The Impact of Sleep Deprivation on Hormones and Metabolism

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Faculty and Disclosures

Introduction

Sleep loss can occur as a result of habitual behavior or due to the presence of a pathological condition that is associated with reduced total sleep time. This column focuses on the impact of behavioral sleep curtailment, an endemic condition in modern society, and provides evidence against the old notion that "sleep is for the mind, and not for the rest of the body."

Prevalence of Sleep Curtailment in Modern Society

Sleep curtailment is a hallmark of modern society, one that is often considered harmless and efficient. The advent of artificial light has permitted the curtailment of sleep to the minimum tolerable and an increase in the time available for work and leisure. In our 24-hour-a-day society, millions work during the night and sleep during the day, a schedule that generally results in substantial sleep loss.

Figure 1 illustrates changes in self-reported sleep duration over the past 50 years. In 1960, a survey of over 1 million people found a modal sleep duration of 8.0-8.9 hours.[1] In 2000, 2001, and 2002, polls conducted by the National Sleep Foundation indicated that the average duration of sleep for Americans had fallen to 6.9-7.0 hours.[2] Overall, sleep duration thus appears to have decreased by 1.5-2 hours during the second half of the 20th century. Today, many people are in bed only 5-6 hours per night on a regular basis.

Figure 1. Self-reported sleep duration, 1960-2002.

The 2 major pathways by which sleep affects the release of hormones are the hypothalamic-pituitary axes and the autonomous nervous system. The release of hormones by the pituitary — the "master" endocrine organ that controls the secretion of other hormones from the peripheral endocrine glands — is markedly influenced by sleep. Modulation of pituitary-dependent hormonal release is partly mediated by the modulation of the activity of hypothalamic-releasing and/or hypothalamic-inhibiting factors controlling pituitary function. During sleep, these hypothalamic factors may be activated — as in the case of growth hormone (GH)-releasing hormone — or inhibited, as is the case for corticotropin-releasing hormone.

The other pathway by which sleep affects peripheral endocrine regulation is via the modulation of autonomic nervous system activity. During deep sleep, sympathetic nervous system activity is generally decreased and parasympathetic nervous system activity is increased. Sleep loss is associated with an elevation of sympathovagal balance, with higher sympathetic but lower parasympathetic tone. Most endocrine organs are sensitive to changes in sympathovagal balance. Well-documented examples are pancreatic insulin secretion and release by the fat cells of leptin, an appetite-suppressing hormone.

A profound and generalized impact of sleep loss on the endocrine system should therefore be expected. Until recently, however, it was considered unlikely that the adverse effects of sleep deprivation on endocrine function would be long-term. The studies from which this notion was drawn examined the effects of only 1 or 2 nights of acute total sleep deprivation. In general, the data suggested that endocrine alterations that occurred during the sleepless night(s) were completely reversed during recovery sleep.

More recently, a few studies have examined the impact on hormones, metabolism, and immune function of the much more common, real-life situation — chronic partial sleep deprivation.[3,4] The earliest study measured hormonal and metabolic parameters in subjects studied after 6 days of sleep restriction (4-hour bedtime) and after full sleep recovery (6 days of 12-hour bedtime).[5] Subsequent studies examined the impact of less severe sleep restriction (6.5 hours per night) over 1 week[6] as well as the effects of short-term sleep curtailment (2 days with 4-hour vs 12-hour bedtime).[7]

Alterations of Pituitary-Dependent Hormones During Sleep Loss

The first effect of partial sleep loss on circulating levels of pituitary-dependent hormones to be documented under various study conditions is an increase in the early evening levels of the stress hormone cortisol.[3,6] Normally at that time of day, cortisol concentrations are rapidly decreasing to attain minimal levels shortly before habitual bedtime. The rate of decrease of cortisol concentrations in the early evening was approximately 6-fold slower in subjects who had undergone 6 days of sleep restriction.
than in subjects who were fully rested.[8] Elevations of evening cortisol levels in chronic sleep loss are likely to promote the development of insulin resistance, a risk factor for obesity and diabetes.

The upper and middle panels of Figure 2 illustrate the impact of sleep restriction on the thyroid axis.[9] After 6 days of 4-hour sleep time, the normal nocturnal thyroid-stimulating hormone (TSH) rise was strikingly decreased, and the overall mean TSH levels were reduced by more than 30%.[9] A normal pattern of TSH release reappeared when the subjects had fully recovered. Differences in TSH profiles between the 2 bedtime conditions were probably related to changes in thyroid hormone concentrations via a negative-feedback regulation, because the free thyroxine index (FT$_4$) was higher in the sleep-restriction condition than in the fully rested condition (middle panels of Figure 2). Thyroid axis function was thus markedly altered by partial recurrent sleep restriction.

