CHAPTER 15

Sleep and Endocrinology

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INTRODUCTION

Endocrinology is a subspecialty of internal medicine that focuses on the physiology and pathology of hormonal release and action. Hormones are chemical messengers that are secreted by endocrine cells, transported in the peripheral circulation and act on other cell types. This chapter will focus on three categories of hormones: 1) hormones of the hypothalamo-pituitary axes, in particular growth hormone (GH), prolactin, cortisol and thyroid-stimulating hormone (TSH), 2) insulin, the major hormone involved in glucose metabolism, and 3) two hormones that play a major role in appetite regulation, leptin and ghrelin.

The present chapter is illustrated in the slide-set 6 presentation from the **Basics of Sleep Guide Slide Sets** (v1.1)[1]; references to slide numbers are provided. We are including a few additional figures illustrating findings that have emerged after the SRS Slide Set became available. **Section A** describes the typical hormonal profiles of young healthy adults. This section will show the impact of two major modulators of endocrine release, the sleep/wake cycle and the circadian process. **Section B** is dedicated to the impact of aging on sleep quality, hormones and glucose metabolism. **Section C** describes the impact of sleep disturbances on endocrine function and metabolism. **Section D** summarizes the effects of sleep deprivation and short sleep duration on hormones and glucose metabolism.

A. SLEEP AND ENDOCRINOLOGY IN HEALTHY YOUNG ADULTS

In humans, the control of the temporal organization of 24-hour profiles of hormones of the hypothalamo-pituitary axes, and more generally of all hormonal profiles, results mainly from the interaction of two time-keeping mechanisms in the central nervous system, i.e., circadian rhythmicity (i.e., intrinsic effects of biological time, irrespective of the sleep or wake state) and sleep/wake homeostasis (i.e., the effect of the sleep or wake state per se, irrespective of time of day). In mammals, endogenous circadian rhythmicity, often referred to as "process C," is generated by a pacemaker located in the paired suprachiasmatic nuclei of the hypothalamus. The sleep "homeostat," also referred to as "process S," is often represented as an hourglass mechanism relating the amount and intensity of sleep to the duration of prior wakefulness. The impact of circadian rhythmicity and sleep homeostasis on pituitary-dependent hormonal release is thought to be mediated by the modulation of the pulsatile activity of the hypothalamic releasing and/or inhibiting factors controlling pituitary function. In addition to the input of circadian rhythmicity and the sleep homeostat, other rhythmic and non-rhythmic events during the day, such as postural changes, stress, food intake and exercise modulate the overall waveform of the temporal patterns of hormone release. The autonomic nervous system (ANS) is another pathway linking the central control of sleep-wake homeostasis and circadian rhythmicity with peripheral endocrine organs (Slide 4').[2]

The circadian pacemaker takes several days to adjust to a large abrupt shift of the sleep-wake and light-dark cycles. Manipulations of the sleep/wake cycle can therefore be used to delineate the respective contributions of the circadian rhythmicity and sleep-wake homeostasis in hormonal profiles. For example, when the sleep period is delayed by 12 hours (12-hour shift protocol), the effects of the circadian modulation in the absence of sleep and the effects of sleep at an abnormal circadian time can be observed. An example of such a protocol is described in Slide 5.[1] The subjects were studied over a 53-hour period including 8 hours of

nocturnal sleep from 23:00 until 7:00, 28 hours of continuous wakefulness including a night of total sleep deprivation, and an 8-hour daytime recovery sleep period from 11:00 until 19:00, thus scheduled 12 hours out of phase with the usual bedtimes. To eliminate the effects of feeding, fasting and postural changes, the subjects remained recumbent throughout the study and meal ingestion was replaced by a continuous glucose infusion at a constant rate.

Roles of Sleep and Circadian Rhythmicity in Modulating the Release of Hypothalamo-Pituitary Hormones

Growth Hormone (GH): The 24-hour profile of plasma GH levels consists of stable low levels abruptly interrupted by bursts of secretion. In men, the most reproducible pulse occurs shortly after sleep onset. When the sleep period is shifted, the major GH pulse is also shifted. GH is thus a hormone primarily controlled by sleep-wake homeostasis. (Slide 6[1]) GH secretory pulses occur preferentially during slow wave sleep (SWS, stages 3 and 4) when slow wave activity (delta frequency range, 0.5-4 Hz) is high (Slide 7[1]). It is important to note that sex differences exist in GH secretion. Indeed, men secrete GH mostly during the first part of the night (when SWS occurs) whereas women secrete GH throughout the 24-hour cycle although a GH pulse associated with the first episode of SWS is generally present (Slide 8[1]). In both young and older men, but not in women, there is a "dose-response" relationship between SWS and nocturnal GH release.

Prolactin: In addition to its important role in the control of lactation in women, prolactin has multiple effects on metabolism and immune function. In both men and women, the 24-h profile of circulating prolactin levels under normal baseline conditions is characterized by a major nocturnal elevation starting shortly after sleep onset and culminating around mid-sleep. Sleep-onset, irrespective of the time of day at which it occurs, has a robust stimulatory effect on prolactin release. The temporal profile of prolactin release, similar to that of GH release, is thus primarily controlled by sleep-wake homeostasis (Slide 9[1]).

