Altered Neuroendocrine Sleep Architecture in Patients With Type 1 Diabetes

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OBJECTIVE — The modulatory influence of nocturnal sleep on neuroendocrine secretory activity is increasingly recognized as a factor critical to health. Disturbances of sleep may arise from and contribute to the disease process in chronically ill patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Using standard polysomnography and repetitive blood sampling, neuroendocrine sleep architecture was assessed under well-controlled nonhypoglycemic conditions in 14 type 1 diabetic patients and 14 healthy control subjects matched for age, sex, and BMI.

RESULTS — As expected, plasma glucose ($P = 0.02$) and serum insulin ($P < 0.001$) levels were constantly higher in type 1 diabetic patients than in healthy subjects throughout the night. Beside these characteristic alterations of glucose metabolism, type 1 diabetic patients displayed higher blood levels of growth hormone ($P = 0.001$) and epinephrine ($P = 0.02$) during the entire night and higher levels of ACTH ($P = 0.01$) as well as a tendency toward higher cortisol levels ($P = 0.072$) during the first night-half, compared with healthy control subjects. Patients spent slightly less time in slow wave sleep ($P = 0.09$) during the first night-half (where this sleep stage predominates), and overall exhibited an increased proportion of stage 2 sleep ($P = 0.01$). Correspondingly, assessment of mood and symptoms after sleep revealed that subjective sleep was less restorative in type 1 diabetic patients than in healthy subjects.

CONCLUSIONS — Our data indicate distinct alterations in the neuroendocrine sleep architecture of patients with type 1 diabetes, which add to the generally adverse impact of the disease on the patients' health.

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The endocrine system is subject to a number of periodic processes reflecting the spectrum of biological rhythms. Apart from the circadian rhythm, nocturnal sleep profoundly influences the release of hormones. Sleep onset is followed by a major burst of growth hormone secretion, a rise in circulating prolactin and leptin levels, and a suppression of hypothalamo-pituitary-adrenal (HPA) secretory activity (1). The late part of nighttime sleep is associated with a sharp rise in HPA secretory activity, whereas release of growth hormone, thyroid-stimulating hormone (TSH), and prolactin is more or less decreased (1).

Whereas neuroendocrine secretion patterns during nighttime sleep have been thoroughly examined in healthy subjects, little is known about the dynamics of hormone release during sleep in patients with type 1 diabetes. Compared with healthy control subjects, patients with type 1 diabetes show elevated growth hormone levels during the first part of the nighttime sleep (2). Also, cortisol levels have been found to be elevated in type 1 diabetic patients in the late evening and slightly lowered in the morning (3). However, these results were obtained in studies with no control for a most important confounding factor, i.e., nocturnal hypoglycemia, which frequently occurs in type 1 diabetic patients (4) and per se increases the secretion of cortisol and growth hormone (5). In the present study, we examined whether the neuroendocrine sleep architecture is changed in type 1 diabetic patients under nonhypoglycemic conditions.

RESEARCH DESIGN AND METHODS

— A total of 14 type 1 diabetic patients (7 women) and 14 healthy control subjects (7 women) matched for age (mean ± SEM 31.3 ± 2.6 and 28.9 ± 1.5 years) and BMI (24.2 ± 0.8 and 23.1 ± 0.7 kg/m^2) participated in the experiments. All subjects had a regular sleep-wake cycle and did not work on night shifts during the 4 weeks before experiments. Habitual sleep duration, as systematically assessed by a standard questionnaire, did not differ between type 1 diabetic patients and healthy subjects (7:25 h ± 7 min [range 6:75–8:25 h] vs. 7:32 h ± 8 min [6:75–8:25 h]; $P = 0.78$). Also, the usual bedtime (22:59 h ± 6 min vs. 23:07 h ± 6 min) and the usual wake up time (06:33 h ± 6 min vs. 06:44 h ± 7 min) were comparable between both groups. Patients with type 1 diabetes were selected to participate only when they had no clinical evidence of diabetes complications. Mean ± SD diabetes duration was 9.3 ± 1.6 years (range 1–23 years) and A1C was 7.7 ± 0.3% (range 6.0–10.0%; upper limit of the normal range 6.7%). Ten patients were receiving an intensive conventional therapy regimen with at least three injections of regular insulin and one to two injections of long-acting insulin per day. The remaining four type 1 diabetic patients were receiving continuous subcutaneous insulin infusion. The mean ± SEM cumulative insulin dose was 54.9 ± 3.9 units/day. 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

