BRIEF REVIEW

SLEEP AND METABOLIC CONTROL: WAKING TO A PROBLEM?

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SUMMARY

1. The aim of the present review is to outline: (i) the association between sleep and metabolism; (ii) how sleep duration influences the development of disease; and (iii) how sex differences, ageing and obesity may potentially influence the relationship between sleep, metabolic control and subsequent disease.

2. Sleep is associated with a number of endocrine changes, including a change in insulin action in healthy young individuals. Sleep duration shows a prospective U-shaped relationship with all-cause mortality, cardiovascular disease and Type 2 diabetes.

3. Chronic sleep restriction is becoming more common. Experimental sleep restriction impedes daytime glucose control and increases appetite.

4. The sex hormones oestrogen and testosterone influence sleep duration and quality and may account for sex differences in the prevalence of sleep-related disorders.

5. Ageing is associated with a decreased sleep duration, decreased muscle mass and impaired insulin action.

6. Obesity impairs insulin action and is associated with the incidence and severity of obstructive sleep apnoea.

7. Sleep plays an integral role in metabolic control. Consequently, insufficient sleep may represent a modifiable risk factor for the development of Type 2 diabetes. The challenge ahead is to identify how sex differences, ageing and obesity could potentially influence the relationship between sleep and metabolism.

Key words: ageing, appetite, diabetes, metabolism, obesity, sex, sleep.

INTRODUCTION

Over the past three decades, there has been a marked world-wide increase in the number of people diagnosed with obesity¹ and Type 2 (adult-onset) diabetes.² The continued rise in childhood obesity and Type 2 diabetes³ will ensure that these metabolic disorders will continue to be of significance to worldwide health for decades to come.

By 2010, diabetes is predicted to affect 221 million people globally, rising 46% from the year 2000.⁴ Diet and exercise are typically the foci of therapy for obesity and Type 2 diabetes. However, emerging evidence suggests that sleep duration may represent a significant modifiable risk factor for the development of cardiovascular and metabolic diseases; in particular, the present review focuses on Type 2 diabetes.

The primary aim of the present paper is to review the available literature investigating the interaction between metabolism and sleep. We also aim to provide information that may guide future research and assist in the formation of evidence-based recommendations concerning the interactions between age, gender and obesity on metabolism and sleep.

SLEEP AND METABOLIC CONTROL

The body attempts to tightly control the level of circulating substrates. Prolonged elevation of circulating glucose, as seen in people with diabetes, can result in micro- and macrovascular compromise. In contrast, very low circulating blood glucose levels impair cognitive function, tissue development and can ultimately induce coma. Glucose is the only substrate that can be metabolized by the brain. As such, it is not surprising that there are multiple feedback pathways maintaining and regulating circulating glucose.

The body balances the post-prandial or hepatic appearance of glucose against the uptake of glucose by skeletal muscle and the liver, signalled by insulin, in order to regulate circulating glucose levels. Glucose control varies diurnally, to accommodate enforced periods of fasting (sleep) and with perceived stress (any action that takes the body from homeostasis), in order to maintain the supply of glucose to the brain. We will now briefly review the putative mechanisms regulating glucose uptake/insulin sensitivity and appetite control, how glucose control and appetite are influenced by sleep and, finally, review data on how these are affected by reduced sleep duration.

Neuroendocrine control of metabolism

During periods of perceived stress, the body moderates the action of insulin in order to preserve levels of circulating glucose. The hypothalamic–pituitary–adrenal axis (HPA) and sympathetic nervous system signal perceived stress on different organs. The products of the HPA axis (cortisol) and sympathetic system (catecholamines) counter the effects of insulin, thus maintaining levels of circulating glucose. Adipose tissue also has a powerful
influence on insulin action through the release of fatty acids and adipocyte-derived hormones, such as resistin, leptin and adiponectin. Adipose tissue is directly involved in the regulation of food intake because leptin provides a signal of satiety to the hypothalamus. Circulating leptin levels counter-regulate levels of ghrelin, a peptide released by the stomach that stimulates appetite. The central nervous system (CNS) has sympathetic and parasympathetic connections with abdominal fat depots, which can influence free fatty acid release and gene expression of the adipokines resistin and leptin. The ability of the CNS to sense metabolic and endocrine signals, alongside innervation of adipose tissue and the HPA axis, provides a feedback loop and control mechanism between the brain, adipose tissue, insulin action and appetite.

