

Sleep deprivation effects on the activity of the hypothalamic–pituitary–adrenal and growth axes: potential clinical implications

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Summary

OBJECTIVES Although several studies have shown that sleep deprivation is associated with increased slow wave sleep during the recovery night, the effects of sleep deprivation on cortisol and growth hormone (GH) secretion the next day and recovery night have not been assessed systematically. We hypothesized that increased slow wave sleep postsleep deprivation is associated with decreased cortisol levels and that the enhanced GH secretion is driven by the decreased activity of the HPA axis.

DESIGN AND SUBJECTS After four consecutive nights in the Sleep Laboratory, 10 healthy young men were totally deprived of sleep during the fifth night, and then allowed to sleep again on nights six and seven. Twenty-four hour blood sampling was performed serially every 30 minutes on the fourth day, immediately following the previous night of sleep and on the sixth day, immediately after sleep deprivation.

MEASUREMENT Eight-hour sleep laboratory recording, including electroencephalogram, electro-oculogram and electromyogram. Plasma cortisol and GH levels using specific immunoassay techniques.

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RESULTS Mean plasma and time-integrated (AUC) cortisol levels were lower during the postdeprivation nighttime period than on the fourth night ($P < 0.05$). Pulsatile analysis showed significant reduction of both the 24 h and daytime peak area ($P < 0.05$) and of the pulse amplitude ($P < 0.01$), but not of the pulse frequency. Also, the amount of time-integrated GH was significantly higher for the first 4 h of the post-deprivation night compared to the predeprivation night ($P < 0.05$). Cross-correlation analyses between the absolute values of the time-series of each hormone value and percentage of each sleep stage per half hour revealed that slow wave sleep was negatively correlated with cortisol and positively correlated with GH with slow wave sleep preceding the secretion of these hormones. In contrast, indices of sleep disturbance, i.e. wake and stage 1 sleep, were positively correlated with cortisol and negatively correlated with GH.

CONCLUSION We conclude that sleep deprivation results in a significant reduction of cortisol secretion the next day and this reduction appears to be, to a large extent, driven by the increase of slow wave sleep during the recovery night. We propose that reduction of CRH and cortisol secretion may be the mechanism through which sleep deprivation relieves depression temporarily. Furthermore, deep sleep has an inhibitory effect on the HPA axis while it enhances the activity of the GH axis. In contrast, sleep disturbance has a stimulatory effect on the HPA axis and a suppressive effect on the GH axis. These results are consistent with the observed hypocortisolism in idiopathic hypersomnia and HPA axis relative activation in chronic insomnia. Finally, our findings support previous hypotheses about the restitution and immunoenhancement role of slow wave (deep) sleep.

It has been clearly demonstrated that sleep deprivation is associated with increased slow wave sleep (SWS) and enhanced activity in the delta band during the recovery night (Webb & Agnew, 1971; Borbely *et al.*, 1981). The effects of sleep deprivation on cortisol secretion the next day and recovery night have not been assessed systematically. Sleep and

particularly SWS has an inhibiting effect on cortisol secretion (Weitzman *et al.*, 1983; Seifritz *et al.*, 1995; Brandenberger *et al.*, 1996; Scheen *et al.*, 1996; Bierwolf *et al.*, 1997). We hypothesized that increased slow wave sleep postsleep deprivation is associated with decreased cortisol levels during the first recovery night compared to baseline.

Stress and the intracerebroventricular administration of corticotropin-releasing-hormone (CRH) in animals is associated with arousal, while glucocorticoid administration or hypercortisolism in humans are associated with sleep disturbance (Sutton *et al.*, 1982; Chrousos & Gold, 1992; Chrousos *et al.*, 1993). Furthermore, melancholic depression in humans is associated with chronic hypersecretion of CRH, hypercortisolism, and sleep disturbance (Gold *et al.*, 1988a, b). Pharmacological therapy of depression leads to normalization of CRH and cortisol secretion and correction of the sleep disturbance, while sleep deprivation temporarily relieves depressive symptomatology (Gold *et al.*, 1988a, b). We hypothesized that sleep deprivation is associated with decreased activity of the HPA axis the next day and night and that this could explain why sleep deprivation relieves depression.

Earlier studies have shown that cortisol secretion is negatively correlated with GH secretion and that the HPA axis has a suppressant effect on the activity of the GH axis (Ghizzoni *et al.*, 1996). Several studies have shown that SWS sleep induced by sleep deprivation is associated with increased amounts of GH secretion (Van Cauter *et al.*, 1992; Scheen *et al.*, 1996). We hypothesized that the enhanced GH secretion during the recovery night is probably driven by the decreased activity of the HPA axis.

Methods

Subjects

Ten young healthy men 20–29 years of age (mean \pm SE, 23.3 ± 0.8), body mass index 25.2 ± 0.8 , were recruited from the community and from the medical and technical staff and students of the Milton S. Hershey Medical Center. They were in good general health, had no sleep complaints or circadian abnormalities, were not taking any medications and were screened in the Sleep Laboratory for sleep disordered breathing, nocturnal myoclonus or other primary sleep disorders. Also, a battery of clinical tests, including full blood count, urinalysis, thyroid indices and electro-cardiogram, were negative for abnormal findings.

