Acute cortisol administration increases sleep depth and growth hormone release in patients with major depression

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Abstract

Acute administration of cortisol increases non-rapid-eye movement (non-REM) sleep, suppresses rapid-eye movement (REM) sleep and stimulates growth hormone (GH) release in healthy subjects. This study investigates whether cortisol has similar endocrine and electrophysiological effects in patients with depression who typically show a pathological overactivity of the hypothalamus–pituitary–adrenal (HPA) system. Fifteen depressed inpatients underwent the combined dexamethasone/corticotropin-releasing hormone test followed by three consecutive sleep EEG recordings in which the patients received placebo (saline) and hourly injections of cortisol (1 mg/KG BW). Cortisol increased duration and intensity of non-REM sleep in particular in male patients and stimulated GH release. The activity of the HPA axis appeared to influence the cortisol-induced effects on non-REM sleep and GH levels. Stimulation of delta sleep was less pronounced in patients with dexamethasone nonsuppression. In contrast, REM sleep parameters were not affected by the treatment. These data demonstrate that the non-REM sleep-promoting effects of acute cortisol injections observed in healthy controls could be replicated in patients with depression. Our results suggest that non-REM and REM sleep abnormalities during the acute state of the disease are differentially linked to the activity of the HPA axis.

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1. Introduction

Exogenously administered glucocorticoids strongly affect sleep architecture and sleep-associated release of growth hormone (GH). Seminal work by Gillin and colleagues (Gillin et al., 1972) and subsequent studies addressing this question in healthy control subjects agreed that an acute administration of glucocorticoids suppresses rapid-eye movement (REM) sleep, and some (Born et al., 1989; Born et al., 1991) but not all studies observed a stimulation of slow-wave sleep (Gillin et al., 1972; Born et al., 1987). The observed discrepancies were probably due to methodological aspects, i.e. synthetic vs. natural steroids, oral vs. iv application, single bolus vs. constant infusion. Several studies of our laboratory showed that acute injections of cortisol stimulate both slow-wave sleep and GH release in young and elderly healthy subjects (Friess et al., 1994; Bohlhalter et al., 1997; Friess et al., 2004). These effects have been attributed to the negative feedback inhibition of cortisol on sleep-disrupting activity of corticotropin-releasing hormone (CRH) and stimulation of sleep-promoting activity of GH-releasing hormone (GHRH) (Friess et al., 1995; Steiger, 2002). Interestingly, the slow-wave sleep enhancing effect by pulsatile cortisol injections was also observed in elderly subjects.
(Bohlhalter et al., 1997) where a hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis is present due to the physiological aging process (Heuser et al., 1994a; Heuser et al., 1996). The results were interpreted as preserved capacity of elderly subjects to respond to acute cortisol administration with respect to sleep depth and GH surge.

Neuroendocrine alterations during the state of a major depression include a characteristic hyperactivity of the HPA axis which is suggested to result from an impaired intracellular signaling of corticosteroid-receptor binding process (Holsboer, 2000). The combined dexamethasone/corticotropin-releasing hormone test (DEX/CRH-test) has been proven as a very sensitive measure for the function of the HPA axis (Heuser et al., 1994b; Modell et al., 1997; Rybakowski and Twardowska, 1999). Here, hyperactivity of HPA axis function is represented by DEX/CRH-test non-suppression, i.e. basal or CRH-induced cortisol is increased though dexamethasone has been given on the day before the test. The major sleep abnormalities in patients with depression are a disturbed sleep initiation and maintenance, reduced amount of non-rapid-eye movement (non-REM) sleep with less slow-wave activity, whereas REM sleep and in particular phasic REM sleep parameters are increased (Lauer et al., 1991; Kupfer et al., 1993; Wichniak et al., 2000). In addition, the sleep-associated secretion of GH is often blunted when compared to age-matched healthy controls (Steiger et al., 1993). Using quantitative sleep EEG analysis distinct abnormalities in the amount, the time course and organization of non-REM sleep have been demonstrated. In particular, a deficit to build up slow-wave activity in the first sleep cycle and a shift of slow-wave pressure into the second cycle were identified as biological markers for response to various treatment regimens and the course of the disease (Luthringer et al., 1995; Buysse et al., 1997; Hoffmann et al., 2000; Nissen et al., 2001).

