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Nocturnal Cortisol Release in Relation to Sleep Structure

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Summary: The relationship between the temporal organization of cortisol secretion and sleep structure is controversial. To determine whether the cortisol profile is modified by 4 hours of sleep deprivation, which shifts slow-wave sleep (SWS) episodes, 12 normal men were studied during a reference night, a sleep deprivation night and a recovery night. Plasma cortisol was measured in 10-minute blood samples. Analysis of the nocturnal cortisol profiles and the concomitant patterns of sleep stage distribution indicates that the cortisol profile is not influenced by sleep deprivation. Neither the starting time of the cortisol increase nor the mean number and amplitude of pulses was significantly different between the three nights. SWS episodes were significantly associated with declining plasma cortisol levels ($p < 0.01$). This was especially revealed after sleep deprivation, as SWS episodes were particularly present during the second half of the night, a period of enhanced cortisol secretion. In 73% of cases, rapid eye movement sleep phases started when cortisol was reflecting diminished adrenocortical activity. Cortisol increases were not concomitant with a specific sleep stage but generally accompanied prolonged waking periods. These findings tend to imply that cortisol-releasing mechanisms may be involved in the regulation of sleep. **Key Words:** Cortisol—Sleep structure—Slow-wave sleep—Sleep deprivation.

The circadian rhythm of cortisol, considered to represent "a paradigm of a circadian rhythm" (1,2), contrasts in its nature to the sleep-related rhythms of several hormones. It is relatively independent of sleep as it is unaltered by short-term manipulations such as sleep reversal, sleep deprivation and abrupt shifts in the sleep period.

Nevertheless, more recent studies provide evidence that sleep contributes to the temporal organization of the cortisol profile (3). Results obtained from studies in depressed patients (4,5) or after transmeridian flight (6) indicate clearly the existence of multiple controls.

Studies correlating specific sleep stages with cortisol secretory episodes have provided contradictory results (7–11). Decreasing cortisol concentrations have often been associated with rapid eye movement (REM) sleep (8,9) and increasing concentrations with wakefulness or light sleep. Also synthetic and natural corticosteroids have been shown to reduce REM sleep and to enhance intermittent wakefulness (12,13). Considering the low cortisol values during the first hours of sleep, when slow-wave sleep (SWS) is present to its greatest degree, an inhibitory role of SWS on cortisol secretion was proposed (3,8) although the quiescent period of adrenocortical activity starts a few hours before sleep onset. From this, it is difficult to conclude that there is any relationship between SWS and cortisol secretion, which is all the more evident as the evening nadir and morning acrophase seem to be synchronized by different mechanisms (14).

The aim of the present investigation was to perform a detailed analysis of nocturnal cortisol profiles with a period of sleep deprivation at the beginning of the night. In this case, the major SWS episodes would be delayed, coinciding with enhanced adrenocortical activity, the rhythm of which was expected to remain unaltered. This study examines the question of whether the temporal organization of the cortisol profile is modulated by a shift in sleep onset and sleep deprivation as previously suggested (15). Secondly, it allows the analysis of cortisol secretory episodes concomitantly with numerous SWS episodes, so that it can be established whether they are related. In addition, the cortisol profile was studied during a recovery night after repeated sleep deprivation.

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MATERIALS AND METHODS

Subjects

Twelve male volunteers participated in this study. They were 19–24 years of age, with a mean weight of 69 ± 2 kg and height of 178 ± 1 cm. The subjects were selected after medical examination and screening tests including: 1) a questionnaire about their usual sleep–wake cycle, 2) an evening–morning test (16), and 3) Eysenck's personality inventory (17). Subjects with sleep disorders or who had experienced time shift or sleep deprivation during the previous weeks, smokers, subjects with signs of underlying disease or those taking medication were excluded from the study. All subjects gave informed written consent.

Procedures

Experiments were performed in an apartment, in which the subjects lived in a controlled thermal environment for 11 days. To become adjusted to the experimental conditions they underwent a habituation night prior to the study. Following an initial period of five reference nights, during which lights were switched off at 2300 hours and the subjects awakened at 0700 hours, the duration of sleep was reduced to 4 hours for 4 consecutive nights (sleeping period between 0300 and 0700 hours). The 10th and 11th nights were recovery nights, when subjects were again allowed to sleep 8 hours, from 2300 to 0700 hours. Endocrinological investigations were limited to the first night of each experimental phase (N1, N6, N10). The time in bed for these nights was from 2100 to 0700 hours.

