Stress, Corticotropin and Behaviour

Neuro
endocrinology

Neuroendocrinology 2001;73:312–321

Received: June 29, 2000
Accepted after revision: January 15, 2001

Hypothalamo-Pituitary-Adrenal Axis Activity Is Related to the Level of Central Arousal: Effect of Sleep Deprivation on the Association of High-Frequency Waking Electroencephalogram with Cortisol Release

Florian Chapotot[a, b] Alain Buguet[b] Claude Gronfier[a]
Gabrielle Brandenberger[a]

[a]Laboratoire des Régulations Physiologiques et des Rythmes Biologiques chez l'Homme, Institut de Physiologie, Faculté de Médecine, ULP, Strasbourg, et [b]Unité de Physiologie de la Vigilance, Département des Facteurs Humains, Centre de Recherches du Service de Santé des Armées 'Emile Pardé', La Tronche, France

Key Words
Arousal · Sleep deprivation · Adrenal steroids · Sleep · Electroencephalography

Abstract
The temporal and quantitative interrelationships between the hypothalamo-pituitary-adrenal (HPA) axis activity and the level of central arousal were studied in 10 healthy young men during daytime wakefulness. Two experimental sessions were conducted randomly between 09.00 and 18.00 h, once after nocturnal sleep and once after a night of total sleep deprivation. Spectral analysis of serial waking electroencephalography (EEG) from a short target fixation task repeated every 10 min was undertaken, along with an estimation of cortisol secretory profiles by deconvolution of plasma radioimmunoassay measures obtained from continuous blood withdrawal with regular sampling at a 10-min interval. Following nocturnal sleep, a temporal association between the HPA axis activity and the waking EEG activity was found, cortisol secretory rate following changes in frontal gamma (20–45 Hz) band power by 10 min (average $R = 0.458$, $p < 0.001$). Although it remained significant (average $R = 0.276$, $p < 0.05$), the association strength decreased significantly following total sleep deprivation ($p < 0.05$, Wilcoxon test). Cortisol plasma level, secretory rate and pulse amplitude were increased as well as waking EEG power in the delta (0.5–5.5 Hz), theta (5.5–8.5 Hz) and gamma frequency bands (all p values <0.05, Student t tests). The sleep deprivation-related increases in cortisol secretory rate and waking EEG gamma activity were quantitatively associated ($R = 0.504$, $p < 0.05$). These results support the existence of a common ultradian regulatory mechanism, co-ordinating HPA axis activity to the level of central arousal in man, which seems involved in the sleep deprivation-induced hyperarousal.

Introduction

The hypothalamopituitary-adrenal (HPA) system has a critical influence on metabolic and behavioural homeostasis [1]. Although it is endogenously controlled, it represents the major mediator of the neuroendocrine response to stress [2]. In man, the level of circulating cortisol, the main glucocorticoid released into the bloodstream by the adrenocortical glands, reflects closely the activity of the

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0028–3835/01/0735–0312$17.50/0

Accessible online at:
www.karger.com/journals/nen

Florian Chapotot
Unité de Physiologie de la Vigilance
24, avenue du Maquis du Grésivaudan, CRSSA 'Emile Pardé', BP 87
F–38702 La Tronche Cedex (France)
Tel. +33 4 76 63 97 15, Fax +33 4 76 63 69 45, E-Mail f.chapotot@softhome.net

HPA axis. Cortisol release is controlled by the hypophyseal adrenocorticotropin hormone (ACTH) and occurs in pulses with a period approximating that of the ultradian alternation of the rapid eye movement (REM)/non-REM sleep cycles [3]. The modulation of secretory burst amplitude [4] determines the circadian rhythmicity of cortisol blood levels, which is characterized by a quiescent phase in the evening and an acrophase in the early morning [5].

Recently, our team conducted a series of experiments using continuous blood withdrawal with regular sampling at 10-min intervals, in order to estimate hormonal secretion from corresponding plasma levels, combined with spectral analysis of the electroencephalogram (EEG) to evaluate the sleeping and waking brain processes. These investigations allowed us to describe in detail the interrelationships between the activity of the central nervous and the HPA systems. Dynamic temporal associations between EEG indices of different brain functions and cortisol secretory rates were demonstrated during nocturnal and diurnal sleep [6] as well as during wakefulness [7]. During sleep, HPA axis activity and EEG power density in the delta frequency range (0.5–3.5 Hz) oscillate reciprocally. Decreases in the latter, indicating an alleviation of sleep, are preceded by rises in cortisol release with an approximate delay of 10 min [6]. During the quiescent phase of the HPA circadian rhythm, which normally occurs in the first half of the night, sleep processes fluctuate independently. It was, therefore, suggested that two distinct generators, which may synchronize in phase opposition when they are simultaneously active, drive independently the HPA axis activity and the sleep process [6]. During daytime wakefulness, following a normal night sleep, cortisol release was found to reflect increases in EEG absolute power of the 13- to 35-Hz frequency band with a 10-min delay [7]. Recorded from anterior cerebral areas in waking subjects, the high-frequency EEG over 20 Hz reflects an ultradian rhythm in daytime arousal [8]. Taken together, these elements favour a functional link between the regulatory mechanisms controlling the HPA axis activity and the level of central arousal.

Although the endogenous circadian pacemaker located in the suprachiasmatic nuclei primarily controls the HPA axis activity, plasma cortisol reaches slightly higher nocturnal levels during sleep deprivation than during sleep [9]. This has been attributed to a weak inhibitory influence of sleep. However, diurnal sleep does not decrease cortisol secretion [10, 11]. Moreover, signs of enhanced HPA axis activity, with a delayed onset of the quiescent secretory phase, were observed in the evening following a sleep deprivation night [12]. Consequently, the HPA axis hyperactivity observed during sleep deprivation cannot be explained by a synchronic inhibitory influence of sleep. Therefore, an interference of stress, or an arousal process, may be envisaged.