Moreover, the sleep-endocrine abnormalities during the state of depression have been causally related to the elevated activity of the HPA axis. Since CRH injections were shown to severely disrupt sleep in humans (Holsboer et al., 1988; Born et al., 1989) and rats (Ehlers et al., 1986, 1997) CRH overactivity is thought to mediate sleep impairment in depression. In line with this hypothesis, a recent clinical observation investigating a CRH1-receptor-antagonist in patients with a major depression showed an improved sleep quality and an increase in slow-wave sleep shortly after initiation of treatment (Held et al., 2004).

Therefore, the present study investigates whether acute administration of cortisol would increase slow-wave sleep as well as sleep-associated release of GH and suppress REM sleep in patients with depression.

2. Methods

2.1. Patients

We recruited $n = 21$ non-obese inpatients (mean BMI 24.9 ± 2.9, range 20.3–29.4) diagnosed as having a major depressive episode without psychotic features (ICD10 F32.2, F33). Patients with a bipolar affective disorder, rapid cycling, recurrent brief depression and dysthymia were excluded (ICD10 F31, F38.10, F34). Patients underwent a careful clinical evaluation to exclude other accompanying severe somatic, neurological or endocrinological diseases or substance abuse. Shift workers and patients having traveled across time zones within the previous 6 weeks were excluded. Patients were free of any psychotropic medication including benzodiazepine hypnotics for a wash out period of at least 5 days prior to the endocrinological testing and at least 7 days prior to the sleep EEG recordings. None of the patients had been pretreated with fluoxetine or diazepam. There was a total number of $n = 6$ drop-out cases (3 male, 3 female); one patient among the drop-outs was diagnosed as rapid cycling, $n = 2$ patients cancelled their agreement before entering the study protocol and $n = 3$ patients refused to participate until the end of the protocol. One patient refused to participate in blood sampling. Therefore, the final sample size was $n = 15$ patients with a severe major depressive episode [8 male, 7 female, age range 33–79 yr, mean (SD) 49.3 (13.9) yr, Hamilton Depression scale 21 items (HAMD): range 18–38, mean 28.5 (6.6)] who were included in the statistical analysis for the sleep data. For technical reasons endocrinological data were only available for $n = 14$ patients. For details of the clinical and demographic data see Table 1.

2.2. Procedure

All investigations were performed at the Max Planck Institute of Psychiatry in Munich. The experimental protocol was approved by the Ethics Committee for Human Experiments of the Bayerische Landesarztekammer (Munich, Germany). Written informed consent was

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HAMD: Hamilton depression score (21 item); Cort$_{\text{max}}$: basal cortisol concentration (ng/ml) at 1500 after dexamethasone suppression; Cort$_{\text{bas}}$: maximum cortisol concentration (ng/ml) after CRH stimulation; S: suppressor ($n = 10$); N: nonsuppressor ($n = 5$).
obtained after the procedures had been fully explained. Throughout the entire study the patients agreed to maintain regular sleep/wake and meal schedules (bedtime: 2300 to 0700; breakfast: 0800 lunch: 1200; dinner: 1800). The sleep investigations extended over four consecutive nights in our sleep laboratory according to a single-blind protocol. To avoid carryover effects of hormone administrations during the preceding DEX/CRH-test or the treatment condition and due to ethical aspects concerning a prolongation of the drug-free investigation period, the study protocol consisted of a constant order of (1) an adaptation night to adapt to the laboratory setting, (2) a simple baseline recording without blood sampling, (3) placebo condition and (4) treatment condition. In both the placebo and treatment conditions an indwelling forearm catheter was inserted at 1830. Blood samples were collected at 20 min intervals from 1900 to 0700. During this time period the patients received saline infusion during the placebo condition and hourly intravenous injections of hydrocortisone (Hoechst AG, 65926 Frankfurt, Germany) in the treatment condition. The total dose of hydrocortisone over all injections was 1 mg/kg BW (20% of the total dose as initial loading dose at 1900, 6% of the total dose every following hour until 0600, slow bolus injections over a 30- to 60-s period).

