Effects of sleep restriction on glucose control and insulin secretion during diet-induced weight loss

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Abstract

Insufficient sleep is associated with changes in glucose tolerance, insulin secretion, and insulin action. Despite widespread use of weight-loss diets for metabolic risk reduction, the effects of insufficient sleep on glucose regulation in overweight dieters are not known. To examine the consequences of recurrent sleep restriction on 24-hour blood glucose control during diet-induced weight loss, 10 overweight and obese adults (3F/7M; mean [SD] age 41 [5] y; BMI 27.4 [2.0] kg/m^2) completed two 14-day treatments with hypocaloric diet and 8.5 or 5.5-h nighttime sleep opportunity in random order 7 [3] months apart. Oral and intravenous glucose tolerance test (IVGTT) data, fasting lipids and free-fatty acids (FFA), and 24-hour blood glucose, insulin, C-peptide, and counter-regulatory hormone measurements were collected after each treatment. Participants had comparable weight loss (1.0 [0.3] BMI units) during each treatment. Bedtime restriction reduced sleep by 131 [30] min/day. Recurrent sleep curtailment decreased 24-hour serum insulin concentrations (i.e. enhanced 24-hour insulin economy) without changes in oral glucose tolerance and 24-hour glucose control. This was accompanied by a decline in fasting blood glucose, increased fasting FFA which suppressed normally following glucose ingestion, and lower total and LDL cholesterol concentrations. Sleep-loss-related changes in counter-regulatory hormone secretion during the IVGTT limited the utility of the test in this study. In conclusion, sleep restriction enhanced 24-hour insulin economy without compromising glucose homeostasis in overweight individuals placed on a balanced hypocaloric diet. The changes in fasting blood glucose, insulin, lipid and FFA concentrations in sleep-restricted dieters resembled the pattern of human metabolic adaptation to reduced carbohydrate availability.

INTRODUCTION

Epidemiological data show an association between self-reported short sleep (<6 h/day) and incident diabetes, however, the reasons of this relationship are not known. Impaired insulin action (insulin resistance) related to excessive adiposity and physical inactivity, and failure

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of pancreatic beta-cells to maintain increased compensatory insulin secretion are important pathogenic mechanisms for the epidemic of type 2 diabetes in the modern world. Experimental data in healthy adults indicate that acute sleep loss can result in decreased glucose tolerance, insulin secretion, and/or insulin sensitivity (1–8). Combining traditional risk behaviors such as overeating and physical inactivity with two weeks of experimental sleep restriction is also accompanied by increased insulin resistance, insufficient beta-cell compensation, and reduced glucose tolerance (9). It has been speculated that activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis may contribute to the observed sleep-loss-related changes in glucose regulation, however, this hypothesis has not received convincing experimental support (1, 4–6, 8, 9).

Behavioral modification including diet-induced weight loss and increased physical activity is a powerful strategy for diabetes prevention and cardiometabolic risk reduction. In addition, early declines in plasma glucose and insulin concentrations in diabetic patients who initiate hypocaloric diet therapy are predictive of a favorable longer-term metabolic response (10). However, despite the widespread use of diet-based interventions to ameliorate metabolic risk, the effects of insufficient sleep on the 24-hour control of plasma glucose in overweight individuals placed on a hypocaloric diet have not been studied. To test the hypothesis that reduced sleep duration may undermine the beneficial effects of caloric restriction on systemic glucose regulation, we obtained measures of glucose tolerance, insulin secretion, and insulin action in overweight adults who were enrolled in a previously described study of sleep and dietary weight loss in our laboratory (11). We also examined whether experimental sleep restriction, designed to approximate the short sleep times of many free-living adults initiating a hypocaloric diet to lose weight (12, 13), will be accompanied by undesirable changes in fasting blood lipids and 24-hour profiles of several glucose counter-regulatory hormones.

METHODS AND PROCEDURES

Study participants

Sedentary non-smokers ages 35–49 years with body mass index between 25 and 32 kg/m^2 and self-reported sleep between 6.5 and 8.5 hours/day were recruited through local advertisements. We excluded volunteers who had: any acute or chronic medical condition; history of irregular menstrual cycles or childbirth during the past year; self-reported sleep problems (Pittsburgh Sleep Quality Index score >10), shift work, variable sleep habits or habitual daytime naps; depressed mood (Center for Epidemiologic Studies of Depression score >15); excessive intake of alcohol (>14 drinks/week for men or >7 for women); use of prescription, over-the-counter, or illicit drugs and supplements that can affect sleep or metabolism; abnormal physical exam or screening test results (complete blood counts, thyroid and comprehensive metabolic panels, 75-g oral glucose challenge, electrocardiogram, and overnight polysomnography to exclude sleep apnea [respiratory disturbance index, RDI   10] or other sleep disorder). Only non-pregnant women were studied and data collection was scheduled during the first phase of their menstrual cycle. Ten participants (3 women and 7 men; 4 African American, 3 Non-Hispanic White, and 3

Hispanic White) completed the study. All of them gave written informed consent and were paid for their participation.

