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Slow Oscillations of Plasma Glucose and Insulin Secretion Rate Are Amplified During Sleep in Humans Under Continuous Enteral Nutrition

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Summary: Concomitant oscillations of plasma glucose and insulin secretion rate with a periodicity of about 80 minutes have been identified in normal humans. To determine whether these slow oscillations are influenced by sleep, peripheral levels of glucose and C-peptide were measured at 10-minute intervals over 24 hours in seven subjects, once with a normal nocturnal sleep from 2300 to 0700 hours, and once with a shifted daytime sleep from 0700 to 1500 hours. The subjects received continuous enteral nutrition and remained supine for the 8 hours preceding blood sampling and throughout the whole experiment. Insulin secretion rate was estimated by deconvoluting peripheral C-peptide levels using an open two-compartment model. The amplitude of glucose and insulin secretion rate oscillations increased by 160% during the 8-hour sleep periods, at whatever time they occurred, whereas the influence of the time of day was not significant. Glucose and insulin secretion rate mean levels were also significantly increased during normal nocturnal sleep compared to the remaining 8-hour waking periods, but this effect did not persist when sleep was shifted to the daytime. The number of oscillations was similar in both experimental series and was not affected by sleep. No systematic concordance was found between glucose and insulin secretion rate oscillations and the rapid eye movement–nonrapid eye movement sleep cycles, despite them having similar periodicities. This study demonstrates that increased amplitude of glucose and insulin secretion rate oscillations is related to sleep rather than to the time of day, without any associated frequency variations. The slightly higher mean glucose levels observed during the nighttime period possibly reflect a weak time-dependent influence. **Key Words:** Glucose—Insulin secretion rate—Ultradian rhythm—Sleep—Enteral nutrition.

Various protocols have enabled the demonstration of time-dependent variations of glucose tolerance, with a higher plasma glucose response to meals or during oral glucose tolerance tests in the afternoon than in the morning (1–4). It has also been demonstrated in humans given a glucose infusion at a constant rate that glucose tolerance diminishes in the evening and reaches a minimum in the middle of the night (5,6). In a recent study (7), Van Cauter further demonstrated that both circadian rhythmicity and sleep influence the 24-hr profiles of glucose and insulin secretion rate (ISR), leading to higher mean levels during nocturnal sleep. However, none of these studies has investigated the effect of sleep on the slow oscillations, with a periodicity of 50–150 minutes, which have been observed in animals and humans for both glucose and ISR. The mechanisms and the physiological significance of these fluctuations, which are best seen in situations characterized by high insulin levels, that is, in response to meals (8–10), during continuous enteral nutrition (11) and during glucose infusion (5,12) are at present uncertain, although in diabetes abnormalities in their temporal organization have been reported. This suggests that the fluctuations may play a role in the pathogenesis of this disorder (13–15).

This study was conducted to determine whether sleep affects the slow oscillations in glucose and ISR in humans under continuous enteral nutrition. Two 24-hour profiles were compared in the same subjects, one of which was obtained under basal conditions with a normal nocturnal sleep and the other after a shift of 8 hours in the sleep period. In addition, because glucose and insulin oscillations and the rapid eye movement

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(REM)–nonrapid eye movement (NREM) sleep cycles have similar periodicities, it was of interest to look for a possible temporal relationship between the two phenomena.

MATERIALS AND METHODS

Subjects

Seven healthy males between 20 and 28 years of age volunteered for the study. All were of normal weight; body mass index was 20.8 ± 1.8 kg/m^2. They had normal routines of work, meals and sleep. They were selected after medical examination and screening tests: a questionnaire on their usual sleep–wake cycle and an evening–morning test. Subjects with sleep disorders or having experienced time-shift or sleep deprivation during the previous weeks, smokers and subjects with signs of underlying disease or those taking medication were excluded from the study. None had a personal or family history of diabetes. Fasting glucose and insulin (mean ± SE) levels were 5.02 ± 0.08 mmol·l^{-1} and 44.5 ± 4.3 pmol·l^{-1}, respectively. They all gave their informed consent and the experiments were approved by the Strasbourg Hospital Ethics Committee.

