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Metabolic effects of sleep disruption, links to obesity and diabetes

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Abstract

Purpose of the review—To highlight the adverse metabolic effects of sleep disruption and to open ground for research aimed at preventive measures. This area of research is especially relevant given the increasing prevalence of voluntary sleep curtailment, sleep disorders, diabetes, and obesity.

Resent findings—Epidemiological studies have established an association between decreased self-reported sleep duration and an increased incidence of type 2 diabetes (T2D), obesity, and cardiovascular disease. Experimental laboratory studies have demonstrated that decreasing either the amount or quality of sleep decreases insulin sensitivity and decreases glucose tolerance. Experimental sleep restriction also causes physiological and behavioral changes that promote a positive energy balance. While sleep restriction increases energy expenditure due to increased wakefulness, it can lead to a disproportionate increase in food intake, decrease in physical activity, and weight gain.

Summary—Sleep disruption has detrimental effects on metabolic health. These insights may help in the development of new preventative and therapeutic approaches against obesity and T2D based on increasing the quality and/or quantity of sleep.

Keywords

sleep deprivation; sleep curtailment; metabolism; insulin sensitivity; glucose tolerance

Introduction

Voluntary sleep curtailment is a prevalent behavior. During the 2013 National Sleep Foundation poll, 21% of the people interviewed in US reported less than 6 h of sleep on workdays. Insufficient sleep syndrome (F-51.12) and sleep deprivation (Z72.820) are recognized diagnoses by international classification of sleep disorders (ICSD-10). In epidemiologic work, short sleep has been associated with an increased prevalence of type 2 diabetes (T2D), obesity, and cardiovascular disease [1],[2], [3] [4], [5] [6], [7] [8], [9].

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Conflicts of interest

There are no conflicts of interest.

Furthermore, obesity has emerged as one of the causal factors for sleep disorder breathing, a condition affecting mainly middle aged men with a prevalence of up to 10-17% depending of the age group [10]. Laboratory studies have provide convincing evidence for a causal link between short sleep and poor sleep quality and adverse metabolic effects although the mechanisms are not well understood. This review will briefly review epidemiologic evidence showing the extent of the problem, but will primarily focus on in-laboratory studies to explore causation and potential mechanisms. The review will highlight experimental work conducted in the last 1-2 years and is not intended to be exhaustive, given the space limitation. Figure 1 shows a simplified schematic of the effect of sleep disruption on physiological and behavioral factors as probable mediators for the increased risk for obesity, T2D, and cardiovascular disease associated with short sleep.

Sleep

Sleep is a naturally recurring state characterized by altered consciousness, inhibited sensory activity, and inhibition of voluntary muscle movement. Sleep architecture is described by the use of electroencephalographic (EEG) and electromyographic criteria. Sleep is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. The American Academy of Sleep Medicine divides NREM sleep further into three stages: N1, N2, and N3 [11]. N1 sleep is characterized by active muscle tone and slow eyes rolling movements. In N2 sleep, sleepers become gradually harder to awaken. This stage is characterized by the presence of sleep spindles and K-complexes. During N3 sleep, the sleeper is less responsive to external stimuli and EEG is characterized by high amplitude waves. REM sleep is characterized by rapid eye movements and skeletal muscles atonia. Healthy nighttime sleep proceeds in four to five 90-min cycles of NREM and REM per night with NREM being more prevalent in the beginning and REM more prevalent toward the end of the night. Sleep is controlled by two primary regulatory processes, the circadian process and the homeostatic drive for sleep that increases with increasing prior wakefulness and decreases during sleep. In humans, the physiological drive for sleep can be overruled by voluntary sleep restriction, or can be disrupted because of environmental factors or sleep disorders such as obstructive sleep apnea (OSA), insomnia, restless leg syndrome, and narcolepsy.

Epidemiological studies

Numerous epidemiological studies have shown that self-reported sleep of less than 6-7 h per night is associated with increased incidence of obesity [1],[2], [3]), diabetes [4], [5], cardiovascular disease [6], [7], and total mortality risk [8], [9]. The relationship between duration of sleep and mortality was described as a U-shaped association with different proposed mechanisms at the either end of the distribution of sleep duration [12]. The analysis from the NHANES study showed association between sleep ≤5-h and clinically identified pre-diabetes [13]. Furthermore, cross-sectional observations of lower leptin and higher ghrelin concentrations in people with short sleep, independent of BMI, have led to the hypothesis that such hormonal changes promote over-eating and lead to increased risk of obesity [14], [15]. Additionally, in persons sleeping less than 8 h, increased BMI was proportional to decreased sleep [14]. The link between short sleep and obesity was

supported by a 16-y longitudinal study [16] in which women who reported to sleep 5 h or less gained 1.14 kg more than those who slept 7 h per night (analyses adjusted for age and BMI).