Study protocol

The protocol was approved by the University of Chicago Institutional Review Board. The experimental design has been described in detail elsewhere (11). Briefly, each participant spent two 14-day periods in the laboratory with scheduled time-in-bed of 8.5 or 5.5 h/night in random order at least 3 months apart (mean ± SD time between treatments: 7 ± 3 months). Sleep was recorded polygraphically every night (Neurofax-1100, Nihon-Kohden, Foothill Ranch, CA) and no daytime naps were allowed. During each treatment, participants consumed the same individualized reduced-energy diet with caloric content (mean ± SD: 1447 ± 227 vs. 1450 ± 236 kcal/day; 8.5 vs. 5.5-h time-in-bed condition) equal to 90% of their resting metabolic rate at the time of screening. Carbohydrate, fat, and protein contributed 48 ± 1, 34 ± 1, and 18 ± 1% of energy. Participants spent most of their waking hours indoors engaged in home-office type work or leisure activities (9).

Following each 14-day treatment period, starting at 20:00 participants remained in their room for 48 h mostly sitting (day 1) or resting semi-recumbent in bed (day 2) with controlled caloric intake (21 ± 2 kcal.kg^{-1}.day^{-1}) including oral (day 1) or intravenous (day 2) doses of glucose at 9:00 and two identical carbohydrate-rich (62% of energy) mixed meals at 14:00 and 19:00 (14). Sleep schedule continued to follow assigned time-in-bed conditions (8.5 or 5.5 hours/night). Blood samples for glucose, insulin, C-peptide, cortisol, epinephrine, norepinephrine, and growth hormone (GH) were collected every 30 minutes during the last 24 hours of this period. A 3-hour 75-g oral glucose tolerance test (OGTT) started at 9:00 on the 1st morning as described previously (9). An insulin-assisted (0.03 units/kg) intravenous glucose tolerance test (IVGTT, 0.3 g/kg) was incorporated into the ongoing 24-hour blood sampling sequence between 9:00 and 12:00 on the 2nd morning as described previously (9).

Assays

Plasma glucose was measured with a bedside glucose analyzer (STAT-2300 Yellow Springs Instruments, Yellow Springs, OH). Serum insulin, C-peptide, cortisol, and growth hormone (GH) concentrations were measured using commercial human chemiluminescent enzyme immunoassays (Immulite 2000, Diagnostic Products, Los Angeles, CA). Plasma epinephrine and norepinephrine were measured by high-pressure liquid chromatography (14). Fasting triglycerides, total, and high-density lipoprotein (HDL) cholesterol concentrations were measured by the clinical laboratory of the University of Chicago Medical Center in serum collected prior to the OGTT. Low-density lipoprotein (LDL) cholesterol concentrations were calculated with the Friedewald formula. Plasma free fatty acids (FFA) were measured in samples collected before and during the OGTT using an enzymatic colorimetric assay (NEFA C-test, Wako Chemicals, Richmond, VA).

Data analysis

The effect of bedtime restriction on post-absorptive and postprandial circulating concentrations of glucose, insulin, C-peptide, cortisol, GH, epinephrine, and norepinephrine

was assessed during the entire 24-hour sampling period, the assigned time-in-bed (nighttime) hours, and the daytime prandial period between 14:00 and 23:00. Insulin secretion rates (ISR) were derived from measured C-peptide concentrations by deconvolution using a two-compartment model for C-peptide distribution and degradation and standard parameters for C-peptide clearance adjusted for individual age, sex, and body surface area (15). Fasting glucose, insulin, and C-peptide concentrations were calculated as the average of −10, −5 and 0 min baseline measurements prior to the morning IVGTT. Fasting blood samples collected before the IVGTT from a line, which was placed the night before, were used to avoid the influence of pain from i.v. catheter insertion in the morning before the OGTT. Estimates of whole-body insulin sensitivity (S_I) and acute insulin response to glucose (AIR_G) during the IVGTT were derived by Minimal model analysis (MINMOD, version 5.01; Bergman & Stefanovski Assoc., Boston, MA). A disposition index (DI) equal to the product of AIR_G and S_I was calculated as a measure beta-cell function adjusted for the degree of insulin resistance. Fasting and 2-h plasma glucose measurements during the OGTT provided additional clinically relevant indices of oral glucose tolerance. The magnitude of FFA suppression during the OGTT was calculated as the difference between the average fasting (−15 and 0 min) and 120–180 min (3rd hour) FFA concentrations and expressed as percent decrease from fasting.

To control for treatment-related changes in body composition, the effect of exposure to 5.5-h vs. 8.5-h time-in-bed (a fixed factor) on measures of glucose tolerance, insulin secretion, and insulin action was analyzed using a mixed linear model with treatment period (1st vs. 2nd) as a repeated measure and final fat and fat-free body mass as time-varying covariates. Similar mixed models controlling for order-of-treatment and differences in final body composition were used to examine the effect of sleep restriction on fasting lipid, FFA, and circulating glucose counter-regulatory hormone concentrations. All statistical analyses were done using SPSS 18.0 (SPSS Inc., Chicago, IL). Data in the text are reported as mean ± SD. Two-sided P<0.05 was considered statistically significant and P-values <0.09 are reported as trends.

