Hypoglycemia Counterregulation During Sleep

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Study Objectives: In insulin-treated patients with diabetes, episodes of severe hypoglycemia often occur during sleep, which might reflect an altered counterregulation and reduced awareness. This study examined the influence of sleep on the counterregulatory response to hypoglycemia in healthy subjects.

Design: Subjects participated in two experimental conditions; statistical tests relied on within subject comparisons.

Setting: University hospital sleep laboratory.

Participants: 15 healthy young men.

Interventions: Hypoglycemia (2.8 mmol/l) was induced for 45 min by insulin infusion once during sleep and once at the same time of night while being awake.

Measurements and Results: Counterregulatory hormone concentrations (epinephrine, norepinephrine, ACTH and cortisol) and sleep recordings were obtained. Differences in the hormonal responses to hypoglycemia between sleep and wake conditions remained non-significant, indicating that sleep does not exert a primary influence on the strength of counterregulation. However, the glycemic threshold for the onset of counterregulation was significantly changed during sleep: The average onset threshold for epinephrine and norepinephrine counterregulation was 3.3 ± 0.1 mmol/l for the wake condition and 2.7 ± 0.1 mmol/l for the sleep condition ($P < 0.001$). A decrease in sleep depth coincided with the onset of the counterregulatory response, with most subjects showing signs of awakening.

Conclusions: During sleep, the organism is less sensitive to hypoglycemia. Hypoglycemia per se has an awakening effect.

Keywords: blood glucose; sleep stages; catecholamines; ACTH; cortisol

Citation: Gais S, Born J, Peters A, et al. Hypoglycemia counterregulation during sleep. *SLEEP* 2003;1:55-9.

INTRODUCTION

TWO DIFFERENT MECHANISMS ARE INVOLVED IN THE ORGANISM'S RESPONSE TO HYPOGLYCEMIC CONDITIONS. First, a counterregulatory hormonal response involving release of epinephrine, glucagon, cortisol, and other hormones directly causes an increase in blood glucose through glycogenolysis, gluconeogenesis, and inhibition of glucose utilization.[1-3] Second, the organism reacts to hypoglycemia by generating behavior aimed at food intake. In humans, in particular, feelings of hunger[4,5] make the individual aware of the need to eat. Both responses are necessary, as the first alleviates an immediate shortage of energy and the second aims at replenishing the body's glucose reserves. These mechanisms are often working improperly in patients with diabetes receiving intensive insulin therapy, which increases the risk of hypoglycemia[6-8] and shifts the threshold for symptoms of hypoglycemia[9,10] and hypoglycemia awareness towards lower glucose levels.[11,12] These hypoglycemic episodes in insulin-treated patients with diabetes occur frequently during sleep.[13-15]

In healthy humans, glucose regulation changes during sleep also. Both blood glucose levels and insulin concentrations are higher during the night as compared to daytime and are higher during nocturnal sleep as compared to nocturnal wakefulness.[16,17] While during wakefulness an 8-h fasting period causes a certain decline in blood glucose, during 8-h of sleep, blood glucose remains relatively constant.[18] Also, glucose tolerance is lower during nighttime, probably due to reduced glucose utilization, decreased insulin sensitivity, and lower insulin secretion rates.[17] Hypoglycemia counterregulation is another aspect of glucose regulation that was shown to be affected by sleep. Growth hormone secretion, which is related to hypoglycemia and can be suppressed by glucose infusion during wakefulness, is not suppressed during sleep.[19,20] And Jones et al[21] observed a decreased epinephrine response to a 40-min period of hypoglycemia during sleep in healthy subjects and in patients with diabetes. In that study, however, only a moderate hypoglycemia was induced. A mean blood glucose level below 3.3 mmol/l was reached only during the last 20 min, and blood glucose never touched 2.8 mmol/l. Thus, glucose levels were probably too high to initiate a full epinephrine response. The present study examined the influence sleep has on hypoglycemia counterregulation as compared to a wake control condition in young healthy subjects. A more pronounced hypoglycemia (2.8 mmol/l) was induced, and concurrent changes in counterregulatory hormones and sleep depth were analyzed.

