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Daytime Sleepiness in Obesity: Mechanisms Beyond Obstructive Sleep Apnea—A Review

Lori A. Panossian, MD; Sigrid C. Veasey, MD

Center for Sleep and Circadian Neurobiology and Department of Medicine, Sleep Division, University of Pennsylvania, Philadelphia, PA

Increasing numbers of overweight children and adults are presenting to sleep medicine clinics for evaluation and treatment of sleepiness. Sleepiness negatively affects quality of life, mental health, productivity, and safety. Thus, it is essential to comprehensively address all potential causes of sleepiness. While many obese individuals presenting with hypersomnolence will be diagnosed with obstructive sleep apnea and their sleepiness will improve with effective therapy for sleep apnea, a significant proportion of patients will continue to have hypersomnolence. Clinical studies demonstrate that obesity without sleep apnea is also associated with a higher prevalence of hypersomnolence and that bariatric surgery can markedly improve hypersomnolence before resolution of obstructive sleep apnea. High fat diet in both humans and animals is associated with hypersomnolence. This review critically examines the relationships between sleepiness, feeding, obesity, and sleep apnea and then discusses the hormonal, metabolic, and inflammatory mechanisms potentially contributing to hypersomnolence in obesity, independent of sleep apnea and other established causes of excessive daytime sleepiness.

Keywords: Obstructive sleep apnea, obesity, hypersomnolence, neurons/metabolism, sleep/physiology

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Excessive daytime sleepiness, obesity and obstructive sleep apnea (OSA) are all prevalent conditions in developed countries. Approximately 6% to 12% of the general population regularly experiences subjective sleepiness, as measured with the Epworth Sleepiness Scale.[1-3] Approximately 60% of adults in many developed countries are overweight, defined as a body mass index (BMI) > 25 kg/m^2, and one-third of adults are obese, defined as a BMI > 30 kg/m^2.[4] In severely obese individuals, defined by a body mass index > 35 kg/m^2, the prevalence of excessive daytime sleepiness approximates 30%.[5] Obesity is the largest risk factor for OSA. The overall prevalence of OSA in the general population is 2% to 4%,[6] and in obese individuals the prevalence of OSA is 30%.[7] Thus, it would seem that OSA alone could potentially explain the high prevalence of sleepiness observed in obese individuals.

Despite the close association between obesity and OSA, studies repeatedly demonstrate weak relationships ($r^2 < 0.3$) between the severity of OSA, as defined by the apnea-hypopnea index (AHI), and the severity of subjective sleepiness, as defined by the Epworth Sleepiness Scale.[8-11] Moreover, many individuals with OSA continue to have some degree of sleepiness despite effective therapy for OSA. Some of this sleepiness may be the consequence of irreversible injury to wake neurons from OSA.[12-15] But are we, as sleep clinicians, overlooking obesity and diet as possible contributors to sleepiness in obese patients?

Residual Sleepiness in Treated Obstructive Sleep Apnea

Upon therapy for OSA, most individuals can expect significant improvements in daytime sleepiness. Indeed, a strong dose-related improvement in sleepiness is observed with usage hours of continuous positive airway pressure (CPAP) therapy.[14,16] However, a significant proportion of people with moderate-to-severe OSA continue to experience excessive sleepiness, even after adequate treatment with CPAP. Prevalence rates vary and have been estimated at 12% to 30% among obese individuals using CPAP ≥ 4 h/night.[14,17] Even with longer nightly treatment times, 30% of obese subjects (mean BMI = 35 kg/m^2) using CPAP ≥ 7 h/night continue to have objective sleepiness measured by the maintenance of wakefulness test, and 20% of subjects have abnormal Epworth scores.[14] Among CPAP users with a BMI > 30, some of the lasting sleepiness might be attributed to comorbid sleep disorders, depression, or sedating medications; for example, Pépin et al. found that prevalence rates of residual sleepiness dropped from 12% to 6% after adjusting for these factors.[16,17] Nevertheless, given the high rates of both OSA and obesity, this relatively low percentage represents large numbers of the general population. Stradling has argued that the prevalence of sleepiness in patients treated for OSA is similar to the prevalence of sleepiness in the general population, both approximately 12%.[18] But what are the causes of excessive daytime sleepiness in 12% of obese OSA patients and 6% to 12% of the general adult population, as well as up to 30% of severely obese patients? At present, there is insufficient evidence to attribute all persistent sleepiness in treated OSA patients to irreversible injury from OSA; thus, we need to explore the possibility of reversible causes of hypersomnolence.

Effects of Bariatric Surgery on Wakefulness

Overall, patients with OSA and excessive daytime sleepiness who undergo bariatric surgery can expect a dramatic improvement in subjective sleepiness.[10,19,20] In a study of severely obese patients with OSA who underwent gastric bypass (n = 56), the Epworth sleepiness score for the group fell from 14 (severe sleepiness) preoperatively to 5 (normal) at one month after surgery, a time when weight loss is expected to be just 10-12 pounds.[21] OSA was not reassessed with polysomnography at the one-month interval, but it is unlikely that this amount of weight loss in severely obese individuals would correct OSA.