Before entering the sleep recordings the patients underwent the combined dexamethasone/CRH (DEX/CRH) test to determine the status of HPA axis function as described elsewhere (Heuser et al., 1994b; Zobel et al., 2001). In short, a single oral dose of DEX 1.5 mg was given at 2300 at the evening before the test. At 0830 next morning cortisol and corticotropin levels were determined. At 1500 prior to the CRH stimulation (fur-

2.4. DEX/CRH-test

The DEX suppression status was based on the cortisol concentrations at 1500 prior to the CRH stimulation (fur-

2.5. Sleep EEG recordings

Polysomnographic sleep recordings were obtained from 2300 to 0700 including a bilateral monopolar central and occipital electroencephalogram (EEG) (C3–A2, C4–A1, Oz–A1), vertical and horizontal electrooculogram, submental electromyogram. The EEG, EOG and EMG signals were filtered (high-pass filter at 0.5 Hz, notch filter at 50 Hz) and digitized (8-bit analog-to-digital converter, sampling rate 100 Hz).

The EEG recordings were visually analyzed according to standardized criteria of Rechtschaffen and Kales (1968) by experienced raters, blind for the treatment condition. The EEG data (C3–A2) were subjected to a sleep-state specific (non-REM/REM) spectral analysis using a fast Fourier transformation (0.4 Hz resolution, EEG power spectrum 0.8 to 19.1 Hz) as described previously (Tagaya et al., 2000). The spectral power data in each frequency bin were accumulated across the delta (0.8–4.3 Hz), theta (4.3–7.8 Hz), alpha (7.8–12.1 Hz), sigma (12.1–16.1 Hz) and beta (16.1–19.1 Hz) range after an artifact exclusion of wakefulness and movement times has been performed.

2.6. Data analysis

Treatment effects on the sleep parameters, EEG data, and hormone data were tested for significance by multivariate analysis of variance (MANOVA) with repeated-measures design. Thereby, treatment was a within-subjects factor with two levels (cortisol vs. placebo). With respect to the sleep parameters and growth hormone levels we additionally tested for the influence of sex and age. In case of significant treatment effects, the identification of the variables that contributed to this effect was carried out by subsequent univariate F-tests. Whenever time was also considered as a within-subjects factor, differences between the various time levels were tested for significance by tests with contrasts.

EEG spectral data were normalized to overcome the high interindividual differences in the absolute power densities by calculating a sleep stage-specific cortisol/placebo index during non-REM sleep (sleep stage 2, 3, 4) and REM sleep for the values in each frequency band (percentage of the corresponding mean value during placebo). In view of the high inter- and intradividual variety of the cycle length, the analysis of the sleep EEG data was based on the mean values over three 160 min periods (thirds of
the night sleep). The statistical analysis of the quantitative EEG data focused on measures indicating the degree of EEG synchronization during non-REM sleep, i.e. the spectral power in the delta frequencies (0.8–4.3 Hz) and the sigma (12.1–16.1 Hz) frequency range (Achermann and Borbely, 1998; Friess et al., 2004).

The hormone concentrations during the DEX/CRH-test and sleep recordings were described by mean locations (ML) over the time period from 1500 to 1615.

For the hormonal variables the area under the curve (AUC) value was used in the statistical analysis. Due to technical reasons (incomplete blood sampling) the statistical analysis of the GH levels had to be restricted to n = 14 patients.

As nominal level of significance, \( \alpha = 0.05 \) was accepted. To keep the type I error \( \leq 0.05 \) all posternori tests were performed at an adjusted level of significance (Bonferroni adjusted alpha). For quantifying and testing associations between the sleep EEG and the hormone data, the Pearson’s product-moment correlation coefficient was used.