METHODS

Subjects

Fifteen men (age 18 – 35 years) participated in the experiments. All were non-smokers and had normal body weight (body mass index 20 – 25 kg/m²) and a regular sleep-wake cycle during the four weeks before the experiment. Subjects were healthy and did not take any medication. Diabetes and hypertension among first- or second-degree relatives was excluded. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee on Research Involving Humans of the University of Lübeck. All subjects gave written informed consent.

Design and Procedure

Following an adaptation night in the laboratory, each subject was tested on two experimental nights, spaced at least four weeks apart. They were told that they had a chance of being subjected to periods of hypoglycemia during the nights, but they did not know whether and when this occurred. On each experimental night, they reported to the laboratory at 20.00 h. Two intravenous catheters were inserted in the distal part of the right and left forearms into the cephalic veins for blood sampling and

Disclosure Statement
Nothing to disclose

Submitted for publication April 2002
Accepted for publication August 2002
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infusion of glucose and insulin. Starting from 22.00 h, subjects received 750 IU heparin per hour to facilitate blood sampling. Electrodes were attached to the scalp [electroencephalogram (EEG)], around the eyes [horizontal and vertical electrooculogram (EOG)] and on the chin [electromyogram (EMG)] for standard polysomnography. Then subjects went to bed at 23.00 h. On one night, lights were turned off at that time to allow for sleep until 07.00 h. On the other night, subjects stayed awake in bed in a half-supine position. During the wake condition, they were allowed to read emotionally and mentally non-straining books. The EEG was monitored for signs of sleep. Experimental conditions were assigned according to a within-subject cross-over design, with half of the subjects starting with the sleep condition and the other half with the wake condition. When subjects in the sleep condition had reached slow-wave sleep (SWS), hypoglycemia was induced by infusion of 4.24 mU/kg body weight (BW) per min regular human insulin (Aventis AG, Frankfurt a. M., Germany) for 2 min. During the following 6 min, the dose was continuously reduced to 1.70 mU/kg BW per min. When blood glucose reached 2.8 mmol/l [33.8 ± 8.0 min (mean ± SE) after onset of insulin infusion], this level was maintained for another 30 min by additional infusion of glucose as necessary. Immediately afterwards, insulin infusion was stopped, and subjects were brought back to normal blood glucose concentrations by glucose infusion. Blood sampling and infusions were carried out via long thin tubes from an adjacent room without disturbing the subjects. Blood glucose was determined online in 5-min intervals by means of a Glucose Analyzer II (Beckman Instruments, Inc., Palo Alto, CA). Every 15 minutes, blood samples were taken and centrifuged immediately. Blood plasma was frozen at –80 °C for subsequent determination of epinephrine (EPI), norepinephrine (NE), and ACTH, and blood serum was frozen for cortisol, insulin, and C-peptide.

EPI and NE concentrations were determined by standard high performance liquid chromatography with electrochemical detection. The sensitivity was 35 pmol/l (interassay variation coefficient: 5.6%) for EPI and 36 pmol/l (6.1%) for NE. ACTH was determined by luminescence immunoassay (Lumitest, Brahms Diagnostica, Berlin, Germany). Cortisol was measured using an enzyme immunoassay (Enzymun-Test Cortisol, Roche Diagnostics, Mannheim, Germany). For insulin, a double-antibody radioimmunoassay (Pharmacia RIA 100, Pharmacia-Upjohn, Milton Keynes, UK) was used. C-peptide was measured by specific radioimmunoassay (Diagnostic Products Corporation, Bad Nauheim, Germany). Polysomnographic recordings were scored offline according to standard criteria.[22]