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Address correspondence to: Lori Panossian, University of Pennsylvania, Translational Research Bldg, 125 S. 31st St.; Tel: (215) 746-4801; Fax: (215) 746-4814; E-mail: lori.panossian@uphs.upenn.edu

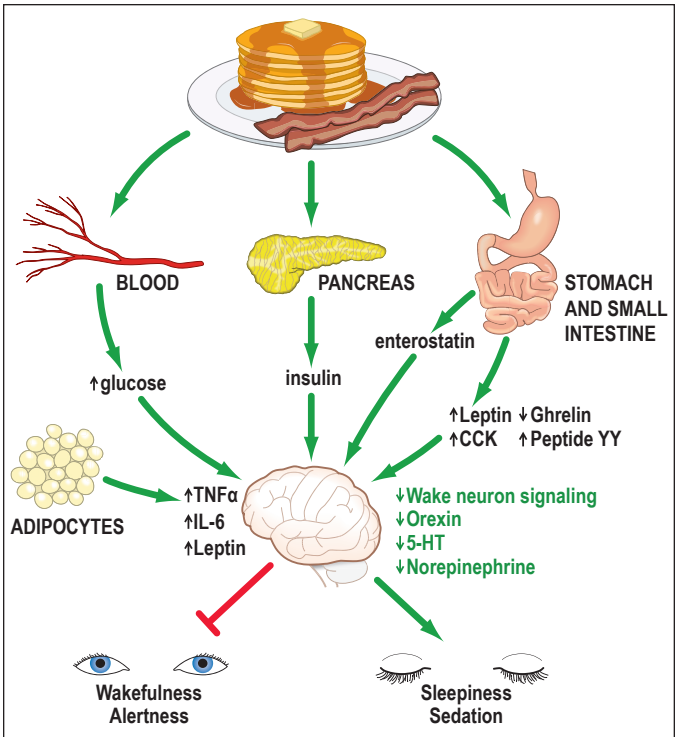

Figure 1—Gut hormones and adipokines with somnogenic effects. (Our example of pancakes with bacon and syrup is only one of many commonly ingested high fat, high sugar meals that could potentially induce the schematized gut and adipose somnogenic responses.) In response to ingestion of high fat, high sugar foods, the plasma carries increased glucose, insulin, leptin, cholecystokinin (CCK), peptide YY, and enterostatin, all of which have somnogenic influences when administered systemically. Increased mass of adipocytes over time will produce increased quantities of tumor necrosis factor-α (TNF-α), interleukin-6, and leptin. These substances have been shown to impair wakefulness, in part, by modulating orexin, serotonin (5-HT), and/or noradrenergic signaling. Which of these and other gut hormones and adipokines play significant roles in impairing alertness requires further study.

Similarly, the group mean Epworth score for subjects undergoing laparoscopic gastric banding (n = 25, mean BMI 53 kg/m^2) fell from 14 to 4 (normal).[10] Interestingly, 17 of the 25 subjects had abnormal Epworth scores of > 10 preoperatively, despite the fact that 12 of these subjects were using CPAP. Postoperatively, no subject had an Epworth > 10, and none were using CPAP. This normalization of sleepiness is surprising in that smaller overall changes in Epworth are realized in response to CPAP therapy for OSA, where a meta-analysis found overall improvements in the Epworth of 2 points.[22] The low overall improvement in Epworth after starting CPAP could, in part, be a consequence of including subjects with minimal sleepiness; however, changes in Epworth following bariatric surgery from 14 to 4-5 are quite dramatic, and doubtless have a profound impact on patient well-being and safety. The effects of bariatric surgery on sleepiness appear to endure; in a study including both gastric bypass and gastroplasty procedures, 88% of individuals 7 years out from their bariatric procedures claimed continued success in alertness.[23] In summary, patients with OSA who undergo bariatric surgery can expect substantial improvements in sleepiness, but unanswered questions include: is the improved alertness a consequence of partial correction of OSA, dietary modification or surgery-induced negative energy balance, and through what molecular mechanisms does bariatric surgery improve wakefulness?

Acute Effects of Food Ingestion on Sleep

An important perspective to consider is whether sleepiness can be modulated acutely by food intake. Regular ingestion of foods with high fat content and significant excess of nutrients can predict excessive daytime sleepiness and poor quality of nocturnal sleep.[24-27] Harnish et al. examined the effects of ingesting a solid meal versus chewing but not ingesting the same food on sleep latency across a series of afternoon naps. They noted shortened sleep latencies (by 2 min) in individuals who ingested the food.[28] In a separate study, subjects were fed carbohydrate-rich, fat-rich, or protein-rich liquid diets. Those ingesting the high carbohydrate meals scored higher for subjective fatigue.[29] Wells et al. examined the effects of acute feeding on sleepiness rather than fatigue using the Stanford Sleepiness Scale.[30] They noted that high-fat meals caused sleepiness and that this sleepiness paralleled levels of cholecystokinin.[31] This sleepiness, however, could not be prevented with a cholecystokinin receptor A antagonist, suggesting other mediators contribute to the sleepiness. A high-fat, high-calorie diet termed the "cafeteria diet" has been shown to increase sleep in rats, with shortened bouts of wakefulness.[32] These effects are at least in part chronic, as the slow wave sleep increase persisted for 3 days after resumption of a normal rodent diet.[32] Hansen et al. found that vagotomy prevented the cafeteria diet-induced sleepiness,[33] and that the diet is associated with acute changes in interleukin-1B mRNA levels in the brain.[34] Thus, food-induced sleepiness may be due to acute hormonal and neuroendocrine effects of a high-fat meal (see Figure 1). High fat content and excessive nutrients ingested on a regular basis could then cause regularly occurring symptoms of excessive sleepiness. For years people attributed the sleepiness after a very large Thanksgiving meal to tryptophan in the turkey typically served at this meal. As it turns out, the amount of tryptophan needed to induce sleep is orders of magnitude larger than the amount ingested in even a very large Thanksgiving dinner.[35] However, a high-glycemic meal acutely increases tryptophan availability.[36] Studies to date examining sleep and obesity have neither provided fine timelines measuring sleepiness across diet variances nor included detailed nutritional logs or controlled for diet. To date, the acute effects of feeding on sleepiness have been examined in lean healthy controls. How obesity influences the acute sleepiness effects of feeding will be interesting to discern.

