Treatment with the CRH₁-receptor-antagonist R121919 improves sleep-EEG in patients with depression

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Abstract

Well documented changes of sleep electroencephalogram (EEG) in patients with depression include rapid eye movement (REM) sleep disinhibition, decreases of slow-wave-sleep (SWS) and increase in wakefulness. Twenty-seven inpatients with major depression were admitted subsequently to a clinical trial with the CRH₁-receptor-antagonist R121919 administered in two different dose escalation panels. A random subgroup of 10 patients underwent three sleep-EEG recordings (baseline before treatment, at the end of the first week and at the end of the fourth week of active treatment). SWS time increased significantly compared with baseline after 1 week and after 4 weeks. The number of awakenings and REM density showed a trend toward a decrease during the same time period. Separate evaluation of these changes for both panels showed no significant effect at lower doses, whereas in the higher doses after R121919 REM density decreased and SWS increased significantly between baseline and week 4. Furthermore positive associations between HAMD scores and SWS at the end of active treatment were found. Although these data might indicate that R121919 has a normalizing influence on the sleep EEG, the design of the study does not allow to differentiate genuine drug effects from those of clinical improvement and habituation to the clinical setting.

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1. Introduction

Neuropeptides including corticotropin-releasing hormone (CRH) play a key role in normal and pathological sleep regulation. (Krueger and Obál, 1993; Steiger and Holsboer, 1997) and exert various influences on behavior, including sleep.

CRH has been reported to enhance wakefulness and to decrease Non-rapid-eye-movement (Non-REM) sleep in rats and rabbits (Opp, 1997; Ehlers et al., 1986; Opp et al., 1989). In healthy young male controls after repetitive hourly intravenous (iv) boluses of 4×50 μg CRH during sleep onset slow-wave-sleep (SWS) decreased (Holsboer et al., 1988), probably due a central action of CRH. This view is supported as acute cortisol administration increased SWS in young and elderly human subjects (Friess et al., 1994; Born et al., 1991; Bohlhalter et al., 1997). It appears likely that this effect is mediated by negative feedback inhibition of central CRH synthesis and release. Furthermore, in the rat, CRH has been shown to enhance rapid-eye-movement (REM) sleep after sleep deprivation (Marrosu et al., 1990). It is thought that CRH overactivity contributes to the well documented aberrancies of sleep electroencephalogram (EEG) in patients with depression (Reynolds and Kupfer, 1987; Steiger, 2002; Ehlers and Kupfer, 1987). Following intracerebroventricular (icv) administration of the CRH antagonist, α-helical CRH, wakefulness decreased while SWS increased in rats (Opp, 1995). Stress induced increases of REM sleep were antagonized following icv α-helical CRH in rats (Gonzalez and Valatx, 1997). Whereas these preclinical data suggest, that overactivity of CRH promotes REM sleep, human studies show ambiguous results. Inhibition of cortisol synthesis by metyrapone followed by an increase of ACTH prompted decreased SWS whereas
REM sleep remained unchanged (Jahn et al., 1996). It is assumed that the changes of ACTH and SWS are mediated by elevated CRH activity. In young normal men, REM sleep was diminished after pulsatile CRH administrations (Holsboer et al., 1988). Since REM suppression was also observed after ACTH and cortisol (Steiger and Holsboer, 1997) it appears likely that the decrease of REM sleep after CRH was mediated by elevated cortisol levels, whereas the decrease of SWS in the same study was thought to be due to a central action of CRH.

In patients with major depression, one of the most consistent neuroendocrine disturbances is the hyperactivity of the HPA system, including elevated secretion of CRH (Holsboer, 2000) and much experimental evidence exists that HPA aberrancies play a key role in the pathophysiology of affective disorders (Holsboer, 1999; Owens and Nemeroff, 1991). Since preclinical data including use of antisense probes directed against CRH1 receptor mRNA and mouse mutants with CRH1 receptor deficiency (Liebsch et al., 1999; Smith, 1998; Timpl et al., 1998) all agree that CRH1 receptors mediate CRH elicited depressive symptoms a selective CRH1 receptor antagonist, R121919 was developed. This compound penetrates the blood–brain barrier and occupies the CRH1 receptor in a dose dependent manner as shown by ex vivo autoradiography in rats (Keck et al., 2001).