RESULTS

Study participants had a mean age of 41 ± 5 y, BMI 27.4 ± 2.0 kg/m², self-reported sleep 7.7 ± 0.7 h/day, CES-D score 4 ± 5, PSQI score 3 ± 2, sleep respiratory disturbance index 3 ± 3 events/hour, and resting metabolic rate 1624 ± 210 kcal/day at the time of screening. Bedtime restriction reduced the 2-week average nighttime sleep of the participants by 2 h 11 min (± 30 min) from 7 h 25 min (± 32 min) per night during the 8.5-h time-in-bed condition to 5 h 14 min (± 6 min) per night during the 5.5-h time-in-bed condition (P<0.01) (11). As reported previously (11), caloric restriction resulted in comparable weight loss (1.0 ± 0.3 BMI units) during each treatment, but more than half of the weight lost during the 8.5-h time-in-bed condition and only a quarter of the weight lost during the 5.5-h time-in-bed condition was fat (Table 1). Instead, sleep restriction resulted in greater loss of fat-free body mass (11).

24-hour blood glucose, insulin, C-peptide and ISR

Figure 1 illustrates the sleep-wake and meal-related changes in blood glucose, insulin, C-peptide, and ISR during each treatment. The 24-hour profile of blood glucose and its average concentration did not change (Figure 1A), whereas 24-hour serum insulin concentrations were significantly lower during the period of recurrent sleep restriction (P<0.03; Figure 1B). Corresponding C-peptide and ISR profiles showed a similar trend towards lower 24-hour mean concentrations during the short-sleep condition (P<0.09 for each; Table 2). Sleep-loss-related declines in insulin, C-peptide, and ISR were clearly present during the scheduled sleep period (P<0.02 for all; Figure 1B–D) and less so during the day, when meal-related hormone concentrations had higher variability and statistical analysis showed only a trend towards lower 60–180 min postprandial insulin concentrations (P<0.06; Figure 1B).

IVGTT and OGTT

Combined exposure to hypocaloric diet and recurrent sleep loss was accompanied by lower blood glucose and insulin concentrations in the morning before the IVGTT (P<0.05; Figure 2). A trend towards similar modest reduction in fasting blood glucose was noted in the morning before the OGTT (P=0.08; Table 2). There was no significant difference in 120-min blood glucose and 3-h area under the OGTT curve for glucose and insulin between the two sleep conditions (Figure 3A and 3B).

Minimal model estimates of insulin secretion and insulin sensitivity were significantly lower at the end of the 5.5-h time-in-bed condition (Table 2). When differences in order-of-treatment and final body composition were controlled for, DI at the end of the 5.5-h time-in-bed condition was reduced by 23% (independent effect of short sleep -523; 95%CI -36 to -1010; P<0.04) and S_I by 26% (independent effect of short sleep -0.9 $(mU/L)^{-1}.min^{-1}$; 95%CI -0.1 to -1.6; P<0.03).

FFA and fasting lipids

Fasting plasma FFA concentrations were higher at the end of the 5.5-h time-in-bed condition (P<0.04; Figure 3C). However, FFA concentrations during the 3rd hour of the OGTT and their percent suppression from fasting remained similar between the two sleep conditions (Table 2). Total and LDL cholesterol concentrations were lower at the end of the short-sleep condition (P<0.04; Table 2), while fasting HDL cholesterol and triglycerides did not differ between treatments.

24-hour profiles of counter-regulatory hormones

Glucose counter-regulatory hormone concentrations showed the expected prandial and sleep-wake related variability characteristic for each variable (Figure 4). Serum cortisol had comparable peak, trough, nighttime, prandial, and 24-hour mean concentrations at the end of each treatment (Figure 4A). When sleep was reduced, the period of relative hypoglycemia (16) during the 2nd hour of the IVGTT (Figure 2) was followed by a rise in cortisol concentrations during hours 4 and 5 after the start of the test (P=0.02; Figure 4A).

Serum GH had comparable nighttime, prandial, and 24-hour mean concentrations at the end of each treatment (Figure 4B). When sleep was restricted, the period of relative hypoglycemia during the 2nd hour of the IVGTT was followed by increased GH concentrations during hours 4 and 5 after the start of the test (P=0.03; Figure 4B).

Plasma epinephrine concentrations were lower during the IVGTT and subsequent prandial period when sleep was reduced (33 ± 12 vs. 25 ± 7 μg/dL; P<0.01; Figure 4C). Despite the lack of such difference during the night, integrated 24-hour epinephrine concentrations were significantly lower during the short-sleep condition (11). Plasma norepinephrine concentrations did not differ between treatments (Figure 4D).

DISCUSSION

This study examined whether sleep restriction, designed to approximate the short sleep times of many adults (12), will have an adverse effect on 24-hour blood glucose control in overweight individuals initiating a hypocaloric diet to lose weight. Using the same balanced hypocaloric diet on two separate occasions with and without recurrent bedtime restriction, we were able to induce comparable weight loss (1.0 BMI unit) while changing the average sleep duration of study participants from >7 h/day (an epidemiologic sleep category with low metabolic risk) to <6 h/day (a category with increased metabolic risk). The experimental results did not support the initial hypothesis. Opposite to predictions, oral glucose tolerance at the end of the short-sleep condition was not compromised and 24-hour glucose homeostasis was maintained with less insulin in the systemic circulation. This enhanced 24-hour insulin economy during the short-sleep condition was accompanied by a modest decline in fasting blood glucose, increased fasting FFA concentrations which suppressed normally after glucose ingestion, and lower total and LDL cholesterol. Although dieters had higher IVGTT estimates of insulin resistance when they slept less, the presence of sleep-loss-related changes in counter-regulatory hormone secretion during the test limited the utility of these estimates.