Sleepiness in Obesity, Independent of OSA

While OSA should be considered the most important contributor to sleepiness in obesity, several studies have demonstrated an association between obesity and sleepiness independent of OSA.[5,8,37,38] Vgontzas et al., compared sleepiness in obese individuals with and without OSA, finding similar prevalences of sleepiness in individuals with and without OSA.[8] Over 50% of non-apneic severely obese subjects without OSA, other sleep disorders, or obesity hypoventilation reported significant daytime hypersomnolence; while only 2% of non-obese non-apneic controls reported daytime sleepiness.[8] To examine objective sleepiness in this group, severely obese (n = 73) and non-obese (n = 45)

subjects without OSA (confirmed by polysomnography the previous night) were given 2 daytime nap opportunities to fall asleep (a modified multiple sleep latency test).[8] The group of obese subjects showed shorter sleep latencies, less wake time after sleep onset during the naps, a greater percentage of the nap time asleep, and more REM sleep, all with $P < 0.01$ values.[8] A more recent study by Sareli et al., examined sleepiness by Epworth scores in all individuals undergoing bariatric surgery at a tertiary medical center.[39] Severe sleepiness (Epworth > 11) was present preoperatively in 26% of subjects with mild OSA and 32% of subjects with moderate-severe OSA, but was also present in 18% of individuals without either OSA or another sleep disorder.

There have been several large cross-sectional trials examining other potential contributors to excessive daytime sleepiness. In one population-based study examining sleepiness in over 5,000 women aged 20-60, Theorell-Haglow et al. found that excessive daytime sleepiness varied significantly with obesity but was also independently related to anxiety/depression, while physical inactivity was associated with fatigue but not overt sleepiness.[40] A more recent study of 400 women identified snoring as a significant independent predictor of sleepiness after controlling for both AHI and BMI.[41] Similarly, Basta et al., found that in obese men with sleep apnea, daytime sleepiness (assessed using the Epworth Sleepiness Scale) was also significantly associated with depression and with physical inactivity after controlling for BMI and medical comorbidities.[42] A large study of over 16,500 men and women found that depression, particularly in younger patients, had the strongest association with daytime sleepiness, followed by BMI and diabetes; presence of sleep apnea had a weaker association with sleepiness in this study.[43]

It is important to recognize that cross-sectional studies demonstrate associations, and it remains unclear whether the sleepiness promotes depression and physical inactivity, whether depression and physical inactivity contribute to increased sleepiness, or whether common mechanisms contribute to both sleepiness and depression. Future studies in which one of the putative factors is modified will help refine relationships. In summary, obesity without OSA is associated with significant daytime hypersomnolence (both subjective and objective) at a greater prevalence than the general population, and in this group, unlike general population studies, other sleep diagnoses have been excluded. The roles that physical inactivity, benign snoring, and depression play in sleepiness deserve further study.

Obesity and Sleep Quality and Duration

Short nocturnal sleep times are a common cause of daytime sleepiness and are considered a risk factor for obesity. Van Cauter and colleagues have shown a clear, direct impact of short sleep time on metabolics, favoring weight gain, increased appetite, and insulin resistance.[44-49] Is it possible, then, that short sleep times explain sleepiness in obesity without OSA? In the daytime nap study cited above, Vgontzas et al., examined nocturnal sleep in this population of obese vs. non-obese individuals, a group in which OSA, obesity hypoventilation, narcolepsy, and other primary sleep disorders had been excluded.[8] Despite increased daytime sleepiness, nocturnal sleep latencies did not differ, and obese subjects at night had only slightly greater wake after sleep onset time by 36 minutes and slightly less REM sleep. While it is unlikely that the reduction in sleep time at night by one-half hour is sufficient to cause profound daytime sleepiness, future studies are needed to carefully phenotype day and nighttime sleep patterns in obese individuals without OSA.

Obesity and Sympathetic Nervous System Overactivity

One physiological response to obesity that could disrupt nocturnal sleep is heightened sympathetic activity in obesity. Obesity and metabolic syndrome are associated with abnormally elevated basal levels of sympathetic nervous system (SNS) activity, which may have the potential to fragment sleep and contribute to daytime sleepiness. Obese individuals, especially those with increased abdominal visceral fat, are more likely to have greater noradrenaline spillover into systemic circulation, elevated urinary noradrenaline levels, and increased efferent muscle sympathetic nerve activity.[50-53] Brain-specific SNS activity has not been measured in the context of obesity. In obesity-prone rats, however, a study found significant decreases in norepinephrine levels and decreased norepinephrine turnover in the hypothalamus (but not the amygdala), coupled with reduced α2-adrenoreceptor binding, suggesting abnormal SNS regulation.[54] Further studies are needed to examine whether brain SNS overactivity contributes to sleep fragmentation and chronic daytime sleepiness in obese individuals.

