HIGHLIGHTED TOPIC | *Physiology and Pathophysiology of Sleep Apnea*

Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes

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Spiegel, Karine, Kristen Knutson, Rachel Leproult, Esra Tasali, and Eve Van Cauter. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol* 99: 2008–2019, 2005; doi:10.1152/japplphysiol.00660.2005.—Chronic sleep loss as a consequence of voluntary bedtime restriction is an endemic condition in modern society. Although sleep exerts marked modulatory effects on glucose metabolism, and molecular mechanisms for the interaction between sleeping and feeding have been documented, the potential impact of recurrent sleep curtailment on the risk for diabetes and obesity has only recently been investigated. In laboratory studies of healthy young adults submitted to recurrent partial sleep restriction, marked alterations in glucose metabolism including decreased glucose tolerance and insulin sensitivity have been demonstrated. The neuroendocrine regulation of appetite was also affected as the levels of the anorexigenic hormone leptin were decreased, whereas the levels of the orexigenic factor ghrelin were increased. Importantly, these neuroendocrine abnormalities were correlated with increased hunger and appetite, which may lead to overeating and weight gain. Consistent with these laboratory findings, a growing body of epidemiological evidence supports an association between short sleep duration and the risk for obesity and diabetes. Chronic sleep loss may also be the consequence of pathological conditions such as sleep-disordered breathing. In this increasingly prevalent syndrome, a feedforward cascade of negative events generated by sleep loss, sleep fragmentation, and hypoxia are likely to exacerbate the severity of metabolic disturbances. In conclusion, chronic sleep loss, behavioral or sleep disorder related, may represent a novel risk factor for weight gain, insulin resistance, and Type 2 diabetes.

obstructive sleep apnea; sympathovagal balance; glucose metabolism; appetite regulation; obesity

CHRONIC PARTIAL SLEEP LOSS: AN ENDEMIC CONDITION

Sleep loss due to voluntary bedtime restriction has become a hallmark of modern society (48–50). Over the past 40 years, self-reported sleep duration of Americans has decreased by 1.5 to 2 h (38, 48–50). The proportion of young adults reporting that they sleep <7 h per night has increased from 15.6% in 1960 to 37.1% in 2001–2002 (38, 49, 50). Today, many Americans sleep only 5–6 h per night (33). Although sleep need is likely to be gender and age dependent, several independent studies involving extension of the bedtime period for prolonged periods of time have concurred that the recommended 8-h bedtime period does not meet the sleep need of healthy young adults (25, 64, 95). Not surprisingly, reports of fatigue and tiredness are more frequent today than a few decades ago (5). A recent study of working women indicated that those reporting sleeping 6 h or less per night were consistently more tired throughout the day than those reporting that they slept 7 h or more (34). Curtailment of bedtime to the

minimum tolerable has become a widespread habit, driven by the demands and opportunities of the modern 24-h society.

Intriguingly, the dramatic increase in the incidence of obesity and diabetes seems to have developed over the same period of time as the progressive decrease in self-reported sleep duration (19, 20, 86). The two secular trends mirror each other over the second half of the 20th century.

Chronic sleep loss may also be the consequence of pathological conditions, including insomnia and sleep-disordered breathing (SDB). The prevalence of both conditions is also increasing, and, as obesity is one of the major risk factors for SDB, the increased prevalence of SDB is associated with the current epidemic of obesity. In middle-aged adults, SDB has been reported to affect 24% of men and 9% of women (98). Although SDB involves sleep fragmentation, respiratory disturbances, and hypoxic stress in addition to sleep loss per se, reduced total sleep time is a major component of this condition. Furthermore, the severity of SDB is exacerbated by restricted bedtimes (54), leading to even greater sleep loss.

Taken together, sleep loss, either behavioral or disease related, affects millions of individuals in our modern society, and recent studies have provided evidence in support of its deleterious impact on glucose metabolism and appetite regu-

lation. The present review focuses on the impact of behavioral sleep loss on the risk of obesity and diabetes and concludes with a brief discussion of the potential role played by sleep loss per se and sleep fragmentation in the metabolic and hormonal alterations that are typical of SDB.

Sleep loss and sleep disturbances could contribute to the development of insulin resistance and Type 2 diabetes either directly by having a deleterious effect on components of glucose regulation or indirectly via a dysregulation of appetite, leading to weight gain and obesity, a major risk factor for insulin resistance and diabetes. In the following section, we provide therefore a brief review of the impact of sleep in the modulation of glucose regulation and the neuroendocrine control of appetite. We then summarize the findings of laboratory and epidemiological studies that have explored the relationship between sleep duration and glucose and appetite regulation. In the final section, we discuss the potential role of sleep loss per se in the metabolic and neuroendocrine disturbances of SDB.

ROLE OF SLEEP IN THE REGULATION OF GLUCOSE METABOLISM

Blood levels of glucose are tightly regulated within a narrow range to avoid hypoglycemia and the associated impairment of the central nervous system as well as to prevent hyperglycemia and the resulting adverse, and eventually life-threatening, effects. Glucose homeostasis depends on the balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as muscle and fat, and non-insulin-dependent tissues, such as the brain. Thus glucose homeostasis is critically dependent on the ability of pancreatic β-cell to release insulin both acutely (i.e., acute insulin response to glucose or β-cell responsiveness) and in a sustained fashion and on the ability of insulin to inhibit hepatic glucose production and promote glucose disposal by peripheral tissues (i.e., insulin sensitivity). Reduced insulin sensitivity, or insulin resistance, occurs when higher levels of insulin are needed to reduce blood glucose levels after the administration of the same amount of exogenous glucose. As will be shown below, both β-cell responsiveness and insulin sensitivity are influenced by sleep.

Although most mammals, whether diurnal or nocturnal, sleep in bouts, human sleep is generally consolidated in a single 7- to 9-h period, and therefore an extended period of fasting must be maintained overnight. In normal subjects, during overnight sleep, blood levels of glucose remain stable or fall only minimally despite the extended fast (87). By comparison, in subjects awake and fasting in a recumbent position, in the absence of any physical activity, glucose levels fall by an average of 0.5–1.0 mM (i.e., 10–20 mg/dl) over a 12-h period (87). Thus a number of mechanisms operative during nocturnal sleep must intervene to maintain stable glucose levels during the overnight fast.