Pituitary-adrenal hormones: The 24-hour profiles of ACTH, a pituitary hormone, and cortisol, the hormone released by the adrenals in response to stimulation by ACTH, occur in close parallelism. Their profiles are characterized by an early morning maximum, declining levels throughout the daytime, a prolonged period of minimal levels, also called the quiescent period, centered around midnight and an abrupt circadian rise during the later part of the night. Drastic manipulations of the sleep-wake cycle only minimally affect the waveshape of these secretory profiles. The 24-hour rhythm of ACTH and cortisol are thus primarily controlled by circadian rhythmicity (Slide 10[1]) although as will be shown later, modest effects of sleep onset, offset and sleep deprivation are clearly present. Sleep onset is consistently associated with a short-term inhibition of cortisol secretion that may not be detectable when sleep is initiated in the morning, i.e., at the peak of corticotropic activity.[3-5] This inhibitory effect appears also during the sleep period and seems to be related to SWS.[6,7] Final awakenings from sleep as well as transient awakenings interrupting the sleep period consistently trigger pulses of cortisol secretion.[6,8,9-12]

Thyroid-stimulating hormone (TSH): Under normal conditions including nighttime sleep, 24-h variations of TSH levels include an early evening elevation that is under circadian control and declining levels following sleep onset that reflect an inhibitory influence of sleep per se. This inhibitory influence of sleep is primarily exerted by SWS and is clearly demonstrated during sleep deprivation, when TSH levels continue to increase until the middle of the usual sleep period. TSH secretion is thus controlled by both circadian rhythmicity and sleep homeostasis (Slide 11[1]).

Gonadotropins: There are important and complex effects of sleep and circadian rhythmicity on gonadotropin release (luteinizing hormone, LH and follicle-stimulating hormone, FSH) and the secretion of testosterone in men and estradiol in women. These effects are different in men and women, and are further influenced by the menstrual cycle in normally cycling women. LH and FSH are secreted in a pulsatile pattern. In adult men, nighttime LH pulsatile activity seems to be related to the REM-NREM cycle. Both LH and FSH show no clear diurnal variation. In adult women, LH pulses are less frequent during sleep in the early follicular phase and early luteal phase, less influenced by sleep during the mid-follicular phase and mid-luteal phase, have a higher amplitude during the late follicular phase and a lower amplitude during late luteal. FSH and estradiol profiles show a circadian pattern with respectively lower and higher values during the sleep period.[2] In men, there is a clear parallelism between cortisol and testosterone profiles during the daytime but in early sleep, testosterone levels increase rapidly whereas cortisol remain low for another 1-2 hours (Slide 12[1]).

Roles of Sleep and Circadian Rhythmicity in Modulating Glucose Metabolism

Glucose tolerance reflects the balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as muscle and adipose tissue, and by non-insulin dependent tissues, such as the brain. When caloric intake is exclusively under the form of an intravenous glucose infusion at a constant rate, hepatic glucose production is inhibited and temporal variations in blood glucose levels represent variations in glucose utilization. In the 12-hour shift protocol (Slide 5[1]), the subjects stayed recumbent such that changes in physical activity were minimal and temporal variations in glucose levels reflected mainly changes in glucose utilization by the brain (Slide 14[1]). During the first half of nocturnal sleep, levels of glucose were increased by approximately 30 percent, indicating a decrease in glucose utilization. During the second half of sleep, glucose levels declined to return to baseline in the morning. These robust changes in glucose levels across the nocturnal period were followed by parallel variations in insulin secretion, with the nocturnal elevation averaging 60%. During sleep deprivation, glucose levels and insulin secretion rose again to reach a maximum at a time corresponding to the beginning of the habitual sleep period, indicating the existence of an intrinsic circadian modulation of glucose regulation. The magnitude of the rise above morning levels was less than that observed during nocturnal sleep. Daytime sleep was associated with marked elevations of glucose levels and insulin secretion, indicating that sleep per se, irrespective of the time of day when it occurs, exerts modulatory influences on glucose regulation (Slide 14[1]).

Temporal Variations in Hormones Involved in Appetite Regulation

The peripheral signals involved in appetite regulations include leptin, a satiety hormone secreted by the adipocytes, and ghrelin, a hunger hormone released primarily from stomach cells. The 24-hour levels of both leptin and ghrelin show clear diurnal variations (Slide 15[1]). The diurnal variation of the satiety hormone leptin is largely dependent on meal intake[13] and therefore shows a morning minimum and increasing levels throughout the daytime culminating in a nocturnal maximum. Nonetheless, under conditions of constant caloric intake such as continuous enteral nutrition, a sleep-related elevation of leptin clearly occurs, irrespective of the timing of sleep.[14] During the daytime, ghrelin levels decrease rapidly after meal ingestion and then increase in anticipation of the following meal. Similar to leptin, concentrations of the hunger hormone ghrelin are increased during the nocturnal Period. Ghrelin levels decrease during the second part of the night despite the absence of food intake suggesting an inhibitory effect of sleep per se. Elevated leptin levels in association with decreasing ghrelin levels during sleep may prevent hunger during the overnight fast.

B. AGE-RELATED CHANGES IN SLEEP AND ENDOCRINOLOGY

Age-Related Changes in Sleep and Hypothalamo-Pituitary Hormones

The normal process of aging involves alterations in both sleep regulation and circadian rhythmicity and thus their control of the temporal organization of endocrine release. Age-related changes in sleep quality (e.g., lighter and more fragmented sleep) contribute to age-related changes of hormonal secretions. In a study comparing young (20-27 years old)) and older (67-84 years old) men, daytime and nighttime levels of both GH and TSH were greatly decreased (Slide 17[1]). Prolactin concentrations were diminished only during the nighttime (Slide 17[1]). The overall waveshape of the cortisol profile was preserved but the amplitude of the rhythm was dampened in older adults (Slide 17[1]). The circadian rises of cortisol and TSH occurred earlier (1-1.5 hr) in older subjects indicating that circadian timekeeping is modified with age, with an advance of circadian phase in conditions of normal entrainment.[15]

A detailed analysis of sleep and hormonal profiles in 149 healthy men 16 to 83 years old, demonstrated a differential chronology of aging for different components of sleep.[16] From young adulthood to midlife, SWS was progressively replaced by lighter stages of sleep without significant changes in sleep fragmentation or REM sleep. From midlife to late life, there was no further significant decrease in SWS. From midlife to late life, sleep became more fragmented at the expense of decreases in both lighter stages of sleep (1+2) and REM sleep. Thus, age-related changes in the amount of SWS and REM sleep occur with different chronologies. (Slide 18[1]). Normal aging is thus associated with reductions in both total sleep time and sleep quality.