Data Analysis

For hormone concentrations, the onset of the counterregulatory response was determined with respect to the first increase in plasma concentrations. The onset was defined as the last sample before respective concentrations increased by more than three SD units as compared to baseline. In addition, baseline adjusted maximum concentrations and areas under the curves (AUCs) were calculated for all hormones for a 120-min interval following the onset of the counterregulatory response. The blood glucose threshold for the onset of hormonal counterregulation was defined by the average blood glucose level during the 15-min interval succeeding the defined onset. This definition provides the best approximation for the glucose level at the time of the true onset of hormonal counterregulation, which occurred somewhere during this 15-min interval. Sleep was analyzed with respect to the onset of the EPI response, which was preferred to other hormones because of its immediate response to hypoglycemia, not relying on intermediate releasing hormones, and because its onset can be clearly determined. Statistical analysis in general relied on ANOVA, including a repeated measures factor for the condition (sleep/wake). A value of $P < 0.05$ was considered significant.

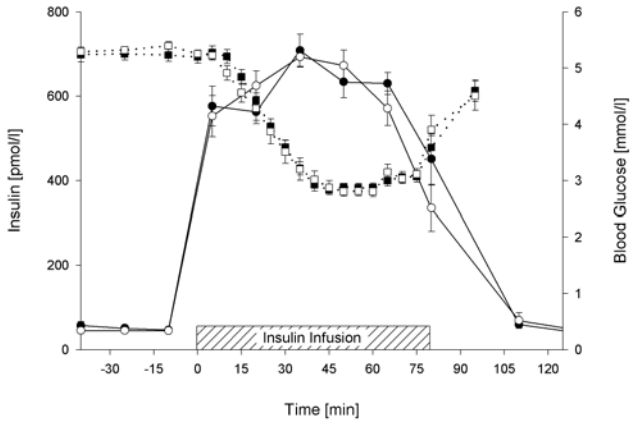

Figure 1—Mean ± SEM serum insulin (circles) and blood glucose concentrations (squares) time-locked to the beginning of insulin infusion. Subjects were tested in two conditions: a sleep condition (open symbols) where the infusion started after the subject had reached SWS and a wake condition (filled symbols) where the infusion started at about the same time of night as in the sleep condition, but subjects remained awake throughout the experiment. The hatched bar marks the duration of insulin infusion.

RESULTS

Blood Glucose and Insulin

During the first 40 min of insulin infusion, blood glucose levels decreased linearly from 5.2 ± 0.1 (mean ± SEM) to 2.8 ± 0.1 mmol/l in both conditions (Figure 1). They stayed at this level for 30 min and afterwards returned rapidly to normoglycemia, due to glucose infusion. The average amount of glucose infused throughout the hypoglycemic phase was equal on both conditions (20.2 ± 1.1 g). Also, insulin levels were completely comparable in both conditions throughout the time of the experiments ($P > 0.50$ for maximum concentrations; $P > 0.60$ for AUCs), and endogenous insulin production as measured by serum C-peptide did not show any differences either ($P > 0.25$ for maximum concentrations; $P > 0.40$ for AUCs).

Epinephrine and Norepinephrine

When blood glucose dropped below a certain level, plasma concentrations of EPI sharply increased (Figure 2A). The onset threshold of this counterregulatory response differed between the sleep and wake condition. Blood glucose levels during the 15 min after the defined onset of EPI counterregulatory secretion averaged 3.3 ± 0.1 mmol/l for the wake condition and 2.7 ± 0.1 mmol/l for the sleep condition ($P < 0.001$). That is, the onset threshold of the EPI response was on average 0.6 mmol/l lower during the sleep condition. The maximum amplitudes of the EPI response were very similar during wakefulness and sleep (4950 ± 570 vs. 4450 ± 550 pmol/l, $P > 0.20$). AUCs of EPI concentration during the 120 min following the onset of the counterregulatory response were slightly larger when subjects were awake than while sleeping (116 ± 12 vs. 98 ± 14 pmol·l^{-1}·min^{-1}; $P = 0.08$). This difference was due to the shorter duration of the counterregulatory response during sleep than wakefulness.

