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The influence of sleep and sleep loss upon food intake and metabolism

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The present review investigates the role of sleep and its alteration in triggering metabolic disorders. The reduction of the amount of time sleeping has become an endemic condition in modern society and the current literature has found important associations between sleep loss and alterations in nutritional and metabolic aspects. Studies suggest that individuals who sleep less have a higher probability of becoming obese. It can be related to the increase of ghrelin and decrease of leptin levels, generating an increase of appetite and hunger. Sleep loss has been closely associated with problems in glucose metabolism and a higher risk for the development of insulin resistance and diabetes, and this disturbance may reflect decreased efficacy of the negative-feedback regulation of the hypothalamic–pituitary–adrenal axis. The period of sleep is also associated with an increase of blood lipid concentrations, which can be intensified under conditions of reduced sleep time, leading to disorders in fat metabolism. Based on a review of the literature, we conclude that sleep loss represents an important risk factor for weight gain, insulin resistance, type 2 diabetes and dyslipidaemia. Therefore, an adequate sleep pattern is fundamental for the nutritional balance of the body and should be encouraged by professionals in the area.

Sleep loss: Food intake: Obesity: Appetite: Diabetes

Introduction

A reduction of sleep time has become common in recent years, guided by the demands and opportunities of modern society[1]. Over the last 40 years, self-reported sleep duration has decreased by 1·5–2 h in the USA[2,3]. The proportion of young adults with a period of sleep shorter than 7 h per d has increased from 15·6 % in 1960 to 37·1 % in 2001–2[2,3].

Recent studies show that the alteration in sleep time can influence various aspects associated with the nutritional and metabolic balance of the body, such as the control of body mass[4–7] and the controls of food intake[8–10], glycaemic levels[1,11,12] and of the levels of cholesterol and TAG[13–15].

Numerous studies have used different methodologies to understand the effects of sleep loss. Sleep deprivation can be total, when no sleep is allowed, or partial, when the retiring time is delayed or the rising time is advanced. In addition, deprivation can last for one or more nights. Results might depend upon the exact nature of the deprivation that is used. Some studies have used shift workers, for example, who might sleep less than day workers, under 5 h on working days[16]. These members of the population have been the main focus of scientific work considering the relationship between sleep and nutrition. Not only might such decreased hours of sleep modify eating behaviour significantly[14,17–22] but also it has been known for some time that the eating habits of night workers during the night shift are altered[23,24].

Individuals that sleep less, including shift workers, have been associated in the longer term with a higher propensity for the development of nutritional problems[25,26], such as obesity and altered metabolism of food[14,17–22,24,27], dyslipidaemias[25,28] and diabetes[12,29–31]. In laboratory studies of healthy young adults submitted to recurrent partial sleep restriction, marked alterations in metabolism, including decreased glucose tolerance and insulin sensitivity[32] and altered metabolism of food[33], have been demonstrated.

Given the need for a better understanding of the nutritional problems resulting from alterations in sleep patterns, the present article discusses the influence of sleep on nutritional and metabolic parameters.

Abbreviations: GH, growth hormone; HPA, hypothalamic–pituitary–adrenal; LPL, lipoprotein lipase; REM, rapid eye movement; SWS, slow-wave sleep; TSH, thyroid-stimulating hormone.

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Obesity and sleep

Landmark studies by Rechtschaffen *et al.*[34] reported that rats submitted to total sleep deprivation (by the disk-over-water method) markedly increased food intake but, nevertheless, lost weight. Many other studies have confirmed these results[35–40]. Recently, however, Martins *et al.*[41] introduced different procedures to allow accurate estimation of food spillage before, during, and after 120 h of sleep deprivation. Their main finding was that, once corrected for spillage, food intake was not significantly increased during sleep deprivation, even though weight loss did occur during the sleep-deprivation period.

In human subjects, recent studies have pointed to a possible involvement of changed sleep hours in altered energy balance of the body and to alterations in the sleep pattern as a contributory factor to increased obesity[1,27,42]. Many recent studies correlate the short duration of sleep with the increase in the BMI, in adults[4,6,7,43–45], children[46–48] and adolescents[49–51]. In a prospective single-age cohort study with 496 young adults, Hasler *et al.*[44] showed an association between short sleep duration and obesity and a negative association between sleep duration and BMI. These associations persisted after controlling for a variety of potentially confounding variables. Reilly *et al.*[47] found, in 8234 children aged 7 years, that sleep duration in the children when aged 30 months was independently associated with the prevalence of obesity at the age of 7 years. Children showing the lowest two quartiles of sleep duration ($<10{\cdot}5$ h and $10{\cdot}5–10{\cdot}9$ h, respectively) were more likely to be obese at age 7 than children in the highest quartile (>12 h).

However, although data from prospective studies and supporting this link are emerging, most of the studies showing an association between short sleeps and obesity have been cross-sectional and do not prove causality. In an attempt to understand better the effect of sleep loss on food intake in man, studies have used models of shift work or jet lag (alterations resulting from rapid crossing of time zones), both of which are situations that alter the sleep pattern and are also associated with alterations in the pattern of food intake[14,17–22,52]. Some studies have reported that obesity tends to occur more frequently in association with shift work than with daytime-only work[14,18,53–56]. During night work[24,57] and after a time-zone transition[24,58], there might be additional problems due to the lack of palatable food[59]. Altered eating habits are a source of concern in night workers, who tend to 'nibble' their way through crisps and chocolate bars during the night shift rather than eat a healthy and substantial meal in the middle of it[60–62]. Waterhouse *et al.*[63] analysed the transient changes in the pattern of food intake following a simulated time-zone transition. Subjects showed significant changes in their pattern of food intake. The distribution of daytime meals was significantly affected on the first post-shift day, with a redistribution of the times that the main, hot meals were eaten.

Even though the mechanisms involved in changed eating habits are not completely understood, it is known that alterations in the sleep–wake schedule affect intracellular circadian clocks – molecular mechanisms that enable the cell, tissue or organism to anticipate diurnal variations in the environment. The environment (of cells and tissues) may include circulating levels of nutrients (for example, glucose, fatty acids and TAG) and various hormones (for example, insulin, leptin, ghrelin, glucocorticoids). As such, alterations in the timing mechanism are likely to induce nutritional changes that may potentiate disrupted metabolism[64] and influence appetite, satiety and, therefore, food intake[33]. It is believed also that problems in adjustment of the biological clock, so impairing the duration and quality of sleep, can also modify food intake[25,58,65].

Therefore, we will approach more precisely the mechanisms by which the sleep loss can lead to the increase of food intake and obesity.

The role of leptin and ghrelin in the control of food intake and sleep

Eating and sleeping are two kinds of behaviour that are essential for the survival of man and higher animals. Whereas it is obvious that these two processes cannot occur at exactly the same time, there appear to be common regulators of both phenomena[66]. With the identification of ghrelin as the endogenous ligand of the growth hormone (GH) secretagogue receptor[67], a new endogenous regulator of food intake and, possibly, also of sleep was found. Later, Bodosi *et al.*[68] described a relationship between sleep, feeding and ghrelin and their antagonist in energy balance, leptin.