Obesity and Medical Conditions Contributing to Sleepiness

In addition to OSA and insufficient or disrupted sleep, there are many potential explanations for sleepiness in obesity, including comorbidities, medications, and metabolic derangements. Greater medical complexity observed in many obese individuals renders identification of factors contributing to excessive daytime sleepiness more difficult. Using multivariate analyses complemented by binary logistic regression in a cross-sectional study, Dixon et al., found several weak but statistically significant variables: glucose and insulin together could *potentially* explain 3% of the sleepiness in severely obese individuals; serum lipids and metabolic syndrome might also explain another 3%.[5] There are few published studies in which medications and illnesses were comprehensively examined as potential sources of sleepiness in obese adults; however, a recent study in children found that neither total sleep time nor OSA significantly explained excessive sleepiness, while obesity, mood disorders, and asthma were strong independent risk factors for excessive sleepiness.[55] Excessive daytime sleepiness is highly prevalent in polycystic ovarian syndrome (PCOS) (45% to 80% of patients), but this may also be explained by the concurrent 30-times higher prevalence of sleep apnea as compared to BMI-matched controls.[56,57] Another potential mechanism by which PCOS may contribute to sleepiness is via insulin resistance. Vgontzas et al., found a strong association between sleepiness in PCOS and the severity of insulin resistance.[57] In support of a relationship between insulin resistance and sleepiness, in a study of 44 subjects Barceló et al., found greater sleepiness in patients with indices of increased insulin resistance. Insulin resistance in this cohort improved with CPAP use.[58] Unfortunately, measures of sleepiness were not reassessed to determine whether improvements in sleepiness temporally coincided with improved insulin sensitivity. Similar findings were reported by Nena et al. in small study comparing newly diagnosed OSA patients matched

for BMI and age; those with insulin resistance and higher glucose were also more likely to be excessively sleepy.[59] However, a recent larger study by Bonsignore et al. found that among 529 patients with OSA, there was no difference in sleepiness between subjects with or without insulin resistance.[60] As noted above, it is difficult to ascertain in cross-sectional studies whether obesity, insulin sensitivity, mood disturbances, and/or asthma contribute to sleepiness. Recently, regular dietary intake of high fat and high calories were found to predict sleepiness and poor nocturnal sleep in women.[61] Clearly, this is an important area of medicine in need of research to better identify the relationships between medical illness, diet, and mood in obesity and daytime sleepiness.

Animal Studies: Effects of Diet-Induced Obesity on Wakefulness

Laboratory rodents do not develop obstructive sleep apnea even with severe weight gain. Thus, animal models can be instrumental in examining the direct relationships between weight or diet and wakefulness, independent of OSA, medications and other health problems. Additionally, dietary intake may be more strictly regulated and monitored. A high-fat diet in adult mice has been shown to disrupt sleep/wake patterns across the 24-h cycle, with more sleep time during the animals' subjective day,[62,63] a pattern similar to that observed in obese humans. Importantly, physical activity, as measured by wheel running, does not differ with high-fat/high-calorie diet in rodents, and, thus, the high-fat diet hypersomnolence cannot be attributed to reduced physical activity. Mice fed a high-fat diet for a longer duration (6 weeks) showed 100 min less wake time/24 h than mice on control diet.[64] Interestingly, the number of behavioral state transitions also increased on high-fat diet, while duration of wake and sleep bouts decreased. These findings reversed with resumption of regular diet and weight loss. In a separate study, the circadian period in mice lengthened with high-fat diet, lengthening within the first week without further change despite significant continued weight gain, suggesting that diet contributes to circadian changes as well.[65] Collectively, these findings demonstrate that high-fat diet and weight gain can impair wakefulness and circadian rhythmicity in animal models, while it remains unclear whether the change in sleep/wake occurs acutely with dietary modification or only chronically after sufficient increase in adipose tissue.

Metabolic Regulation of Wakefulness

Neurobiology of wakefulness

Wakefulness is regulated primarily by homeostatic, circadian and metabolic influences. There have been several recent, thorough reviews covering homeostatic and circadian control of sleep and wakefulness to which the reader is referred.[66-69] The goal of this section is to integrate metabolic regulation of wakefulness with the neurobiology of wakefulness. Overall, optimal wakefulness, or alertness, requires simultaneous inactivation of sleep-active neuronal groups and activation of wake-active and target neurons. The classification of neurons as wake-active neurons is based on neuronal unit recordings across sleep/wake states in animals and responses to activation of the groups. Wake-active neurons have been defined as neuronal groups that demonstrate greater activity in waking with clear reductions in sleep, and when the collective group is activated, wakefulness is enhanced. Recent studies have demonstrated unique responses to environmental or physiological stimuli across wake neuron groups.[70,71] Wake-active neurons include basal forebrain and brainstem cholinergic neurons, hypothalamic orexinergic and histaminergic neurons, and subsets of the brainstem dopaminergic, serotoninergic, and noradrenergic neuronal groups. Medications that antagonize signaling for any one of the wake neuromodulators can impair alertness. For example, anticholinergic, antihistaminergic, antidopaminergic, and some serotoninergic antagonist medications that penetrate the blood-brain barrier can have pronounced sedating effects. Transgenic absence of any 1, 2, or 3 of these wake neuromodulators has very little effect, however, on total wakefulness/24 h, although effects on wakefulness bout length, timing of wakefulness, and wake responses to various stimuli are affected.[72-74]

Orexinergic neurons are unique wake-active neurons in several regards. Significant but incomplete loss of orexinergic neurons can result in hypersomnolence in the subjective day and disrupted or fragmented sleep,[75] while more extensive loss of orexinergic neurons results in narcolepsy with cataplexy.[76,77] As described below, these neurons are intimately involved in feeding behavior and metabolic responses. It is of interest that sleep patterns in obesity (daytime sleepiness and fragmented nocturnal sleep) are consistent with orexin dysfunction.

