The Interactions Between Sleep, Metabolism, and Obesity

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We are currently facing an obesity pandemic for which there are no easy solutions. This is because the factors that have contributed to this pandemic are complex and incompletely understood. One contributing factor that has attracted much interest is shorter sleeping hours. Several large epidemiological studies of adults and children from different countries have demonstrated an association between short sleep duration and obesity. From the Wisconsin Sleep Cohort Study and sleep laboratory studies, the mechanisms for this association may include alterations in the circulating levels of several metabolic hormones (leptin, ghrelin, cortisol, insulin, and growth hormone) that could result in increased appetite and changes in body weight and composition. Short sleep duration may also alter energy expenditure. Although the full mechanisms for the association between short sleep duration and obesity are currently under investigation, it can be argued that encouraging adequate sleep should be added to other lifestyle measures to help prevent obesity. *Int J Sleep Wakefulness* 2007;1(1):20–9.

The burden of obesity

Obesity is a global public health problem [25]. A recent report from the World Health Organization estimated that, in 2005, >1 billion people worldwide were overweight and >300 million were obese [26]. The report forecasts that the number of overweight individuals will reach 1.5 billion by 2015. In the US and other western countries, obesity is expected to become the most common preventable cause of death [27]. Most alarming has been a dramatic rise in the number of children who fit the criteria necessary for the diagnosis of obesity, not least because childhood obesity tracks into adulthood [28]. Data from the Center for Disease Control and Prevention in the US show that the prevalence of children aged 6–19 years old who were considered to be overweight increased from 4–5% in 1963–1970 to 15% in 1999–2000 [29]. Major contributors to the morbidity and mortality associated with obesity include concomitant insulin resistance, type 2 diabetes mellitus, sleep-disordered breathing, and cardiovascular disease [25].

Although there is a strong genetic contribution to obesity, it is believed that the current obesity pandemic is largely driven by environmental factors that alter the balance between energy intake and energy expenditure. Unfortunately, current interventions aimed at altering food selection (with different diets encouraging alterations in different macronutrients) and calorie intake (e.g. smaller portions), and increasing physical activity, have not resulted in long-term weight loss and maintenance. This is because our understanding of factors that influence individuals to choose and over-consume...
particular foods, affect a person’s desire/ability to undertake physical activity, and help maintain long-term motivation needs to be improved. Although there are insufficient robust data from children, data from adults in the US suggest that the trend in obesity has coincided with a trend in shorter sleeping hours (Fig. 1) [30]. This may be a coincidence, but several sources of evidence suggest that sleep may affect both sides of the energy balance equation, resulting in obesity.

### Population studies link sleep duration with obesity

Several large population studies have identified a significant dose–response relationship between short sleep duration, obesity, and metabolic disturbances across all age groups and several ethnic groups [3,5–24,31,32]. The studies in children and adolescents have recently been summarized and reviewed [21]. Table 1 lists the studies in adults and their key findings. Interestingly, several studies in adults report a U-shaped relationship between sleep duration and body weight, suggesting that both short and long sleepers are susceptible to obesity. Some studies have suggested that there are differences in the sleep duration–obesity relationship in males and females. Importantly, there are now several prospective studies reporting an association between short sleep duration and obesity. While it has been argued that the impact of short sleep duration on body weight is small, this does not equate with being biologically meaningless. In the Wisconsin Sleep Cohort Study (WSCS) population [20], for example, a loss of 3 h of sleep from a baseline of approximately 8 h was associated with an average 4–5% higher body weight – this difference being comparable to the average weight loss that can be achieved with lifestyle changes or any of the currently available anti-obesity drugs [33]. Similar differences in body weight have been reported from a longitudinal study of young adults [9]. Since weight gain is associated with only a minor daily energy excess (as little as 100 kilocalories), and we know that even modest reductions in body weight (5–10%) can reduce the complications of obesity such as type 2 diabetes [34], the change in body weight with shorter sleep is likely to be clinically meaningful. Although the relationship between sleep and body weight is U-shaped in older adults, a clear negative linear relationship between sleep duration and body mass index (BMI) has been seen in large, more homogeneous studies of young adults and children [21]. This sleep–obesity association has been consistently observed and has been shown to be independent of potential confounders such as television viewing and self-reported physical activity. Importantly, a recent large birth cohort study from the UK, the Avon Longitudinal Study of Parents and Children (also called “Children of the 90s”) has identified that short sleep duration at an early age of 30 months predicts obesity at age 7 years [21,32]. Given that sleep is important in neurodevelopment,
it can be hypothesized that short sleep duration at a young age may somehow alter the brain’s hypothalamic appetite circuitry. Other studies have identified associations between sleep duration, insulin resistance, diabetes mellitus, and increased cardiovascular risk [4,31].