Sleep and glucose control

During sleep, the body must maintain circulating blood glucose levels so that the brain continues to receive adequate substrates, despite the absence of food intake (for a review, see Van Cauter et al.). Results from studies using continuous venous infusion of glucose show that both nocturnal and daytime sleep induce glucose intolerance (Fig. 1), as shown by an increase in circulatory glucose (20–30%) and insulin levels (20–30%). A proportion of the decreased glucose uptake is probably attributable to decreased muscle tone, reduced glucose requirement by the brain during slow-wave sleep and the release of growth hormone during slow-wave sleep (Fig. 1). Sleep is also associated with an increased rhythmicity of insulin release. Despite these changes, it is apparent that the body adapts to reduced food intake during sleep by inducing a degree of peripheral insulin resistance. During the later stages of sleep, insulin action improves, normalizing circulating glucose levels in preparation for wakefulness and food intake.

The relationship between sleep and appetite is an emerging research field, growing as the understanding of neuroendocrine control of caloric intake builds. Individuals in the Wisconsin Sleep Cohort (n = 1024) show an association between shorter sleep durations and reduced leptin and elevated ghrelin levels, suggesting that sleep restriction may increase appetite. Furthermore, leptin levels appear to be markedly increased by being asleep, but are also under circadian control, with levels lowest in the morning and highest in the evening, promoting the feeling of hunger in the morning and satiety in the evening (Fig. 1). Sleep is also associated with an increased rhythmicity of insulin release. Despite these changes, it is apparent that the body adapts to reduced food intake during sleep by inducing a degree of peripheral insulin resistance. During the later stages of sleep, insulin action improves, normalizing circulating glucose levels in preparation for wakefulness and food intake.

The first large-scale study to provide evidence that abnormal sleep durations were associated with health outcomes was the Cancer Prevention Study in 1964. Analyses of over 1 million participants revealed that individuals with 7 h self-reported sleep duration had the lowest risk of death from cancer and other causes. This finding has been replicated in subsequent studies and has led to the hypothesis that chronic sleep restriction is associated with increased risk of diabetes and obesity.

THE IMPORTANCE OF SLEEP: EPIDEMIOLOGY

According to the Centers for Disease Control and Prevention, chronic sleep restriction is increasing in the US (www.cdc.gov/mmwr; accessed 23 September 2005). If chronic sleep restriction is increasing elsewhere and is definitively shown to cause diabetes and/or obesity, then it is likely to become recognized as an important determinant of population health.

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the lowest mortality in 17 of the 18 age-sex groups. Regularly sleeping less than 7 h, or more than 7 h, was associated with increased mortality, after controlling for insomnia and use of sleeping pills. The follow-up Cancer Prevention Study II (CPSII) observed 1.1 million people prospectively over 6 years from 1982.21 Again, both short and long self-reported sleep durations were independently and prospectively associated with increased risk of mortality after controlling for 31 covariates, including a range of comorbidities and body mass index (BMI). These observations have also been reported by a number of other smaller studies22,23 (see Table 1 for a selected summary). Collectively, these studies expose a U-shaped relationship between sleep duration and all-cause mortality, suggesting that there may be an optimal sleep duration for healthy living.24

More specific studies have examined the relationship between sleep duration and metabolic/cardiovascular complications (Table 1). Interestingly, the same U-shaped relationship exists between sleep duration and the incidence of Type 2 diabetes,25,26 coronary artery disease27 and hypertension,28 independent of a number of confounding variables. Cross-sectional analyses 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 (SDB),29 a condition that may also independently influence glucose control.30,31

The studies in Table 1, although not a complete review, present the consistent relationship between sleep duration and both all-cause mortality and metabolic/cardiovascular compromise. However, it should be noted that all these studies use subjective reports as an estimation of sleep duration. The measurement error associated with single subjective reports may potentially dilute the real effect of sleep restriction on morbidity/mortality because people may over- or underestimate their true sleep durations. Sleep durations may also have changed over the study periods.

