Early report

Impact of sleep debt on metabolic and endocrine function

Karine Spiegel, Rachel Leproult, Eve Van Cauter

Summary

Background Chronic sleep debt is becoming increasingly common and affects millions of people in more-developed countries. Sleep debt is currently believed to have no adverse effect on health. We investigated the effect of sleep debt on metabolic and endocrine functions.

Methods We assessed carbohydrate metabolism, thyrotropic function, activity of the hypothalamo-pituitary-adrenal axis, and sympathovagal balance in 11 young men after time in bed had been restricted to 4 h per night for 6 nights. We compared the sleep-debt condition with measurements taken at the end of a sleep-recovery period when participants were allowed 12 h in bed per night for 6 nights.

Findings Glucose tolerance was lower in the sleep-debt condition than in the fully rested condition ($p<0·02$), as were thyrotropin concentrations ($p<0·01$). Evening cortisol concentrations were raised ($p=0·0001$) and activity of the sympathetic nervous system was increased in the sleep-debt condition ($p<0·02$).

Interpretation Sleep debt has a harmful impact on carbohydrate metabolism and endocrine function. The effects are similar to those seen in normal ageing and, therefore, sleep debt may increase the severity of age-related chronic disorders.

Lancet 1999 **354:** 1435–39

Introduction

Voluntary sleep curtailment has become common. "Normal" average sleep duration has decreased from about 9 h per night in 1910 to about 7·5 h currently[1] to create maximum time for work and leisure activities·[2] Additionally, to meet the demands of around-the-clock production, many shift workers sleep, on average, less than 5 h per work day.[3] Sleep curtailment is purported to be harmless and efficient. It has been suggested that a "normal" night's sleep of about 8 h is composed of a 4–5 h period of core sleep, including most of deep non-rapid-eye-movement (non-REM) sleep, and optional sleep.[4] It has been proposed that optional sleep could be progressively removed without inducement of increased daytime sleepiness, mood changes, or detectable decline in cognitive function.[4] Some studies have shown that participants could adapt to a progressive curtailment of their usual sleep period by 2–3 h per night with no substantial alterations in mood and vigilance,[4,5] but other studies have provided strong evidence to the contrary.[6] Experimental extension of the time spent in bed to 14 h per day over 1 month showed that a normal 8 h night does not meet the sleep needs of healthy young adults, who may carry a substantial sleep debt even in the absence of obvious efforts to curtail sleep.[7]

No study has assessed the potential health impact of chronic sleep debt. Despite well documented modulation by sleep of metabolic and endocrine regulation,[8] immune function,[9] and cardiovascular variables,[10] the consensus is that sleep is for the brain, not for the rest of the body,[4,11] and that sleep debt has little or no effect on peripheral function.[4,12] We investigated metabolic and hormonal variables in people in whom sleep had been restricted and extended.

Methods

Protocol

The protocol was approved by the University of Chicago Institutional Review Board and all participants gave written informed consent.

We included 11 healthy young men aged 18–27 years, who spent 16 consecutive nights in the clinical research centre, during which we restricted and extended the time they spent in bed. On the first 3 nights they spent 8 h in bed from 2300 h to 0700 h (baseline, days B1–B3), for 6 nights they were in bed for 4 h from 0100 h to 0500 h (sleep-debt condition, days D1–D6), and on the last 7 nights they were in bed for 12 h from 2100 h to 0900 h (sleep-recovery condition, days R1–R7) to recover from the sleep debt and to regain the number of bedtime hours lost during the period of sleep restriction. In all conditions, the time in bed was centered around 0300 h. We assessed carbohydrate metabolism and hormonal profiles at the end of the sleep-debt and sleep-recovery conditions, and compared sleepiness, sympathovagal balance, and saliva free-cortisol concentrations in all three conditions.