Sleep deprivation, which is accompanied by a deterioration of cognitive and psychomotor performance [13], also affects the sleeping and waking brain electrogenesis. For instance, along with an increase in EEG slow-wave activity during recovery sleep [14], especially in anterior cerebral areas [15], sleep deprivation increases waking EEG powers in the high-frequency range in proportion to prior wakefulness duration [16]. These changes in EEG high frequencies affect preferentially frequencies over 20 Hz (data not shown) and are thought to represent an increase in arousal counteracting an enhanced sleep pressure. It can, therefore, be expected that sleep deprivation-induced changes in HPA axis activity could be related to changes in the level of central arousal.

The aim of the present study was thus to determine whether (1) sleep deprivation disrupts the temporal association between the HPA axis activity and waking EEG indices of arousal which was previously observed following nocturnal sleep, and (2) changes induced by one night of sleep deprivation on the HPA axis and waking EEG activities may be associated.

Materials and Methods

Subjects

Twelve healthy young males (21–27 years of age) gave their informed written consent to participate in the study, which was approved by the local ethics committee. In questionnaires, they reported stable sleep schedules with a good sleep-wake quality and were selected after a medical examination. Two subjects presenting a sleep efficiency below 80% (sleep efficiency = 100 · TST/SPT; TST = total sleep time; SPT = sleep period time) during the experimental nocturnal sleep episode analyzed by polysomnography were subsequently excluded from the study, the analysis being carried out on the remaining 10 individuals.

Protocols

Experiments were performed in two individual soundproof and air-conditioned rooms, electrophysiological signals being monitored in an adjacent control room. The subjects were studied twice in a random order with a 1- to 2-month interval. In both experiments, they arrived at 18.00 h and spent two consecutive nycthemera in the laboratory, the first nycthemeron for adaptation, the second representing the experimental session. They slept between 23.00 and 07.00 h during the adaptation night and were either totally sleep-deprived (prolonged wakefulness, W session) or allowed to sleep between 23.00 and 07.00 h (S session) during the experimental night. During the daytime, they remained awake and supine in a dim light (< 100 lx) and were submitted to a series of short tasks from 09.00 to

15.00 h on the adaptation phase and from 09.00 to 18.00 h on the experimental phase. Between tasks, subjects were free to read, listen to music, and watch television or converse with the investigators. Standardized meals were taken at 07.00, 12.00 and 19.00 h. At 16.00 h, i.e. 2 h before the experimental phase, an indwelling venous catheter was inserted under local cutaneous anaesthesia to allow for 24-hour continuous blood withdrawal.

Serial Task

The serial task, consisting in a 70-second target visual fixation, was repeated every 10 min. The target was a spot fixed on the wall at 2 m ahead of the subjects. Prior to the procedure, subjects were instructed to stay awake and to avoid movements and any particular mental or physical effort apart from fixing the target. Simple verbal instructions were given to the subjects 30 s before the task started, when the task started and at the end. The subjects were under closed circuit video monitoring to control proper execution of the task. When any behavioural sign of drowsiness was suspected (eyelids lowering or eyes rolling), the instruction to stay awake was repeated.

Electrophysiological Recordings

Continuous polysomnographic recordings were carried out during the experimental nocturnal sleep and the two daytime waking sessions. One hour before starting each recording session, silver-silver chloride electrodes were fixed with collodion according to the 10/20 international system [17]. The left frontal, central and parietal EEG derivations (F_3, C_3, P_3, respectively) and the right central derivation (C_4) were referenced to the contralateral mastoid apophyses (A_2 and A_1, respectively). One transversal electro-oculographic and one chin electromyographic derivation were used for sleep monitoring and artefact detection. After high-pass (0.5 Hz) and low-pass (45 Hz) filtering, signals were recorded at a 256-Hz sampling rate using a 12-bit analog-to-digital converter.

Sleep Stage Scoring and Waking EEG Analysis

Classical sleep stage scoring [18] and quantitative analysis of the serial waking EEG were performed with the ERA-Profiler® 2.1 software package (PhiTools®, Grenoble, France). Artefacts (eye blinks, movements and electrode detachments) were detected through combining digital filtering and background-dependent amplitude thresholds and were subsequently inspected by an expert. The 2-second EEG epochs with artefacts did not exceed 25% of the recording sequences and were discarded from further analysis. The first 10 s of each 70-second task were also discarded to allow for the subjects to accommodate. Absolute power (μV^2) spectra of the four EEG derivations were computed between 1 and 45 Hz on the remaining 2-second epochs using a fast Fourier transform algorithm and were subsequently averaged in each task, resulting in a mean estimate of the EEG spectra every 10 min. The EEG power spectral arrays were then smoothed using a 30-min moving average window. A visual inspection of the individual power spectra allowed to determine the frequency limits of five frequency bands: delta (0.5–5.5 Hz), theta (5.5–8.5 Hz), alpha (8.5–13.5 Hz), beta (13.5–20 Hz) and gamma (20–45 Hz). These limits did not exactly match the classical frequency bands but corresponded more to the limits obtained by principal component analysis of waking EEG recording [19]. Absolute power in each frequency band was computed by summing up powers in the 0.5-Hz frequency bins belonging to the corresponding frequency band, the upper bin being excluded.

Blood Sampling and Plasma Measurements

During the 24-hour experimental phase, blood was withdrawn continuously from 18.00 to 18.00 h on the following day using a peristaltic pump (Ismatec®, Bioblock Scientific, Strasbourg, France). Samples were drawn every 10 min into tubes containing EDTA-K_2 (1 mg/ml), a maximum of 200 ml of blood per subject being withdrawn during the experiment. Samples were immediately centrifuged at 4°C and the plasma stored at –25°C. Plasma cortisol concentrations were measured by radio-immunoassay (RIA) (Diagnostic System Laboratories, Webster, Tex., USA). The assay sensitivity was 0.2 μg/dl; intra-assay coefficient of variation was 10% under 6 μg/dl and 4% above 6 μg/dl. All samples from a given subject were measured in the same assay.