From these findings, many studies have clearly indicated that the reduction in total sleep time is associated with two parallel endocrine behaviours that can significantly alter food intake: the reduction of the anorexigenic hormone leptin[7,69–71] and the increase of the orexigenic hormone ghrelin[7,33,68]. In individuals who sleep less, this combination of changes results in increased hunger and food intake[33]. In an experiment carried out by Spiegel *et al.*[33], sleep deprivation in men was associated with an increase of 28 % in ghrelin levels, a reduction of 18 % in the leptin levels and increases of 24 % in hunger and 23 % in appetite (Fig. 1).

Leptin is a protein composed of 167 amino acids, and it is produced mainly by the adipose tissue[72]. Leptin provides the regulating centre in the brain with information about energy balance, and its release is associated with the promotion of satiety[73–80]. Elevated leptin levels at times of metabolic excess activate an anorexigenic pathway, the peptide precursor pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript peptide (CART), and reduce activity in orexigenic pathways, neuropeptide Y (NPY) and agouti-related peptide (AgRP). Low leptin levels, occurring at times of nutrient deficit, result in a reduction of inhibitory influences on NPY/AgRP neurons, a lack of activation of POMC/CART-containing neurons and an overall increase in orexigenic signalling[81,82] (see Fig. 2).

Recent studies with animals have suggested that leptin might participate in the regulation of sleep, systematically reducing rapid eye movement (REM) sleep and influencing non-REM sleep[83]. Other work has postulated a direct influence of leptin release on sleep, since the levels of this hormone are higher during sleep than when awake[84]. Some

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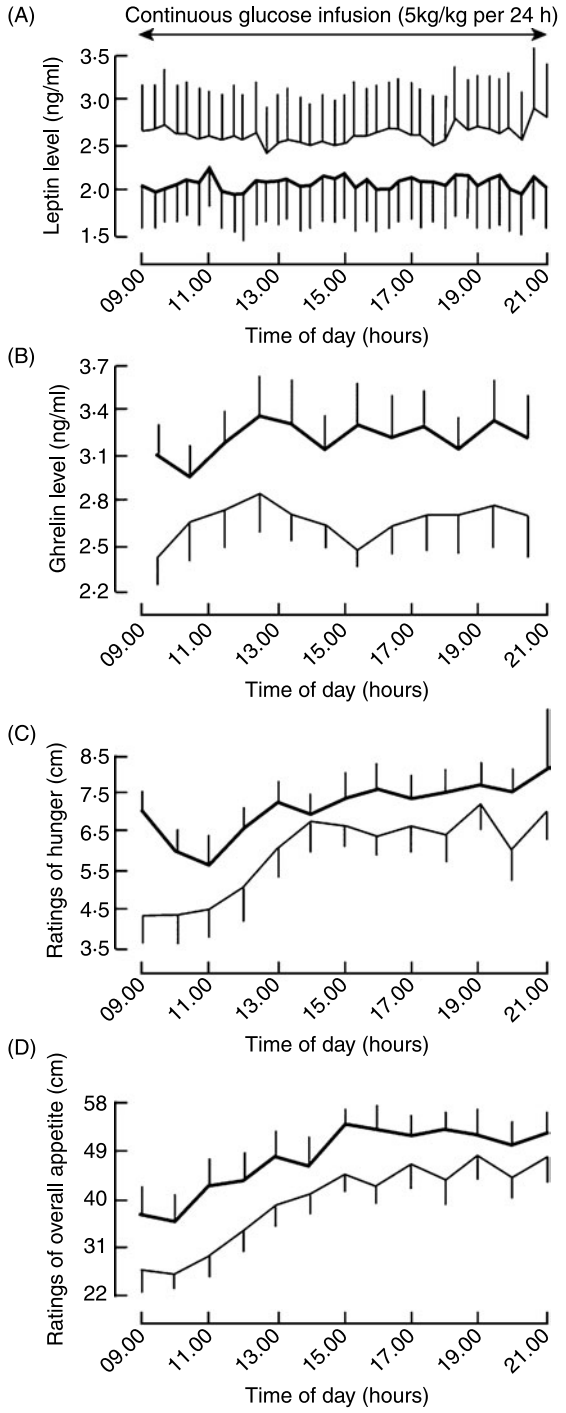

Fig. 1. Effect of sleep duration on daytime leptin levels (A), ghrelin levels (B), hunger (C) and appetite (D). (A) Daytime (09.00 to 21.00 hours) profiles of leptin after 2 d with 4 h in bed (—) or 2 d with 10 h in bed (—). Mean leptin levels were 18 % lower when sleep was restricted. (B) Daytime (09.00 to 21.00 hours) profiles of ghrelin from nine of the twelve participants after 2 d with 4 h in bed or 2 d with 10 h in bed. Mean ghrelin levels were 28 % higher in the afternoon and early evening (12.00 to 21.00 hours) when sleep was restricted. (C) Ratings of hunger (0–10 cm visual analogue scale) and (D) overall appetite (0–70 cm visual analogue scale) after 2 d with 4 h in bed or 2 d with 10 h in bed. When sleep was restricted, ratings of hunger and overall appetite increased by 24 and 23 %, respectively. Values are means, with their standard errors represented by vertical bars. (From Spiegel *et al.*[71]; used with permission from the *Annals of Internal Medicine*.)

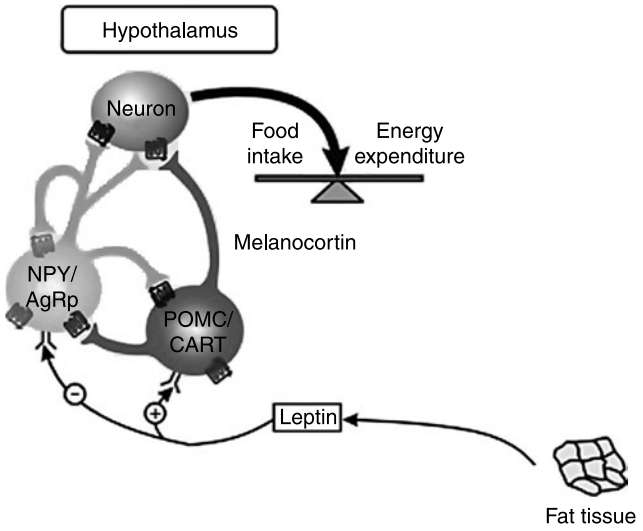

Fig. 2. Central control of food intake. Leptin stimulates pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript peptide (POMC/CART) neurons and inhibits neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons. The result of these opposing actions is the stimulation of food intake and energy expenditure. (Adapted from Gale *et al.*[229].)

evidence suggests that this nocturnal increase is partly a response to the intake of food that took place during the day[85]. It is believed, however, that sleep *per se* can affect the regulation of leptin, since studies have shown that the elevation observed during sleep persists in subjects receiving continuous enteral nutrition, even when sleep occurs during the daytime[71,84].