Studies of nighttime glucose tolerance during sleep have used intravenous glucose infusion at a constant rate or continuous enteral nutrition and have sampled glucose and insulin without awakening the subjects (70, 71, 85). Confounding effects of food ingestion and prolonged fasting are thus avoided by replacing the normal caloric intake with a constant input, thereby creating a steady-state condition with levels of glucose and insulin secretion within the physiological range,

although under conditions that are clearly artificial. In particular, prolonged glucose infusion results in a marked inhibition of endogenous glucose production.

Figure 1 shows mean profiles of blood glucose and insulin secretion rates obtained in normal subjects who were studied at bed rest for a 53-h period including a period of nocturnal sleep, 28 h of continuous wakefulness, and a daytime period of recovery sleep. Caloric intake was replaced by intravenous glucose infusion at a constant rate. A marked decrease in glucose tolerance (reflected in higher plasma glucose levels) is apparent during nocturnal 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%. Maximum levels occur around the middle of the sleep period. During the first half of the sleep period, the increase in plasma glucose is followed by a >50% increase in insulin secretion. Under these experimental conditions, the major underlying cause of the glucose increase is decreased glucose utilization. It is estimated that about two-thirds of the fall in glucose utilization during early sleep is due to a decrease in brain glucose metabolism (7) related to the predominance of slow-wave sleep (SWS), which is associated with a 30–40% reduction in cerebral glucose metabolism relative to waking. The remainder of the fall in glucose uptake is thought to reflect decreased peripheral utilization. Diminished muscle tone during sleep and rapid anti-insulin-like effects of the sleep-onset growth hormone (GH) pulse (46) are both likely to contribute to this decrease in peripheral glucose uptake.

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, reflecting an increase in glucose uptake. This increase is partially due to the increase in wake and rapid eye movement (REM) stages (66). Indeed, glucose utilization during REM sleep and waking is higher than during non-REM sleep (7, 8, 42–44). The hypoglycemic activity of previously secreted insulin during early sleep could also contribute to the decline of glucose levels during late sleep. 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 (55).

The distinct mechanisms regulating glucose metabolism during the early part of nocturnal sleep vs. the later part of nocturnal sleep predict that the response to partial sleep deprivation will differ from the response to total sleep deprivation. Indeed, during partial sleep deprivation, SWS is relatively well preserved and other mechanisms that contribute to prevent glucose levels from falling in the early part of sleep despite the extended fast are also preserved (e.g., nocturnal GH secretion), and thus nocturnal glucose levels are similar to those observed during sleep. In contrast, during total sleep deprivation, nocturnal glucose levels are lower than during sleep, although this difference may be reverted in the morning as delayed effects of counterregulatory mechanisms come into play.

ROLE OF SLEEP IN THE REGULATION OF APPETITE

Although it appears obvious that sleep plays an important role in energy balance, our understanding of the role of sleep in
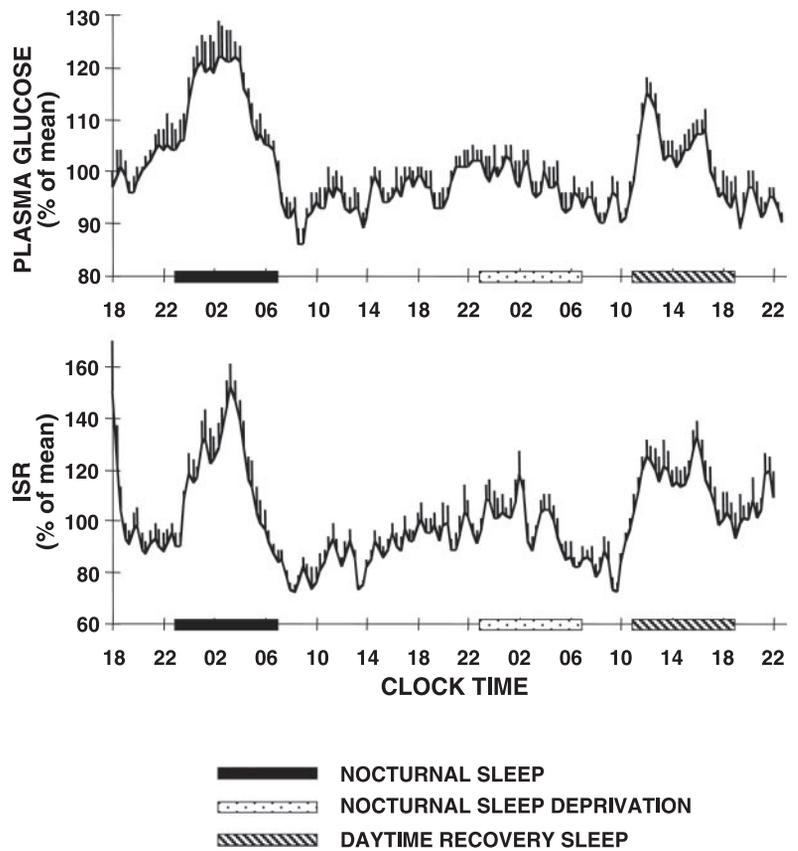
Fig. 1. Mean (+SE) profiles of glucose and insulin secretion rates (ISR) in a group of 8 normal young men (aged 20–27 yr) studied during a 53-h period including 8 h of nocturnal sleep, followed by 28 h of sleep deprivation including a period of nocturnal sleep deprivation, and 8 h of daytime recovery sleep. Data were obtained at 20-min intervals under continuous glucose infusion. (Adapted from Ref. 84.)