NE concentrations, in principle, followed the same course as those of EPI, although the increase was much smaller and less clear-cut (Figure 2B). The onset threshold for the NE response was also shifted on average by 0.6 mmol/l blood glucose (3.4 ± 0.3 and 2.8 ± 0.1 mmol/l for the wake and sleep conditions, respectively; $P < 0.05$). Maximum amplitudes of the NE response appeared to be slightly enhanced during wakefulness as compared to sleep, but this difference remained non-significant (1.81 ± 0.11 vs. 1.61 ± 0.11 nmol/l; $P = 0.10$). AUCs showed a significantly larger NE secretion in the wake than sleep condition (0.03 ± 0.004 vs. 0.02 ± 0.004 nmol·l^{-1}·min^{-1}; $P = 0.05$) due to the longer duration of the counterregulatory response during wakefulness.

ACTH and Cortisol

The ACTH counterregulatory response during sleep also started at a significantly lower blood glucose level (2.6 ± 0.04 mmol/l) than when

subjects were awake (2.9 ± 0.08 mmol/l; $P < 0.01$). Again, peak amplitudes of the ACTH counterregulatory response did not differ between wake and sleep conditions (35 ± 5 pmol/l vs. 36 ± 4 pmol/l; $P > 0.80$). AUCs for the 120 min interval following the onset of counterregulation showed a comparable amount of ACTH secretion during the wake and sleep conditions (0.93±0.14 pmol·l^{-1}·min^{-1} vs. 0.83±0.14 pmol·l^{-1}·min^{-1}; $P = 0.20$; Figure 2C).

The blood glucose threshold for the onset of the cortisol counterregulatory response was the same as for ACTH. Compared to the sleep condition, the maximum cortisol response tended to be higher during the wake condition (570 ± 20 vs. 540 ± 20 nmol/l; $P = 0.08$). Also, the AUCs differed significantly (26 ± 1 vs. 22 ± 1 nmol·l^{-1}·min^{-1}; $P < 0.001$), indicating a distinctly prolonged cortisol secretory response to hypoglycemia during wakefulness as compared to sleep (Figure 2D).

Sleep

Comparing the depth of sleep during the 20-min period before the onset of EPI counterregulatory secretion to a 20-min period afterwards shows a distinct change toward more shallow sleep after the onset of EPI counterregulation. While the subjects spent more than 50% of the interval before the EPI response in SWS (stages 3 and 4), there was only a marginal amount of stage 3 sleep and no stage 4 sleep left afterwards. On the other hand, the proportion of light sleep (stages 1 and 2) and wakefulness was 92% afterwards. Also, nine of the 15 subjects woke up after the onset of the EPI response, and 13 subjects reached sleep stage 1. In contrast, during the interval before the onset of the hormonal response, only one subject showed signs of wakefulness. In all subjects, the decrease in sleep depth took place during the 15-min interval delimiting the onset of the counterregulatory EPI response. Figure 3 shows the cumulative number of epochs of wakefulness beginning 20 min before the onset of the EPI counterregulatory response. It shows a dramatic increase in epochs of wakefulness starting at about the same time as the EPI counterregulation.