Protocol

Each subject participated in a sleep deprivation experiment that lasted seven days. After four consecutive nights in the Sleep

Laboratory (1 adaptation night and 3 baseline nights), the subjects were deprived of sleep during the entire fifth night, while they were allowed to sleep again on nights six and seven. The subjects stayed awake in the presence of nursing or technical staff and total wake time before the first recovery night was 40 h. Twenty-four hour blood sampling was performed serially every 30 minutes on the fourth day (predeprivation) and sixth day, the latter immediately following sleep deprivation. An indwelling catheter was inserted in the antecubital vein about 30 minutes before the first blood sample. The catheter was kept patent with small amounts of heparin. During the sleep recording period, blood was collected outside the subjects' room through a perforation in the wall, via extra tubing, in order to decrease sleep disturbance from the blood sampling technique. During the day, blood samples were taken in the Clinical Research Center of the University Hospital of the Milton S. Hershey Medical Center. The timing of the subjects' meals (lunch at 1200 h and dinner at 1800 h) as well as the amount and composition of food intake were similar on the two days of blood sampling. The study was approved by the Institutional Review Board and each subject signed a written consent form.

Sleep recordings

Sleep laboratory recording was carried out in a sound-attenuated, light-and temperature-controlled room which has a comfortable bedroom-like atmosphere. During this evaluation, each subject was monitored continuously for 8 hours (2200–0600 h). The sleep schedule in the sleep laboratory was similar to the subjects' normal sleep schedule. A standard sleep recording using the standardized 10–20 system, including electro-oculogram (EOG) recorded from the outer canthi of both eyes and referred to the same mastoid and to each other, was made (Rechtschaffen & Kales, 1968). The electromyogram (EMG) was recorded bipolarly from the submental muscle. The sleep recordings were amplified using standard clinical polygraphs (Grass Instrument Co., Model 78d & e). The sleep records were scored independently of any knowledge of the experimental condition according to standardized criteria (Rechtschaffen & Kales, 1968).

Sleep parameters assessed from the sleep recordings included sleep induction (sleep latency or SL); sleep maintenance (wake time after sleep onset or WTASO); total wake time (TWT) which is the sum of sleep latency and WTASO; % ST which is total sleep time as percentage of time in bed; percentage of the various sleep stages (REM, 1, 2, 3 and 4 combined [SWS]) which is calculated as the minutes in each stage as the percentage of total sleep time; and REM latency which is the interval from sleep onset to the first REM period.

Hormone assays

Blood collected from the indwelling catheter was transferred to a heparinized tube and refrigerated until centrifugation (within 3 h). The supernatant was frozen at -20° until assay for the hormones. Cortisol and GH levels were measured by specific immunoassay techniques as previously described (Chrousos *et al.*, 1984; Magiakou *et al.*, 1994). The low limit of detection was 17.66 nmol/l for cortisol and 0.2 mU/l for GH. The intra- and inter-assay coefficients were, respectively, 4.6% and 6% for cortisol and 3.3% and 5.1% for GH.

Pulse analysis

The plasma cortisol and GH concentrations obtained were analysed for the presence of pulses by the Detect programme (Oerter *et al.*, 1986; Genazzani & Rodbard, 1991). The detection of pulses by Detect is based on the calculation of a mathematical model of the predicted variance of the raw data. The most accurate way of calculating this model of variance is based on the intra- and inter-assay coefficients of variation of the hormonal assay. This programme reveals significant pulses as follows: (1) analysis of first derivatives of data for the detection of rapid events, and (2) fitting of linear segments for the detection of slow events. Data from each subject were analysed using Detect, with a nominal value of $P=0.01$ for positive peak detection. The programme calculates separately the one-tailed Student's t -value for the desired P -value (in our case $P=0.01$) and number of degrees of freedom for 1 derivative, 2, 3, or 4 derivatives in a row. Samples were analysed for 24-h mean serum hormone concentration, peak area, peak amplitude, and number of peaks per unit of time. Also, the peak area was calculated separately for the daytime period (0800–2200 h) and the nighttime period (2200–0600 h).

Time-integrated cortisol

The amount of time-integrated cortisol was calculated by the trapezoid method (integrated AUC) for the 24-h period, the daytime period (0800–2200 h) and the nighttime period (2200–0600 h).

Cross-correlation analysis

To search for time-ordered relations between cortisol, GH and sleep stages, analysis of correlations between the absolute values of the time series of each hormone value and percentage of each sleep stage per 30 minutes time intervals of the corresponding night was performed. These cross-correlation analyses were computed between cortisol and GH values and percentage wakefulness, stage 1, and 2 sleep, REM sleep

and SWS in every 30 minutes interval at various time lags covering the 8-h period of study. For example, if release of a hormone B is regulated by a sleep stage A (e.g. A is the releasing sleep stage and B is the affected hormone), then one might expect the concentration-time series of hormone B to lag (follow) in time, quantitatively, the percentage-time series of sleep stage A. Cross-correlation was computed after lagging the concentration time series of hormone B relative to the percentage time series of sleep stage A. If we call r_k the coefficient of correlation between the time series of the hormone concentration and the percentage of sleep stage at lagtime k for one subject, then the mean r_k of all subjects was considered significant when it exceeded zero by more than 2.00 SE ($P<0.05$ level of significance). The SE at each time point was calculated from the individual values of r_k s for the 10 subjects at the lagtime k . All correlations were performed using Statview software for the Macintosh computer (Abacus Concepts, Inc., Berkeley, CA).

Statistical analysis

Data were expressed as mean \pm SE. Differences between pre- and post-sleep deprivation values were examined using paired two-tailed Student t -test.

Results

Sleep pre- and post-sleep deprivation

On postdeprivation (night 6) compared to predeprivation (nights 2–4), subjects demonstrated significantly shorter sleep latencies and a higher percentage of slow wave sleep (Table 1).