modulating caloric intake is relatively limited. In rodents, food shortage or starvation results in decreased sleep (13) and, conversely, total sleep deprivation leads to marked hyperphagia (60). 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 (80). Hypocretin neuronal activity and hypocretin-1 release are stimulated by sleep deprivation (18, 97). Hypocretin-containing neurons in the lateral hypothalamus project directly to the locus coeruleus and to other brain stem and hypothalamic arousal areas. These neurons also interact with the leptin-responsive neuronal network involved in balancing food intake and energy expenditure. Leptin, a hormone released by the adipocytes, provides information about energy status to regulatory centers in the hypothalamus (1). Circulating leptin concentrations in humans show a rapid decline or increase in response to acute caloric shortage or surplus, respectively (11, 36). These changes in leptin levels have been associated with reciprocal changes in hunger (11). The 24-h leptin profile shows a marked nocturnal rise, which is partly dependent on meal intake (67). Nevertheless, a study using continuous enteral nutrition to eliminate the impact of meal intake showed the persistence of a sleep-related leptin elevation, although the amplitude was lower than during normal feeding conditions (72). Prolonged total sleep deprivation results in a decrease in the amplitude of the leptin diurnal variation (47). Systemic administration of leptin to normally fed rats results in an increase of SWS and a decrease in REM sleep (73). Ghrelin, a peptide produced predominantly by the stomach, is also involved in energy balance regulation, but, in contrast to the anorexigenic effects of leptin, ghrelin stimulates appetite (30). The 24-h profile of ghrelin levels shows a marked nocturnal rise, which is only modestly dampened when subjects are sleep deprived (15). Ghrelin injections stimulate SWS and slow-wave activity in humans (96).

IMPACT OF SLEEP RESTRICTION ON GLUCOSE AND APPETITE REGULATION: LABORATORY STUDIES

The first laboratory studies that examined glucose tolerance or food intake during sleep deprivation all used the paradigm of total sleep deprivation for extended periods of time (62). Landmark studies by Rechtschaffen and collaborators reported that rats submitted to total sleep deprivation by the disk-over-water method markedly increased food intake but nevertheless lost weight (61). Fasting levels of glucose were not altered. These rodent studies concluded that prolonged total sleep deprivation did not affect glucose metabolism and that the hyperphagia was a normal response to increased energy expenditure. In humans, a number of early studies of acute total sleep deprivation (39, 52, 89, 92), sometimes in association with increased physical activity, noted a decrease in glucose tolerance and, more than a decade ago, VanHelder and Radomski (88) reported that "the major metabolic perturbations accompanying sleep deprivation . . . are an increase in insulin resistance and a decrease in glucose tolerance." These alterations were observed during total sleep deprivation for >40 h. In 1997, Dinges and Chugh (14) noted increased food intake in subjects confined to the laboratory and permitted ad libitum

access to food during 3 days of total sleep deprivation. Despite their potentially important physiological and clinical implications, these observations did not receive much attention, probably because such extreme sleep deprivation paradigms were very unlikely to occur in the general population.

The first study designed to address the hormonal and metabolic consequences of the much more common condition of recurrent partial sleep restriction was performed in 11 young healthy men studied after 6 days of sleep restriction with 4-h bedtimes (0100 to 0500) followed by 7 days of sleep recovery with 12-h bedtimes (2100 to 0900) (76). At the end of the week of sleep extension, the subjects slept on average 9 h 3 min ± 15 min, indicating that they had mostly recovered from their sleep debt. Examination of glucose metabolism included an intravenous glucose tolerance test (IVGTT) administered in the morning at the end of each bedtime condition followed by a 24-h period of blood sampling during which caloric intake was limited to identical carbohydrate-rich meals presented at 5-h intervals.

Figure 2 depicts the daytime profiles of glucose, insulin, homeostasis model assessment (HOMA, defined as the nor-

malized product of insulin concentration multiplied by the glucose concentration), leptin, and sympathovagal balance obtained from recordings of interbeat intervals at the end of sleep restriction and at the end of sleep recovery. Marked alterations in these physiological variables were observed in the morning hours. After 6 days of 4-h bedtimes, the overall glucose response after breakfast ingestion was increased (Fig. 2, shaded areas) and the peak of the response was on average higher by 15 mg/dl, indicating decreased glucose tolerance during sleep loss. The magnitude of this difference in peak glucose levels is similar to that observed between young and old adults and suggests that these young sleep-deprived subjects may have responded to an oral glucose tolerance test in a manner consistent with a diagnosis of impaired glucose tolerance (23). No significant change was observed for the amount of insulin secreted. When the integrated glucose and insulin responses were examined using the HOMA index, the area under the curve from 0900 to 1030 was >50% larger when the subjects were in the state of sleep debt than when they were fully rested. Even though the HOMA index has been validated as a measure of insulin resistance only during a fasting state, these results
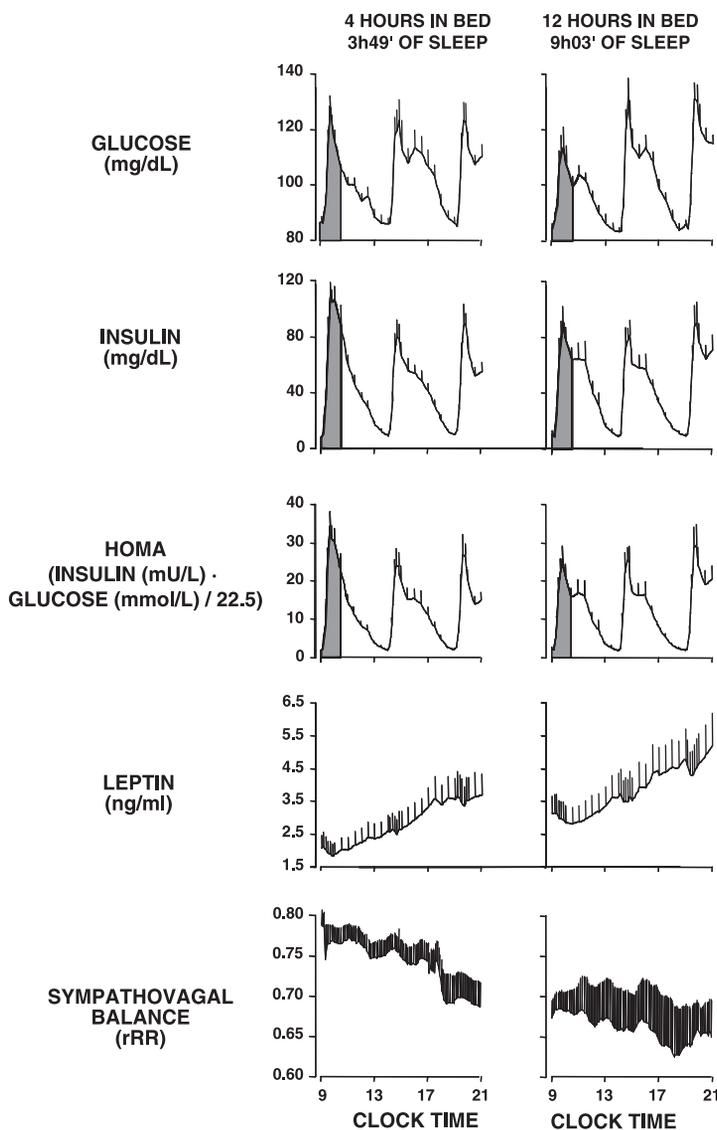