Evidence from other laboratory studies has shown that both chronic, partial sleep deprivation[70] and acute sleep deprivation[69] might cause a reduction in the serum concentration of leptin. Spiegel *et al.*[71] evaluated the pattern of leptin secretion in eleven male individuals subjected to a shortened sleep time (4 h) for six nights. Mean and maximum values of leptin were lower (by 19 and 26 %, respectively) during sleep restriction, compared with the same individuals when they had normal sleep (8 h), suggesting that sleep plays an important role in leptin secretion. Sleep restriction seems to change the capacity of leptin to respond to the body's energy balance and to produce the satiety signal when the energy needs have been adequately met[71]. Also, Taheri *et al.*[7] observed, in a cross-sectional study carried out with 1024 volunteers, that short sleep was associated with low leptin levels, with a decrease of 15·5 % predicted for habitual sleeps of 5 *v.* 8 h. Chaput *et al.*[86] found a cross-sectional association between short sleep duration and leptin levels in a sample of 323 men and 417 women aged 21–64 years. When compared with adults reporting 7–8 h of sleep per d, and after adjustment for age, sex, and physical activity level, the adjusted OR for overweight or obesity was 1·38 (95 % CI 0·89, 2·10) for those with 9–10 h of sleep and 1·69 (95 % CI 1·15, 2·39) for those with 5–6 h. However, all of these significant differences disappeared after statistical adjustment for plasma leptin levels.

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An impact of sleep duration on leptin levels could involve several mechanisms. Considering that leptin release is inhibited by the sympathetic nervous system[87], another possibility is that sleep restriction results in a reduction in leptin levels due to increased sympathetic activity[71]. Alterations in the regulation of cortisol and sympatho–vagal balance, the two most important neurobiological markers of stress, were clear when individuals were studied for 6 d of sleep restriction[71]. A negative association between changes in leptin levels and cortisol during sleep restriction is well documented in the literature, possibly indicating a suppressive effect of leptin on the hypothalamic–pituitary–adrenal (HPA) axis[88–90].

A parallelism between the diurnal and pulsatile variations in thyroid-stimulating hormone (TSH) and leptin levels has been reported in healthy young adults[91]. Spiegel *et al.*[71] observed a positive association between 24 h variations in leptin and TSH after sleep restriction, which provides compelling evidence for a role for leptin in the physiological regulation of the thyrotropic axis. Evidence suggests that TRH neurons may be regulated by leptin[90], and a stimulatory effect of leptin on TSH release has been suggested in man[91–93] and shown in rodents. In contrast, many other studies have reported negative findings in the role of physiological concentrations of thyroid hormones on leptin regulation[71,94,95].

It has been suggested that the reduction in leptin levels after sleep restriction might be an adaptation to increased energy needs, due to the increase in wake time[71]. Studies involving accurate measurements of energy balance in individuals submitted to chronic partial sleep loss are necessary, to rule out the possibility that the state of sleep restriction entails a significant increase in energy expenditure.

A close relationship between leptin and ghrelin, another hormone influenced by sleep, has been described. Ghrelin is a peptide composed of twenty-eight amino acids, produced mainly by the endocrine glands of the stomach[67] and duodenum[67], and by a number of brain structures[96]. This hormone increases in periods of fasting[97], triggering the sensation of hunger[97–99] in the arcuate nucleus[100], stimulating gastrointestinal motility[101] and promoting the deposition of lipids[102]. The arcuate nucleus is involved in the central control of food intake[103], and ghrelin is the only substance that is found endogenously in mammals and that increases hunger and appetite when administered to human subjects[104–109]. This hormone contributes to preprandial hunger[110] and plasma concentrations of ghrelin are inversely correlated with the amount of food ingested[68]. Ghrelin is thought to be significantly involved in the neuroendocrine network that regulates energy balance in at least two ways. First, it acts as a peripheral hormone from the stomach that, along with other signals such as insulin or leptin, informs the central energy balance control when energy stores diminish, and also increases orexigenic drive and decreases energy expenditure. Its second involvement is as a hypothalamic neuropeptide, expressed in a previously unidentified population of neurons adjacent to the third ventricle and between the ventromedial hypothalamus, the dorsal hypothalamus, the paraventricular nucleus, and the arcuate nucleus. Efferents of ghrelin-expressing neurons project to key circuits involved in the regulation of central energy balance and may offset the activity of orexigenic neuropeptide Y/Agouti-related protein with anorectic pro-opiomelanocortin neurons and so modulate the output of the efferent pathway[97].

Current evidence indicates that ghrelin is also a sleep-promoting factor[111], inducing slow-wave sleep (SWS) and the nocturnal secretion of GH[112]. It is well documented that there is an increase in the levels of ghrelin during sleep, followed by a decrease in the morning, some hours before breakfast. The cause of this profile remains to be clarified, since it is anomalous that the levels of a hormone that stimulates hunger are increased during sleep. It has been suggested that ghrelin might produce other metabolic and endocrine functions that remain to be ascertained[112].

As in the case of leptin, sleep seems to influence the pattern of ghrelin secretion, since high levels of this hormone follow the curtailment of sleep in human subjects[33]. Spiegel *et al.*[33] showed that the curtailment of sleep (to 4 h) in twelve healthy men for a period of 2 d was associated with an increase of almost 28 % in the diurnal levels of ghrelin. Bodosi *et al.*[68], in a study with rats, analysed plasma and hypothalamic concentrations of ghrelin before and after sleep deprivation. They observed that levels of hypothalamic ghrelin changed during and after sleep deprivation, increasing during sleep deprivation and decreasing afterwards to levels below baseline. Plasma ghrelin, on the other hand, showed increased levels both during[71] and after sleep deprivation[111]. Based on this evidence, it has been postulated that high levels of ghrelin in response to sleep deprivation might be a normal response of the body to a greater need for energy intake, as a result of the longer time the individual has remained awake. This hypothesis requires further investigation[33]. Therefore, high ghrelin levels can contribute to an increase of hunger and food intake during sleep loss.

These differences in leptin and ghrelin are likely to increase appetite, possibly explaining the increased BMI observed in individuals with short sleep duration[7]. The current literature indicates that the decrease of leptin and increase of ghrelin levels are considered to be the main factors that trigger the increase of hunger when the sleep pattern is altered[33]. Fig. 3 shows how sleep deprivation might change the pattern of ghrelin and leptin and energy balance.