A common complaint of shift workers is disrupted sleep. Night shift work was associated with short sleep (average 4.8 h [17], reviewed in [18]). An epidemiological study in 1,806 workers showed a relative risk for coronary heart disease in shift workers of 1.5 compared to day workers [19]. In a study conducted in 2,860 male workers, the relative risk for T2D for the 2-shift workers and 3-shift workers compared to daytime workers was increased [20]. Additionally, in 4,328 workers evaluated, shift work was a risk factor for weight gain [21].

Observational studies have shown an association between OSA, narcolepsy, insomnia, and restless leg syndrome with insulin resistance and decreased glucose tolerance [22]. Strength of epidemiologic studies is that people are studied in their natural environment and large numbers are included. The main limitations are that causation cannot be established and results are typically based on self-reported sleep duration.

Laboratory studies

Sleep deprivation can be caused by diminished sleep duration [23], [24], [25], and/or diminished sleep quality [26]. Laboratory studies have provided convincing evidence that even short-term decreases in sleep quantity or quality can have deleterious effects on glucose regulation, can interfere with the secretion of anabolic hormones (growth hormone [27], prolactin [28], testosterone, [29]) alter the amount and timing of catabolic hormones (glucocorticoids [23], catecholamines, [30]) change food regulation (food preferences [31], timing of food consumption [32], quantity of food) and have effects on the immune system.

In one of the first studies to determine the effects of partial sleep deprivation, sleep restriction to 4 h TIB for 6 nights (as compared to a 12-h TIB recovery period) caused a decrease in glucose tolerance as measured by intravenous glucose tolerance test (IVGTT) [23]. The sleep debt condition also resulted in lower thyrotropin, elevated evening cortisol, and an increase in a measure of sympathovagal balance. Additionally, partial sleep restriction to 4 h TIB for 2 nights caused an 18% reduction in the anorexigenic hormone leptin, a 28% elevation in the orexigenic factor ghrelin, and a near 24% increase in hunger and appetite ratings with preference for calorie-dense higher carbohydrate content food when caloric intake was kept constant [31]. Sleep restriction can also affect *ex vivo* insulin sensitivity in white adipose tissue [33]. The effect of sleep restriction to 4.5 h compared to 8.5 h in bed for 4 nights on a step in the insulin-signaling pathway (phosphorylation of Akt) was evaluated in abdominal fat. The insulin concentration required to achieve half-maximal stimulation of phosphorylation of Akt (pAkt), expressed as the ratio over total Akt (tAkt), was used as a measure of cellular insulin sensitivity. Sleep restriction increased the required insulin concentration to achieve half-maximal pAkt/tAkt response 3-fold, demonstrating impaired insulin signaling in abdominal fat tissue after partial sleep restriction. This effect was concurrent with a decrease in whole body insulin sensitivity, as estimated by IVGTT.

Even a single night of partial sleep restriction is sufficient to reduce insulin sensitivity. Sleep restriction to 4 h TIB compared to 8.5 h TIB resulted in increased endogenous glucose

production assessed by euglycemic hyperinsulinemic clamp, indicating hepatic insulin resistance [34]. Additionally, sleep restriction decreased glucose disposal rate during the clamp, reflecting decreased peripheral insulin sensitivity. Consequently, the rate of glucose infusion was decreased by 25%.

Not only healthy individuals are negatively affected by sleep restriction, but also relevant patient groups. In patients with type 1 diabetes, 1 night of sleep restriction to 4 h TIB vs. 8.5 h TIB resulted in decreased glucose disposal, reflecting decreased insulin sensitivity, estimated by hyperinsulinemic clamp [35]. Short sleep decreased the rate of glucose infusion by 21%, while endogenous glucose production during the clamp test was not altered.

A study conducted in adolescent boys showed that sleep restriction to 4 h TIB for 3 nights vs. 9 h TIB increased insulin resistance as estimated by HOMA-IR by 65% [36]*. Apparently, the negative effects of sleep restriction on glucose regulation starts from a young age, which suggest that preventive measures should be started early in life.

In conditions of a negative energy balance, sleep curtailment to 4 h TIB for 3 nights vs. 9h TIB did not lead to decreased insulin sensitivity, but may predispose to overeating via separate mechanisms for men and women [37].