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Abbreviations: AUC, area under the curve; EWL, adjective checklist (Eigenschaftswörterliste); HPA, hypothalamo-pituitary-adrenal; REM, rapid eye movement; SWS, slow wave sleep, TSH, thyroid-stimulating hormone; TST, total sleep time; WASO, awake after sleep onset.

written informed consent before participation.

After an adaptation night in the sleep laboratory including the placement of two intravenous catheters and electrodes for standard polysomnography, each subject was tested on one experimental night. During the night, spontaneous hypoglycemia (<3.9 mmol/l) was prevented by infusion of 20% glucose solution whenever necessary, which was the case in five patients.

On the day of the experimental night, subjects reported to the laboratory at 2000 h. Two intravenous catheters were inserted, one into a vein in the back of the hand for infusion of glucose and the other one into an antecubital vein of the other arm for blood sampling. Electrodes were attached to the scalp (electroencephalogram), around the eyes (horizontal and vertical electrooculogram), and on the chin (electromyogram) for polysomnography. Subjects went to bed and lights were turned off at 2300 h. Wake up time was 0630 h. The entire bed period time was monitored by the experimenters via video observation. In the case of awakening before lights on, subjects stayed in bed until 0630 h. Blood was sampled every 30 min via long thin tubes from an adjacent room without disturbing the subject's sleep. Mood and tiredness were assessed by an adjective checklist in the evening (between 2030 and 2050 h) and in the next morning between 0650 and 0710 h.

Sleep recordings

Polysomnographic recordings were scored offline according to standard criteria (6). The following sleep parameters were determined for the first and second night-halves (i.e., end of first half and beginning of second half at 0300 h) as well as for the total nights: total sleep time (TST) (time spent in sleep stages 1, 2, 3, and 4, and REM sleep between sleep onset and final awakening); time spent awake after sleep onset (WASO); time spent in stage 1, stage 2, stage 3, stage 4, and slow wave sleep (SWS) (defined as the sum of stage 3 and stage 4); and REM sleep (in minutes and percentage of TST) as well as movements (defined as the sum of movement times and arousals, as a percentage of 30-s epochs) and movement times (as a percentage of TST).

Mood

A standardized adjective check list (EWL) was used to assess mood and feelings of fatigue (7). It consists of a total of 123 adjectives describing the subject's actual mood on 14 dimensions: "activation," "deactivation," "fatigue," "numbness," "extraversion," "introversion," "self-assuredness," "well-being," "agitation," "sensibility," "anger," "anxiousness," "depressiveness," and "dreaminess." For each adjective, the subject indicated whether or not it reflected aspects of his or her current mood. For each dimension, the numbers of adjectives that were marked by the subject to correctly indicate his or her current mood were counted.