Protocol

Experiments were performed in soundproof, air-conditioned sleep chambers. The subjects were studied twice in a random order, with a 1- to 2-month interval between experiments, one of which was under basal conditions with normal nocturnal sleep from 2300 to 0700 hours and the other after an acute 8-hour delay in the sleep–wake cycle, which was obtained by total sleep deprivation during the night followed by 8 hours of daytime sleep from 0700 to 1500 hours. A catheter was inserted at 1400 hours under local anesthesia into an antecubital vein and was kept patent with heparinized solutions. To avoid the influence of repeated meal intake, the subjects received continuous enteral nutrition, which began 8 hours before blood sampling (Sondalis, ISO, Sopharga, Puteaux, France; 50% carbohydrate; 35% fat; 15% protein; 90 Cal·h^{-1}). Electrodes were attached for the following uninterrupted electrophysiological recordings: two electroencephalograms, two electrooculograms, one electromyogram and one electrocardiogram. Sleep stages were scored from the polygraphic recordings according to established criteria (16). The subjects remained supine for the 8 hours preceding blood sampling and throughout the whole experiment. When awake, the subjects read, listened to music and watched television. During the night of sleep deprivation, they were kept under continuous surveillance and conversed with an experimenter.

Blood sampling and plasma sample measurements

Blood was taken continuously for 24 hours, from 2300 (day 1) to 2300 hours (day 2), using a peristaltic pump (Ismatec, Bioblock Scientific, Strasbourg, France). The blood was collected in an adjoining room and sampled into tubes containing EDTA-Na_2 (1 mg·ml^{-1}) and aprotinin (500 kIU·ml^{-1}) at 10-minute intervals. A maximum of 220 ml blood was removed during the 24 hours and this produced no significant change in hematocrit. Samples were immediately centrifuged at 4°C and the plasma was stored at −25°C. Plasma glucose levels were measured in duplicate with a glucose oxidase method (Boehringer, Mannheim, Germany). The intraassay coefficient of variation (CV) was 2%. Plasma C-peptide levels were determined in duplicate by radioimmunoassay (RIA) (International CIS, Division France, Gif-sur-Yvette, France). The intraassay CV was 12.0% for values below 265 pmol·l^{-1}, 7.1% for values between 265 and 850 pmol·l^{-1} and 5.5% for values between 850 and 4,000 pmol·l^{-1}. All samples from one individual were analyzed in a single assay.

Data analysis

Insulin secretion rate

The ISR during each 10-minute interval was derived from the plasma levels of C-peptide smoothed by the robust least square method of Cleveland, using a two-compartment model as proposed by Eaton et al. (17). This deconvolution method is based on the fact that insulin and C-peptide are co-secreted in equimolar concentrations and that C-peptide, which is not extracted by the liver, has a constant metabolic rate even under non-steady-state conditions. The kinetic parameters for C-peptide distribution and metabolism described by Shapiro et al. (12) were used.

Pulse analysis of 24-hour profiles of plasma glucose levels and ISR

The individual 24-hour glucose and ISR profiles were analyzed using the computer program ULTRA (18,19). This algorithm eliminates all peaks for which either the increment or the decrement does not reach a certain threshold. The threshold for pulse detection was set at two times the CV for glucose. Peaks of ISR were considered as significant if both the increment and the decrement were greater than two times the upper limit of the CV for C-peptide assays. Significant pulses of glucose and ISR were considered to be concomitant if their peaks occurred within 20 minutes of each other.

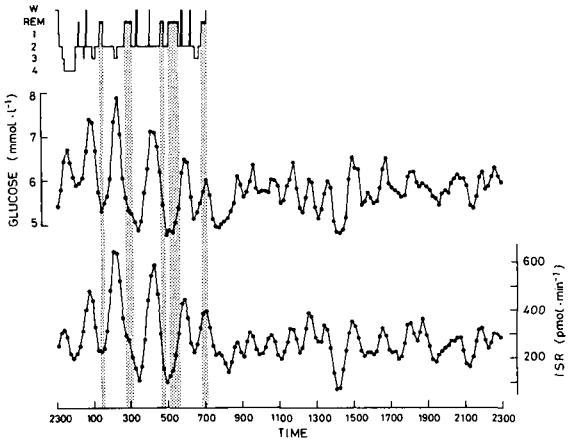

FIG. 1. Individual 24-hour profiles of plasma glucose levels and insulin secretion rate (ISR) with normal nighttime sleep. REM sleep lies in shaded areas.

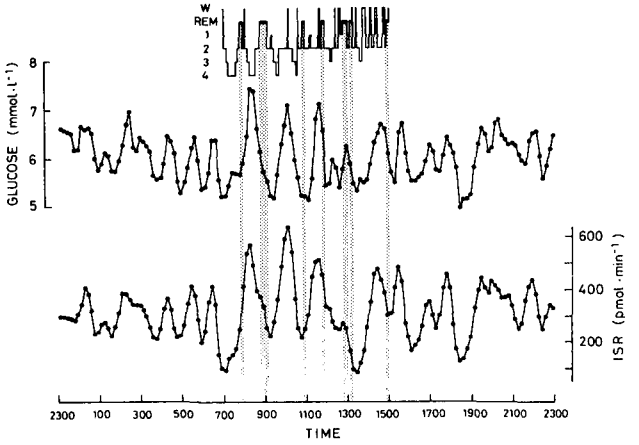

FIG. 2. Individual 24-hour profiles of plasma glucose levels and insulin secretion rate (ISR) with shifted daytime sleep. REM sleep lies in shaded areas.