Six subjects performed the experiment at 20°C and six others were exposed to 35°C after the reference period. Preliminary statistical analyses showed no difference in sleep parameters or endocrinological data between the two groups, which is in accordance with previous results (18). Therefore data from all 12 subjects were pooled for analysis.

Blood sampling and plasma measurements

Blood samples were collected continuously throughout the night in an adjoining room over 10-minute periods using a peristaltic pump. Samples were taken in ethylenediaminetetraacetate (EDTA) tubes and immediately centrifuged at 4°C, and the plasma was removed and stored at −25°C.

Plasma cortisol was measured by radioimmunoassay (RIA) using a method based on that of Vescei et al. (19). The cortisol antiserum was prepared against a bovine serum albumin cortisol-21-acetate-3-O-carboxymethyl oxime conjugate. The detection limit was 14 nmol/l. The intra-assay coefficient of variation (CV) for the duplicates assayed was 2% above 400 nmol/l, 4% between 170 and 400 nmol/l, 10% between 110 and 170 nmol/l and 20% for levels less than 110 nmol/l. All samples from a given night were analyzed in the same assay.

Sleep analysis

Polygraphic sleep recordings included two electroencephalograms, two electrooculograms, one electromyogram and one electrocardiogram. They were scored at 30-second intervals using standardized criteria (20). On this basis total sleep time, total duration of SWS and total duration of REM sleep were quantified. The onset of a REM sleep phase was defined as the beginning of a REM sleep episode that had a duration of at least 1 minute. Two REM sleep or SWS episodes were considered distinct from one another if they were separated by one or more blood sampling periods. The relationship between cortisol levels and sleep stages was estimated by calculating (10 minutes) the percentage of time spent in a given stage for each blood sampling period.

Data analysis

Cortisol peaks were identified using the pulse analysis program ULTRA (21), which eliminates all peaks of plasma concentration for which either the increment or the decrement does not exceed a threshold set at three times the intra-assay coefficient of variation in the relevant concentration range. Simulation studies (22) have indicated that for series involving few and/or small pulses and especially for raw data as used here, the threshold of three CV is appropriate to minimize both false-positive and false-negative errors. It is clear that for peak analysis the sampling frequency and technique is of major importance. Compared to discrete sampling, some of the rapid oscillations may not have been picked up using the continuous blood withdrawal method, but it is advantageous in that it does not disregard the 10-minute intersample period. The significant oscillations were analyzed in relation to the sleep stages, which were classified into either ascending or nonascending phases defined by the pulse-detection program.

The association of REM sleep onset or SWS and hormone pulse phases was tested by χ^2, taking the relative proportions of 10-minute samples in ascending and nonascending phases into account throughout the total monitoring time. The decline of cortisol levels during SWS phases was evaluated using a one-tailed Student's t test with Bonferroni's correction for multiple comparisons.

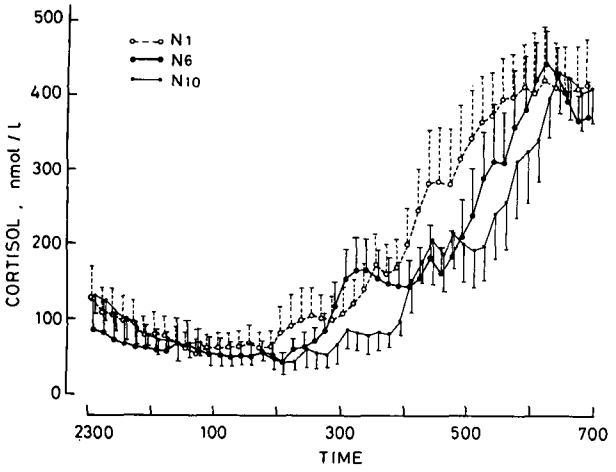

FIG. 1. Mean ± SE plasma cortisol curves (n = 12) for the reference night (N1), the deprivation night (N6) and the recovery night (N10).