Sleep deprivation seems to increase not only appetite but also the preference for foods containing more energy[7,113]. Spiegel *et al.*[33] showed that the appetite for energy-rich nutrients with high carbohydrate content, including sweets, salty snacks and starchy foods, increased by 33–45 %; by contrast, appetite for fruits, vegetables and high-protein nutrients was less affected. Lennernas *et al.*[114] observed a great preference for the intake of ‘fast food’ and energy-rich snacks during the nocturnal working hours in night workers. The preference for such foods is a source of great concern since, in addition to presenting a hormone pattern that predisposes to an increased energy intake[33], individuals with sleep loss (common in night workers) tend to meet this need with foods of low nutritional quality[115–119].

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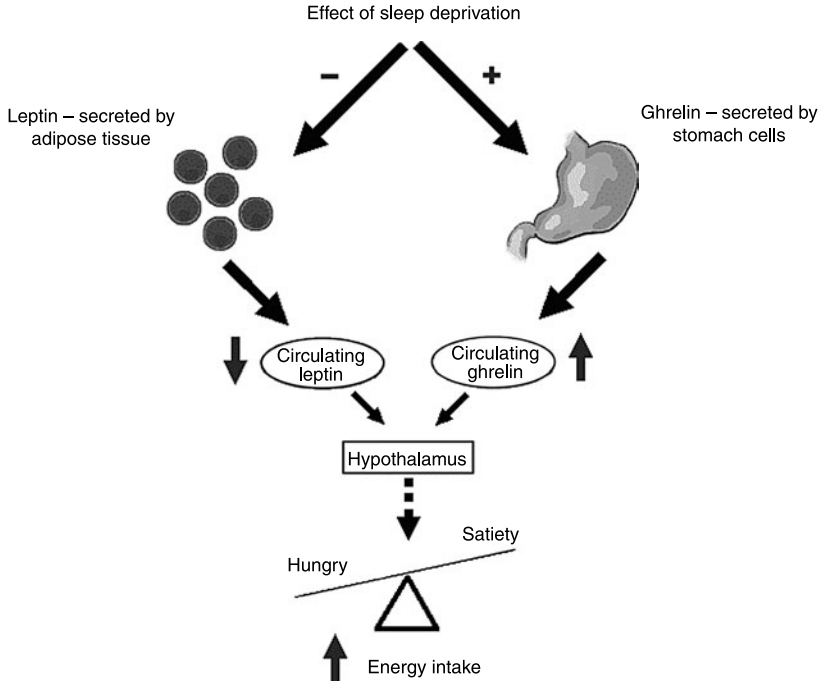

Fig. 3. Changes in the pattern of ghrelin and leptin release and energy balance produced by sleep deprivation.

This altered food intake can result from inadequate eating facilities during the night shift but, whatever its cause, it increases the risks of obesity[26], dyslipidaemias[28] and CVD[115–119].

Sleep duration might represent a major risk factor for the development of weight gain and one that can be modified fairly easily. Unfortunately, most studies that describe hormonal and behavioural changes capable of increasing food intake have been acute interventions, and so it has not been possible to establish what would be their long-term effects. Indeed, there are many other neuropeptides that have stronger effects on food intake, and which have not been measured in sleep-loss studies. Even so, the new studies should lead to a better understanding of the role of sleep in the mechanisms that control hunger and satiety. Also, it is suggested that new studies, to measure the effect of sleep-promoting interventions on appetite and body weight, are required. Even so, the current findings suggest that changes in the levels of leptin and ghrelin, due to sleep curtailment, cause changes in food intake. That is, sleep duration can be added to the environmental factors that are prevalent in our society and that contribute to weight gain and obesity. It might be that a better night's sleep will become a goal in future attempts to combat obesity.

Sleep and energy expenditure

Sleep duration may alter the balance between energy intake and energy expenditure. With regard to energy expenditure, excessive daytime sleepiness and fatigue, resulting from sleep loss (tiredness without increased sleep propensity), have been associated with obesity and have a significant impact on individual wellbeing and public safety[120]. Taheri[121] stated that excessive daytime fatigue and sleepiness could contribute to reduced daytime physical activity, which many believe is a major contributor to the current obesity pandemic. Knutson[50] found that about 40 % of 12–16 year olds reported waking up tired; this could have a serious adverse effect on daily physical activity. Additionally, physical activity has a beneficial effect on sleep, suggesting a negative synergy between poor sleep and low physical activity.

Gupta *et al.*[49] studied a tri-ethnic cross-section sample of male and female adolescents, aged 11–16 years (Heartfelt Study). Data obtained from 24 h wrist actigraphy showed that obese adolescents experienced less sleep than non-obese adolescents ($P < 0{\cdot}01$). For each hour of lost sleep, the odds of obesity increased by 80 %. Sleep disturbance was not directly related to obesity in the sample, but influenced physical activity levels ($P < 0{\cdot}01$). Daytime physical activity diminished by 3 % for every hour increase in sleep disturbance. Other studies, measuring energy expenditure in both sexes, at different ages and following sleep loss, are needed to understand better these relationships[71,87].

Influence of sleep on glucose metabolism

In man, the homeostatic control of plasma glucose results in a strictly controlled balance between the distribution of glucose (originating in the liver in the post-absorptive state or from the intestine in the postprandial state) and the use of glucose by the tissues such as muscles, adipose tissue and the brain. This control prevents the development of hypoglycaemia or hyperglycaemia[1,122].

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In order to investigate differences in glucose control during sleep and waking periods, a number of recent studies have measured glucose levels of individuals in both states[123]. In normal subjects during an overnight sleep, blood levels of glucose remain stable or fall only minimally despite the extended fast[122]. By comparison, in subjects awake and fasting in a recumbent position during the daytime period, and in the absence of any physical activity, glucose levels fall by an average of 0·5–1·0 mM (i.e. 100–200 mg/l) over a 12 h period[122]. Thus, a number of mechanisms must operate during nocturnal sleep to maintain stable glucose levels during the fasting period[1].

Glucose homeostasis is critically dependent on the ability of pancreatic β-cells to release insulin both acutely (i.e. the acute insulin response to glucose, 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 a given amount of exogenous glucose[1]. Insulin resistance can lead to a marked decrease in glucose tolerance (reflected in higher plasma glucose levels). It is well established that insulin sensitivity, insulin resistance and glucose tolerance vary across the 24 h cycle and can be influenced by a lack of sleep[122].

Recent studies have described a significant impairment in glucose control in individuals who have alterations in their sleep pattern[1,32,124]; these subjects are more susceptible to the onset of insulin resistance[1,32] and type 2 diabetes[1,32,125]. Therefore, it is appropriate to address the mechanisms involved in the impaired glucose metabolism by disruption of the sleep–wake rhythm.

Glucose metabolism during sleep

Studies of nocturnal glucose tolerance during sleep – determined by the balance of insulin secretion and insulin action – have used intravenous glucose infusion at a constant rate, or continuous enteral nutrition, and have sampled glucose and insulin without waking the subjects[126–128].