Lancel et al. (2001) recently showed that the CRH1 receptor antagonist R121919 attenuates stress elicited sleep disturbances in rats, particularly in those with high innate anxiety. The effects of CRH1 antagonism by R121919 on human sleep patterns however are unknown. We hypothesized that CRH1 receptor antagonism is capable of counteracting sleep-EEG changes in patients with depression. We now report on the effects of four week treatment with the CRH1 receptor antagonist R121919 on the sleep EEG in patients with depression.

2. Methods

Over the course of 13 months 27 patients were selected from referrals to the Clinical Department of the Max Planck Institute of Psychiatry for treatment of a major depressive episode with the CRH1 receptor antagonist R121919. The detailed study design and the results of the clinical trail as well as ethical regulations have been reported elsewhere (Zobel et al., 2000). In these patients all met the DSM IV criteria for major depression. The severity of depression was evaluated by the Hamilton Depression Scale (21-items version, Hamilton) one day before medication and on day 29 of medication. A random subgroup of 10 patients underwent three sleep EEG recordings. During the screening period all psychoactive medication was stopped for a minimum of at least for 7 days. Pretreatment with monoamine oxidase inhibitors, fluoxetine or slow release neuroleptics had to be discontinued for at least 1 month and treatment with corticosteroids or electroconvulsion within 3 months prevented study inclusion. Each patient spent five nights in a sleep-laboratory over the period of 30 days of R121919 medication: two nights before medication (baseline), one night during the early treatment period (first week) and two nights at the end of the treatment period (day 29 and 30). The 1st and the 4th night was an adaptation night to the laboratory setting. The patients were enrolled in two dose-escalation panels. In panel A the dose range was increased from 5 to 20 and 40 mg and in panel B the dose was escalated from 40 to 60 and 80 mg every 10 days terminating at 30 days. R121919 was administered as a daily oral dose at 8.00 h. For safety reasons the first 10 patients were recruited into panel A, completing the lower doses before the initiation of panel B. Dose escalation took place on day 11 and day 21 of the study. An initiated 3rd panel with a higher dose of R121919 (80–160 mg) was terminated early for technical reasons. One patient was treated with the increased dose of R121919 and was able to participate in the complete set of polysomnographic sleep recordings. Complete sets of polysomnographic recordings (baseline, first week under treatment, end of treatment period) were available for five patients from panel A and four patients from panel B. In order to achieve an acceptable sample size for a between-groups comparison we merged the four patients from panel B with the one patient treated with the higher dose regimen of R121919 (80/120/160 mg). Demographic data of the patients are given in Table 1.

Conventional sleep-EEG findings as well as the power of the δ, θ, α, σ and β wavebands were compared between baseline and the first week of treatment (immediate sleep response) and between baseline and the end of the treatment period (subchronic sleep response).

In a first exploratory analysis we compared the results between baseline and the first week of treatment and the end of the treatment period pair-wise using Wilcoxon matched pairs tests, respectively. In order to identify

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data of the patients</th>
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<tbody>
<tr>
<td></td>
<td>Panel A</td>
</tr>
<tr>
<td></td>
<td>(5 patients)</td>
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<tr>
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<td>2 males</td>
</tr>
<tr>
<td></td>
<td>3 females</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
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<tr>
<td>DSM IV 296.32</td>
<td>2 patients</td>
</tr>
<tr>
<td>DSM IV 296.33</td>
<td>1 patient</td>
</tr>
<tr>
<td>HDRS screening</td>
<td>24.0±3.2</td>
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<td>HDRS last day of med.</td>
<td>11.2±5.7</td>
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significant changes we evaluated these changes separately for the two groups, panel A and panel B.

As there are no standard non-parametric tests available for the determination of interactions between change under treatment and dose group, we conducted a parametric two-way analysis of variance for repeated measures. Changes between the baseline results and the first week results and the results at the end of the treatment period were assessed by single contrasts. All results are presented as means and standard deviations.