RESULTS

Sleep patterns

Partial sleep deprivation affected the distribution of sleep stages during the subsequent 4 hours, during which sleep was allowed, in comparison to the typical pattern displayed during the reference night. The latency of sleep onset decreased (23 ± 5 vs. 13 ± 4 minutes; $p < 0.05$) and the total duration of SWS, related to the total time asleep, increased (21% vs. 31%; $p < 0.001$), whereas the proportion of REM sleep did not change significantly (21% vs. 19%; ns).

Also during the recovery night, certain parameters of the sleep pattern were altered. Comparison with the reference night pointed out that the total time spent asleep increased (401 ± 16 vs. 452 ± 7 minutes; $p < 0.01$) as well as the total duration of SWS (81 ± 7 vs. 102 ± 6 minutes; $p < 0.05$) and the total duration of REM sleep (86 ± 8 vs. 106 ± 8 minutes; $p < 0.05$). When expressed as a percentage of time spent asleep, these durations did not differ between the reference and recovery nights.

Nocturnal cortisol profiles

The mean cortisol curves obtained for the subjects did not differ between the three nights in their general pattern (Fig. 1). During the deprivation night, the mean cortisol levels were not significantly different from the mean levels of the reference night either during the first or the second half of the night. During the recovery night, a lower level was observed during the second half of the night as shown in Table 1.

TABLE 1. *Cortisol levels for the 3 nights*[a]

	2300–0300 hours	0300–0700 hours
N1	83 ± 17	301 ± 33
N6	64 ± 17	257 ± 22
N10	69 ± 11	232 ± 25**[b]

[a] Values are mean ± SE.
[b] Significant difference from the corresponding time period of the reference night N1: **$p < 0.01$.

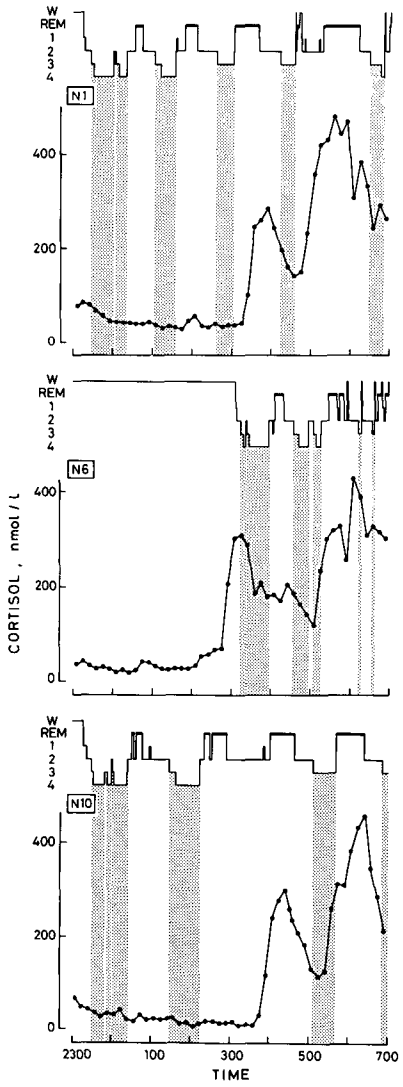

FIG. 2. Example of individual cortisol profiles for the three nights: reference (N1), sleep deprivation (N6) and recovery (N10) with the patterns of sleep stage distribution. SWS phases are represented by shaded areas.

Figure 2 illustrates the curves obtained for one representative subject for the three nights displaying cortisol oscillations of high amplitude during the second half of each night.

A detailed pulse analysis of the individual curves by the program ULTRA allowed the secretory episodes to be precisely located and a comparison of the number and amplitude between the three nights (Table 2) to be made. This analysis demonstrated that the mean

TABLE 2. *Analysis of cortisol pulses*

Nights	Time of sleep onset	Number of pulses	Mean amplitude (nmol/l)	Onset of the first cortisol increase
N1	23 hours 37 ± 8 minutes	4 ± 1	246 ± 36	1 hour 55 ± 30 minutes
N6	3 hours 13 ± 4 minutes	4 ± 1	204 ± 22	1 hour 55 ± 30 minutes
N10	23 hours 14 ± 2 minutes	4 ± 1	232 ± 28	2 hours 25 ± 30 minutes

number of secretory episodes per night remained constant (4 ± 1) and that their mean amplitude did not significantly differ between N1 (246 ± 36 nmol/l), N6 (204 ± 22 nmol/l) and N10 (232 ± 28 nmol/l).