On days B1, D1–D4, and R1–R4, participants were allowed to leave the clinical research centre to attend to their normal activities, but had to return by 1900 h, before dinner, and remain in the clinical research centre until 0900 h, after breakfast. We asked participants to eat lunch at 1400 h and not to deviate from their normal daily routines. Sleep during the daytime was not allowed. We verified compliance through wrist activity recordings (Gaehwiler Electronics, Hombrechtikon, Switzerland). On days B2–B3, D5–D6, and R5–R6, participants rested in bed continuously in the clinical research centre. During scheduled waking hours they watched television, read, conversed with staff, worked on lap-top computers, or played board games. An investigator was present continuously to monitor wakefulness. Participants ate carbohydrate-rich (62%) meals every 5 h during these days (ie, at 0900 h, 1400 h, and 1900 h). We recorded beat-to-beat (RR) heart-rate intervals with the Mini-Logger (Mini-Mitter Co Inc, Sunriver, OR, USA) via a polar chest belt (polar heart rate monitor, Polar cic inc, Port Washington, NY, USA). During waking hours, participants rated their degree of sleepiness once every hour on the Stanford Sleepiness Scale.

On days B3, D6, and R6, we took saliva samples every 30 min from 1500 h to bedtime to measure free cortisol concentrations (Salivette, Sarstedt, Rommelsdorf, Germany). On days D5 and R5, we did intravenous glucose tolerance tests at 0900 h. On days D6 and R6, blood samples were collected every 10–30 min for 24 h to measure glucose and hormone concentrations. Because of limitations on the volume of blood that could be drawn, we could not do intravenous glucose tolerance tests and 24 h blood sampling during baseline days B1–B3.

Department of Medicine, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA
(K Spiegel PhD, R Leproult BS, E Van Cauter PhD)

Correspondence to: Dr Eve Van Cauter
(e-mail: evcauter@medicine.bsd.uchicago.edu)

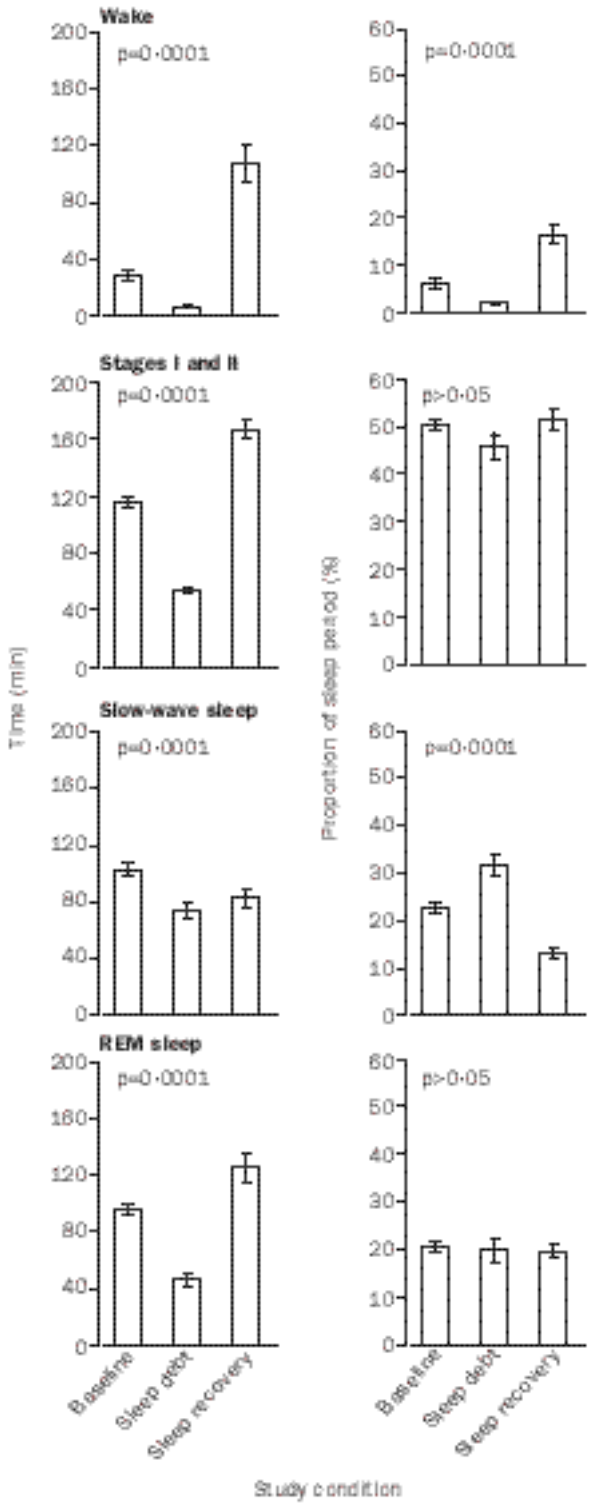

Figure 1: **Impact of sleep duration on sleep stages during last 2 nights of each condition**
Data are mean (SE).