Sleep EEG analysis: Polygraphic recordings were performed from 23:00 to 07:00 h and consisted of two EEGs (C3-A2, C4-A1; time constant 0.3 s, low-pass filtering 70 Hz), vertical and horizontal electro-oculograms (EOG), an electromyogram (EMG) and an electrocardiogram (ECG). The EEG signals were filtered (EEG: high pass 0.53 Hz, −3 dB; low pass 70 Hz, −3 dB; −12 dB octave, band-stop between 42 and 62 Hz, −3 dB) and transmitted by an optical fiber system to the polygraph (Schwartzer, ED 24). By means of a personal computer, EEG signals were additionally sampled by an 8-bit analog-to-digital converter at a sampling rate of 100 Hz and stored on disk for further spectral analysis. Sleep EEGs were rated visually according to standard criteria (Rechtschaffen and Kales, 1968) by an experienced rater who was blind to the study protocol. Parameters used were: SOL—sleep onset latency [sleep onset defined as the first epoch of 30 s containing stages 2, 3, 4 or REM sleep (min)]; SPT—sleep period time (interval from sleep onset until final awakening, including intermittent time spent awake) (min); TST—total sleep time (SPT—intermittent time spent awake) (min); time spent in each of the following sleep stages during the SPT Awake, Non-REM stages 1–4, SWS—slow wave sleep (non-REM stages 3 and 4), REM; REM latency [interval from onset until the first epoch containing stage REM (min)]; REM density (the average ratio of 3-s mini-epochs of REM sleep including REMs to the total number of 3-s mini-epochs of REM sleep.)

Sleep EEG spectral analysis: As described in detail elsewhere (Steiger et al., 1993) spectral analysis was initially performed on the distinct frequency ranges δ (0.5–4.5 Hz), θ (4.5–8.0 Hz), α (8.0–11.8 Hz), σ (11.8–15.2 Hz) and β (15.2–20.0 Hz) and thereafter using the single frequency.

3. Results

3.1. Sleep–EEG analysis

In the first exploratory analysis we compared the results between baseline, the first week and the end of the treatment for all three panels using a Wilcoxon matched pairs test regardless of the dose. The Wilcoxon matched pairs test revealed significant increases of time spent in stage 4 and SWS at the first week as well as at the end of treatment, compared with baseline (stage 4: baseline 9.5 ± 3.3 min vs. first week 16.1 ± 19.7 min, \( P < 0.05 \); vs. end 17.9 ± 21.7 min, \( P < 0.05 \); SWS: baseline 40.9 ± 26.6 min vs. first week 49.0 ± 31.0 min, \( P < 0.05 \); vs. end 54.6 ± 32.1 min, \( P < 0.05 \)). Furthermore a trend of a reduced REM latency in the first week was observed (baseline 54.3 ± 22.8 min vs. first week 39.5 ± 25.4 min, \( P = 0.09 \)). A significant decrease of the number of awakenings and a trend of a decrease of REM density were observed between baseline and the end of the treatment period (number of awakenings: baseline 20.7 ± 10.6 min vs. end 15.3 ± 7.7 min, \( P < 0.01 \); REM density: baseline 4.5 ± 1.9 vs. end 3.9 ± 7.6, \( P = 0.09 \)).

After identifying significant changes for the complete group of patients we evaluated these changes separately for the two groups panel A and panel B. In panel A no changes were observed, whereas we found significant changes in panel B: (1) a reduced REM latency in the first week of treatment (baseline 63.2 ± 16.0 min vs. first week 32.7 ± 26.4 min, \( P < 0.05 \)), (2) a trend to an increase of stage 4 in the first week of treatment (baseline 17.9 ± 14.6 min vs. first week 27.2 ± 20.7 min, \( P = 0.08 \)), (3) a decrease of REM density at the end of treatment (baseline 4.2 ± 1.3 1/min vs. first week 3.0 ± 0.1 1/min, \( P < 0.05 \)), (4) a significant increase of SWS (baseline 58.4 ± 16.4 min vs. end 71.7 ± 17.5 min, \( P < 0.05 \)) and a trend to an increase of stage 4 at the end of the treatment period (baseline 17.9 ± 14.6 min vs. end 28.0 ± 23.2 min, \( P < 0.05 \)).