Statistical analysis

Analysis of variance for repeated measures and paired *t* tests with Bonferroni procedure for multiple comparisons were used to assess the statistical difference between the mean values, the mean number of pulses and their absolute amplitude. Three periods were considered: 2300–0700 hours (P1); 0700–1500 hours (P2) and 1500–2300 hours (P3). The results are expressed as means ± SE. For the examination of associations between glucose and ISR oscillations and sleep stages, the different episodes of each sleep stage lasting at least 20 minutes were related to the slopes of glucose and ISR variations. Two sleep episodes were considered distinct from one another if they were separated by one or more blood sampling periods (at least 10 minutes). For glucose and ISR values, the linear regression was calculated for three successive sample points during the various sleep episodes. Sample 0 was set at the nearest point to the beginning of the sleep stage. Sample points 1 and 2 corresponded to the two subsequent samples. The slopes were compared with the nonparametric Hodges-Lehmann aligned rank test (20). This statistical test is an extension of the Wilcoxon/Mann-Whitney test. The purpose of the alignment procedure (calculation of the deviations from each subject's mean) prior to the ranking is to remove the between-subject variability. Calculations performed on the ranks lead to the derivation of a statistic z, which is normally distributed. Paired comparisons of the ranked slopes were achieved using the Bonferroni procedure. Two-tailed probabilities were reported because the hypothesis did not predict the direction of the differences.

RESULTS

Individual 24-hour profiles

Figure 1 gives the 24-hour profiles of plasma glucose levels and ISR for one individual with normal nighttime sleep and Fig. 2 gives the profiles obtained with shifted daytime sleep. As previously described (11), synchronous oscillations with a mean periodicity of about 80 minutes were observed throughout the 24 hours in all the subjects studied under continuous enteral nutrition.

Pulse analysis of the individual profiles revealed about 18 oscillations/24 hours of plasma glucose and ISR, both under basal conditions and after the shift in the sleep period (Table 1). The number of the oscillations was similar in both experimental series and was not affected either by sleep or by the time of day.

In contrast, increased amplitude of glucose and ISR

TABLE 1. *Effect of an 8-hour shift in the sleep period on the number (mean ± SE) of significant pulses of plasma glucose and insulin secretion rate (ISR) in seven subjects*

Experimental conditions	24 hours	2300–0700 hours	0700–1500 hours	1500–2300 hours
Nighttime sleep (2300–0700 hours)				
Plasma glucose	18.1 ± 0.6	5.7 ± 0.4	6.4 ± 0.4	6.0 ± 0.2
ISR	16.6 ± 0.8	5.3 ± 0.4	6.1 ± 0.4	5.1 ± 0.3
Daytime sleep (0700–1500 hours)				
Plasma glucose	18.4 ± 0.6	6.3 ± 0.3	6.1 ± 0.3	6.0 ± 0.3
ISR	16.1 ± 0.5	5.6 ± 0.2	5.6 ± 0.4	5.0 ± 0.2

TABLE 2. *Effect of an 8-hour shift in the sleep period on the absolute amplitude (mean ± SE) of significant pulses of plasma glucose and insulin secretion rate (ISR) in seven subjects*

Experimental conditions	24 hours	2300–0700 hours	0700–1500 hours	1500–2300 hours
Nighttime sleep (2300–0700 hours)				
Plasma glucose (mmol·l^{-1})	1.1 ± 0.1	1.4 ± 0.2	1.1 ± 0.1	0.9 ± 0.1
ISR (pmol·minute^{-1})	210 ± 9	267 ± 15	175 ± 12	188 ± 12
Daytime sleep (0700–1500 hours)				
Plasma glucose (mmol·l^{-1})	1.1 ± 0.1	0.8 ± 0.1	1.6 ± 0.1	1.1 ± 0.1
ISR (pmol·minute^{-1})	238 ± 17	161 ± 16	326 ± 26	228 ± 16

oscillations was observed during sleep, irrespective of the experimental conditions, whereas the influence of the time of day independently of sleep was not significant (Table 2). The sleep-associated increase was 150% during normal nighttime sleep and 170% during shifted daytime sleep for both glucose and ISR compared to the two remaining 8-hour waking periods. This difference between night- and daytime sleep was not statistically significant. In individual subjects, the amplitude of the oscillations could be as high as 2.5 mmol·l^{-1} for glucose and 450 pmol·minute^{-1} for ISR.

