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Temporal relationships between pulsatile cortisol secretion and electroencephalographic activity during sleep in man

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Abstract

A temporal link between slow wave sleep and low or decreasing cortisol release has been previously demonstrated. This relationship was re-evaluated in 15 healthy male subjects using spectral analysis of their sleep electroencephalogram (EEG). EEG activity in the delta, theta, alpha and beta bands was cross-correlated with cortisol secretory rates at 10-min intervals. For the period of pulsatile cortisol secretion, an inverse relationship was found with the delta band with an average cross-correlation coefficient of –0.505 ($P < 0.0001$). Variations in cortisol secretory rates coincided with or anticipated opposite variations in delta wave activity by 10 or 20 min. A significant positive correlation was found with theta activity, but alpha and beta bands did not elicit any systematic association with cortisol profiles. These results demonstrate a temporal association between cortisol secretory pulses and delta wave activity in man, suggesting the existence of a central control common to both variables. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

The cortisol rhythm, generally considered to be mainly under endogenous circadian control, seems to be not entirely independent of sleep processes (Van Cauter and Refetoff, 1985). The low cortisol secretion during the first few hours of the night has generally been attributed to an inhibitory effect of slow wave sleep (SWS) present in high density at that period of time (Weitzman et al., 1983; Born et al., 1988). Not all results are consistent with this hypothesis, all the more that the quiescent period of cortisol secretion has already begun before sleep onset. Nevertheless, it has been found that the onset of SWS episodes was associated with diminished adrenocortical activity (Follenius et al., 1992; Weibel et al., 1995) and that this association still persists in case of alterations of cortisol profiles as observed in night workers (Weibel et al., 1996) or in sleep disorders (Brandenberger et al., 1996).

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All of these previous studies evaluating relationships between sleep and either plasma cortisol levels or secretory rates were based on traditional methods of recording and analysing sleep stages. Spectral analysis of the sleep electroencephalogram (EEG) by means of Fast Fourier Transformation (FFT) is a more useful tool in delineating dynamic events such as sleep processes (Achermann and Borbely, 1987; Aeschbach and Borbely, 1993) and in determining temporal relationships with hormonal secretion.

In the present study, a refined analysis of the temporal relationship between nocturnal cortisol secretory pulses and the EEG frequency bands was performed.

2. Methods

2.1. Subjects and design

Fifteen healthy male volunteers (aged 20–28 years) gave informed consent to participate in the study, which was approved by the local Ethical Committee. Subjects with sleep disorders, with signs of underlying disease or those

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taking medication were excluded from the study. The experiments were performed in soundproof rooms. The subjects underwent habituation for one night-session prior to the study, to become adjusted to the experimental conditions. Lights were switched off at 23:00 h and the subjects were awakened at 07:00 h. Blood sampling and sleep recordings were carried out during this period.

2.2. Blood sampling and plasma measurements

Four hours before the beginning of the recordings, a catheter was inserted under local anaesthesia into an antecubital vein. Blood was sampled continuously using a peristaltic pump and collected in EDTA-K_2 tubes in an adjoining room over 10-min periods. The samples were immediately centrifuged at 4°C and the plasma was stored at −25°C until assay. Plasma cortisol was measured by radioimmunoassay using commercial assay kits (Ciba Corning Diagnostics S.A., Cergy-Pontoise, France). The detection limit was 2 ng/ml. The intra-assay coefficient of variation for the duplicate samples was 4% above 60 ng/ml and 10% for levels below 60 ng/ml. All samples taken from a given subject were analysed in the same assay.

2.3. Sleep analysis

Sleep recordings were performed using two EEG derivations (C3-A2 and C4-A1), one chin electromyographic derivation and one horizontal electro-oculographic derivation (upper canthus of one eye versus lower canthus of the other eye).

For all-night spectral analysis, the EEG signal was converted from analogue to digital with a sampling frequency of 128 Hz and stored on a computer hard disk. Subsequently, spectra were computed for consecutive 2-s periods using an FFT-algorithm (Cooley and Tuckey, 1965). The values for 15 consecutive 2-s periods were averaged to yield power density values for 30-s periods. The spectral parameter studied was relative power (% of the global EEG band (0.5–35 Hz)) for the delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz) and beta (13–35 Hz) bands.

2.4. Data analysis

The secretory rate of cortisol during each 10-min interval was derived from the corresponding plasma level using deconvolution analysis based on a two-compartment model for distribution and degradation. The same half-lives of hormone elimination were used for all subjects (Kerrigan et al., 1993). A detailed description of the procedure has been given previously (Weibel et al., 1995). The statistical error propagation of the uncertainty in data measurements was taken into account in the determination of the secretory profile. Significant cortisol secretory pulses occurring during the night were identified using a modification of the computer algorithm ULTRA (Van Cauter, 1981).