Feeding and sleeping: restricting one influences the other

Recent studies have identified profound effects of either sleep restriction on feeding or of food restriction on sleep. Less sleep has been shown to affect leptin and ghrelin levels and appetite, although some results have been conflicting. In two studies where leptin levels were measured at multiple time points throughout the day and food intake was controlled, several days of sleep deprivation or restriction to 4 h/night in young healthy men resulted in increased appetite and decreased leptin levels, with flattening of circadian peaks in leptin.[78,79] In fact, shortening the sleep time by just 1.5 h/night for 2 weeks is sufficient to markedly increase appetite and caloric intake.[80] Ghrelin increases in parallel with increased appetite.[81] By contrast, more recent studies have found either increased or unchanged leptin levels during sleep restriction or deprivation.[81-84] Some of these studies also found no changes in hunger or appetite, but Bosy-Westphal et al. demonstrated a 20% increase in calorie intake despite unchanged hunger ratings.[83,84] These discrepancies may partly be due to differences in experimental conditions, with some studies taking less frequent measurements of leptin levels,[81,82,84] not controlling for food intake,[82,84] or shorter time periods of sleep loss.[81,83] Stress from the experimental procedure may also affect leptin levels: Pejovic et al. used minimally stressful conditions and found that after 1 night of sleep deprivation, there was no change in cortisol or cardiovascular parameters but significant increases in leptin levels; whereas subjects in the Spiegel et al. study had elevated cortisol levels and potentially more stress, which may have affected their leptin levels.[79,83] Short-term sleep restriction in young healthy adults also promotes insulin resistance, impaired glucose tolerance, and obesity.[85,86] Insufficient sleep in combination with physical inactivity impedes weight loss in overweight individuals matched for caloric intake.[87]

Table 1

Gut Hormone	Feeding Response	Variance with Obesity	Acute Effect on Sleep/Wake
Amylin	↑ with carbohydrates and protein ingestion	Unknown	Unknown
Cholecystokinin	↑ with fat and protein ingestion	Unknown	↑ sleep
Enterostatin	↑ with fat ingestion	Unknown	May ↑ sleep
Ghrelin	Suppressed with food intake	Levels are ↓ in obese individuals	In normals, ↑ sleep
GLP-1	↑ with glucose	Attenuated in obesity	Unknown
Neurotensin	↑ with fat ingestion	Unknown	In basal forebrain: ↑ REM sleep and waking
Obestatin	Suppressed by food intake	Cleavage product form preproghrelin mRNA	Minor effects on sleep/wake
Oxyntomodulin	↑ with carbohydrate and fat ingestion	Unknown	Unknown
PACAP	↑ in response to serum glucose	Unknown	↑ wake and ↓SWS
Peptide YY	↑ with fat, fiber, glucose ingestion	Unknown	↑ sleep with peripheral administration
Adipokines		**Variance with Obesity**	**Effect on Sleep/Wake**
Adiponectin		Reduced	Unknown
Angiotensin II		Increased	Reduced REM sleep
Apelin		Increased	Unknown
ASP		Increased	Unknown
IL-6		Increased	Central administration increases NREM sleep
Leptin		Increased (yet leptin resistant)	Reduced REM sleep
MCP-1		Increased	Unknown
Omentin		Reduced	Unknown
Resistin		Increased	Unknown
TNF-α		Increased	Increased NREM sleep
TGF-β		Increased	Subtle slowing of waking electroencephalogram
Visfatin		Increased	Unknown

While sleep restriction influences feeding and weight, food deprivation modulates wakefulness. Jacobs and McGinty found that complete food deprivation in adult rats had little effect for the first 4-5 days, but thereafter sleep bouts progressively shortened and total wakefulness increased.[88] After 6-11 days of food deprivation, rats had no discernable sleep. Sleep in this study, however, was only measured for 3 h midday. A subsequent study in rats measuring sleep across the 24-h cycle confirmed that the increased wake response to food deprivation followed weight loss, supporting a wakefulness response to loss of available nutrients at the cellular level.[89] Similarly, in humans, arousal from sleep is an important protective response to potentially life-threatening hypoglycemia, particularly in individuals with insulin-dependent diabetes mellitus.[90] In summary, there is a pronounced wakefulness response to extreme food deprivation and/or to significant weight loss, and as noted in a previous section, acute increases in caloric intake can reduce wakefulness. It would be of interest to determine whether conversion to a healthy lower calorie diet in obese individuals would improve daytime sleepiness.

Peripheral metabolic regulation of sleep

A vast number of proteins and peptides, termed gut hormones and adipokines, respond to food ingestion and body fat, respectively. In general, gut hormones change acutely with feeding, while adipokines may change acutely or chronically with changes in adipose deposition and long-term energy balance. A similar bidirectional relationship exists for feeding-related gut hormones and adipokines and sleep/wake activity. Table 1 summarizes the feeding and sleep wake responses for both gut hormones and adipokines and notes the proteins and peptides for which effects have not been reported. It is important to note that not all sleep and circadian related hormones and neuropeptides are modified by feeding or obesity, and many require further study.[91]

Leptin and ghrelin influence sleep/wake activity and show acute changes with feeding patterns. Leptin is produced peripherally by adipocytes and influences metabolism through its effects on the central nervous system. Very high doses of leptin (systemically) can increase slow wave sleep in rats.[92] While leptin levels are higher in obesity, leptin resistance is common. Whether endogenous leptin in obese individuals contributes to

sleepiness has not been determined. A mouse model of leptin resistance was developed with a mutant form of the leptin receptor LRb. The mice are obese, hyperphagic, insulin resistant, and have decreased wake time and sleep fragmentation, but whether the reduced wake times are a consequence of diet, obesity, or leptin signaling has not been established.[8,93] Future studies are needed to modulate endogenous leptin in obese individuals and then determine the relative importance of endogenous leptin on wakefulness in obesity.