Fig. 2. Mean (+SE) daytime profiles of glucose, insulin, homeostasis model assessment (HOMA; the normalized product of insulin concentration multiplied by the glucose concentration), leptin, and sympathovagal balance obtained in 11 young healthy men after 6 days of bedtimes restricted to 4 h per night (*left*) and after 6 days of sleep extended to 12 h per night (*right*).

are suggestive of decreased insulin sensitivity in the morning in a state of a sleep debt. When sleep was restricted, mean leptin levels were 19% lower and the duration of the rise from morning nadir to nocturnal acrophase was decreased by nearly 1.5 h. The amplitude of the 24-h variation was on average 20% lower than during sleep extension. These marked differences in 24-h regulation of leptin levels between the two bedtime conditions occurred despite similar amounts of caloric intake and physical activity as well as stable body mass index (BMI). Sleep restriction, compared with sleep extension, tended to be associated with higher values of the coefficient of autocorrelation of successive beat-to-beat intervals over the 24-h period, reflecting lower levels of heart rate variability due to an elevation of cardiac sympathetic activity and/or a decrease in parasympathetic activity (9, 35, 53). The impact of sleep restriction on sympathovagal balance was particularly important in the morning and early afternoon and showed a 16–19% increase, respectively.

Glucose metabolism was further examined during a frequently sampled IVGTT performed after 5 days of sleep curtailment and after 6 days of sleep recovery. The glucose, insulin, and C-peptide profiles are shown in Fig. 3. Glucose tolerance, estimated as the rate of decrease of glucose levels after intravenous glucose injection from *time 0* to +19 min, was ~40% lower on the fifth day of sleep restriction than on the fifth day of sleep extension. Importantly, although this estimation of glucose tolerance was in the normal range for young healthy men when the subjects were fully rested, it was in the range observed in older adults with impaired glucose tolerance when the subjects were in the state of sleep debt (21, 57). The insulin profiles show a biphasic pattern; the first phase corresponds to the rapid release of insulin stored in the β-cells, whereas the second phase is triggered by the injection at *time t* = 20 min of tolbutamide, a drug that stimulates the production and release of insulin from the β-cells. The first phase of insulin secretion was reduced by nearly 30%, whereas the second phase (estimated as the area under the curve above

baseline levels from *t* = 19 min until the end of the test) was increased. Measurements of the plasma levels of C-peptide, a peptide that is coreleased with insulin in equimolar amounts, provide a more accurate estimation of insulin secretion than insulin concentration themselves. The first phase of C-peptide secretion was reduced by 25–30%. In contrast, the second phase increased by nearly 20%.

Analysis of the glucose and insulin responses using the minimal model revealed a 30–40% decrease in glucose effectiveness, a measure of non-insulin-dependent glucose utilization. Changes in the insulin sensitivity index obtained by minimal model analysis were nonsignificant. The "disposition index," which is calculated as the product of acute insulin response to glucose and insulin sensitivity index and is considered to be a predictor of diabetes risk (4), was decreased by an average of 37% in the state of sleep debt compared with the fully rested state.

It is likely that the adverse impact of sleep loss on glucose tolerance involves multiple pathways. Because the brain is a major site of non-insulin-dependent glucose uptake, the decrease in glucose effectiveness is likely to reflect decreased brain glucose utilization, consistent with PET studies that have shown reduced brain glucose utilization in sleep-deprived subjects (76, 82). Pancreatic β-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. Our recordings of heart rate variability indeed support a shift toward higher sympathovagal balance when the subjects were sleep restricted compared with fully rested (Fig. 2, *bottom*). Disturbances in the secretory profiles of the counterregulatory hormones, GH and cortisol, may also contribute to the alterations in components of glucose regulation observed during sleep loss. We previously reported that 6 days of sleep restriction were associated with an extended duration of elevated nighttime GH concentrations and with an increase in
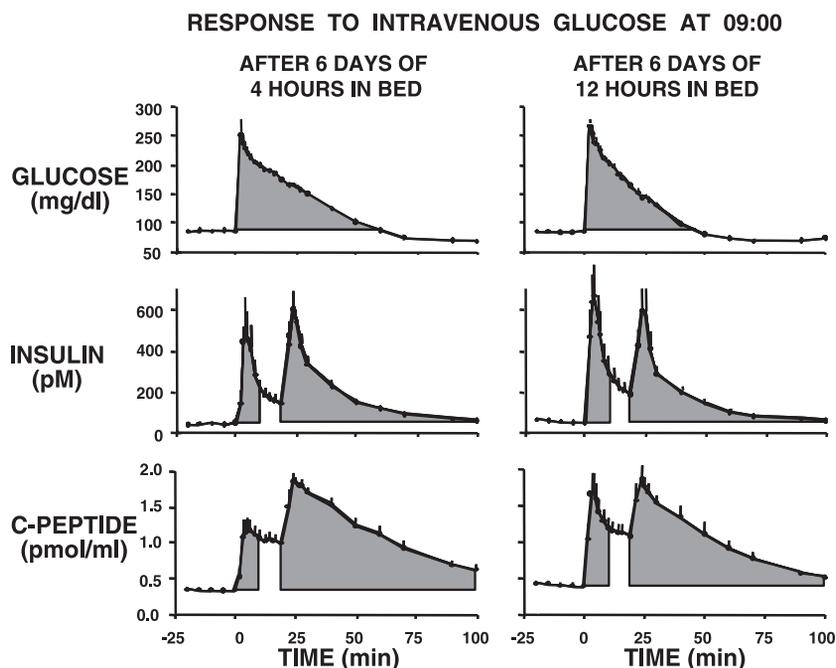

Fig. 3. Mean (+SE) glucose, insulin, and C-peptide profiles obtained in healthy young men during an intravenous glucose tolerance test performed at the end of sleep curtailment to 4-h bedtimes (*left*) and at the end of sleep extension to 12-h bedtimes (*right*). (Adapted from Ref. 76.)

evening cortisol levels. The extended exposure of peripheral tissues to higher GH levels may adversely affect glucose regulation by inducing a rapid decrease in muscular glucose uptake, and elevated evening cortisol concentrations are likely to result in reduced insulin sensitivity on the following morning (56).