Blood assays

Plasma glucose was measured by means of the Glucose Analyzer II (Beckman Instruments, Palo Alto, CA). The following assays were used to measure circulating hormone levels: serum insulin: radioimmunoassay (Pharmacia Insulin RIA 100; Pharmacia Diagnostics, Uppsala, Sweden) with an interassay coefficient of variation (CV) <5.8% and an intra-assay CV <5.4%; plasma ACTH: luminescence immunoassay (Lumitest; Brahms Diagnostica, Berlin, Germany) with an interassay CV <5.1% and intra-assay CV <3.2%; serum cortisol: enzyme immunoassay (Enzymun-Test Cortisol; Roche Diagnostics, Mannheim, Germany) with an interassay CV <3.9% and intra-assay CV <2.0%; serum growth hormone: radioimmunoassay (HGH; Diagnostic Products, Los Angeles, CA) with an interassay CV <3.4% and intra-assay CV <1.6%; plasma epinephrine and norepinephrine: standard high-performance liquid chromatography with an interassay and intra-assay CV for epinephrine <5.6% and <2.9% and for norepinephrine <6.1% and <2.6%; serum prolactin: chemiluminescent immunometric assay (Immulite, Diagnostic Products) with an interassay CV <9.5% and intra-assay CV <5.9%; serum leptin: radioimmunoassay (LINCO Research) with an interassay CV <4.0% and intra-assay CV <3.0%; and serum TSH: immunometric assay (Immulite) with an interassay CV <10.0% and intra-assay CV <6.2%.

Statistical analysis

Values are presented as means ± SEM. Hormonal data were analyzed by ANOVA including the repeated-measures factors "time" for multiple measurements during the night and "group" for differences between type 1 diabetic patients and healthy control subjects. Area under the curve (AUC) measures calculated for the entire night as well as separately for the first (2330–0300 h) and the second (0300–0630 h) night-half were compared between groups using unpaired Student's *t* tests. The same test was used to compare sleep data between groups. Data from the adjective check list were analyzed by ANOVA, including a repeated-measures factor time (evening versus morning) and group (type 1 diabetic patients versus control subjects). Pearson correlation analyses were performed to examine the relationships between sleep stages and AUC for growth hormone, cortisol, and ACTH. $P < 0.05$ was considered significant.

RESULTS

Sleep

Table 1 summarizes polysomnographic data. TST (395 ± 15 vs. 404 ± 10 min; $P = 0.93$) as well as sleep onset latency (11 ± 1 vs. 12 ± 1 min; $P = 0.50$) did not differ between type 1 diabetic patients and healthy subjects. Interestingly, REM sleep latency, i.e., the time between REM sleep and falling asleep, was significantly longer in the type 1 diabetic patients than in healthy control subjects (132 ± 15 vs. 98 ± 8 min; $P = 0.05$). In both type 1 diabetic patients and healthy subjects, SWS predominated during the first night-half, whereas REM sleep was more prevalent during the second night-half, reflecting the typical pattern of nocturnal sleep architecture. Compared with the control subjects, type 1 diabetic patients tended to spend less time in SWS during the first night-half ($P = 0.09$). During both the first ($P = 0.04$) and the second ($P = 0.04$) night-halves, type 1 diabetic patients spent significantly more time in sleep stage 2 than the healthy subjects. Sleep parameters of the five type 1 diabetic patients requiring glucose infusion to prevent spontaneous hypoglycemia did not differ from those in the nine patients who did not require glucose infusion (TST 412.6 ± 12.8 vs. 397.6 ± 14.5 min; $P = 0.51$; WASO 2.0 ± 1.0 vs. 1.3 ± 0.6%, $P = 0.57$; S1 12.5 ± 1.2 vs. 14.2 ± 2.6%, $P = 0.64$; S2 55.0 ± 3.2 vs. 58.3 ± 2.8%, $P = 0.48$; SWS 15.5 ± 4.6 vs. 12.5 ± 2.9%, $P = 0.58$; REM 14.8 ± 2.7 vs. 13.4 ± 2.2%, $P = 0.69$; movements 10.5 ± 3.0 vs. 12.8 ± 2.5%, $P = 0.58$; movement times 0.7 ± 0.2 vs. 0.6 ± 0.2%, $P = 0.68$).