Cortisol Secretory Rates and Secretory Pulses

Cortisol secretory rates were estimated from cortisol plasma levels using a deconvolution procedure [5]. A two-compartment model for hormone distribution and degradation was applied with half-lives of 5 and 65 min. The distribution volume 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 standard deviation associated with each estimated secretory rate. Significant pulses of cortisol secretion were determined using a modification of the ULTRA detection algorithm [20]. Significant increases and decreases in cortisol secretory rates were considered when the sum of the standard deviations associated with the successive time points exceeded a threshold of 3 times the RIA error. The secretory parameters of cortisol release determined in each individual were the total number of pulses, the average pulse amplitude and duration and the average interpulse interval.

Statistical Analysis

Only the frontal derivation, a site at which the high frequency EEG activity has been shown to reflect the level of central arousal [8], was used for the analyses.

Temporal relationships between daytime (09.00–18.00 h) cortisol secretion and waking EEG powers were determined in both the nocturnal sleep (S) and prolonged wakefulness (W) sessions by using a 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 standard deviation of the data). Cross-correlation coefficients between all pairs of chronological series were computed using MATLAB® 5.3 (Scientific Software, Sèvres, France) for 10-min lags falling between –30 and +30 min, each lag corresponding to a temporal measure. A χ^2 test of homogeneity was performed in each session with individual transformed coefficients [21]. If homogeneity was assumed, individual cross-correlation coefficients were averaged using Fisher's z transform producing an average estimate of the correlation [22]. The cross-correlation coefficients obtained from the two experimental sessions were compared using the Wilcoxon signed-rank test for matched pairs.

Changes in the temporal profiles of cortisol plasma level and secretory rates between the two sessions were determined on time series averaged by 30-min samples and expressed as relative changes (%) from a common baseline average. This baseline average was calculated for each individual between 18.00 and 23.00 h on the first day before any significant sleep or sleep deprivation had occurred. Significant effects were assessed by a 2-way ANOVA for repeated measures with session and time as factors and post hoc half-hourly

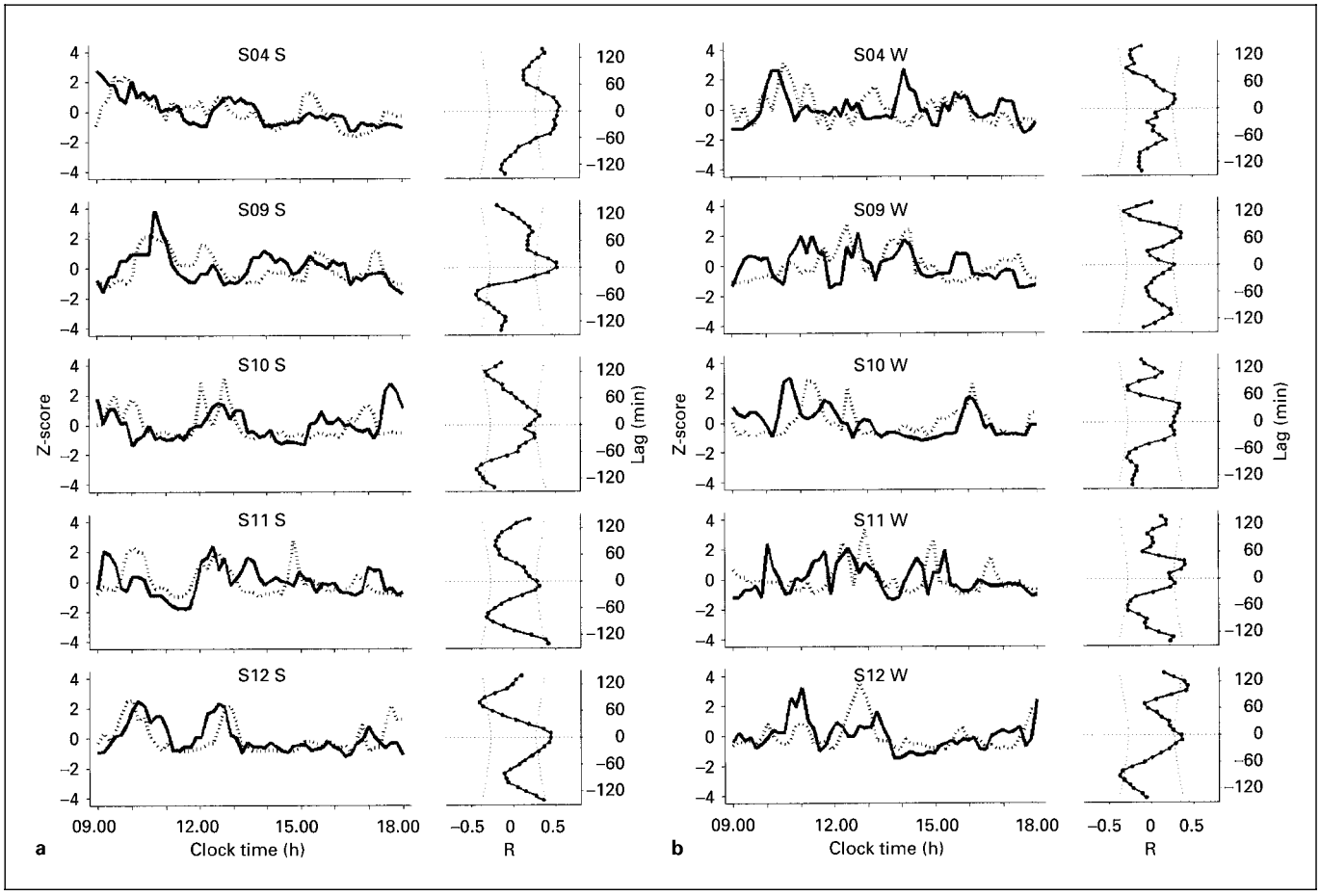

Fig. 1. Individual profiles of the left frontal waking EEG gamma activity (20–45 Hz absolute power; ——) and the concomitant cortisol secretory rate (·····) with the corresponding cross-correlation plots in 5 subjects during daytime wakefulness between 09.00 and 18.00 h. **a** Individual profiles obtained after nocturnal sleep (S). **b** Individual profiles obtained during prolonged wakefulness (W). Time series are expressed in z-scores.

comparisons using the Student paired t test. Changes in the average cortisol secretory parameters determined between 23.00 and 18.00 h and in waking EEG power of the different frequency bands, available only during the daytime (09.00–18.00 h), were assessed using the Student paired t test after transformations yielding normal residual distributions. Differences were considered to be significant when the p value was below 0.05. All results were expressed as mean ± standard error of the mean (SEM).

