Entrainment of Ultradian Oscillations in the Secretion of Insulin and Glucagon to the Nonrapid Eye Movement/Rapid Eye Movement Sleep Rhythm in Humans*

WERNER KERN, SYLVIA OFFENHEUSER, JAN BORN, AND HORST L. FEHM

Departments of Clinical Neuroendocrinology and Internal Medicine, University of Luebeck, D-23538 Luebeck, Germany

ABSTRACT

The cause of ultradian oscillations in the secretion of glucagon and insulin with a period length between 70–140 min has been attributed to feedback mechanisms of glucose and insulin. Influences of the central nervous system on these ultradian glucagon and insulin oscillations remained to be elucidated.

In the present study on one occasion, concentrations of glucose, glucagon, insulin, and GH were determined at 15-min intervals from 2100–0700 h in 16 healthy subjects while they were infused with saline solution. On another occasion, concentrations of these hormones during nocturnal sleep were determined in 10 of these subjects while they were constantly infused with glucose (4.5 mg/kg/min). The order of the treatments (placebo vs. glucose) was balanced across subjects, and experiments were performed in a double blind manner. Significant glucagon and insulin peaks were determined by the peak detection algorithm Cluster. Sleep was recorded somnographically.

During the infusion of saline solution, glucagon concentrations showed spontaneous oscillations, with a mean periodicity of 107.9 ± 13.2 min. During the constant infusion of glucose, oscillations of similar periodicity (110.1 ± 10.3 min) were observed for insulin. The phases of glucagon and insulin secretory activity on the respective nights were entrained to the nonrapid eye movement (non-REM)/REM sleep cycle. Significant increases in the concentrations of glucagon ($\chi^2 = 5.23; P < 0.02$) and insulin ($\chi^2 = 7.32; P < 0.01$) generally fell into epochs of non-REM sleep, with a preference for the beginning of the epochs, whereas decreasing concentrations of those hormones coincided significantly with epochs of REM sleep ($P < 0.05$). The time spent in the different sleep stages was not altered during glucose infusion.

In conclusion, ultradian oscillations of insulin and glucagon concentrations are modulated by central nervous system mechanisms entraining secretory pulses of the a- and $\beta$-cells of the endocrine pancreas to the non-REM sleep epochs of the non-REM/REM sleep cycle. (J Clin Endocrinol Metab 81: 1541-1547, 1996)
Subjects and Methods

Subjects

Sixteen healthy men of normal body weight (±10%), aged 18–34 yr (mean, 25.5 yr), voluntarily participated in the experiments. None was taking any drugs, and none had a personal or family history of diabetes or sleep disturbances. The men were required to get up before 0700 h on the days before experimental nights, not to take any naps during the day, and to abstain from coffee and alcoholic beverages. They were acclimated to the experimental sleep condition by spending 1 night under the conditions of the experiment, including the placement of catheters and the infusion of placebo (saline solution). The study was approved by the committee on research involving human subjects of the University of Ulm, and each man gave written informed consent.

Procedure

The experiments took place in an air-conditioned, electrically shielded room. Upon arrival at the laboratory at 1900 h, subjects were prepared for somnopolygraphic recording and blood sampling. Lights were turned off at 2300 h, and continuous recordings and blood samples were obtained until 0700 h, when the subjects were awakened. Blood samples for determination of blood glucose, serum insulin, glucagon, GH, and C peptide (measured only in five subjects) concentrations were taken every 15 min via an iv forearm catheter connected to a long thin tube (1.5-mL volume), which enabled blood collection from an adjacent room without disturbing the subject’s sleep.

Subjects were studied on 2 occasions, during which placebo (150 mEq/L NaCl solution) or glucose (4.5 mg/kg/min) was infused at a constant rate. For infusions of glucose and placebo, a second iv forearm catheter was placed in the other arm. The infusions started at 2100 h. The 2 experimental sessions for a subject were at least 1 week apart. Six subjects completed only the placebo night. The order of treatments (placebo vs. glucose) was balanced across the remaining 10 subjects. Experiments were performed in a double blind manner. On the morning after experimental nights, subjects were asked whether they believed that they had been infused with placebo or glucose.