3. Results

3.1. Sleep architecture and continuity

In the cortisol condition one patient did not reach sleep stage 3 or 4. We therefore considered this record as an outlier and replaced its values with missing values (see Table 2). The analysis of aggregated sleep parameters revealed a significant main effect of treatment [Wilks’ multivariate analysis of variance; effect of treatment: \( F(7,7) = 11.81; p = 0.002 \); effect of sex: \( F(6,7) = 1.09; n.s.; \) interaction effect of treatment and sex: \( F(7,7) = 1.19; n.s.; \) effect of covariate age: \( F(6,7) = 1.43; n.s. \)] that could be attributed to the effects on the duration of non-REM sleep (univariate F-tests, \( p < 0.05 \)). Subsequent testing on sleep stages revealed that the treatment induced a significant increase in the duration of stage 2 sleep and slow-wave sleep [Wilks’ multivariate analysis of variance; effect of treatment: \( F(3,10) = 5.72; p = 0.015 \); univariate F-tests \( p < 0.05 \)]. With respect to slow-wave sleep, we observed a significant interaction effect of treatment and sex [\( F(1,11) = 9.2; p = 0.011 \)]. Though there were no significant gender differences in slow-wave sleep in each condition the cortisol-induced increase in slow-wave sleep was significantly higher in male patients [\( t \)-test for paired samples; mean (SD); male (n = 6): 39.3 (26.5) vs. 81.5 (47.3) min.; \( p < 0.01 \); female (n = 7): 34.6 (38.3) vs. 41.4 (33.2) min; n.s.].

There were no other measures of sleep continuity or sleep architecture including sleep onset latency, tonic and phasic REM sleep parameters differed significantly between the placebo condition and the cortisol administration (see Table 2). In a second step, we repeated the analysis after exclusion of n = 4 patients with a latency between DEX administration and beginning of the placebo night shorter than 72 h. We could replicate the treatment effect in the reduced sample [Wilks’ multivariate analysis of variance; effect of treatment: \( F(3,8) = 4.38; \) sign of

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<td>SOL</td>
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<td>REM density</td>
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</table>

Data represent mean (SEM) in minutes (except of SEI) for the placebo and cortisol condition. SPT = Sleep period time; TST = total sleep time; SEI = sleep efficiency index; SOL = sleep onset latency; \(^{1}\)statistical comparisons by MANOVA.

\( F = 0.042 \) in terms of a significant increase in stage 2 and SWS in the verum condition (univariate F-tests, \( p < 0.05 \)).

3.2. Spectral composition of the sleep EEG

To avoid collinearities in the data we analyzed the power spectra in two separate MANOVAs delta and sigma power and on the other hand theta, alpha and beta power were considered as dependent variables. The statistical comparison of delta and sigma power between placebo and cortisol as well as between thirds of the nights revealed significant main effects of treatment and time [Wilks multivariate test of significance; treatment: \( F(2,13) = 4.34; \) sign of \( F = 0.036 \); effect of time: \( F(4,11) = 28.56; \) sign of \( F < 0.0001 \)], and a marginal interaction effect [\( F(4,54) = 2.30; \) sign of \( F = 0.07 \)] as well. All effects were significant on the delta EEG activity only [mean(SD) delta power 2300–0700: 200.2(131.7) vs. 223.8(134.1) \( \mu \text{V}^2 \); univariate F-tests, \( p < 0.05 \)]. During the first third of the night delta EEG activity in the cortisol condition increased significantly compared to placebo [2300–0140: 248.7(166.6) vs. 307.3(186.6) \( \mu \text{V}^2 \); tests with contrasts; \( p < 0.05 \); see Fig. 1] obtaining its smallest value in the last third of the night. None of the other power spectra showed significant differences neither between the treatments nor between the night thirds. As expected, there was a significant effect of time on the delta power with respect to night thirds (tests with contrasts, \( p < 0.05 \)).