The results show a large interindividual variability in the starting time of the early morning increase in adrenocortical activity (Table 2). Comparing the first significant plasma cortisol increase, no significant difference could be found between mean onset time during the three nights. Mean values were 1 hour 55 ± 30 minutes, 1 hour 55 ± 30 minutes and 2 hour 25 ± 30 minutes, respectively, for N1, N6 and N10. Thus cortisol began to increase before sleep onset during the deprivation night N6. The tendency of a delayed cortisol increase during N10 did not reach the level of significance.

Relationship between cortisol secretory episodes and sleep stages

REM sleep

For the 36 nights studied, pulse-by-pulse analysis of all the individual nocturnal cortisol profiles showed that 73% of REM sleep phases started during a nonascending portion of a cortisol pulse. Although 27% started during an ascending portion of a cortisol pulse, which reflects active secretion, a χ^2 test taking the relative proportion of ascending and nonascending phases of the cortisol peaks into account shows that the deviation from chance in the association of REM onsets and nonascending phases is still significant ($p < 0.05$) (Table 3). In fact 10% among these 27% ascending phases gave evidence of a shouldering of the cortisol curve at the time of REM sleep onset, suggesting a transient reduction of the secretion. Even when REM sleep started in a well-defined nonascending phase, the REM sleep episode often continued after plasma cortisol had begun to increase again, especially in the early morning hours.

Slow-wave sleep

During the first half of the reference and recovery nights SWS phases were numerous and the plasma cortisol level was very low. This prevented analysis of the relationship between SWS and cortisol secretory episodes. Thus, only the second half of the night (0300–0700 hours) was considered, although SWS phases at this time are generally short and sleep is less deep. Sleep deprivation till 0300 hours meant that the main SWS phases, appearing soon after sleep onset, coincided with the time of enhanced cortisol secretion.

Figure 3 illustrates the mean temporal distribution of SWS and cortisol in relation to the onset of SWS episodes, N6 and N1–N10 being treated as two separate groups. Following sleep deprivation (N6), mean plasma cortisol clearly decreased during the first 20 minutes of SWS and subsequently increased. Student's *t* test with Bonferroni's correction for multiple comparisons revealed a significant decrease in cortisol values in the two 10-minute samples following the 0-sample, which corresponds to SWS onset ($p < 0.01$). For the subsequent sample, mean cortisol increased and the difference became nonsignificant. This was because the SWS phases were of various length (10–60 minutes), but an equal number of sample points following each SWS onset were considered. Thus, for short SWS phases, only two or three sample points were within the SWS episode. For 31% of the SWS phases, especially those of long duration, cortisol had begun to rise before the end of the SWS phase.

During the second half of the night, without sleep deprivation (N1, N10), SWS periods were shorter and comprised of fewer stage 4 phases. Nevertheless, the mean cortisol values also decreased significantly ($p < 0.01$) in two 10-minute samples following SWS onset.

TABLE 3. *Relationship between cortisol oscillations and sleep stages during the 0300–0700-hour period for the three nights*

	Plasma cortisol			
	Ascending phases	Nonascending phases	Deviation from chance association	
10-minute cortisol samples	331	533		
REM sleep onset[a]	34	93	$\chi^2 = 4.8$	$p < 0.05$
SWS[b]	5	68	$\chi^2 = 27.6$	$p < 0.001$
SWS[c]	8	59	$\chi^2 = 18.6$	$p < 0.001$

[a] Ten-minute period during which sleep stage started.
[b] First 10-minute period following REM sleep onset.
[c] Second 10-minute period following REM sleep onset.