Data reduction and analysis

Insulin, glucagon, GH, and C peptide were measured by RIA (insulin: Pharmacia Insulin RIA 100, Pharmacia Diagnostics, Uppsala, Sweden; intraassay coefficient of variation, 4.5%; glucagon: Hermann Biermann Diagnostica, Bad Nauheim, Germany; intraassay coefficient of variation, 4.4%; GH: BioMerieux, Nuertingen, Germany; intraassay coefficient of variation, 5% between 1.5–60 µg/L; C peptide: C-Peptide-RIA, Hermann Biermann Diagnostica, Bad Nauheim, Germany; intraassay coefficient of variation, 2%). The interassay coefficient of variation was below 10% in all assays. All samples from the same subject were determined in duplicate in the same assay. Plasma glucose was measured in duplicate with a Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA), with a coefficient of variation smaller than 1%. Sleep stages were determined from recordings of electroencephalogram, electrooculogram, and electromyogram, which were scored offline according to the criteria described by Rechtschaffen and Kales (28).

For each night, sleep onset latency with reference to 2300 h, sleep time, total time spent in the different sleep stages (awake, sleep stages 1–4, and REM sleep), and latency of the sleep stages with reference to sleep onset were determined. The amount of time in slow wave sleep (SWS) was defined as the sum of sleep stages 3 and 4. The percentages of time spent in the different sleep stages and average plasma concentrations of blood glucose, insulin, glucagon, and GH were calculated for the total sleep time and, in addition, separately for the first and second halves of sleep time.

Significant secretory pulses of glucagon, insulin, and (in five subjects) C peptide were analyzed by a peak detection algorithm (Cluster), thereby excluding fluctuations due to assay variations (29). Of importance was a further analysis comparing the temporal distribution of phases of increasing and decreasing concentrations of these hormones, i.e. for each sleep stage the time of decreasing vs. increasing concentrations of the hormone was determined to decide whether secretory activity of the respective hormone coincides with the occurrence of a particular sleep stage. Significant increases and decreases in this analysis were defined by Cluster analysis with respect to changes within 15 min that, respectively, exceeded the assay variability. In addition, for each significant peak, the sleep stage at the time of peak onset (defined by Cluster analysis) was determined. Results are indicated as the mean ± se. Statistical evaluation was based on two-tailed Wilcoxon tests. P < 0.05 was considered significant.

Results

Sleep recordings

Table 1 summarizes results concerning sleep parameters. Total sleep time, percentage of sleep spent in different sleep stages, and latencies of the different sleep stages during infusion of placebo indicated normal undisturbed sleep. The infusion of 4.5 mg/kg/min glucose did not change any of the sleep parameters significantly. The mean length of the nonREM/REM cycles was 123.6 ± 5.8 min during the infusion of glucose and 116.7 ± 7.9 min on the placebo nights.

Subjects were, in general, unable to correctly identify the treatment they had received.

Blood glucose, insulin, glucagon, and GH concentrations

Table 2 summarizes concentrations of blood glucose, insulin, glucagon, and GH averaged across total sleep time and separately for the first and second halves of sleep time during the infusion of placebo and 4.5 mg/kg/min glucose. During