3.3. GH and cortisol levels

There were significant main and interaction effects of the factors treatment and time on the AUC values of GH [Wilks’ multivariate analysis of variance; effect of treatment: \( F(1,13) = 14.39; \) sign of \( F = 0.002 \); effect of time: \( F(2,12) = 12.38; \) sign of \( F = 0.001 \); effect of treatment by time: \( F(2,12) = 4.83; \) sign of \( F = 0.029 \)]. Cortisol injections
significantly stimulated GH secretion during the total observation period [mean(SD) AUCGH 1900–0700: 32.1(4.8) vs. 62.6(10.7) ng/ml min⁻¹; p < 0.05]. Tests with contrast revealed a significant increase of the GH release in the presleep period starting shortly after the cortisol injections [AUCGH 1900–2300: 6.9(2.2) vs. 35.2(7.3) ng/ml min⁻¹; p < 0.05; see Fig. 2]. GH release in the first half [AUCGH 2300–0300: 22.7(6.4) vs. 31.6(11.3) ng/ml min⁻¹] and the second half of night sleep [AUCGH 0300–0700: 6.6(1.5) vs. 9.3 (1.7) ng/ml min⁻¹] was not affected significantly by the treatment. After exclusion of n = 4 patients with a latency between DEX administration and beginning of the placebo night shorter than 72 h this result was confirmed [Wilks’ multivariate analysis of variance; effect of treatment: F(2,8) = 14.3; sign of F = 0.003]. The cortisol injections resulted in a marked increase in the circulating cortisol levels [AUCcort 1900–0700: 131.4(12.1) vs. 267.7(62.3) ng/ml min⁻¹; F(1,13) = 16.06; p < 0.001]. There was no interaction effect of treatment and sex with respect to the hormone levels.

Finally, we were interested whether the treatment effects on GH and sleep EEG data were associated with each other, but failed to find any significant relation between both measures.

Fig. 1. Effects of cortisol on non-REM power spectrum. Data are expressed as mean percentage of the mean power values (SEM) during total non-REM sleep in the placebo night; black line depicts cortisol (n = 15) and grey line depicts placebo condition (n = 15).

Fig. 2. Nocturnal growth hormone and cortisol release. Mean (SEM) of growth hormone (upper panel) and cortisol (lower panel) plasma concentration; black line depicts cortisol (n = 14) and grey line depicts placebo condition (n = 14); grey bar indicates polysomnographic recording.

Fig. 3. Function of HPA axis and delta EEG-activity. Data are expressed as mean percentage of mean power values (SEM) during total non-REM sleep in the placebo condition; black line depicts cortisol and grey line depicts placebo condition separated for “nonsuppressors” (left panel) and “suppressors” (right panel) according to the function of the HPA axis.
3.4. Function of HPA axis

According to their basal cortisol values in the DEX/CRH-test (see Table 1) we characterized patients as “non-suppressors” \((n = 5)\) or “suppressors” \((n = 10)\) (Heuser et al., 1994b). In the group of DEX/CRH test “non-suppressors” the disturbed function of HPA axis included an excessive release of cortisol when compared to the group of “suppressors” [mean(SD) CRH-induced cortisol 1500–1615: 186.0(49.4) vs. 26.6(10.2) ng/ml]. However, due to the small number in one of the subgroups we tried to explain some obtained results only exploratory. We observed that the increase in non-REM delta power induced by cortisol was more pronounced in patients defined as “suppressors” when compared to “nonsuppressors” (see Fig. 3).

4. Discussion

This study demonstrates that a short term administration of cortisol significantly changes the sleep architecture and the sleep associated GH release in the state of an acute and severe major depression. Cortisol increased the duration and intensity of non-REM sleep resulting in a higher amount of delta EEG activity. The cortisol-induced increase in slow-wave sleep was significantly higher in male patients. The treatment markedly stimulated the GH release in the presleep period, though this effect occurred independently of the changes in sleep EEG. Other measures of sleep architecture and sleep continuity were not significantly affected. In particular, we could not confirm the REM sleep suppressing effect of cortisol observed in our previous studies in healthy and elderly subjects (Friess et al., 1994; Bohlhalter et al., 1997; Friess et al., 2004).