Extended sleep duration has also been shown to be independently associated with mortality.21–23 Although we review the plausible mechanisms to explain why short sleep may be harmful, there is neither evidence nor consensus as to probable mechanisms for why long sleep may be harmful. Long sleep may be a correlate of any number of harmful conditions or a very early marker of chronic disease. For instance, long sleep duration is associated with lower socioeconomic status and depression.32 Additional non-controlled factors that are found with low-socioeconomic status (i.e. residual confounding) may go much of the way in explaining why long sleep is associated with harm. Some of these include poor housing, healthcare, diet and low levels of physical activity. The relationship between long sleep duration and mortality is an area that will require further investigation over the coming years.

Other unidentified factors may better explain why poor outcomes, diabetes in particular, are associated with short sleep. As such, it is necessary to look for experimental evidence to confirm the findings of these large observational studies.

THE IMPORTANCE OF SLEEP RESTRICTION: MECHANISMS

Glucose control

Despite the substantial epidemiological evidence associating sleep restriction with impaired glucose control, only two well-controlled laboratory trials have been performed to date. The first of these studies observed the effect of sleep restriction for 6 days (4 h sleep opportunity/night) followed by 7 days recovery sleep (12 h sleep opportunity/night) in 11 healthy young men.33 Intravenous glucose tolerance tests (IGTT) revealed that the area under the curve of the integrated glucose and insulin curves was > 50% greater when subjects were sleep restricted, relative to the sleep extension state. The same research group again studied glucose and insulin in response to a frequently sampled IGTT following 2 days of sleep restriction in 12 healthy young males.34 Findings from this investigation showed that sleep restriction produced an approximate 40% reduction in glucose tolerance following sleep restriction. Importantly, although values were in the normal range when fully rested, sleep-restricted subjects showed glucose levels comparable to older individuals with impaired glucose tolerance.

Appetite

In addition to the impairment of glucose control, sleep restriction appears to be accompanied by an alteration in appetite control.34 In the same experiment described above of only 2 nights of sleep restriction to 4 h per night in 12 healthy young men, the peak leptin concentration and 24 h variation are, respectively, reduced by 19 and 20%.34 At the same time, ghrelin concentration was increased and the resultant ghrelin-to-leptin ratio increased by > 70%. Interestingly, 70% of the change in reported hunger could be explained by the ghrelin-to-leptin ratios, suggesting a strong neuroendocrine control of food intake. This also seemed to result in a > 30% greater desire for calorie-dense foods, such as cake and potatoes.34 The increased caloric intake would relate to a 350–500 kcal/day caloric excess and, thus, increasing weight gain, which, in turn, will further influence glucose control and the development of obesity.

SEX DIFFERENCES AND SLEEP

Sleep: General

There are significant differences in the prevalence of sleep disorders between men and women, suggesting that sleep physiology could possibly be influenced by sex (for a more detailed review, see Manber and Armitage35). Women have a greater prevalence of insomnia16 and men have approximately twice the prevalence of sleep apnoea.17 Aside from sleep disorders, men and women report different levels of satisfaction with their sleep, with women typically reporting decreased subjective sleep quality compared with age-matched male subjects, irrespective of age.38,39 Differences in perceived sleep quality include taking longer to fall asleep (sleep latency) and more awakenings during the sleep period. In contrast with self-reports, objective assessments typically demonstrate better sleep in females compared with males. Middle-aged and elderly women experience higher sleep quality, more slow-wave sleep (SWS), more REM sleep and fewer awakenings compared with age-matched males.39,40 Even the sleep complaints commonly associated with menopause may be largely subjective, with the largest study using polysomnography, the gold-standard objective measure of sleep, finding that objective sleep quality is better during and after menopause than before it.41 In younger subjects, fewer gender differences have been demonstrated, but females have been reported to experience shortened sleep latencies,32 fewer awakenings,32 less SWS in the second half of the night42 and overall higher sleep quality compared with males. As
**Table 1**  Excess risk of mortality and morbidity with different durations of sleep: risk expressed relative to a reference of 7 or 8 h sleep per night (see legend for a guide as to whether values are hazard/odds ratio or relative risk)