Mood

Data from the adjective check list (summarized in Table 2) revealed that feelings of numbness increased across the night in

Table 1—*Sleep parameters during the first and the second halves of the night*

	Type 1 diabetic patients	Healthy subjects	*P* value
First night-half			
TST (min)	202.8 ± 0.8	201.7 ± 1.6	0.83
WASO (%)	0.7 ± 0.3	1.5 ± 0.8	0.25
Stage 1 (%)	11.9 ± 1.7	17.8 ± 3.3	0.59
Stage 2 (%)	58.6 ± 3.1	47.5 ± 4.0	0.04
SWS (%)	21.3 ± 3.7	24.7 ± 3.3	0.09
REM (%)	7.5 ± 1.5	8.6 ± 1.8	0.38
Movement (%)	12.3 ± 2.0	12.7 ± 2.2	0.33
Movement time (%)	0.7 ± 0.2	0.5 ± 0.2	0.52
Second night-half			
TST (min)	194.6 ± 9.1	208.4 ± 7.4	0.69
WASO (%)	3.1 ± 1.6	3.9 ± 2.2	0.21
Stage1 (%)	16.3 ± 2.4	20.3 ± 4.9	0.27
Stage 2 (%)	52.6 ± 3.0	46.6 ± 5.4	0.04
SWS (%)	8.3 ± 2.3	7.0 ± 2.0	0.66
REM (%)	20.0 ± 2.3	22.2 ± 2.5	0.27
Movement (%)	13.0 ± 1.7	17.8 ± 3.4	0.68
Movement time (%)	0.6 ± 0.2	0.5 ± 0.2	0.54
Entire night			
TST (min)	395 ± 15	404 ± 10	0.93
WASO (%)	1.8 ± 0.8	2.6 ± 1.1	0.52
Stage 1 (%)	14.2 ± 1.7	19.2 ± 3.3	0.34
Stage 2 (%)	55.6 ± 2.4	47.2 ± 4.1	0.01
SWS (%)	14.7 ± 2.6	14.9 ± 2.3	0.75
REM (%)	13.9 ± 1.5	15.5 ± 1.3	0.58
Movement (%)	12.4 ± 1.7	15.1 ± 2.3	0.23
Movement time (%)	0.6 ± 0.1	0.5 ± 0.1	0.50

Data are means ± SEM. Percent values refer to TST. *P* values derive from unpaired Student's *t* test.

type 1 diabetic patients but not in healthy subjects ($P < 0.001$ for group × time interaction). Also, whereas fatigue decreased across the night in healthy subjects, it increased in the type 1 diabetic patients ($P = 0.05$ for group × time).

Plasma glucose and insulin

Plasma glucose ($P = 0.02$) (Fig. 1*A*) and serum insulin ($P < 0.001$) (Fig. 1*B*) levels were higher in type 1 diabetic patients than in healthy subjects throughout the night. Although plasma glucose levels appeared to decline during the night, this change was not statistically confirmed because of its great variability ($P > 0.32$ for respective main and interaction effects). Serum insulin concentration decreased across the night ($P < 0.001$ for time main effect) with a distinctly more pronounced decrease in the type 1 diabetic patients ($P = 0.009$ for group × time).

ACTH, cortisol, and growth hormone

Plasma ACTH (Fig. 1*C*) and serum cortisol (Fig. 1*D*) levels increased in both type 1 diabetic patients and healthy subjects during the night ($P < 0.001$ and $P = 0.002$ for time main effects, respectively). Overall, plasma ACTH levels were higher in type 1 diabetic patients than in healthy control subjects ($P = 0.05$), and a similar pattern was observed for average serum cortisol levels, although this difference was not significant ($P = 0.16$). During the first night-half, the $AUC_{2330-0300\,h}$ for ACTH was significantly higher (256 ± 39 vs. 163 ± 13 pmol · l^{-1} · min^{-1}; $P = 0.01$) and the $AUC_{2330-0300\,h}$ for cortisol tended to be higher (14,624 ± 3,603 vs. 8,123 ± 1,230 nmol · l^{-1} · min^{-1}; $P = 0.07$) in type 1 diabetic patients than in healthy control subjects. During the second night-half, $AUC_{0300-0630\,h}$ for ACTH (509 ± 53 vs. 392 ± 62 pmol · l^{-1} · min^{-1}; $P = 0.16$) and cortisol (29,571 ± 4,306 vs. 23,797 ± 4,055 nmol · l^{-1} · min^{-1}; $P = 0.36$) did not differ between groups.

