Endocrine Physiology in Relation to Sleep and Sleep Disturbances

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Chapter 26

Abstract

Sleep exerts important modulatory effects on most components of the endocrine system. Pathways mediating the impact of sleep on peripheral endocrine function and metabolism include the activity of the hypothalamic releasing and inhibiting factors on pituitary hormone release and the autonomous nervous system control of endocrine organs. Modulatory effects of sleep on endocrine release are not limited to the hormones of the hypothalamic-pituitary axes; these effects are also observed for the hormones controlling carbohydrate metabolism, appetite regulation, and water and electrolyte balance. Sleep loss is associated with disturbances of hormone secretion and metabolism, which may have clinical relevance, particularly as voluntary partial sleep curtailment has become a highly prevalent behavior in modern society. Reduced sleep quality also adversely affects endocrine release and metabolism. Evidence suggests that part of the constellation of hormonal and metabolic alterations that characterize normal aging may reflect the deterioration of sleep quality. Major metabolic diseases such as obesity, type 2 diabetes, and polycystic ovary syndrome are all associated with sleep disturbances, which may promote the development or exacerbate the severity of the condition. Strategies to reverse decrements in sleep quality may have beneficial effects on endocrine and metabolic function.

MODULATION OF ENDOCRINE FUNCTION BY SLEEP–WAKE HOMEOSTASIS AND CIRCADIAN RHYTHMICITY

In healthy adults, reproducible changes of essentially all hormonal and metabolic variables occur during sleep and around wake–sleep and sleep–wake transitions. These daily events reflect the interaction of central circadian rhythmicity and sleep–wake homeostasis. Thus, the dual control of sleep timing and quality by circadian processes (i.e., Process C) and sleep–wake homeostasis (i.e., Process S) is readily reflected in the modulatory effects exerted by sleep on endocrine and metabolic function. Pathways by which central circadian rhythmicity and sleep-wake homeostasis affect peripheral endocrine function and metabolism include the modulation of the activity of the hypothalamic releasing and inhibiting factors and the autonomous nervous system control of endocrine organs. Findings from genome-wide association studies also support a role of circulating melatonin levels on specific endocrine targets, including the pancreatic beta cells.[1-3] The relative contributions of circadian timing compared with homeostatic control in the regulation of the temporal organization of hormone release vary from one endocrine axis to another. Similarly, modulatory effects of the transitions between wake and sleep (and vice versa) and between non–rapid eye movement (NREM) and rapid eye movement (REM) stages also vary from one hormone to another.

Circadian oscillations can be generated in many peripheral organs, including tissues that release endocrine signals such as adipocytes and pancreatic beta cells.[4] These "local" oscillators appear to be under the control of the central pacemaker in the suprachiasmatic nuclei either directly via neural and endocrine signals, or indirectly via its control of behavioral rhythms such as the sleep–wake cycle and the rhythm of feeding. The possible involvement of these peripheral oscillators on the temporal organization of endocrine release and metabolic function during waking and sleeping remains to be investigated.

To differentiate between effects of circadian rhythmicity and those subserving sleep–wake homeostasis, researchers have used experimental strategies that take advantage of the fact that the central circadian pacemaker takes several days to adjust to a large sudden shift of sleep–wake and light–dark cycles (such as occur in jet lag and shift work). Such strategies allow for the effects of circadian modulation to be observed in the absence of sleep and for the effects of sleep to be observed at an abnormal circadian time. Figure 26-1 illustrates mean profiles of hormonal concentrations, glucose levels, and insulin-secretion rates (ISR) observed in healthy subjects who were studied before and during an abrupt 12-hour delay of the sleep–wake and dark–light cycles. To eliminate the effects of feeding, fasting, and postural changes, the subjects remained recumbent throughout the study, and the normal meal schedule was replaced by intravenous glucose infusion at a constant rate.[5]

As shown in Figure 26-1, this drastic manipulation of sleep had only modest effects on the wave shape of the cortisol profile, in sharp contrast with the immediate shift of the growth hormone (GH) and prolactin (PRL) rhythms that followed the shift of the sleep–wake cycle. The temporal organization of thyroid-stimulating hormone (TSH) secretion appears to be influenced equally by circadian and sleep-dependent processes. Indeed, the evening elevation of TSH levels occurs well before sleep onset and has been shown to reflect circadian phase. During sleep, an inhibitory process prevents TSH concentrations from rising further. Consequently, in the absence of sleep, the nocturnal TSH elevation is markedly amplified. Both sleep and time of day clearly modulated glucose levels and ISR. Nocturnal elevations of glucose and ISR occurred even when the subjects were sleep deprived, and recovery sleep at an abnormal circadian time was also associated with elevated glucose and ISR. This pattern of changes in glucose levels and ISR reflected changes in glucose use because, when glucose is infused exogenously, endogenous glucose production is largely inhibited.

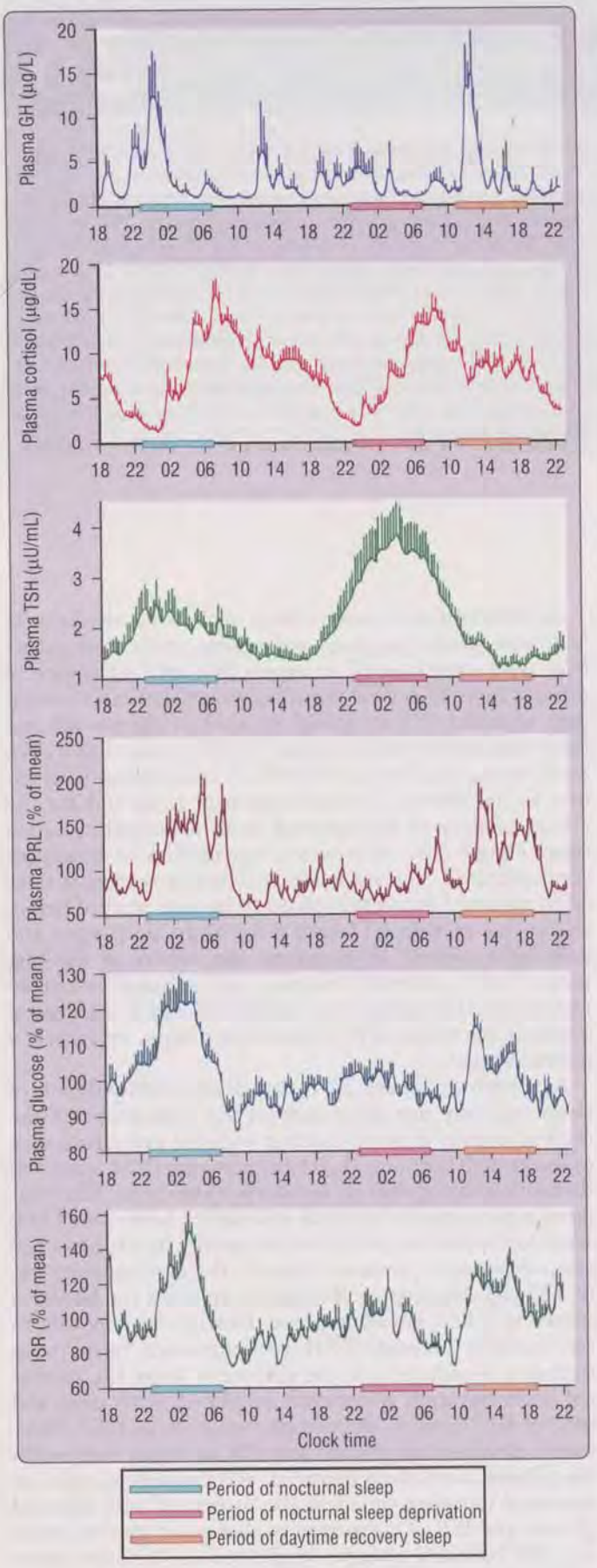

Figure 26-1 From top to bottom: Mean 24-hour profiles of plasma growth hormone (GH), cortisol, thyrotropin (TSH), prolactin (PRL), glucose, and insulin secretion rates (ISR) in a group of eight healthy young men (20 to 27 years old) studied during a 53-hour period including 8 hours of nocturnal sleep, 28 hours of sleep deprivation, and 8 hours of daytime sleep. The vertical bars on the tracings represent the standard error of the mean (SEM) at each time point. The *blue bars* represent the sleep periods. The *red bars* represent the period of nocturnal sleep deprivation. The *orange bars* represent the period of daytime sleep. Caloric intake was exclusively under the form of a constant glucose infusion. Shifted sleep was associated with an immediate shift of GH and PRL release. In contrast, the secretory profiles of cortisol and TSH remained synchronized to circadian time. Both sleep-dependent and circadian inputs can be recognized in the profiles of glucose and ISR. (Adapted from Van Cauter E, Spiegel K. Circadian and sleep control of endocrine secretions. In: Turek FW, Zee PC, editors. Neurobiology of sleep and circadian rhythms. New York: Marcel Dekker; 1999; and Van Cauter E, Blackman JD, Roland D, et al. Modulation of glucose regulation and insulin secretion by sleep and circadian rhythmicity. J Clin Invest 1991;88:934-942.)

First we will review the interactions between sleep and endocrine release in the hypothalamic-pituitary axes and the roles of sleep in carbohydrate metabolism, appetite regulation, and hormone control of body-fluid balance. Table 26-1 provides basic information about the hormones that will be discussed in this chapter. We then summarize the growing body of evidence linking decrements of sleep duration or quality that occur with sleep restriction, in sleep disorders, or as a result of normal aging, and disturbances of endocrine and metabolic function. Lastly, we review recent evidence linking disorders of sleep–wake regulation and metabolic and endocrine diseases, including obesity, type 2 diabetes, and polycystic ovary syndrome (PCOS). For a review of sleep abnormalities in other endocrine diseases, the reader is referred to Chapter 125.

THE GROWTH HORMONE AXIS

Pituitary release of GH is stimulated by hypothalamic GH-releasing hormone (GHRH) and inhibited by somatostatin. In addition, the acylated form of ghrelin, a peptide produced predominantly by the stomach, binds to the growth hormone secretagogue (GHS) receptor and is a potent endogenous stimulus of GH secretion.[6] There is a combined and probably synergic role of GHRH stimulation, elevated nocturnal ghrelin levels, and decreased somatostatinergic tone in the control of GH secretion during sleep. Although sleep clearly involves major stimulatory effects on GH secretion, the hormones of the somatotropic axis, including GHRH, ghrelin, and GH, in turn appear to be involved in sleep regulation.[7]

In healthy adult subjects, the 24-hour profile of plasma GH levels consists of stable low levels abruptly interrupted by bursts of secretion. The most reproducible GH pulse occurs shortly after sleep onset.[8] In men, the sleep-onset GH pulse is generally the largest, and often the only, secretory pulse observed over the 24-hour span. In women, daytime GH pulses are more frequent, and the sleep-associated pulse, although still present in the vast majority of individual profiles, does not account for the majority of the

Table 26-1 Origin and Main Action of Hormones

HORMONE	MAIN SECRETING ORGAN	MAIN ACTION IN ADULTS
Growth hormone (GH)	Pituitary gland	Anabolic hormone that regulates body composition
Prolactin (PRL)	Pituitary gland	Stimulates lactation in women; pleiotropic actions
Adrenocorticotropic hormone (ACTH)	Pituitary gland	Stimulates release of cortisol from adrenal cortex
Cortisol	Adrenal cortex	Stress hormone, antiinsulin effects
Thyroid-stimulating hormone (TSH)	Pituitary gland	Stimulates the release of thyroid hormones from the thyroid gland
Luteinizing hormone (LH)	Pituitary gland	Stimulates ovarian and testicular function
Follicle-stimulating hormone (FSH)	Pituitary gland	Stimulates ovarian and testicular function
Testosterone	Gonads	Stimulates spermatogenesis
Estradiol	Ovaries	Stimulates follicular growth
Insulin	Pancreas	Regulates blood glucose levels
Melatonin	Pineal gland	Hormone of the dark that transmits information about the light–dark cycle
Leptin	Adipose tissue	Satiety hormone regulating energy balance
Ghrelin	Stomach	Hunger hormone regulating energy balance