Subsequent analysis of variance revealed a significant effect of time and a significant interaction between time and treatment group (panel A vs. panel B) for the REM latency. However, this effect seems to be attributable to baseline differences between the two groups of patients (Table 2). The REM density was similar between the two groups of patients at baseline. However, patients of panel B showed a distinctly reduced REM density at the end of the treatment period, which was not the case in the patients of panel A. This group difference in change over time results in a significant interaction between change (end of treatment–baseline) and the group factor (Fig. 1).

The amount of SWS in the second half of the night changed between baseline and the first week of treatment differently between the two groups, which is expressed by a significant interaction between the respective change term (first week–baseline) and the group factor (see Fig. 2). SWS in the second half of the night increased significantly in panel B at the end of treatment. Correspondingly, we observed a significant main effect of time for the time spent in SWS during the
total night indicating an overall increase in SWS (Table 2). In the complete set of 20 patients (Zobel et al., 2000) the increase in SWS was accompanied by a distinct reduction of the total score and of the sleep items sub-scale of the Hamilton Depression Rating Scale (HDRS, see Fig. 3). Similarly high associations between SWS and the HDRS total Score ($r_{\text{Kendal}} = -0.748, P = 0.002$) and the HDRS sleep items Score ($r_{\text{Kendal}} = -0.706, P = 0.005$) were found at the end of the treatment period in the subgroup of patients which participated in the sleep recordings. This association was not found at baseline (see Fig. 4).

3.2. EEG spectral analysis

We also analyzed the power of the spectral wavebands $\delta$, $\theta$, $\alpha$, $\sigma$ and $\beta$ of the three study nights. For technical reasons the spectral baseline results of one patient from panel B were not available. Therefore, the
Fig. 2. Slow wave sleep (2nd half of the night) analysis of variance (min) of the three examinations (baseline, first week, end of treatment) compared for panel A \( (n=5) \) and panel B \( (n=5) \). Panel B showed a significant increase of SWS (2nd half of the night) between baseline and the first week of treatment \((1)-(0), \text{time}\times\text{panel}^{**}\). \( **P<0.01 \).

Fig. 3. The total score and the sleep items subscale score of the Hamilton Depression Rating Scale (HDRS) for baseline and end of treatment compared for panel A \( (n=10) \) and panel B \( (n=10) \). Both scores decreases significantly \((\text{time}^{**})\) which was more pronounced in panel B \([\text{time}\times\text{panel}^{*} (*)]\). \( **P<0.01; *P<0.05; (*) P<0.10 \).

Fig. 4. Association between SWS (min) and the Hamilton Depression Rating Scale (HDRS) at the end of treatment with R121919.
number of patients with spectral data in all of the three study nights was reduced to \( N = 4 \) in panel B. In an exploratory analysis, we did not find any significant changes between baseline and the first week or the end of treatment (Wilcoxon matched pairs tests), neither for the complete group of patients nor separately for panel A or panel B. Trends \( (P < 0.10) \) suggesting marginal reduction in alpha power in panel B at the end of treatment as well as a slight increase in sigma power in panel A but not in panel B could be observed. However, the result of the analysis of variance did not reveal any significant effects or trends suggesting any changes in the time or interactions with the group factor.

4. Conclusions

The major findings of our study were increases in SWS and decreases in REM density during treatment of patients with depression with the CRH 1 receptor antagonist R121919. Additionally, a decrease in the number of awakenings could be observed at the end of the treatment for the entire group of patients. A positive association between SWS and the HDRS score at the end of the treatment period was also found.

Decreases in SWS and increases of wakefulness and REM density are key symptoms of sleep dysfunction in patients with depression (Reynolds and Kupfer, 1987; Steiger, 2002). The hypothesis that CRH overactivity contributes through activation of the CRH 1 receptor to these aberrancies is supported by this study since treatment with R121919 improved sleep-quality and in particular normalized some of the sleep-EEG changes characteristic of depression.