Van Cauter *et al.*[11] evaluated glucose and insulin secretion rates in a group of eight normal young men (aged 20–27 years) during constant glucose infusion, including an 8 h period of nocturnal sleep. During nocturnal sleep, levels of glucose and insulin secretion increased by 31 ± 5 and 60 ± 11 %, respectively, and returned to baseline in the morning. During the first half of the sleep period, the increase in plasma glucose was followed by a 50 % increase in insulin secretion. Under these experimental conditions, the major underlying cause of the glucose increase is decreased glucose utilisation[11]. The profiles of peripheral glucose and insulin concentrations observed in this study confirmed and extended the findings of previous studies, which had shown decreased glucose tolerance in the evening as compared with the morning[129–133].

It is estimated that about two-thirds of the fall in glucose utilisation during early sleep is due to a decrease in brain glucose metabolism[134], which is related to the predominance of SWS and associated with a 30–40 % reduction in cerebral glucose metabolism relative to waking values. The remainder of the fall in glucose uptake is thought to reflect decreased peripheral utilisation. Diminished muscle tone during sleep and rapid anti-insulin-like effects of the sleep-onset GH pulse[135] are both likely to contribute to this decrease in peripheral glucose uptake. During the latter part of the night, glucose tolerance begins to improve, and glucose levels progressively decrease toward morning values, reflecting an increase in glucose uptake. This increase in glucose uptake is partially due to the increases in wakefulness and REM stages[136]. Indeed, glucose utilisation during REM sleep and waking is higher than during non-REM sleep[134,137–140]. Finally, the latter part of the night appears also to be associated with increased insulin sensitivity[11,141].

Glucose metabolism during sleep loss

Some evidence has indicated that diabetes is more likely to occur in individuals who experience sleep loss. In a longitudinal study over a 10-year period, Suwazono *et al.*[142] investigated the effect of alternating shifts on the onset of diabetes mellitus in Japanese workers (*n* 3203) compared with day-shift workers (*n* 2426). The OR for the development of diabetes mellitus in the alternating-shift group compared with the day-shift group was 1·35 (95 % CI 1·05, 1·75), indicating that alternating shifts are an independent risk factor for the onset of diabetes mellitus. Morikawa *et al.*[143] analysed the risk of diabetes mellitus in 2860 men in a factory in Japan over the course of 8 years. They found a significantly increased risk of diabetes mellitus for the two-shift, but not three-shift, system, using white-collar workers as a reference group. More specific studies have examined the relationship between sleep duration and diabetes. Trenell *et al.*[144] found the same U-shaped relationship between sleep duration and the incidence of type 2 diabetes[29,145], independent of confounding variables. Analysis of cross-section data from the Sleep Heart Health Study also revealed that reduced sleep duration was associated with an increased prevalence of type 2 diabetes and insulin resistance, after controlling for sleep-disordered breathing[12], a condition that may also independently influence glucose control[146,147].

Several studies have shown major changes in glucose tolerance under conditions of sleep restriction or deprivation[1,32,122,148–150]. In a laboratory study, Spiegel *et al.*[32] analysed the glucose tolerance (measured by an intravenous bolus of glucose; 300 mg/kg body mass) in eleven young men after time in bed had been restricted to 4 h per night for six nights. The authors compared the sleep-debt condition with measurements taken at the end of a sleep-recovery period (fully rested condition) when participants had been allowed 12 h in bed per night for six nights. They observed that glucose tolerance was lower in the sleep-loss condition than in the fully rested condition. Sookoian *et al.*[151] studied 877 day workers and 474 rotating-shift workers. In comparison with day workers, rotating-shift workers had elevated fasting insulin and an increased homeostasis index, which is a measure of insulin resistance.

To define the roles of circadian rhythmicity (intrinsic effects of time of day, independent of the sleep or wake

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condition) and sleep (intrinsic effects of the sleep condition, irrespective of the time of day) on the 24 h variation in glucose tolerance, Van Cauter *et al.*[11] evaluated glucose and insulin secretion rates during a 53 h period −8 h of nocturnal sleep, followed by 28 h of sleep deprivation including a period of nocturnal sleep deprivation, and then 8 h of daytime recovery sleep. During sleep deprivation, glucose levels and insulin secretion rose to reach a maximum at a time corresponding to the beginning of the habitual sleep period. The magnitude of the rise above morning levels averaged 17 (SD 5) % for glucose and 49 (SD 8) % for calculated insulin secretion. Serum insulin levels did not parallel the circadian variation in insulin secretion, indicating the existence of an approximate 40 % increase in insulin clearance during the night. Daytime sleep was associated with a 16 (SD 3) % rise in glucose levels, a 55 (SD 7) % rise in insulin secretion and a 39 (SD 5) % rise in serum insulin. The profiles observed under these conditions indicate unequivocally that both circadian rhythmicity and sleep modulate glucose regulation[11] (Fig. 4).

Further studies are necessary to evaluate whether there is a difference in glucose metabolism following intravenous infusion or oral intake of glucose or other kinds of carbohydrates under conditions of sleep deprivation. It is also important that the impact of chronic sleep debt be clarified[1]. Mander *et al.*[124] observed that healthy individuals of both sexes, whose sleep had been curtailed (to less than 6·5 h per night) for a minimum period of 6 months, had a response to intravenous glucose similar to that of individuals who had slept longer (7·5–8·5 h), but at the cost of having markedly higher insulin secretion. This finding suggests that there might be a mechanism of metabolic adaptation when sleep debt becomes chronic. If this is the case, the initial impairment to glucose tolerance and to the responsiveness of β-cells might foster the subsequent development of insulin resistance[1].

There are other explanations for the changes in glucose metabolism during conditions of sleep loss. Cortisol, whose 24 h rhythm is noteworthy for its robustness and persistence under a large variety of pathological conditions, is a hormone that plays an important role in glucose metabolism. A modest elevation in cortisol levels during the night was present in elderly and adult individuals who had been sleep deprived[152–155]. In both groups, the nocturnal elevation of cortisol could reflect an impairment of feedback inhibition on the HPA axis[156].

Spiegel *et al.*[32] observed, in eleven young men after time in bed had been restricted to 4 h per night for six nights (sleep-debt condition), that the evening cortisol concentrations were raised ($P = 0{\cdot}0001$) and the activity of the sympathetic nervous system was increased ($P < 0{\cdot}02$). The sleep-debt condition, compared with the sleep-recovery condition (12 h in bed per night for six nights), was associated with alterations in the 24 h profile of plasma cortisol, including a shorter quiescent period and raised concentrations in the afternoon and early evening ($P = 0{\cdot}0001$). This latter disturbance may reflect decreased efficacy of the negative-feedback regulation of the HPA axis.