| Parameter | Placebo | Glucose |
|-----------|---------|---------|
| Time (min) |         |         |
| Sleep onset | 18.7 (12.5) | 8.2 (3.6) |
| Sleep time | 462.3 (12.5) | 472.8 (3.6) |
| %, total |         |         |
| W | 3.2 (2.4) | 3.5 (2.1) |
| S1 | 7.1 (1.4) | 8.4 (2.4) |
| S2 | 49.9 (3.3) | 50.6 (1.5) |
| S3 | 10.9 (1.6) | 10.4 (1.3) |
| S4 | 10.0 (0.8) | 8.0 (1.8) |
| SWS | 20.9 (1.9) | 18.4 (2.7) |
| REM | 18.8 (1.9) | 18.9 (2.0) |
| %, first half |         |         |
| W | 1.1 (0.9) | 0.4 (0.3) |
| S1 | 7.6 (2.4) | 11.4 (3.6) |
| S2 | 44.4 (4.9) | 50.1 (3.9) |
| S3 | 16.9 (2.5) | 14.2 (2.6) |
| S4 | 19.4 (1.7) | 14.8 (3.3) |
| SWS | 36.6 (3.0) | 29.0 (4.2) |
| REM | 11.0 (2.3) | 9.5 (2.6) |
| %, second half |         |         |
| W | 5.5 (3.9) | 0.6 (4.1) |
| S1 | 6.5 (1.3) | 5.4 (2.2) |
| S2 | 55.9 (3.9) | 52.1 (3.0) |
| S3 | 19.4 (1.7) | 13.7 (2.6) |
| S4 | 0.9 (0.4) | 1.3 (0.8) |
| SWS | 5.7 (1.7) | 8.0 (2.0) |
| REM | 26.8 (3.3) | 25.3 (3.5) |
| Latency (min) |         |         |
| S2 | 4.7 (1.3) | 7.7 (2.2) |
| SWS | 20.9 (5.6) | 25.2 (6.0) |
| REM | 147.1 (18.4) | 164.5 (22.8) |

Values are the mean ± se. Latency was measured with reference to sleep onset. There were no significant (P > 0.05) differences for any of the parameters between the placebo and glucose conditions.
On 29 July 2018.

The mean pulse amplitude was 15.8 ± 3.5 pg/L, corresponding to 53.8% of the average concentration of insulin during these nights. In 5 subjects, C peptide levels were also measured. On the nights during constant glucose infusion, all significant insulin peaks were accompanied by significant C peptide peaks.

Of increasing and decreasing insulin and glucagon concentrations. REM sleep significantly coincided with decreasing concentrations of insulin and glucagon, i.e. a diminished synchronous secretory activity of the α- and β-cells of the pancreas and non-REM sleep significantly coincided with increasing concentrations of both hormones, i.e. an increased synchronous secretory activity of the endocrine pancreas. Moreover, the peak onset of 40 (representing 97.6%) of the 41 significant insulin peaks fell into a phase of non-REM sleep (2 = 5.23; P < 0.02; see Fig. 1 for examples of individual profiles; Fig. 2). Although periods of intermittent wakefulness appeared to be generally short, these periods were significantly associated with decreasing concentrations of insulin.

To further evaluate the temporal relationship between the secretory activities of the α- and β-cells of the pancreatic islets and central nervous system sleep processes, the distribution of onsets of secretory pulses across the non-REM/KEM cycle was determined for glucagon and insulin (Fig. 2). For this purpose, non-REM/KEM cycles were divided into 10 periods of equal length, each representing 10% of a cycle. As indicated in Fig. 2, the onsets of secretory pulses were not evenly distributed across the sleep cycle. For both hormones they were almost absent during REM sleep, but the greatest number of secretory pulses started in the beginning of the non-REM epoch of a sleep cycle [glucagon: \(\chi^2 = 8.69; P < 0.01\); insulin: \(\chi^2 = 15.76; P < 0.001\); for the comparison of REM sleep (representing about 20% of a non-REM/REM sleep cycle) and the non-REM sleep phase immediately after REM sleep (which also comprised 20% of a sleep cycle).