DISCUSSION

The present data show that sleep has an influence on blood glucose regulation independent of time of day effects: With a steady decline in blood glucose concentration, during sleep, the onset of a counterregulatory hormonal response was delayed, until a significantly lower blood glucose concentration was reached. Also, there was an effect of hypoglycemia on sleep: Coinciding with the onset of counterregulation, sleep depth decreased. Most subjects even awoke during hypoglycemia. Our results show in healthy humans that a double strategy to compensate for hypoglycemia is followed during sleep: On one hand, hormonal counterregulation elevates blood glucose via stimulation of gluconeogenesis, glycogenolysis, and inhibition of glucose utilization, and on the other hand, the subject is aroused from sleep as a prerequisite for any food intake behavior. Most important, data show that sleep apart from impeding behavioral counterregulation, also delays hormonal counterregulation upon hypoglycemia. The onset threshold of the EPI and NE responses to hypoglycemia is shifted during sleep by about 0.6 mmol/l towards lower glucose levels, that of ACTH and cortisol by about 0.3 mmol/l. This finding shows that metabolic processes are regulated differently during sleep and wakefulness. If this finding can be confirmed in patients with diabetes, it has a special significance because these patients frequently experience hypoglycemia and, in addition, show the onset of hormonal counterregulation at lower glucose levels in conjunction with hypoglycemia unawareness during wakefulness.[23-25]