Profiles of plasma GH and cortisol in young men and older men of similar body mass index (BMI, 24.1 ± 0.6 kg/m^2 and 24.1 ± 0.8 kg/m^2, respectively) were examined to explore the possible role of the age-related alterations in sleep in age-related changes in the secretory pattern of these two hormones[16] (Slide 19[1]). The major GH pulse occurred during early sleep for both age groups but GH levels were markedly reduced in old age (Slide 19[1]). The chronology of age-related changes of GH secreted during sleep paralleled that

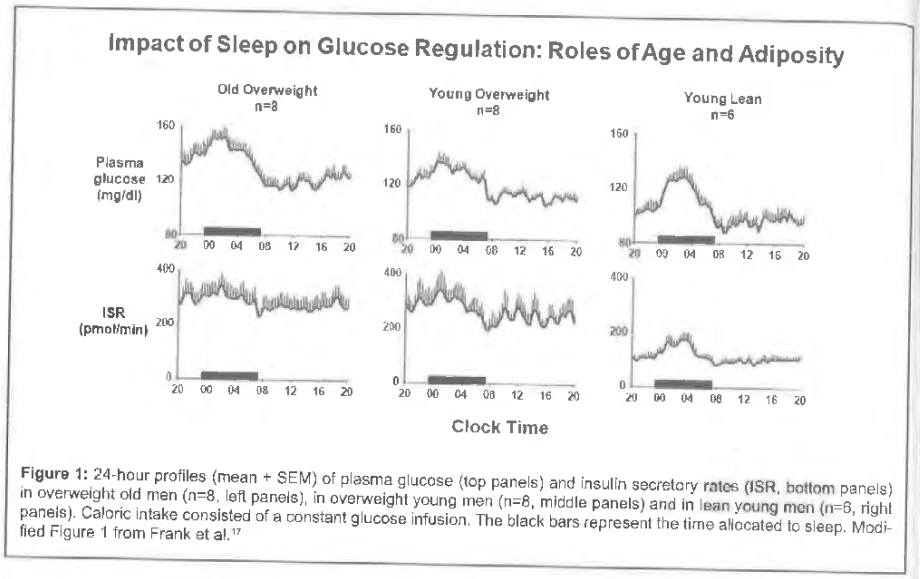

Figure 1: 24-hour profiles (mean + SEM) of plasma glucose (top panels) and insulin secretory rates (ISR, bottom panels) in overweight old men (n=8, left panels), in overweight young men (n=8, middle panels) and in lean young men (n=6, right panels). Caloric intake consisted of a constant glucose infusion. The black bars represent the time allocated to sleep. Modified Figure 1 from Frank et al.[17]

of the amount of SWS (Slide 20[1]). Indeed, GH secretion was markedly diminished from early adulthood to midlife. From midlife to late life, GH secretion further decreased but at a slower rate. The overall waveshape of the cortisol profile was preserved with age. Indeed, both young and older adults exhibited an early morning cortisol elevation, declining levels throughout the daytime and a nocturnal quiescent period (Slide 19[1]). But higher age was associated with an elevation of evening cortisol levels. Age-related changes of the nocturnal minimum of cortisol and the amount of REM sleep appeared later in life and followed the same chronology, i.e., the disturbances developed from midlife to old age (Slide 21[1]).[16]

To examine the relationship between SWS and GH secretion during sleep, two similar groups of subjects (matched for age and BMI) were selected for their difference in the amount of SWS. The group with higher amount of SWS had also higher nocturnal secretion of GH (Slide 22[1]).[16]

To examine the relationship between REM and nocturnal nadir of cortisol concentrations, subjects matched for age and BMI were split in two groups, one with high amount of REM sleep and one with low amount of REM sleep. The group with higher amount of REM sleep had also lower nocturnal minimum of cortisol. Thus, there is an inverse relationship between the amount of REM sleep and the level of the nocturnal minimum of cortisol[16] (Slide 23[1]).

Age-Related Changes in Glucose Metabolism

Aging is associated with alterations in glucose metabolism, with decreases in both insulin sensitivity and insulin secretion, and increased diabetes risk. There is also evidence that brain glucose utilization decreases with aging. Figure 1 (modified from[17]) represents the 24-hour mean (+SEM) profiles of glucose and insulin during a constant intravenous glucose infusion in 3 groups of subjects; old overweight (mean ± SD: age of 65 ± 5 years, BMI of 29 ± 2 kg/m^2), young weight-matched (age of 25 ± 4 years, BMI of 28 ± 3 kg/m^2) and young lean (age of 25 ± 2 years, BMI of 22 ± 1 kg/m^2) men. Glucose levels were highest for the old overweight group, intermediate for the young weight-matched controls and lowest for the young lean subjects, indicating that both increased adiposity and age per se affect glucose control. Similar insulin levels were observed for the old overweight and young weight-matched, but the temporal variations in insulin failed to mirror the glucose changes and overall insulin levels were markedly higher when compared to young lean men. Therefore, older adults were more insulin resistant than their weight-matched young controls since for the same amount of insulin, they exhibited higher glucose levels.[17]

