

Cortisol Secretion Is Related to Electroencephalographic Alertness in Human Subjects during Daytime Wakefulness*

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ABSTRACT

To determine whether human hypothalamo-pituitary-adrenal axis activity is related to the alertness level during wakefulness, 10 healthy young men were studied under resting conditions in the daytime (0900–1800 h) after an 8-h nighttime sleep (2300–0700 h). A serial 70-sec gaze fixation task was required every 10 min throughout the daytime experimental session. The corresponding waking electroencephalographic (EEG) segments were submitted to quantitative spectral analysis, from which EEG β activity (absolute power density in the 13–35 Hz frequency band), an index of central alertness, was computed. Blood was collected continuously through an indwelling venous catheter and sampled at 10-min intervals. Plasma cortisol concentrations were measured by RIA, and the corresponding secretory rates were determined by a deconvolution procedure.

Analysis of individual profiles demonstrated a declining tendency for EEG β activity and cortisol secretory rate, with an overall temporal relationship indicated by positive and significant cross-correlation coefficients between the two variables in all subjects (average $r = 0.565$, $P < 0.001$). Changes in cortisol secretion lagged behind

fluctuations in EEG β activity, with an average delay of 10 min for all the subjects. On the average, 4.6 ± 0.4 cortisol secretory pulses and 4.9 ± 0.5 peaks in EEG β activity were identified by a detection algorithm. A significant, although not systematic, association between the episodes in the two variables was found: 44% of the peaks in EEG β activity (relative amplitude, near 125%; $P < 0.001$) occurred during an ascending phase of cortisol secretion, cortisol secretory rates increasing by 40% ($P < 0.01$) 10-min after peaks in EEG β activity. However, no significant change in EEG β activity was observed during the period from 50 min before to 50 min after pulses in cortisol secretion.

In conclusion, the present study describes a temporal coupling between cortisol release and central alertness, as reflected in the waking EEG β activity. These findings suggest the existence of connections between the mechanisms involved in the control of hypothalamo-pituitary-adrenal activity and the activation processes of the brain, which undergoes varying degrees of alertness throughout daytime wakefulness. (*J Clin Endocrinol Metab* 83: 4263–4268, 1998)

CORTISOL is released in pulses by adrenocortical glands under pituitary ACTH control, with a periodicity of 80–110 min in man (1). The 24-h pattern of cortisol levels shows an early-morning acrophase and an evening nadir (2). This is the consequence of an amplitude modulation of ACTH secretory bursts (3), probably driven by the supra-chiasmatic nucleus of the hypothalamus, which controls CRH and arginine vasopressin cells of the paraventricular nucleus (4). Although cortisol secretion is known to be primarily under a circadian influence (5), independent of sleeping and waking, several studies in humans have suggested that sleep, especially slow-wave sleep, may exert an inhibitory influence on cortisol secretion (6, 7). Other authors argue that an underlying mechanism decreases cortisol se-

cretion and facilitates sleep onset and slow-wave sleep installation (8–10). Dynamic relationships have been described between human sleep electroencephalographic (EEG) activity, which reflects central nervous sleep processes, and cortisol secretory activity (11, 12). Sleep deepening, indicated by an increase in EEG slow wave activity (SWA or δ activity between 0.5–4 Hz), has been shown to be preceded by or concomitant with a decrease in cortisol secretory rates (11). These results confirmed that alternations between rapid-eye-movement (REM) sleep and non-REM sleep are associated with changes in cortisol secretion (8, 13). Consequently, the existence of common mechanisms influencing both the central nervous system and the hypothalamo-pituitary-adrenal (HPA) axis should be physiologically relevant during sleep, if not during both sleep and wakefulness.