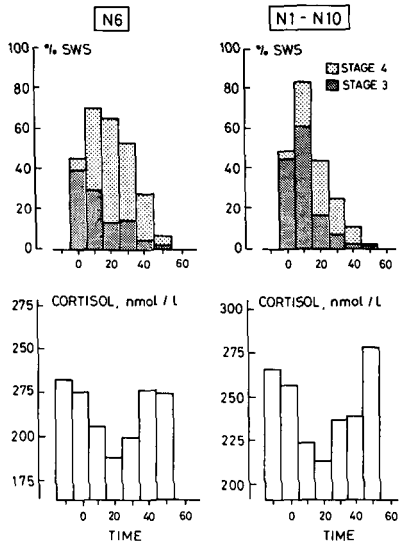

FIG. 3. Mean temporal distribution of SWS and cortisol in relation to the onset of SWS episodes (time 0). Left panel: period following 4 hours of sleep deprivation (N6); right panel: period following 4 hours of sleep (N1 and N10).

The pulse-by-pulse analysis of cortisol allowed a more precise determination of the relationship between cortisol variation and each SWS phase. This analysis was performed during the 0300–0700-hour period of all nights studied (N1, N6, N10). Seventy-three SWS phases occurred during the 36 half-nights considered and 56% of these phases coincided with a cortisol decrease, 36% with no change and 8% with a cortisol increase. χ^2 tests were performed separately on two cortisol samples, the first corresponding to the time interval after which SWS started and the second following this time interval. These measurements showed that the deviation from chance in the association between SWS and nonascending cortisol phases was highly significant ($p < 0.001$) (Table 3).

Cortisol increases did not coincide with a specific sleep stage. They occurred as frequently during stage 2, during REM sleep, as at the end of SWS phases and accompanied generally prolonged waking periods.

DISCUSSION

The results of the present study provide evidence of a temporal relationship between adrenocortical secretion, sleep quality and sleep structure. Previous observations obtained after diverse manipulations of the sleep–wake cycle, such as reversal (23), shortening (24), transmeridian flight (6,14), night work (25) or temporal isolation (26), led to the conclusion that sleep may influence adrenocortical activity, and Weitzman et al. (3) suggested that sleep could have an inhibitory effect on cortisol secretion. Our results obtained during the recovery night, in which the total sleep time was enhanced, support this observation. However, this effect is not apparent in normal conditions, where cortisol levels are already low before sleep onset. Even so, under conditions of partial sleep deprivation our results gave no evidence of enhanced secretory activity during the prolonged waking period. The decrease in mean cortisol level during the recovery night was due to a decrease during the second half of the night only. These results agree with the hypothesis of Van Cauter and Refetoff (14), who suggested that different mechanisms would synchronize the morning acrophase and the evening nadir.

The influence of sleep deprivation on the temporal distribution of cortisol secretory episodes is not clearly established (3,11,15,27,28). The large inter- and intraindividual differences observed for cortisol between nights could account for some discrepancies. In addition, sleep processes and adrenocortical activity are not strongly correlated but only linked by a temporal relationship. Thus, the experimental design afforded a great number of night studies and suited profile analyses. After sleep deprivation, significant modification of the cortisol profile was identified by the pulse analysis performed in this study.

An association between REM sleep and periods of low adrenal cortex secretory activity has been reported (8). Our results show that a significant proportion of REM sleep phases started at a time of unchanged or decreasing cortisol levels, but the REM episode often persisted after cortisol increased again. These findings are in accordance with a previously demonstrated temporal relationship between adrenocorticotropic hormone (ACTH) and REM sleep onset (29), but the percentage of REM sleep phases starting during cortisol increases was higher than that previously found for ACTH. This may be explained by the time lag existing between ACTH and cortisol secretion (30) and the relatively high percentage of REM sleep phases occurring at ACTH peak levels.

The shouldering of cortisol curves sometimes observed at the time of REM sleep onset corresponds to a transient decrease in secretion, too short to be registered as a separate plasma peak by the pulse analysis technique used, which affords not only a significant increment but also a significant decrement. A higher sampling rate or discrete sampling may have identified additional significant cortisol peaks, especially during the early morning hours.