Quantitative relationships between daytime (09.00–18.00 h) cortisol secretion and waking EEG powers were determined by linear regression analysis on the amount of changes in each parameter across the S and W sessions. In an attempt to make all scores comparable for all subjects, each individual change was removed from an estimate of the individual effect. A set of individually aligned data was obtained by considering relative changes in the two experimental sessions as compared to the individual mean between sessions.

Results

Temporal Relationships between Cortisol Secretion and Waking EEG Activity

Temporal relationships between cortisol release and frontal waking EEG activity were evaluated for all frequency bands using the individual cortisol plasma levels and secretory rates. In the S and W sessions, the most significant temporal association within the time range under study (± 30 min lags) was found between cortisol secretory rate and waking EEG absolute power in the gamma frequency band (fig. 1).

In the S session, cross-correlation analysis between cortisol secretory rate and the left frontal waking EEG gamma band power indicated a systematic temporal relation-

Table 1. Highest individual cross-correlation coefficients between daytime cortisol secretory rate and left waking EEG gamma band (20–45 Hz) power after one night of sleep

Subject	Lag, min	R
S02 S	10	0.601***
S04 S	10	0.562***
S05 S	20	0.491***
S06 S	–10	0.468***
S07 S	30	0.313*
S08 S	30	0.490***
S09 S	0	0.528***
S10 S	20	0.315*
S11 S	–10	0.308*
S12 S	0	0.448***
Average	10	0.458***
χ^2	8.21	Homogeneity

* $p < 0.05$; *** $p < 0.001$.

Table 2. Highest individual cross-correlation coefficients between daytime cortisol secretory rate and left waking EEG gamma band (20–45 Hz) power after one night without sleep

Subject	Lag, min	R
S02 W	30	0.214
S04 W	20	0.300*
S05 W	30	0.287*
S06 W	30	0.269*
S07 W	30	0.288*
S08 W	–30	–0.019
S09 W	0	0.291*
S10 W	30	0.333*
S11 W	30	0.407**
S12 W	–10	0.362**
Average	16	0.276*
χ^2	6.75	Homogeneity

* $p < 0.05$; ** $p < 0.01$.

ship with positive cross-correlation coefficients significant in all individuals between lag –30 and 30 min. For each subject, the highest coefficient with its corresponding time lag is given in table 1. With all individual coefficients being homogeneous ($\chi^2 = 8.21$, $p > 0.05$), an average cross-correlation coefficient was computed and found to be highly significant (average $R = 0.458$, $p < 0.001$). The individual time lags, lying between –10 and 30 min and averaging 10 min, indicated that fluctuations in EEG gamma activity tended to precede that of cortisol secretory rate by an average of 10 min. Figure 1a illustrates five individual z-score profiles of EEG gamma band power with regard to the concomitant cortisol secretory rate and the corresponding cross-correlation plot during daytime waking in the S session.

In the W session, the temporal relationship between cortisol secretory rate and EEG gamma band power was no longer systematic but still persisted in 8 subjects out of 10. The individual cross-correlation coefficients between lag –30 and 30 min (table 2) were homogeneous ($\chi^2 = 6.75$, $p > 0.05$) and resulted in a significant average correlation ($R = 0.276$, $p < 0.05$) with an average lag of 16 min. Figure 1b illustrates the z-score profiles of EEG gamma activity and cortisol secretory rate in the W session for the same 5 individuals presented for the S session. The cross-correlation coefficients obtained between waking EEG gamma band power and cortisol secretory rate were significantly reduced ($p < 0.05$) in the W session as compared to the S session, whereas no change occurred for the lag between the two variables.

Effects of Sleep Deprivation on Cortisol Secretion

During both experimental sessions, the mean cortisol plasma level shown in figure 2 exhibited similar temporal profiles with a quiescent phase lasting approximately until 03.00 h, an increasing episodic pattern between 03.00 and 08.00 h and a decline from the morning to the late afternoon. During the W session, cortisol plasma levels were significantly increased between 06.00 and 07.30, 08.30 and 10.00 and 13.00 and 17.00 h when compared to the S session (interaction effect: $F_{(37,333)} = 1.96$, $p = 0.001$; all post hoc p values < 0.05) as shown in the mean half-hourly profiles illustrated in figure 2. Mean cortisol plasma levels (6.5 ± 0.4 vs. 9.2 ± 0.57 μg/dl, $p < 0.05$, +45.6 ± 11.2%) and secretory rate (30.3 ± 1.9 vs. 39.9 ± 2.2 μg/min, $p < 0.05$, +35.3 ± 10.5%) between 23.00 and 18.00 h were also significantly increased, as illustrated in figure 3a. The average secretory pulse amplitude (80.8 ± 10.6 vs. 105.2 ± 6.9 μg·min^{-1}, $p < 0.05$) was marked by an increase of 46.5 ± 18.5% in the W session as compared to the S session. However, the number of pulses was similar in both sessions (6.4 ± 0.3 vs. 6.2 ± 0.5, $p = 0.751$), as was the average interpulse interval (138.1 ± 5.8 vs. 141.6 ± 9.9 min,