The observed cortisol-induced increase in the duration of non-REM sleep is in line with the results of our previous studies in young and elderly healthy controls (Friess et al., 1994, 2004; Bohlhalter et al., 1997). By means of a quantitative EEG analysis we were now able to demonstrate that the cortisol injections resulted in a higher degree of EEG synchronization during non-REM sleep also in patients with major depression. In parallel to the effects seen in healthy subjects the cortisol-induced increase in non-REM sleep intensity in patients with depression could be interpreted as a possible result of the negative feedback inhibition on the activity of the HPA axis via suppression of CRH in brainsites relevant for regulation of sleep. Likewise acute cortisol stimulates the somatotrophic axis. Thus, the sleep regulating reciprocal interaction of the HPA and hypothalamic-pituitary-somatotropin axis would be shifted towards the sleep-promoting effects of GHRH (Steiger et al., 1992; Kerkhofs et al., 1993; Steiger, 2002). The observed increase in slow-wave sleep predominated in male patients, which is in line with a previous study on the sleep-endocrine effects of GHRH in patients with depression. The sleep-promoting effects of GHRH were restricted to male patients whereas female patients showed a decreased amount of non-REM sleep (Antonijevic et al., 2000). On the other hand, female gender is associated with a higher basal activity of the HPA axis, a steeper decline in sleep intensity within the first half and less sleep intensity in the second half of the night (Antonijevic et al., 1999). Therefore, the basal activity of the HPA axis appears to weaken the impact of GHRH on sleep regulation. In our study, however, gender distribution was balanced both in patients characterized as “suppressors” \((5m:5f)\) and “nonsuppressors” \((3m:2f)\). Moreover, there is some evidence that the cortisol-induced negative feedback inhibition is less efficient in patients with a pathological overactivity of the HPA axis though statistical comparison was not possible due to the small sample size. According to the corticosteroid-receptor-hypothesis of depression HPA overactivity results from an impaired intracellular signaling process of corticosteroid-receptor binding suggested as the key mechanism in the pathogenesis of the disease (Holsboer, 2000). Thus, the patients where HPA impairment is minor according to DEX/CRH-test outcome seem to be more sensitive to the effects of cortisol at least with respect to the non-REM sleep-promoting effect of the steroid. Therefore, CRH suppression may be the major mechanism mediating the observed effects of cortisol on non-REM sleep.

However, other factors may have potentially influenced the effect of gender, e.g. age, severity of depressive symptoms, basal level of delta power in the placebo night and stimulated levels of GH in the verum night. Stimulated GH levels and HAMD scores were pretty similar between male and female patients [mean(SD) stimulated GH: male: 1.73(0.72) vs. female: 1.95(1.32) ng/ml; HAMD: male: 29.1(5.0) vs. female: 28.0(8.5)]. Yet, age and basal delta power did not differ significantly between female and male patients mean levels of both parameters were slightly higher in female patients \([age: male: 45.4(9.3) vs. female: 53.9(17.4) yr; delta power: male: 194.6(113.6) vs. female: 268.6(158.5) \text{\mu V}^2\)\]. Therefore, the pronounced SWS-promoting effect of cortisol in male patients may have been also influenced by their younger age and lower amount of delta power in the placebo night.

We were not able to replicate the REM sleep suppressing effects of acute cortisol injections in the present sample of patients with depression that were clearly seen in our previous studies in young and elderly healthy controls (Friess et al., 1994, 2004; Bohlhalter et al., 1997). It has been repeatedly demonstrated that an acute treatment with natural and synthetic glucocorticoids reduces the duration of REM sleep in healthy controls (Gillin et al., 1972; Feinberg et al., 1984; Fehm et al., 1986; Born et al., 1987, 1989, 1991). In addition, a recent study on the effects of CRH1-receptor-antagonist R121919 in patients with depression strongly suggests that CRH overexpression contributes to REM sleep disinhibition ( Held et al., 2004) as one of the most characteristic sleep abnormality due to the disease (Lauer et al., 1991; Kupfer et al., 1993; Wichniak et al., 2000). The mean REM density in our patients was elevated. However there was no reduction of mean REM latency.
when compared to the values of healthy subjects (Lauer et al., 1991). We expected that the REM sleep suppressive effects of cortisol seen in healthy subjects would be more prominent in patients with depression since the treatment would attenuate the REM promoting of CRH via negative feedback. We did not observe significant changes in the duration, spectral composition or phasic components of REM sleep. The latter parameter, however, was only assessed during total night sleep so that we might have missed a significant effect of the treatment on REM density in the first REM period. The failure of cortisol to suppress REM sleep in our study indicates that other factors next to CRH participate in the REM sleep dysregulation during the acute state of the disease. In particular, an increased cholinergic and/or decreased aminergic neurotransmission were suggested to mediate REM sleep disinhibition in patients depression according to the reciprocal interaction model (Berger et al., 2003). As already mentioned, however, our patients exhibited only moderate signs of a REM sleep disinhibition though they were severely depressed (mean Hamilton 28.5). To further address this question a future study should only include patients with depression showing clear signs of an overactive HPA system function on the one hand and/or REM sleep disinhibition on the other hand.