We recorded sleep polygraphically during the last 2 nights of baseline, the last 2 nights of the sleep-debt condition, and the first night and the last 2 nights of the sleep-recovery condition. The recordings were scored in sleep stages—wake, I, II, III, IV, and REM—according to standard criteria.[13] Sleep onset and final awakening were defined as the first and last 20 s scored II, III, IV, or REM, and the sleep period as the time between sleep onset and final awakening. Total sleep time was the sum of stages I, II, III, IV, and REM.

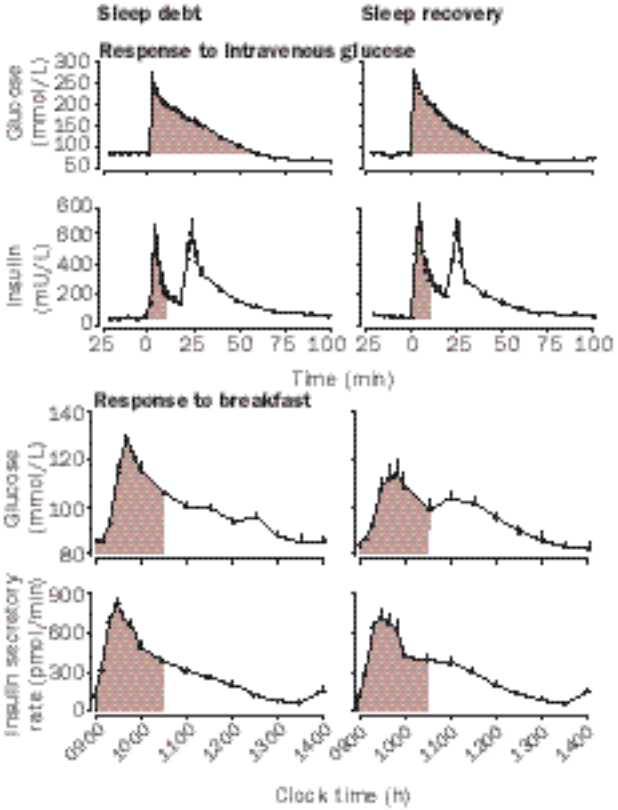

Figure 2: **Mean (SE) profiles of blood glucose and serum insulin during intravenous glucose tolerance test, and glucose and insulin responses to breakfast**

Assays and measurements

Glucose concentrations were assayed at bedside (Model 23A, Yellow Springs Instrument Company, Yellow Springs, OH, USA), with a coefficient of variation of less than 2%. We measured serum insulin by RIA, with a limit of sensitivity of 20 pmol/L and an average within-assay coefficient of variation of 5%. Plasma C-peptide concentrations were measured by RIA, with a detection limit of 0·02 pmol/L and an average within-assay coefficient of variation of 6%.[14] We assayed thyrotropin by chemiluminescent enzyme immunoassay (Immulite, Diagnostics Products Corporation, Los Angeles, CA, USA) with a limit of sensitivity of 0·002 μIU/mL and an average within-assay coefficient of variation of 5%. Free thyroxine concentrations were estimated by deriving the free thyroxine index from the total serum thyroxine concentration and the resin thyroxine ratio. We measured total cortisol concentrations in plasma and free cortisol concentrations in saliva by RIA (Orion Diagnostica, Finland); the lower limit of sensitivity was 20 nmol/L in plasma and 1 nmol/L in saliva and the average within-assay coefficients of variation were 4% and 6%, respectively. The quiescent period of cortisol secretion was determined as the period during which plasma cortisol concentrations were lower than 138 nmol/L. For all variables, all samples from each participant were measured in the same assay.