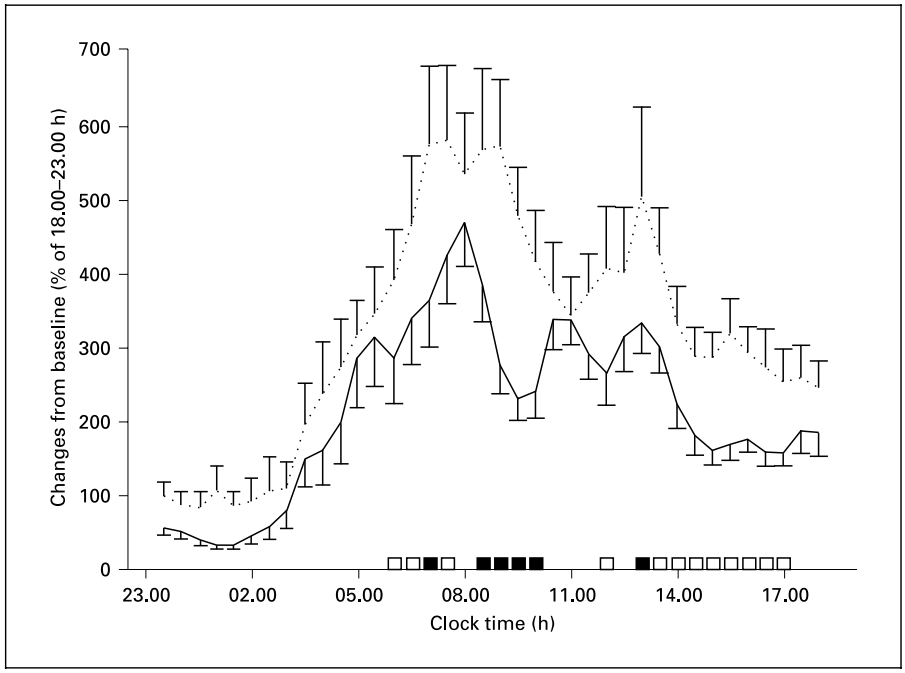

Fig. 2. Average (mean ± SEM) cortisol plasma profiles between 23.00 and 18.00 h during the S (——) and W (·····) sessions. Data were averaged by 30-min samples and expressed as relative variations from the common reference period (18.00–23.00 h). White and black squares indicate significant differences between the two experimental sessions ($p < 0.05$; $p < 0.01$, respectively, Student t test).

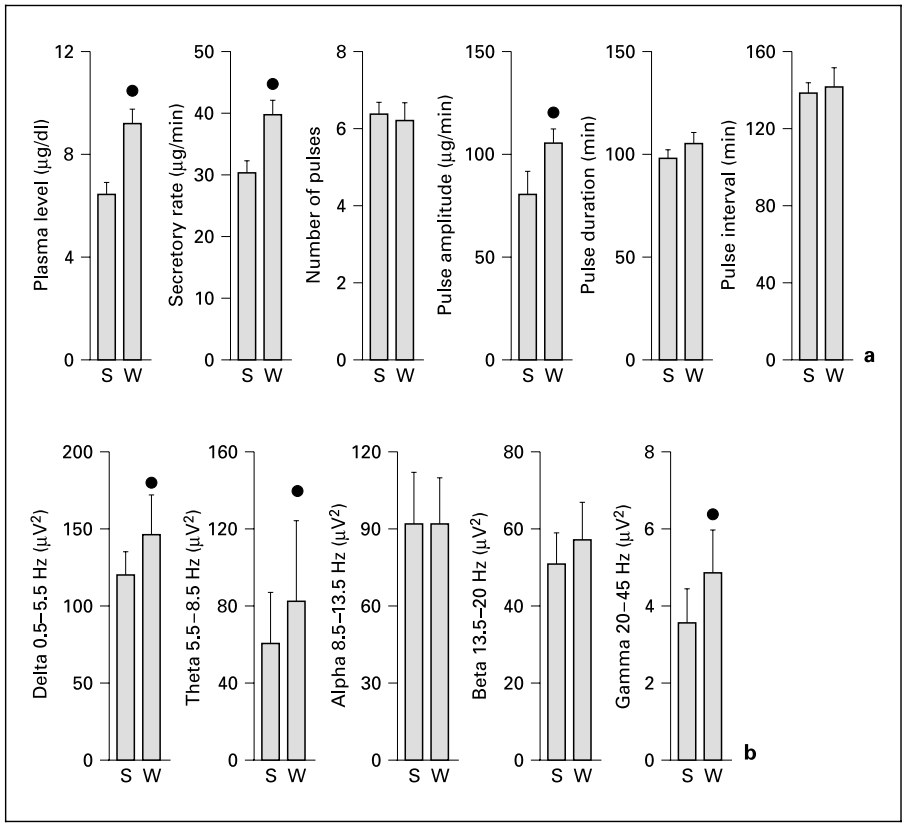

Fig. 3. Average (mean ± SEM) cortisol secretory parameters between 23.00 and 18.00 h (**a**) and waking EEG powers of the left frontal derivation between 09.00 and 18.00 h (**b**) during the S and W sessions. Significant differences ($p < 0.05$, Student t test) between the two experimental sessions are indicated (●).