Effect of sleep restriction on energy expenditure

In a study measuring energy expenditure (EE) by a whole room calorimetry, total sleep deprivation for 40 h increased the 24-h EE by 7% as compared to a baseline day including 8 h time in bed (TIB) [38]. In this same study, hourly EE was on average 32% higher during wakefulness versus scheduled baseline sleep. In a different study, partial sleep restriction to 5 h TIB as compared to 9 h TIB for 5 nights increased daily EE by 5% as measured by whole room calorimetry [39]**. In a third study, short sleep with 4 h TIB compared to 8 h TIB for 3 nights increased 24-h EE by 5% as measured by whole room calorimetry [40]. While these three studies show that sleep restriction increases EE, this increase appears to be smaller compared to the increased energy intake when food is freely available. In the second study, food intake was 6% greater in the sleep restricted compared to control condition, i.e., the increase in energy intake was larger than the increase in EE, resulting in a larger increase in body weight [39]**.

When energy expenditure was measured by doubly labeled water technique, sleep curtailment for 14 nights to 5.5 h TIB (vs. 14 nights with 8.5 h TIB) [32] and for 5 nights to 4 h TIB (vs. 5 nights with 9 h TIB) [41] did not show significant differences in 24-h EE. The discrepancies in the findings of whether or not there is an effect of sleep restriction on EE may be explained by the higher sensitivity of whole room calorimetry used to estimate EE (0.5-2%) as compared to that of doubly labeled water method (6-8%) [39]**).

Other effects of sleep restriction

One week with 5.7 h TIB compared to 8.5 h TIB affected the genes associated with circadian rhythms (PER1, PER2, PER3, CRY2, CLOCK, NR1D1, NR1D2, RORA, DEC1, CSNK1E), sleep homeostasis (IL-6, STAT3, KCNV2, CAMK2D), oxidative stress (PRDX2, PRDX5), and metabolism (SLC2A5, GHRL, ABCA1), as assessed by

transcriptome analysis [42]*. Biological processes affected by sleep restriction included chromatin modification, gene-expression regulation, macromolecular metabolism, and inflammatory, immune and stress responses. Effect of sleep loss on inflammatory cytokines was evaluated in a study with 50-h total sleep deprivation, where sleep loss caused an increase in the pro-inflammatory cytokine TNF-alpha compared to a baseline 8-h night of sleep, but no changes in interleukin-6, cortisol, or CRP [43]. Moreover, partial sleep restriction to 4 h for 5 nights compared to a control group who slept 8 h/night led to changes in leukocyte RNA expression assessed by whole genome microarrays complemented with pathways and transcription factors analysis [44]. Sleep restriction altered the expression of 117 genes. Fifteen of the 25 most up-regulated pathways included those for B-cell activation, interleukin-8 production, and NF-kB signaling. If such activation is maintained during prolonged partial sleep restriction, this would lead to chronic, low level inflammation that could contribute to detrimental health conditions, including cardiometabolic disease.

Effect of sleep quality on glucose regulation

Not only decreases in sleep duration, but also in sleep quality have been demonstrated to adversely influence glucose regulation. The effects of sleep fragmentation on glucose regulation was studied by interrupting sleep using auditory and mechanical (vibrations) stimuli irrespective of sleep stage (30/h). Following two nights of sleep fragmentation, insulin sensitivity as assessed by IVGTT was decreased and morning cortisol was increased [45]. A different study evaluated the effect of sleep stage-specific disruption on glucose control. Slow wave suppression for 3 nights without significant changes in wake time and total sleep time resulted in decreased insulin sensitivity without compensatory increase in insulin release [26]. OSA is a sleep disorder that combines sleep fragmentation and hypoxemia. In addition to the adverse effects of sleep fragmentation and decreased sleep quality with OSA, hypoxemia itself has been shown to negatively affect glucose metabolism. Experimentally induced intermittent hypoxemia in 13 healthy volunteers for 5 h during wakefulness as compared to normoxia resulted in a decrease in insulin sensitivity as assessed by IVGTT [46]. Knowing that sleep fragmentation also impairs insulin sensitivity, hypoxia during OSA may increase that effect and contribute to development of diabetes.

Effect of circadian misalignment on glucose regulation

In addition to the effects of quantity and quality of sleep, also the timing of sleep (and thereby of the resultant fasting episode among other behavioral factors) appears to have an effect on glucose regulation. Circadian misalignment induced by inversion of the sleep/wake and fasting/feeding cycle by 12 h relative to the timing of the central circadian pacemaker during a forced desynchrony protocol, increased postprandial plasma glucose despite increased insulin, decreased leptin, reduced sleep efficiency, and inverted the cortisol and melatonin profiles relative to the behavioral cycle [47]. Statistical analysis suggested that the effects of misalignment could not be merely explained by the decrease in sleep efficiency [47], while the effects could also not be explained by a difference in slow wave sleep [48]. In a different study, a 2.5-wk history of combined circadian misalignment (forced desynchrony) plus sleep restriction (5.6h TIB/24h) compared to a baseline 10-h TIB and 9 recovery days with 10 h TIB resulted in increased glucose and decreased insulin concentrations following a mixed meal, indicating decreased pancreatic beta-cell function