The association between short sleep duration, metabolic hormones, and appetite

Most population studies have relied on self-reported sleep duration rather than objective measures, suggesting that the association between sleep duration and obesity may not be truly accurate i.e. time in bed does not equate with time asleep and does not take into account any sleep disturbance. Reported sleep measures are likely to be most accurate for children due to parental reporting [35,36]. So far, there has only been one study using short-term actigraphy in adolescents to objectively determine sleep duration and disturbance and their interaction with obesity [37]. Additionally, it may be argued that the association between short sleep duration and changes in body weight is a

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Design</th>
<th>Key findings</th>
</tr>
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<tbody>
<tr>
<td>Vioque et al., 2000 [22]</td>
<td>Spain</td>
<td>1772</td>
<td>Cross-sectional</td>
<td>Prevalence OR for obesity 0.43 (95% CI 0.27–0.67) for sleeping ≥9 h vs. ≤6 h; prevalence OR for obesity was 24% lower for each additional sleeping h/day.</td>
</tr>
<tr>
<td>Shigeta et al., 2001 [18]</td>
<td>Japan</td>
<td>437</td>
<td>Cross-sectional</td>
<td>Sleeping ≤6 h was associated with BMI ≥25 kg/m² (OR 1.98, 95% CI 1.03–3.82) vs. &gt;6 h sleep.</td>
</tr>
<tr>
<td>Kripke et al., 2002 [12]</td>
<td>USA</td>
<td>1.1 million</td>
<td>Epidemiological survey; Cancer Prevention Study II</td>
<td>U-shaped relationship between sleep duration and obesity in women, but linear relationship for men from baseline sleep duration of 7 h.</td>
</tr>
<tr>
<td>Heslop et al., 2002 [10]</td>
<td>UK</td>
<td>6797 (baseline)</td>
<td>Cross-sectional analysis from cohort study</td>
<td>Short sleep duration associated with obesity at baseline and at second screening.</td>
</tr>
<tr>
<td>Taheri et al., 2004 [20]</td>
<td>USA</td>
<td>721</td>
<td>Cross-sectional; Wisconsin Sleep Cohort Study</td>
<td>U-shaped relationship between sleep duration and obesity; short sleep duration was associated with higher ghrelin and lower leptin levels.</td>
</tr>
<tr>
<td>Cournot et al., 2004 [7]</td>
<td>France</td>
<td>3127</td>
<td>Cross-sectional; Vieillissement et Santé au Travail study</td>
<td>Mean BMI was higher in women reporting sleep duration &lt;6 h vs. ≥6 h (24.4 kg/m² vs. 23.4 kg/m²); no association in men.</td>
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<tr>
<td>Patel et al., 2004 [14]</td>
<td>USA</td>
<td>82 969 (women)</td>
<td>Prospective; Nurses Health Study</td>
<td>U-shaped relationship between sleep duration and BMI in women</td>
</tr>
<tr>
<td>Hasler et al., 2004 [9]</td>
<td>Switzerland</td>
<td>496</td>
<td>Prospective; Zurich Cohort Study</td>
<td>Trend for negative association between average change in weight gain and average change rate in sleep duration.</td>
</tr>
<tr>
<td>Vorona et al., 2005 [24]</td>
<td>USA</td>
<td>924</td>
<td>Cross-sectional, primary care center-based</td>
<td>Overweight and obese patients slept less than those of normal weight.</td>
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<tr>
<td>Gangwisch et al., 2005 [8]</td>
<td>USA</td>
<td>9588</td>
<td>Cross-sectional; National Health and Nutrition Examination Survey</td>
<td>Those aged 32–49 years who slept &lt;7 h had a higher BMI vs. those who slept ≥7 h.</td>
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<tr>
<td>Singh et al., 2005 [19]</td>
<td>USA</td>
<td>3158</td>
<td>Cross-sectional, telephone interview</td>
<td>U-shaped relationship between sleep duration and obesity, but only significant for shorter sleep hours.</td>
</tr>
<tr>
<td>Patel et al., 2006 [16]</td>
<td>USA</td>
<td>68 183 (women)</td>
<td>Prospective; Nurses Health Study</td>
<td>Women sleeping ≤5 h/day gained 1.14 kg and women sleeping 6 h/day gained 0.71 kg more than those sleeping 7 h/day over 16 years, no relation between sleep duration and calorie intake or reported physical activity.</td>
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<tr>
<td>Kohatsu et al., 2006 [11]</td>
<td>USA</td>
<td>990</td>
<td>Cross-sectional survey, rural population</td>
<td>Weeknight self-reported sleep duration negatively correlated with BMI (beta=−0.42; 95% CI −0.77 to −0.07).</td>
</tr>
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BMI: body mass index; CI: confidence interval; OR: odds ratio.
spurious or a surrogate marker for another factor that impinges on body weight regulation. However, in addition to the extensive epidemiological data suggesting a link between short sleep duration and obesity, recent evidence has begun to suggest a mechanistic link involving metabolic hormones. Emerging evidence from longitudinal analyses in adults and children also suggest that short sleep duration may precede the development of obesity [16,38]. It is likely that different mechanisms operate in the sleep–obesity link in adult long sleepers compared with short sleepers; therefore, further study of long sleepers is necessary.