In contrast to prior sleep deprivation studies with unrestricted food intake when morning reductions in insulin secretion and sensitivity resulted in higher prandial glucose concentrations (4, 8, 9), there was no deterioration in oral glucose tolerance of our weight-reduced subjects at the end of the short-sleep condition (Figures 1 and 3). In addition, disposal of oral carbohydrate did not require higher insulin concentrations when sleep was curtailed – a result, which suggests that their systemic insulin sensitivity was not reduced (Figures 1 and 3). Indeed, since circulating insulin concentrations tended to be lower 60 to 180 min after meal ingestion at the end of the 5.5-h time-in-bed condition (P<0.06; Figure 1), one could speculate that dieters may have had somewhat higher insulin-independent glucose disposal (e.g. via splanchnic uptake) or systemic insulin sensitivity when their sleep was curtailed.

The rate of insulin secretion required to control plasma glucose concentrations during the nighttime fasting period was significantly reduced at the end of the 5.5-h time-in-bed condition (Figure 1). Sleep conserves energy and carbohydrate during the night, whereas overnight sleep deprivation results in 20–30% higher energy expenditure, systemic glucose

disposal, and need for endogenous glucose production (17, 18). Higher respiratory quotient measurements during sleep restriction (19) and repeated disruption of sleep (20) suggest that partial sleep loss may also lead to use of relatively more energy from carbohydrate - indeed, the respiratory quotient of our study participants was elevated when their sleep was curtailed (11). Systemic glucose availability in the postabsorptive state is maintained primarily by glycogenolysis and gluconeogenesis in the liver. This aspect of hepatic metabolism is very sensitive to small changes in insulin and the decline in overnight ISR could enhance endogenous glucose production when weight-reduced dieters slept less (11, 17–20). Interestingly, lean adults with chronic sleep insufficiency (difficulty initiating or maintaining sleep) were also found to have lower fasting insulin concentrations (21). Although several glucose counter-regulatory hormones can amplify endogenous glucose production by inhibiting insulin secretion, there were no changes in integrated nighttime concentrations of cortisol, GH, and plasma catecholamines at the end of the short-sleep condition (Figure 4). In contrast, overnight acylated ghrelin concentrations were increased when dieters slept less (11). This hormone has inhibitory effects on insulin secretion and may enhance endogenous glucose production to support the extended nighttime needs of sleep-restricted dieters (22–25).

The modest decline in plasma glucose concentrations after a 14-hour nighttime fast at the end of the short-sleep condition also suggests that dieters used more energy from carbohydrate when their sleep was curtailed. The combination of improved insulin economy and lower fasting blood glucose seen in this study resembles the human metabolic adaptation to reduced carbohydrate availability (26). Importantly, increased availability of dietary carbohydrate in the setting of negative energy balance reduces the loss of body protein (27). Since the hypocaloric diet and the length of overnight fasting were the same during both treatments, if dieters needed more energy from carbohydrate when their sleep was curtailed, this may have contributed to their increased loss of lean body mass (Table 1) (11).

The decline in fasting LDL and total cholesterol concentrations is also consistent with the presence of a more pronounced carbohydrate deficit (28) at the end of the short-sleep condition. In addition, lower insulin levels promote lipolysis and the rise in fasting FFA concentrations during the short-sleep condition fits well with the observed decline in nighttime ISR. Oxidation of relatively less fat for energy when sleep was curtailed (11) could also contribute to the increase in fasting FFA. However, higher fasting FFA were not associated with increased triglyceride or decreased HDL cholesterol concentrations, suggesting that circulating FFA were cleared efficiently via non-oxidative disposal during the short-sleep condition (29, 30). Higher fasting FFA concentrations also enhance hepatic gluconeogenesis, but may impair insulin-mediated glucose uptake in muscle (31, 32). However, FFA suppression during the OGTT did not differ between the two treatments and adipose tissue insulin resistance or FFA-mediated reduction in muscle insulin sensitivity were not likely to have an adverse effect on glucose regulation during the prandial period of this study (33–35).

At odds with their enhanced 24-hour insulin economy, sleep-restricted dieters had higher IVGTT estimates of insulin resistance. This discrepancy highlights the important limitations

of the IVGTT in sleep-restricted dieters and requires careful consideration (9). Most notably, the pattern of counter-regulatory hormone secretion during the test was altered when dieters slept less and such transient changes can lead to erroneous estimates of insulin sensitivity (16). In addition, administration of acylated ghrelin in healthy volunteers results in decreased insulin-mediated disposal of intravenous glucose and transient increases in cortisol and GH (23, 25). The greater rise of acylated ghrelin in sleep-restricted dieters during the IVGTT (11) is consistent with the observed changes in cortisol and GH (Figure 4) and raises the possibility that the increase in insulin resistance during the test may reflect the influence of these hormones on Minimal model estimates (16).