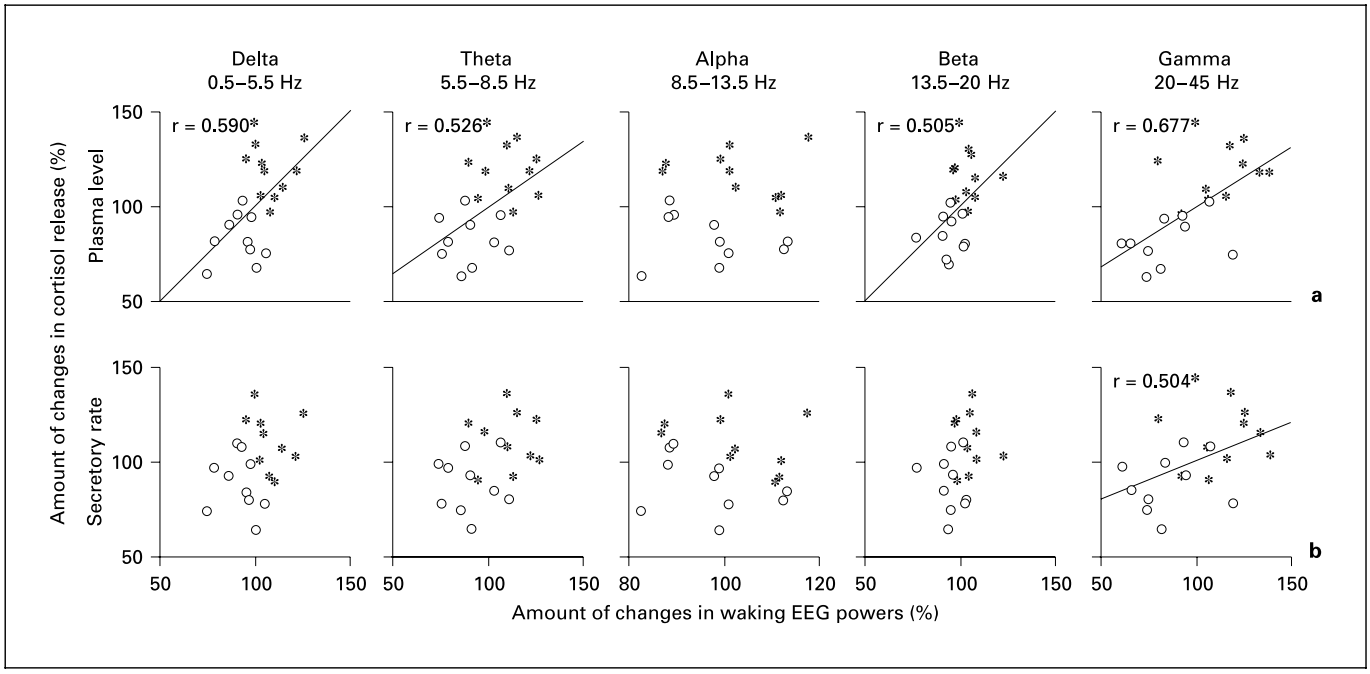

Fig. 4. Linear regression between the amount of changes in daytime (09.00–18.00 h) cortisol release and left frontal waking EEG powers across the S and W sessions. Individual changes in cortisol plasma level, secretory rate and EEG power in the different frequency bands were determined in reference to the individual mean of the two sessions. Individual changes in the S session (○) and W session (*) are shown. The best-fit line and regression coefficient are represented for significant associations only.

p = 0.796) and pulse duration (97.4 ± 4.7 vs. 105.2 ± 5.7 min, p = 0.409).

Effects of Sleep Deprivation on Waking EEG Activity

The daytime waking EEG of the left frontal derivation between 09.00 and 18.00 h exhibited significant differences between the S and W sessions. Sleep deprivation significantly increased EEG power in the delta (120 ± 14.4 vs. 146.4 ± 24.8 μV^2, p = 0.025), theta (60.4 ± 26.8 vs. 82.4 ± 42.4 μV^2, p = 0.037) and gamma (3.6 ± 0.8 vs. 4.8 ± 1.2 μV^2, p = 0.035) frequency bands (fig. 3b). In the beta frequency band, only a tendency for increased EEG power (50.4 ± 8.4 vs. 56.8 ± 9.6 μV^2, p = 0.055) was found. There was no significant change in the alpha frequency band (91.2 ± 20.4 vs. 91.6 ± 18.4 μV^2, p = 0.382) between the experimental sessions.

Quantitative Relationships between Cortisol Secretion and Waking EEG Activity

The amount of changes in cortisol plasma level and secretory rate between the two experimental sessions was significantly correlated with changes in frontal EEG power of the gamma frequency band (fig. 4). Positive linear regression coefficients were found, indicating that sleep deprivation-related changes in cortisol plasma level (R = 0.677, $p < 0.05$) and secretory rate (R = 0.504, $p < 0.05$) occurred in the same way as changes in EEG gamma activity. Plasma level, but not secretory rate, also showed a significant correlation coefficient with changes in the delta (R = 0.590, $p < 0.05$), theta (R = 0.526, $p < 0.05$) and beta (R = 0.505, $p < 0.05$) frequency bands.

Discussion

During daytime wakefulness, the HPA axis activity was associated temporally with indices of central arousal as cortisol secretory rates followed fluctuations in frontal waking EEG gamma band power by 10 min. After one night of sleep deprivation this temporal relationship persisted, although its strength was weaker. Prolonged wakefulness increased plasma cortisol levels at night and on the following daytime phase. This was related to an increased amplitude of cortisol secretory pulses without any modification in their number, duration or interval. In parallel, sleep deprivation increased daytime waking EEG power

in the delta, theta and gamma frequency bands of the frontal cerebral area. The sleep deprivation-related changes in cortisol release were significantly associated with the changes in frontal waking EEG gamma activity. This indicates that the ultradian and homeostatic regulatory mechanisms of brain arousal and that of HPA axis activity are tightly related, suggesting that both systems may partly share common regulatory elements.

The temporal relationship between HPA axis and waking EEG activities observed in the present study relates closely to our previous finding of a positive 10-min delayed association between cortisol release and EEG power in the 13- to 35-Hz frequency range [7]. In the latter study, the EEG derivations analyzed were chosen individually either from the left or the right central location and the EEG parameter was selected arbitrarily from the classical frequency bands. In the present study, the waking EEG spectrum was divided into different frequency bands on the basis of its temporal dynamics. A frontal lcoation, for which frequencies over 20 Hz reflect an ultradian rhythm in daytime arousal, was chosen [8]. By doing so, the present results show that fluctuations in frontal waking EEG activity of the higher frequency component (>20 Hz) are followed systematically by changes of cortisol secretory rate with an approximate delay of 10 min. This positive temporal association weakened but persisted after one night of sleep deprivation. Assuming that cortisol release follows that of ACTH by approximately 10 min [4], central cortical activation and activation of the HPA axis at the hypothalamic paraventricular level are likely to be time-locked, probably under the influence of a common central regulatory mechanism. However, while sleep deprivation did not affect the phase delay between HPA axis activity and brain arousal, it significantly weakened their association. This weakened association indicates that the temporal link between HPA axis and central activation is only partial, although it certainly depends on a common regulatory mechanism.