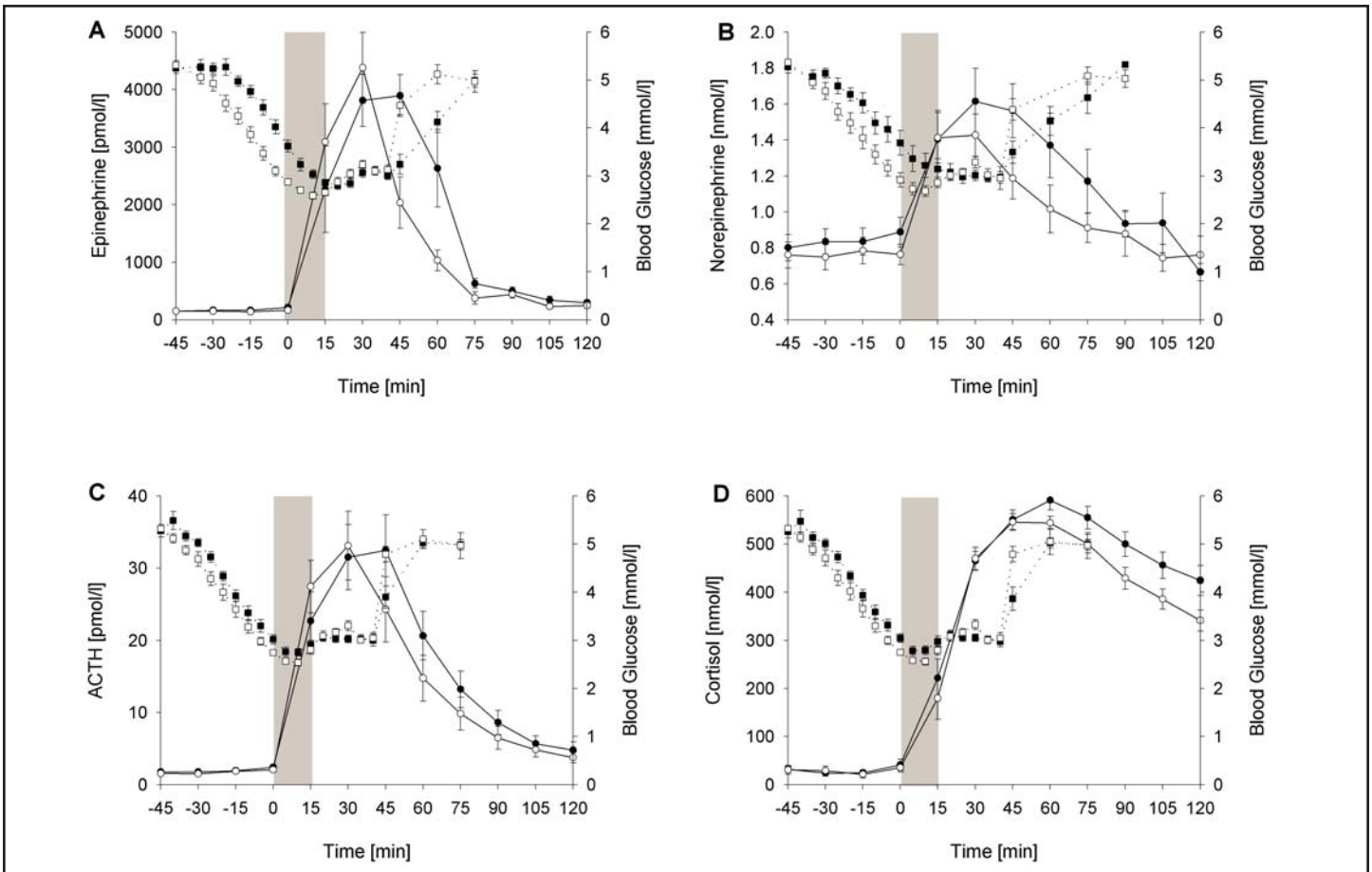

Figure 2—Circles / solid lines show mean ± SEM plasma EPI (A), NE (B), ACTH (C), and cortisol (D) concentrations time-locked to the beginning of the counterregulatory hormone secretion during the sleep (open) and wake conditions (filled). Squares / dotted lines show in each panel the blood glucose concentrations during sleep (open) and wake conditions (filled). The shaded area represents the 15-min interval containing the true onset of hormone secretion. The difference between glucose levels of the sleep and wake conditions during this interval represents the difference in the onset threshold for the counterregulatory response. The glucose curves differ slightly for the four hormones because they are synchronized to the response onset for each hormone.

Since the influence of sleep may add in these patients to the deficient hypoglycemic counterregulation,[21] the threat that hypoglycemia poses to these patients is larger during sleep than wakefulness.

Comparing the hormonal responses between sleep and wake conditions revealed that maximum plasma concentrations of EPI and ACTH achieved during counterregulation were comparable for both conditions. Maximum concentrations of NE and cortisol were slightly higher during the wake than the sleep condition. However, these differences did not reach significance. This pattern indicates that sleep does not primarily affect the strength of the counterregulatory hormonal response. Once activated, this response appears to proceed in a rather stereotyped fashion. Slight but non-significant differences in the maxima of NE and cortisol might result from the fact that these systems become activated at different baseline levels during sleep and wakefulness.[26] It cannot be ruled out that during longer lasting hypoglycemic periods these differences become more pronounced. However, the primary difference between the sleep and wake condition is the glycemic threshold for triggering the hormonal response during sleep, which is shifted towards lower glucose levels.

At first glance, this conclusion is in contrast with recent results by Jones et al[21] who reported on a suppressed counterregulatory response during sleep. However, some differences in the course of hypoglycemia can be found between those and the present experiments. (1) In that study, blood glucose concentrations during hypoglycemia stayed well above the level of 2.8 mmol/l achieved here. (2) The lowest levels were not reached until the end of the experiment, leaving no time for detecting a strong hormonal response. (3) None of the subjects included in that study woke up during the hypoglycemic period, indicating that the glycemic threshold for awakening was not reached. (4) Only subjects who were awake showed substantial increases in EPI concentrations. Together, this suggests that most of the subjects in the sleep condition indeed did not reach the glycemic threshold for initiating any hormonal counterregulation. From this perspective, the data of Jones et al are entirely in accordance with the finding presented here, that sleep shifts the onset threshold for counterregulation towards lower glucose levels. In a further study, Bendtson et al[27] examined the effects of a more pronounced hypoglycemia (1.5 – 1.9 mmol/l). Consonant with the present data, those authors concluded that no difference in hypoglycemia counterregulation exists between patients who were awake (during the day) and those who were asleep (during the night). Thus, although glycemic thresholds are shifted towards lower glucose levels during sleep, sleep does not appear to restrain hormonal counterregulation once these thresholds are reached.