Serum growth hormone levels showed a maximum in the beginning of

Table 2—*Mood assessed by an adjective check list on 14 dimensions (translated from German) before and after the nighttime sleep*

	Type 1 diabetic patients		Healthy subjects		*P* value		
	Evening	Morning	Evening	Morning	Time	Group	Time × group
Activation	0.40 ± 0.08	0.25 ± 0.08	0.40 ± 0.08	0.40 ± 0.09	0.18	0.45	0.13
Deactivation	0.22 ± 0.06	0.28 ± 0.08	0.20 ± 0.06	0.22 ± 0.07	0.38	0.64	0.62
Fatigue	0.28 ± 0.07	0.38 ± 0.06	0.32 ± 0.07	0.21 ± 0.04	0.87	0.35	0.05
Numbness	0.07 ± 0.04	0.34 ± 0.05	0.13 ± 0.04	0.13 ± 0.06	0.001	0.18	<0.001
Extroversion	0.63 ± 0.05	0.59 ± 0.08	0.57 ± 0.08	0.54 ± 0.08	0.51	0.54	0.85
Introversion	0.17 ± 0.08	0.16 ± 0.08	0.13 ± 0.05	0.11 ± 0.05	0.77	0.62	0.91
Self-assuredness	0.59 ± 0.07	0.56 ± 0.09	0.51 ± 0.08	0.54 ± 0.08	0.91	0.61	0.63
Well-being	0.54 ± 0.09	0.49 ± 0.09	0.65 ± 0.08	0.70 ± 0.07	0.91	0.16	0.25
Agitation	0.18 ± 0.05	0.09 ± 0.04	0.19 ± 0.07	0.10 ± 0.03	0.01	0.91	0.90
Sensibility	0.10 ± 0.06	0.04 ± 0.03	0.04 ± 0.02	0.00 ± 0.00	0.13	0.89	0.98
Anger	0.08 ± 0.04	0.07 ± 0.05	0.05 ± 0.04	0.01 ± 0.01	0.14	0.22	0.82
Anxiousness	0.08 ± 0.04	0.07 ± 0.05	0.05 ± 0.04	0.01 ± 0.01	0.252	0.38	0.45
Depressiveness	0.11 ± 0.06	0.08 ± 0.07	0.04 ± 0.02	0.01 ± 0.01	0.07	0.29	0.81
Dreaminess	0.18 ± 0.07	0.33 ± 0.07	0.20 ± 0.07	0.25 ± 0.06	0.41	0.29	0.14

Data are means ± SEM. *P* values are derived from ANOVA including a repeated measures factor "time" (evening versus morning) and a factor "group" (type 1 diabetic patients versus healthy control subjects).