Ghrelin, secreted in the stomach during fasting, has variable effects on sleep/wake activity, depending upon age and sex and location (and/or dosage) of administration. Acute systemic ghrelin administration in young adult men enhanced sleep, while in women and older men showed no effect.[94,95] In contrast, acute ghrelin administered directly into the lateral hypothalamus in rats powerfully induces wakefulness.[96] Feeding and obesity can acutely and chronically reduce ghrelin levels, respectively.[97,98] Whether the chronically reduced ghrelin levels in obesity contribute to the sleep fragmentation observed in obese individuals would also be interesting to explore.

Cholecystokinin (CCK) is synthesized in the gut and within the central nervous system. Peripheral CCK increases in response to high-caloric, high-fat foods. When administered intraperitoneally in rats, CCK increases slow wave NREM sleep significantly,[99] while administration of a CCK antagonist (at the CCK-A receptor) reduces feeding-induced sleep in rats.[100] CCK-B antagonists have little to no effect on sleep.[101] Thus, acute CCK-A activation may occur more frequently in individuals who are regularly consuming a high-caloric diet and is a plausible contributor to sleepiness in obesity.

Insulin, released upon food ingestion, can cause somnolence, but only at very high doses.[102] Whether insulin in nondiabetic obese individuals might contribute to somnolence is unclear. Peptide YY, both a gut hormone and neuropeptide, is released in response to high fat, glucose, and/or fiber intake. When administered peripherally, this peptide enhances slow wave sleep,[103] and thus could also contribute to sleepiness in obese individuals on high-caloric diets. Enterostatin, acutely released upon ingestion of fatty foods, may also contribute to postprandial sleepiness, but duration of effects, particularly on wakefulness, are not known. When injected peripherally in rats, behavioral quiescence in a sleep posture is increased.[104] As summarized in Figure 1, many gut hormones may contribute acutely with feeding to sleepiness in obesity and deserve further study. To advance this work, clinical and animal trials are needed, in which the effects of blocking endogenous activity of each of the more promising candidate gut hormones on wakefulness are determined.

The only adipokines (Table 1) studied for sleep/wake effects to date are cytokines. TNF-α increases sleep and centrally administered IL-6 increases sleep. In a small pilot study (n = 8) subjects with obesity and OSA, a TNF-α antagonist markedly improved sleepiness.[105] High-fat diet in obese males can substantially increase IL-6 with little immediate change in TNF-α, followed by a reduction in TNF-α 4 h postprandially.[106] Adiponectin-1 receptors are present in several wake related brain regions, including the cholinergic basal forebrain and locus coeruleus, and thus may affect sleep and wakefulness.[107] Changes in adiponectin-1 signaling are expected to occur on a chronic basis with changes in response to changes in energy stores and adiposity.

Hypothalamus: interface for sleep and feeding responses

The hypothalamus serves as a major regulator of energy homeostasis, influencing glucose and insulin levels, feeding, and energy expenditure behaviors.[108] Central to energy homeostasis are the hypothalamic anorexigenic (feeding suppressant) and orexigenic (feeding stimulant) neuropeptides. Anorexigenic peptides include cocaine- and amphetamine-regulated transcript (CART), α-melanocyte-stimulating hormone (αMSH), and melanin concentrating hormone (MCH); several of these have physiological effects consistent with a role in obesity-related sleepiness. CART promotes physical activity and wakefulness.[109] The leptin resistance observed in obesity is expected to reduce CART transcription, thereby contributing to excessive somnolence. αMSH may have wake promoting or sleep fragmenting effects.[110] Obese adolescents have low levels of αMSH that may contribute to obesity hypersomnolence. MCH seems to have somnogenic effects; central administration of MCH1 antagonists increases wake, while MCH null mice show increased wakefulness.[111] Diet-induced obesity increases MCH levels in the hypothalamus of rats,[112] supporting the concept that MCH might also contribute to somnolence in obesity. Orexigenic peptides include NPY, Agouti-related peptide (AgRP), orexin-A, and to a lesser extent, orexin-B. It is important to recognize that while orexin stimulates appetite acutely, it also significantly increases metabolic rate and energy expenditure chronically, and in doing so, the long-term effect of orexin is prevention of obesity. AgRP increases orexin mRNA and stimulates food intake, effects that are expected to promote wakefulness; however, this neuropeptide is unchanged or increased peripherally in obesity.[113] In summary, while many of the hypothalamic feeding related peptides are expected to influence wakefulness, the roles of each of the hypothalamic neuropeptides in acute (postprandial) or chronic excessive daytime sleepiness in obesity have not been determined.

Orexinergic neurons influence wake response to food availability and intake

Orexinergic neurons in the lateral hypothalamus (LH) are involved in diverse physiological processes, including feeding, wakefulness and glucose regulation.[114] They are sensitive to glucose levels: prepro-orexin mRNA is increased in response to hypoglycemia occurring with food deprivation.[115,116] In contrast, food deprivation with normoglycemia does not influence prepro-orexin mRNA.[115] Orexin is largely an excitatory neurotransmitter that acts by binding to two types of G protein-coupled receptors, the orexin-1 receptor (OX1R) and the orexin-2 receptor (OX2R), found throughout the brain. Fasting increases levels of OX1R and OX2R mRNA and protein in the rat hypothalamus. Fasting also increases c-fos in histaminergic wake neurons in the hypothalamus, but whether this is related to changes in OX1 signaling is not known. Transgenic absence of orexin in animals impairs the wakefulness response to food restriction.[117] Also, the clinical syndrome of narcolepsy with orexin deficiency has been associated with metabolic alterations, including increased rates of insulin resistance, metabolic syndrome, and obesity, possibly related to decreased energy expenditure.[118,119] Collectively, these findings support a significant role for orexinergic neurons

in mediating the behavioral and physiologic responses to acute nutrient deprivation (i.e., increased wakefulness and activity).