There are bidirectional interactions between several hormones and circadian and homeostatic sleep mechanisms. The release of hormones may be tied to sleep (e.g. growth hormone secretion during slow-wave sleep), transitions between sleep stages (e.g. plasma renin activity having troughs during rapid eye movement [REM] sleep and peaks in non-REM [NREM] sleep), and transitions between sleep and wakefulness (e.g. cortisol being highest on awakening). Additionally, hormones have an effect on sleep in their own right. In the WSCS, it was hypothesized that the link between short sleep duration and obesity could be mediated by alterations in circulating leptin and ghrelin levels, two opposing hormones in appetite regulation (Fig. 2) [20,39].

Leptin is an 16 kDa, 167 amino acid, secreted protein that is primarily produced by adipose tissue [39–42]. The rate of leptin secretion and its plasma concentration are correlated with total fat mass. Considerable information has been gained about the various physiological functions of leptin by examining differences between wild-type rodents and their counterparts with single gene mutations causing either the suppression of normal leptin production or the expression of dysfunctional leptin receptors. These mutant animals are hyperphagic, exhibit obesity, and are usually insulin resistant. In the few humans with leptin system gene mutations, the greatest impact of leptin deficiency appears to be on appetite rather than energy expenditure [43].

Leptin is an important peripheral signal that allows the organism to maintain body weight at a particular set point despite daily fluctuations in food intake and energy expenditure. In starvation, leptin levels fall, resulting in activation of hypothalamic neuronal circuits that adapt energy intake, energy expenditure, and behavior such that loss of fat mass is minimized. Weight gain results in increased leptin levels that act on the hypothalamic neuronal circuitry to induce a reduction in fat mass. Excessive weight gain is associated with adipose tissue expansion and high circulating leptin levels. It has been proposed that, in obesity, a defect in the transport mechanism of leptin into the central nervous system may occur, resulting in the observed leptin resistance. Therefore, low leptin levels in states of energy deficit are a greater biological signal than high leptin levels [41]. Weight loss results in leptin deficiency and, interestingly, adaptations to reduced body weight are reversible with low-dose leptin administration [44,45].

Leptin circulates bound to a soluble receptor. As well as food intake and changes in energy balance, leptin levels are
regulated by several factors, including negative regulation by the sympathetic nervous system [46]. Levels of leptin, but not its soluble receptor, show circadian changes; they are low during the day but rise in the night during sleep (leptin levels peak at about 2 AM). Although the leptin amplitude is diminished in parenterally-fed individuals, this rhythm is not eliminated [47]. The diurnal leptin pattern has been reported to mirror changes in body temperature and parallel plasma insulin and glucose levels. In obese individuals, there is a sharper rise in leptin levels during the night compared with the rise in lean individuals [48].