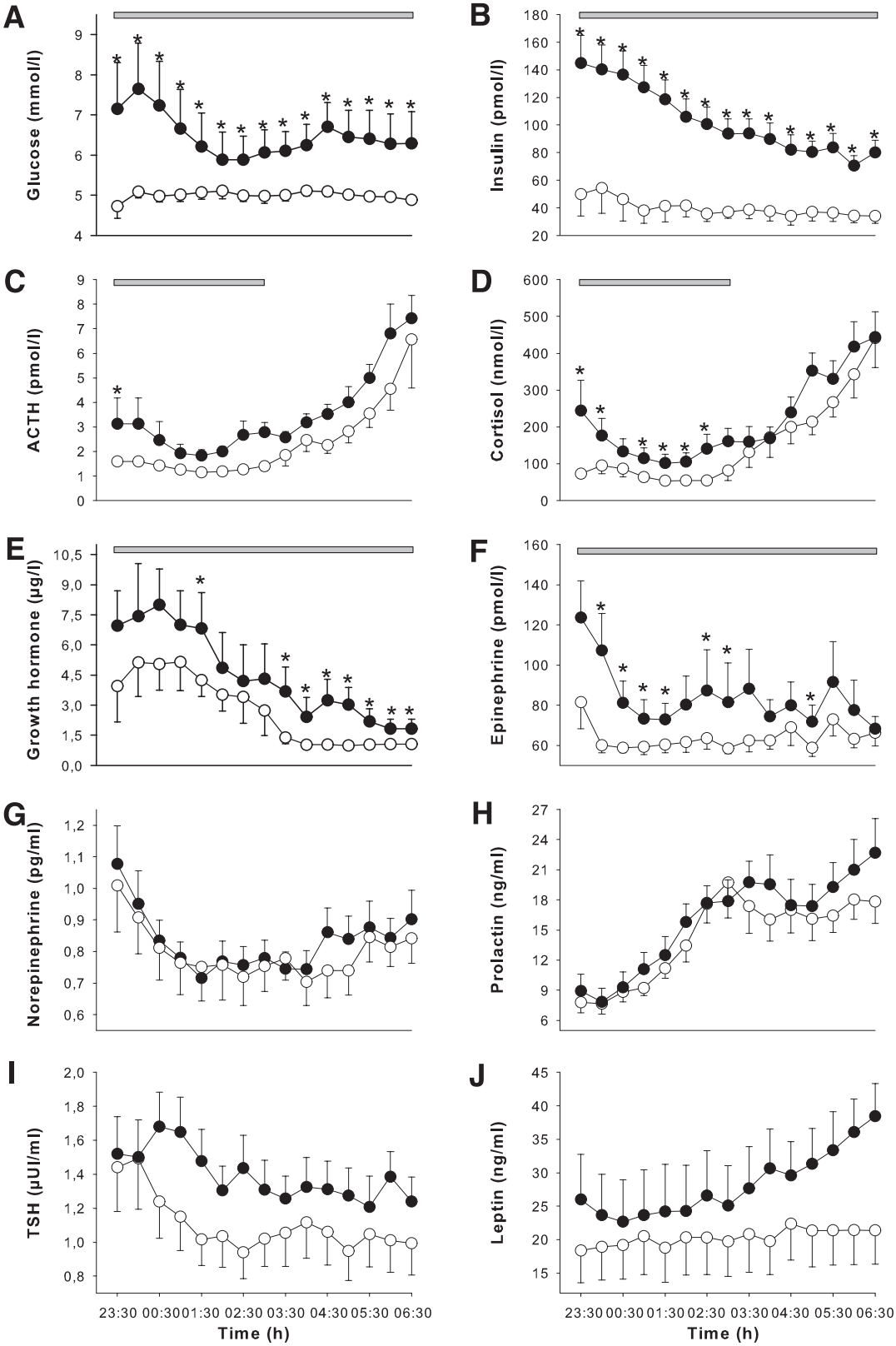

Figure 1—*Mean ± SEM levels of glucose (A), insulin (B), ACTH (C), cortisol (D), growth hormone (E), epinephrine (F), norepinephrine (G), prolactin (H), leptin (I), and TSH (J) in type 1 diabetic patients (●) and 14 healthy control subjects matched for sex, age, and BMI (○) during a 7-h nighttime sleep period. Gray horizontal bars indicate intervals (first or second night-half or entire night) of significantly ($P < 0.05$, as derived from ANOVA) increased hormone levels in type 1 diabetic patients compared with control subjects. *$P < 0.05$ derived from unpaired Student's t test.*

the night at about 0030 h and continuously decreased thereafter in both type 1 diabetic patients and healthy subjects ($P = 0.001$ for time main effect) (Fig. 1*E*). Overall, growth hormone levels were significantly higher in type 1 diabetic patients than in control subjects ($P = 0.05$ for group main effect). $AUC_{2330-0630\ h}$ for the entire night (951 ± 173 vs. 640 ± 89 $\mu g \cdot l^{-1} \cdot min^{-1}$; $P = 0.03$) as well as $AUC_{0300-0630\ h}$ for the second night-half (291 ± 72 vs. 126 ± 14 $\mu g \cdot l^{-1} \cdot min^{-1}$; $P = 0.016$) were higher in type 1 diabetic patients than in control subjects.