Orexinergic neurons: response to feeding-related peptides and glucose

The response of orexinergic neurons to feeding may occur, in part, through leptin signaling. Most orexinergic neurons have leptin receptors; leptin effects may also be secondary via the arcuate nucleus or other lateral hypothalamic neurons.[117,120] Neurons in the lateral hypothalamic area expressing leptin receptors have been characterized, and were found to have direct GABAergic (most likely inhibitory) projections onto orexin neurons in response to leptin administration.[120] It can be hypothesized that elevated leptin in the setting of excessive nutrient intake may increase inhibitory inputs to orexin neurons, resulting in diminished orexin signaling and associated declines in physical activity and wakefulness. Alternatively, leptin resistance in obesity can reduce prepro-orexin transcription[120] (Figure 2). Mice deficient in leptin have reduced orexin-A and -B levels and less orexinergic signaling, while orexin signaling normalizes upon leptin administration.[120-122] Similarly, mice that transgenically lack leptin receptor expression in lateral hypothalamic neurons projecting to orexinergic cells have evidence of chronically disrupted orexinergic signaling. These mice are phenotypically obese, have less locomotor activity, and may also be more sleepy, although sleep was not directly measured in this study.[123] Obesity in humans is frequently associated with leptin resistance and aberrant leptin signaling, phenotypically resembling leptin deficient animal models (Figure 2). Of note, serum orexin levels in obese humans are low and are increased by weight loss, temporally coinciding with resolution of leptin resistance.[124] These longer-term effects of leptin on orexin signaling may also involve synaptic plasticity.[125,126] It is possible that the different modulatory effects of leptin on orexin neurons may facilitate increased food-seeking behavior in the acute setting during fasting (when leptin levels drop and orexin neuronal firing increases) and may also protect against obesity in the chronic setting by increasing energy expenditure (with leptin causing increased orexin neuropeptide gene transcription).

Ghrelin effects on orexin neurons also influence feeding behavior (Figure 2). Axon terminals that contain ghrelin, originating from the hypothalamic arcuate nucleus, synapse onto and excite orexinergic neurons.[127] Ghrelin outside the central nervous system also activates orexin neurons in the lateral hypothalamus.[128] Orexin is required to elicit ghrelin-induced feeding behavior.[127,128]

Extracellular concentrations of glucose can acutely influence orexin neuronal activity. In brain slice under low glucose conditions, analogous to a physiological hypoglycemic state, orexin neurons exhibit increased firing rates.[129] Conversely, high extracellular glucose hyperpolarizes and inhibits orexin neuron firing.[130] The adjacent sleep-promoting MCH neurons have a synergistic response to high glucose, with increased firing rates.[130] In general, the glucose-mediated changes in orexinergic neuron excitability are short-lived, lasting for just minutes after the change in glucose.[131] It is likely that the combined inhibition of orexin and activation of MCH neurons contributes to excessive sleepiness during hyperglycemia. The mechanism for glucose inhibition of orexin neurons has not yet been fully elucidated. Evidence suggests that in orexin neurons, glucose acts extracellularly to influence neuronal activity.[131]

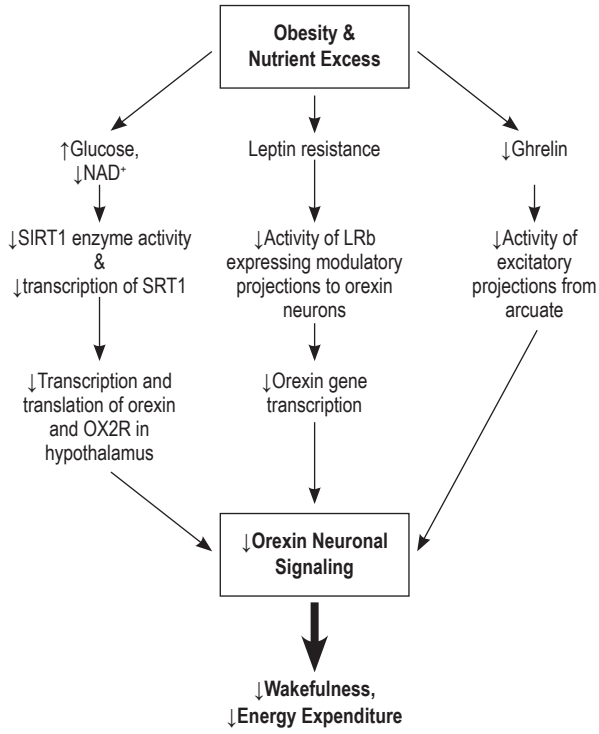

Figure 2—Diet and energy balance in the regulation of orexinergic neurons. Orexin plays a central role in energy homeostasis and maintenance of wakefulness, and may be affected by glucose, leptin and/or ghrelin signaling. Alterations in SIRT1 in response to energy surplus may also affect orexin neuron activity. The net effect is one of decreased orexinergic signaling with a phenotype of reduced wakefulness and energy expenditure. NAD^+, nicotinamide adenine dinucleotide; OX2R, orexin 2 receptor; LRb, leptin receptor.