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Sample size</th>
<th>Outcome</th>
<th>3 h (95% CI)</th>
<th>4 h (95% CI)</th>
<th>5 h (95% CI)</th>
<th>6 h (95% CI)</th>
<th>7 h (95% CI)</th>
<th>8 h (95% CI)</th>
<th>9 h (95% CI)</th>
<th>≥ 10 h (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Prevention Study II: Women</td>
<td>6 years</td>
<td>636 095</td>
<td>All-cause mortality*</td>
<td>1.33 (1.08–1.64)</td>
<td>1.11 (1.01–1.22)</td>
<td>1.07 (1.01–1.13)</td>
<td>1.07 (1.03–1.11)</td>
<td>Ref</td>
<td>1.13 (1.09–1.16)</td>
<td>1.23 (1.17–1.28)</td>
<td>1.23 (1.17–1.28)</td>
</tr>
<tr>
<td>Cancer Prevention Study II: Men</td>
<td>6 years</td>
<td>480 841</td>
<td>All-cause mortality*</td>
<td>1.19 (0.96–1.47)</td>
<td>1.17 (1.06–1.28)</td>
<td>1.11 (1.05–1.18)</td>
<td>1.08 (1.04–1.11)</td>
<td>Ref</td>
<td>1.12 (1.09–1.15)</td>
<td>1.17 (1.13–1.21)</td>
<td>1.34 (1.28–1.40)</td>
</tr>
<tr>
<td>Japan Collaborative Cohort: Women</td>
<td>10 years</td>
<td>60 158</td>
<td>All-cause mortality†</td>
<td>–</td>
<td>1.83 (1.20–2.81)</td>
<td>1.18 (0.90–1.53)</td>
<td>1.17 (0.99–1.39)</td>
<td>Ref</td>
<td>1.35 (1.17–1.56)</td>
<td>1.57 (1.26–1.96)</td>
<td>2.12 (1.67–2.68)</td>
</tr>
<tr>
<td>Japan Collaborative Cohort: Men</td>
<td>10 years</td>
<td>43 852</td>
<td>All-cause mortality‡</td>
<td>–</td>
<td>0.88 (0.44–1.78)</td>
<td>1.07 (0.83–1.38)</td>
<td>1.11 (0.95–1.28)</td>
<td>Ref</td>
<td>1.19 (1.07–1.32)</td>
<td>1.27 (1.08–1.48)</td>
<td>1.75 (1.46–2.09)</td>
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<tr>
<td>Nurses Health Study</td>
<td>10 years</td>
<td>71 617</td>
<td>All-cause mortality§</td>
<td>–</td>
<td>–</td>
<td>1.12 (0.68–1.84)</td>
<td>0.91 (0.65–1.28)</td>
<td>0.83 (0.60–1.14)</td>
<td>Ref</td>
<td>1.45 (0.89–2.36)</td>
<td>–</td>
</tr>
<tr>
<td>Sleep Heart Health Study</td>
<td>Cross-sectional</td>
<td>1486</td>
<td>Type-2 diabetes**</td>
<td>–</td>
<td>–</td>
<td>2.51 (1.57–4.02)</td>
<td>1.66 (1.15–2.39)</td>
<td>Ref</td>
<td>1.79 (1.08–2.96)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Massachusetts Male Ageing</td>
<td>15 years</td>
<td>1139</td>
<td>Type-2 diabetesδ</td>
<td>–</td>
<td>–</td>
<td>1.95 (1.06–3.58)</td>
<td>1.95 (1.06–3.58)</td>
<td>Ref</td>
<td>1.41 (0.78–2.55)</td>
<td>3.12 (1.53–6.37)</td>
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<tr>
<td>Nurses Health Study</td>
<td>10 years</td>
<td>70 026</td>
<td>Type-2 diabetes†</td>
<td>–</td>
<td>–</td>
<td>1.18 (0.96–1.44)</td>
<td>1.10 (0.97–1.25)</td>
<td>1.02 (0.91–1.16)</td>
<td>Ref</td>
<td>1.29 (1.05–1.59)</td>
<td>–</td>
</tr>
<tr>
<td>Nurses Health Study</td>
<td>10 years</td>
<td>71 617</td>
<td>Coronary artery disease†</td>
<td>–</td>
<td>–</td>
<td>1.39 (1.05–1.84)</td>
<td>1.18 (0.98–1.43)</td>
<td>1.10 (0.92–1.31)</td>
<td>Ref</td>
<td>1.37 (1.02–1.85)</td>
<td>–</td>
</tr>
<tr>
<td>Nurses Health Study</td>
<td>10 years</td>
<td>71 617</td>
<td>Non-fatal MI‡</td>
<td>–</td>
<td>–</td>
<td>1.52 (1.08–2.14)</td>
<td>1.32 (1.05–1.65)</td>
<td>1.23 (0.93–1.52)</td>
<td>Ref</td>
<td>1.35 (0.93–1.95)</td>
<td>–</td>
</tr>
<tr>
<td>Nurses Health Study</td>
<td>10 years</td>
<td>71 617</td>
<td>Fatal CHD§</td>
<td>–</td>
<td>–</td>
<td>1.12 (0.68–1.84)</td>
<td>0.91 (0.65–1.28)</td>
<td>0.83 (0.60–1.14)</td>
<td>Ref</td>
<td>1.45 (0.89–2.36)</td>
<td>–</td>
</tr>
<tr>
<td>National Health and Nutrition (US)</td>
<td>9 years</td>
<td>4810</td>
<td>HT§</td>
<td>–</td>
<td>–</td>
<td>1.32 (1.02–1.71)</td>
<td>1.01 (0.82–1.23)</td>
<td>Ref</td>
<td>1.12 (0.84–1.50)</td>
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</tr>
</tbody>
</table>