Catecholamines

Overall, plasma epinephrine levels tended to be higher in type 1 diabetic patients than in control subjects ($P = 0.05$ for group main effect) (Fig. 1*F*). Comparison of AUCs revealed significantly higher epinephrine levels in type 1 diabetic patients compared with control subjects during the entire night (17,443 ± 2,077 vs. 13,669 ± 663 $\mu g \cdot l^{-1} \cdot min^{-1}$; $P = 0.02$) and also during the first night-half (9,070 ± 1,061 vs. 6,903 ± 429 $\mu g \cdot l^{-1} \cdot min^{-1}$; $P = 0.04$). In contrast, there was no evidence for any group difference in plasma norepinephrine concentrations ($P > 0.6$ for all comparisons) (Fig. 1*G*).

Prolactin, leptin, and TSH

Serum prolactin ($P < 0.001$ for time main effect) (Fig. 1*H*) and serum leptin concentrations ($P = 0.02$) (Fig. 1*I*) increased in both type 1 diabetic patients and healthy subjects during the night, without any significant difference in this increase between groups ($P > 0.1$ for all comparisons). AUCs for prolactin and leptin revealed similar results with no difference between groups ($P > 0.2$). Serum TSH levels decreased during the night ($P < 0.001$ for time main effect) (Fig. 1*J*) but also did not differ between type 1 diabetic patients and healthy subjects (all $P > 0.32$). There was also no difference in AUCs for TSH between groups (all $P > 0.25$).

Correlation analyses

In pooled data of both the type 1 diabetic patients and the healthy control subjects, $AUC_{2330-0300\ h}$ for ACTH was correlated with plasma glucose levels ($r = 0.378$; $P = 0.05$), whereas $AUC_{2330-0300\ h}$ for cortisol was correlated with serum insulin levels ($r = 0.463$; $P = 0.01$). Cortisol levels during the first part of the night were inversely correlated with the amount of SWS in healthy control subjects ($r = -0.569$, $P = 0.03$), but not in type 1 diabetic patients ($r = -0.126$, $P = 0.67$). There were no other significant correlations between sleep stages and hormone levels.

In patients with type 1 diabetes, $AUC_{2330-0300\ h}$ for cortisol was correlated with A1C levels ($r = 0.562$, $P = 0.04$), whereas total night $AUC_{2330-0630\ h}$ for cortisol was correlated with the duration of type 1 diabetes ($r = 0.585$, $P = 0.03$). There were no other significant correlations between A1C, disease duration, sleep stages, and hormonal levels in type 1 diabetic patients (all $P > 0.12$).

CONCLUSIONS — Our data show discrete alterations in the neuroendocrine sleep architecture of type 1 diabetic patients. Whereas growth hormone and epinephrine levels were increased during the whole night in type 1 diabetic patients, concentrations of HPA hormones were elevated mainly during the first night-half. The hormonal changes were accompanied by a tendency toward more shallow sleep in type 1 diabetic patients with decreased amounts of SWS during the first night-half and an overall increased proportion of stage 2 sleep throughout the night. Also, increased numbness and fatigue point to a weakened restorative effect of sleep in type 1 diabetic patients.

Our findings of increased levels of HPA hormones and growth hormone in type 1 diabetic patients are in line with previous studies (2,3). However, only one of these studies assessed sleep architecture via polysomnographic recordings, and none included an approach to prevent nocturnal hypoglycemia, which represents a major confounder of hormonal activity. With careful control for glucose levels in the patient group, our study shows that increased HPA secretory activity, enhanced growth hormone levels, and lighter sleep in type 1 diabetic patients do not depend on the occurrence of hypoglycemic episodes.