The temporal relationship between cortisol secretion and EEG activity in the different frequency bands, starting with the onset of the first significant cortisol pulse, was quantified by using a cross-correlation analysis on both series transformed into Z-scores. Before this calculation, the spectral variables were smoothed with a median filter of 20 points in order to obtain one point every 10-min corresponding to the cortisol secretory rate measured at 10-min intervals. The normality of the spectral and cortisol distributions was assessed using the Shapiro and Wilk's test. A natural logarithmic transformation for the spectral values (Gasser et al., 1982) and a square root transformation for the cortisol secretory rates were retained. These normalised data were then transformed into Z-scores ($Z\text{-score} = (x - m)/\sigma$; where x is the value, m the mean value and σ the standard deviation of the normalised values. This method enables the comparison between chronological series which are not expressed in the same units. The cross-correlation coefficients were computed for lags [−3], [−2], [−1], [0], [+1], [+2] and [+3] between the two Z-score transformed series, each lag corresponding to a 10-min blood sampling interval. After a χ^2 homogeneity test (Snedecor and Cochran, 1980), individual correlation coefficients were averaged using Fisher's 'z' transformation in order to yield a common estimate of the correlation (Edwards, 1957).

3. Results

The nocturnal secretory profiles of cortisol demonstrated a low secretory activity during the first part of the night, followed by a pronounced pulsatile secretion with increasing pulse amplitude towards the morning. During the quiescent period of cortisol secretory activity, the EEG activity exhibited large variations, in particular a high delta wave activity. The quantification of the relationship between the variations of EEG activity and pulsatile cortisol secretion was limited to the period which began with the onset of the first significant nocturnal secretory pulse determined for each subject, the duration of this period being subject-dependent. The highest individual cross-correlation coefficients between cortisol secretory rates and the different EEG bands and the corresponding lags are given in Table 1. Cortisol secretory rates were negatively correlated with the delta band in all subjects. The maximum coefficients were found to be significant in 12 of the 15 subjects for lags lying between [−2] and [0] excepted for one subject which presented a positive lag. These negative time lags indicated that cortisol secretion was concomitant or anticipated delta waves by 10–20 min, i.e. when cortisol increased, the delta wave activity decreased at the same time or 10–20 min later. The homogeneity of the correlation coefficient allowed to calculate an average coefficient which was found to be −0.505 ($P < 0.0001$). On the opposite, the cortisol secretory rates were positively correlated with the theta band in all subject, and with a statistical significance in 10 of the 15 subjects. These coefficients

Table 1
Highest coefficients of cross-correlation between cortisol secretory rates and spectral EEG bands.

Subject	No.	Delta		Theta		Alpha		Beta	
		Lag	*r*	Lag	*r*	Lag	*r*	Lag	*r*
1	38	−1	−0.481**	−1	0.467**	−1	0.422**	0	0.292
2	46	−1	−0.478***	0	0.514***	+1	0.277	0	0.465**
3	41	−1	−0.516***	0	0.497***	+2	0.640***	+1	0.678***
4	41	−2	−0.214	0	0.255	+1	0.295	+1	0.251
5	34	0	−0.724***	0	0.598***	+1	0.627***	+2	0.518**
6	31	−2	−0.513**	+1	0.390*	−1	−0.561**	−2	−0.463**
7	27	+2	−0.360	+2	0.363	+2	0.333	+1	0.182
8	33	0	−0.404*	−1	0.298	+1	−0.194	+2	0.259
9	33	0	−0.470**	0	0.455**	0	0.198	+1	−0.181
10	45	0	−0.745***	0	0.702***	+1	0.388**	+1	0.202
11	37	−2	−0.491**	−2	0.443**	+2	0.455**	+1	0.217
12	23	0	−0.658***	+1	0.574**	+2	−0.471*	+1	−0.406*
13	33	−1	−0.308	0	0.361*	−2	−0.443**	−1	−0.379*
14	24	0	−0.492**	0	0.353	+1	0.508*	+1	0.511**
15	17	0	−0.482*	0	0.134	+1	0.248	0	0.626**
χ			19.52		14.18		79.17		73.74
Average-*r*			−0.505		0.456		Non-homogeneity		Non-homogeneity

Cross-correlation coefficients were calculated for lags [−3], [−2], [−1], [0], [+1], [+2] and [+3], each corresponding to a 10-min blood sampling interval. For negative lags, cortisol secretion anticipated spectral EEG activity; for positive lags, cortisol lagged behind spectral activity. Average-*r* were computed after a Fisher's '*z*' transformation on the individual cross-correlation coefficients after having obtained the significance of the χ^2-test of homogeneity. No., number of 10-min plasma samples following the onset of the first significant cortisol secretory pulse.
$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

were lower than for delta band, but were homogeneous with an average coefficient of +0.456 ($P < 0.0001$). The lags were comprised between [−2] and [+2]. No systematic correlation was found between cortisol and alpha or beta bands since the coefficients did not elicit homogeneity and were sometimes positive and sometimes negative. The closest cross-correlation and the more systematic relationship in the time lag was found between cortisol secretion and delta wave activity.