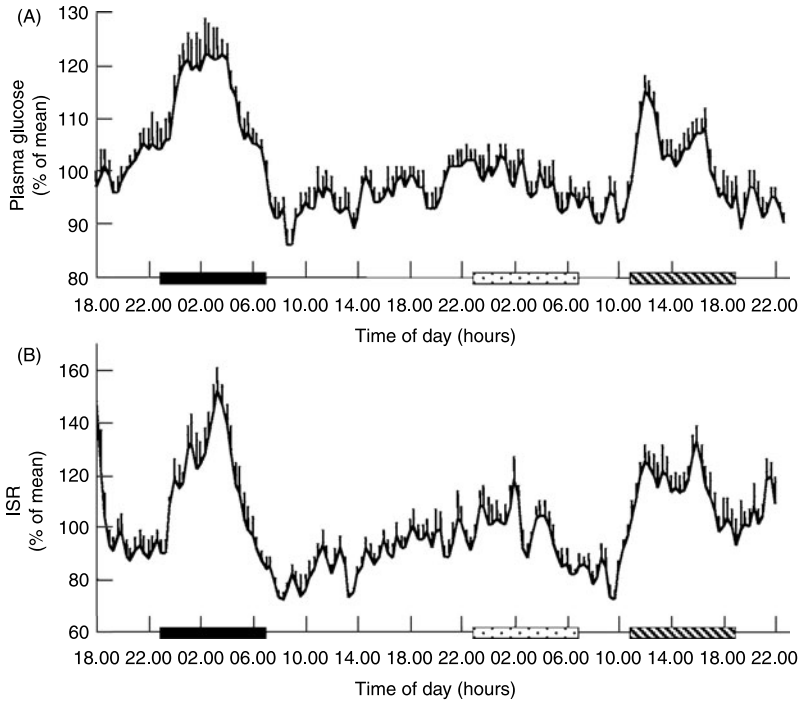

Fig. 4. Profiles of glucose (A) and insulin secretion rates (ISR) (B) in a group of eight normal young men (aged 20–27 years) studied during a 53 h period including 8 h of nocturnal sleep (■), followed by 28 h of sleep deprivation including a period of nocturnal sleep deprivation (⚄) and 8 h of daytime recovery sleep (▧). Data were obtained at 20 min intervals under continuous glucose infusion. Values are means, with their standard errors represented by vertical bars. (Adapted from Van Cauter *et al.*[11]; cited by Spiegel *et al.*[1]; used with permission from the *Journal of Applied Physiology*.)

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Cortisol has an immediate effect on the secretion of insulin, producing an inhibition in the absence of changes in glucose concentration[141]. This effect has been demonstrated in both *in vitro*[157–162] and *in vivo* studies[163–166].

One of the slower effects of a rise in cortisol levels is the onset of insulin resistance 4–6 h afterwards[156]. Therefore, the normal nocturnal elevation of cortisol levels might adversely affect glucose regulation during the night and the following day. In the long term, it might contribute to age-related reductions in glucose tolerance and insulin sensitivity. The hypothesis also suggests that the normal elevation of plasma cortisol at night, when the HPA axis is normally inhibited, would result in deleterious metabolic effects that are stronger than those that take place due to a similar elevation during the morning, when the HPA axis is fully activated[156]. A slow reduction of cortisol concentration in the afternoon is consistent with altered hippocampal mechanisms that control the negative feedback upon the HPA axis[32]. On the other hand, some studies rule out the possibility that the circadian variations in cortisol concentrations contribute to the diurnal variation in glucose tolerance, since this tolerance is higher in the morning (when cortisol levels are high) and lower in the first half of the night (when cortisol levels are low)[130,165]. The coincidences of increased insulin sensitivity with high cortisol levels in the morning, and of decreased insulin sensitivity with low cortisol levels in the evening, appear to contradict the well-known adverse effects of glucocorticoids on insulin sensitivity. However, this interpretation is based on the assumption that alterations of insulin resistance are an immediate consequence of changes in cortisol concentrations[122].

Disorders in the profile of GH secretion might also contribute to the alterations in glucose regulation observed during sleep loss. GH is secreted in a series of pulses throughout the whole 24 h cycle, with greater changes in concentration, due to more frequent and larger secretory pulses, taking place during sleep[167]. In normal adults, peak plasma concentrations of GH take place during the first half of sleep, in association with the time of most SWS[167–170]. The amount of GH secreted during the first episode of SWS is quantitatively related to the duration[171,172] and the intensity[173] of the SWS. The rapid anti-insulin-like effects of the GH pulse[135] are responsible for reducing glucose uptake by the peripheral tissues[1].

Considering the importance and the multiplicity of the metabolic actions of GH, even when there are only minor changes in the secretion profile over the course of the 24 h, these could be associated with significant peripheral effects[174]. Plat *et al.*[156] showed that sleep restriction was associated with a longer elevation of GH and an increase in cortisol levels during the night. Sleep-onset GH secretion is thought to facilitate the maintenance of stable overnight glucose levels despite the prolonged fasting condition[122]. Indeed, studies that have used intravenous administrations of a low dose of synthetic GH to mimic physiological pulsatile release have shown that a primary effect is a rapid decrease in muscular glucose uptake[135,175]. Spiegel *et al.*[174] evaluated a semi-chronic partial sleep loss (sixteen consecutive nights in the clinical research centre, including three nights with 8 h bedtime from 23.00 to 07.00 hours, six nights with bedtime limited to a 4 h period from 01.00 to 05.00 hours, and seven nights with 12 h bedtime from 21.00 to 09.00 hours) on the 24 h GH profile. Eleven young men were studied after six nights of restricted bedtimes (01.00 to 05.00 hours) and after seven nights of extended bedtimes (21.00 to 09.00 hours, the fully rested condition). After 1 week of sleep restriction, the biphasic nature of nocturnal GH release resulted in an extended period of elevated GH concentration compared with fully rested conditions. This extended exposure of peripheral tissues to higher GH levels may have adversely affected glucose regulation[156].

All these mechanisms suggest an important impairment in glucose metabolism during sleep, especially in individuals submitted to sleep restriction or deprivation[32]. With humans spending a significant proportion of their lives asleep, it is not surprising that the body compensates for these periods of enforced fasting by manifesting a degree of peripheral insulin resistance, thereby maintaining circulating glucose levels. Likewise, there appears to be value in maintaining levels of circulating glucose during periods of perceived stress, in order to sustain cognitive and metabolic function[144].

These results highlight the fact that dietary care is fundamental in those individuals who are more susceptible to glucose metabolic disorders such as diabetes and insulin resistance. Accordingly, the intake of carbohydrates near bedtime should be minimal, since the little evidence that does exist suggests that intake at 22.00 hours entails a considerably stronger insulin and glucose response compared with the same intake at 10.00 hours[176]. This response is compatible with the considerable insulin resistance observed during the night[177]. In addition, it has been suggested that the intake of large amounts of food at night, during the circadian phase when there is lowest insulin sensitivity, might generate effects that predispose individuals to the onset of other metabolic disorders[177].