Both age-related changes in the secretion of counterregulatory hormones (decrease of GH release and elevation of evening levels of cortisol) and in sleep duration and quality are likely to play a role in the decrease of glucose tolerance during normal aging.[18]

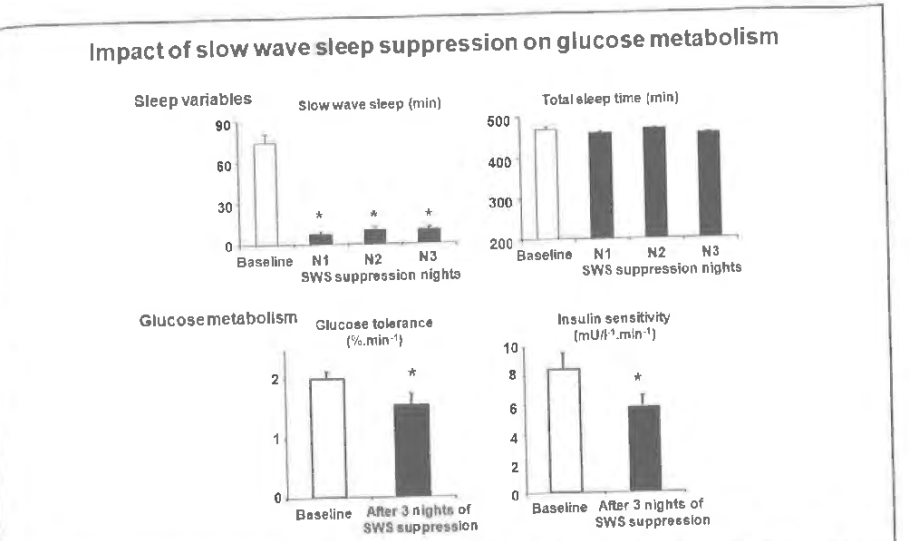

Figure 2: Results from the slow-wave sleep (SWS) suppression study. The top panels show the SWS (left panel) and the total sleep time (right panel) during an undisturbed night (baseline) and during the 3 nights of SWS suppression (N1, N2 and N3). The lower panels show glucose tolerance and insulin sensitivity after undisturbed nights (Baseline) and after 3 nights of SWS suppression. The asterisks indicate a significant difference with the undisturbed nights. Modified and combined Figures 1 and 3 from Tasali et al.[21]

C. IMPACT OF REDUCED SLEEP QUALITY AND SLEEP DISORDERS ON ENDOCRINE FUNCTION AND METABOLISM

Full Arousals Interrupting Sleep in Healthy Young Adults

Awakenings that interrupt sleep coincide consistently with declining prolactin levels[19] (Slide 26[1]) and with increased levels of cortisol and TSH[20] (Slide 27[1]). Increased dopaminergic tone has been implicated in the decline of prolactin levels. Fragmented sleep is thus associated with lower nocturnal prolactin levels, and higher nocturnal cortisol and TSH levels.

Impact of Low SWS Due to Micoarousals

A recent study[21] demonstrated major alterations of glucose metabolism in young healthy subjects in whom sleep quality was experimentally decreased by suppressing SWS via acoustic stimulation without inducing full arousals. An intravenous glucose tolerance test was performed after 2 nights of undisturbed sleep and after 3 nights of SWS suppression. Figure 2 shows the results for sleep variables (SWS and total sleep time) and glucose metabolism (glucose tolerance and insulin sensitivity). SWS decreased by 90% during the 3 nights of SWS suppression, reaching levels observed in older adults, and was replaced by stage 2 and REM sleep, without a significant change in the amount of total sleep time. Both glucose tolerance and insulin sensitivity were decreased by about 25% after 3 nights of SWS suppression, as compared to the undisturbed nights condition. Importantly, the decreases in insulin sensitivity were correlated with the reductions in SWS. The 24-hour cortisol profile was not affected by the microarousals induced to suppress SWS but daytime sympathetic nervous activity was markedly enhanced. These findings demonstrate that reduced intensity of non-REM sleep without change in sleep duration may adversely affect glucose regulation. These findings suggest that conditions involving low amounts of SWS (such as normal aging, obesity and sleep-disturbed breathing) are likely to be associated with increased diabetes risk.

Insomnia

Despite the high prevalence of insomnia, there is very little information on endocrine function and metabolism in insomniacs. One small, but well-documented

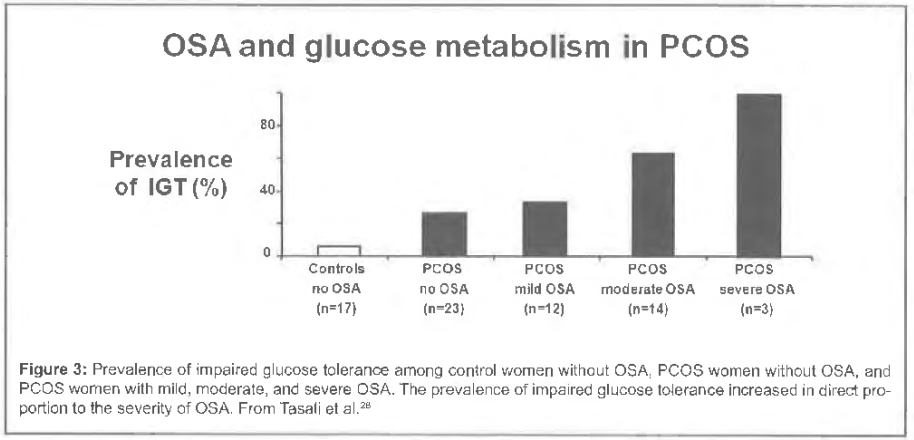

Figure 3: Prevalence of impaired glucose tolerance among control women without OSA, PCOS women without OSA, and PCOS women with mild, moderate, and severe OSA. The prevalence of impaired glucose tolerance increased in direct proportion to the severity of OSA. From Tasali et al.[28]

study showed that insomniacs have an elevated 24-hour mean cortisol level when compared to age- and BMI-matched controls without sleep disturbances. The greatest differences are observed in the evening and during the first part of the night. (Slide 29[1]) The degree of sleep disturbance plays a role in determining the endocrine alteration since among insomniacs, higher cortisol levels in the evening and throughout the nighttime period were observed only for those with low total sleep time (Slide 30[1]).[22]