24-hour secretory output. Sleep onset elicits a pulse in GH secretion whether sleep is advanced, delayed, or interrupted and reinitiated. The mean GH profile shown in Figure 26-1 illustrates the maintenance of the relationship between sleep onset and GH release in subjects who underwent a 12-hour delay shift of the sleep–wake cycle. There is a consistent relationship between the appearance of delta waves in the EEG and elevated GH concentrations and maximal GH release occurs within minutes of the onset of slow-wave sleep (SWS).[8,9] In healthy young men, there is a quantitative correlation between the amount of GH secreted during the sleep-onset pulse and the duration of the slow-wave episode.[10] Pharmacologic stimulation of SWS with oral administration of low doses of gamma-hydroxybutyrate (GHB), a drug used for the treatment of narcolepsy, as well as with ritanserin, a selective 5-hydroxytryptamine ($5\text{-}HT_2$) receptor antagonist, results in increases in GH secretion.[11,12] Sedative hypnotics that are ligands of the $GABA_A$ receptor such as benzodiazepines and imidazopyridines, do not increase nocturnal GH release, consistent with their lack of stimulation of slow-wave activity.[13]

The mechanisms that underlie the relationship between early sleep and GH release are unclear. The significance of this relationship is that anabolic processes in the body are synchronized to a state when behavioral rest occurs and when cerebral glucose use is at its lowest point.[14] There is good evidence to indicate that stimulation of nocturnal GH release and stimulation of SWS reflect, to a large extent, synchronous activity of at least two populations of hypothalamic GHRH neurons.[14] Sleep-onset GH secretion appears to be primarily regulated by GHRH stimulation occurring during a period of decreased somatostatin inhibition of somatotropic activity. Indeed, in humans, GH secretion during early sleep may be nearly totally suppressed by administration of a GHRH antagonist.[15] The late evening and nocturnal hours coincide with the trough of a diurnal variation in hypothalamic somatostatin tone[16] that is likely to facilitate nocturnal GH release. It is also possible that ghrelin plays a role in causing increased GH secretion during sleep because the normal 24-hour ghrelin profile shows a marked nocturnal increase peaking in the early part of the night.[17,18]

The upper panel of Figure 26-1 shows that the secretion of GH is increased during sleep independently of the circadian time when sleep occurs and that sleep deprivation results in greatly diminished release of this hormone. However, a slight increase may be observed during nocturnal sleep deprivation, indicating the existence of a weak circadian component that could reflect, as discussed earlier, lower somatostatin inhibition. Following a night of total sleep deprivation, GH release is increased during the daytime such that the total 24-hour secretion is not significantly affected.[19] Again, the mechanisms underlying this compensatory daytime secretion are unknown, but they could involve decreased somatostatinergic tone or elevated ghrelin levels.

Marked rises in GH secretion before the onset of sleep have been reported by several investigators.[20-22] Presleep GH pulses may reflect the presence of a sleep debt, as they occur consistently after recurrent experimental sleep restriction.[23] The short-term negative feedback inhibition exerted by GH on its own secretion may also explain observations of an absent GH pulse during the first slow wave period, when a secretory pulse occurred before sleep onset. Awakenings interrupting sleep have an inhibitory effect on GH release.[24,25] Thus, sleep fragmentation generally decreases nocturnal GH secretion.

THE CORTICOTROPIC AXIS

Activity of the corticotropic axis—a neuroendocrine system associated with the stress response and behavioral activation—may be measured peripherally via plasma levels of the pituitary adrenocorticotropic hormone (ACTH) and of cortisol, the adrenal hormone directly controlled by ACTH stimulation. The plasma levels of these hormones decline from an early morning maximum throughout the daytime and are near the lower limit of most assays in the

late evening and early part of the sleep period. Thus, sleep is normally initiated when corticotropic activity is quiescent. Reactivation of ACTH and cortisol secretion occurs abruptly a few hours before the usual waking time.

The mean cortisol profile shown in Figure 26-1 illustrates the remarkable persistence of this diurnal variation when sleep is manipulated. Indeed, the overall waveshape of the profile is not markedly affected by the absence of sleep or by sleep at an unusual time of day. Thus, the 24-hour periodicity of corticotropic activity is primarily controlled by circadian rhythmicity.

Nevertheless, modulatory effects of sleep or wake have been clearly demonstrated. Indeed, a number of studies have indicated that sleep onset is reliably associated with a short-term inhibition of cortisol secretion,[5,26] although this effect may not be detectable when sleep is initiated at the time of the daily maximum of corticotropic activity, that is, in the morning.[27] Under normal conditions, because cortisol secretion is already quiescent in the late evening, this inhibitory effect of sleep, which is temporally associated with the occurrence of slow-wave sleep,[28-30] results in a prolongation of the quiescent period. Therefore, under conditions of sleep deprivation, the nadir of cortisol secretion is less pronounced and occurs earlier than under normal conditions of nocturnal sleep. Conversely, awakening at the end of the sleep period is consistently followed by a pulse of cortisol secretion.[5,25,31]

During sleep deprivation, the rapid effects of sleep onset and sleep offset on corticotropic activity are obviously absent, and, as may be seen in the profiles shown in Figure 26-1, the nadir of cortisol levels is higher than during nocturnal sleep (because of the absence of the inhibitory effects of the first hours of sleep), and the morning maximum is lower (because of the absence of the stimulating effects of morning awakening). Overall, the amplitude of the rhythm is reduced by approximately 15% during sleep deprivation as compared to normal conditions.

In addition to the immediate modulatory effects of sleep–wake transitions on cortisol levels, nocturnal sleep deprivation, even partial deprivation, results in an elevation of cortisol levels on the following evening.[32] Sleep loss thus appears to delay the normal return to evening quiescence of the corticotropic axis. This endocrine alteration is remarkably similar to that occurring in normal aging, where increases in evening cortisol levels of similar magnitude are consistently observed. This interpretation is consistent with findings in normal subjects submitted to recurrent partial sleep restriction, as discussed later.

THE THYROID AXIS

Daytime levels of plasma TSH are low and relatively stable and are followed by a rapid elevation starting in the early evening and culminating in a nocturnal maximum occurring around the beginning of the sleep period.[30,33] The later part of sleep is associated with a progressive decline in TSH levels, and daytime values resume shortly after morning awakening. The first 24 hours of the study illustrated in Figure 26-1 are typical of the diurnal TSH rhythm. Because the nocturnal rise of TSH occurs well before the time of sleep onset, it probably reflects a circadian effect. However, a marked effect of sleep on TSH secretion may be seen during sleep deprivation (clearly seen in Fig. 26-1), when nocturnal TSH secretion is increased by as much as 200% over the levels observed during nocturnal sleep. Thus, sleep exerts an inhibitory influence on TSH secretions, and sleep deprivation relieves this inhibition.[30,34]

Interestingly, when sleep occurs during daytime hours, TSH secretion is not suppressed significantly below normal daytime levels. Thus, the inhibitory effect of sleep on TSH secretion appears to be operative when the nighttime elevation has taken place, indicating once again the interaction of the effects of circadian time and the effects of sleep. When the depth of sleep at the habitual time is increased by prior sleep deprivation, the nocturnal TSH rise is more markedly inhibited, suggesting that SWS is probably the primary determinant of the sleep-associated fall.[30] Awakenings interrupting nocturnal sleep appear to relieve the inhibition of TSH and are consistently associated with a short-term TSH elevation.

Circadian and sleep-related variations in thyroid hormones have been difficult to demonstrate, probably because these hormones are bound to serum proteins and thus their peripheral concentrations are affected by diurnal variations in hemodilution caused by postural changes. However, under conditions of sleep deprivation, the increased amplitude of the TSH rhythm may result in a detectable increase in plasma triiodothyronine (T_3) levels, paralleling the nocturnal TSH rise.[35] If sleep deprivation is continued for a second night, then the nocturnal rise of TSH is markedly diminished as compared with that occurring during the first night.[35,36] It is likely that following the first night of sleep deprivation, the elevated thyroid hormone levels, which persist during the daytime period because of the prolonged half-life of these hormones, limit the subsequent TSH rise at the beginning of the next nighttime period. Data from a study of 64 hours of sleep deprivation suggest that prolonged sleep loss may be associated with an upregulation of the thyroid axis, with lower levels of TSH and higher levels of thyroid hormones.[37] As discussed in the section on chronic sleep restriction, this was indeed the case in a study of the endocrine and metabolic effects of a sleep debt resulting from bedtime curtailment to 4 hours per night for 6 nights.[38,39]

The inhibitory effects of sleep on TSH secretion are time dependent, and that may cause, under specific circumstances, elevations of plasma TSH levels that reflect the misalignment of sleep and central circadian timing. In a study examining the course of adaptation to an abrupt 8-hour advance of the sleep–dark period in healthy young men,[40] TSH levels increased progressively because daytime sleep failed to inhibit TSH and nighttime wakefulness was associated with large circadian-dependent TSH elevations. As a result, mean TSH levels following awakening from the second shifted sleep period were more than twofold higher than during the same time interval following normal nocturnal sleep. This overall elevation of TSH levels was paralleled by a small increase in T_3 concentrations.[40] This study demonstrated that the subjective discomfort and fatigue often referred to as "jet-lag syndrome" are associated not only with a desynchronization of bodily rhythms but also with a prolonged elevation of a hormone concentration in the peripheral circulation.

PROLACTIN SECRETION

Under normal conditions, PRL levels undergo a major nocturnal elevation starting shortly after sleep onset and culminating around midsleep. Decreased dopaminergic inhibition of PRL during sleep is likely to be the primary mechanism underlying this nocturnal PRL elevation. In adults of both sexes, the nocturnal maximum corresponds to an average increase of more than 200% above the minimum level.[35] Morning awakenings and awakenings interrupting sleep are consistently associated with a rapid inhibition of PRL secretion.[35]

Studies of the PRL profile during daytime naps or after shifts of the sleep period have consistently demonstrated that sleep onset, irrespective of the time of day, has a stimulatory effect on PRL release. This is well illustrated by the profiles shown in Figure 26-1, in which elevated PRL levels occur both during nocturnal sleep and during daytime recovery sleep, whereas the nocturnal period of sleep deprivation was not associated with an increase in PRL concentrations. However, the sleep-related rise of PRL may still be present, although with a reduced amplitude, when sleep does not occur at the normal nocturnal time. Maximal stimulation is observed only when sleep and circadian effects are superimposed.[41-43] A close temporal association between increased prolactin secretion and slow wave activity is apparent.[44] However, in contrast to the quantitative correlation between amount of slow wave activity and amount of GH release that has been evidenced in men, no such "dose-response" relationship has been demonstrated for prolactin. Awakenings interrupting sleep inhibit nocturnal PRL release.[44]

Benzodiazepine and imidazopyridine hypnotics taken at bedtime may cause an increase in the nocturnal PRL rise, resulting in concentrations near the pathological range for part of the night.[45,46] This is illustrated for triazolam and zolpidem in Figure 26-2. Neither triazolam nor zolpidem has any effect on the 24-hour profiles of cortisol, melatonin, or GH. A recent report showed that chronic treatment of insomnia with the melatonin receptor agonist ramelteon also increases prolactin release in women, but not in men.[47]