Fat metabolism during sleep

Recent studies have shown that night workers, with chronic sleep loss, are more predisposed to fat metabolism disorders[9,14,15,28,54,55,178,179]. These individuals present higher serum levels of TAG[9,14,28,54,55,179] and cholesterol[14,15,178] compared with day workers (Table 1).

It is widely recognised that environmental factors, especially feeding, are critical for the development of those problems, and night workers have inadequate eating habits that might contribute to these problems[28,115–118]. Nevertheless, another body of evidence suggests that the problems might be triggered by metabolic disorders that do not depend on food intake[28]; rather, they are a pathogenic effect induced by a mismatch between circadian rhythms, environmental factors and social stress[180]. In other words, the difficulties might arise from a clash between the body clock and the environment[181]. Therefore, we shall now consider alterations of fat metabolism that are triggered by disruption of the sleep–wake rhythm.

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Table 1. Lipid profile disturbances in shift workers

Study	Sample	Design	Results
Ghiasvand *et al.* (2006)[15]	Shift and day workers (*n* 158 and *n* 266 respectively)	Epidemiological study	High total- cholesterol levels: +72·2 % in shift workers and +50·8 % in day workers High LDL-cholesterol levels: +37·3 % in shift workers and +25·4 % in day workers
Van Amelsvoort *et al.* (2004)[228]	Shift and day workers (*n* 239 and *n* 157 respectively)	Cohort	Decreased LDL:HDL-cholesterol ratio: −0·13 mmol/l in day workers and −0·33 mmol/l in shift workers
Karlsson *et al.* (2003)[14]	Day workers and three-shift workers in two plants (*n* 665 and *n* 659 respectively)	Cross-sectional data	High TAG levels: +32·5 % in shift workers and +25·1 % in day workers Low HDL-cholesterol levels: +7·6 % in shift workers and +3·9 % in day workers
Karlsson *et al.* (2001)[18]	Shift and day workers (*n* 7909 and *n* 19 576 respectively)	Cross-sectional data	High TAG levels: +31·5 % in shift workers and +28·5 % in men day workers aged 40 years; +13·7 % in shift workers and +9·6 % in women day workers aged 40 years; +30 % in shift workers and +25·5 % in women day workers aged 60 years Low HDL-cholesterol levels: +26·7 % in shift workers and +17·9 % in men day workers aged 30 years; +27·8 % in shift workers and +20·6 % in men day workers aged 60 years; +18·3 % in shift workers and +8·6 % in women day workers aged 30 years; +14·7 % in shift workers and +10·8 % in women day workers aged 50 years
Nakamura *et al.* (1997)[9]	Three-shift workers, two-shift workers and day workers used as a control group (*n* 33, *n* 27 and *n* 239 respectively)	Cross-sectional study for an industrial male, blue-collar population	High mean total cholesterol levels: 5·70 (SD 1·19) mmol/l in three-shift workers, 4·81 (SD 1·01) mmol/l in two-shift workers and 4·98 (SD 0·95) mmol/l in day workers
Romon *et al.* (1992)[28]	Shift workers and day workers used as control (*n* 73 and *n* 73 respectively)	Cross-sectional survey	High TAG levels: 1·26 mmol/l in shift workers and 1·03 mmol/l in day workers Cholesterol and HDL-cholesterol levels: similar for both groups
Nagaya *et al.* (2002)[56]	Day- and shift workers (*n* 2824 and *n* 826 respectively)	Cross-sectional study	High TAG levels:levels: +28·7 % in day workers and +31·2 % in shift workers
Knutsson *et al.* (1988)[55]	Shift- and day workers (*n* 361 and *n* 240 respectively)	Cross-sectional study	High TAG levels: 1·61 mmol/l in shift workers and 1·43 mmol/l in day workers

Circadian control of fat metabolism

The supply of TAG from the adipocytes results from a balance between the uptake and release of NEFA. These fatty acids are formed by the hydrolysis of circulating TAG by the lipoprotein lipase (LPL) enzyme[182] and by the lipolysis of TAG into NEFA and glycerol by hormone-sensitive lipase[183]. These processes are reciprocally regulated, suggesting an inverse relationship between the activities of LPL and hormone-sensitive lipase[184].

Dramatic diurnal variations in adipocyte lipolysis and lipogenesis occur in mammals. When an animal sleeps, rates of lipolysis increase, resulting in increased release of NEFA into the circulation. In contrast, when an animal is awake, rates of lipolysis decrease, with a concomitant increase in lipogenesis. Diurnal variations in adipose TAG turnover have been explained primarily in terms of reciprocal changes in neurohumoral influences promoting lipolysis and lipogenesis[64]. According to the 'lipogenic–lipolytic' theory of Armstrong[115], daytime food intake is associated with glucose metabolism and fat deposition, and nocturnal fasting with fat metabolism. It follows that fat metabolism will be more active during the night and fat oxidation takes place mainly at this time[167,185].

Hormones that acutely affect lipolysis in human adipocytes are catecholamines (adrenaline and noradrenaline) and insulin[186]. Circulating GH also plays a fundamental role in the regulation of fat metabolism[187,188], generally increasing energy flow in the lipid transportation system by stimulation of lipolysis in adipose tissue[189,190]. Some authors suggest that GH is the main hormone in the control of lipolysis. Interestingly, peak production of this hormone occurs during the night, suggesting that this might be the pathway through which lipolysis is stimulated during sleep[191]. In addition to increases in GH concentration, adrenocorticotropin[192] and prolactin[193] also rise and then fall during the night, and have also been implicated in the regulation of lipolysis[194,195]. These results support the view that the circadian variations of several endocrines modulate both fat deposition and utilisation during a 24 h period.

Circadian rhythm of lipid tolerance and cholesterol biosynthesis

TAG concentrations in the blood show a circadian variation, with maximum values around 03.00 to 04.00 hours and minimum values at noon[196]. Morgan *et al.*[197] observed a marked increase of plasma TAG during the night and its dissociation into two significant components. The first was related to the internal body clock, and the second to the time after waking. This increase in TAG is possibly due to an impairment in lipid tolerance during the night – that is, an impaired postprandial TAG clearance[198] – in turn due to insufficient insulin activity at this time[196,197,199]; the result will be a reduction in the activity of LPL and decreased hydrolysis of plasma TAG[200]. Consequently, concentrations of TAG in the blood will be high during the night[14,200].

Other possible causes of nocturnal lipid intolerance are that the clearance of TAG from the circulation, or the suppression of hepatic synthesis and/or secretion of TAG, is impaired[198]. Lemberger *et al.*[201] state that the α-sub-type hepatic PPAR indirectly influences TAG hydrolysis, and so affects the levels of circulating TAG, via regulation of the synthesis of apo CIII (a lipoprotein fraction that is an inhibitor of LPL).