Sleep-Disordered Breathing (SDB)

Sleep disorder breathing (SDB) is one of the most common sleep disorders and obstructive sleep apnea (OSA) is the most common form of SDB. A few studies have examined the effects of Continuous Positive Airway Pressure (CPAP), the treatment of choice for OSA, on pituitary hormone secretions. In untreated apneic patients, GH, a mostly sleep-dependent hormone, is decreased, especially during nighttime. A clear increase of GH levels during the first few hours of sleep has been demonstrated in apneic patients during the first night of CPAP treatment (Slide 31[1]).[23] It is likely that the restoration of sleep-related GH release in early sleep reflects the restoration of SWS. Studies on the effects of OSA and CPAP treatment on cortisol are limited and not consistent. One study[24] showed a decrease in the at-night cortisol levels after 3 months of CPAP treatment. In addition, CRH administration increased ACTH but not cortisol in obese sleep apneics patients.[24,25]

OSA is associated with elevated levels of leptin, after controlling for the degree of adiposity. OSA patients are thought to be more leptin resistant than similarly obese subjects who do not have OSA. In a few studies, a reduction of leptin levels following CPAP treatment was observed.[26]

A large body of evidence has shown that SDB is an independent risk factor for insulin resistance and diabetes, after controlling for BMI, age, sex and other potential confounders. The evidence comes from epidemiologic studies, clinic-based studies and studies of CPAP treatment of patients with OSA.[27]

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects about 5% of women. Insulin resistance is considered as a hallmark of this disorder. Women with PCOS often have impaired glucose tolerance and tend to develop type 2 diabetes at an early age. PCOS women are 7 times more likely to have OSA than similarly obese non-PCOS women.[28] PCOS women with OSA are markedly more insulin resistant than those without OSA after controlling for age, BMI and ethnicity while PCOS women without OSA present only minimal increases in insulin resistant relative to similarly obese women. The degree of metabolic alterations in PCOS is highly correlated with the presence and severity of OSA. Figure 3 shows that the prevalence of impaired glucose tolerance increases in direct proportion to the severity of OSA. Thus, insulin resistance in PCOS appears to be largely determined by the presence of OSA. PCOS is comprised of two sub-phenotypes: PCOS with OSA and PCOS without OSA, each with distinct metabolic alterations. A study including eight women with PCOS and OSA assessed by polysomnography demonstrated that the severity of SDB is strongly associated with glycosylated hemoglobin, a measure of glucose tolerance (Slide 32[1]).[29]

D. IMPACT OF SLEEP DEPRIVATION AND SLEEP RESTRICTION

Sleep Loss and Hypothalamo-Pituitary Hormones

Acute sleep deprivation results in drastically diminished nocturnal secretion of sleep-related hormonal release, i.e., GH and prolactin, whereas circadian-related hormones such as cortisol are only minimally affected by sleep loss. Since TSH profiles are under the control of both circadian- and sleep-related processes with sleep having an inhibitory influence on TSH levels, total sleep deprivation results in a major elevation of nocturnal TSH levels (Slide 34[1]).[30] Although the diurnal variation of cortisol levels is preserved with sleep loss, evening cortisol levels are significantly higher on the evening following one night of partial or total sleep deprivation than on the previous day at the same clock time (Slide 35[1]).[31] Therefore, sleep loss over one night, whether total or partial, appears to delay the normal return to low levels of the corticotropic axis.

Except for cortisol, the impact of sleep loss on hypothalamo-pituitary hormonal profiles is very different when sleep loss is partial and recurrent instead of acute (Slide 36[1]).[32] The most reproducible and often the largest GH pulse in normal adult men appears during early sleep, in temporal association with the first phase of SWS. Acute total sleep deprivation essentially suppresses nocturnal GH secretion. After a semi-chronic partial sleep restriction of 6 consecutive nights of 4 hours allocated to sleep, a GH pulse prior to sleep onset is observed, contrasting with the usual single nocturnal GH pulse in early sleep seen with a normal 8-hour night of sleep (Slide 38[1]). This extended period of elevated GH concentrations in the semi-chronic sleep restriction condition could have had an adverse impact on glucose tolerance.[33]

TSH profiles observed in young healthy subjects under conditions of normal nocturnal sleep with 8-hour bedtimes are characterized by low and relatively stable daytime levels followed by a rapid elevation starting in the early evening and culminating in a nocturnal maximum occurring around the beginning of the sleep period. The TSH levels then gradually decline during sleep to reach daytime values shortly after awakening. The inhibitory influence exerted on TSH during sleep is clearly revealed by the profiles observed in the same subjects during acute total sleep deprivation. Indeed, maximal TSH levels are nearly twice as high during nocturnal wakefulness than during nocturnal sleep. In contrast, after sleep restriction to 4 hours for 6 consecutive nights, the nocturnal TSH elevation is markedly dampened and the total amount of TSH secreted is reduced (Slide 40[1]). The blunting of the nocturnal TSH increase and reduced 24-hour TSH levels after recurrent sleep restriction may represent the effect of high thyroid hormone levels since a concomitant elevation of total free thyroxin index was observed.[34]