Although sleep EEG has been extensively studied (14), the time course of the waking EEG activity has been studied far less, because of artifacts contaminating EEG recordings. However, diurnal fluctuations of the human background EEG, a neurophysiological indicator of the brain's functional state (15), have been shown to occur spontaneously, with patterns depending on the EEG spectrum frequency band

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(16, 17). Indeed, homeostatic wake-dependent and circadian components of the EEG have been recently identified (18). Moreover, it has been shown that daytime temporal changes in different frequency bands of the waking EEG occur periodically (19, 20), with an ultradian periodicity of 70–120 min (21), comparable with that of cortisol release (1). From a neurophysiological point of view, EEG β activity (13–35 Hz) is observed during wakefulness and REM sleep. It is controlled by the thalamus and generated by the desynchronization of cortical neurons in response to cognitive processes and attention requirements (22, 23). This specific activity is considered to be an index of the level of brain activation, because increased alertness has been shown to be associated with EEG desynchronization (23, 24).

Therefore, the coupling of HPA axis activity and the level of central alertness was examined during wakefulness using a 70-sec gaze fixation task, performed every 10 min, with EEG and plasma cortisol measurements being taken simultaneously.

Subjects and Methods

Subjects

Ten healthy males, between 21 and 27 yr old, with a standard body mass index ($21.7 \pm 0.9 \text{ kg/m}^2$), volunteered and gave their informed written consent after the approval of the protocol by the local ethics committee. They were selected, after a medical examination, based on their sleep schedules and quality. All evening- or morning-type people and subjects with sleep disorders or jet-lag experience, shift work, or sleep deprivation during the preceding weeks were excluded from the study. A preliminary EEG test was performed to exclude subjects exhibiting more than 10 eye blinks per minute. Subjects having low sleep efficiencies (<80%), during the night preceding the daytime measures of alertness, were excluded from the analyses.

Protocol

Experiments were performed in two soundproof air-conditioned rooms, with blood samples collected and electrophysiological signals monitored in an adjacent room. Closed-circuit television allowed constant supervision of the subjects. Special attention was given to avoid intercurrent sleep episodes. When awake, the subjects were maintained in dim light (<100 lux). They slept in the laboratory for two consecutive nights, from 2300–0700 h, each night being followed by a daytime period during which they remained supine and were submitted to a serial 70-sec gaze-fixation task. This task was repeated every 10 min, from 0900–1500 h, during the habituation period (day I) and from 0900–1800 h during the experimental period (day II). Between gaze-fixation periods, the subjects read, listened to music, watched television, or conversed with an experimenter. They received standardized meals at 0700 h, 1200 h, and 1900 h. At 1600 h on day I, a catheter was inserted under local anesthesia into an antecubital vein and was kept patent with heparinized solutions, allowing the subjects to remain supine until the end of the experiment. Electrodes for polygraphic recordings were attached 1 h before the beginning of each recording period and detached at the end of the procedure. Polygraphic sleep recordings were performed during the night, from day I to day II.

Waking-EEG recordings

Continuous waking-EEG recordings were performed with electrodes attached with collodion and placed according to the 10/20 international system (25) using both central EEG derivations (C_3 and C_4), referenced to the contralateral mastoid apophysis (A_2 and A_1 , respectively). One transversal electrooculographic derivation and 1 chin electromyographic derivation were attached for artifact control (26). After high-pass (0.3 Hz) and low-pass (35 Hz) filtering, EEG signals were converted to numeric with a sampling frequency of 256 Hz and then stored on a

computer hard disk. EEG data were then imported into ERA (Phitools, Grenoble, France), a Matlab 5.2 (The MathWorks, Natick, MA) software package for polysomnographic and quantitative EEG analyses. Subsequently, spectra were computed for each consecutive 2-sec epoch using a fast Fourier transform algorithm (27). Median spectra were computed over the 2-sec epochs falling in the last 60 sec of each gaze fixation task. From poorly artifacted recordings, this procedure allows data averaging, without the interference of ectopic values. The first 10 sec of each task were not taken into account, to let the subjects accommodate to the task. Missing values related to accidental electrode detachment represented less than 5% of the total recording samples and were linearly interpolated. Spectral time series were then smoothed using a weighted moving-average window of three points. The spectral parameter considered was the absolute power density, expressed in μV^2 , in the 13–35 Hz frequency band (EEG β activity), because it has been shown to constitute a good index of the physiological level of alertness (24). Each subject was informed 30 sec in advance (t_{-30}) that the task was going to start, the beginning (t_0) and the end (t_{70}) of each task being communicated orally. The task was repeated 54 times from 0900–1800 h on day II. Before the beginning of the recording procedure, the subject was asked to comply with the following instructions: Do not move and do not make any particular mental or physical effort except for keeping your eyes open, looking in front of you, and staying awake.