[49]. To test directly whether circadian misalignment *per se* has adverse effects on metabolism, the effect of a combination of prior circadian misalignment and sleep loss was compared to the same degree of sleep loss alone [50]*. Sleep restriction to 5 h TIB/24h for 8 days reduced insulin sensitivity compared to baseline in both the aligned and misaligned conditions. In women, no significant difference was found in parameters derived from IVGTT when aligned and misaligned conditions were compared. However, in the larger group of men, the relative decrease in insulin sensitivity following misalignment was nearly twice as large (-58%) as compared to following the aligned condition (-32%, P=0.01). Despite the greater decrease in insulin sensitivity following circadian misalignment, the beta-cell response was similar in the two experimental conditions.

Conclusion

Experimental sleep restriction alone or in combination with misalignment, and decreases in sleep quality negatively affect glucose regulation. Sleep curtailment alters energy expenditure, weight regulation, gene-expression, and inflammatory cytokine levels. The effects of sleep restriction are observed in healthy individuals with varying age and gender and in patients with medical conditions such as type 1 diabetes. In patients with obstructive sleep apnea, the combination of disrupted sleep with hypoxia may have even worse effects on glucose metabolism. The effect of sleep on the progression of many other medical conditions and their treatment is unknown. Despite the convincing evidence for the deleterious effects of decreased sleep quality and quantity, there is a paucity of research performed to test sleep extension or sleep improvement as a therapeutic approach to improve metabolic health in individuals who have acquired or are at risk for developing obesity, diabetes, or cardiovascular disease.

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Key points

- Decreased sleep duration is associated with obesity, diabetes and cardiovascular disease
- Controlled laboratory studies have shown that decreased quantity and quality of sleep negatively affects glucose regulation and alters food intake and energy balance
- Large-scale field studies and controlled in-laboratory studies are needed to assess whether sleep interventions targeting the improvement of the quality and quantity of sleep will improve metabolic health

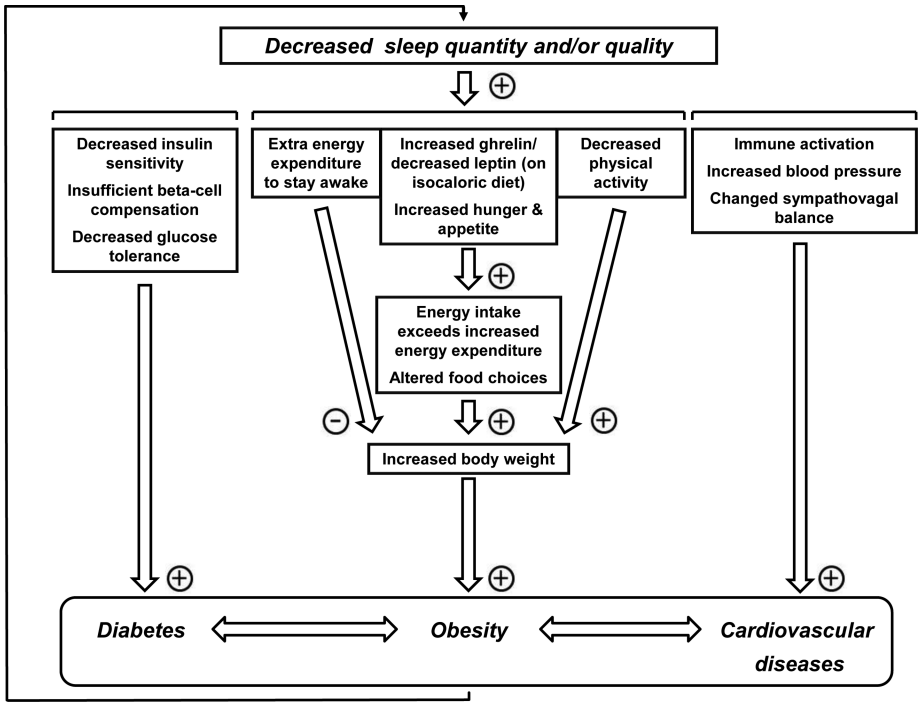

Fig. 1. Effects of sleep deprivation, links to obesity, diabetes, and cardiovascular disease

Epidemiological studies have shown an association between decreased sleep duration and diabetes, obesity, and cardiovascular disease. Controlled in-laboratory studies have provided evidence for a causal link and physiological mechanisms by which decreased quantity and/or quality of sleep may lead to the development of those medical conditions.