We confirmed the deleterious impact of sleep restriction on glucose metabolism in a follow-up study using a randomized crossover design (77). Twelve healthy men were investigated after two consecutive nights of 10 h in bed (2200 to 0800) and after two consecutive nights of 4 h in bed (0100 to 0500). This design addressed some of the limitations of the previous study (76), namely the possibility of an order effect (sleep restriction preceded sleep recovery) and the use of a rather severe amount of sleep restriction (6 nights of 4-h bedtimes). After the second night of each bedtime condition, caloric intake was replaced by an intravenous glucose infusion at a constant rate to avoid fluctuations of hunger and appetite related to meal ingestion. The subjects completed validated visual analog scales for hunger and appetite for various food categories throughout the daytime period, and blood samples were obtained at 20-min

intervals for the measurement of glucose, insulin, leptin, and ghrelin.

The daytime profiles of glucose, insulin, ghrelin-to-leptin ratio, and craving for foods with high carbohydrate content obtained after the second night of each bedtime condition are illustrated in Fig. 4. Even though sleep duration was manipulated for only two nights, the glucose and insulin profiles obtained during continuous glucose infusion were consistent with the results obtained during IVGTT in the previous study (see Fig. 3). In the early part of the day, after 2 days of short bedtimes, glucose levels were higher and insulin levels were lower than after 2 days of long bedtimes. Appetite for calorie-dense foods with high carbohydrate content (examples listed on the scale included cake, candies, cookies, ice cream, pastry, bread, pasta, cereal, potatoes, chips) was increased by >30% when the subjects had short sleep vs. extended sleep (77). The ghrelin-to-leptin ratio was elevated by >70%. Importantly, there was a robust relationship between the increase in hunger during sleep restriction and the increase in the ratio of ghrelin to leptin (77). An analysis of variance revealed that the decrease in leptin was a stronger predictor of changes in hunger
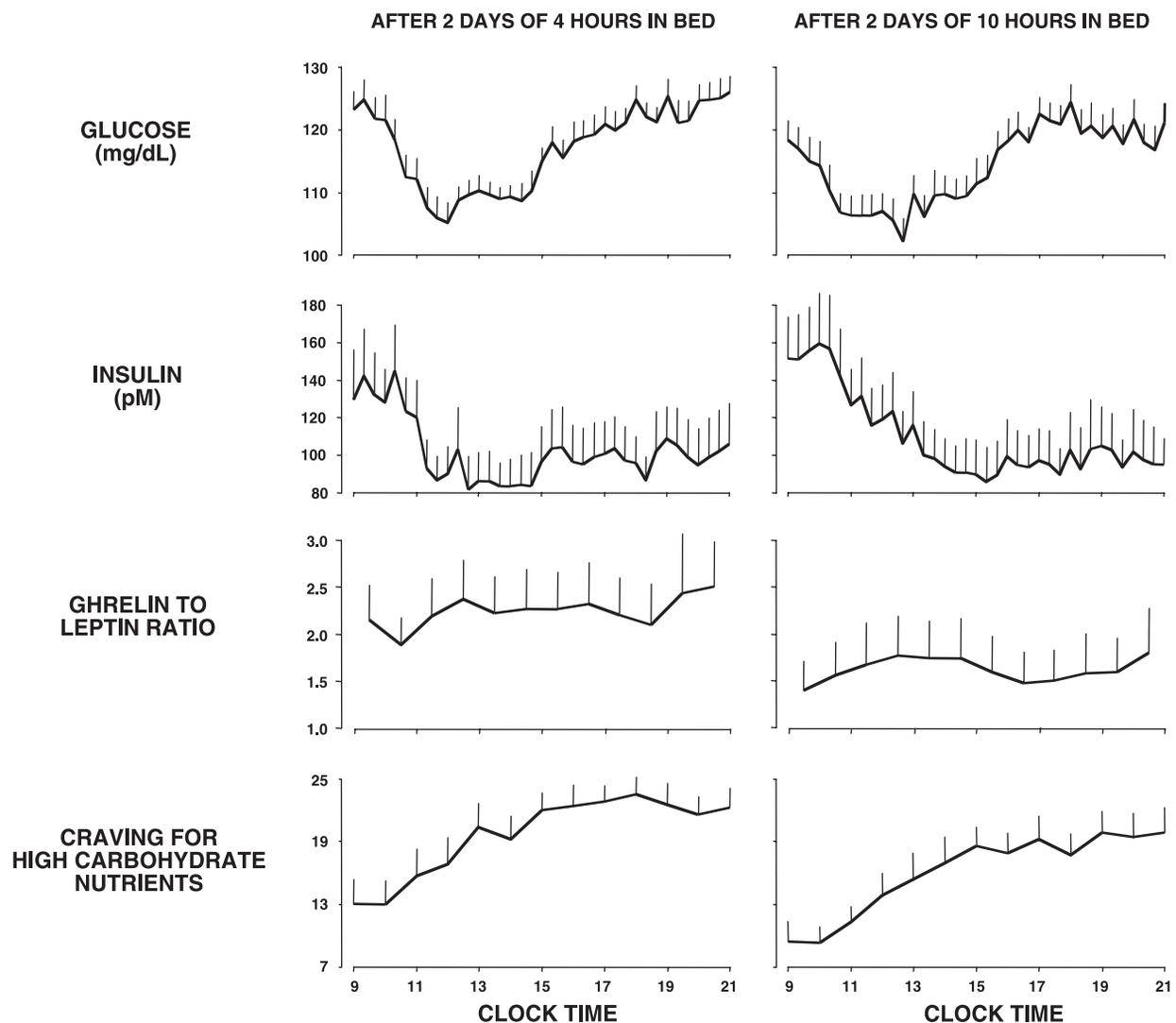