Studies involving the hepatic lipase enzyme suggest that its activity is positively related to serum concentrations of TAG[202] and that hypertriacylglycerolaemia is a characteristic of hepatic lipase deficiency[203]. Moreover, this enzyme has been implicated in impairment of the postprandial clearance of lipoproteins[204]. Consequently, it is possible that reduced levels of hepatic lipase at night might also contribute to nocturnal lipid intolerance[198].

Advances of the sleep–wake cycle[205] and simulated shift work[206] have both revealed an increase in the postprandial response of TAG in the night. It is known that factors such as the rate of gastric emptying, TAG hydrolysis in the intestine, and intestinal motility might influence the rate of TAG flow into the circulation[207], and insulin resistance has also been suggested to be a factor contributing to this increase in postprandial TAG[208]. Since LPL has a reduced activity at night and plays an important role in the regulation of postprandial TAG clearance[209], higher levels of TAG are observed after food intake at night compared with the daytime[199].

The decrease of lipid tolerance in the night-time can cause high levels of TAG in the circulation, especially in association with food intake. Traditionally, fasting plasma TAG concentrations have not been recognised as an independent risk factor affecting the pathogenesis and progression of CHD[210]. However, more recent epidemiological evidence suggests that the relative importance of TAG as a risk factor for CHD may have been underestimated. A large meta-analysis of seventeen population-based prospective studies showed that plasma TAG concentration was an independent risk factor for CHD[211]. This analysis also showed that plasma TAG concentrations were particularly important in relation to CHD risk in women; an increase in plasma TAG concentration increased cardiovascular risk by 76 % in women compared with 32 % in men[211].

Current evidence[185,212] indicates that the rates of endogenous cholesterol biosynthesis in man are subject to large changes over the course of the day[185,212–214] and increase at night. The concentration of HDL-cholesterol also shows a circadian variation, which is phased opposite to that of TAG, with minimum values at around 04.00 hours and maximum values around noon[196]. Miettinen[213] observed an increase in the cholesterol precursors squalene and lanosterol, with maximum values found between midnight and 04.00 hours. Parker *et al.*[185] observed a nocturnal increase in plasma levels of mevalonate, a precursor of cholesterol biosynthesis whose production is controlled by hydroxymethylglutaryl-CoA reductase[215], and these were correlated with the rate of cholesterol production[216–218].

The behaviour of cholesterol metabolism in human subjects during sleep deprivation[219] and rotating-shift systems[53] has led to the suggestion that changes in the sleep–wake and/or light–dark cycles might be involved. On the other hand, Cella *et al.*[220] observed that, with alterations in the sleep–wake and/or light–dark cycles but with no changes to meal times, the diurnal pattern of cholesterol

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synthesis was unaltered; this result shows that the rhythm is more strongly regulated by meal times rather than by the sleep–wake and light–dark cycles. However, in other studies carried out upon animals, both the circadian rhythm and meal times played important roles in the regulation of the diurnal variation of cholesterol synthesis[205]. It has also been found that eating at night leads to an increase in the LDL:HDL ratio[25].

The increase of GH in SWS might be associated with the increase in cholesterol synthesis during the night[167,185]. Takahashi *et al.*[167] and Parker *et al.*[185] have suggested that GH might have a direct regulating effect on cholesterol synthesis due to the strong temporal association between the increases of GH and mevalonate in the night. The hypothesis is that β-oxidation, which also is increased during the night, might be the pathway for the oxidation of the NEFA to supply the two carbon fragments necessary to condense and form hydroxymethylglutaryl-CoA, the immediate precursor of mevalonate[167,185]. However, Boyle *et al.*[221] and Cella *et al.*[220] observed that an abrupt change in sleep time, with the resulting change in release of GH, was not associated with detectable changes in cholesterol synthesis.

Cella *et al.*[220] showed that TSH, normally inhibited by nocturnal sleep, had a peak coinciding with the maximum rate of cholesterol synthesis on days with normal amounts of sleep at night; by contrast, a twofold increase in the amplitude of the TSH rhythm was observed during sleep deprivation[222–224]. This major alteration in the profile of TSH concentration was associated with a modest elevation in the peak of the rhythm of cholesterol synthesis, and these simultaneous changes were reflected in an increase in the cross-correlation between them[220]. These observations support the view that TSH might exert an effect on cholesterol synthesis, mainly during sleep deprivation[220]. Under normal sleep–wake conditions, the diurnal variation in secretion of thyroid hormone has a low amplitude and its circadian rhythm might go undetected[224,225]. During sleep deprivation, by contrast, a nocturnal increase in this hormone parallels an increase of TSH[225]. Since the activity of the hydroxymethylglutaryl-CoA reductase enzyme is influenced by this thyroid hormone[226,227], it is conceivable that the activation of the pituitary–thyroid axis during sleep deprivation exerts a modest influence on cholesterol synthesis[220].

Therefore, it is possible that the normal increases in levels of TAG and cholesterol at night is accentuated by sleep loss and abnormal nocturnal food intake, thus contributing to the risk of CVD. Many studies show that physiological events that control lipid metabolism are strongly influenced by the sleep–wake cycle. Thus, it is reasonable to suppose that interruption of the sleep–wake cycle, resulting in a decreased sleep time, can impair lipid metabolism. This impairment is demonstrated in studies that show that shift workers, who sleep less than 5 h on their working days[16], have a greater frequency of disorders of lipid metabolism.

The role of sleep loss in fat metabolism is an exciting new field of study, and is believed to result in an increased incidence of dyslipidaemias. Elucidation of the mechanisms involved might have profound implications for an understanding of these disorders. In the future, it will be necessary to investigate whether these processes have an impact on both susceptibility to dyslipidaemias and on susceptibility to the development of the potentially debilitating co-morbidities associated with disorders of fat metabolism. Nevertheless, it might prove difficult to show unequivocally that there is a causal relationship between sleeps of short duration and problems with lipid metabolism.

Conclusion

We conclude that sleep affects the body's nutritional control, and that alterations to an individual's sleep pattern might stimulate food intake and so contribute to the onset of disorders of glucose and fat metabolism. Sleep loss also contributes to the onset of insulin resistance, type 2 diabetes and obesity, as direct consequences of the influence of sleep on glucose metabolism and of an alteration in feeding behaviour generated by appetite dysregulation. It is also important to acknowledge that the laboratory analyses do not prove causality between sleeps of short sleep duration and diabetes. However, the current experimental literature involves only very small numbers of participants who are nearly all men and young. Experimental evidence from older individuals and from women of all ages is required to confirm that sleep loss causes metabolic problems in the population as a whole. The increase in blood lipids during the night, associated with altered eating patterns, seems to contribute to the onset of dyslipidaemias. Indeed, not only adequate sleep time but also balanced eating habits are of fundamental importance for the maintenance of health, and both should be encouraged by health professionals. In particular, individuals with chronic sleep loss, such as night workers, deserve specific nutritional advice. Further studies are required so that the detailed needs of these individuals can be better understood.

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