In the WSCS population, circulating leptin levels were higher in women and were positively correlated with BMI [20]. After adjustment for age, sex, and BMI, leptin levels were positively correlated with insulin levels, but negatively correlated with insulin sensitivity and ghrelin levels. Other associations included diastolic blood pressure, smoking, and blood urea nitrogen levels [20].

Ghrelin is a 28-amino acid peptide hormone synthesized by the stomach [49]. It circulates as active and inactive forms. Active ghrelin is acetylated and lipophilic, and therefore can cross the blood–brain barrier. Acute administration of small doses of ghrelin, either systemically or directly into the brain, dramatically increases food intake in rats [50,51]. Chronic systemic administration of ghrelin to rodents results in weight gain and increased fat mass. In addition, ghrelin appears to have an effect on energy expenditure. Calorimetry has suggested that administration of ghrelin causes an increase in respiratory quotient in rodents, but ghrelin negatively correlated with energy expenditure in humans [52]. Several lines of evidence suggest that the primary site of action of stomach-derived ghrelin is within the hypothalamus, an important brain region in the regulation of appetite, energy expenditure, temperature regulation, control of pituitary hormone secretion, water balance, reproduction, and physiological responses to emotional stimuli. Compared with the stomach (where ghrelin-synthesizing cells have been identified as X/A-like cells in the oxyntic glands), much smaller quantities of ghrelin have been observed in the hypothalamic arcuate nucleus and other brain regions [49]. Most current evidence regarding ghrelin’s biology stems from studies of its actions as a hormone; however, the individual roles of central and peripheral ghrelin in the regulation of food intake and energy expenditure remain to be determined.

Plasma ghrelin appears to be pulsatile (ultradian secretion) and displays a diurnal rhythm with highest levels at night during sleep [48]. The nocturnal peak in ghrelin is diminished in obese individuals. During the day, plasma ghrelin levels rise before meals, while systemic ghrelin infusion results in hunger [51,53,54]. Ghrelin is therefore believed to be the “hunger hormone”. Ghrelin levels are lower after partial gastrectomy, explaining to some extent the success of this procedure in reducing appetite and promoting weight loss. Subjects with Prader–Willi syndrome, which is associated with voracious appetite, have elevated ghrelin levels [55]. In view of the actions of exogenous ghrelin described above, it is likely that changes in endogenous ghrelin represent an adaptive response to fasting, promoting food intake and favoring fat deposition.

In the WSCS study, circulating total ghrelin levels were higher in women and negatively correlated with BMI. After adjustment for age, sex, and BMI, ghrelin was negatively correlated with leptin but positively correlated with adiponectin levels (adiponectin is adipocyte-derived and its levels are negatively correlated with fat mass and positively correlated with insulin sensitivity) and insulin sensitivity [20]. Other associations that were found with ghrelin levels included high-density lipoprotein (HDL) cholesterol, creatinine levels, and alcohol intake [20].

In the WSCS population, significant associations were found between serum ghrelin and leptin levels and sleep duration that were independent of age, sex, and BMI (Table 2) [20]. Short sleep duration was associated with low leptin (with a predicted reduction in leptin of 15.5% for habitual sleep of 5 h vs. 8 h), and high ghrelin (with a predicted increase in ghrelin of 14.9% for nocturnal/polysomnographic sleep of 5 h vs. 8 h), independent of BMI [20]. These relationships remained following correction for multiple possible confounding factors including age, sex, BMI, morningness–eveningness tendencies, self-reported exercise, and sleep-disordered breathing [20,56]. These hormone changes are usually observed in reaction to food restriction and weight loss, and are typically associated with increased appetite. The hormone changes observed with sleep duration require comparison with changes after calorie restriction, and similar changes in leptin to those observed with sleep loss have been reported with both acute and long-term calorie deficits [46]. For example, in a study of 50 overweight and obese female volunteers (aged 18–50 years; BMI 25–32 kg/m²; who were put on a calorie-restricted diet over 3 weeks, the women lost approximately 3.9% of their BMI (p<0.001) and this was associated with a 13.6% increase in levels of ghrelin (p<0.01) [unpublished data from Taheri, University of Bristol, Bristol, UK]. Therefore, high circulating ghrelin and low circulating leptin provide powerful signals to the hypothalamus to promote food intake (Fig. 2). The fact that gastric bypass surgery is associated with low ghrelin levels suggests that lowering ghrelin levels by ensuring adequate sleep may have a significant effect on weight loss.