The stimulation of GH release by acute cortisol administration in patients with depression confirmed our previous results in young and elderly healthy controls (Friess et al., 1994; Bohlhalter et al., 1997) though the effects in the present study were limited to the presleep period. Concerning the underlying neuronal mechanism a direct stimulatory effect of cortisol on GH gene transcription (Karin et al., 1990; Treacy et al., 1991) as well as indirect effects via an increased synthesis of GHRH receptors have been described (Seifert et al., 1985). The question, however, why disturbed function of the HPA axis appeared to influence the cortisol-induced effects on sleep but not on GH release cannot be answered by the present study. Since this study confirmed the dissociation of the treatment-induced effects on both measures (Friess et al., 2004) the present results support the previous suggestions that the relation of neuronal GH promoting mechanisms to slow-wave sleep is not as strong as it has been assumed up to now. Approximately one third of highly synchronized non-REM periods are not associated with a significant GH secretion (Van Cauter and Plat, 1996; Van Cauter et al., 1998). Therefore, the cortisol-induced increase in sleep intensity and stimulation of GH may have been driven by different mechanisms activating hypothalamic GHRH pathways. Whereas the control of pituitary GH release prior to sleep primarily involves GHRH-containing neurons of the arcuate nucleus, the pathways controlling the GHRH-driven increase in non-REM sleep may originate in other regions of the mediobasal hypothalamus, i.e. within the ventromedial nucleus (Meister and Hulting, 1987).

The placebo and verum condition were applied in a fixed and subsequent order. Therefore, an adaptation effect on the sleep quality has to be considered. We investigated patients with a severe degree of depressive symptoms who were not treated with antidepressant drugs. The patients spent two nights (adaptation and baseline night) in the sleep lab before entering the placebo and verum condition. A further lengthening of the experimental protocol and thus the drug-free period would have been unjustifiable. A previous study on the influence of sleep recordings in patients with depression suggested an attenuated first night effect. The reduction of slow-wave sleep due to adaptation is not as prominent as in healthy subjects. There were less differences in the sleep parameters between the first, second and third recordings in depressed inpatients (Toussaint et al., 2000). Therefore, it is unlikely that the observed increase in sleep depth in the fourth recording night (verum condition) is due to a prolonged adaptation to the experimental setting. In addition, it has to be questioned whether the DEX/CRH-test could have affected the sleep structure. In most of the patients the latency between the administration of DEX and the sleep EEG recording of the placebo night was longer than the half life time of DEX (=72 h; mean ± SD 108 ± 73.7 h). However, there were n = 4 patients where the latency between DEX administration and placebo night was shorter than 72 h. After exclusion of these patients the statistical comparison confirmed the slow-wave sleep enhancing as well as GH stimulating effect of cortisol administration. The half life time of CRH is very short and the stimulated cortisol levels typically come back to baseline within several hours (Heuser et al., 1994b). Therefore, a carryover effect of the preceding endocrinological testing on the results of the experiment is unlikely.

In summary, a short term administration of cortisol increased sleep intensity and GH surge in patients with a major depression. These effects were not related to each other but appeared to be influenced by changes in the set-point of the HPA axis. Future studies should clarify whether the stimulated amount of highly synchronized non-REM sleep would be a suitable phenotype reflecting the function of glucocorticoid receptor signaling in the course of the disease.

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Conflict of interest

All authors declare that they have no conflict of interests.

Contributors

Dagmar Schmid recruited the patients, organized the study and wrote the manuscript. Elisabeth Friess designed the present study, wrote the protocol, supervised the performance of the study and contributed substantially to the manuscript. Christoph Lauer and Florian Holsboer...
initiated the study and contributed substantially to the design of the study. Manfred Uhr analyzed the plasma levels of ACTH, cortisol and growth hormone. Hans Brunner and Alexander Yassouridis analysed the sleep EEG data and undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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