Blood sampling and plasma measurements

During the last 24-h period, blood was withdrawn continuously, from 1800 h (day I) to 1800 h (day II), using a peristaltic pump (Ismatec, Bioblock Scientific, Strasbourg, France), and was sampled (every 10 min) into tubes containing EDTA- K_2 (1 mg/mL). A maximum of 200 mL blood per subject was removed during the experiment. Samples were immediately centrifuged at 4 C, and the plasma was stored at -25 C . Plasma cortisol concentrations were measured by RIA (Diagnostic Systems Laboratories, Inc., Webster, TX). The assay sensitivity was 0.2 pg/mL; the intraassay coefficient of variation was 10% under 6 pg/mL and 4% above 6 pg/mL. All samples from each subject were measured in the same assay.

Determination of cortisol secretory rates

Cortisol secretory rates were estimated from the corresponding cortisol plasma levels using a deconvolution procedure. A two-compartment model for hormone distribution and degradation was applied with half-lives of 5 and 65 min. The distribution vol was set at 53 dL for all subjects, and the fraction associated with the first compartment was 80%. Statistical error propagation of uncertainty in plasma level measurements was taken into account in the determination of the SD associated with each estimated secretory rate.

Regression analysis

Trends in the time series of cortisol secretory rate and EEG β activity, throughout daytime, were assessed by a first-order regression analysis. The slopes and their corresponding significance levels were computed for all individuals.

Cross-correlation analysis

Daytime temporal relationships between cortisol secretory rate and EEG β activity were determined by cross-correlation analysis, with series transformed into Z-scores [$Z\text{-score} = (x - \mu) / \sigma$, where x is the original data, μ the mean value, and σ the SD of the data]. Cross-correlation coefficients between the two chronological series were computed for 10-min lags falling between -20 and $+20$ min, each lag corresponding to an experimental measurement period. For positive lags, EEG β activity would anticipate cortisol secretion; conversely, for negative lags, cortisol secretion would precede EEG β activity. A χ^2 test of homogeneity was computed with individual transformed coefficients (28). When homogeneity was assumed for the whole group, individual correlation coefficients were averaged, using Fisher's transform, yielding an average estimate of the correlation (29).

Peak detection

Significant peaks in EEG β activity and pulses of cortisol secretion were identified using a modification of the detection algorithm ULTRA (30). Increases and decreases in cortisol secretory rates and EEG β absolute power density were considered significant when the sum of the SDS associated with the successive time points exceeded a subject-dependent threshold. This threshold was set at a constant percentage of the variance of the time series (25% for cortisol secretory rate and 15% for EEG β activity). The detection threshold of cortisol secretory pulses was chosen so as to always exceed the error associated with the radio-immunological measurement method. For each significant peak in EEG β activity and pulse of cortisol secretory rate, the time of occurrence of the crest (maximal peak value), the onset of the ascending phase, and the offset of the descending phase were determined.

Mean peak analyses

After the detection of peaks in EEG β activity and of pulses in cortisol secretory rate, the average peak in each variable was computed with regard to the level in the concurrent variable. For each subject, all peaks or pulses were aligned by their crest and averaged, point by point, from 50 min before to 50 min after the crest. To obtain an average peak for the entire group of subjects, the 10 individual mean peaks were expressed as a percentage of the individual mean peak level and were subsequently averaged among subjects. Percentages from the individual mean peaks were processed by a one-way ANOVA for repeated measures, with time as the factor. *Post hoc* comparisons of the different time points were performed with a Dunnett *t*-test in reference to a control value corresponding to the mean of the peaks in the time range under study (100%).