Table 1 Nighttime sleep pre- and post-sleep deprivation in normal male volunteers

	Nights 2–4	Night 6
SL	28.4 \pm 5.5	7.9 \pm 1.3**
WTASO	43.3 \pm 10.3	37.2 \pm 12.5
TWT	71.7 \pm 9.1	45.1 \pm 12.6
% ST	85.1 \pm 1.9	90.6 \pm 2.6
% Stage 1	9.4 \pm 2.1	5.2 \pm 1.3
% Stage 2	50.8 \pm 2.6	43.3 \pm 3.1
% SWS	18.8 \pm 2.9	29.0 \pm 3.7*
% REM	21.0 \pm 1.3	22.4 \pm 1.7
REM Latency	102.9 \pm 5.3	92.4 \pm 18.8
# REM Periods	3.8 \pm 0.2	4.3 \pm 0.3
REM Duration	23.7 \pm 1.7	23.3 \pm 2.3

Data represent mean \pm SE. * $P<0.05$; ** $P<0.01$.

Also, total wake time and percentage of stage 1 sleep tended to be lower postdeprivation ($P = 0.1$).

Twenty-four hour secretion of cortisol pre- and post-sleep deprivation

Mean 24-h plasma cortisol levels were lower, but not significantly so, postdeprivation. During the postdeprivation nighttime period, mean plasma cortisol levels were significantly lower compared to the predeprivation night (4th night) (157.3 ± 11.0 vs. 176.6 ± 13.8 nmol/l, $P < 0.05$) (Table 2, Fig. 1). Pulsatile analysis showed significant reduction of the 24 h peak area (7134.8 ± 447.0 vs. 8323.9 ± 491.1 nmol/l. minutes, $P < 0.05$) and the pulse amplitude (1103.6 ± 74.5 vs. 1534.0 ± 99.3 nmol/l. minutes, $P < 0.01$), but not of the pulse frequency (6.6 ± 0.4 vs. 5.6 ± 0.4 , $P > 0.05$). Finally, the amount of time-integrated cortisol, as calculated by the trapezoid method (integrated AUC), was lower during the nighttime postdeprivation than the nighttime predeprivation (71471.9 ± 4745.5 vs. 80165.5 ± 5989.8 nmol/l. minutes, $P < 0.05$).

Twenty-four hour secretion of growth hormone pre- and post-sleep deprivation

The growth hormone (GH) levels were increased during the nighttime postdeprivation period compared to the nighttime predeprivation period (Table 3, Fig. 2). Specifically, mean plasma GH levels tended to be higher during the postdeprivation nighttime period than during the predeprivation nighttime (3.4 ± 0.6 vs. 2.6 ± 0.4 mU/l, $P = 0.1$). The difference was

stronger for the first 4-h of the nighttime period (5.4 ± 1.2 vs. 3.8 ± 0.8 mU/l, $P = 0.07$). Also, the amount of time-integrated GH, as calculated by the trapezoid method (integrated AUC), tended to be higher during the postdeprivation than during predeprivation nighttime (1676.4 ± 276.2 vs. 1331.6 ± 210.6 mU/l. minutes, $P = 0.1$). The difference was significant for the first 4-h of the nighttime period (1285.8 ± 294.8 vs. 886.2 ± 163.6 mU/l. minutes, $P < 0.05$). Pulsatile analysis showed no significant differences between pre- and postdeprivation with regard to 24-h peak area, pulse amplitude or pulse frequency. The nighttime secretion of the hormone tended to be higher during post- compared to pre-deprivation (50.0 ± 9.2 vs. 36.6 ± 6.6 mU/l, $P < 0.1$).

Correlation analyses

Cortisol and GH. A significant negative correlation was observed between cortisol and GH pre- and post-sleep deprivation at lag times 0 ($r = -0.22$) and 30 ($r = -0.25$) minutes, respectively, with cortisol leading GH. Also, there was a positive correlation between cortisol and GH pre- and post-sleep deprivation at 6.5 ($r = 0.26$) and 7.5 ($r = 0.25$) hours, respectively, with GH leading cortisol (Fig. 3). Finally, there was a positive correlation between cortisol and GH post-sleep deprivation peaking at lag time 15 h, with cortisol leading GH ($r = 0.17$).

Cortisol and sleep stages pre- and post-sleep deprivation. No significant correlation was observed predeprivation between SWS and cortisol. However, a significant negative correlation was observed postdeprivation between SWS and cortisol

	Pre-deprivation	Post-deprivation	P-value
Mean values (nmol/l)			
24 h	231.8 ± 13.8	212.4 ± 8.3	$=0.08$
Daytime (0800–2200 h)	240.0 ± 19.3	226.2 ± 13.8	ns
Nighttime (2200–0600 h)	176.6 ± 13.8	157.3 ± 11.0	<0.05
Time-integrated AUC (nmol/l. minutes)			
24 h	282334.0 ± 18104.6	261933.9 ± 9079.9	$=0.1$
Daytime (0800–2200 h)	202165.7 ± 16396.7	190462.0 ± 11016.7	ns
Nighttime (2200–0600 h)	80165.5 ± 5989.8	71471.9 ± 4745.5	<0.05
Pulsatile analysis			
24 h peak AUC (nmol/l. minutes)	8323.9 ± 491.1	7134.8 ± 447.0	<0.05
Daytime (0800–2200 h)	5244.9 ± 355.9	4442.0 ± 449.7	<0.05
Nighttime (2200–0600 h)	1865.1 ± 198.6	1713.3 ± 173.8	ns
average AUC/peak (nmol/l. minutes)	1534.0 ± 99.3	1100.8 ± 74.5	<0.01
# peaks	5.6 ± 0.4	6.6 ± 0.4	$=0.063$

Table 2 Overall and pulsatile cortisol release pre- and post-sleep deprivation

Data represent mean \pm SE.