Average GH concentrations during total sleep time and

### Table 2. Concentrations of blood glucose, insulin, glucagon, and GH for total sleep time and separately for first and second halves of sleep time during infusion of 4.5 mg/kg · min glucose from 2100–0700 h compared to the placebo condition (n = 10)

| Parameter | Placebo | Glucose | P value |
|-----------|---------|---------|---------|
| Total sleep time | | | |
| Glucose (mmol/L) | 5.11 (0.16) | 7.72 (0.26) | <0.005 |
| Insulin (pmol/L) | 49.2 (4.2) | 190.2 (31.2) | <0.005 |
| Glucagon (ng/L) | 44.9 (4.1) | 34.2 (3.5) | <0.005 |
| GH (μg/L) | 3.4 (0.4) | 3.9 (0.8) | NS |
| First half of sleep time | | | |
| Glucose (mmol/L) | 4.90 (0.18) | 7.57 (0.37) | <0.005 |
| Insulin (pmol/L) | 51.0 (6.0) | 192.6 (37.2) | <0.005 |
| Glucagon (ng/L) | 42.2 (4.2) | 35.3 (3.5) | <0.05 |
| GH (μg/L) | 6.2 (0.9) | 5.4 (0.9) | NS |
| Second half of sleep time | | | |
| Glucose (mmol/L) | 5.32 (0.13) | 7.87 (0.21) | <0.005 |
| Insulin (pmol/L) | 46.8 (4.2) | 187.2 (30.6) | <0.005 |
| Glucagon (ng/L) | 47.5 (4.4) | 33.2 (3.7) | <0.005 |
| GH (μg/L) | 0.6 (0.1) | 2.4 (0.8) | NS |

Values are the mean ± se.
During the first and second halves of sleep time did not significantly differ between the glucose and placebo conditions (Table 2). Also, peak latency (placebo, 86.3 ± 12.3 min; glucose, 83.3 ± 10.3 min) and peak values (placebo, 9.8 ± 1.2 μg/L; glucose, 10.7 ± 1.9 μg/L) for the rise in GH concentrations after sleep onset were nearly identical during the infusions of placebo and glucose. To examine whether the increase in GH secretion at sleep onset had a phase-setting effect on the synchronization of insulin oscillations with non-REM/REM sleep cycles, mean profiles of blood glucose and serum insulin, glucagon, and GH concentrations were calculated. These profiles, shown in Fig. 3, however, did not give any evidence for such an effect, as the sleep-related increase in the GH concentration at the beginning of a night was accompanied by only a very slight increase in the blood glucose concentration, and serum insulin levels did not change. (Due to the substantial variations in the length of non-REM/REM cycles and interpeak intervals among subjects the ultradian oscillation of these hormones are hardly visible in the mean profiles.)

**Discussion**

This study aimed at investigating temporal relationships between the secretory activity of the α- and β-cells of the pancreas islets and central nervous system sleep processes. Under basal conditions, during infusion of placebo, glucagon concentrations showed, as in previous studies (6, 10), regular oscillations, with a mean periodicity of 107.9 min, indicating a spontaneous synchronous secretion of a great number of
INSULIN AND GLUCAGON SECRETION DURING SLEEP

65 glucagon peaks

NonREM

REM

41 insulin peaks

NonREM

REM

NonREM/REM cycle, %

0 10 20 30 40 50 60 70 80 90 100

NonREM/REM cycle, %

0 10 20 30 40 50 60 70 80 90 100

FIG. 2. Time of onset of a total of 65 glucagon pulses during placebo (in 16 nights; upper panel) and 41 insulin pulses during glucose infusion (in 10 nights; lower panel) during the non-REM/REM sleep cycle. The non-REM/REM cycle was divided into 10 epochs of equal duration, each representing 10% of the total cycle length. The onsets of glucagon ($\chi^2 = 5.23; P < 0.02$) and insulin pulses ($\chi^2 = 7.32; P < 0.01$) were not randomly distributed across the sleep cycle. They were nearly absent during REM sleep epochs and accumulated in the beginning of the non-REM sleep epoch of a non-REM/REM sleep cycle.