Recently, data from human laboratory studies using the partial sleep restriction paradigm have suggested that sleep...
restriction is associated with changes in metabolic hormones (cortisol, growth hormone, insulin, leptin, and ghrelin), increased appetite, and an increased desire for high carbohydrate food [57,58]. This laboratory work suggests that as little as 2–3 nights of sleep restriction can have profound effects on metabolic hormones and appetite [58]. In addition, laboratory studies have suggested a reduction in insulin sensitivity with sleep restriction and, interestingly, it has recently been argued that insulin resistance may actually have a role in the development of obesity [60]. One problem with the available laboratory studies is the use of different sleep restriction paradigms; this is to be expected as this is a novel area of investigation and will be clarified with the increasing research into this topic.

It is clear that data from large population and laboratory studies point to a novel physiological interaction between sleep and metabolism. However, leptin and ghrelin are unlikely to be the only hormones involved. Other metabolic hormones such as peptide tyrosine tyrosine (PYY) [61,62] and hormones whose secretion is associated with sleep and circadian rhythms (e.g. cortisol) are known to have profound effects on appetite and/or body composition and may be affected by changes in sleep duration or quality. Furthermore, changes in these hormones may augment the adverse metabolic consequences of obesity, including insulin resistance and diabetes. To fully understand the physiological interaction between sleep and metabolism, additional human studies are essential, especially studies that investigate individuals with varying sleep durations. These studies will complement studies investigating experimental sleep deprivation in individuals of average sleep duration. Unfortunately, there are few animal models of human sleep. Rodents, which are commonly used to study obesity, do not have consolidated sleep like humans.

Sleep duration and energy expenditure
Sleep deprivation has long been used as a method to gain insights into the biological significance of sleep. While short-term non-pharmacological sleep deprivation is feasible in humans, because of ethical reasons, long-term total sleep deprivation (TSD) has only been performed on experimental animals. Studies in rats using the “disk-over-water” method have provided important insights into the impact of sleep deprivation on health (Fig. 3) [63–66]. It should be noted that in these studies the yoked control also experienced an element of sleep deprivation. The TSD rats died 11–32 days after beginning deprivation having consistently displayed several abnormalities: extreme debilitated appearance, edema of paws, skin lesions, motor weakness, ataxia, and an inability to generate high electroencephalograph amplitude. Interestingly, TSD also resulted in increased food intake but greater energy expenditure, ultimately leading to weight loss. During the late stages of sleep deprivation, the TSD rats had reduced body temperature, reduced plasma thyroxine, and increased plasma norepinephrine.

Changes in energy balance occur early in the TSD model; within a few days of the initiation of TSD, rats exhibit an increase in waking body temperature and, consequently, energy expenditure. TSD rats increase food consumption to compensate for this, yet they lose weight, indicating a dramatic increase in energy expenditure. During the latter part of TSD when death is imminent, energy expenditure increases in conjunction with declining body temperature, suggesting massive heat loss. Interestingly, the deleterious effects of sleep deprivation can be postponed by a high-calorie diet. Therefore, increased food intake is thought to be an adaptive response to the increased energy expenditure during TSD, but the degree to which increased food intake can counteract the increase in energy expenditure is limited, since survival time in these studies was predicted by the rate