For the intravenous glucose tolerance test we started taking blood samples at 0900 h and drew samples every 5 min for 20 min, at which time we administered an intravenous bolus of glucose 300 mg/kg bodyweight. We took further blood samples at 2 min, 3 min, 4 min, 5 min, and 6 min, then every 2 min until 16 min, then at 19 min, 22 min, 24 min, 25 min, 27 min, and 30 min, then every 10 min until 100 min, and then every 20 min until 180 min. At 20 min, we gave all participants intravenous tolbutamide 125 mg/m^2 body surface area. We calculated glucose tolerance as the linear slope of the natural log of plasma glucose compared with time between 5 min and 19 min after the glucose injection. Insulin sensitivity and glucose effectiveness were estimated by minimal-model analysis.[15] The acute insulin

response to glucose was calculated as the mean increment of the insulin response compared with baseline from 2 min to 10 min.

After meal ingestion, we derived insulin secretion rates mathematically from plasma C-peptide concentrations with a two-compartment model with parameter values adjusted for sex, age, and body surface area.[16] The glucose and insulin responses to each meal were quantified by the areas under the curves during the first 90 min after the meal was presented.

After correction for artefactual values (heart-rate intervals >1700 ms or <400 ms), we calculated the autocorrelation coefficient RR intervals (ie, Pearson's correlation coefficient between RRn and RRn+1) over each 5 min period of recording. This measure of heart-rate variability is closely correlated with a well-documented marker of sympathovagal balance, the ratio of low-frequency to high-frequency power in the frequency spectrum of RR intervals.[17]

Statistical analysis

All values are expressed as mean (SE). We compared baseline, sleep-debt, and sleep-recovery conditions by ANOVA for repeated measures, with pairwise contrasts tested by Fisher's procedure. All calculations were done on StatViewSE+ software (version 1.04A).

Results

Mean total sleep time during the last 2 nights of each study condition was 7 h 14 min (SE 5 min) at baseline, 3 h 49 min (2) in the sleep-debt condition, and 9 h 3 min (15) in the sleep-recovery condition. The duration of awakenings during sleep time decreased from 29 min (5) at baseline to 5 min (1) during the last 2 nights of the sleep-debt condition and increased to 106 min (14) during the last 2 nights of the sleep-recovery condition (p=0·0001). Adaptation to sleep debt and recovery was achieved through proportional compression or extension of lighter stages (I and II) of non-REM sleep, such that the proportion of the sleep period spent in these stages remained constant. By contrast, the proportion of deep non-REM sleep (stages III and IV, or slow-wave sleep) was highest during the sleep-debt condition, which shows an increased pressure for slow-wave sleep. The loss of REM during the sleep-debt condition was proportional to the decrease in sleep period. Therefore, slow-wave sleep seemed to be better preserved than that for REM sleep during sleep debt. The mean increase in REM sleep during the first recovery night was 137 min (7) compared with the previous night, whereas the mean rebound of slow-wave sleep was only 41 min (8, p=0·0001; figure 1).

Glucose and insulin responses at the end of sleep recovery were in the normal range for young healthy men. During the sleep-debt condition, responses were consistent with a clear impairment of carbohydrate tolerance (figure 2). The rate of glucose clearance after injection was nearly 40% slower in the sleep-debt condition than in the sleep-recovery condition (1·45 [0·31] *vs* 2·40% per min [0·41], p<0·02). Glucose-tolerance values of around 1·60% per min are typical in older adults with impaired glucose tolerance,[18] whereas values of 2·2–2·9% per min are typical of fit young adults.[19] Glucose effectiveness, which quantifies the ability of glucose to mediate its own disposal independently of insulin,[15] was 30% lower in the sleep-debt condition than after the sleep-recovery condition (1·7 [0·2] *vs* 2·6%/min [0·2], p<0·0005). This difference in glucose effectiveness is nearly identical to that reported between groups of patients with non-insulin-dependent diabetes and normoglycaemic white men (1·4 *vs* 2·6%/min).[15] The acute insulin response to glucose was 30% lower in the