The cooccurrence of low cortisol levels and numerous SWS episodes during the first half of the night led some authors to propose that SWS may exert an inhibitory effect on cortisol secretion (3,7,9,15) or that the offset of SWS episodes perhaps acts as a trigger for the nocturnal cortisol rise (8). However, a normal

nighttime sleep does not favor detailed study of the relationship, as low cortisol secretion coincides with major SWS episodes. On the contrary, partial sleep deprivation during the first half of the night provides a much more interesting model. Thus, the major SWS phases were delayed, again appearing soon after sleep onset, but coinciding in this case with enhanced cortisol secretion. The results clearly indicated that SWS phases are associated with diminished adreno-cortical activity. Although from this temporal relationship it cannot be concluded that SWS has an inhibitory influence on cortisol secretion, neither can the reverse be concluded. Some observations in patients tend to imply that cortisol-releasing mechanisms or cortisol itself may be involved in the regulation of sleep. Patients with hypercortisolism showed diminished amounts of SWS (31), whereas patients with adrenocortical insufficiencies (32) displayed increased amounts of SWS. Also, patients with endogenous depression were found to have increased nocturnal plasma cortisol levels and less SWS episodes (5).

Despite the 10-minute blood sampling time with regard to the sleep scoring period of 30 seconds, it appears that the cortisol decrease often slightly preceded SWS onset. This does not agree with an inhibitory action for SWS on cortisol secretion but it rather indicates that enhanced adrenocortical activity prevents sleep deepening. Also, before the end of some of the longer-lasting SWS episodes, plasma cortisol was already found to increase, perhaps preparing for the transition to lighter sleep, as enhanced cortisol concentration was shown to be associated with more shallow sleep (8,9).

In conclusion, this study demonstrates that SWS episodes as well as REM sleep onset are temporally related to decreased cortisol secretion, which reflects decreased pituitary activity. Moreover, cortisol increases do not seem to be related to any specific sleep stage.