Fig. 4. Mean (+SE) daytime profiles of glucose, insulin, ghrelin-to-leptin ratio, and craving for high-carbohydrate nutrients obtained in 12 young healthy men after 2 days of 4-h bedtimes (*left*) or after 2 days of 10-h bedtimes (*right*).

than the increase in ghrelin. Nearly 70% of the variance in increased hunger could be accounted for by the increase in the ghrelin-to-leptin ratio. Nevertheless, a role for additional humoral factors regulating hunger and appetite such as cholecystokinin, adiponectin, and peptide YY 3-36, a peptide released into the peripheral circulation by the intestinal L-cells after food intake, in the complex pathways linking sleep loss and food intake cannot be excluded. If the increase in hunger and appetite ratings observed during sleep restriction translates into a commensurate increase in food intake, this would correspond to a caloric excess of 350–500 kcal/day for a young normal-weight sedentary adult and would result in a high risk of clinically significant weight gain.

Similar findings were obtained simultaneously in a large epidemiological study that obtained laboratory measures including polysomnographic assessments of sleep and morning fasting levels of plasma leptin and ghrelin as well as sleep diaries in over 1,000 subjects (79). As summarized in Table 1, despite the differences in study design, the two studies were remarkably concordant in finding a decrease in the satiety hormone leptin and an increase in appetite-stimulating ghrelin with short sleep (77, 79).

In summary, two well-controlled laboratory studies in relatively small groups of healthy young men submitted to sleep curtailment for 2–6 days have indicated that short-term sleep restriction results in a marked decrease in glucose tolerance to intravenous glucose and reduced insulin release. Alterations in glucose and insulin responses to carbohydrate-rich meals observed after 6 days of short sleep were suggestive of a decrease in insulin sensitivity. Further work is needed to evaluate differences in the impact of sleep loss on glucose metabolism when exogenous glucose input is oral and gastrointestinal factors come into play, compared with intravenous. Whether the adverse effects of sleep restriction on glucose metabolism would also be found in women and older adults and whether some degree of adaptation might occur if sleep restriction continued during a more extended period of time, i.e., months or years, are important open questions. Preliminary data have shown that young healthy subjects of both genders who voluntarily curtail their sleep on a chronic basis, i.e., <6.5 h per night for at least 6 mo, have a glucose response to intravenous glucose similar to that of subjects with habitual bedtimes between 7.5 and 8.5 h, but at the cost of markedly higher insulin secretion (41). Thus the nearly 40% reduction in glu-

cose tolerance to intravenous glucose and the decrease in the acute insulin response observed after short-term sleep restriction appears to result in the long run in a reduction in insulin sensitivity. When sleep loss becomes more chronic, adaptation seems to occur, as the initial impairment of glucose tolerance and of β-cell responsiveness subside and insulin resistance develops. In contrast, the impact of sleep loss on appetite regulation seems to be similar under acute or chronic conditions, as both short-term laboratory studies of experimental sleep restriction (75, 77) and studies of habitual short sleepers show an upregulation of orexigenic ghrelin and a downregulation of anorexigenic leptin (79).

Figure 5 provides a schematic representation of the mechanisms by which sleep deprivation may result in increased risk of insulin resistance and diabetes either by directly affecting parameters of glucose tolerance or indirectly via a disturbance in appetite regulation, leading to increased food intake and weight gain.

SLEEP DURATION AND RISK OF OBESITY AND DIABETES: EPIDEMIOLOGICAL EVIDENCE

In recent years, an increasing number of epidemiological studies have reported an association between sleep duration and BMI. A 2000 report from Spain observed that those reporting sleeping 6 h or less per day had an increased risk of obesity after controlling for sex, age, and other factors, and this group also had a higher mean BMI (27.7 vs. 24.9 kg/m² for those sleeping ≥9 h per day) (91). In 2002, an analysis of a survey conducted in 1982 in over one million subjects from the Cancer Prevention Study II demonstrated a significant U-shaped association between BMI and self-reported sleep duration among women and a negative monotonic association among men (37). Interestingly, this association was present even though the mean BMI for the sleep duration categories ranged from 24.5 to 26.5 kg/m², thus indicative of a very low proportion of obese participants at the time of the survey. The Wisconsin Sleep Cohort Study, which was a population-based study that included over 1,000 subjects, observed a U-shaped association between average sleep duration based on 6-day sleep diaries and BMI, after adjustment for age and sex (79). The data were collected beginning in 1995, and mean BMI for the sleep duration categories were all above 30 kg/m² after adjustment for age and sex. A sleep duration of 7.7 h predicted

Table 1. *Impact of sleep restriction on leptin and ghrelin levels*

	Laboratory Study	Epidemiological Study
	Spiegel et al. (77)	Taheri et al. (79)
	Within-subject comparison	Across-subject comparison
	2 days of 4-h bedtimes vs. 2 days of 10-h bedtimes	Usual sleep time of 5 h vs. 8 h
	$n=12$	$n=1{,}024$
	age: 22 ± 2 yr	age: 53 ± 8 yr
	100% men	54% men
Change in leptin (satiety hormone)	−18%*	−16%†
Change in ghrelin (appetite hormone)	+28%*	+15%†