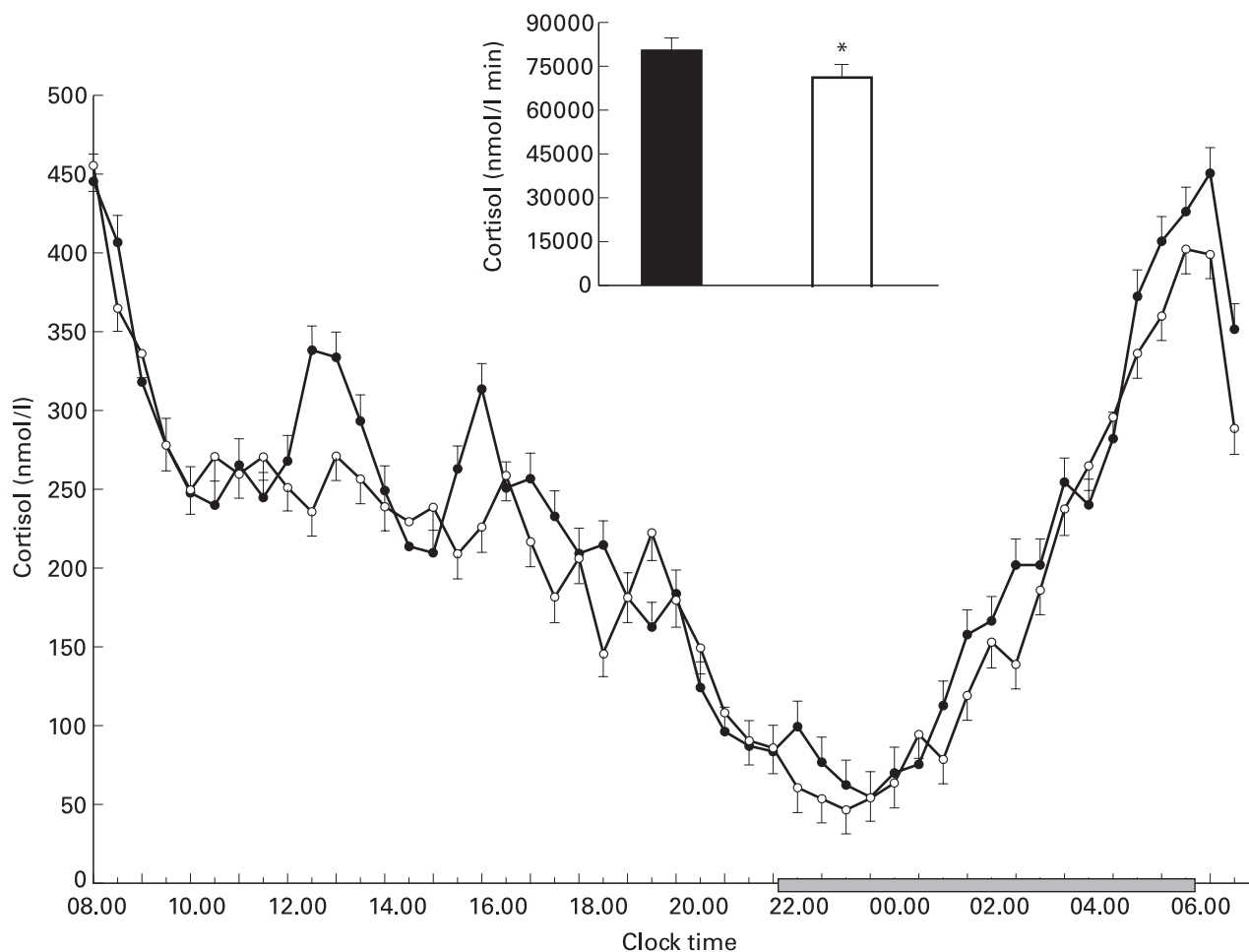


Fig. 1 Diurnal variation (mean \pm SE) in plasma cortisol concentrations in 10 healthy men pre- (●) and post- (○) sleep deprivation. Samples were taken every 30 minutes through an indwelling IV catheter. Inset, integrated nighttime AUC pre- (■) and post- (□) sleep deprivation. * $P < 0.05$.

peaking at lag time 0 minutes, with SWS leading cortisol ($r = -0.46$) (Fig. 4). Also, significant positive correlations were observed postdeprivation between SWS and cortisol at lag time 6.5 h with SWS leading cortisol ($r = 0.30$) and at lag time 3 h with cortisol leading SWS ($r = 0.16$).

A positive correlation was observed between wake and cortisol pre- and post-sleep deprivation, peaking in both conditions at lag time 7.5 h ($r = 0.26$, $r = 0.19$, respectively), with wake leading cortisol. Also, a negative correlation was observed between wake and cortisol pre- and post-sleep deprivation, peaking in both conditions at lag time 1.5 h ($r = -0.25$, $r = -0.23$, respectively), with wake leading cortisol. In addition, a positive correlation was observed between stage 1 sleep and cortisol pre- and post-sleep deprivation peaking at 1.5 h ($r = 0.19$) and 2 h ($r = 0.12$), respectively, with stage 1 sleep leading cortisol.