Metabolic Regulation of Other Wake-Active Neurons

Serotoninergic dorsal raphe neurons and noradrenergic locus coeruleus neurons are important wake-active neuron groups whose activity is also influenced by metabolism. Like orexinergic neurons, locus coeruleus neurons are activated by hypoglycemia. In addition to hypoglycemia, noradrenergic neurons in the locus coeruleus (and also in the nucleus solitarius tract in the brainstem) are activated by exercise and send efferent signals to the ventromedial hypothalamus to enhance fat oxidation.[132] While dorsal raphe serotoninergic neuron activity is not altered with changes in glucose, leptin can inhibit serotonin synthesis and reduce firing rates of dorsal raphe neurons.[133] Conversely, during low nutrient conditions when ghrelin levels rise, ghrelin can directly depolarize dorsal raphe neurons and stimulate serotonin signaling to the hypothalamus, increasing feeding behavior.[134] In summary, metabolic status modulates firing rates in these wake-active neuronal groups with resultant changes in wakefulness behavior. Whether these changes occur in direct response to metabolic sensors in serotoninergic and noradrenergic wake neurons or secondarily in response to reduced orexinergic input should be determined.

SIRT1 Mediation of Metabolic Responses in Wake-Active Neurons

SIRT1 is a metabolically sensitive deacetylase that influences a vast array of cellular proteins and transcription. SIRT1 ac-

tivity is dependent upon NAD+ as a key substrate. The NAD+/NADH ratio is a measure of energy availability and redox in a cell. Recently, we identified SIRT1 in all wake-active neurons.[135] In energy surplus, NAD+ decreases, and SIRT1 activity declines.[136] Conversely, hypoglycemia upregulates SIRT1 enzyme activity. Transcription of the SIRT1 gene also increases in hypoglycemia, as demonstrated in a study of cultured non-neuronal cell lines by Zhang et al.[137] Low glucose leads to reductions in the amount of NADH available to facilitate the binding of transcriptional repressor molecules to the SIRT1 promoter region.[137] Disinhibition of the SIRT1 promoter then leads to increased SIRT1 transcription (Figure 2).[137]

SIRT1 is necessary for optimal health and functioning of wake-active neurons. Transgenic absence or reduction and conditional knock down of brain SIRT1 impair wakefulness.[135] Reduced brain SIRT1 imparts significant injury to wake neurons: reduced neurotransmitter transcription and translation, loss of dendrites, axons, and boutons.[135] Transgenic absence of SIRT1 reduces orexin neuron firing, body temperature, and physical activity.[138] Thus, chronic reductions in SIRT1 (which also occur with normal aging) are expected to have deleterious (chronic) effects on orexinergic neurons and therefore on wakefulness.

In the brain, SIRT1 plays a critical role in the body's response to food deprivation. Several studies have demonstrated elevated SIRT1 levels and enzymatic activity in the hypothalamus of fasting animals,[138-140] together with increased neuronal firing in the lateral and dorsomedial hypothalamus, areas important in regulating alertness and feeding behavior.[138] SIRT1 also increases transcription and translation of OX2R in these neurons,[138] and we have shown that loss of SIRT1 reduces translation and transcription of prepro-orexin. Fasting in rats and mice typically results in acutely increased physical activity, thought to represent food-seeking behavior. SIRT1 is required for this behavioral effect: increasing SIRT1 levels enhances these changes, while knocking out SIRT1 in the brain prevents the increase in food-seeking physical activity.[138,141] SIRT1 is also required for ghrelin-induced feeding and stimulates transcription of the orexigenic peptides AgRP and NPY in response to ghrelin signaling.[142] The relationship between hypothalamic SIRT1 and fasting may vary based on subtypes of hypothalamic neurons, however, as another study has found a fasting-related decline in SIRT1 protein levels in the arcuate nucleus of the hypothalamus.[143] In summary, high caloric food intake and/or obesity may reduce SIRT1 activity in orexinergic and other hypothalamic neuronal groups, compounding reduced orexinergic signaling via leptin resistance and reduced ghrelin signaling (Figure 2). Understanding these complex relationships and relative roles for each putative factor is expected to advance therapies to treat sleepiness in obese individuals.

CONCLUSION

Impaired alertness can be a prominent symptom in individuals with obesity and can have a significant impact on safety and quality of life. In obese individuals, OSA should be considered the most important cause of hypersomnolence, and diagnosis and treatment are high priority. There are, however, many obese individuals with sleepiness persisting despite therapy for OSA, and there are obese individuals without OSA for which sleepiness is a major concern. A growing body of clinical and animal model evidence supports the concept that both obesity and diet can directly contribute to sleepiness. Research in this field, as summarized in this review, has begun to elucidate the complex interrelationships between circulating systemic hormones and neuronal signaling pathways in the CNS. While studies have successfully identified candidate molecules for hypersomnolence in obesity, additional studies are needed to more firmly establish key molecular mechanisms involved, to discern acute and chronic effects of feeding and obesity, and to guide targeted treatments for maintaining optimal wakefulness while chronic metabolic disturbances are fully corrected.

ABBREVIATIONS

αMSH, α-melanocyte-stimulating hormone
AgRP, Agouti-related peptide
AHI, apnea-hypopnea index
BMI, body mass index
CART, cocaine- and amphetamine-regulated transcript
CCK, cholecystokinin
CPAP, continuous positive airway pressure
LH, lateral hypothalamus
MCH, melanin concentrating hormone
OSA, obstructive sleep apnea
OX1R, orexin-1 receptor
OX2R, orexin-2 receptor
PCOS, polycystic ovarian syndrome
SNS, sympathetic nervous system

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