The left column reports the leptin and ghrelin changes obtained in young healthy men during a laboratory study that used a randomized crossover design involving 2 days of 4-h bedtimes and 2 days of 10-h bedtimes (77). The right column reports the leptin and ghrelin changes obtained in a population of >1,000 men and women (79) when habitual sleep duration was 5 h vs. 8 h. Despite the differences in study design, the two studies are remarkably concordant in finding a decrease in the satiety hormone leptin and an increase in appetite-stimulating ghrelin with short sleep. *Body mass index unchanged; †after controlling for body mass index.
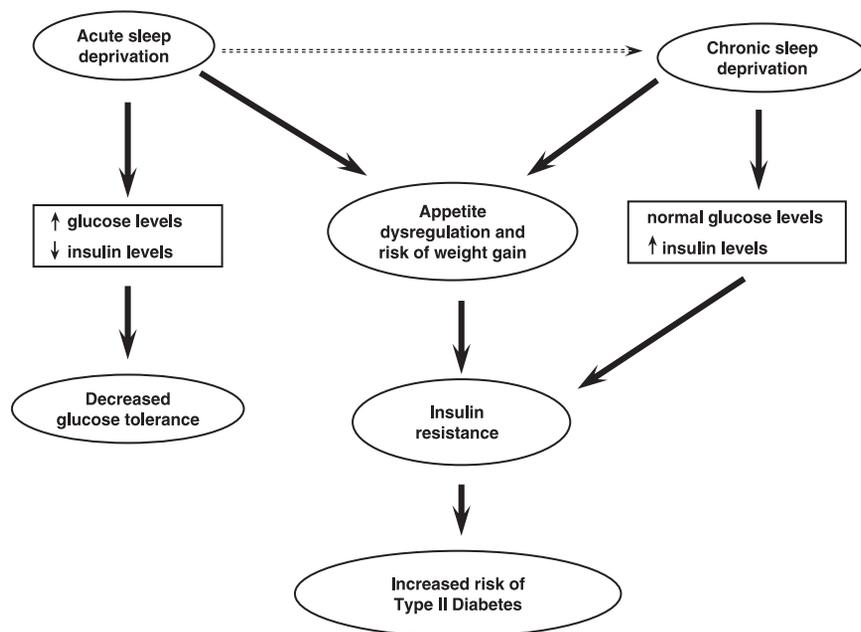
Fig. 5. Putative mechanisms by which sleep deprivation may result to weight gain, altered glucose metabolism, and Type 2 diabetes.

the lowest mean BMI (79). A 13-year prospective study in almost 5,000 subjects demonstrated that self-reported sleep duration is negatively associated with risk of obesity after controlling for age, education, physical activity, and other factors (29). Furthermore, this study showed that the average self-reported sleep duration from four interviews conducted over 13 years was negatively associated with the yearly rate of change in BMI with higher average sleep durations being associated with a smaller BMI increase (29). Finally, a study of 924 adults from the United States found that overweight (BMI 25–29.9 kg/m^2) and obese (BMI 30–39.9 kg/m^2) participants report sleeping less than subjects with a normal BMI (93).

Similar associations between sleep duration and BMI have been observed in adolescents and children as well. A French case-control study found that short sleep duration was associated with increased risk of obesity in 5-yr-old children after controlling for television viewing and parental overweight (40). A study of 383 adolescents in Texas found a significant negative association between total sleep time over one 24-h period of actigraphy recording and risk of obesity (BMI >85th percentile for age and sex and a percentage body fat ≥25% for men or ≥30% for women) after controlling for age, sex, sexual maturation, and ethnicity (24). In this sample, an hour decrease in sleep duration was associated with an increase in risk of obesity by 80% (24). In Japan, a study of 6- to 7-yr-old children observed a dose-response relationship between short sleep durations (reported by the parents) and obesity after controlling for age, sex, parental obesity, physical activity, TV watching, frequency of eating breakfast, and frequency of snacking (68). Finally, a study of over 8,000 children in the United Kingdom reported that sleep duration at age 30 mo (as reported by a parent) was associated with obesity (BMI ≥95th percentile for age and sex) at age 7 yr after adjusting for maternal education, energy intake at 3 yr of age, and sex (63).

A few studies have reported an association between sleep and risk of diabetes. The Nurses Health Study revealed a significant association between short sleep at baseline and risk of developing symptomatic diabetes 10 years later after adjust-

ment for shift work in 1988, hypercholesterolemia, hypertension, smoking, snoring, exercise, alcohol, depression in 1992, postmenopausal hormone use, and family history of diabetes (2). In Sweden, ~6,400 men who were nondiabetic at baseline were followed for almost 15 years, and difficulty sleeping at baseline significantly predicted development of Type 2 diabetes after controlling for age, BMI at screening, changes in BMI until follow-up, baseline glucose, follow-up time, physical activity, family history of diabetes, smoking, social class, and alcohol intake (51). A prospective study of over 8,000 adults in Germany with a mean follow-up period of 7.5 yr observed that difficulty maintaining sleep at baseline was associated with increased risk of incident Type 2 diabetes at follow-up even after controlling for age, education, parental history of diabetes, smoking, alcohol, hypertension, physical activity, dyslipidemia, history of angina pectoris, and BMI (45). Finally, the Sleep Heart Health Study recently demonstrated an increased risk of Type 2 diabetes or impaired glucose tolerance among participants who reported sleeping 6 h or less or 9 h or more per night after adjustment for age, sex, ethnicity, study size, and waist circumference (22).

In summary, eight independent studies have indicated that chronic short and/or poor sleep may increase the risk of obesity, and four studies have found an increased risk of Type 2 diabetes with short sleep.

POSSIBLE ROLE OF SLEEP LOSS AND SLEEP FRAGMENTATION IN OSA-RELATED METABOLIC DISTURBANCES

There is growing evidence from both clinical and epidemiological studies suggesting that disrupted sleep, as occurs in obstructive sleep apnea (OSA), is independently associated with abnormalities that comprise the metabolic syndrome including insulin resistance, hypertension, dyslipidemia, and an increased risk of diabetes (12, 32, 58, 59, 78, 81). Metabolic consequences of OSA will be addressed in another article of this issue of the Journal. Here, we will specifically discuss the

possible role of sleep loss (i.e., reduced total sleep time) and sleep fragmentation (i.e., lack of sleep continuity) in the development of metabolic morbidities associated with OSA. OSA also involves respiratory stress in addition to sleep loss and sleep fragmentation, and hypoxia and hypercapnia also result in increases in sympathetic nerve activity (74, 94) and adverse effects on glucose regulation (17, 27, 28, 32, 51, 58, 59, 81, 90). Importantly, in the present context of endemic behavioral sleep restriction, the severity of SDB is exacerbated by short bedtimes (54), leading to even greater sleep loss and fragmentation.