<table>
<thead>
<tr>
<th>Method</th>
<th>Sleep variable</th>
<th>n</th>
<th>coefficient</th>
<th>p value</th>
<th>n</th>
<th>coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysomnography</td>
<td>Sleep efficiency (proportion)</td>
<td>856</td>
<td>-5.1</td>
<td>0.05</td>
<td>1017</td>
<td>0.15</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Wake after sleep onset (h)</td>
<td>856</td>
<td>0.81</td>
<td>0.05</td>
<td>1017</td>
<td>-0.041</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Total sleep time (h)</td>
<td>856</td>
<td>-0.69</td>
<td>0.008</td>
<td>1017</td>
<td>0.047</td>
<td>0.13</td>
</tr>
<tr>
<td>Diary</td>
<td>Average nightly sleep (h)</td>
<td>617</td>
<td>-0.52</td>
<td>0.13</td>
<td>709</td>
<td>0.12</td>
<td>0.006</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>Usual sleep (h)</td>
<td>855</td>
<td>-0.096</td>
<td>0.72</td>
<td>1015</td>
<td>0.089</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 2. Relationships between sleep variables and ghrelin and leptin, adjusted for age, sex, body mass index, and time of sample storage (adapted from [20]). Leptin and ghrelin levels were square-root transformed. Ghrelin, which is an important short-term regulator of food intake, was found to be associated with polysomnographic (short-term) sleep measures. Leptin, a long-term regulator of food intake, was correlated with measures of long-term sleep (from questionnaire and sleep diary).
The hypothalamic hypocretin (orexin) system

The lateral hypothalamic hypocretin (orexin) neuropeptide system, known to be abnormal in the sleep disorder narcolepsy, may be key to the interaction between short sleep duration and metabolism [71–73]. Most cases of narcolepsy–cataplexy cases are associated with undetectable hypocretin levels in the cerebrospinal fluid. Post mortem studies have shown absence of hypocretin precursor mRNA expression in brains from patients with narcolepsy–cataplexy. Hypocretin (orexin) neurons are located in the perifornical area and have connections with the hypothalamic arcuate and paraventricular nuclei, important areas for appetite, hormone, and autonomic nervous system regulation. Several studies have reported an association between narcolepsy and excess body weight in the face of reduced appetite [74–77]. Therefore, absent hypocretin (orexin) neurotransmission, as seen in narcolepsy, is believed to result in reduction in energy expenditure, but this requires more careful study. Hypocretin (orexin) neurons are important in the maintenance of wakefulness. They respond to sleep deprivation by activation (Fig. 4) and

Figure 3. The disk-over-water method of sleep deprivation in the rat. When the totally sleep deprived (TSD) rat goes to sleep, this activates the computer to turn the motor and if the TSD rat does not awaken, it lands in the water surrounding the disk. The control rat is also sleep-deprived but gets an opportunity to sleep when the TSD rat is awake. This technique highlighted a potential association between sleep and metabolism. This model is, however, inadequate for studying the mechanisms for the interaction between human sleep and metabolism. Compare this with the human situation where sleep is consolidated, environmental temperature is regulated, and there is free access to high-calorie food.

of energy expenditure increase early in deprivation. These results indicate a critical role for sleep in maintaining the ability to thermoregulate during both sleep and wake states. This link is given further credence by the fact that both phylogenetically small mammals and juveniles, which have less thermal stability and thus face greater thermoregulatory challenges, generally sleep more than larger (and older) mammals [67].

It is difficult to reproduce the effects of partial chronic sleep loss as seen in humans in rodent models, which do not have consolidated sleep. Furthermore, it is difficult to have ideal control animals for such experiments. Nevertheless, the disk-over-water method and other approaches have been used to study the impact of sleep deprivation on metabolic hormones. Hormonal studies with sleep deprivation models in rodents have, however, shown conflicting changes in leptin, ghrelin, and corticosterone.