Sleep Loss and Glucose Metabolism

In modern societies, sleep loss has become more and more common over the past few decades. Most individuals choose to curtail their sleep to spend more time at work, commuting to and from work or involved in leisure activities. To evaluate the impact of a semi-chronic partial sleep deprivation on various hormones, 11 young healthy subjects underwent a 16-day protocol, the "Sleep Debt Study" (Slide 37[1]). They started with a baseline period (3 nights of 8 nighttime hours allocated to sleep), followed by a period of sleep restriction (6 nights of 4 nighttime hours allocated to sleep) and a period of sleep extension (7 nights of 12 hours allocated to sleep) to pay the sleep debt that accumulated during the sleep restriction period. At the end of the sleep restriction and at the end of the sleep extension, blood sampling at frequent intervals was conducted for 24 hours under controlled conditions with the subjects remaining at bed rest and receiving three identical carbohydrate-rich meals as their only caloric intake.

In the Sleep Debt Study, glucose response to breakfast was higher after sleep restriction, as compared to the sleep extension condition, despite similar insulin secretory rates (Slide 42[1]).[34] In the same protocol, the volunteers underwent an intravenous glucose tolerance test after 5 days of sleep restriction and 5 days of sleep extension. The rate of decrease of glucose levels after intravenous glucose injection, an index of glucose tolerance, was nearly 40% slower after sleep restriction than after sleep extension. The profile of insulin shows a biphasic pattern: the first phase corresponds to the rapid release of insulin stored in the beta cells whereas the second phase corresponds to the release of insulin newly synthesized. The first phase of insulin secretion was markedly reduced after sleep restriction, as compared to sleep extension. Analysis of the glucose and insulin responses by a mathematical model[35] demonstrated a 30% decrease in glucose effectiveness, a measure of non-insulin dependent glucose utilization. Insulin sensitivity was lower in the sleep debt condition but the changes did not reach statistical significance (Slide 43[1]).[34]

The adverse effect of sleep loss on glucose tolerance probably involves multiple pathways (Slide 44[1]). Because the brain is a major site of non-insulin-dependent glucose uptake, the decrease in glucose effectiveness

Chapter 15: Sleep Pearl

A 26-year-old woman presents with complaints of nighttime awakenings and daytime sleepiness for over 6 months. She maintains a regular bedtime and wake time, allowing 7 hours of time in bed and thinks that she sleeps for about a total of 5-6 hours. She has been told that she snores by friends. She does not have a regular bed partner. Past medical history is significant for depression. Irregular menstrual periods, weight gain of about 25 lbs over past 2 years, severe acne, and more than usual facial hair. Medications include Sertraline and multi- vitamins. Examination is remarkable for BMI=32 and elevated blood pressure.

In addition to insufficient sleep, an endocrine disorder should be considered as part of the differential diagnosis in this patient. The history of hirsutism (excessive hair growth), weight gain, irregular menstrual cycles, elevated blood pressure, and snoring in a young woman, suggest polycystic ovary syndrome (PCOS). PCOS is characterized by insulin resistance and increase production of androgen which can lead to acne, excessive hair growth, weight gain, and problems with ovulation. Obesity and the high levels of androgen increase the risk of obstructive sleep apnea. Therefore, women with PCOS have greater chances of developing several serious diseases, including type 2 diabetes, cardiovascular disease and obstructive sleep apnea. Furthermore, depression and insomnia are also more prevalent among women with PCOS than in the general population.

This Sleep Pearl was provided by Phyllis C. Zee, MD, PhD, FAASM, Northwestern University Medical School, Chicago, IL

is likely to reflect decreased brain glucose utilization, consistent with PET studies that have shown reduced brain glucose utilization in sleep-deprived subjects.[38] Disturbances in the secretory profiles of the counterregulatory hormones, cortisol and GH, may also contribute to the alterations in components of glucose regulation observed during sleep loss. Pancreatic beta-cell function is influenced by autonomic nervous activity, with sympathetic activation inhibiting and parasympathetic activation stimulating insulin release. Thus, the reduction in acute insulin response to intravenous glucose could be related to the alteration in sympathovagal balance. In the sleep restriction condition, heart rate variability, estimated via the auto-correlation coefficients of the inter-beat-intervals, was indeed higher over the 24-hour period, as compared to the sleep extension condition (Slide 45[1]).[37] The impact of sleep restriction on sympathovagal balance was particularly important in the morning. This increase in sympathetic versus parasympathetic tone is the most probable cause of the decreased beta-cell responsiveness in the sleep debt condition, and may also negatively affect other functions such as cardiac function, blood pressure regulation and kidney function.

These well controlled laboratory studies have some limitations such as the sample size and short duration of recurrent sleep restriction. The findings were confirmed in a recent study performed in an independent laboratory, showing that one week of sleep restriction to 5 hours per night in healthy men resulted in reduced insulin sensitivity as assessed by the hyperinsulinemic euglycemic clamp.[38] A recent paper[39] showed that, in older adults who report sleeping at least 8.5 hours (but actually sleep 7 to 7.5 hours based on actigraphy), 8 weeks of bedtime restriction (resulting in a decrease in total sleep time by an average of 62 min as compared to an average of 24 min in the control group) did not improve glucose tolerance, as assessed by serum glucose level obtained 2-hour post oral glucose administration. This study indicates that being a long sleeper or trying to sleep longer by spending more time in bed has no benefit on glucose metabolism in older adults. This supports the view that the increased mortality/morbidity of long sleepers is not directly a consequence of sleep but rather a consequence of other underlying factors.