The studies reviewed in the preceding sections clearly indicate that reduced total sleep time, in the absence of sleep fragmentation or breathing abnormalities, can lead to alterations in parameters of glucose tolerance and dysregulation of appetite. In the two laboratory studies (75–77), sleep efficiency was indeed very high when the subjects had only 4-h bedtimes and sleep continuity was optimal. The observed impairment of glucose tolerance with reduced total sleep time in the absence of sleep fragmentation (75, 76) suggests that sleep loss per se could be a significant contributor to insulin resistance in OSA (17, 27, 28, 32, 51, 58, 59, 81, 90). Similarly to short sleepers without OSA (79), patients with OSA display higher ghrelin levels that decrease to levels only slightly higher than BMI-matched controls after only 2 days of continuous positive airway pressure (CPAP) treatment (26). In contrast, the observed reduction in leptin levels with short sleep is not consistent with the hyperleptinemia, which is characteristic of OSA. Although leptin levels are reduced in short sleepers

without OSA irrespective of BMI (79), patients with OSA have elevated leptin levels, and CPAP treatment partly corrects this abnormality (10, 26, 31, 65, 69).

Studies of glucose tolerance and/or insulin resistance after CPAP treatment of OSA have not all shown an improvement of metabolic parameters. Negative findings may have been related to the relatively short duration of treatment (which ranged from 1 night to a maximum of 6 mo) that may have been insufficient to correct the insulin resistance developed after years of SDB. But another factor that could play a role in the persistence of metabolic abnormalities despite CPAP treatment of OSA is the fact that even the most compliant patients rarely use CPAP for >5–6 h per night and therefore some degree of sleep loss persists.

OSA is invariably associated with sleep fragmentation, which also commonly results in decreased amount of SWS. To date, there are only very few studies that have specifically examined the possible role of sleep fragmentation or altered sleep architecture on metabolic disturbances. In one experimental paradigm using auditory stimuli to fragment sleep, Bonnet et al. (6) found that, in healthy young men, sleep disruption was accompanied by increased metabolic rate (derived from O_2 uptake and CO_2 output) throughout the night compared with a nondisturbed baseline night. In another study, experimental suppression of SWS using acoustic stimuli in healthy subjects resulted in elevation of plasma catecholamine levels that was correlated with the degree of sleep fragmentation (83). A possible interpretation of these findings could be that sleep fragmentation augments sympathetic nervous activ-
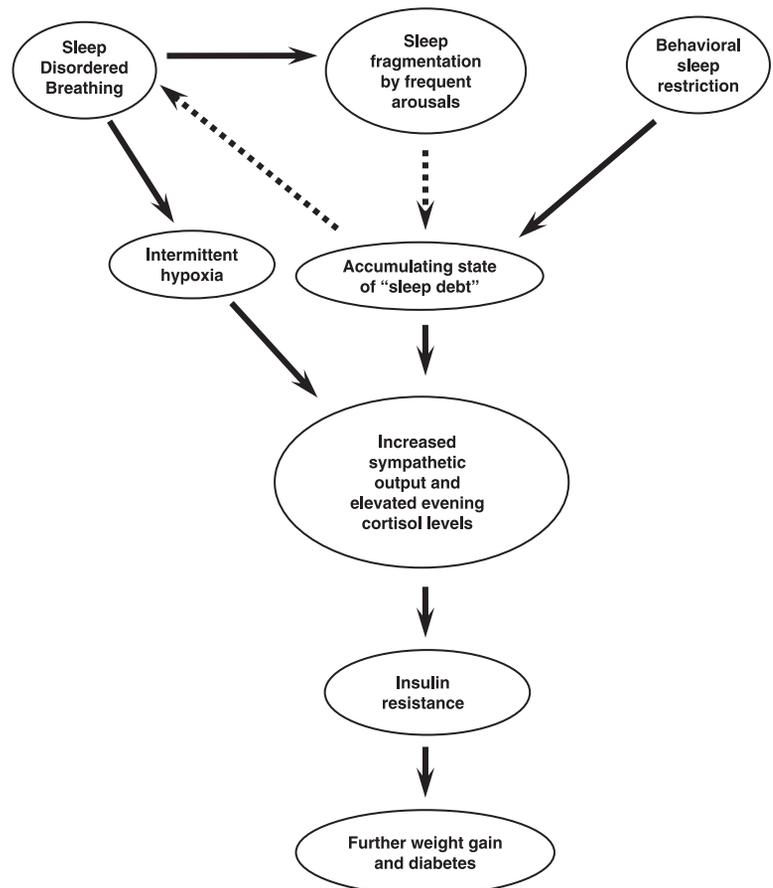
Fig. 6. Potential mechanisms underlying the development of insulin resistance and diabetes in patients with sleep disordered breathing.

ity, which in turn results in higher metabolic rate during sleep and elevated catecholamine secretion. Indeed, the presence of abnormally high sympathetic output has been proposed as the mediating mechanism in the causal link between OSA and insulin resistance (74). In this context, it is noteworthy that sleep loss without sleep fragmentation also increases sympathetic nervous activity (see Fig. 2). In a recent study in patients with the burnout syndrome, a syndrome characterized by emotional exhaustion, depersonalization, and low personal accomplishment, which is often associated with sleep disorders (3), Ekstedt et al. (16) reported that microarousals during sleep were the best predictors of increased morning cortisol levels and hyperlipidemia. Clearly, further studies of experimental sleep fragmentation are needed to validate the hypothesis that sleep fragmentation without reduction in total sleep time may adversely affect metabolic and endocrine function and could play a role in the metabolic abnormalities observed in patients with OSA.

Figure 6 summarizes the putative mechanisms that may act in concert to result in the increased risk of insulin resistance, obesity, and diabetes in patients with SDB. In this increasingly prevalent syndrome, a feedforward cascade of negative events generated by the combined sleep loss, both behavioral and disease related, sleep fragmentation, and hypoxia is likely to steadily increase the severity of metabolic disturbances. Most likely mediating mechanisms involve elevations of sympathetic neural activity and evening cortisol levels.

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