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REFERENCES

1. Krieger DT, Aschoff J. Endocrine and other biological rhythms. In: De Groot LJ, ed. *Endocrinology.* New York: Grune and Stratton, 1979;3:2079–109.
2. Krieger DT. *Endocrine rhythms. Comprehensive endocrinology series.* New York: Raven Press, 1979.
3. Weitzman ED, Zimmerman JC, Czeiler CA, Ronda J. Cortisol secretion is inhibited during sleep in normal men. *J Clin Endocrinol Metab* 1983;56:352–8.
4. Linkowski P, Mendlewicz J, Golstein J, Copinshi G, Leclercq R, Brasseur M, Van Cauter E. The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. *J Clin Endocrinol Metab* 1985;61:429–43.
5. Jarrett DB, Coble PA, Kupfer DJ. Reduced cortisol latency in depressive illness. *Arch Gen Psychiatry* 1983;40:506–11.
6. Desir D, Van Cauter E, Fang V, Martino E, Jadot C, Spire JP, Noel P, Refetoff S, Copinshi G, Golstein J. Effects of "jet lag" on hormonal pattern. I. Procedures, variations in total plasma proteins and disruption of adrenocorticotropin–cortisol periodicity. *J Clin Endocrinol Metab* 1981;52:628–41.
7. Kupfer DJ, Bulik CM, Jarrett DB. Nighttime plasma cortisol secretion and EEG sleep: are they associated? *Psychiatry Res* 1983;10:191–9.
8. Born J, Kern W, Bieber K, Fehm-Wolfsdorf G, Schiebe M, Fehm HL. Night-time plasma cortisol secretion is associated with specific sleep stages. *Biol Psychiatry* 1986;21:1415–24.
9. Fehm K, Bieber K, Benkowitsch R, Fehm-Wolfsdorf G, Voigt KH, Born J. Relationships between sleep stages and plasma cortisol: a single case study. *Acta Endocrinol* 1986;111:264–70.
10. Steiger A, Herth J, Holsboer F. Sleep electroencephalography and the secretion of cortisol and growth hormone in normal controls. *Acta Endocrinol* 1987;116:36–42.
11. Born J, Schenk U, Späth-Schwalbe E, Fehm HL. Influences of partial REM sleep-deprivation and awakenings on nocturnal cortisol release. *Biol Psychiatry* 1988;24:801–11.
12. Gillin JC, Jacobs LS, Fram DH, Snyder F. Acute effect of a glucocorticoid on normal human sleep. *Nature* 1972;237:398–9.
13. Fehm HL, Benkowitsch R, Kern W, Fehm-Wolfsdorf G, Pauschinger P, Born J. Influences of corticosteroids, dexamethasone and hydrocortisone on sleep in humans. *Neuropsychobiology* 1986;16:198–204.
14. Van Cauter E, Refetoff S. Multifactorial control of the 24-hour secretory profiles of pituitary hormones. *J Endocrinol Invest* 1985;8:381–91.
15. Born J, Muth S, Fehm HL. The significance of sleep onset and slow wave sleep for nocturnal release of growth hormone and cortisol. *Psychoneuroendocrinology* 1988;13:233–43.
16. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness–eveningness in human circadian rhythm. *Int J Chronobiol* 1976;4:97–110.
17. Eysenk HJ, Eysenk SBG. *Inventaire de personnalité d'Eysenk (EPI). Traduction et adaptation par Ganansia K.* Paris: Ed. du Centre de Psychologie Appliquée, 1971.
18. Brandenberger G, Follenius M, Di Nisi J, Libert JP, Simon C. Amplification of nocturnal oscillations in PRA and aldosterone during continuous heat exposure. *J Appl Physiol* 1989;66(3): 1280–6.
19. Vescei P, Peuke B, Katzy R, Black L. Radioimmunological determination of plasma cortisol. *Experientia* 1972;8:1104–6.
20. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects.* Washington DC: US Government Printing Office, 1968.
21. Van Cauter E. Quantitative methods for the analysis of circadian and episodic hormone fluctuations. In: Van Cauter E, Copinshi G, eds. *Human pituitary hormones: circadian and episodic variations.* The Hague: Nyhoff, 1981.
22. Van Cauter E. Estimating false-positive and false-negative errors in analysis of hormonal pulsatility. *Am J Physiol* 1988;254: E786–94.
23. Weitzman ED, Goldmacher D, Kripke DF, McGregor P, Kream J, Hellman F. Reversal of sleep–waking cycle: effect on sleep stage pattern and neuroendocrine rhythms. *Trans Am Neurol Assoc* 1968;93:153–7.
24. Weitzman ED, Nogeire C, Perlow M, Fukushima D, Sassin JF, McGregor P, Gallagher TF, Hellman L. Effects of a prolonged 3 hour sleep–wake cycle on sleep stages, plasma cortisol, growth hormone and body temperature in man. *J Clin Endocrinol Metab* 1974;38:1018–30.
25. Touitou Y, Motohashi Y, Reinberg A, Touitou C, Bourdeleau P, Bogdan A, Auzeby A. Effect of shift work on the night-time secretory patterns of melatonin, prolactin, cortisol and testosterone. *Eur J Appl Phsyiol* 1990;60:288–92.
26. Weitzman ED, Czeisler CA, Zimmerman JC, Morre-Ede MC. Biological rhythms in man: relationship of sleep–wake, cortisol,

growth hormone and temperature during temporal isolation. In: Martin JB, Reichlin S, Bick K, eds. *Neurosecretion and brain peptides.* New York: Raven Press, 1981:475–99.
27. Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W. Delayed sleep phase syndrome: a chronological disorder withi sleep onset insomnia. *Arch Gen Psychiatry* 1981;38:737–45.
28. Weitzman ED, Boyar R, Kapen S, Hellman L. The relationship of sleep and sleep stages to neuroendocrine secretion and biological rhythms in man. In: Greep R, ed. *Recent progress in hormone research.* New York: Academic Press, 1975:399–440.
29. Follenius M, Brandenberger G, Simon C, Schlienger JL. REM sleep in humans begins during decreased secretory activity of the anterior pituitary. *Sleep* 1988;11(6):546–55.
30. Follenius M, Simon C, Brandenberger G, Lenzi P. Ultradian plasma corticotropin and cortisol rhythms: time-series analyses. *J Endocrinol Invest* 1987;10:261–6.
31. Krieger DT, Glick SM. Sleep EEG stages and plasma growth hormone concentration in states of endogenous hypercortisolemia or ACTH elevation. *J Clin Endocrinol Metab* 1974;39: 986–1000.
32. Gillin JC, Jacobs LS, Snyder F, Henkin RI. Effects of decreased adrenal corticosteroids: changes in sleep in normal subjects and patients with adrenal cortical insufficiency. *Electroencephalogr Clin Neurophysiol* 1974;36:283–9.