Coincidence analysis

When the mean peak analysis revealed significant results, the association between the crest in one variable and the ascending phases in the concurrent variable was tested. This was performed by a χ^2 test, taking into account the relative proportion of 10-min samples in the different phases throughout the duration of the experiment.

In all statistical analyses, differences were considered to be significant when the *P* value was less than 0.05. All results are expressed as mean \pm SEM. Only data from day II, during which electrophysiological and endocrine variables were measured simultaneously, were concerned with statistical analyses. In all analyses, EEG data were chosen from the least artifacted derivation (C_3 or C_4).

Results

EEG β activity profiles

Profiles of EEG β activity were characterized by a mean level of $6.0 \pm 1.1 \mu V^2$ (showing a large interindividual variability) and by a diurnal coefficient of variation of $19.3 \pm 1.9\%$ (which indicated noticeable variations during the daytime). For both cortisol secretory rate and EEG β activity, regression analysis on individual profiles demonstrated significant linear trends throughout daytime for almost all subjects. Table 1 gives the individual slopes with their corresponding significance level for the two variables. A majority of subjects exhibited negative and significant slopes (nine subjects for cortisol secretory rates and eight for EEG β activity). During the 9-h waking period, 4.9 ± 0.5 peaks in EEG β activity and 4.6 ± 0.4 pulses of cortisol secretion were identified.

Cross-correlation analysis

Cross-correlation analysis between cortisol secretory rate and EEG β activity revealed significant and positive coefficients in all individuals. For each subject, the highest coefficient, with its corresponding time lag, is given in Table 2. All individual coefficients being homogeneous ($\chi^2 = 8.10$,

TABLE 1. Individual slopes of cortisol secretory profiles and waking EEG β activity (13–35 Hz absolute power density)

| Subject | Cortisol secretion | EEG β activity |
|---------|-----------------------|-----------------------|
| | Slope ($\mu g/h^2$) | Slope ($\mu V^2/h$) |
| 1 | 6.1 | 0.03 |
| 2 | -46.3 ^a | -0.68 ^a |
| 3 | -19.9 ^b | -0.03 ^b |
| 4 | -20.3 ^b | -0.09 ^c |
| 5 | -20.6 ^b | -0.14 ^a |
| 6 | -35.6 ^a | -0.05 ^b |
| 7 | -29.9 ^b | -0.04 ^c |
| 8 | -30.6 ^b | 0.03 |
| 9 | -21.5 ^b | -0.20 ^a |
| 10 | -39.3 ^b | -0.17 ^a |

^a *P* < 0.001.

^b *P* < 0.01.

^c *P* < 0.05.

TABLE 2. Highest individual cross-correlation coefficients between cortisol secretory rate and waking EEG β activity (13–35 Hz absolute power density)

| Subject | Lag (min) | r |
|----------|-----------|--------------------|
| 1 | -10 | 0.569 ^a |
| 2 | 0 | 0.623 ^a |
| 3 | 0 | 0.480 ^a |
| 4 | 20 | 0.640 ^a |
| 5 | 0 | 0.634 ^a |
| 6 | 20 | 0.560 ^a |
| 7 | 20 | 0.380 ^b |
| 8 | -10 | 0.638 ^a |
| 9 | 10 | 0.436 ^a |
| 10 | 0 | 0.631 ^a |
| Average | 10 | 0.565 ^a |
| χ^2 | 8.10 | Homogeneity |

^a *P* < 0.001.

^b *P* < 0.01.

^c *P* < 0.05.

P > 0.5), an average cross-correlation coefficient was computed and found to be highly significant (average *r* = 0.565, *P* < 0.001). The individual time lags, lying between -10 and +20 min, indicated that fluctuations in EEG β activity tended to precede that of cortisol secretory rate. Figure 1 illustrates four individual Z-score profiles of EEG β activity with regard to the corresponding cortisol secretory rate during the daytime waking period.