*Hazard ratios were adjusted for age, race, education, occupation, marital status, exercise level, smoking at baseline, years of smoking, church-going, fat and fibre intake, insomnia frequency, subjective ‘sickness’, ‘upset’, body mass index (BMI), leg pain, history of heart disease, hypertension, cancer, diabetes, stroke, bronchitis, emphysema, kidney disease, sleeping pills, antihypertensives, diuretics, Tylenol and Tagamet.21

†Relative risk was adjusted for age, perceived mental stress, depressive symptoms, smoking, drinking, physical activity, BMI, marital status, education and any history of myocardial infarction (MI), stroke or cancer.23

**Figures are odds ratio and were controlled for age, sex, race/ethnicity, severity of sleep disordered breathing, study site and waist girth.29

δ, men only and relative risk was adjusted for age group, hypertension, smoking, self-rated health status, waist and education (all baseline).25

§, women only and relative risk was adjusted for BMI, shift work (from 1988), hypercholesterolaemia, smoking, snoring, exercise, alcohol consumption, depression (from 1992), aspirin use (from 1988) postmenopausal hormone use, family history of MI, Type 2 diabetes and hypertension.21

1Hazard ratios adjusted for daytime sleepiness, depression, physical activity, alcohol consumption, salt consumption, smoking, pulse rate, gender, age, education, ethnicity, diabetes and being overweight/obese.24
such, the differences in both sleep duration and quality of sleep in men and women suggest that sex differences may play a role in the relationship between sleep and metabolic control. To date, no studies have investigated whether gender changes the effects of sleep restriction on metabolic control.