At the same time, the possibility that a transient postabsorptive rise in peripheral insulin resistance contributed to the lower S_I of sleep-restricted dieters cannot be entirely dismissed. Previous studies have detected signs of increased insulin resistance in the morning after one or more nights of total or partial sleep deprivation (3, 5–8). However, when followed over time, sleep-loss-related changes in morning blood glucose and insulin concentrations do not persist during the rest of the day (4, 8). These transient changes (when participants switch from a fasting to a fed metabolic state) are quite different from the sustained 24-hour changes in insulin secretion and action in obese insulin-resistant individuals (36), and may not have the same implications with regards to diabetes risk. Even if present in this study, such transient rise in systemic (possibly muscle) insulin resistance had to be offset by increased non-insulin-mediated (e.g. splanchnic) glucose uptake (37) because glucose tolerance and serum insulin concentrations of sleep-restricted dieters during the OGTT did not change (Figure 1). For example, when glucose is given intravenously, the contribution of splanchnic organs (primarily liver and gut) to overall glucose uptake is small and >90% of insulin-mediated glucose disposal reflects uptake by peripheral tissues (primarily muscle) (38). In contrast, splanchnic uptake has a significant role in controlling plasma glucose concentrations after oral carbohydrate intake (39). Unfortunately, IVGTT indices of non-insulin-mediated glucose disposal become unreliable when insulin secretion changes (40) and could not be used in this study. This further weakened the ability of our Minimal model IVGTT analysis to capture any changes in insulin-mediated vs. non-insulin-mediated glucose disposal in sleep-restricted dieters.

In summary, recurrent sleep restriction enhanced 24-hour insulin economy without compromising glucose tolerance and 24-hour glucose homeostasis in overweight adults placed on a hypocaloric diet to lose weight. This was accompanied by a modest decline in fasting blood glucose, lower total and LDL cholesterol, and higher fasting FFA concentrations which suppressed normally after glucose ingestion. Together, these changes resemble the pattern of human metabolic adaptation to reduced carbohydrate availability consistent with the notion that dieters used more energy from carbohydrate when their sleep was curtailed (11). Thus, a relative carbohydrate deficit may have contributed to the increased loss of lean body mass and reduced satiety of our sleep-restricted dieters (11, 27) – important consequences, which could undermine the long-term success of dietary weight-loss therapy. However, due to the high cost and technical difficulty of such experiments, this discussion is based on the detailed laboratory evaluation of a small number of subjects during a limited period of time. Additional studies are needed to examine the effects of insufficient sleep on endogenous glucose production, insulin-mediated and non-insulin-

mediated glucose disposal, and oxidative substrate metabolism in weight-reduced individuals.

