ELSEVIER

Sleep Medicine 9 Suppl. 1 (2008) S23–S28

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

Metabolic consequences of sleep and sleep loss

Eve Van Cauter[a,*], Karine Spiegel[b], Esra Tasali[a], Rachel Leproult[a]

[a]*Department of Medicine, University of Chicago, Chicago, IL, USA*
[b]*INSERM/UCBL – U628, Physiologie intégrée du système d'éveil, Département de Médecine Expérimentale, Faculté de Médecine, Université Claude Bernard Lyon 1, 69373 Lyon Cedex 08, France*

Abstract

Reduced sleep duration and quality appear to be endemic in modern society. Curtailment of the bedtime period to minimum tolerability is thought to be efficient and harmless by many. It has been known for several decades that sleep is a major modulator of hormonal release, glucose regulation and cardiovascular function. In particular, slow wave sleep (SWS), thought to be the most restorative sleep stage, is associated with decreased heart rate, blood pressure, sympathetic nervous activity and cerebral glucose utilization, compared with wakefulness. During SWS, the anabolic growth hormone is released while the stress hormone cortisol is inhibited. In recent years, laboratory and epidemiologic evidence have converged to indicate that sleep loss may be a novel risk factor for obesity and type 2 diabetes. The increased risk of obesity is possibly linked to the effect of sleep loss on hormones that play a major role in the central control of appetite and energy expenditure, such as leptin and ghrelin. Reduced leptin and increased ghrelin levels correlate with increases in subjective hunger when individuals are sleep restricted rather than well rested. Given the evidence, sleep curtailment appears to be an important, yet modifiable, risk factor for the metabolic syndrome, diabetes and obesity. The marked decrease in average sleep duration in the last 50 years coinciding with the increased prevalence of obesity, together with the observed adverse effects of recurrent partial sleep deprivation on metabolism and hormonal processes, may have important implications for public health.

Keywords: Sleep deprivation; Glucose metabolism; Diabetes; Appetite regulation; Leptin; Ghrelin; Obesity

1. Sleep patterns in society

For a variety of reasons, either by lifestyle choice, imposed by work or family demands, or due to physical or psychological problems, chronic sleep deprivation is increasingly common in our hectic modern society [1,2]. Societal changes, such as an increase in television viewing and internet use, have impacted sleep patterns, leading to chronic sleep deprivation in a substantial proportion of the population [1]. Over the past 50 years, sleep duration in adults and adolescents has decreased by 1.5–2 hours per night, and more than 30% of Americans between the ages of 30 and 64 report sleeping less than 6 hours per night [3]. In addition to societal impact, the aging of the population in Western countries is associated with a decrease in average sleep duration as older adults obtain on average 2 hours less sleep per night than younger adults, a deficit that is independent of the increased incidence of age-related disorders which can impact sleep patterns [4,5]. Furthermore, the quality of sleep declines with age, with a major reduction in the duration of slow wave sleep (SWS) and increased sleep fragmentation [4].

* Corresponding author. Department of Medicine, MC 1027, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA. Tel.: +1 773 702 0169; fax: +1 773 702 7686.
E-mail address: evcauter@medicine.bsd.uchicago.edu (E. Van Cauter).

2. Hormone release is modulated by sleep

SWS or deep sleep occurs during stages 3 and 4 of non-rapid eye movement (REM) sleep and is thought to be the most restorative of all sleep stages. Most slow wave activity occurs in the first two sleep cycles (approximately the first 3 hours of sleep), and the total amount of SWS per night is drastically reduced with age. Several important physiological activities only occur during the SWS, including a reduction in heart rate, blood pressure, sympathetic nervous activity and an increase in vagal tone [6]. SWS is also associated with a decrease in brain glucose metabolism [7]. Additionally, SWS exerts major modulatory effects on endocrine release. The release of the hormones of the hypothalamamic–pituitary–adrenocortical (HPA) system is inhibited [8], whereas the release of growth hormone (GH) and prolactin is increased. Both GH and cortisol have important roles in glucose metabolism. Laboratory studies have shown that the levels of these metabolic hormones are adversely affected by acute total sleep deprivation [9]. Studies in normal sleepers have shown that nocturnal GH release is reduced in individuals who are totally sleep deprived, but subsequently increases during daytime recovery sleep (with the reverse observed for cortisol release) [2].

1389-9457/08/$ – see front matter

An analysis of data from a series of studies was undertaken to determine the chronology of age-related changes in sleep duration and sleep quality in 149 healthy men, and whether sleep changes were associated with hormonal alterations [4]. The study found that the mean percentage of SWS decreased from 18.9% during early adulthood (age 16–25 years) to 3.4% during midlife (age 36–50 years), but remained unchanged from midlife to late life (age 71–83 years). Also, a significant decrease in sleep duration was observed across the age groups: each 10-year increment in age was associated with a 28-minute decrease in sleep duration ($P < 0.001$). The reductions in SWS observed with age were associated with a significant decline in GH secretion both from early to midlife ($P < 0.001$) and from midlife to late life ($P < 0.02$), and reductions in GH secretion were significantly associated with reductions in SWS independent of age ($P < 0.001$) [4].