Appetite regulation

Independent of adiposity, body fat composition or BMI, women have been shown to have significantly higher fasting leptin levels than men.44,45 Many studies in children, with ages ranging from 5 to 19 years, show that fasting leptin levels are consistently higher in females than males, independent of measures of adiposity.46–48 Repeated sampling throughout the day has revealed that women consistently have leptin levels double that of men, but women maintain nearly identical 24 h and ultradian patterns to men.49 Further studies have shown that sex hormones, in particular oestrogens, can influence adipose tissue function through specific receptors.50,51 As such, oestrogen may play an important role in circulating leptin, possibly through increased adipose tissue expression of the ob gene and increase leptin secretion.52,53

Ghrelin was first discovered in 199954 and, thus, only a limited number of studies has investigated sex differences, with even fewer looking at changes with sleep. Men with hypogonadism present with reduced circulating ghrelin levels, which are normalized after testosterone treatment.55 Women with and without polycystic ovary syndrome show an inverse relationship between androstendione levels and ghrelin,56 suggesting an association between sex hormones and ghrelin. Although sex differences in circulating ghrelin may13 or may not57 exist during wakefulness, during sleep there does not appear to be any difference.19 However, it should be noted that there is a lack of consensus about changes in ghrelin during sleep,19,58 although these may be methodological as opposed to physiological differences and, as such, further examinations are warranted.

Cortisol

The literature does not clearly show a sex difference in circulating cortisol over a 24 h period. Small studies suggest that there are no differences between men and women. However, a larger, better-powered study revealed that women in young adulthood demonstrated lower variation in circulating cortisol over 24 h than men.59 The reduced 24 h variation in cortisol in young women was attributed to decreased circadian amplitude and increased rate of return to baseline. Interestingly, the sex differences observed in young adults were amplified with ageing,59 suggesting that the decline in HPA axis function accompanying ageing may be different between men and women.

Sex hormones

The differences in sleep characteristics between men and women may be explained by differences in the levels of sex hormones and/or by secondary factors, such as regional fat distribution. Two of the major hormones involved in sleep differentiation between men and women are progesterone and oestrogen.

Exogenous administration of progesterone produces sedative effects in both women60 and men.61 Oestrogen replacement therapy (ERT) has been shown to reduce sleep disturbance and insomnia62,63 and produce shortened sleep latencies, reduced nocturnal restlessness plus reduced wake after sleep onset (WASO).64 It is hypothesized that the beneficial effects of oestrogen on sleep are mediated via a reduction in climacteric symptoms, in particular, hot flushes.65 However, the effects of oestrogen on sleep may not be mediated only via a reduction in climacteric symptoms. For instance, ERT administration has been reported to improve sleep in asymptomatic perimenopausal women.64 It has been proposed that increased oestrogen levels may improve sleep by reducing the impact of stress or nocturnal disturbances.64,65 Given the large number of women experiencing sleep disturbance and consequent decreases in waking functions, this is an area of significant concern that has not, to date, been adequately addressed.

In contrast, increased levels of testosterone, achieved via exogenous administration, have been reported to increase sleep disturbance in older men.66 It may be hypothesized that, in females, the increase in endogenous testosterone levels coincident with the decrease in oestrogen levels associated with peri- and menopause may also contribute to the increased prevalence of SDB after menopause.67

AGEING AND SLEEP

Sleep: General
An increase in the prevalence of sleep disturbance is commonly associated with increasing age in both males and females (for a quantitative review, see Ohayon et al.68). The most commonly reported sleep difficulties in individuals aged 55 years or older include an increased number of awakenings across the night69 and an increased time to return to sleep.70,71 Factors that may underlie this increased prevalence include depression, anxiety, pain, sleep disorders and other medical disorders that disturb sleep and menopause.72,73

Appetite regulation

Ageing is ordinarily characterized by decreased rhythmicity and peak amplitude of circadian rhythms.74 Although fasting leptin levels are elevated in the elderly,75 the circadian variation in leptin has been shown to be preserved with ageing, presenting an earlier acrophase and dampened peak compared with BMI-matched middle-aged individuals.76 Other studies have reported that ageing influences factors controlling leptin release,77 such as body temperature,78 growth hormone79 and cortisol.80 Ageing is associated with an increase in adipose tissue,81 suggesting that circadian variation in leptin may be suppressed by the increased adiposity accompanying ageing. In addition, as people age, adipocytes appear to become less sensitive to catecholamines81 and insulin,82 both influential factors in adipocyte function.