Acknowledgements

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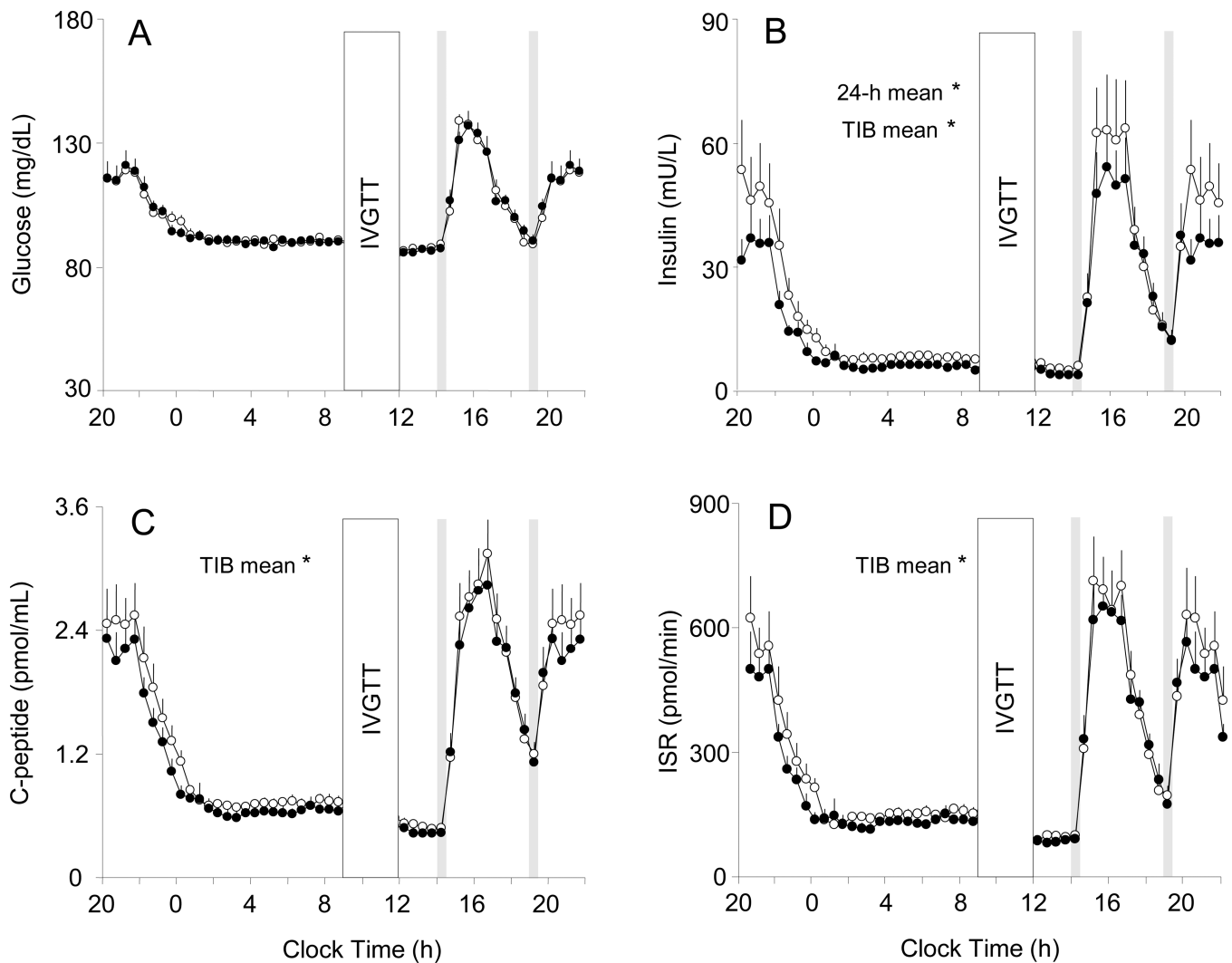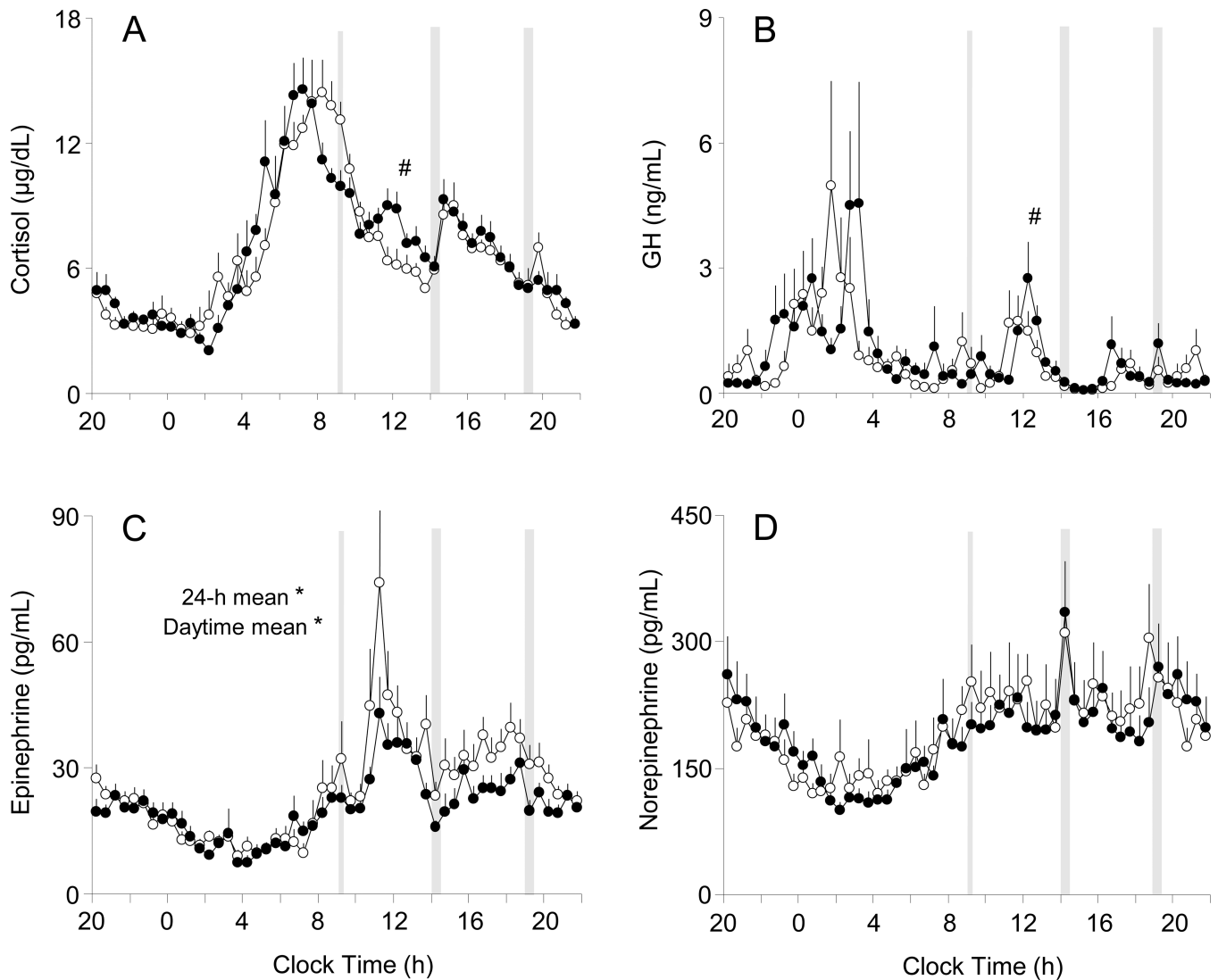
Figure 1.
Mean (+SE) 24-h profiles of circulating plasma glucose (**A**), serum insulin (**B**) and C-peptide concentrations (**C**), and corresponding insulin secretion rate (ISR) derived by deconvolution analysis (**D**) at the end of the 8.5-h (open circles) and 5.5-h (solid circles) bedtime condition (n=10). The time of the intravenous glucose tolerance test is marked by a vertical white bar; lunch and dinner are marked by vertical grey bars. To improve clarity, data collected between 20:00 and 22:00 are double plotted at the beginning and the end of the time axis. * P<0.05 for effect of sleep condition based on mixed model analysis controlling for treatment order and body composition.