Mean peak and coincidence analyses

The analysis of the mean peak in EEG β activity, Fig. 2A, showed a significant effect of time on the corresponding cortisol secretory rates ($F_{(11,90)} = 2.28$, *P* < 0.05). Peak related increases in EEG β activity occurred at -10 min, 0 min, and +10 min from the crest; and they averaged +15%, +25%, and +15%, respectively, over the mean peak level (*P* < 0.001). The corresponding increases in cortisol secretory rate, occurring at the time of the crest in EEG β activity (0 min), averaged +30% over the mean pulse level (*P* < 0.05) and reached a maximum 10 min later, about +40% over the mean pulse level (*P* < 0.01). On the other hand, the mean cortisol secretory pulse, as illustrated in Fig. 2B, was not accompanied by any significant increase or decrease in the corresponding levels of EEG β activity ($F_{(11,90)} = 1.16$, n.s.). Numerical re-

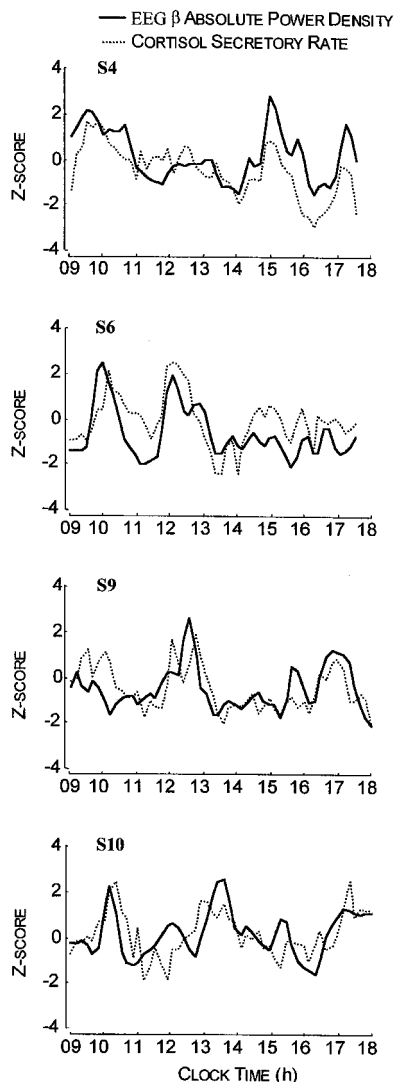


FIG. 1. Individual profiles of waking EEG β activity (13–35 Hz absolute power density) and cortisol secretory rate in four subjects during the daytime waking period. Time series are expressed in Z-score.

sults of these analyses are summarized in Table 3. Coincidence analysis between the crest of EEG β activity peaks and the different phases of cortisol secretory pulses indicates that 44% of the crest in EEG β activity peaks occurred during an ascending phase of cortisol secretory rate. Taking into account the relative proportion of ascending and nonascending phases in cortisol secretory rate during the experimental period (22%), this association was highly significant ($\chi^2 = 13.72$, $P < 0.001$).

Discussion

This study presents a new aspect of the regulatory mechanisms involved in the maintenance of alertness throughout the waking period. Endogenous waking EEG β activity (absolute power density in the 13–35 Hz frequency band) and cortisol secretion exhibit similar declining profiles during daytime, with concomitant episodic variations (increases in EEG β activity being associated with 10-min delayed in-