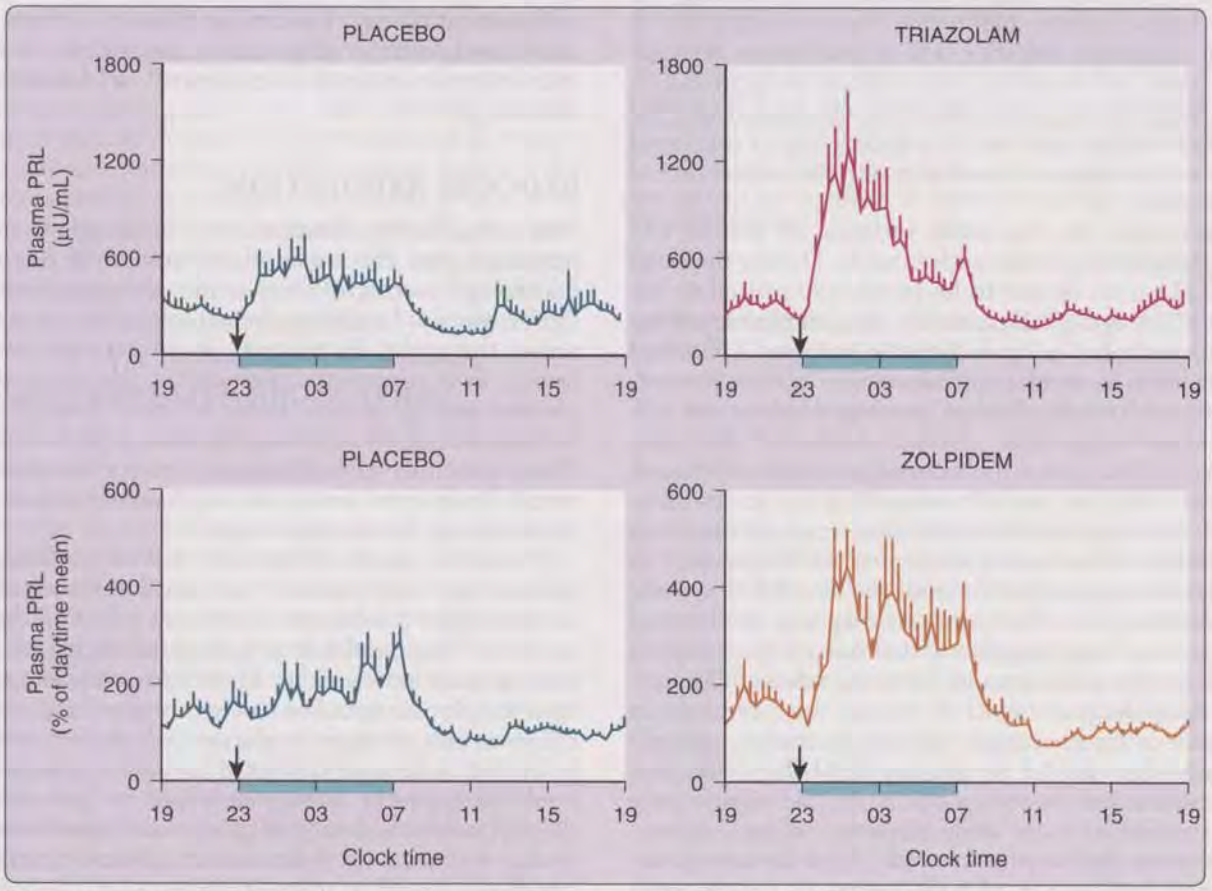

Figure 26-2 Effects of commonly used hypnotics on the 24-hour profile of plasma prolactin (PRL) in healthy young subjects. Data are mean plus standard error of the mean. Samples were collected at 15- to 20-minute intervals. Sleep was polygraphically recorded. *Top*, effects of bedtime administration of triazolam (0.5 mg). *Bottom*, effects of bedtime administration of zolpidem (10 mg). Both benzodiazepine and nonbenzodiazepine hypnotics cause transient hyperprolactinemia during the early part of sleep. Time in bed is denoted by the *blue bars*. *Arrows* denote time of drug administration. (Data from Copinschi G, Van Onderbergen A, L'Hermite-Balériaux M, et al. Effects of the short-acting benzodiazepine triazolam taken at bedtime on circadian and sleep-related hormonal profiles in normal men. Sleep 1990;13:232-244; Copinschi G, Akseki E, Moreno-Reyes R, et al. Effects of bedtime administration of zolpidem on circadian and sleep-related hormonal profiles in normal women. Sleep 1995;18:417-424; and Van Cauter E, Spiegel K. Circadian and sleep control of endocrine secretions. In: Turek FW, Zee PC, editors. Neurobiology of sleep and circadian rhythms. New York: Marcel Dekker; 1999.)

There is evidence from animal studies that PRL is involved in the humoral regulation of REM sleep.[48] The primary effect is a stimulation of REM sleep, which appears to be dependent on time of day. Recent findings indicate that prolactin deficient mice have decreased REM sleep.[49]

THE GONADAL AXIS

The relationship between the 24-hour patterns of gonadotropin release and gonadal steroid levels varies according to the stage of maturation, and it is gender dependent in young adulthood (for review see Van Cauter et al.[35]).

Prior to puberty, luteinizing hormone (LH) and follicle-stimulating hormone are secreted in a pulsatile pattern, and an augmentation of pulsatile activity is associated with sleep onset in a majority of both girls and boys. The increased amplitude of gonadotropin release during sleep is one of the hallmarks of puberty. Both sleep and circadian rhythmicity contribute to the nocturnal elevation of gonadotropin pulses in pubertal children. As the pubescent child enters adulthood, the daytime pulse amplitude increases as well, eliminating or diminishing the diurnal rhythm. In pubertal girls, a diurnal variation of circulating estradiol levels, with higher concentrations during the daytime instead of the nighttime, becomes apparent. It has been suggested that the lack of parallelism between gonadotropin and estradiol levels reflects an approximate 10-hour delay between gonadotropin stimulation and the subsequent ovarian response. In pubertal boys, a nocturnal rise of testosterone coincides with the elevation of gonadotropins.

In adult men, the day–night variation of plasma LH levels is dampened or even undetectable. During the sleep period, LH pulses appear to be temporally related to the REM–NREM cycle.[50] Despite the low amplitude of the nocturnal increase in gonadotropin release, a marked diurnal rhythm in circulating testosterone levels is present, with minimal levels in the late evening, a robust rise following sleep onset and maximal levels in the early morning.[51,52] Thus, the robust circadian rhythm of plasma testosterone may be partially controlled by factors other than LH. The nocturnal rise of testosterone appears temporally linked to the latency of the first REM episode,[53] as plasma levels continue to rise until the first REM episode occurs. A robust rise of testosterone may also be observed during daytime sleep, suggesting that sleep, irrespective of time of day, stimulates gonadal hormone release.[54] Experimental sleep fragmentation in young men resulted in attenuation of the nocturnal rise of testosterone, particularly in subjects who did not achieve REM sleep.[55] Androgen concentrations in young adults decline significantly during periods of total sleep deprivation and recover promptly once the sleep is restored.[54,56] In contrast, pharmacological suppression of testosterone in healthy men appears to have no effect on the total amount and overall architecture of nighttime sleep.[57]

In women, the 24-hour variation in plasma LH is markedly modulated by the menstrual cycle.[58,59] In the early follicular phase, LH pulses are large and infrequent, and a marked slowing of the frequency of secretory pulses occurs during sleep, suggestive of inhibitory effect of sleep on pulsatile gonadotropin-releasing hormone (GnRH) release. Awakenings interrupting sleep are usually associated with a pulse of LH concentration.[60] In the midfollicular phase, pulse amplitude is decreased, pulse frequency is increased, and the frequency modulation of LH pulsatility by sleep is less apparent. Pulse amplitude increases again by the late-follicular phase. In the early luteal phase, the pulse amplitude is markedly increased, the pulse frequency is decreased, and nocturnal slowing of pulsatility is again evident. In the mid- and late-luteal phase, pulse amplitude and frequency are decreased, and there is no modulation by sleep.

In older men, the amplitude of LH pulses is decreased but the frequency is increased and no significant diurnal pattern can be detected.[61-63] The circadian variation of testosterone persists, although markedly dampened.[63] The sleep-related rise is still apparent in older men, but its amplitude is lower and the relationship to REM latency is no longer apparent.[64] It is likely that decreased sleep quality as occurs in aging as well as in sleep disorders (e.g., obstructive sleep apnea) plays a role in the dampening of the sleep-related testosterone rise.

In postmenopausal women, gonadotropin levels are elevated, but they show no consistent circadian pattern.[65] A number of studies[66-68] have indicated that estrogen replacement therapy has modest beneficial effects on subjective and objective sleep quality, particularly in the presence of environmental disturbance[69] or sleep-disordered breathing.[66,67,70]

GLUCOSE REGULATION

The consolidation of human sleep in a single 7- to 9-hour period implies that an extended period of fast must be maintained overnight. Despite the prolonged fasting condition, glucose levels remain stable or fall only minimally across the night. In contrast, if subjects are awake and fasting in a recumbent position, in the absence of any physical activity, glucose levels fall by an average of 0.5 to 1.0 mmol/L (± 10 to 20 mg/dL) over a 12-hour period.[71] Thus, a number of mechanisms that operate during nocturnal sleep must intervene to maintain stable glucose levels during the overnight fast.

The lower panels of Figure 26-1 show profiles of blood glucose and ISR obtained in normal subjects who were studied under conditions of constant glucose infusion,[76] a condition that results in a marked inhibition of endogenous glucose production. Thus, when subjects receive a constant glucose infusion, changes in plasma glucose levels reflect mainly changes in glucose use. A marked decrease in glucose tolerance (reflected in higher plasma glucose levels) is apparent during nighttime as well as daytime sleep. A smaller elevation of glucose and insulin also occurs during nocturnal sleep deprivation, indicating an effect of circadian-dependent mechanisms.

During nocturnal sleep, the overall increase in plasma glucose ranged from 20% to 30%, despite the maintenance of rigorously constant rates of caloric intake. Maximal levels occur around the middle of the sleep period. During the later part of the night (i.e., at the time of the so-called dawn phenomenon), glucose tolerance begins to improve, and glucose levels progressively decrease toward morning values. The mechanisms underlying these robust variations

in set-point of glucose regulation across nocturnal sleep are different in early sleep and late sleep.

Under conditions of constant glucose infusion, the decrease in glucose tolerance during the first half of the sleep period is reflected in a robust increase in plasma glucose, which is followed by a more than 50% increase in insulin secretion. It is estimated that about two thirds of the fall in glucose use during sleep is due to a decrease in brain glucose metabolism[72] related to the predominance of slow wave stages, which are associated with a 30% to 40% reduction in cerebral glucose metabolism as compared to the waking state.[73] (See Chapter 18.) The last third of the fall would then reflect decreased peripheral use. Diminished muscle tone during sleep and rapid antiinsulin-like effects of the sleep-onset GH pulse are both likely to contribute to decreased peripheral glucose uptake. The nocturnal elevation of melatonin levels could contribute to the nocturnal decrease in glucose tolerance because of an inhibitory effect of melatonin on insulin release from beta cells.[2,74] During the later part of the sleep period, glucose levels and insulin secretion decrease to return to presleep values, and this decrease appears to be partially due to the increase in wake and REM stages.[75] Indeed, glucose use during the REM and wake stages is higher than during NREM stages.[73] In addition, several other factors may also contribute to the decline of glucose levels during late sleep. These include the hypoglycemic activity of previously secreted insulin during early sleep, the increased insulin-independent glucose disposal due to transient mild hyperglycemia, and the quiescence of GH secretion and thus the rapid attenuation of the short-term inhibitory effects of this hormone on tissue glucose uptake. Finally, the later part of the night appears to be associated with increased insulin sensitivity, reflecting a delayed effect of low cortisol levels during the evening and early part of the night.[76]

SLEEP AND APPETITE REGULATION

Sleep plays an important role in energy balance. In rodents, food shortage or starvation results in decreased sleep[77] and, conversely, total sleep deprivation leads to marked hyperphagia.[78] The identification of hypothalamic excitatory neuropeptides, referred to as hypocretins or orexins, that have potent wake-promoting effects and stimulate food intake, has provided a molecular basis for the interactions between the regulation of feeding and sleeping.[79,80] Orexin-containing neurons in the lateral hypothalamus project directly to the locus coeruleus and other brainstem and hypothalamic arousal areas, where they interact with the leptin-responsive neuronal network involved in balancing food intake and energy expenditure. Orexin-containing neurons are active during waking and quiescent during sleep. Orexin activity is inhibited by leptin, a satiety hormone, and stimulated by ghrelin, an appetite promoting hormone.

