhythmicity of feeding/fasting fluctuations in the gut microbiome [20]**.

Experimental circadian misalignment can lead to changes in the presence of bacterial communities that can promote increased energy absorption from food ingestion and subsequent increases in energy balance [19]**. In a study including mouse models, as well as two human subjects, jet lag induced intestinal dysbiosis due to altered feeding rhythmicity, promoting glucose intolerance, and these effects were transferrable from humans to germ-free mice [19]**.

Novel countermeasures: time-restricted feeding

Countermeasure strategies to disrupted feeding patterns during circadian misalignment have been proposed in which an attempt is made to restrict feeding to the biological day, regardless of when sleep/wake occurs. This idea of “chrononutrition” has been discussed within the context of obesity since studies have shown that eating at the “wrong” time of day can induce weight gain, even in the face of identical caloric intake.

In a mouse model, Yasumota et al recently reported that only 1 week of a high-fat, high-sucrose diet restricted to the light, or inactive phase, led to higher food consumption, reduced wheel running and increased fat accumulation in the liver as compared to animals fed the same diet restricted to the dark, active phase [22]*. In this study, there was also an uncoupling of the circadian expression of glucose- and lipid-related genes between peripheral metabolic tissues. Specifically, metabolic gene expression in the liver shifted to match the food intake schedule, whereas the temporal pattern of gene expression in muscle remained relatively unchanged.

In addition, in a mouse model of jetlag, a twice-weekly advance of 6 hours was sufficient to induce obesity under normal chow, *ad libitum* feeding conditions. In contrast, restricting feeding to a fixed 12-hour window protected jetlagged animals from the induction of obesity, despite isocaloric intake [23]*. Interestingly, the 12 hours of fixed feeding did not systematically occur during the active phase, but consisted of a set 12-hour window that did not shift when the mice were advanced, which resulted in the food availability window

occurring during the light phase in some parts of the protocol, and during the dark phase at others. In this study, the benefit of fixed feeding may be due to the intermittent restriction of food to the active phase at some time-points throughout the protocol, rather than *ad libitum* feeding during the entire 14-week experiment.

In another murine study, a systematic analysis of the protective effects of time-restricted feeding (TRF) of diverse diets, as well as of the effectiveness of TRF in the face of preexisting obesity, was conducted [24]**. Chaix et al compared “unhealthy” diets (fat + sucrose, high-fructose and high-fat) to normal chow diets using differing durations of access to food. TRF reduced body fat accumulation, lowered inflammation and improved glucose tolerance, compared to *ad libitum* feeding. An important aspect to consider regarding TRF is the length of the fasting period. In the current study, the benefits of TRF were proportional to the duration of the fast, which may provide metabolic tissues with a necessary rest and repair period not provided by *ad libitum* food availability [24]**.

TRF has also been shown to partially restore normal gut microbial fluctuations as compared to *ad libitum* eating, since eating at the wrong circadian time results in the subsequent appearance of nutrients in the gut during the biological night when the body is not prepared to receive them [20]**.

Finally, using a mobile application in humans, it was revealed that healthy non-shift-workers eat frequently and erratically during waking hours [25]**. In half of this cohort, dietary intake exceeded 14.75 hours over the course of the day. In a small subset of overweight individuals (n=8), participants were instructed to reduce eating duration from >14 hours to 10-11. After the 16-week intervention, body weight was significantly reduced, which persisted for 1 year. In addition, an improvement in sleep was reported. The benefits of TRF may result from the restoration of the feeding/fasting rhythm, reduction in “metabolic jetlag” resulting from later eating on weekends as compared to weekdays, from improved sleep, or from reduced caloric intake. As the authors point out, TRF may be an inadvertent way to reduce caloric intake that is more effective and less expensive than other behavioral modifications.

Consistent with this hypothesis, a study examining 270 patients who underwent bariatric surgery reported that weight loss effectiveness after surgery was related to the timing of the main meal. Weight loss after surgery was characterized by three different patterns: successful, as defined as a greater than 50% loss of excess body weight; primarily poor weight-loss-responders, characterized by sustained limited weight loss, and secondarily poor weight-loss-responders, characterized by a successful initial weight loss but subsequent weight regain with a final excess body weight loss <50% [26]**.

Obesity-related variables, such as pre-surgical total energy expenditure, sleep duration, chronotype, caloric intake and macronutrient distribution, were similar among groups. However, the percentage of late eaters (those who ate their main meal after 15:00) was significantly higher in the group considered primarily poor weight-loss-responders than in both secondarily poor weight-loss-responders and good weight-loss-responders after an average follow-up time of 6 years [26]**.

Future research should also examine whether improvements in sleep, or even time-restriction of *specific* macronutrients, may play a role in the observed health benefits of TRF.

Conclusions

Insufficient sleep and circadian misalignment are novel, modifiable risk factors for the development of obesity. During the review period, we have seen significant advances into the identification of the mechanisms that link insufficient sleep to obesity: hunger, appetite and subsequent food choices in adolescents are altered during insufficient sleep; the lingering metabolic effects of insufficient sleep during development have been examined; and a novel appetite regulating mechanism—the endocannabinoid system—has been implicated in the link between sleep loss and hunger and appetite. Finally, the effects of insufficient sleep and circadian misalignment on the gut microbiome and host metabolism have been examined and findings suggest that changes in feeding rhythms may promote increased energy absorption from food.

As mechanisms continue to be elucidated, more effective countermeasure strategies can be tested and implemented, as evidenced by the concept of chrononutrition and the protective effects of TRF. Of course, the best intervention is to avoid sleep loss and circadian misalignment altogether. However, sleep loss and/or circadian misalignment are often unavoidable in our modern, 24-hour society and it is important to develop potential countermeasure strategies to the development of obesity and its comorbidities.

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Key Points

- Sleep restriction during childhood and young adulthood may have long-term consequences on metabolic health.
- Insufficient sleep leads to poor dietary choices and altered hormones involved with hunger and appetite, including ghrelin and the endocannabinoid receptor ligand 2-arachidonoylglycerol (2-AG).
- Circadian misalignment as occurs with shiftwork leads to poor dietary choices and reduced energy expenditure, which may both contribute to an increased risk for obesity.
- Circadian variations are present in the structure of the gut microbiome and depend on the composition of dietary intake of the host; circadian misalignment can lead to increases in the presence of bacterial communities that can promote energy absorption from food and subsequent weight gain.
- Time-restricted feeding to a shorter period during the biological day may be an effective countermeasure strategy to the health impairments associated with erratic eating patterns and eating at night in both shift work and non-shift work populations.