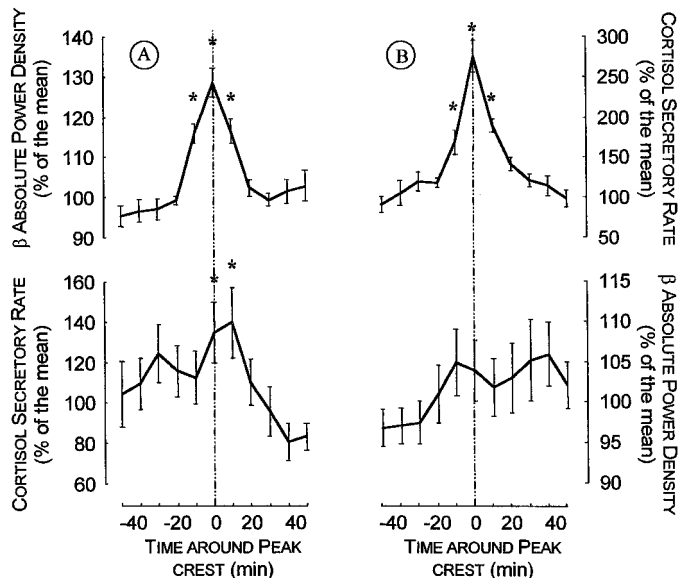


FIG. 2. Mean peak analyses: mean peak in waking EEG β activity (13–35 Hz absolute power density) with regard to the corresponding cortisol secretory rate (A), and mean pulse in cortisol secretory rate with regard to the corresponding waking EEG β activity (B) [* Significant differences from the mean level (100%), $P < 0.05$].

creases in cortisol secretory rate). However, peaks in EEG β activity are significantly, but not systematically, associated with cortisol secretory pulses. These results indicate that daytime cortisol secretion, under a multifactorial control, is related to the activation processes of the brain, which undergoes varying degrees of alertness throughout daytime wakefulness.

The finding that EEG β activity showed a declining episodic pattern during the daytime does not corroborate the findings of previous studies in which a linear increase in EEG β activity was reported as hours of wakefulness accumulated (16, 31–32). However, these findings were based on EEG measurements performed every 1–2 h; and such infrequent sampling intervals may obviously obscure the characterization of a rapidly changing EEG activity. In contrast to protocols used in previous studies, constant bed rest prevented postural and exercise effects. Control of the preceding sleep EEG recordings also prevented sleep loss effects, by excluding subjects with poor sleep efficiencies from the study. In fact, an increase in EEG β activity has been shown to correspond to a homeostatic effect of sleep deprivation and has been interpreted as evidence of an increasing effort to maintain wakefulness (31). The parallel decrease observed from morning to evening in both EEG β and HPA axis activities should therefore correspond to the declining phase of a circadian rhythm. Indeed, if fatigue factors related to the consecutive fixation tasks would interfere, EEG β activity should rather increase, to maintain a sustained wakefulness state. Concerning circadian variations in the waking EEG, conflicting results have been published. Whereas a previous study reported a pronounced circadian rhythm in EEG β activity with lower values during the night hours (33), Aeschbach *et al.* (18), during a constant routine protocol, did not find a significant circadian component in this EEG

TABLE 3. Mean peak analyses between cortisol secretory rate and waking EEG β activity (13–35 Hz absolute power density)

| Time effect | Mean peak in waking EEG β activity | | Corresponding cortisol secretory rate | | Mean pulse of cortisol secretion | | Corresponding waking EEG β activity | |
|-------------------|--|-----------------------|---------------------------------------|-----------------------|----------------------------------|----------|---|-----------------------|
| ANOVA | F 14.23 (11, 90) | | F 2.28 (11, 90) | | F 22.70 (11, 90) | | F 1.16 (11, 90) <i>P</i> n.s. | |
| t-test Time (min) | % of the mean | <i>P</i> ^b | % of the mean | <i>P</i> ^c | % of the mean | <i>P</i> | % of the mean | <i>P</i> ^a |
| -50 | 96.9 | n.s. | 97.2 | n.s. | 83.8 | n.s. | 99.2 | |
| -40 | 97.7 | n.s. | 102.1 | n.s. | 96.9 | n.s. | 99.4 | |
| -30 | 96.6 | n.s. | 113.9 | n.s. | 110.4 | n.s. | 99.8 | |
| -20 | 97.6 | n.s. | 110.5 | n.s. | 108.8 | n.s. | 103 | |
| -10 | 112.9 | <i>a</i> | 112.3 | n.s. | 154.7 | <i>a</i> | 106.6 | |
| 0 | 124.8 | <i>a</i> | 130.9 | <i>b</i> | 252.9 | <i>a</i> | 105.7 | |
| 10 | 113.1 | <i>a</i> | 138.3 | <i>c</i> | 174.1 | <i>a</i> | 103.9 | |
| 20 | 100.4 | n.s. | 111.5 | n.s. | 130.7 | n.s. | 104 | |
| 30 | 98.4 | n.s. | 96.2 | n.s. | 111.8 | n.s. | 105.4 | |
| 40 | 99.5 | n.s. | 81 | n.s. | 106 | n.s. | 106.1 | |
| 50 | 99.4 | n.s. | 91 | n.s. | 91.1 | n.s. | 104.1 | |