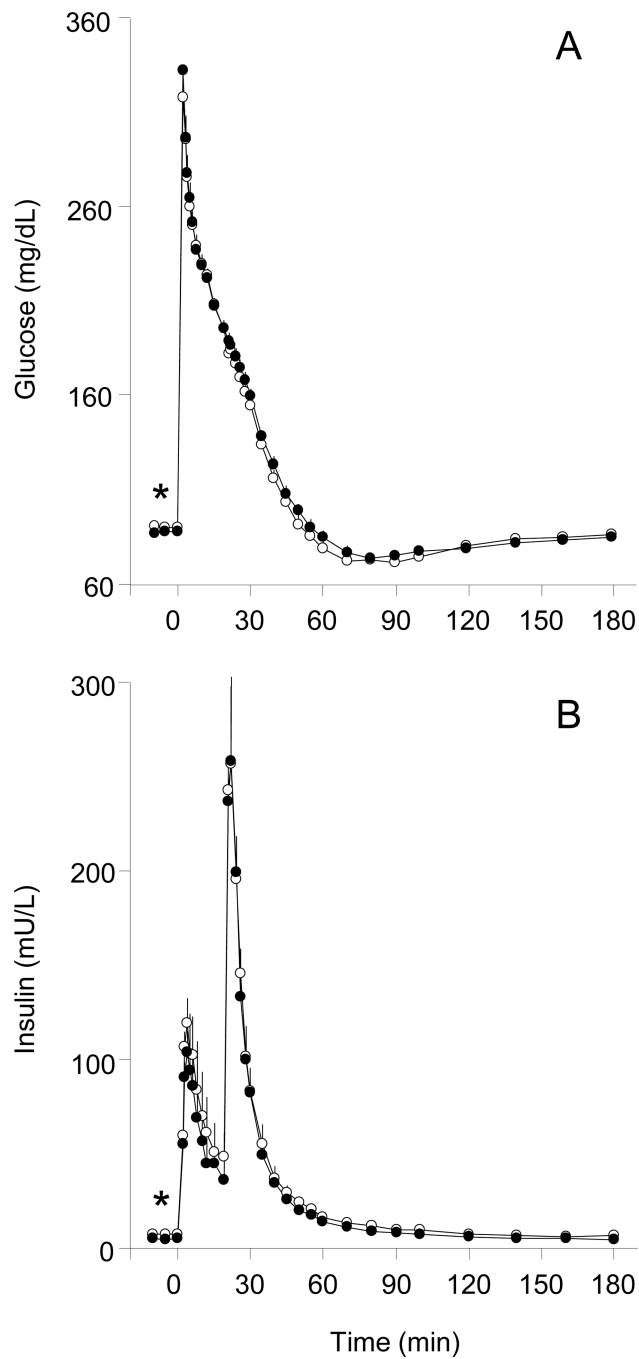
Figure 2.
Mean (+SE) concentrations of plasma glucose (**A**) and serum insulin (**B**) during the 3-h intravenous glucose tolerance test at the end of the 8.5-h (open circles) and 5.5-h (solid circles) bedtime condition (n=10). * P<0.05 for effect of sleep condition on fasting concentrations based on mixed model analysis controlling for treatment order and body composition.
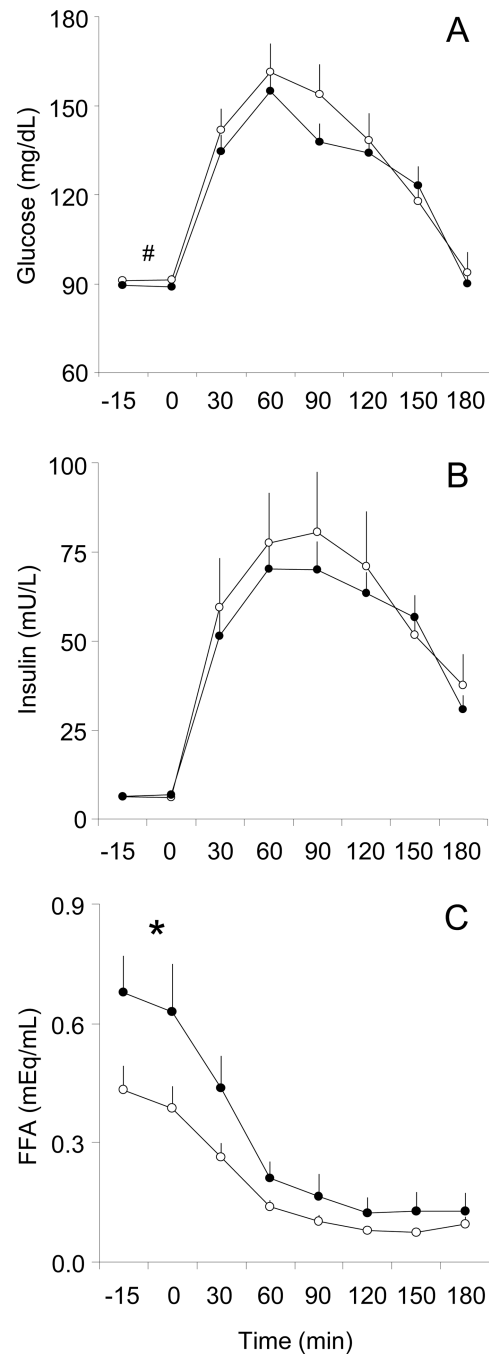
Figure 3.
Mean (+SE) concentrations of plasma glucose (**A**), serum insulin (**B**) and plasma free fatty acids, FFA, (**C**) during the 3-h oral glucose tolerance test at the end of the 8.5-h (open circles) and 5.5-h (solid circles) bedtime condition (n=10). * $P<0.05$ and # $P<0.06$ for effect of sleep condition on fasting concentrations based on mixed model analysis controlling for treatment order and body composition.