Leptin, a hormone released by the adipocytes, provides information about energy status to regulatory centers in the hypothalamus.[81] Circulating leptin concentrations in humans show a rapid decline or increase in response to acute caloric shortage or surplus, respectively. These changes in leptin levels have been associated with reciprocal changes in hunger. The 24-hour leptin profile shows a marked nocturnal rise, which is partly dependent on meal intake.[82] The upper panel of Figure 26-3 shows a typical 24-hour profile of plasma leptin levels in a normal man. The nocturnal elevation of leptin has been thought to suppress the hunger during the overnight fast. Although daytime food intake plays a major role in the nocturnal rise of leptin, a study using continuous enteral nutrition to eliminate the impact of meal intake showed the persistence of a sleep-related leptin elevation, though the amplitude was lower than during normal feeding conditions.[83] Prolonged total sleep deprivation results in a decrease in the amplitude of the leptin diurnal variation.[84]

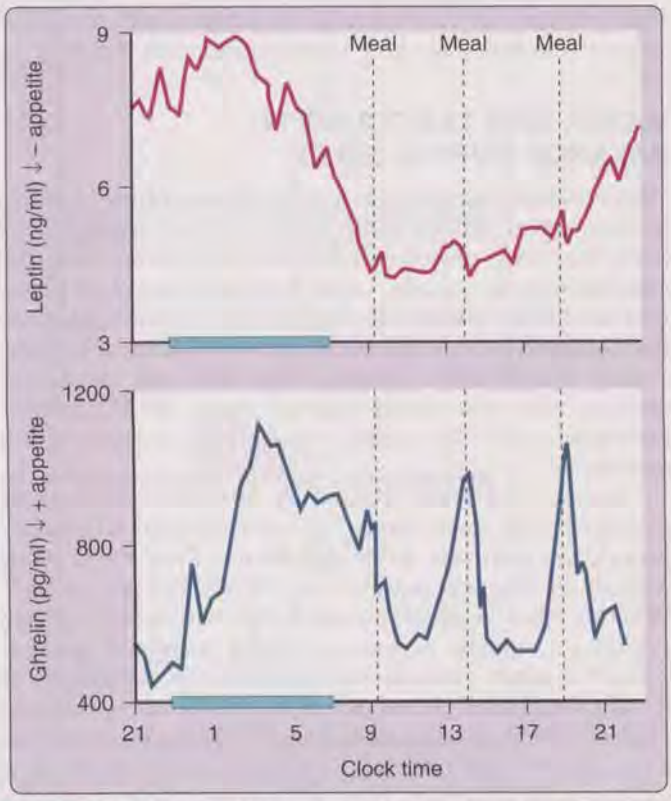

Figure 26-3 Typical 24-hour profiles of plasma leptin *(top)* (an appetite-suppressing hormone) and ghrelin *(bottom)* (a hunger-promoting hormone) from a healthy lean young man. Time in bed is denoted by the *blue bars*. The *vertical lines* denote the time of presentation of identical high-carbohydrate meals. (Unpublished data.)

Ghrelin is also involved in regulating energy balance[6] and stimulating appetite.[85] Daytime profiles of plasma ghrelin levels are primarily regulated by the schedule of food intake: Levels rise sharply before each designated meal time and fall to trough levels within 1 to 2 hours after eating. A study examining spontaneous meal initiation in the absence of time- and food-related cues provided good evidence for a role for ghrelin in meal initiation.[86] The 24-hour profile of ghrelin levels shows a marked nocturnal rise, which is only modestly dampened when subjects are sleep deprived.[17] The nocturnal ghrelin rise partly represents the rebound of ghrelin following the dinner meal. Despite the persistence of the fasting condition, ghrelin levels do not continue to increase across the entire sleep period and instead decrease during the later part of the night. The lower panel of Figure 26-3 illustrates a

representative 24-hour profile of ghrelin from a normal subject who ingested three carbohydrate-rich meals.

WATER AND ELECTROLYTE BALANCE DURING SLEEP

Water and salt homeostasis is under the combined control of vasopressin, a hormone released by the posterior pituitary, the renin-angiotensin-aldosterone system, and the atrial natriuretic peptide. Urine flow and electrolyte excretion are higher during the day than during the night, and this variation partly reflects circadian modulation. In addition to this 24-hour rhythm, urine flow and osmolarity oscillate with the REM–NREM cycle. REM sleep is associated with decreasing urine flow and increasing osmolarity.

Vasopressin release is pulsatile but without apparent relationship to sleep stages.[87] Levels of atrial natriuretic peptide are relatively stable and do not show fluctuations related to the sleep–wake or REM–NREM cycles.[88] Whether the levels of plasma atrial natriuretic peptide exhibit a circadian variation is still a matter of controversy.[88] A close relationship between the beginning of REM episodes and decreased activity has been consistently observed for plasma renin activity.[87,89-91] Figure 26-4 illustrates the 24-hour rhythm of plasma renin activity in a subject studied during a normal sleep–wake cycle and in a subject studied following a shift of the sleep period. A remarkable synchronization between decreased plasma renin activity and REM stages is apparent during both sleep periods.[92] This relationship was confirmed in studies with selective REM-sleep deprivation in healthy subjects.[93]

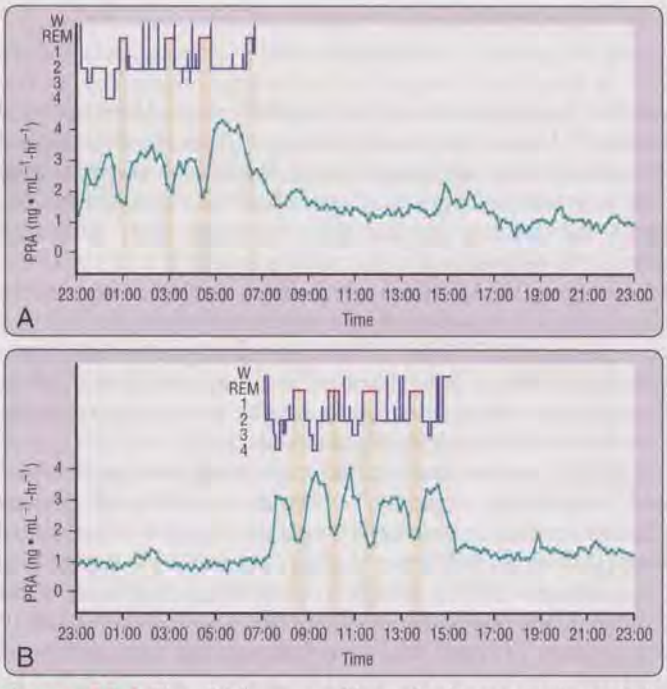

Figure 26-4 The 24-hour profiles of plasma renin activity sampled at 10-minute intervals in a healthy subject. **A**, Nocturnal sleep from 23:00 to 07:00. **B**, Daytime sleep from 07:00 to 15:00 after a night of total sleep deprivation. The temporal distribution of stages wake (W); REM; 1, 2, 3, and 4 are shown above the hormonal values. The oscillations of plasma renin activity are synchronized to the REM–NREM cycle during sleep. (From Brandenberger G, Follenius M, Goichot B, et al. Twenty-four hour profiles of plasma renin activity in relation to the sleep-wake cycle. J Hypertens 1994;12:277-283.)

Increases in plasma renin activity parallel increases in slow-wave EEG activity.[94] In conditions of abnormal sleep architecture (e.g., narcolepsy, sleeping sickness), the temporal pattern of plasma renin activity faithfully reflects the disturbances of the REM–NREM cycle.[87] A well-documented study[95] has delineated the mechanisms responsible for oscillations of plasma renin activity during sleep. The initial event is a reduction in sympathetic tone, followed by a decrease in mean arterial blood pressure and an increase in slow-wave activity. The rise in plasma renin activity becomes evident a few minutes after the increase in slow-wave activity. During REM sleep, sympathetic activity increases, whereas renin and slow-wave activity decrease and blood pressure becomes highly variable.

The increased release of renin during sleep is associated with elevated levels of plasma aldosterone.[96] Acute total sleep deprivation dampens the nighttime elevation of plasma aldosterone and increases natriuresis.[97]

CHRONIC SLEEP RESTRICTION: IMPACT ON ENDOCRINE AND METABOLIC FUNCTION

Voluntary sleep curtailment has become a very common behavior in modern society. Data from the 2008 "Sleep in America" poll indicate that although working adults report a sleep need of an average of 7 hours and 18 minutes to function at best, 44% of them sleep fewer than 7 hours and 16% sleep fewer than 6 hours on a typical weeknight.[98] Sleep times in European countries appear to follow a similar trend.[99] The cumulative sleep loss per workweek of a substantial portion of the adult population may correspond to as much as one full night of sleep deprivation. Several laboratory studies involving extension of the bedtime period for prolonged periods of time have provided evidence that the "recommended 8-hour night" does not meet the sleep need of healthy young adults, who may carry a substantial sleep debt even in the absence of obvious efforts at sleep curtailment.[100-102]

Although the impact of various durations of acute total sleep deprivation on endocrine function and glucose metabolism has been documented in multiple studies, the much more common condition of partial chronic sleep restriction has not received nearly as much attention. The following subsections review, respectively, the laboratory and epidemiologic evidence supporting an adverse impact of recurrent partial sleep restriction on hormones, glucose metabolism, and body weight regulation.

Laboratory Studies

Figure 26-5 summarizes the hormonal and metabolic findings of the first "sleep debt study"[39] which examined the impact of 6 days of sleep restriction to 4 hours per night as compared to 6 days of sleep extension to 12 hours per night in a group of healthy young men.[23,38,39] The findings suggest that sleep restriction has adverse effects on multiple endocrine axes as well as on glucose metabolism.