GH and sleep stages pre- and post-sleep deprivation. There was a significant positive correlation between SWS and GH concentration pre- and post-sleep deprivation at lag times 30 ($r = 0.37$) and 0 ($r = 0.32$) minutes, respectively with SWS leading GH (Fig. 5). Also, there was a negative correlation between SWS and GH concentration pre- and post-sleep deprivation peaking at 2.5 ($r = -0.10$) hours and 6.5 ($r = -0.14$) hours, respectively, with SWS leading GH. In addition, there was a negative correlation between SWS and GH concentration post-sleep deprivation, peaking at 4.5 h, with GH leading SWS ($r = -0.10$).

There was a negative correlation between wake and GH post-sleep deprivation, peaking at 0 minutes ($r = -0.20$). Also, wake and GH concentration was positively correlated pre- and post-sleep deprivation, peaking in both conditions at 2 h, with wake leading GH ($r = 0.28$, $r = 0.23$, respectively). Finally, there was a negative correlation between stage 1 sleep and GH

	Pre-deprivation	Post-deprivation	P-value
Mean values (mU/l)			
24 h	1.4 ± 0.2	1.8 ± 0.4	ns
Daytime (0800–2200 h)	0.8 ± 0.2	1.0 ± 0.6	ns
Nighttime (2200–0600 h)	2.6 ± 0.4	3.4 ± 0.6	=0.1
1st half of the night	3.8 ± 0.8	5.4 ± 1.2	=0.073
Time-integrated AUC (mU/l. minutes)			
24 h	2058.0 ± 378.6	2636.0 ± 594.6	ns
Daytime (0800–2200 h)	656.6 ± 224.6	883.8 ± 495.8	ns
Nighttime (2200–0600 h)	1331.6 ± 210.6	1676.4 ± 276.2	=0.1
1st Half of the Night	886.2 ± 163.6	1285.8 ± 294.8	<0.05
Pulsatile analysis (mU/l. minutes)			
24 h peak AUC	56.6 ± 12.4	77.0 ± 18.6	ns
Daytime (0800–2200 h)	29.0 ± 16.0	69.4 ± 49.8	ns
Nighttime (2200–0600 h)	36.6 ± 6.6	50.0 ± 9.2	=0.099
Average AUC/peak	22.8 ± 3.8	31.4 ± 6.6	ns
# Peaks	2.6 ± 0.5	2.6 ± 0.4	ns

Table 3 Overall and pulsatile GH release pre- and post-sleep deprivation

Data represent mean ± SE.

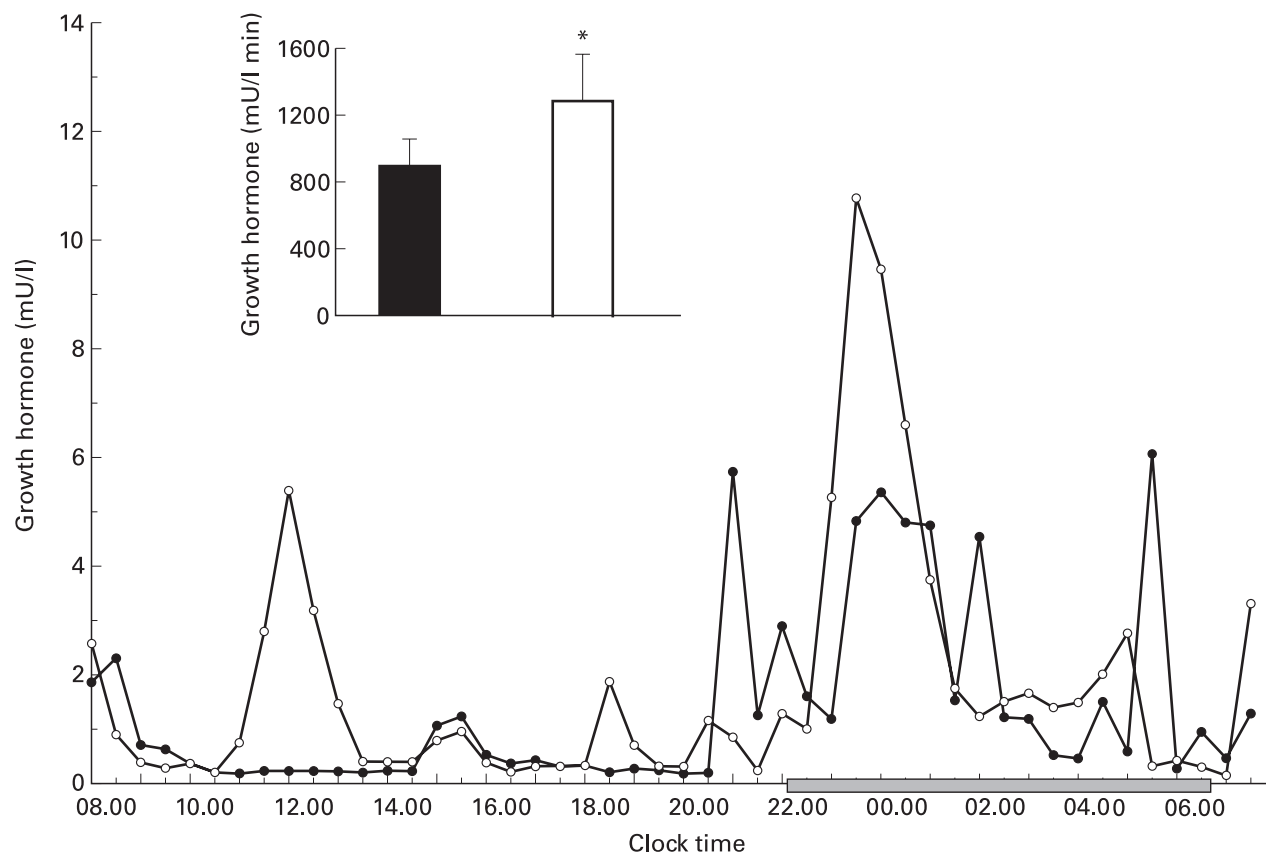


Fig. 2 Diurnal variation (mean ± SE) in plasma GH concentrations in 10 healthy men pre- (●) and post- (○) sleep deprivation. Samples were taken every 30 minutes through an indwelling IV catheter. Inset, integrated AUC for the first half of the night pre- (■) and post- (□) sleep deprivation. * $P < 0.05$.