The decreased food intake with ageing has been associated with a reduction in circulating ghrelin.83 Other studies have failed to repeat these observations75 and suggest that concurrently elevated levels of insulin and leptin may account for the low sensitivity to ghrelin in the elderly. The strong correlation between ghrelin and BMI with ageing84 supports the notion that ghrelin may be influenced by other factors associated with adiposity, such as circulating levels of insulin and leptin. Irrespective of whether
ghrelin is suppressed or not, the high levels of leptin associated with ageing are likely to dominate over the effects of ghrelin, thus suppressing appetite. Further studies looking at the circadian variation of ghrelin with ageing alongside identifying differences in the different isoforms of ghrelin are required.

Cortisol

Age-related changes in cortisol activity may be derived from a number of mechanisms (for a review, see Ferrari et al.95). The HPA feedback control can be influenced by ageing centrally (the degeneration of neurons sensitive to cortisol can produce changes in cortisol levels and activity) and peripherally (reduced sensitivity of target tissues owing to decreased steroid receptor numbers or reactivity). Typically, with increasing age, a decrease in the amplitude of the circadian rhythm of peripheral cortisol is observed.84 In addition, nocturnal elevations in cortisol levels in elderly subjects compared with younger subjects have been reported.84 However, the increase in nocturnal cortisol levels may be related to the increased degree of sleep disturbance commonly reported with increasing age.87

Sex hormones

A possible sex–age–sleep interaction exists, with the onset of the menopause producing significant endocrine changes,88 in particular in sex hormones (see Sex differences and sleep section). For instance, whereas men gradually become increasingly prone to SDB, women have a more abrupt increase in risk associated with menopause.89 Men also experience an age-dependent decline in levels of circulating testosterone.89 The decrease in testosterone alongside a decrease in sleep duration/quality would appear paradoxical. Consequently, it is likely that factors other than testosterone dominate sleep in elderly men.

OBESITY AND SLEEP

Sleep: General

The close association between weight gain and the development of SDB means that very little is known about the direct effect of weight gain and obesity on sleep after controlling for the effects of SDB (for a review, see Young et al.89). Characterized by repeated occlusion of the upper airway during sleep, SDB results in periods of intermittent hypoxaemia85 and is also independently associated with impaired glucose control.31 The repeated arousals characterized by SDB directly affect sleep architecture and induce sleep fragmentation. It remains to be determined what the direct effect of obesity is on sleep.

Appetite regulation

Because leptin is released by adipose tissue, it is not surprising that the accumulation of adipose tissue influences circadian variation of leptin levels. Body mass index or body fat mass have both been reported to be positively correlated with serum leptin concentrations.92 Frequent sampling of leptin over a 24 h period shows that circulating levels of leptin are consistently elevated with obesity,93 with higher leptin concentration per kg fat mass, suggesting increased expression of genes relating to leptin production (ob).94 The literature is not clear on whether obesity influences circadian variation in leptin.93,94 Weight loss does produce a decrease in circulating leptin, creating a paradox where the stimulus for satiety decreases alongside weight loss, thus increasing the desire to eat and the propensity for weight regain.95 This reinforces the need for observing multiple endocrine markers for appetite regulation during weight loss.

Levels of circulating ghrelin are reported to be decreased with obesity96 and improve with weight loss.97 The increase in 24 h plasma ghrelin profiles after weight loss, elevation before feeding and reduction after a meal is consistent with the role of ghrelin in long-term bodyweight regulation.97 In contrast with non-obese individuals, obesity has been shown to impair the normal elevation of ghrelin in the evening.93