The data show an increased awakening concurrently with the beginning of hypoglycemia counterregulation. As spontaneous awakenings at this time of night are highly unusual, these awakenings are probably caused by hypoglycemia. It might also be possible that the awakenings are induced not by hypoglycemia but the increased levels of insulin during the hypoglycemic clamp. This possibility could only be ruled out by a euglycemic hyperinsulinemic control study. It is however not likely that high levels of insulin caused the awakenings because Kern et al[28] could not find changes in sleep stages related to endogenous insulin release in humans, and insulin in animal studies increases SWS.[29] Within the bounds of this experiment, it is impossible to determine whether there is a causal relationship between awakening and the onset of the counterregulatory hormonal response. Blood was sampled at a temporal resolution of 15 min. Since the onset of the hormonal counterregulation and the decrease in sleep depth fell exactly into the same 15-min interval, no causal relationship can be inferred. If the EPI response preceded awakening, then one of the functions of EPI release during sleep could be to bring hypoglycemia to the awareness of the subject. A similar function has been proposed for the counterregulatory EPI response during the wake state, based on observations that most initial symptoms of hypoglycemia are mediated by EPI.[30] Warning the individual of hypoglycemic states might even be the reason why the adrenomedullary EPI response to hypoglycemia originally developed, as the suppression of EPI does not alter the course of hypoglycemia in healthy humans.[31] On the other hand, awakening may be a necessary prerequisite for initiating hormonal counterregulation. The changed onset threshold for the counterregulatory response might then protect sleeping subjects from awakening upon minor nightly hypoglycemia. The most probable explanation, however, is that both hormonal counterregulation and awakening upon hypoglycemia are commonly controlled by a superordinate central nervous mechanism presumably residing in caudal hindbrain regions.[32-34] Such a mechanism could jointly control brainstem arousal centers responsible for awakening as well as sympathetic and pituitary-adrenal counterregulation. Given that thresholds for hypoglycemia awareness are shifted towards lower glucose levels in many diabetic patients, a systematic examination of awakening thresholds during hypoglycemia in those patients is strongly needed to unravel the mechanisms underlying the danger of sleep associated hypoglycemia in this disease.

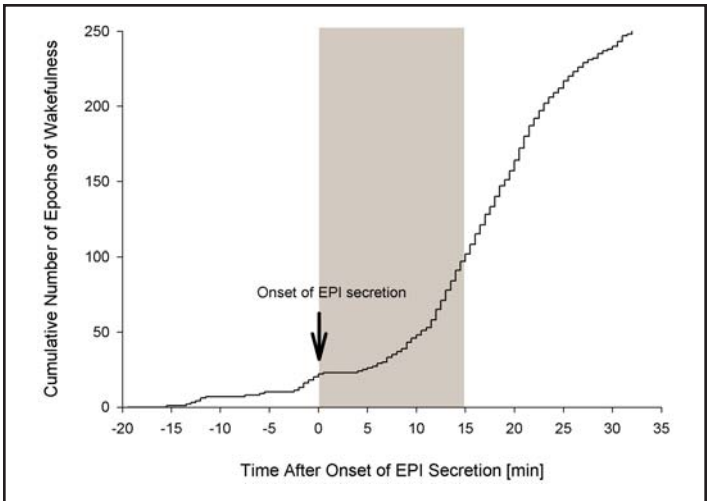

Figure 3—Cumulative number of 30-s epochs of wakefulness during an interval beginning 20 min before the onset of the counterregulatory EPI response. The shaded area represents the 15-min interval containing the true onset of the EPI secretion.

ABBREVIATIONS

ACTH: adrenocorticotropic hormone
ANOVA: analysis of variance
AUC: area under the curve
BW: body weight
EEG: electroencephalogram
EMG: electromyogram
EOG: electrooculogram
EPI: epinephrine
NE: norepinephrine
REM: rapid eye movement
SEM: standard error of the mean
SWS: slow-wave sleep

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