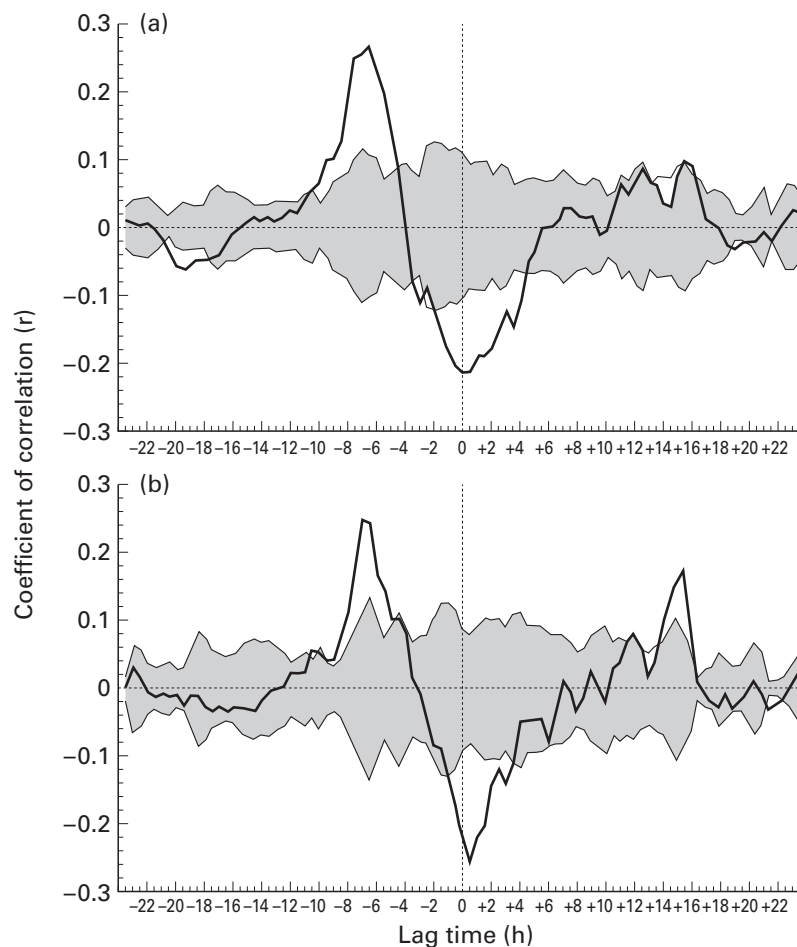


Fig. 3 Cross-correlation analysis between cortisol and GH over the 24-h study period (a) pre- and (b) post-sleep deprivation. The solid line represents the mean of the individual values of the coefficients of correlation r_k for all 10 subjects at each lagtime k . The grey area represents 2 SE, displayed above and below zero, and indicates the limits of significance for cross-correlation at the $P = 0.05$ level. Therefore, significant correlation at any lagtime is achieved when the solid line falls outside the grey area. (See Subjects and methods).

concentration pre- and post-sleep deprivation, peaking at 0 minutes in both conditions, with stage 1 sleep leading GH ($r = -0.18$, $r = -0.21$, respectively).

Discussion

Our primary finding is that sleep deprivation results in a significant decrease in plasma cortisol levels the next day and recovery night. Also, GH secretion after sleep deprivation is increased primarily during the recovery night. The decrease of the HPA axis activity postsleep deprivation appears, to a large extent, to be related to the increased amount of SWS during the recovery night. Furthermore, our results do not support the notion that acute sleep deprivation represents a stress associated with activation of the stress system of which HPA axis is a major component. Previous studies have shown that cortisol secretion is either not or minimally affected by sleep following prolonged wakefulness (Moldofsky *et al.*, 1989; Van Cauter & Turek, 1994; Scheen *et al.*, 1996). The difference of our

findings from these reports may be a result of either methodological differences (variable sampling, ad lib design, analysis focused on circadian rhythmicity) (Moldofsky *et al.*, 1989) or that the focus of an earlier study was on daytime sleep after a night of sleep deprivation (Scheen *et al.*, 1996). Two more recent studies reported either no change in cortisol secretion the day and the night following sleep deprivation (Brun *et al.*, 1996) or elevated cortisol levels the next evening (Leproult *et al.*, 1997). The former was presented in an abstract form, thus making difficult a comparison and discussion of its methodology and findings to those of our study. The latter, studied subjects in a constant recumbent condition, who were given calories intravenously in the form of glucose and who were sampled entirely differently from our study. Specifically, we sampled our subjects for 24 h, twice, before and immediately after sleep deprivation, while they performed sampling during and after sleep deprivation for a total of 32 h. These methodological differences may explain the somewhat contradicting results of these two studies.