As future directions, research studies are needed to determine if longer sleep duration could improve glucose metabolism in diabetics.

Sleep Loss and Appetite Regulation

In the Sleep Debt Study, both the mean leptin levels and the amplitude of the diurnal variation were decreased after sleep restriction in comparison with the sleep extension condition despite stable BMI, and identical amounts of caloric intake and physical activity (Slide 41[1]). The difference in maximal leptin levels between the state of sleep debt and the fully rested state was similar to what has been reported after 3 days of dietary restriction by ±900 Kcal per day.[40] Sleep restriction therefore alters the ability of leptin to accurately signal caloric need and produces an internal misperception of insufficient energy intake. The reduced leptin levels during the 4-h bedtime condition may therefore lead to increased food intake when food is available *ad libitum*.

Twelve healthy men (22 ± 2 years old) participated in another study (Slide 47[1]) involving 2 randomized experimental conditions, either 2 consecutive nights of 10 hours in bed (from 22:00 until 8:00) or 2 consecutive nights of 4 hours in bed (from 1:00 until 5:00). After receiving a standard hospital dinner at 19:00 on the evening of the second night, the subjects remained at bed rest and blood samples were obtained at 20 min intervals from 8:00 until 21:00 after the 2nd night. Caloric intake was kept constant and consisted of an intravenous glucose infusion at a constant rate. From 9:00 to 21:00, the subjects completed validated visual analog scales for hunger and appetite. Mean daytime leptin levels were 19% lower after 2 days of 4 hours bedtimes, as compared to 2 days of 10-hour bedtimes, whereas afternoon and evening ghrelin levels showed a 24% increase (Slide 48[1]). Ratings of hunger and global appetite were increased by 19% and 20%, respectively, with short sleep duration (Slide 49[1]). Importantly, the increase in hunger from the 10 hours to the 4 hours bedtime condition was highly correlated with the increase in the ratio of ghrelin to leptin concentrations (Slide 50[1]).[41] If the increase in hunger was to translate into a commensurate increase in food intake, it would correspond to a caloric excess of 350 to 500 Kcal/day for a young normal weight / sedentary adult. This excess in caloric intake could result in a high risk of clinically significant weight gain. A recent study comparing food intake in overweight middle-aged adults after 2 weeks of either sleep restriction (-1.5 hours per night) or extension (+1.5 hours per night) demonstrated a significant increase in caloric intake from snacks in the short sleep condition.[42] Consistent with findings from laboratory studies, an epidemiologic study [43] has reported similar differences in leptin and ghrelin levels when habitual short sleep duration was compared to normal sleep duration in a population of more than 1000 men and women, controlling for various factors such as age and BMI. Indeed, short sleep was associated with low leptin (15.5% lower leptin for nocturnal sleep of 5 hours vs. 8 hours) and with high ghrelin (14.9% higher ghrelin for nocturnal sleep of 5 hours vs. 8 hours) (Slide 51[1]).

Sleep Duration and Hormonal Characteristics

Nine of the 11 subjects who participated in the Sleep Debt Study were evaluated one year later during an 8-h bedtimes condition, using the exact same experimental procedures. Identical amounts of caloric intake, similar levels of physical activity and stable BMI were applied in this additional study condition. When the 3 bedtimes conditions (4 hours, 8 hours and 12 hours) were compared, decreasing sleep duration was associated with increasingly stronger alterations in hormonal characteristics (Slide 46[1]).[37] An inverse dose-response relationship was observed between evening cortisol levels and sleep duration. The mean leptin levels, the nocturnal leptin acrophase and the amplitude of the diurnal variations varied markedly with bedtime duration, in a dose-response manner. An inverse dose-response relationship between sleep duration and the post-breakfast homeostasis model assessment (HOMA) values was observed. HOMA is the normalized product of the insulin concentration by the glucose concentration. It increases when glucose tolerance is decreased and/or when insulin sensitivity is decreased.

CONCLUSION

There is ample evidence to indicate that sleep duration and quality affect endocrine function. The effects of sleep on hypothalamo-pituitary endocrine secretions may be stimulatory (GH, prolactin for example) or inhibitory (cortisol, TSH for example). Glucose metabolism and appetite regulation are also markedly dependent on sleep duration. Decreases in sleep duration and sleep quality, as occur in aging, in sleep disorders, but also as the result of voluntary behaviors, have a major deleterious impact on hormonal characteristics, and on glucose and appetite regulation.

ABBREVIATIONS

BMI = Body Mass Index
CPAP = Continuous Positive Airway Pressure
GH = Growth Hormone
SWS = Slow Wave Sleep (Stages 3 and 4)
TSH = Thyroid-Stimulating Hormone

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REFERENCES

1. Leproult R, Spiegel K, Van Cauter E. SRS Basics of Sleep Guide (Slide Sets): Editors, CJ Amlaner and OM Buxton, 2008.
2. Van Cauter E, Copinschi G. Endocrine and other biological rhythms. In: DeGroot L, Jameson J, eds. Endocrinology. 4th ed. Philadelphia: W.B. Saunders, 2006:235-56.
3. Weitzman ED, Zimmerman JC, Czeisler CA, Ronda JM. Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab 1983;56:352-8.
4. Born J, Muth S, Fehm HL. The significance of sleep onset and slow wave sleep for nocturnal release of growth