^a *P* < 0.001.^b *P* < 0.01.^c *P* < 0.05.

activity. Discrepancies between these results may therefore be attributable either to the experimental conditions or to the different procedures used for rhythm identification.

The various analytical methods used in the present study to assess temporal relationships between cortisol secretory rate and EEG β activity all demonstrate the existence of a significant coupling of the two physiological variables. Cross-correlation reveals an overall temporal relationship with fluctuations in EEG β activity being followed by parallel changes in cortisol secretion, with an average delay of 10 min. This analysis estimates the overall coordinate behavior of two time series but does not adequately estimate temporal links between discrete events occurring in these series, such as pulses of cortisol secretion and peaks in EEG β activity. Indeed, large concomitant peaks in the two chronological series may influence the correlation, masking the effects of nonsynchronized small peaks, even when they are more numerous. Taking into account the limitations of this method, the association between the two variables was further assessed by two different analyses. The mean peak analysis indicated that peaks in EEG β activity were associated with consecutive increases in the amount of cortisol released into the bloodstream, with a delay of 10 min. In contrast, reciprocal mean peak analysis showed that pulses in cortisol secretion were not significantly associated with changes in EEG β activity in the time range under study (± 50 min). A coincidence analysis finally revealed an association between the crest of peaks in EEG β activity and the ascending phases in cortisol secretion. This association, however, far from being systematic, indicates that peaks in EEG β activity do not always precede pulses of cortisol secretion, so that cortisol secretory pulses may also occur by stimulation from separate origins.

The temporal dynamic of EEG β activity and cortisol secretion, by displaying parallel changes, emphasized the importance of fluctuating vigilance states in the regulation of endocrine systems. These findings, concerning variations in central alertness and HPA activity during the waking period, have to be examined with regard to previous sleep-endocrine analyses. Indeed, a robust inverse

relationship has been reported between cortisol secretory rates and EEG δ activity, observed during non-REM sleep (11, 34). This activity is generated by thalamocortical and corticocortical circuits, and it corresponds to a synchronized brain state. It has been reported to oscillate reciprocally with EEG β activity throughout REM and non-REM sleep (35). By inference, it may be suggested that HPA axis activity runs parallel to the central alertness level of which EEG β activity is an indicator. However, the relationship between cortisol secretion and EEG β activity has not yet been demonstrated during sleep.

The question now rises as to whether HPA axis activity may be related to other EEG indices of cerebral functions, as would be the case with the limbic system, which is implied in memory processes and from which EEG θ activity (4–8 Hz frequency band) originates. This brain structure has been demonstrated to process corticosteroid feedback control over diurnal oscillations of HPA secretion (36). To respond to such questions, further research is needed, concerning the interrelationships between the different generators of EEG rhythmic activities during wakefulness.

The present finding of a temporal coupling between EEG β activity and cortisol secretion suggests the involvement of HPA hormones in the regulation of the brain activation level. It is now well known that fast EEG rhythms in the 13–35 Hz frequency range increase in sleep-deprived humans (18, 31–32). Sleep deprivation may therefore constitute an adapted design for testing the robustness of the interaction between central nervous processes of alertness and HPA axis, because an increase in cortisol levels has been reported as a result of sleep loss (37). To a certain extent, it may be hypothesized that HPA axis activity and EEG β activity represent two elements of an arousal system through which a psychoneuroendocrine regulation of alertness takes place within the whole brain-body.

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