Taken together with our previous findings of a negative association between HPA axis and sleep EEG delta (0.5–3.5 Hz) activities [6, 23], the findings of a positive association between cortisol release and waking EEG gamma (20–45 Hz) activity is not contradictory if one considers the inverse relationship between EEG delta (0.3–3 Hz) and beta (20–28 Hz) band powers in the non-REM and REM sleep alternation [24]. Although it remains to be demonstrated directly, a positive relationship between high-frequency EEG and HPA axis activities may also be observed during sleep.

Contrasting results have been published concerning the effect of sleep deprivation on the corticotropic axis in healthy men. While an increase in plasma cortisol levels has been reported on the evening following a one-night sleep deprivation [12, 25], other authors did not observe any change [26–29] or reported evidence of a decreased HPA axis activity [30, 31]. The lack of control of experimental parameters such as activity and posture and the low temporal resolution used in these latter studies probably accounts for the discrepancies. The decrease in plasma or urinary cortisol reported by Åkerstedt et al. [31] and Kant et al. [30] occurred after 48 h or more of prolonged wakefulness suggesting that cortisol response to sleep deprivation may be biphasic. Consequently, our results extend the findings of Leproult et al. [12] and Spiegel et al. [25] and indicate that cortisol release is enhanced by sleep deprivation during the first night but also on the following daytime waking phase. The observed increases in cortisol plasma levels and pulse amplitude are probably related to an increased amplitude of ACTH secretory bursts [4]. Exactly how this is accomplished in vivo is unknown, but it may be due to an increased stimulation by hypothalamic secretagogues such as CRH and/or AVP.

Consistent with earlier reports [32–34], sleep deprivation in subjects with the eyes open resulted in an increased EEG activity of the lower and higher frequency range with no change in the intermediate alpha frequency band. However, while an increased high-frequency waking EEG activity has been reported for the 13- to 25-Hz frequency band over central cerebral areas [32], our results indicate that, for the left frontal derivation studied here, this increase affected mainly the gamma (20–45 Hz) frequency range. During waking, EEG low frequencies are considered to reflect thalamocortical inhibitory processes [35] and have been shown to increase continuously during 40 h of prolonged wakefulness, well reflecting the increasing sleep pressure [34]. In comparison, EEG high frequencies reflect traditionally cortical activation [35]. The increase in high-frequency EEG activity observed during sleep deprivation has been proposed to reflect the effort of the subjects to stay awake [16]. However, while the systematic artefact rejection procedure discarded any craniofacial electromyographic contamination, an endogenous physiological reaction increasing arousal to counteract an enhanced sleep pressure may also be proposed to take into account the sleep deprivation-related increase in waking EEG high-frequency activity. As a matter of fact, an increased activity of the noradrenergic brainstem locus coeruleus involved in the control of cortical arousal [36] may play an important role. In depressed patients,

an enhanced activity of the brainstem locus coeruleus, which stimulates hypothalamic noradrenergic receptors in the paraventricular nuclei, has been suggested [37] to account for the increase in plasma cortisol levels after sleep deprivation. A similar mechanism can also explain the co-ordinated effect of sleep deprivation both on the indexes of central arousal and corticotropic activity. However, changes in other neuromodulators are obviously not excluded. The brain CRH system must also be considered. It is involved in the regulation of physiological waking by inducing EEG arousal and HPA axis activation [38] and increases during sleep deprivation [39].

In conclusion, a common regulatory mechanism coordinating the activity of the human central nervous sleep-wake processes and the HPA system is suggested. The present findings are also consistent with the idea that sleep deprivation induces an emergency reaction with increased arousal both at the central and peripheral levels. Interestingly, as for the corticotropic activity [30, 31], the high-frequency waking EEG activity increases during the first 48 h of sleep deprivation and then declines (unpubl. observation). The decreases in high-frequency EEG activity and cortisol release after two consecutive nights of sleep deprivation would indicate that sleep deprivation induces a short-term and transient hyperarousal which is not maintained throughout extended periods of prolonged wakefulness.

Acknowledgments

The authors thank Daniel Joly, Jean Ehrhart, Béatrice Reinhardt and Michèle Simeoni for experimental assistance. They are indebted to Dr. Anne Charloux and Dr. Evelyne Lonsdorfer for medical assistance and Dr. Alain Muzet for providing sleep facilities at the CEPA in Strasbourg. They thank Dr. Eve Van Cauter for providing the ULTRA software. This work was supported by a grant of the Institut Electricité Santé (Paris, France), partner of the electricity profession.