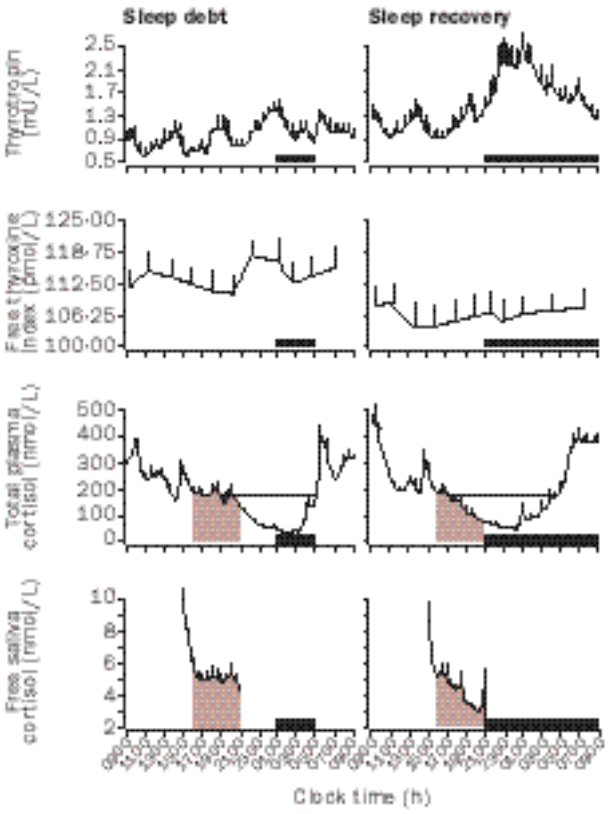

Figure 3: **Thyrotropin concentrations, free thyroxin index, and plasma and saliva cortisol concentrations in sleep-debt and sleep-recovery conditions**
Horizontal lines show quiescent periods of cortisol secretion.

sleep-debt condition than in the deep-recovery condition (304 [95] *vs* 432 pmol/min [110], p<0·04). A decrease in acute insulin response to glucose is an early marker of diabetes.[20] Differences in the acute insulin response to glucose of a magnitude similar to that seen between the sleep-debt and the fully rested conditions have been described in ageing[21] and gestational diabetes.[22] Differences in insulin sensitivity were not significant.

The glucose response after breakfast was higher in the sleep-debt condition than in the sleep-recovery condition (p=0·05), despite similar insulin secretory responses (figure 2). The difference in peak glucose concentrations in response to breakfast between the sleep-debt and sleep-recovery conditions (0·8 mmol/L) is similar to that seen between young and old adults (age 20–36 *vs* 60–72 years), and translates into about 1·1 mmol/L difference in glucose concentrations 120 min after the beginning of a standard glucose tolerance test.[23] This comparison suggests that, in the sleep-debt condition, the response to a morning standard oral glucose tolerance test would be consistent with current diagnostic criteria for impaired glucose tolerance. Profiles of blood glucose and insulin secretion in response to lunch and dinner did not differ significantly between conditions.

Other measurements taken during the study suggest possible mechanisms underlying the decrease in glucose tolerance associated with sleep loss. The decrease in acute insulin response to glucose could be related to an alteration in the importance of sympathetic (inhibitory) and parasympathetic (stimulatory) control of pancreatic function. Estimations of sympathovagal balance derived from recordings of heart-rate variability were significantly higher in the sleep-restriction condition than in the sleep-