Does sleep deprivation alter the energy balance in humans? To answer this, total and partial sleep deprivation studies have been carried out [57,58,68]. It is difficult to bring about sufficient days of TSD in humans to observe similar effects on energy expenditure as observed in the TSD rat model. However, the loss of a single night of sleep in humans does not typically result in an increase in mean core body temperature. Humans normally experience a drop in core body temperature at night, half of which is due to sleep, the other half of which is circadian. Therefore, the loss of sleep at night results in an inability to lose the resultant excess heat. Failure of thermoregulation and a disruption of sleep in humans have been observed in quadriplegics who lack an ability to actively thermoregulate (this disruption was beyond that caused by sleep apnea in these subjects) [69]. Other changes that have been observed during short-term TSD include an increase in sympathetic nervous system activity, a decreased ability to curtail heat loss in a cool environment [70], and an increase in hunger, which may reflect an increased energy need or a mismatch between energy need and food-seeking behavior. Collectively, these results indicate that short-term TSD is likely to cause a disruption in thermoregulation and energy balance in humans. However, the effects of prolonged partial changes in sleep duration are unknown. The major components of energy expenditure are resting (basal) metabolic rate, thermogenic effect of ingested food, and activity-related energy expenditure (exercise and non-exercise activity thermogenesis [NEAT]). The most variable component is activity-related energy expenditure; it is likely that sleep has an impact on this component as it results in fatigue, but this needs to be confirmed by future studies.
are sensitive to peripheral metabolites (glucose and lipids) and metabolic hormones (leptin and ghrelin). Hypocretin (orexin) neurons have been shown to be involved in the regulation of both food intake and energy expenditure, but the effect on the latter may be more important. Furthermore, there may be reciprocal connections between these neurons and peripheral hormones through alterations in sympathetic nervous system activity. Unfortunately, the hypocretin peptides can only be reliably measured in cerebrospinal fluid, making studies in humans difficult. Moreover, it would be difficult to image these neurons since they are few in number and located in a small part of the brain.

**Potential mechanisms and research agenda**

Figure 5 summarizes the potential mechanisms for the sleep–metabolism interaction. These mechanisms need to be clarified by well-designed population and laboratory studies. Since this interaction is complex, it is likely that multiple interrelated factors operate downstream of sleep duration.
and that these combine to result in the observed phenotype (obesity). Sleep duration may alter the balance between energy intake and energy expenditure by affecting both sides of the equation. To investigate this further, we need to answer several fundamental questions. TD in rats results in increased energy expenditure, but the effect in humans remains to be determined. Could chronic sleep loss also result in increased energy expenditure in humans, and if so, which components of energy expenditure are altered [78]? Sleep loss results in fatigue and excessive daytime sleepiness. Could this fatigue contribute to reduced daytime physical activity? Sleep loss results in alterations in several hormones including leptin, ghrelin, insulin, and cortisol. Could these hormonal changes contribute to selection of calorie-dense food, excessive food intake, alterations in energy expenditure, and insulin resistance? What other hormones/cytokines are involved (e.g. PYY, adiponectin, resistin, visfatin, interleukin-6 [79], and tumor necrosis factor-α)? How does sleep loss translate into all the above changes? Is it through alterations in sympathetho-vagal balance?

Conclusion

There is now sufficient population data to suggest an important association between short sleep duration and obesity. Several potential mechanisms for this relationship have been proposed above and these need to be investigated methodically. Despite our incomplete understanding of the mechanisms and neural circuitry involved, we have to examine the public health implications of our current knowledge. Voluntary sleep restriction is not likely to be the only cause of the current obesity pandemic and it is too simplistic to expect obese individuals to lose weight simply by sleeping more. It may prove difficult to unequivocally prove a causal relationship between short sleep duration and obesity as we are dealing with highly complex physiological systems and current animal models are inadequate. Additionally, it may be difficult to extend sleep for prolonged periods, as is reflected by the scarcity of publications in this area. Intervention studies using sleep extension for weight loss cannot be placebo controlled or blinded, and once obesity occurs the situation is compounded by the occurrence of sleep-disordered breathing [56]. Furthermore, the optimal sleep duration is unclear [80]. It has been argued that the impact of sleep on body weight is likely to be more important in the prevention of obesity in children [21]. We know that short sleep duration at a young age is associated with later obesity and can ensure that parents are educated regarding the importance of sleep so that their children can be provided with the appropriate opportunity and environment for adequate sleep. Good sleep could, for example, be promoted by removal of gadget distractions such as televisions and computers from bedrooms and restricting their use, observance of strict bedtimes, and other sleep hygiene measures [21]. There is little risk in including advice regarding adequate sleep as part of other lifestyle approaches such as healthy eating and physical activity, and any opportunity to halt and reverse the obesity pandemic should not be lost.

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