Figure 2. Levels of thyroid-stimulating hormone (TSH), free thyroxine index, and leptin in sleep-deprived vs well-rested subjects. From top to bottom, 24-hour (+SEM) profiles of TSH, free thyroxine indexes, and leptin in healthy young subjects when submitted to partial sleep restriction for 6 days (4-hour sleep times; mean total sleep time during previous 2 nights, 3 hours 49 minutes; left panels) and after full sleep recovery (12-hour sleep times for 6 nights; mean total sleep time during previous 2 nights, 9 hours 3 minutes; right panels). The black bars represent the sleep periods.[3,10]

The temporal organization of GH secretion is also altered by chronic partial sleep loss.[7] The normal single GH pulse occurring shortly after sleep onset splits into 2 smaller pulses, 1 before sleep and 1 after sleep; as a result, the peripheral tissues are exposed to high GH levels for an extended period of time, which, because GH has anti-insulin-like effects, could also have an adverse impact on glucose tolerance.

Impact of Sleep Loss on Hormones Controlling Appetite

Sleeping and feeding are intricately related. Animals faced with food shortage or starvation sleep less,[48] conversely, animals subjected to total sleep deprivation for prolonged periods of time increase their food intake markedly.[9] Recent studies in humans have shown that the levels of hormones that regulate appetite are profoundly influenced by sleep duration. Sleep loss is associated with an increase in appetite that is excessive in relation to the caloric demands of extended wakefulness.

The regulation of leptin, a hormone released by the fat cells that signals satiety to the brain and thus suppresses appetite, is markedly dependent on sleep duration. After 6 days of bedtime restriction to 4 hours per night, the plasma concentration of leptin was markedly decreased, particularly during the nighttime.[10] The magnitude of this decrease was comparable to that occurring after 3 days of restricting caloric intake by approximately 900 kcal/day. But the subjects in the sleep-restriction condition received identical amounts of caloric intake and had similar levels of physical activity as when they were fully rested. Thus, leptin levels were signaling a state of famine in the midst of plenty.

In a later study, the levels of ghrelin, a peptide that is secreted by the stomach and stimulates appetite, were measured with the levels of leptin after 2 days of sleep restriction (4 hours of sleep) or sleep extension (10 hours of bedtime).[5] The subjects also assessed their levels of hunger and appetite at regular intervals. Sleep restriction was associated with reductions in leptin (the appetite suppressant) and elevations in ghrelin (the appetite stimulant) and increased hunger and appetite, especially an appetite for foods with high-carbohydrate contents. Similar findings were obtained simultaneously in a large epidemiologic study in which sleep duration and morning levels of leptin and ghrelin were measured in over 1,000 subjects.[11] The Table summarizes the remarkable concordance between the results of the 2 studies. Despite the differences in study design, both studies found a decrease in the satiety hormone leptin and an increase in appetite-stimulating ghrelin with short sleep.

Sleep loss therefore seems to alter the ability of leptin and ghrelin to accurately signal caloric need and could lead to excessive caloric intake when food is freely available. The findings also suggest that compliance with a weight-loss diet involving caloric restriction may be adversely affected by sleep restriction.

During the second half of the 20th century, the incidence of obesity has nearly doubled, and this trend is a mirror image of the decrease in self-reported sleep duration illustrated in Figure 1. The discovery of a profound alteration in the neuroendocrine control of appetite in conditions of sleep loss is consistent with the conclusions of several epidemiologic studies that revealed a negative association between self-reported sleep duration and body mass index. Taken together, the current evidence suggests a possible role for chronic sleep loss in the current epidemic of obesity.

Metabolic Implications of Recurrent Sleep Curtailment

Recent work also indicates that sleep loss may adversely affect glucose tolerance and involve an increased risk of type 2 diabetes.

In young, healthy subjects who were studied after 6 days of sleep restriction (4 hours in bed) and after full sleep recovery, the levels of blood glucose after breakfast were higher in the state of sleep debt despite normal or even slightly elevated insulin responses.[8] The difference in peak glucose levels in response to breakfast averaged ±15 mg/dL, a difference large enough to suggest a clinically significant impairment of glucose tolerance.
These findings were confirmed by the results of intravenous glucose tolerance testing. Indeed, the rate of disappearance of glucose post injection — a quantitative measure of glucose tolerance — was nearly 40% slower in the sleep-debt condition than after recovery, and the acute insulin response to glucose was reduced by 30%. Glucose tolerance measured at the end of the recovery period was similar to that reported in an independent study in young, healthy men, but glucose tolerance in the state of sleep debt was comparable to that reported for older adults with impaired glucose tolerance. Thus, less than 1 week of sleep restriction can result in a prediabetic state in young, healthy subjects. Of note, the adverse impact of sleep deprivation on glucose tolerance demonstrated in laboratory studies is consistent with the finding of an increased risk of symptomatic diabetes with short sleep in a cohort study of women.

Multiple mechanisms are likely to mediate the adverse effects of sleep curtailment on parameters of glucose tolerance, including decreased cerebral glucose utilization, increases in sympathetic nervous system activity, and abnormalities in the pattern of release of the counterregulatory hormones cortisol and GH.

**Conclusion**

Clearly, sleep is not only for the brain but also for the rest of the body. Recent evidence suggests that sleep loss, a highly prevalent — and often strongly encouraged — condition in modern society could be a risk factor for major chronic diseases, including obesity and diabetes.

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