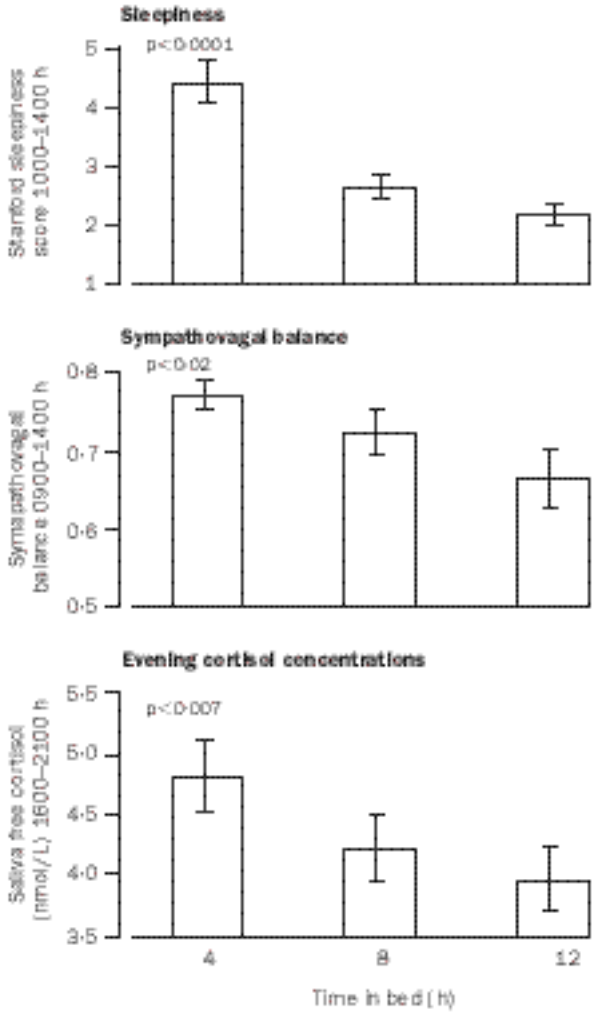

Figure 4: **Mean (SE) values of sleepiness, sympathovagal balance, and saliva cortisol concentrations for all three conditions**

recovery condition (mean sympathovagal balance during the interval 0900–1400 h was 0·77 [0·02] *vs* 0·66 [0·04], p<0·02). The brain is a major site of non-insulin-dependent glucose uptake.[24] In normal people studied at rest after an overnight fast, a decrease in glucose effectiveness is likely to represent a decrease in the brain's use of glucose. Therefore, the high degree of sleepiness seen on day 5 of the sleep-debt condition compared with sleepiness on day 5 of the sleep-recovery condition (mean Stanford Sleepiness Scores 4·4 [0·4] *vs* 2·1 [0·2], p<0·0005) seemed to be associated with lower cerebral glucose uptake, consistent with a study that showed a 7% decrease of global cerebral metabolic rate per day of total sleep deprivation on positron emission tomography.[25]

Changes were seen in thyrotropic function and activity of the hypothalamo-pituitary-adrenal axis (figure 3). The normal rise in thyrotropin at night was strikingly decreased in the sleep-debt condition compared with that in the sleep-recovery condition, and the overall 24 h mean thyrotropin concentration was significantly decreased (0·95 [0·10] *vs* 1·43 mU/L [0·18] p<0·01). Differences in thyrotropin profiles between the two conditions are probably related to changes in thyroid-hormone concentrations, since the free thyroxin index was higher in the sleep-debt condition than in the sleep-recovery condition (9·1 [0·3] *vs* 8·5 µg/dL [0·3], p<0·01). Previous studies have shown that total sleep deprivation is associated, during the first night, with a striking increase in thyrotropin secretion that lessens during the next 2–3 nights, presumably because of negative-feedback effects from slowly rising concentrations of thyroid hormones.[26,27] Similar mechanisms probably underlie the raised free thyroxin index and decreased thyrotropin concentrations we saw in the sleep-debt condition.

Sleep debt was, compared with the sleep-recovery condition, associated with alterations in the 24 h profile of plasma cortisol, including a shorter quiescent period (537 [44] *vs* 634 min [24], p<0·03) due largely to a delay in its onset of nearly 1·5 h (at 1930 [47 min] *vs* 1701 h [43], p<0·04) and raised concentrations in the afternoon and early evening (p=0·0001, figure 3). This latter disturbance, which we have shown previously in conditions of acute total and partial sleep loss,[28] may reflect decreased efficacy of the negative-feedback regulation of the hypothalamo-pituitary-adrenal axis. Based on the analysis of the concentrations of free cortisol in saliva, the rate of decrease of free cortisol concentrations between 1600 h and 2100 h was about six times slower in the sleep-debt condition than in the sleep-recovery condition (0·07 [0·13] *vs* 0·43 nmol/L [0·13] every hour, p<0·01). Rises in cortisol concentrations in the afternoon and early evening, similar to those seen in the sleep-debt condition, are typical of normal ageing.[29,30]

The non-invasive measures of sleepiness scores, estimations of sympathovagal balance, and concentrations of free cortisol in saliva were compared for all three durations of time in bed (figure 4). Post-hoc comparisons showed that 4 h in bed were associated with higher degrees of sleepiness (p<0·01), a trend towards higher sympathetic activity (p<0·12), and higher afternoon cortisol (p<0·03) than 8 h in bed (baseline).