Although the full clinical impact of chronic sleep deprivation on metabolic hormone release is yet to be determined, evidence indicates that dysfunction of glucose metabolism, obesity and increased diabetes risk are all likely outcomes [9].

3. Effect of sleep deprivation on carbohydrate metabolism and diabetes risk

Sleep appears to play an important role in the control of blood glucose levels, and recurrent partial sleep deprivation has been shown to have detrimental effects on carbohydrate metabolism and endocrine function [9,10]. A sleep debt study compared glucose metabolism in 11 young men undergoing periods of enforced partial sleep deprivation (4 hours sleep per night), sleep extension (12 hours sleep per night) and "normal" sleep as a baseline (8 hours sleep per night). During the sleep-restriction period, the individuals had significantly impaired glucose tolerance ($P < 0.04$; measured using the intravenous glucose tolerance test [IVGTT]), and significant reductions in their acute insulin response to glucose ($P = 0.05$) and in glucose effectiveness ($P < 0.0005$), compared with those observed when they were fully rested [10]. Insulin sensitivity was also reduced (5.41 versus 6.73×10^4/min/μU/mL), but this was not statistically significant [10]. The disposition index, a product of the acute insulin response to glucose and insulin sensitivity [11] and a marker of diabetic risk used in genetic studies [12], was significantly lower following sleep restriction than when the individuals were fully rested ($P = 0.0006$) [10].

Another study in young healthy adults showed that suppression of SWS without any reduction in total sleep time resulted in decreased insulin sensitivity, reduced glucose tolerance and increased risk of type 2 diabetes, suggesting that a reduction in SWS (such as that seen in the elderly and in many obese individuals), independent of the overall duration of sleep, may be particularly important for normal glucose metabolism [13]. The mechanisms by which sleep deprivation impacts glucose tolerance are thought to be multifactorial, including decreased brain glucose utilization, alterations in the sympatho-vagal balance, increased evening cortisol and extended night-time GH secretion, and proinflammatory processes [14].

The impact of short sleep duration on the risk of diabetes has been shown in several epidemiological studies, with a significant increase in incidence of diabetes in individuals who have difficulty in maintaining sleep or who experience chronic short sleep duration [15–17]. The largest of these, the prospective 10-year Nurses Health Study in 70,026 women [15], showed that individuals who slept 5 hours per night or less had a significantly higher risk of being diagnosed with diabetes (odds ratio [OR] 1.57, 95% CI: 1.28–1.92) compared with those who slept 8 hours per night, although this association was not significant after adjustment for obesity and other confounding factors (OR 1.18, 95% CI: 0.96–1.44). However, the increase in the risk of *symptomatic* diabetes with ⩽5 hours sleep per night versus 8 hours remained significant even after adjustment (OR 1.34, 95% CI: 1.04–1.72), suggesting that, although diabetes risk is increased by obesity (which appears to be more prevalent in short sleepers and, conversely, may result in poor sleep quality), insufficient sleep may be a risk factor for more severe diabetes [15].

Data from laboratory and epidemiological studies suggest that in addition to changes in glucose/carbohydrate metabolism, the relationship between sleep deprivation and diabetes risk may also involve upregulation of appetite and decreased energy expenditure, both of which can lead to obesity, itself a major risk factor for diabetes [14].

4. Sleep duration and appetite regulation

Food intake is controlled by the neuroendocrine system which is itself controlled by the central nervous system [18]. Long-term regulators of food intake include insulin and leptin, which are released in proportion to the amount of body fat. These hormones exert sustained inhibitory effects on food intake while increasing energy expenditure [18]. Ghrelin, on the other hand, is an appetite stimulating hormone released by cells in the stomach. In the non-pathological state, ghrelin levels rise rapidly before meals and fall equally rapidly after food intake (Figure 1). Both ghrelin and leptin are part of the orexin system, which integrates control of feeding, wakefulness and energy expenditure in the body, and they exert their influence on the central nervous system via receptors in the "appetite center" of the brain: the ventromedial and arcuate nuclei of the hypothalamus. Although the exact mechanisms are unclear, leptin and ghrelin are thought to act in parallel as opposing metabolic counterparts for body mass homeostasis [19].

Sleep duration plays an important role in the regulation of leptin and ghrelin levels in humans: several studies have shown that recurrent partial sleep deprivation and chronic short sleep are associated with a significant decrease in levels of leptin and increase levels of ghrelin (Figure 2A) [20–23]. In a randomized, cross-over study, 2 nights of short sleep (4 hours) were compared with 2 nights of long sleep (10 hours) on metabolic parameters. Results showed that a