Cortisol

Recent evidence suggests that obesity, whether central or subcutaneous, is related to disturbances in the HPA axis (for a review, see Dallman et al.98). Patients with Cushing’s syndrome and subclinical Cushing’s, a condition characterized by central obesity, present with increased cortisol output, dyslipidaemia, insulin resistance and cardiovascular disease risk.99 Although obesity is not generally associated with a change in daytime cortisol levels100 or cortisol at waking,101 obesity is associated with a delayed wake-related increase in cortisol (wake + 30 min).102 Despite the apparent normality of daytime circulating cortisol, obesity is associated with an increased turnover of cortisol.100 The physiological relevance of increased cortisol following waking and in obesity is not known. It is possible that the orexigenic effects of cortisol may produce an elevation of leptin in order to regulate appetite.102

Sex hormones

Obesity is accompanied by a number of endocrine changes, including an alteration in circulating hormone levels. These alterations are the product of altered hormone secretion, metabolism, transport and/or impaired action at the target tissue (for a more detailed review, see Pasquali103). In women, obesity influences sex steroid (e.g. oestrogen, progesterone) balance, irrespective of whether the woman is pre- or post-menopausal. Circulating androgens and oestrogen are influenced directly by obesity and indirectly through sex hormone binding globulin (SHBG). The SHBG binds strongly to testosterone and, to a lesser extent, with oestradiol,104 preventing metabolism and maintaining circulating hormone levels. In women, SHBG is inversely related to central obesity. In turn, the reduction in SHBG produces an increased clearance of SHBG-bound steroids, such as testosterone. In comparison, men show decreasing testosterone with increasing obesity.105 Similar to women, the reduction in testosterone is typically associated with a decrease in SHBG.106

CONCLUSIONS AND COMMENT

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 inducing a degree of peripheral insulin resistance, therefore maintaining circulating glucose levels. Likewise, it appears logical to maintain levels of circulating glucose during periods of perceived stress, in order to sustain cognitive and metabolic function. In line with these observations, acute reduction of sleep duration decreases peripheral insulin sensitivity and promotes hunger, an
 appropriate stress response. If decreased insulin action and increased caloric intake are sustained for any period of time, they may influence the development of Type 2 diabetes and weight gain. Outside the controlled laboratory environment, cross-sectional and prospective population-based cohorts reveal that self-reported sleep durations of less than or more than 7 h are associated with increased risk of metabolic diseases and mortality.25,29,31 Combined, these physiological, experimental and epidemiological studies provide substantial evidence of a relationship between sleep, metabolic control and the development of disease. However, even in large and well-designed epidemiological cohort studies, significant associations between short sleep durations and morbidity/mortality should not be interpreted in isolation as final proof that chronic sleep restriction causes morbidity. Even though the existing experimental evidence confirms that the associations in the cohort studies could be causal, more experimental evidence is needed. The current experimental literature involves only very small numbers of participants who are all men and all young (<35 years). The cohorts, in contrast, include much older people and also women. The epidemiological study evidence we have presented suggests that there are important sleep and endocrine differences between men and women and between older and younger people. Experimental evidence from older people and in women of all ages is required to confirm the suggestion from the observational studies that sleep restriction causes poor glucose control and is thus a likely causal factor in the development of Type 2 diabetes and weight gain.

What remains to be determined is how these findings translate into meaningful guidelines. It is clear that sex/stress hormones, obesity and ageing influence sleep duration/quality, either independently or interdependently. The sex hormones oestrogen and testosterone affect sleep duration and sleep quality. Ageing is associated with decreased sleep duration and an alteration in circulating sex hormones. Obesity appears to suppress circadian endocrine variation and circulating sex hormones. With such a pronounced variation in these groups, future studies are required to address how the relationship between sleep duration and metabolic control are influenced by sex, age and obesity, either individually or in combination. Irrespective of these comments, sleep duration presents a potentially major modifiable risk factor for the development of impaired glucose control and weight gain. The challenge for the coming years is to better understand the specificity and sensitivity of sleep and metabolic control in the general population.

ACKNOWLEDGEMENTS

The authors acknowledge the support of the Woolcock Institute of Medical Research. This work was supported by the National Health and Medical Research Council of Australia (no. 352483). NLR was supported by a Howard Florey Centenary Research Fellowship (no. 307719) and NSW BioFirst awards for this work.

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