Mean 24-hour profiles of plasma glucose levels and ISR

Figure 3 shows the mean 24-hour profiles of plasma glucose levels and ISR from the group of seven subjects with normal nocturnal sleep from 2300 to 0700 hours (top) and with daytime sleep from 0700 to 1500 hours after a night of sleep deprivation (bottom).

During normal nocturnal sleep, mean glucose levels were slightly but significantly higher (108%) compared to the remaining 8-hour waking periods, whereas mean levels were not affected when sleep occurred during the daytime (Table 3). A within-factor ANOVA on the mean glucose levels revealed a significant difference on the period factor, with a significant effect of time of day but no effect of sleep. For ISR, higher mean levels were observed when nighttime periods were considered. The ANOVA performed on the ISR data showed a significant condition–period interaction.

Relationship with the internal sleep structure

The relationship between sleep structure and variations of glucose and ISR was analyzed by using paired two-tailed comparisons of the slopes during the various sleep stages. The results of the three planned comparisons are shown in Table 4. No significant variation for glucose or for ISR was found for any sleep stage.

DISCUSSION

In this study, we demonstrated that the slow oscillations in the 60–150-minute period range of plasma glucose levels and ISR are amplified during sleep at whatever time it occurs. These oscillations observed previously in humans under continuous enteral nutrition (11) exhibit a 160% increase in their amplitude during sleep, without associated modulation of their frequency and without any systematic association with the different sleep stages. Of interest, the mean levels of plasma glucose were slightly higher during the nighttime period, possibly reflecting a weak time-dependent influence, but the amplitude of the oscillations was not modulated by this influence.

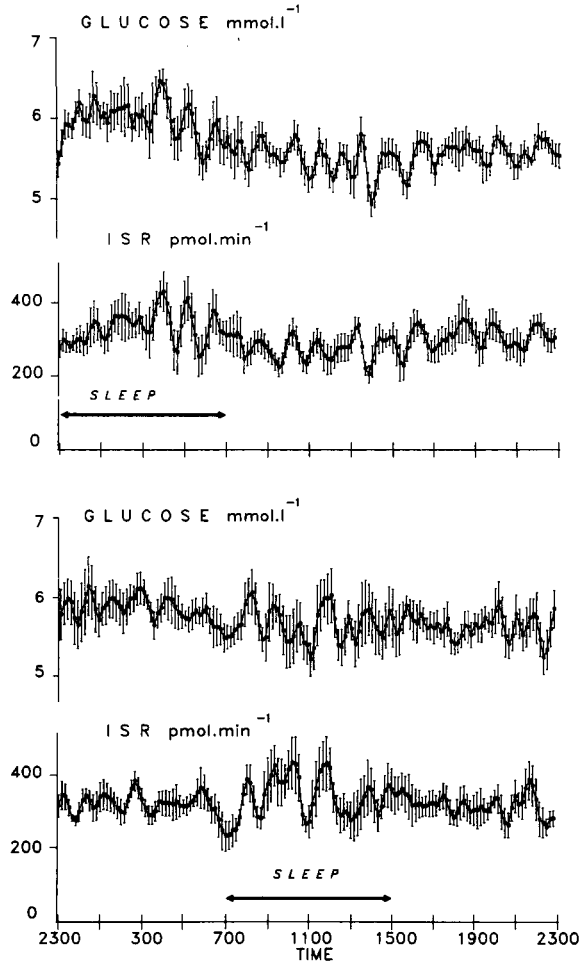

FIG. 3. Effect of an 8-hour delay in the sleep–wake cycle on the mean (± SE) 24-hour profiles of plasma glucose levels and insulin secretion rate (ISR) in seven subjects.

TABLE 3. *Effect of an 8-hour shift in the sleep period on the mean ± SE plasma glucose levels and insulin secretion rate (ISR) in seven subjects*

Experimental conditions	24 hours	2300–0700 hours	0700–1500 hours	1500–2300 hours
Nighttime sleep (2300–0700 hours)				
Plasma glucose (mmol·l^{-1})	5.7 ± 0.1	6.0 ± 0.1	5.5 ± 0.1	5.6 ± 0.1
ISR (pmol·minute^{-1})	307 ± 18	334 ± 16	279 ± 16	307 ± 26
Daytime sleep (0700–1500 hours)				
Plasma glucose (mmol·l^{-1})	5.7 ± 0.1	5.9 ± 0.2	5.7 ± 0.1	5.6 ± 0.1
ISR (pmol·minute^{-1})	328 ± 16	324 ± 15	340 ± 16	320 ± 21