Fig. 1 shows two individual profiles which illustrate the association between cortisol secretory profiles and delta relative power after *Z*-score transformation. An increase in the cortisol secretory rate was associated with a decrease in the delta relative power.

4. Discussion

The comparison of nocturnal cortisol secretion and sleep EEG spectral activities demonstrates an even closer association than could be previously inferred from conventional sleep stage analyses. The cortisol rhythm is known to be mainly under circadian control, and the beginning of the night is a period of low, quiescent adrenocortical activity. The results clearly indicate that during this quiescent period, delta wave activity was greatest. However, for the period of pulsatile cortisol release, cortisol secretory variations were concomitant or anticipated opposite variations in delta wave activity by 10–20 min. The cross-correlation analysis performed in this study demonstrated that sleep deepening was associated with decreasing cortisol secretion and conversely

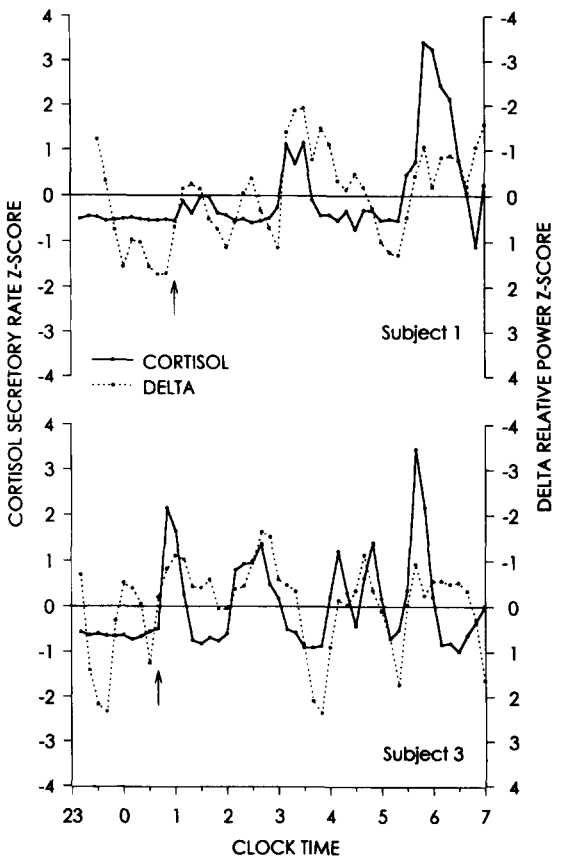

Fig. 1. Concomitant delta relative power and cortisol profiles after *Z*-score transformation in two representative subjects during the night. For delta relative power, the scale is inverted. The arrow indicates the onset of the pulsatile portion of the cortisol secretory profile.

that the lightening of sleep was accompanied by increasing cortisol secretion.

To describe the sleep EEG as a series of discrete stages tends to obscure the fact that sleep is a continuous oscillatory process. Spectral analysis allows a more refined exploration of the sleep process, in particular the assessment of dynamic aspects and the quantitative estimation of EEG activities. Also, in contrast to the majority of previous studies, the present results are based on secretory rates calculated from peripheral plasma concentration by numerical deconvolution. Thus the two procedures used in this study allowed the synchrony between active cortisol secretion and delta wave activity to be accurately estimated and their correlation to be quantified.

Cross-correlation analysis revealed that a temporal link exists between cortisol secretory rates and delta and theta bands of the EEG activity. This indicates a close relationship between cortisol secretion and sleep depth. The temporal coupling of cortisol secretion and of delta relative power is of variable strength depending on the individual subject. This may be evidence of a complex underlying relationship that can be accounted for by a variety of interfering regulatory factors. Significant cross-correlations between the two variables were at a maximum when the two variables were concomitant or showed a negative lag of 10–20 min depending on the subject. Thus, variations in cortisol secretory rates coincided with or anticipated variations in delta wave activity. These observations do not support the hypothesis that there exists an inhibitory action of SWS on cortisol secretion, as has been stated in previous studies (Weitzman et al., 1983). Also whether the inverse may be inferred remains questionable. Nonetheless, the dynamic description of delta wave activity and thus the refined analysis of its temporal coupling with cortisol secretion found in most subjects, allowed an assessment of the existence of a central control common to both variables.

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