References

1 Munck A, Guyre PM, Holbrook NJ: Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984;5:25–44.
2 Selye H: The Stress of Life. New York, MacGraw-Hill, 1956.
3 Follénius M, Simon C, Brandenberger G, Lenzi P: Ultradian plasma corticotropin and cortisol rhythms: Time series analysis. J Endocrinol Invest 1987;10:261–266.
4 Veldhuis JD, Iranmanesch A, Johnson ML, Lizarralde G: Amplitude, but not frequency, modulation of adrenocorticotropin secretory bursts gives rise to the nyctohemeral rhythm of the corticotropic axis in man. J Clin Endocrinol Metab 1990;71:452–463.
5 Van Cauter E, Van Coeverden A, Blackman J: Modulation of neuroendocrine release by sleep and circadian rhythmicity; in Yen SCC, Vale WW (eds): Neuroendocrine Regulation of Reproduction. Norwell, Serono Symposia, 1990, pp 113–122.
6 Gronfier C, Chapotot F, Weibel L, Jouny C, Brandenberger C: Pulsatile cortisol secretion and EEG delta waves are controlled by two independent but synchronized generators. Am J Physiol 1998;275:E97–E100.
7 Chapotot F, Gronfier C, Jouny C, Muzet A, Brandenberger G: Cortisol secretion is related to electroencephalographic alertness in human subjects during daytime wakefulness. J Clin Endocrinol Metab 1998;83:4263–4268.
8 Chapotot F, Jouny C, Muzet A, Buguet A, Brandenberger G: High frequency waking EEG: Reflection of a slow ultradian rhythm in daytime arousal. Neuroreport 2000;11:2223–2227.
9 Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J: Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab 1983;56:352–355.
10 Weibel L, Follénius M, Spiegel K, Ehrhart J, Brandenberger G: Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. Sleep 1995;18:549–556.
11 Pietrowsky R, Meyer R, Kern W, Born J, Fehm HL: Effects of diurnal sleep on secretion of cortisol, luteinizing hormone, and growth hormone in man. J Clin Endocrinol Metab 1994; 78:683–687.
12 Leproult R, Copinschi G, Buxton O, Van Cauter E: Sleep loss results in an elevation of cortisol levels the next evening. Sleep 1997;20:865–870.
13 Horne JA: Why We Sleep: The Function of Sleep in Human and Other Mammals. Oxford, Oxford University Press, 1988.
14 Feinberg I, Floyd TC, March JD: Effects of sleep loss on delta (0.3–3 Hz) EEG and eye movement density: New observations and hypotheses. Electroencephalogr Clin Neurophysiol 1987;67:217–221.
15 Cajochen C, Foy R, Dijk DJ: Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. Sleep Res Online 1999;2:65–69.
16 Corsi-Cabrera M, Arce C, Ramos J, Lorenzo I, Guevara MA: Time course of reaction time and EEG while performing a vigilance task during total sleep deprivation. Sleep 1996;19:563–569.
17 American Electroencephalographic Society: Guidelines for standard electrode position nomenclature. J Clin Neurophysiol 1991;8:200–201.
18 Rechtschaffen A, Kales A: A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, US Government Printing Office, 1968.
19 Kubicki S, Herrmann WM, Fichte K, Freund G: Reflections on the topics: EEG frequency bands and regulation of vigilance. Pharmakopsychiatry 1979;12:237–245.
20 Van Cauter E: Quantitative methods for the analysis of circadian and episodic hormone fluctuations; in Van Cauter E, Copinschi G (eds): Human Pituitary Hormones: Circadian and Episodic Variations. The Hague, Nijhoff, 1981, pp 1–25.
21 Snedecor G, Cochran W: Statistical Methods. Ames, Iowa States University Press, 1980.
22 Edwards AL: Testing hypotheses about correlation coefficients; in Edwards AL (ed): Experimental Design in Psychological Research. New York, Rinehart, 1957, pp 133–138.

23 Gronfier C, Brandenberger G, Chapotot F, Weibel L, Jouny C, Follénius M: Cortisol pulsatility and delta wave activity during sleep in man; in Touitou Y (ed): Biological Clocks: Mechanisms and Applications. Amsterdam, Elsevier Science, 1998, pp 577–580.
24 Uchida S, Maloney T, Feinberg I: Beta (20–28 Hz) and delta (0.3–3 Hz) EEGs oscillate reciprocally across NREM and REM sleep. Sleep 1992;15:352–358.
25 Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435–1439.
26 Moldofsky H, Lue FA, Davidson JR, Gorczynski R: Effects of sleep deprivation on human immune functions. FASEB J 1989;3: 1972–1977.
27 Salin-Pascual RJ, Ortega-Soto H, Huerto-Delgadillo L, Camacho-Arroyo I, Roldan-Roldan G, Tamarkin L: The effect of total sleep deprivation on plasma melatonin and cortisol in healthy human volunteers. Sleep 1988;11:362–369.
28 Gary KA, Winokur A, Douglas SD, Kapoor SC, Zaugg L, Dinges DF: Total sleep deprivation and the thyroid axis: Effects of sleep and waking activity. Aviat Space Environ Med 1996;67:513–519.
29 Dinges DF, Douglas SD, Zaugg L, Campbell DE, McMann JM, Whitehouse WG, Orne EC, Kapoor SC, Icaza E, Orne MT: Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. J Clin Invest 1994;93:1930–1939.
30 Kant GJ, Genser SG, Thorne DR, Pfalser JL, Mougey EH: Effects of 72-hour sleep deprivation on urinary cortisol and indices of metabolism. Sleep 1984;7:142–146.
31 Åkerstedt T, Palmblad J, de la Torre B, Marana R, Gillberg M: Adrenocortical and gonadal steroids during sleep deprivation. Sleep 1980;3: 23–30.
32 Lorenzo I, Ramos J, Arce C, Guevara MA, Corsi-Cabrera M: Effects of total sleep deprivation on reaction time and waking EEG activity in man. Sleep 1995;18:346–354.
33 Dumont M, Macchi MM, Carrier J, Lafrance C, Hébert M: Time course of narrow frequency bands in the waking EEG during sleep deprivation. Neuroreport 1999;10:403–407.
34 Aeschbach D, Matthews JR, Postolache TT, Jackson MA, Giesen HA, Wehr TA: Two circadian rhythms in the human electroencephalogram during wakefulness. Am J Physiol 1999; 277:R1771–R1779.
35 Steriade M, Gloor P, Llinas RR, Lopes da Silva FH, Mesulam MM: Basic mechanisms of cerebral rhythmic activities. Electroencephalogr Clin Neurophysiol 1990;76:481–508.
36 Aston-Jones G, Bloom FE: Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1981;1:876–886.
37 Baumgartner A, Riemann D, Berger M: Neuroendocrinological investigations during sleep deprivation in depression. II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. Biol Psychiatry 1990;28:569–587.
38 Chang FC, Opp MR: Blockade of corticotropin-releasing hormone receptors reduces spontaneous waking in the rat. Am J Physiol 1998; 275:R793–R802.
39 Fadda P, Fratta W: Stress-induced sleep deprivation modifies corticotropin releasing factor (CRF) levels and CRF binding in rat brain and pituitary. Pharmacol Res 1997;35:443–446.