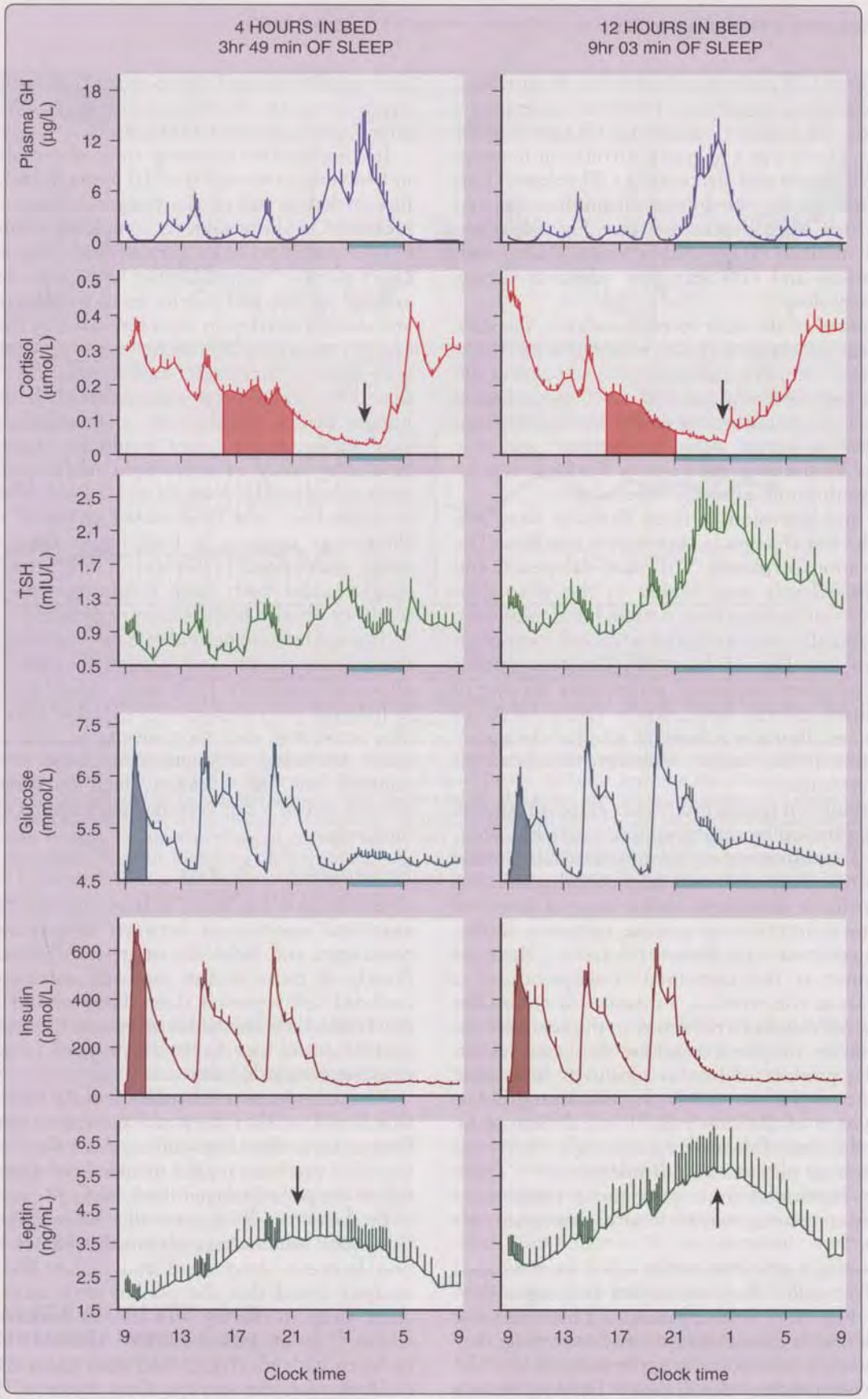

Figure 26-5 The 24-hour profiles of plasma GH, plasma cortisol, plasma TSH, plasma glucose, serum insulin and plasma leptin levels in 11 healthy young men who were studied after 1 week of bedtime restriction to 4 hours per night *(left panels)* and 1 week of bedtime extension to 12 hours per night *(right panels)*. The *blue bars* represent the bedtime period. On the cortisol profiles, the *blue areas* show the increase in evening cortisol levels and the *arrows* indicate the timing of the nadir. On the glucose and insulin profiles, the blue area shows the response to the morning meal. On the leptin profiles, the *arrows* indicate the timing of the nocturnal acrophase. (From Spiegel K, Leproult R, Van Cauter E. Impact of a sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-1439; Spiegel K, Leproult R, Colecchia E, et al. Adaptation of the 24-hour growth hormone profile to a state of sleep debt. Am J Physiol 2000;279:R874-R883; and Spiegel K, Leproult R, L'Hermite-Balériaux M, et al. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 2004;89:5762-5771.)

The sleep-onset GH pulse was observed in all individual profiles for both sleep conditions. However, after partial sleep restriction, all subjects exhibited a GH pulse prior to sleep onset. There was a negative correlation between presleep GH secretion and sleep-onset GH release. This profile of GH release is quite different from that observed during acute total sleep deprivation (see Fig. 26-1, top panels), where minimal GH secretion occurs during nocturnal wakefulness and GH secretion rebounds during daytime recovery sleep.

When compared to the fully rested condition, the state of sleep debt was associated with alterations of the 24-hour profile of cortisol, including a shorter quiescent period and elevated levels in the evening (see Fig. 26-5, second panel shaded areas). This alteration was similar to that observed after acute total or partial sleep deprivation[32] and may reflect decreased efficacy of the negative feedback regulation of the hypothalamic-pituitary-adrenal axis.[39]

Restriction and extension of sleep duration were also associated with clear changes in thyrotropic function. The nocturnal elevation of plasma TSH was dampened and thyroid hormone levels were higher in the sleep debt state.[39] Previous studies have demonstrated that total sleep deprivation is initially associated with a marked increase in TSH secretion (see Fig. 26-1), which becomes smaller when sleep deprivation continues, presumably because of negative feedback effects from slowly rising levels of thyroid hormones. Similar mechanisms are likely to underlie the alterations in thyrotropic function after recurrent partial sleep restriction.

Bedtime curtailment results in a higher glucose response to breakfast despite similar insulin secretion (see Fig. 26-5, lower panels). The difference in peak postbreakfast glucose levels between the sleep debt and fully rested conditions (i.e., ± 15 mg/dL) is consistent with a state of impaired glucose tolerance. Intravenous glucose tolerance testing confirms this deterioration in glucose tolerance.[39] Reduced glucose tolerance is the combined consequence of a decrease in glucose effectiveness, a measure of noninsulin dependent glucose use, and a reduction in the acute insulin response to glucose despite a trend for decreased insulin sensitivity. The product of insulin sensitivity and acute insulin response to glucose, that is, the disposition index, a validated marker of diabetes risk,[103] was decreased by nearly 40% in the state of sleep debt, reaching levels typical of populations at an elevated risk of diabetes.[104,105] These findings were confirmed in a subsequent randomized crossover study comparing two 10-hour nights versus two 4-hour nights.[106]

Mean levels of the satiety hormone leptin were reduced by 20% to 30% under sleep restriction as compared to extension (see Fig. 26-5, lowest panels).[38] This effect size of sleep restriction is comparable to that occurring after three days of dietary restriction by approximately 900 kcal per day under normal sleep conditions.[107] Further, there is a clear dose-response relationship between sleep duration and characteristics of the leptin profile[38] (Fig. 26-6, upper panels). Indeed, mean leptin levels gradually increase from 4 hours to 8 hours and to 12-hour bedtime condition. Importantly, these differences in leptin profiles occur despite identical amounts of caloric intake, similar sedentary conditions, and stable weight. A reduction of peak leptin levels has also been reported in volunteers studied after 7 days of 4-hour bedtimes.[108]

In a randomized crossover study of two nights of 4 hours in bed versus two nights of 10 hours in bed, daytime profiles of leptin and of the hunger hormone ghrelin were measured, and the subjects completed validated scales for hunger and appetite for various food categories (Fig. 26-6, lower panel).[109] Overall leptin levels were decreased by an average of 18% and ghrelin levels were increased by 28%, and the ghrelin:leptin ratio increased by more than 70%. Hunger showed a 23% increase, and appetite for nutrients with high carbohydrate content was increased by more than 30% when sleep was restricted. If this increase in hunger were to translate into a commensurate increase in food intake, weight gain would be expected. A recent laboratory study of overweight middle-aged adults who were submitted to 2 weeks of 1.5 hour of sleep extension or restriction in a randomized crossover design indeed showed an increase in food intake from snacks during sleep restriction.[110] However, the participants gained weight under both sleep conditions and differences in leptin or ghrelin levels were not detected.

Two epidemiologic studies have confirmed and extended these findings with observations of reduced leptin levels, after controlling for body mass index (BMI) or adiposity, in habitual short sleepers.[111,112] Higher ghrelin levels were also associated with short sleep.[111] A subsequent smaller study involving only postmenopausal women did not confirm the link between sleep duration, leptin, and ghrelin levels,[113] but very few participants had short sleep durations.

Epidemiologic Studies

Over the past ten years, a large number of studies have examined associations between sleep duration and the prevalence and incidence of type 2 diabetes and obesity. Nearly all these studies explored existing data sets that included self reported sleep duration and none of them determined whether short sleep was the result of bedtime curtailment or was due to the presence of a sleep disorder or other co-morbidities.

Four cross-sectional studies found a significant association between short sleep and the risk of diabetes.[114-117] In four of six prospective studies, short sleep at baseline was found to predict a higher incidence of diabetes.[118-123] The follow-up period ranged from 10 to 18 years.

By the end of 2008, more than 40 cross-sectional epidemiological studies have provided evidence for an association between short sleep and higher BMI. One meta-analysis found that the pooled odds ratio (OR) linking short sleep to obesity was 1.89 in children and 1.55 in adults.[124] Another meta-analysis reported an OR of 1.58 in children with short sleep duration and an OR of 1.92 in children with the shortest sleep duration.[125] A systematic review concluded that short sleep duration appears independently associated with weight gain, particularly in younger age groups.[126] A cross-sectional analysis that uniquely assessed sleep duration by wrist actigraphy in more than 6,000 men and women, ages 67 to 99 years, and showed that, compared to sleeping 7 to 8 hours per night,