Our data do not allow conclusions regarding cause-effect relationships. Nevertheless, it is tempting to speculate that the increase in HPA secretory activity during the first night-half is a result of diminished SWS and increased sleep stage 2 during this time, because SWS has been demonstrated to actively inhibit HPA secretory activity (8). However, reduced SWS in type 1 diabetic patients should be associated with decreased rather than increased growth hormone levels, because the release of growth hormone during sleep is closely connected to SWS and electroencephalogram synchronization (9). Also, in light of the moderate size of the reduction in SWS, it is unlikely that the observed changes in neuroendocrine activity in type 1 diabetic patients are a mere result of alterations in central nervous system sleep regulation.

As demonstrated in our study, patients with type 1 diabetes frequently display elevated levels of plasma glucose and insulin owing to the fact that even sophisticated regimens of insulin substitution do not perfectly mimic the physiological regulation of plasma glucose and insulin secretion. Apart from discrete hypoglycemic episodes that were prevented in our experiments, slightly but persistently elevated concentrations of glucose and insulin can likewise stimulate HPA activity and the release of epinephrine. Previous studies in healthy subjects indeed showed a stimulatory influence of insulin on HPA secretory activity (10) and circulating epinephrine (11) during daytime wakefulness. Also, both type 1 and type 2 diabetic patients display overall increased HPA activity during spontaneous activity as well as in stimulation and suppression tests (3,12–14). Some of those studies suggest that increased HPA secretory activity depends on the strength of glycemic control, i.e., the degree of hyperglycemia (3,12–14). Epinephrine levels have also been found to be elevated in type 1 diabetes (15–17). However, the influence of hyperglycemia and hyperinsulinemia on neuroendocrine sleep architecture has not been directly assessed so far. Comparing effects of human and porcine insulin on sleep under nonhypoglycemic conditions in type 1 diabetic subjects, Roth et al. (18) observed reduced power in the 14-Hz spindle frequency range when the patients were switched from porcine to human insulin. Also, patients receiving human insulin felt less relaxed after sleep. However, this study did not include a control of healthy subjects without insulin administration, which hampers the interpretation of the results.

Although our study points for the first time to an alteration in neuroendocrine sleep architecture in patients with type 1 diabetes under nonhypoglycemic conditions, it does not allow any conclusion about the underlying pathophysiological mechanisms. Here, further studies with control for glycemia as well as for insulinemia (possibly by applying hyperinsulinemic-euglycemic clamp technique) are required to dissociate a potential influ-

ence of these factors from the influence of type 1 diabetes itself. However, from the clinical point of view, our results appear to be of particular interest because they were obtained under conditions that, with exception of the systematic prevention of hypoglycemia, resemble real-life conditions in type 1 diabetic patients being characterized by various degrees of hyperglycemia and hyperinsulinemia.

The elevation in blood concentrations of epinephrine, ACTH, cortisol, and growth hormone observed here in type 1 diabetic patients during sleep hints at a generally increased activity of neuroendocrine stress systems in these patients. Besides the presence of hyperglycemic and hyperinsulinemic conditions, psychological factors such as the burden of the disease could contribute to activation of stress systems. However, assessment of mood did not indicate any alterations in well-being and self-confidence in type 1 diabetic patients, and patients also did not show any signs of sleep disruption such as increased WASO, stage 1, or movements, which renders this possibility unlikely.

Our results are of clinical relevance for patients with type 1 diabetes. Both chronic disturbances of sleep (19–22) and activity of neuroendocrine stress systems (23,24) have been implicated in increased morbidity and mortality. On this background, we suggest that some of the adverse effects of type 1 diabetes on general health are mediated by changes in sleep and associated neuroendocrine activity which, hence, might become another target for therapeutic interventions in type 1 diabetic patients.

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