FIG. 3. Mean profiles ($\pm$SE) of blood glucose and serum insulin, glucagon, and GH averaged across the 10 subjects during constant infusion of placebo (●) and glucose (4.5 mg/kg/min; ○). Due to the substantial variations in the length of non-REM/REM cycles and interpeak intervals among subjects, the ultradian oscillations of these hormones are hardly visible in the mean profiles. These profiles do not give any evidence for a phase-setting effect of the increase in GH concentrations at the beginning of the night on the synchronization of insulin oscillations with non-REM/REM sleep cycles.

pancreatic α-cells. Stimulation of insulin secretion by constant infusion of glucose, as expected, invoked ultradian oscillations of serum insulin levels with a mean periodicity (110.1 min) comparable to that reported in several previous studies (7–11, 30). Notably, periodicity of oscillations of insulin concentrations (during stimulation with glucose) and glucagon concentrations (under basal condition) were almost identical.

C Peptide concentrations were measured in five of the subjects. Cluster indicated that on these nights all significant insulin peaks were accompanied by significant peaks in C peptide concentrations. This finding is in line with several foregoing studies investigating the slower ultradian oscillations of insulin concentrations in humans in response to meals (7), during continuous enteral nutrition (9), as well as during constant glucose infusion (10, 11). In all of those situations, oscillations of insulin and C peptide concentrations ran in parallel. The results together suggest these oscillations to reflect a synchronous secretory activity of the endocrine pancreas rather than periodic changes in the clearance rate of insulin.

It has been suggested that the ultradian oscillations in insulin concentrations are an inherent feature of the insulin-glucose feedback mechanism, with a delay between increases in insulin secretion and the resulting reduction of glucose levels (15, 31). However, if these oscillations were solely due to a delay in the feedback effect of glucose on insulin secretion, insulin peaks during a constant rate infusion of glucose would have been expected to be randomly distributed across episodes of non-REM and REM sleep. Actually, however, nearly all insulin secretory peaks originated during non-REM sleep, preferentially in the beginning of these epochs. Also, increasing concentrations of insulin were significantly associated with phases of non-REM sleep, indicating that the synchronized secretory activity of β-cells is linked to the presence of non REM sleep. By contrast, decreasing insulin concentrations, reflecting a diminished secretory activity, significantly coincided with the occurrence of REM sleep.
The ultradian oscillations in glucagon concentrations under basal conditions also were not randomly distributed across the night. Again, nearly all glucagon secretory peaks originated during non-REM sleep, preferentially in the beginning of these phases. In contrast, REM sleep significantly coincided with decreasing glucagon concentrations. Because under fasting baseline conditions, oscillations in blood glucose concentrations were virtually absent, it is unlikely that the oscillations of glucagon secretion reflect delays in the feedback effect linking glucose and glucagon. Rather than a neuronal influence, the secretory function of this sleep stage is modulated by the central nervous system. By contrast, during REM sleep an inhibitory central nervous system influence appears to diminish pancreatic activity. The sudden increase in the number of secretory pulses originating in the very beginning of a non-REM sleep epoch suggests inhibition to be active during the preceding REM sleep, which is released immediately upon the occurrence of subsequent non-REM sleep.

In principle, a temporal association between the non-REM/REM sleep cycle and secretory activity of the endocrine pancreas. Thus, rather than a direct stimulatory effect of non REM sleep on the secretory activity of the endocrine pancreas, such a temporal pattern indicates a permissive function of this sleep stage. By contrast, during REM sleep, an inhibitory central nervous system influence appears to diminish pancreatic activity. The sudden increase in the number of secretory pulses originating in the very beginning of a non-REM sleep epoch suggests inhibition to be active during the preceding REM sleep, which is released immediately upon the occurrence of subsequent non-REM sleep.

In summary, slightly elevated glucose and insulin concentrations did not affect sleep in humans. Yet, the present results demonstrate a temporal link between central nervous system sleep processes and the secretory activity of α- and β-cells, with this activity being inhibited during REM sleep and increased during non-REM sleep. This association between non-REM/REM sleep cycles and ultradian fluctuations of glucagon and insulin secretory activity reflects a regulatory influence of brain structures involved in sleep regulation on pancreatic endocrine secretory activity. It is of interest to determine to what extent this temporal relationship is disturbed under pathological conditions, e.g. in patients with noninsulin-dependent diabetes mellitus and sleep disturbances.

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