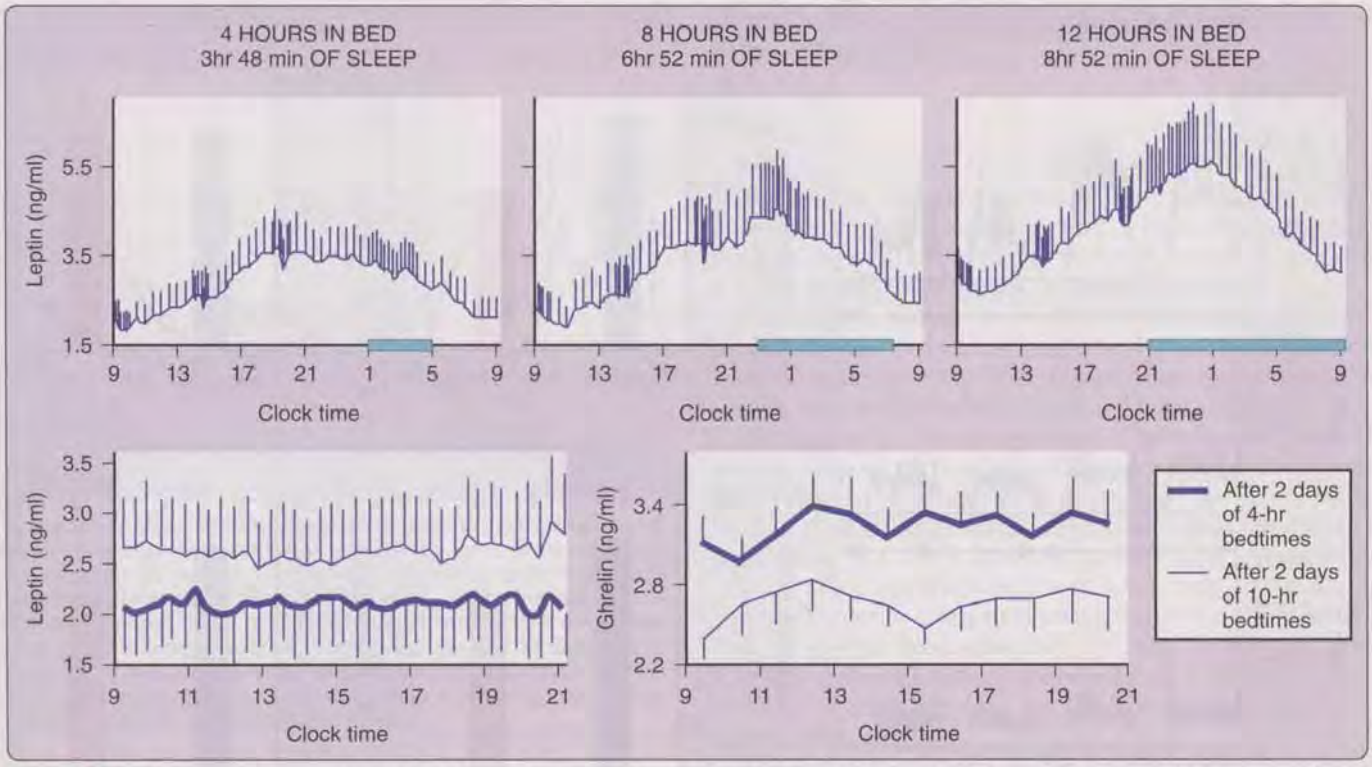

Figure 26-6 *Upper panel,* mean (± SEM) 24-hour leptin profiles obtained after 6 days of 4 hours, 8 hours, and 12 hours in bed in 9 healthy lean men studied at bed rest who ate 3 identical carbohydrate-rich meals. At the end of these bedtime conditions, the subjects slept an average of 3 hours 48 minutes in the 4-hour in bed condition, 6 hours 52 minutes in the 8-hour in bed condition, and 8 hours 52 minutes in the 12-hour in bed condition. Note that all the characteristics of the 24-hour leptin profile (overall mean, nocturnal maximum, amplitude) gradually increased from the 4-hour to the 12-hour bedtime condition. The *blue bars* represent the sleep periods. (From Spiegel K, Leproult R, L'Hermite-Balériaux M, et al. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 2004;89:5762-5771). *Lower panel,* mean (± SEM) daytime profiles of plasma leptin and ghrelin observed in healthy subjects after 2 days with 4-hour bedtimes or 2 days with 10-hour bedtime. Caloric intake was exclusively under the form of a constant glucose infusion. (From Spiegel K, Tasali E, Penev P, Van Cauter E. Sleep curtailment results in decreased leptin levels, elevated ghrelin levels and increased hunger and appetite. Annals Int Med 2004;141(11):846-850.)

sleeping fewer than 5 hours was associated with a BMI that was, on average, 2.5 kg/m^2 greater in men and 1.8 kg/m^2 in women, after adjusting for multiple potential confounders.[127] Finally, 9 of 10 longitudinal studies on sleep duration and obesity risk in children and adults, found that shorter sleep durations are associated with an increased risk for overweight and obesity a few years later.[128,129]

This body of epidemiologic evidence supports the hypothesis that sleep curtailment may be a nontraditional lifestyle factor contributing to the epidemic of obesity.[130]

REDUCED SLEEP QUALITY AND SLEEP DISORDERS: IMPACT ON ENDOCRINE AND METABOLIC FUNCTION

Experimental Reduction of Sleep Quality

Early studies have been consistent in showing that experimentally-induced full awakenings interrupting nocturnal sleep consistently trigger pulses of cortisol secretion.[25,131,132] Furthermore, in an analysis of cortisol profiles during daytime sleep, it was observed that 92% of spontaneous awakenings interrupting sleep were associated with a cortisol pulse.[132]

Aging and sleep disorders are associated with reduced sleep quality, including lower amounts of SWS without systematic decrease in sleep duration. The initiation of SWS is associated with a decrease in cerebral glucose use, stimulation of GH secretion, inhibition of cortisol release, decreased sympathetic nervous activity and increased vagal tone. (See Chapter 20 for autonomic measures.) All these correlates of SWS affect total body glucose regulation, suggesting that low amounts of SWS may be associated with reduced glucose tolerance.

A study tested this hypothesis by selectively suppressing SWS (using acoustic stimuli) in healthy young adults and examining the impact on the response to intravenous glucose injection.[133] The amount of SWS was reduced by nearly 90%, similar to what occurs over the course of four decades of aging. Such low levels of SWS are also typical of moderate to severe obstructive sleep apnea (OSA). Importantly, this intervention did not reduce total sleep duration. Slow-wave activity was markedly reduced

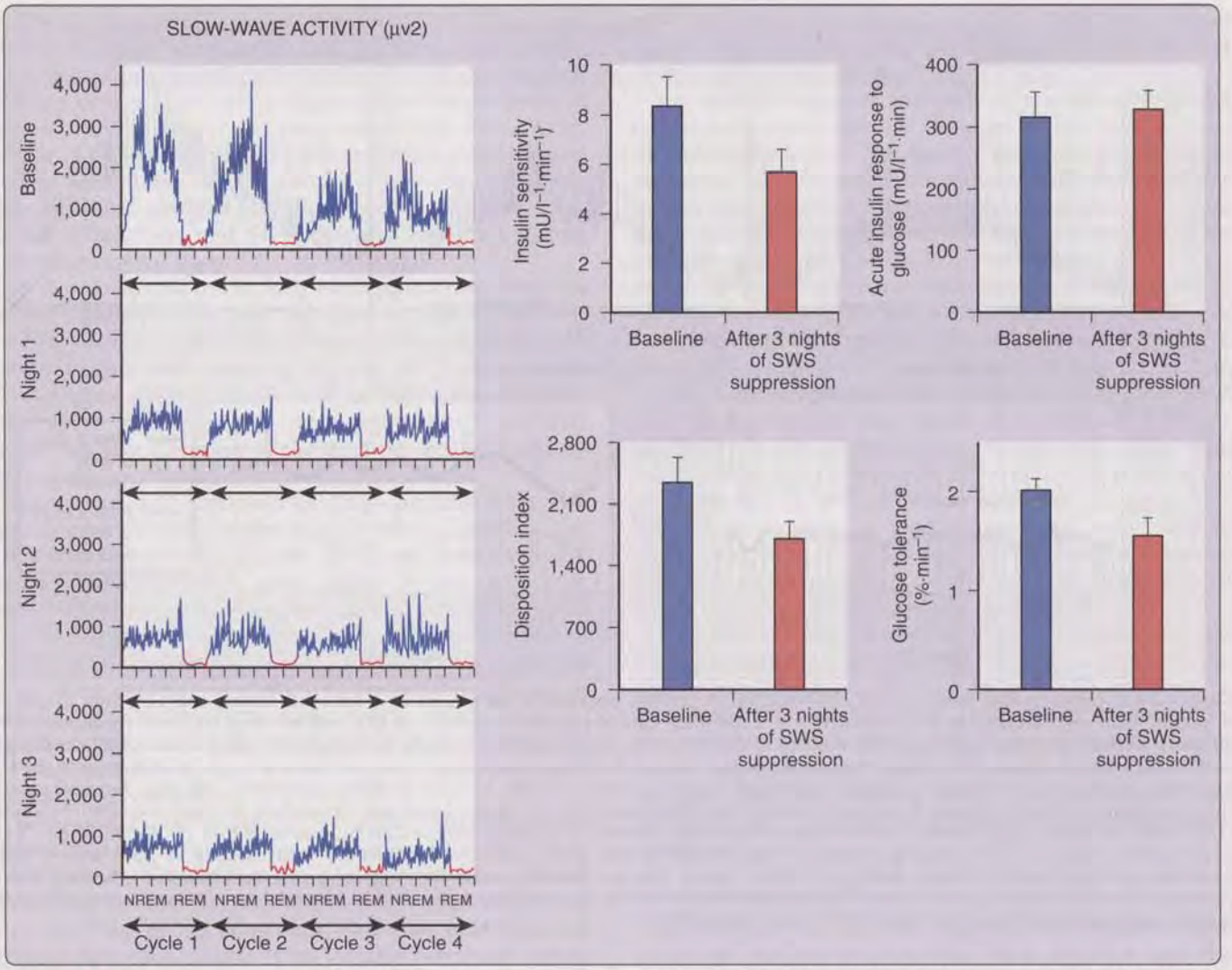

Figure 26-7 *Left panel*, mean (± SEM) profiles of slow-wave activity (μV^2) for the first four NREM–REM sleep cycles (NREM1, NREM2, NREM3, and NREM4) during baseline and in each experimental night of slow-wave activity suppression (Night 1, Night 2, Night 3). Slow-wave activity was markedly and similarly reduced in each experimental night compared to baseline, and the largest reductions were achieved during the first two NREM cycles. *Right panel*, mean (± SEM) insulin sensitivity, acute insulin response to glucose, disposition index, and glucose tolerance at baseline and after 3 nights of slow-wave sleep (SWS) suppression. (From Tasali E, Leproult R, Ehrmann D and Van Cauter E. Slow wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci USA 2008;105(3):1044-1049).

in each experimental night compared to baseline (Fig. 26-7, left panels). After 3 nights of SWS suppression, insulin sensitivity was decreased by ~25% (Fig. 26-7, right panels), reaching the level reported in older adults and in populations at high risk for diabetes.[134] This decrease in insulin sensitivity was not compensated for by an increase in insulin release, because acute insulin response to glucose remained virtually unchanged. Consequently, diabetes risk, as assessed by the disposition index was lower and glucose tolerance was reduced, reaching the range typical of impaired glucose tolerance. These laboratory findings demonstrate that reduced sleep quality, without change in sleep duration, may adversely affect glucose regulation.

In this study where SWS was suppressed while carefully avoiding full awakenings, cortisol levels were not affected at any time of the day or night.[133] An increase in daytime sympathovagal balance, as assessed by spectral analysis of heart rate variability, was identified as one of the possible mechanisms mediating the adverse impact of SWS suppression on glucose metabolism.

Studies in Population and Clinic-Based Samples

A number of cross-sectional as well as prospective epidemiologic studies (reviewed in detail in references 104 and 128) have provided evidence for an association between self-reported poor sleep quality, and the prevalence or incidence of diabetes, after controlling for age, BMI, and various other confounders. Of note, in 6 of 7 prospective studies that examined self-reported problems (such as difficulty initiating or maintaining sleep, use of sleeping pills,

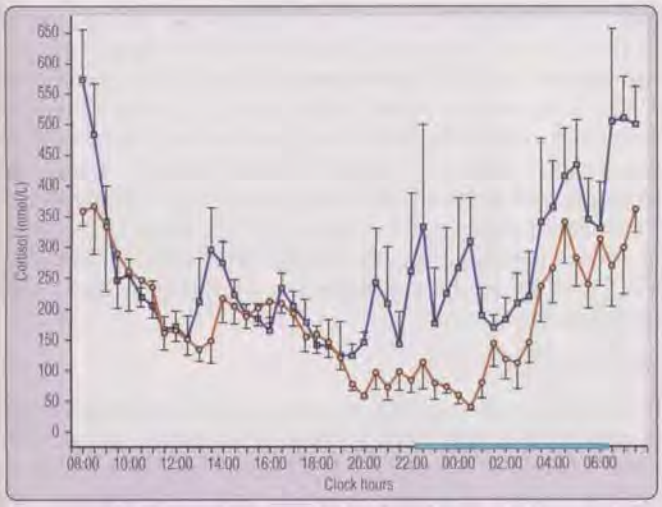

Figure 26-8 Mean 24-hour profiles of plasma cortisol in young people with insomnia with low total sleep time *(blue squares)* as compared to young people with insomnia with high total sleep time *(orange circles)*. The *blue bar* indicates the sleep-recording period. The error bars indicate standard error of the mean (SEM). (From Vgontzas A, Bixler EO, Lin HM, et al. Chronic insomnia is associated with neurohumoral activation of the hypothalamo-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 2001;86:3787-3794).

or insomnia complaint), poor sleep quality was associated with an increased risk of diabetes.[119,120,123,135-138]

Two clinic-based studies have examined the relationship between sleep duration and quality and glycemic control in type 2 diabetes. The first study administered the Pittsburgh Sleep Quality questionnaire to 161 African-American diabetic patients.[115] Higher perceived sleep debt or lower sleep quality were associated with poorer glycemic control after controlling for age, sex, BMI, insulin use, and the presence of complications.[115] Importantly, the magnitude of these effects of sleep duration or quality was comparable to that of commonly used oral antidiabetic medications. The second study used actigraphy in 47 diabetic patients and 23 nondiabetic controls under free-living conditions.[170] After adjusting for age, gender, and schooling, measures of sleep fragmentation were significantly higher in the patients with diabetes, and glycemic control correlated inversely with sleep efficiency.