Discussion

Less than 1 week of sleep curtailment in healthy young people is associated with striking alterations in metabolic and endocrine function. Therefore, although the primary function of sleep may be cerebral restoration, sleep debt also has consequences for peripheral function that, if maintained chronically, could have long-term adverse effects on health. Decreased carbohydrate tolerance and increased sympathetic tone are well-recognised risk factors for the development of insulin resistance, obesity, and hypertension.[31] Raised cortisol concentrations in the evening are thought to reflect an impairment of the negative-feedback control of the hypothalamo-pituitary-adrenal axis and to be involved in age-related insulin resistance and memory impairments.[32,33] The metabolic and endocrine alterations seen during the sleep-debt condition therefore mimic some of the hallmarks of ageing, which suggests that chronic sleep loss could increase the severity of age-related pathologies, such as diabetes and hypertension.

For metabolic and endocrine variables derived from measurements in blood, sleep debt could be compared only with the sleep-recovery condition and not with the baseline condition because of limitations on blood withdrawal. For non-invasive measures such as subjective sleepiness, sympathovagal balance, and concentrations for free cortisol in the saliva, however, baseline values were intermediate between the sleep-debt and the sleep-recovery conditions, which suggests that the fully rested

state may represent a better functional condition than that achieved by the "normal" 8 h bedtime. Previous studies have shown that 8 h in bed may not be sufficient to satisfy the sleep needs of normal young adults.[7]

Our data further identify putative pathways by which the impact of sleep debt on the central nervous system could be translated to the periphery. Increases in sympathetic compared with parasympathetic tone, which we interpret as the most probable cause of decreased β-cell responsiveness in the sleep-debt condition, may negatively affect cardiac function, regulation of blood pressure, and kidney function. A decrease in non-insulin-dependent glucose uptake is likely to reflect decreased cerebral use of glucose, which suggests another pathway linking central and peripheral manifestations of sleep debt. Diminished brain glucose uptake results in increased exposure of peripheral tissues to higher glucose concentrations, which, under chronic conditions, will probably facilitate the development of insulin resistance in predisposed individuals. The slower decrease of cortisol concentrations in the afternoon was consistent with altered hippocampal mechanisms that control negative-feedback regulation of the hypothalamo-pituitary-adrenal axis. Metabolic and cognitive function could therefore be adversely affected under chronic conditions.[32,33]

Irrespective of the underlying mechanisms, when compared with the sleep-recovery condition, sleep debt, which is experienced by a substantial proportion of people in more-developed countries, is clearly associated with metabolic and endocrine alterations that may have physiopathological consequences in the long term.

Contributors

Eve Van Cauter was primarily responsible for the overall design of the study, supervised its execution, and reviewed each step of data analysis. Eve Van Cauter and Karine Spiegel were jointly responsible for data interpretation and preparation of the paper. Rachel Leproult provided assistance in all recording procedures and the execution of the study. Rachel Leproult and Karine Spiegel did the computerised data analysis. Karine Spiegel was primarily responsible for the execution of all parts of the study, from recruitment to data collection.

Acknowledgments

The study design was developed in collaboration with members of the Research Network on Mind-Body Interactions of the MacArthur Foundation, Chicago, IL, USA. We thank M L'Hermite-Balériaux for expert assistance with hormonal assays; P Penev and E Colecchia for analysis of heart-rate variability; the volunteers for their participation, patience, and cooperation; and the staff of the Clinical Research Center of the University of Chicago for assistance.

This study was supported by a grant from the Research Network on Mind-Body Interactions of the MacArthur Foundation, by grant F49620–94–1–0203 from the US Air Force Office of Scientific Research, Bollings AFB, MD, USA, and by grants RO1 DK–41814 and PO1 AG–11412 from the National Institutes of Health (NIH), Bethesda, MD, USA. The General Clinical Research Center of the University of Chicago is supported by grant RR–00055 from the NIH, Bethesda. Glucose, insulin and C-peptide assays were supported by the Diabetes Research and Training Center of the University of Chicago (grant NIH P60 DK20595).

References

1 Webb WB, Agnew HW. Are we chronically sleep deprived? *Bull Psychon Soc* 1975; **6:** 47–48.

2 Broman JE, Lundh LG. Hetta J. Insufficient sleep in the general population. *Neurophysiol Clin* 1996; **26:** 30–39.

3 Bliwise DL. Historical change in the report of daytime fatigue. *Sleep* 1996; **19:** 462–64.

4 Horne J. Why we sleep. Oxford: Oxford University Press, 1988: 1–1–319.

5 Freidmann J, Globus G, Huntley A, Mullaney D, Naitoh P, Johnson L. Performance and mood during and after gradual sleep reduction. *Psychophysiology* 1977; **14:** 245–50.