Figure 4.
Mean (+SE) 24-h profiles of circulating cortisol (**A**), growth hormone, GH (**B**), epinephrine (**C**), and norepinephrine (**D**) concentrations measured every 30 minutes at the end of the 8.5-h (open circles) and 5.5-h (solid circles) bedtime condition (n=10). The timing of intravenous glucose administration (IVGTT), lunch, and dinner is marked by vertical grey bars. To improve clarity, data collected between 20:00 and 22:00 are double plotted at the beginning and the end of the time axis. * $P<0.05$ for effect of sleep condition based on mixed model analysis controlling for treatment order and body composition; [#] $P<0.05$ for the time interval 4–5 h after the start of the IVGTT.

Table 1

Treatment-related changes in sleep duration and loss of body weight and adiposity

	8.5-h TIB	5.5-h TIB
Total sleep time (h:min/day)	7:25 (0:32)	5:14 (0:06)*
Initial body weight (kg)	82.0 (11.2)	80.5 (10.3)
Initial body mass index (BMI, kg/m^2)	27.5 (2.2)	27.1 (2.0)
Weight loss (kg)	2.9 (1.4)	3.0 (1.0)
(%)	3.5 (1.2)	3.7 (1.0)
Fraction of weight loss as fat (%)	56 (35)	25 (24)#
Final fat-free mass (kg)	54.1 (10.7)	53.1 (10.3)#
Final body fat (kg)	25.0 (6.3)	24.4 (6.4)

Data are mean (SD) values; N=10. 8.5-h TIB and 5.5-h TIB: 8.5 and 5.5-h time-in-bed conditions.

*
P<0.01 by paired t-test;

#
P<0.01 for the effect of sleep restriction (5.5-h vs. 8.5-h TIB condition as fixed effect) based on mixed model analysis with treatment period as repeated measure and initial fat and fat-free body mass as time-varying covariates.

Table 2

Measures of glucose regulation and blood lipids

	8.5-h TIB	5.5-h TIB
24-h glucose, insulin and C-peptide		
24-h mean glucose (mg/dL)	99 (3)	99 (2)
24-h mean insulin (mU/L)	20 (10)	16 (6)[*]
24-h mean C-peptide (pmol/mL)	1.28 (0.31)	1.17 (0.28)[#]
24-h mean insulin secretion (pmol/min)	271 (78)	244 (64)[#]
TIB mean glucose (mg/dL)	92 (3)	90 (4)
TIB mean insulin (mU/dL)	9 (4)	6 (2)[*]
TIB mean C-peptide (pmol/mL)	0.79 (0.15)	0.63 (0.22)[*]
TIB mean insulin secretion (pmol/min)	149 (27)	125 (43)[*]
Oral glucose tolerance test		
Fasting glucose (mg/dL)	91 (4)	89 (6)[#]
120-min glucose (mg/dL)	139 (28)	134 (14)
3-h AUC glucose (mg.dL^{-1}.min)	24041 (3562)	23102 (2027)
3-h AUC insulin (mU.L^{-1}.min)	10856 (6106)	9908 (2764)
Fasting FFA (mEq/mL)	0.41 (0.18)	0.65 (0.33)[*]
FFA 120–180 min (mEq/mL)	0.07 (0.03)	0.10 (0.12)
FFA supression (%)	79 (13)	84 (12)
Intravenous glucose tolerance		
Fasting glucose (mg/dL)	90 (3)	88 (4)[*]
Fasting insulin (mU/dL)	7 (3)	5 (2)[*]
Fasting C-peptide (pmol/mL)	0.71 (0.15)	0.62 (0.21)[*]
S_I (mU/L)$^{-1}$.min^{-1}	3.5 (1.5)	3.0 (1.1)[*]
AIR_G (mU.L^{-1}.min)	743 (489)	647 (378)
DI	2237 (1066)	1719 (627)[*]
Fasting blood lipids		
Total cholesterol (mg/dL)	181 (43)	169 (33)[*]
LDL cholesterol (mg/dL)	114 (40)	104 (34)[*]
HDL cholesterol (mg/dL)	45 (11)	47 (7)
Triglycerides (mg/dL)	105 (33)	90 (24)

Data are mean (SD) values; N=10. TIB: time in bed; AUC: area under the curve; S_I: insulin sensitivity index; AIR_G: acute insulin response to glucose; DI: disposition index; FFA: free fatty acids; ISR: insulin secretion rate.

[*] P<0.05 and

[#] P<0.09 for the effect of sleep restriction (5.5-h TIB vs. 8.5-h TIB) on measured variables using mixed linear model analysis controlling for crossover study design (treatment period as repeated measure) and final fat and fat-free body mass as time-varying covariates.