hormone (GH) and cortisol. Psychoneuroendocrinology 1988;13:233-43.
5. Weibel L, Follenius M, Spiegel K, Ehrhart J, Brandenberger G. Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. Sleep 1995;18:549-56.
6. Follenius M, Brandenberger G, Bardasept J, Libert J, Ehrhart J. Nocturnal cortisol release in relation to sleep structure. Sleep 1992;15:21-7.
7. Gronfier C, Luthringer R, Follenius M, et al. Temporal relationships between pulsatile cortisol secretion and electroencephalographic activity during sleep in man. Electroencephalogr Clin Neurophysiol 1997;103:405-8.
8. Van Cauter E, van Coevorden A, Blackman JD. Modulation of neuroendocrine release by sleep and circadian rhythmicity. In: Yen S, Vale W, eds. Advances in neuroendocrine regulation of reproduction. Norwell: Serono Symposia USA, 1990:113-22.
9. Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S, Polonsky KS. Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. J Clin Invest 1991;88:934-42.
10. Spath-Schwalbe E, Gofferje M, Kern W, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. Biol Psychiatry 1991;29:575-84.
11. Pruessner JC, Wolf OT, Hellhammer DH, et al. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci 1997;61:2539-49.
12. Caufriez A, Moreno-Reyes R, Leproult R, Vertongen F, Van Cauter E, Copinschi G. Immediate effects of an 8-h advance shift of the rest-activity cycle on 24-h profiles of cortisol. Am J Physiol Endocrinol Metab 2002;282:E1147-53.
13. Schoeller DA, Cella LK, Sinha MK, Caro JF. Entrainment of the diurnal rhythm of plasma leptin to meal timing. J Clin Invest 1997;100:1882-7.
14. Simon C, Gronfier C, Schlienger JL, Brandenbergor G. Circadian and ultradian variations of leptin in normal man under continuous enteral nutrition: Relationship to sleep and body temperature. J Clin Endocrinol Metab 1998;83:1893-9.
15. van Coevorden A, Mockel J, Laurent E, et al. Neuroendocrine rhythms and sleep in aging men. Am J Physiol 1991;260:E651-E61.
16. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000;284:861-8.
17. Frank S, Roland DC, Sturis J, et al. Effects of aging on glucose regulation during wakefulness and sleep. Am J Physiol 1995;269:E1006-E16.
18. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. Endocr Rev 1997;18:716-38.
19. Van Cauter E. Hormones and sleep. In: Kales A, ed. The Pharmacology of Sleep. Berlin: Springer Verlag, 1995:279-306.
20. Van Cauter E, Spiegel K. Circadian and Sleep Control of Hormonal Secretions. In: Turek FW, Zoe PC, eds. Regulation of Sleep and Circadian Rhythms. New York: Marcel Dekker, Inc., 1999:397-425.
21. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A 2008;105:1044-9.
22. Vgontzas AN, Bixler EO, Lin HM, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 2001;86:3787-94.
23. Saini J, Krieger J, Brandenberger G, Wittersheim G, Simon C, Follenius M. Continuous positive airway pressure treatment: Effects on growth hormone, insulin and glucose profiles in obstructive sleep apnea patients. Hormone Metab Res 1993;25:375-81.
24. Vgontzas AN, Pejovic S, Zoumakis E, et al. Hypothalamic-pituitary-adrenal axis activity in obese men with and without sleep apnea: effects of continuous positive airway pressure therapy. J Clin Endocrinol Metab 2007;92:4199-207.
25. Lanfranco F, Gianotti L, Pivetti S, et al. Obese patients with obstructive sleep apnoea syndrome show a peculiar alteration of the corticotroph but not of the thyrotroph and lactotroph function. Clin Endocrinol 2004;60:41-8.
26. Harsch IA, Konturek PC, Koebnick C, et al. Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. Eur Respir J 2003;22:251-7.
27. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. Chest 2008;133:496-506.
28. Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93:3878-84.
29. Tasali E, Van Cauter E, Ehrmann DA. Relationships Between Sleep Disordered Breathing and Glucose Metabolism in Polycystic Ovary Syndrome. J Clin Endocrinol Metabolism 2006.
30. Buxton O, Spiegel K, Van Cauter E. Modulation of endocrine function and metabolism by sleep and sleep loss. Sleep Med 2002:59-69.
31. Leproult R, Copinschi G, Buxton O, Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. Sleep 1997;20:865-70.
32. Spiegel K, Leproult R, Van Cauter E. Metabolic and Endocrine Changes. In: Kushida C, ed. Sleep Deprivation: Basic Science, Physiology, and Behavior. New York: Marcel Dekker, 2005:293-318.
33. Spiegel K, Leproult R, Colecchia EF, et al. Adaptation of the 24-h growth hormone profile to a state of sleep debt. Am J Physiol Regul Integr Comp Physiol 2000;279:R874-83.
34. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-9.
35. Bergman RN. Minimal model: perspective from 2005. Horm Res 2005;64 Suppl 3:8-15.
36. Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res 2000;9:335-52.
37. Spiegel K, Leproult R, L'Hermite-Baleriaux M, Copinschi G, Penev P, Van Cauter E. Leptin levels are dependent on sleep duration: Relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 2004;89:5762-71.
38. Buxton O, Pavlova M, Reid E, Simonson D, Adler G. Sleep restriction for one week reduces insulin sensitivity measured using the euglycemic hyperinsulinemic clamp technique. Sleep 2008;31:A107.
39. Zielinski MR, Kline CE, Kripke DF, Bogan RK, Youngstedt SD. No effect of 8-week time in bed restriction on glucose tolerance in older long sleepers. J Sleep Res 2008;17:412-9.
40. Chin-Chance C, Polonsky KS, Schoeller D. Twenty-four hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake. J Clin Endocrinol Metabolism 2000;85:2685-91.
41. Spiegel K, Tasali E, Penev P, Van Cauter E. Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels and increased hunger and appetite. Ann Intern Med 2004;141:846-50.
42. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr 2008.
43. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1:e62.

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