These results differ to some extent from those of several investigators who have shown that glucose levels or glucose tolerance are subject to nycthemeral variations. It has been shown repeatedly that plasma glucose responses to meals, to oral glucose and to an intravenous glucose load are higher in the evening than in the morning (1–4). It has also been described that glucose tolerance decreases in the evening, reaching a minimum around the middle of the night (5,6). In a recent study delaying the sleep period by 12 hours, Van Cauter et al. reported that both circadian rhythmicity and sleep modulate glucose and ISR profiles obtained from humans during continuous glucose infusion (7). These time-dependent variations could not be clearly seen in the present study, even when the morning and evening mean levels and the oscillation amplitude were analyzed and compared over 4-hour periods (i.e. 0700–1100 hours vs. 1900–2300 hours). A modest time-dependent influence was only revealed when the mean glucose and ISR levels of the 8-hour nighttime periods were considered. Differences in the experimental protocols, such as 12-hour sleep delay versus 8-hour sleep delay or constant glucose infusion versus constant enteral nutrition, may account for the variations between the results.

It is now evident that most of the 24-hour endocrine rhythms are under multifactorial control, combining an internal oscillator and sleep-related influences, and that the relative importance of both factors differs widely between hormones (21,22). Often, amplitude modulation of the secretory bursts is sufficient to create a 24-hour rhythm; examples of this include luteinizing hormone and adrenocorticotropin (23). In contrast, certain rhythms, for example thyroid stimulating hormone, growth hormone and B-endorphin, are generated by diurnal variations in both secretory-burst amplitude and frequency. A diurnal variation in secretory-burst frequency alone has not been demonstrated for any pituitary hormone in normal humans. It has recently been suggested that distinct neuroendocrine mechanisms give rise to the variations in frequency and in amplitude of the secretory bursts (23). The present study, which demonstrates amplitude variations of plasma glucose and ISR oscillations contrasting with a constant frequency, supports this hypothesis. This is also suggested by the recent demonstration in pancreas transplant recipients that low-frequency pulse period was normal but pulse amplitude was increased (24).

TABLE 4. *Paired two-tailed comparisons of the different sleep stages, concerning the slopes of glucose and insulin secretion rate (ISR) variations for the seven subjects during night- and daytime sleep. The z values are the normal approximations of the Hodges-Lehmann test. No significant difference was found for any sleep stage*

	Glucose		ISR	
	z	p	z	p
Nighttime sleep				
SWS[a] vs. REM sleep	1.35	ns	1.28	ns
SWS vs. Stage 2	0.59	ns	0.61	ns
REM vs. Stage 2	1.20	ns	2.33	ns
Daytime sleep				
SWS vs. REM sleep	0.45	ns	0.27	ns
SWS vs. Stage 2	0.51	ns	0.89	ns
REM vs. Stage 2	0.55	ns	1.41	ns

[a] Slow-wave sleep.

The close proximity of sleep-controlling mechanisms and the hypothalamus has orientated most of the research into the relations between sleep and hormones towards hormones of the hypothalamo-pituitary axis. At present the effect of sleep on other endocrine systems has received little attention, and recent findings suggest this research needs expanding. It has been demonstrated that renin, an enzyme of the renin-angiotensin system is a biological marker of the NREM–REM sleep cycle (25), and in a previous study (7) mean glucose and insulin levels have been shown to be influenced by sleep. In the present study, individual glucose and ISR oscillations were examined in parallel with the NREM–REM sleep phases, because they show similar periodicities and because cerebral blood flow and glucose metabolism in animals differ depending on the sleep stage, being highest during REM and lowest during NREM sleep (26). However, neither glucose nor ISR oscillations appeared to be associated with any particular sleep stage.

The exact mechanisms by which the oscillations in

glucose and ISR are amplified during sleep are not known. This amplification of the oscillations is not accompanied by an important increase in mean levels, as is seen during sleep in the case of prolactin or plasma renin activity, for which such an increase is more pronounced. This amplification may be attributed to a different sensitivity of glucose to feedback from insulin, increased amplitude of glucose counterregulatory hormone pulses, decreased glucose utilization and production during sleep (27), changes in the gut's absorption or a combination of these factors. Another possibility would be that wakefulness dampens oscillations that are disclosed during sleep. Further studies are necessary to elucidate the precise mechanisms controlling glucose and ISR pulses during sleep and wakefulness in normal humans and in diabetic patients.

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