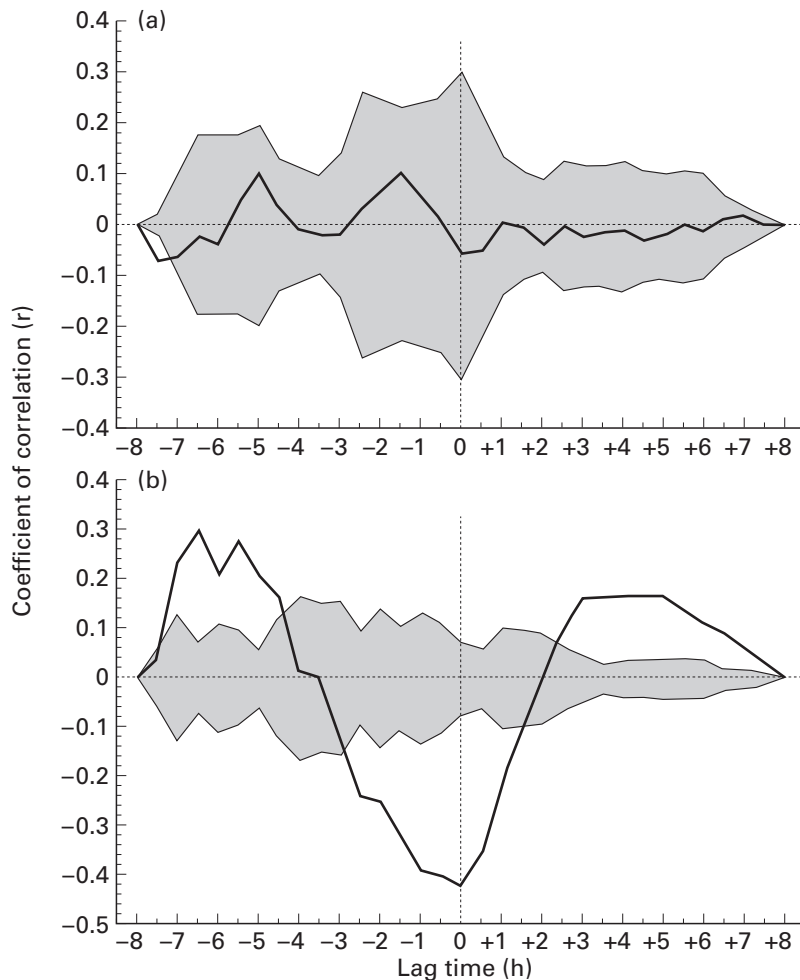


Fig. 4 Cross-correlation analysis between cortisol and slow wave sleep over the 8-h night period (a) pre- and (b) post-sleep deprivation. The solid line represents the mean of the individual values of the coefficients of correlation r_k for all 10 subjects at each lagtime k . The grey area represents 2 SE, displayed above and below zero, and indicates the limits of significance for cross-correlation at the $P=0.05$ level. Therefore, significant correlation at any lagtime is achieved when the solid line falls outside the grey area. (See Subjects and methods).

Slow wave sleep, an index of sleep depth, was negatively correlated to cortisol levels over time, at lag time 0h postsleep deprivation, with SWS leading cortisol. In contrast, slow wave sleep was positively correlated to GH levels over time, at lag time 30 and 0 minutes pre- and post-sleep deprivation, respectively, with SWS leading GH. These results indicate that slow wave sleep has an inhibitory effect on cortisol secretion, which is more pronounced in the first recovery night following sleep deprivation; in contrast, SWS enhances the secretion of GH. It is possible that the enhanced GH secretion following sleep deprivation is driven by the inhibition of the HPA axis activity induced by the increased amount of SWS, since HPA axis has been shown to regulate GH secretion under normal conditions (Ghizzoni *et al.*, 1996). The negative correlation between SWS and GH at lag time 2.5 h and 6.5 h pre- and post-sleep deprivation, respectively, could be the mirror image of the preceding positive correlation.

Stage 1 sleep, which is associated with sleep disturbance,

was positively correlated to cortisol levels over time, at a lag time of 1.5–2.5 h, with stage 1 leading cortisol. The positive correlation between wake and cortisol at 7.5 h lag time could reflect the fact that wake is high early at night, whereas cortisol plasma levels are high late at night. The strong negative correlation of wake and stage 1 with GH at 0 h lag time indicates that sleep disturbance is associated with inhibition of GH axis during the nighttime. The positive correlation between wake and GH at a lag time of 2 h reflects the lag between the wake before sleep onset and the occurrence of SWS. Indeed, SWS is positively correlated with GH at a lag time of only 30 minutes

Overall, our analysis indicates that deep sleep is associated with inhibition of the HPA axis, while it is associated with enhancement of the activity of the GH axis. The inhibition of the HPA axis and the activation of the GH axis appear to correlate with the amount of SWS. In contrast, sleep disturbance appears to be associated with activation of the HPA axis and suppression of the GH axis activity. These results are