6 Dinges D, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep* 1997; **20:** 267–77.

7 Wehr TA, Moul DE, Barbato G, et al. Conservation of photoperiod-responsive mechanisms in humans. *Am J Physiol* 1993; **265:** R846–57.

8 Van Cauter E, Spiegel K. Hormones and metabolism during sleep. In: Schwartz WJ, ed. Sleep science: integrating basic research and clinical practice. *Monogr Clin Neurosci* 1997: **15:** 144–74.

9 Dinges DF, Douglas SD, Hamarman S, Zaugg L, Kapoor S. Sleep deprivation and human immune function. *Adv Neuroimmunol* 1995; **5:** 97–110.

10 Parmeggiani P. The autonomic nervous system in sleep. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: WB Saunders, 1994: 194–203.

11 Benington JH, Heller HC. Restoration of brain energy metabolism as the function of sleep. *Prog Neurobiol* 1995, **45:** 347–60.

12 Bonnet, MH. Sleep deprivation. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: WB Saunders, 1994: 50–67.

13 Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: Government Printing Office, 1968.

14 Faber OK, Binder C, Markussen J, et al. Characterization of seven C-peptide antisera. *Diabetes* 1978; **27** (suppl 1)**:** 170–77.

15 Bergman RN. Lilly Lecture 1989: toward physiological understanding of glucose tolerance—minimal model approach. *Diabetes* 1989; **38:** 1512–27.

16 Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels: comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 1992, **41:** 368–77.

17 Otzenberger H, Gronfier C, Simon C, et al. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am J Physiol* 1998, **275:** 946–50.

18 Garcia GV, Freeman RV, Supiano MA, Smith MJ, Galecki AT, Halter JB. Glucose metabolism in older adults: a study including subjects more than 80 years of age. *J Am Geriatr Soc* 1997, **45:** 813–17.

19 Prigeon RL, Kahn SE, Porte D Jr. Changes in insulin sensitivity, glucose effectiveness, and B-Cell function in regularly exercising subjects. *Metabolism* 1995, **44:** 1259–63.

20 Kahn CR. Etiology and pathogenesis of type II diabetes mellitus and related disorders. In: Becker K, ed. Principles and practice of endocrinology and metabolism. Philadelphia: JB Lippincott, 1995: 1210–16.

21 Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and B-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 1993; **42:** 1663–72.

22 Catalano PM, Tyzbit ED, Wolfe RR, et al. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am J Physiol* 1993; **264:** E60–67.

23 Gumbiner B, Polonsky KS, Beltz WF, Wallace P, Brechtel G, Fink RI. Effects of aging on insulin secretion. *Diabetes* 1989; **38:** 1549–56.

24 Kahn CR. Glucose homeostasis and insulin action. In: Becker KL, ed. Principles and practice of endocrinology and metabolism, 2nd edn. Philadelphia: JB Lippincott, 1995: 1198–02.

25 Thomas M, Balkin T, Sing H, Wesensten N, Belenky G. 14th European Congress on Sleep Research 1–332. Madrid: Blackwell Science, 1998.

26 Allan JS, Czeisler CA. Persistence of the circadian thyrotropin rhythm under constant conditions and after light-induced shifts of circadian phase. *J Clin Endocrinol Metab* 1994; **79:** 508–12.

27 Van Cauter E, Sturis J, Byrne MM, et al. Demonstration of rapid light-induced advances and delays of the human circadian clock using hormonal phase markers. *Am J Physiol* 1994; **266:** E953–63.

28 Leproult R, Copinschi G, Buxton O, Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep* 1997; **20:** 865–70.

29 Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab* 1996; **81:** 2468–73.

30 Kern W, Dodt C, Born J, Fehm HL. Changes in cortisol and growth hormone secretion during nocturnal sleep in the course of aging. *J Gerontol* 1996; **51A:** M3–9.

31 Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 1996; **334:** 374–81.

32 Dallman MF, Strack AL, Akana SF, et al. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. *Front Neuroendocrinol* 1993, **14:** 303–47.

33 McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; **338:** 171–79.