Insomnia

There have been remarkably few studies of hormonal and metabolic variables in subjects with physician-diagnosed insomnia. A well-documented study[139] in patients with insomnia revealed that those with decreased total sleep time have higher cortisol levels across the night (Fig. 26-8). It is unclear whether this relative hypercortisolism is the result of sleep fragmentation and the associated sleep loss, or, alternatively, whether hyperactivity of the corticotropic axis is causing hyperarousal and insomnia. Recent views on chronic insomnia propose that it is a disorder of hyperarousal during both the night and the daytime, with associated hyperactivity of the hypothalamic-pituitary-adrenal axis.[140] A recent study involving 14 patients with insomnia found decreased nocturnal ghrelin levels, providing evidence for a possible dysregulation of energy balance in this patient population.[141]

OSA

There is a growing body of evidence linking OSA to abnormalities of glucose metabolism, including insulin resistance and glucose intolerance. For a summary of the present state of knowledge, refer to Chapter 114 of this volume as well as to recent reviews.[142,143]

Obstructive sleep apnea is also associated with disturbances in the control of weight and appetite regulation. Indeed, patients with OSA appear more predisposed to weight gain than similarly obese subjects without OSA.[144] Consistent with the upregulation of ghrelin observed following sleep restriction in healthy subjects,[109,111,145] patients with OSA—who usually have decreased total sleep time—have higher ghrelin levels. Elevated leptin levels, after controlling for BMI, are also consistently observed in OSA.[144] This hyperleptinemia in OSA is in contrast with the lower leptin levels that occur following sleep restriction in normal lean subjects[38,108,109] and in chronic short sleepers without OSA independently of BMI and adiposity.[111,112] Hyperleptinemia in OSA is thought to reflect leptin resistance.[144]

Successful treatment of OSA by continuous positive air pressure (CPAP) should lead to a reduction in leptin resistance, a decrease in ghrelin levels, and thus weight loss. Only two studies have measured ghrelin levels after CPAP treatment and both reported a decrease in ghrelin levels.[146,147] However, the findings on the effect of CPAP on body weight and visceral adiposity are mixed. Weight loss has been reported in one study after 6 months of CPAP,[148] whereas another study found no weight loss after one year of CPAP use.[149] Six months of CPAP therapy added to a weight reduction program have not resulted in greater weight loss.[150] If weight loss is important, loss of visceral fat is by far more relevant from a metabolic point of view. Again, the studies are scarce and provide conflicting results.[151-153]

AGE-RELATED SLEEP ALTERATIONS: IMPLICATIONS FOR ENDOCRINE FUNCTION

Normal aging is associated with pronounced age-related alterations in sleep quality, which consist primarily of a marked reduction of SWS (stages 3 and 4), a reduction in REM stages, and an increase in the number and duration of awakenings interrupting sleep (see Chapter 3). There is increasing evidence that these alterations in sleep quality may result in neuroendocrine disturbances, suggesting that some of the hormonal hallmarks of aging may partly reflect the deterioration of sleep quality.[154]

GH Axis

There are mutual interactions between somatotropic activity and sleep that are evident both in youth and older age. Sex and age differences are illustrated in the upper panels of Figure 26-9. In normal young men, there is a "dose-response" relationship between slow-wave sleep/slow-wave activity (SWS/SWA) and GH secretion, and

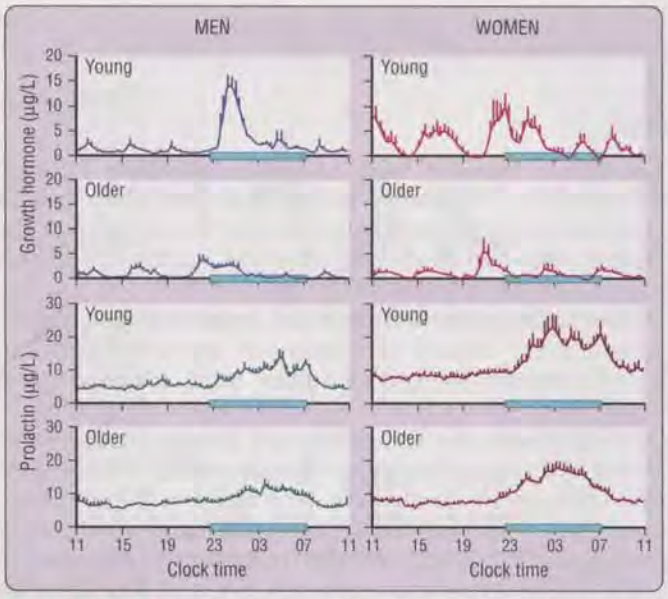

Figure 26-9 *Upper panels*, mean 24-hour profiles of plasma growth hormone in healthy young (18-33 years old) and older (51 to 72 years old) men *(left)* and women *(right)*. Young women were studied in the follicular phase of the menstrual cycle. Older women were postmenopausal and not on hormone replacement therapy. The *blue bars* represent the sleep periods. *Lower panels*, mean 24-hour profiles of plasma prolactin in the same subjects. (From Van Cauter E, Plat L and Copinschi G. Interrelations between sleep and the somatotropic axis. Sleep 1998;21:533-566; Latta F, Leproult R, Tasali E, et al. Sex differences in nocturnal growth hormone and prolactin secretion in healthy older adults: relationship with sleep EEG variables. Sleep 2005;28:1519-1524; and Caufriez A, Leproult R, L'Hermite-Balériaux M, et al. A potential role for endogenous progesterone in modulation of growth hormone, prolactin and thyrotropin secretion during normal menstrual cycle. Clin Endocrinol 2009;71:535-542).

the sleep-onset GH pulse is often the largest pulse observed over the 24-hour span. In normal young women, daytime GH pulses are more frequent and the sleep-onset pulse, while generally present, is smaller.[155,156] The GH profiles shown in Figure 26-9 illustrate gender differences in healthy older adults. In both gender groups, a significant amount of GH secretion occurs in the late evening, before habitual bedtime, at a time when GH secretion is usually quiescent in young adults.[157] Such presleep GH pulses may appear in young subjects when studied in a state of sleep debt.[23] In older men, but not women, the quantitative relationship between SWS/delta activity and sleep-onset GH release persists. In contrast, in older women, presleep GH release inhibits both the amount of GH secreted during sleep and sleep consolidation as evidenced by negative correlations between presleep GH secretion and sleep maintenance.[157]

The impact of aging on the amount of SWS and on GH release occurs with a similar chronology characterized by major decrements from early adulthood to midlife (Fig. 26-10).[158] Reduced amounts of SWS were found to be a significant predictor of reduced GH secretion in middle life and late life, independently of age. The observation that in older adults, levels of insulin-like growth factor (IGF-1), the hormone secreted by the liver in response to stimulation by GH, are correlated with the amounts of SWS,[159] is consistent with this finding. The relative GH deficiency of elderly adults is associated with increased fat tissue and visceral obesity, reduced muscle mass and strength, and reduced exercise capacity. The persistence of a consistent relationship between SWS and GH secretion in older men suggests that drugs that reliably stimulate SWS in older adults may represent a novel strategy for GH replacement therapy.

Prolactin Secretion

In both men and women, the majority of the daily release of prolactin occurs during sleep, irrespective of age. The lower panels of Figure 26-9 illustrate typical profiles in healthy nonobese young and older men and women. The sex difference is apparent both during daytime and nighttime in young adulthood but in older age only nighttime levels are affected. A nearly 50% dampening of the nocturnal PRL elevation is evident in elderly men and women.[160] This age-related endocrine alteration may partly reflects the increased number of awakenings (which inhibit PRL release) and decreased amounts of REM stages (which stimulate PRL release).[157]

Besides its role in the control of lactation and parental behavior, prolactin has multiple actions, including on metabolism and immunoregulation. Age-related alterations in sleep architecture and their clear impact on nocturnal prolactin release could thus impact healthy aging.

Pituitary-Adrenal Axis

There are highly consistent, sex-specific alterations in the diurnal pattern of basal cortisol secretion across the lifetime.[161] Figure 26-11 shows 24-hour profiles typical of younger and older men and women. In young adulthood, overall cortisol levels are lower in women than in men because the female response to the early morning circadian signal is slower and of lesser magnitude and the return to quiescence is more rapid. In men, the nocturnal quiescent period is shorter and the early morning elevation is higher and more prolonged. During aging, there appears to be a progressive decline in the endogenous inhibition of nocturnal cortisol secretion in both men and women, as reflected by a delay of the onset of the quiescent period and higher nocturnal cortisol levels.

In contrast to the rapid decline of SWS and GH secretion from young adulthood to midlife, the impact of age on REM sleep, sleep fragmentation, and evening cortisol levels does not become apparent until later in life. As illustrated in Figure 26-10, REM sleep, wake after sleep onset, and evening cortisol levels follow the same chronology of aging, that is, no alteration until midlife, and then a steady rise from midlife to old age.[158] There is a significant negative relationship between the loss of REM sleep in old age and the inability to achieve or maintain the quiescence of the corticotropic axis. Both animal and human studies have indicated that deleterious effects of hypothalamic-pituitary-adrenal hyperactivity are more pronounced at the time of the trough of the rhythm than at the time of the peak. Therefore, modest elevations in evening cortisol levels could facilitate the development of central and