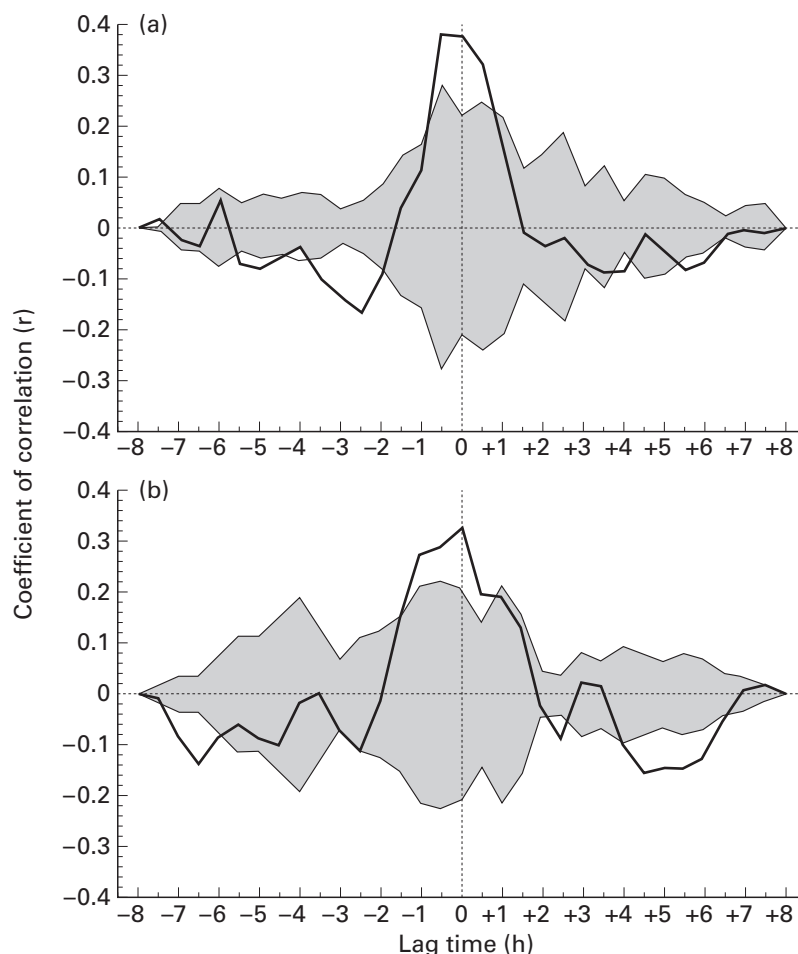


Fig. 5 Cross-correlation analysis between GH and slow wave sleep over the 8-h night period (a) pre- and (b) post-sleep deprivation. The solid line represents the mean of the individual values of the coefficients of correlation r_k for all 10 subjects at each lagtime k . The grey area represents 2 SE, displayed above and below zero, and indicates the limits of significance for cross-correlation at the $P = 0.05$ level. Therefore, significant correlation at any lagtime is achieved when the solid line falls outside the grey area. (See Subjects and methods).

consistent with our preliminary findings of subtle hypocortisolism and inferred CRH deficiency in patients with idiopathic hypersomnia, a condition of increased daytime sleepiness and deep nocturnal sleep (Vgontzas *et al.*, 1997). Also, they support the previously reported findings that in chronic insomnia 24-h urinary free cortisol excretion was positively related to indices of sleep disturbance, i.e. amount of wakefulness. (Vgontzas *et al.*, 1998).

The reciprocal relation of the activities of HPA and GH axes were confirmed in a cross-correlation analysis which demonstrated that cortisol and GH were strongly negatively correlated with each other over time, with cortisol leading GH. The relation did not change following one night of sleep deprivation. This finding replicates in adults previous findings on the relation of the two hormones in children (Ghizzoni *et al.*, 1996). This reciprocal relation may reflect the negative effects of glucocorticoids on the central noradrenergic system (Chrousos & Gold, 1992) and/or the positive effects of CRH on hypothalamic somatostatin secretion (Peterfreund & Vale,

1983). The strong positive correlation between the two hormones observed at lag time of 6.5–7.5 h could either reflect the temporal difference of their circadian phase or be the mirror image of the negative correlation observed in cross-correlation analyses.

Our findings may have pathophysiological implications with regard to the effects of sleep and sleep deprivation in humans. Melancholic depression is associated with HPA axis activation and cortisol hypersecretion (Gold *et al.*, 1988a). Its temporary improvement following sleep deprivation has been replicated by many investigators. However, the mechanism through which sleep deprivation improves the mood of depressed patients is unknown. Previous findings on the effect of sleep deprivation on cortisol secretion in healthy humans or depressed patients are inconsistent. Sleep deprivation in healthy humans was associated with either no change (Poland *et al.*, 1972; Kant *et al.*, 1984) or a significant decrease of urinary glucocorticoid excretion (Akerstedt *et al.*, 1980). In patients with depression, two studies have shown an increase of cortisol secretion

during the night of sleep deprivation (Baumgartner *et al.*, 1990; Bouhuys *et al.*, 1990), while a third one showed no change of plasma cortisol the morning after sleep deprivation (Ebert *et al.*, 1994). However, these studies did not extend their measures of cortisol the next day and night following sleep deprivation. Our findings that sleep deprivation leads to lower cortisol levels postdeprivation (primarily during the subsequent night of sleep) suggest that lowering the level of HPA activity, which is increased in depression, may be the mechanism through which sleep deprivation improves the mood of depressed individuals.

In addition, our findings shed new light on an old controversy in the sleep field which is whether sleep has a restitutive role (Adam & Oswald, 1983; Horne, 1983). Our findings tend to support that sleep, particularly SWS, by decreasing cortisol (a catabolic hormone) and increasing GH (an anabolic hormone) has a positive role on several systems and organs in terms of the daily 'wear and tear.' Previous findings have suggested a possible link between SWS and the immune system (Krueger *et al.*, 1985; Moldofsky *et al.*, 1986). Activation and suppression of the HPA axis, respectively, inhibits or enhances the immune-mediated inflammatory reaction (Chrousos, 1995). Our results suggest that increased amounts of SWS lead to lower levels of cortisol, which in turn may enhance immune function in humans.

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