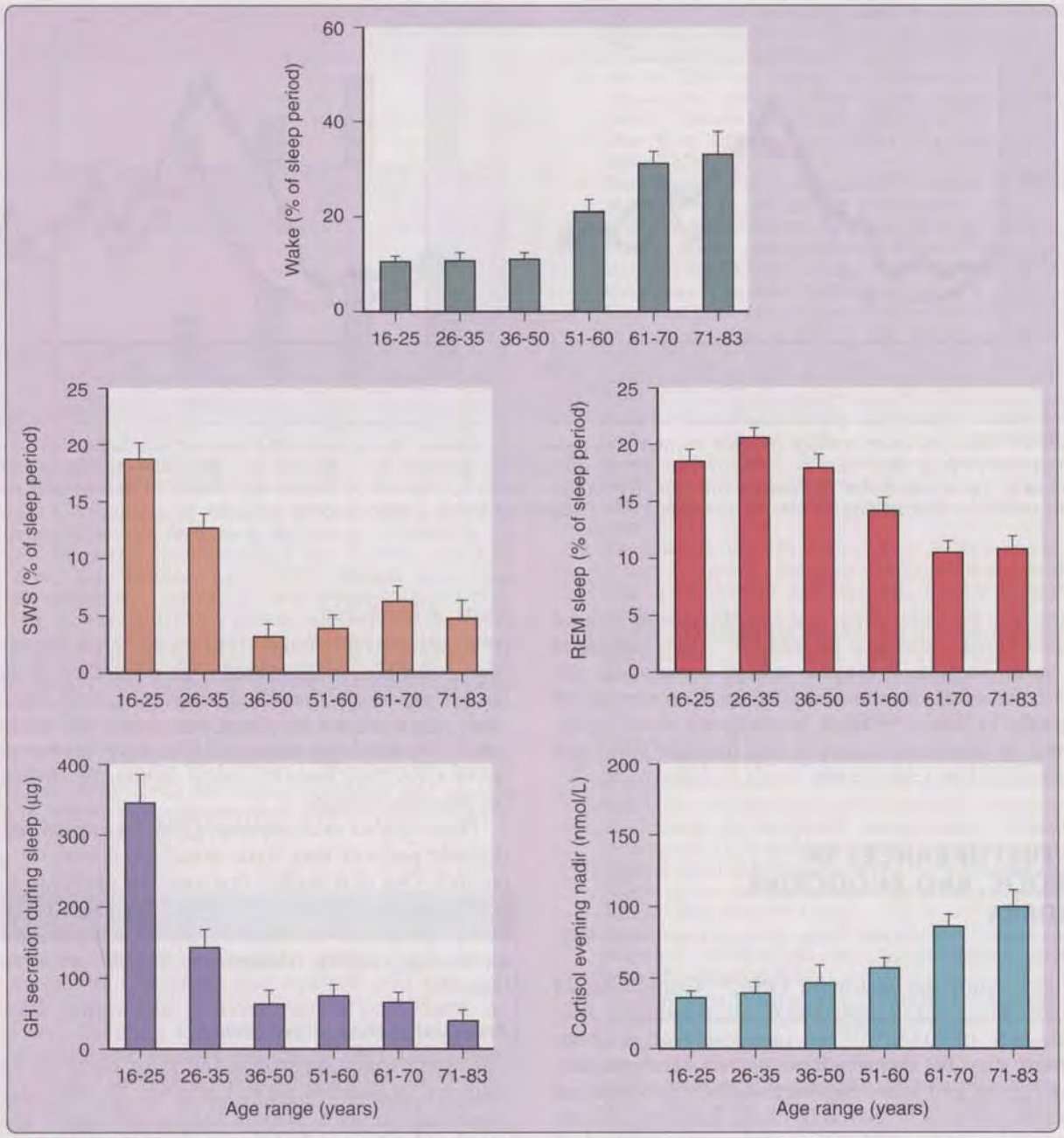

Figure 26-10 Mean (SEM) amounts of wake after sleep onset *(top panel)*, slow-wave sleep (stages III and IV, *middle left panel*), REM sleep *(middle right panel)*, growth hormone (GH) secretion during sleep *(lower left panel)* and nadir of plasma cortisol concentrations *(lower right panel)* by age group in 149 healthy nonobese men. Sleep stages are expressed as a percentage of the sleep period, defined as the time interval between sleep onset and final morning awakening. (From 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;284:861-868.)

peripheral disturbances associated with glucocorticoid excess, such as memory deficits and insulin resistance, and further promote sleep fragmentation.

Pituitary-Gonadal Axis

A progressive decline in testosterone levels occurs with aging in normal men. Starting at 30 to 40 years of age, testosterone concentrations decrease by 1% to 2% per year. In elderly men, the diurnal variation of testosterone is still detectable, but the nocturnal rise is markedly dampened.[51] One study indicated that the considerable interindividual variability of testosterone levels in healthy elderly men might be partly related to differences in sleep quality.[162] Indeed, both total and free (i.e., biologically active) morning testosterone levels were significantly correlated with total sleep time achieved during a night of laboratory polysomnography. A difference in total sleep time between 4.5 and 7.5 hours translated into a clinically meaningful difference in total testosterone levels, as concentrations around 200 to 300 ng/dL are considered to be

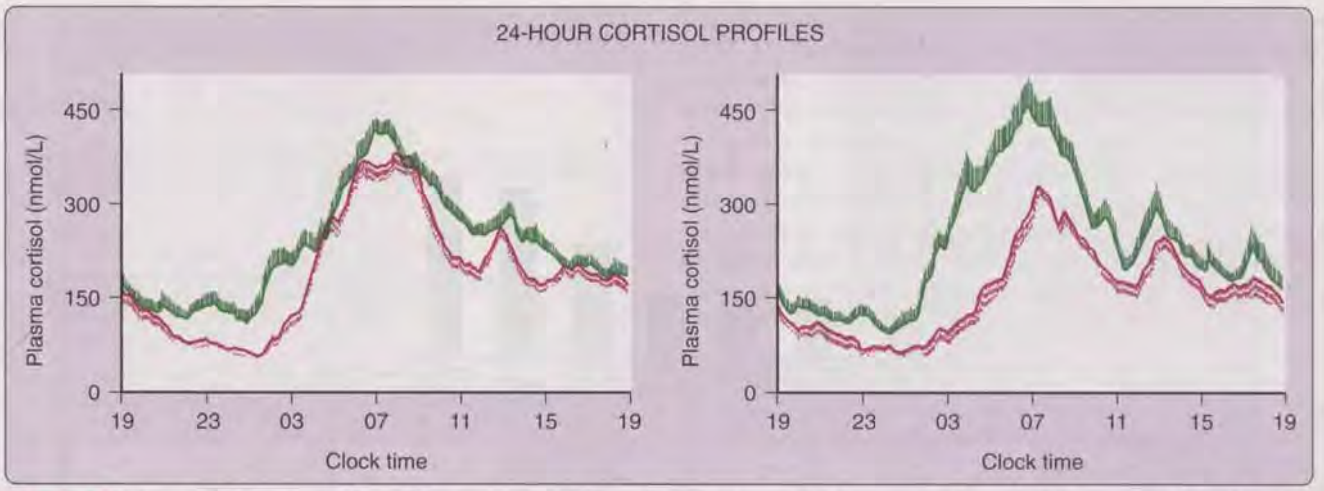

Figure 26-11 Mean 24-hour cortisol profiles in men *(left panel)* and women *(right panel)* 50 years of age and older ($n = 25$ and $n = 22$, respectively; *green lines*) as compared to 20- to 29-year-old subjects ($n = 29$ and $n = 20$, respectively; *red lines*). The *shaded area* at each time point represents the SEM. (From Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab 1996;81:2468-2473.)

borderline-low for older men, and concentrations around 500 to 700 ng/dL represent midnormal values typical of healthy young adults. A similar robust correlation was found with the usual amount of nighttime sleep monitored by actigraphy at home.[162] Thus, it is important to inquire about poor or insufficient sleep in the interpretation and management of low testosterone levels in older men.

SLEEP DISTURBANCES IN METABOLIC AND ENDOCRINE DISORDERS

Obesity

Obesity is a major risk factor for OSA.[163] Complaints of daytime sleepiness may be present in obese subjects even in the absence of OSA.[164-167] In obese subjects without OSA, there may be disturbances in sleep architecture, including lighter and more fragmented sleep as compared to nonobese controls.[165] Severely obese patients without OSA may have significantly shorter sleep latencies than lean age-matched controls.[164] Excessive daytime sleepiness has been found in 35% of obese subjects (BMI 40 ± 6 kg/m^2) without OSA compared to 2.7% in age-matched nonobese controls.[167] It has been proposed that excessive daytime sleepiness and fatigue (i.e., tiredness without increased sleep propensity) in obese individuals without OSA could be due to a disruption of sleep homeostasis caused by elevated levels of proinflammatory cytokines released by visceral fat (interleukin-6 and tumor necrosis factor-α).[168] In a cohort of 1300 middle-aged men and women who had one night of laboratory polysomnography, 47% of obese subjects reported subjective sleep disturbances (insomnia, sleep difficulty, excessive daytime sleepiness) as compared to 26% of nonobese individuals. Thus, the association between short sleep and high BMI evidenced in multiple epidemiologic studies may partly reflect the high prevalence of sleep disturbances and emotional stress.[169]

Type 2 Diabetes

As mentioned previously, there is evidence indicating that type 2 diabetes is associated with poor sleep quality, both by self report and based on actigraphy.[115,170] There is also emerging evidence for a high prevalence of OSA in diabetics.[171-175] It has been suggested that the presence and severity of OSA may have clinically significant adverse effects on glycemic control.

There is also evidence that CPAP treatment of OSA in diabetic patients may have beneficial effects on glycemic control. Out of 6 studies that assessed glycemic control in a total number of nearly 150 diabetic patients with OSA, 5 were positive.[176-180] Notably, the negative study reported an average nightly therapeutic CPAP use of only 3.6 hours.[181]

Polycystic Ovary Syndrome

Polycystic ovary syndrome, the most common endocrine disorder of premenopausal women, is characterized by hyperandrogenism, obesity, insulin resistance, and an elevated risk of type 2 diabetes. Insulin resistance is often referred to as a hallmark of PCOS. Obstructive sleep apnea is present in at least 50% women with PCOS.[182-187] Insulin resistance and reduced glucose tolerance in women with PCOS are largely due to the presence of OSA.[185] Both the prevalence of impaired glucose tolerance and the degree of insulin resistance increase in direct proportion to the severity of OSA (Fig. 26-12). Women with PCOS who have preserved normal glucose tolerance are not more insulin resistant than non-PCOS control women. Thus, PCOS appears to be comprised of two subphenotypes: PCOS with OSA and PCOS without OSA. Polycystic ovary syndrome with OSA is clearly associated with a higher risk of diabetes.[185] Thus, assessment of OSA in PCOS is highly recommended because the correction of OSA may greatly improve the prognosis. Unfortunately, most clinicians who treat PCOS today are not yet aware of the high risk of OSA in patients with PCOS, and that obesity is not a prerequisite.[188,189]

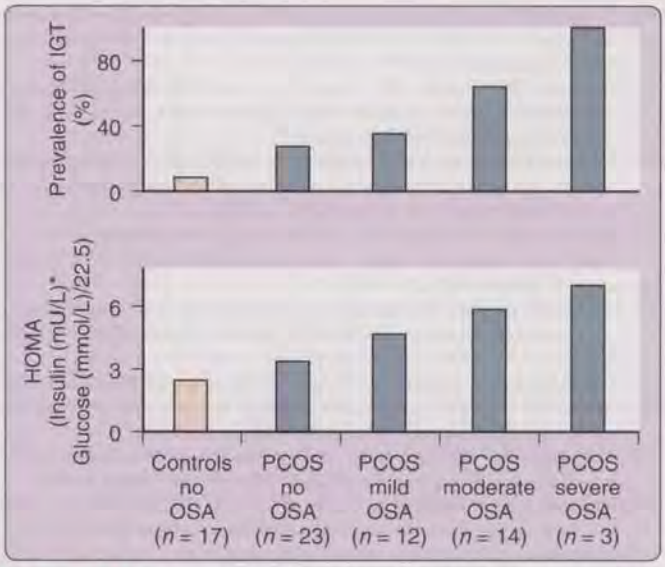

Figure 26-12 Prevalence of impaired glucose tolerance (IGT), *top* and degree of insulin resistance, *bottom* as assessed by the HOMA index, in control women without OSA, women with PCOS without OSA, and women with PCOS women with mild (5<AHI<15), moderate (15<AHI<30), and severe (AHI≥15) OSA. As expected, women with PCOS with or without OSA displayed a higher prevalence of IGT and increased insulin resistance than control women without OSA. Among women with PCOS, the prevalence of IGT and degree of insulin resistance increased in direct proportion to the severity of OSA. AHI, apnea-hypopnea index; HOMA, homeostasis model assessment; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome. (From Tasali E, Van Cauter E, Hoffman L, Ehrmann DE. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with the polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93:3878-3884).

❖ Clinical Pearl

Sleep exerts marked modulatory effects on most components of the endocrine system and has an important impact on glucose regulation. There is rapidly accumulating evidence from both laboratory and epidemiologic studies indicating that sleep loss and poor sleep quality are associated with hormonal disturbances and an increased risk of obesity and diabetes. Sleep disorders may also exacerbate the severity of an existing condition. Findings suggest that part of the constellation of hormonal and metabolic alterations that characterize normal aging may reflect the deterioration of sleep quality. Strategies to improve sleep quality may have beneficial effects on endocrine and metabolic function.

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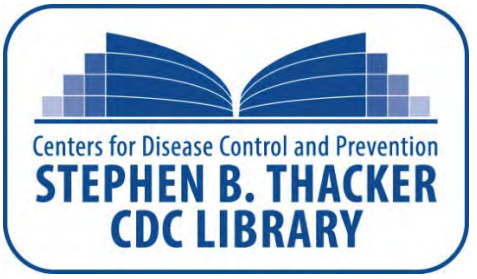

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