Overall, in all the patients examined, the increase of SWS was observed within the first few days of active medication. This observation suggests an early onset of the action of the compound on sleep. It appears that SWS continues to increase during the treatment period, since the highest mean value was found at the end of the treatment period. This change can be primarily attributed to an increase in one of the components of SWS, in particular, stage 4 (deep SWS). Separate inspection of the panels revealed, that in panel A at baseline, SWS time was lower than in panel B. In panel A the increase of SWS was less pronounced than in panel B that is in line with a dose-dependent effect of the drug on SWS.

The increase of SWS after treatment with R121919 is consistent with previous reports on decreases of SWS after CRH administration in humans and animals. In young healthy male control subjects SWS decreased after repetitive iv boluses of CRH around sleep onset (Holsboer et al., 1988). In animals SWS was reduced after icv CRH (Ehlers et al., 1986; Opp et al., 1989).

SWS was reduced after icv CRH. In the Lewis rat, a strain with reduced CRH synthesis, SWS is increased and wakefulness reduced in comparison to strains with normal CRH synthesis (Opp, 1997), which again is consistent with the observed effect of the CRH antagonist \( \alpha \)-helical CRH, that increased SWS in rats (Opp, 1995). A reciprocal interaction of CRH and GHRH in sleep regulation is supported by many studies and in patients with depression a reduction of the GHRH:CRH ratio due to CRH overactivity is thought to result in more shallow sleep (Ehlers and Kupfer, 1987; Steiger and Holsboer, 1997).

In addition to a decrease of SWS, an increase of wakefulness and a disturbed sleep continuity are frequent symptoms in depression. Depressed patients often complain about sleep fragmentation and therefore the observed decrease of the number of awakenings after R121919 is clinically relevant. Similarly, we have previously found a decrease of the number of awakenings in elderly healthy women and men following pulsatile iv administration of GHRH (Guldner et al., 1997). These findings have led to the hypothesis that during normal aging, the GHRH:CRH ratio is decreased due to declining activity of GHRH secretory neurons. It appears likely that a decrease of the number of awakenings is a common effect of the normalization of the GHRH:CRH ratio, either by R121919 in the present study in depressed patients or by GHRH in the elderly subjects in our previous trial. Notably there was a non-significant trend of the intermittent awake time to decrease at the end of the treatment period with R121919.

Elevated REM density is one of the most robust sleep-EEG changes in patients with depression (Lauer et al., 1991). In addition to short REM latency and prolonged first REM sleep period, elevated REM density is one component of REM sleep disinhibition in depression. Several findings suggest that CRH promotes REM sleep. For example, CRH augmented the rebound of REM sleep after REM deprivation in rats (Marrosu et al., 1990). In rats, stress induces an increase of REM sleep probably via CRH. This effect was antagonized by the \( \alpha \)-helical CRH antagonist (Gonzalez and Valatx, 1997). The present finding of a decrease in REM density after R121919 supports the hypothesis that CRH contributes to the increase of REM density in depression via CRH 1 receptors. In panel B REM density decreased significantly at the end of active treatment whereas panel A showed no effect again indicating that the higher dose of the drug is more effective.

In the absence of a placebo control design it cannot be ruled out that the effects on the sleep EEG might due to clinical improvement and habituation to the clinical setting.

However, it appears unlikely that the changes of sleep EEG are simply consequences of serial testing and/or the concomitant improvement of psychopathology. The latter theory is also contradicted by the observation that
the sleep EEG of drug-free depressed patients does not change between acute depression and recovery (Giles et al., 1989). In another study the EEG measures which are most characteristically altered during depression failed to be normalized after full clinical remission. Furthermore stage 4 decreased and the number of awakenings increased significantly between acute depression and remissions. (Steiger et al., 1989). Recently a polysomnographic assessment of the long term course of major depression showed that a persistent increase of REM density and a decrease of SWS were significantly associated with an increased risk for relapse of depression the follow up period. This finding suggests that both parameters are reflective of a neurobiological “scar” of depression (Hemmeter et al., 2002). In our study, the CRH 1 receptor antagonist R121919 seems to be capable of increasing SWS and decreasing REM-density. In that respect, the specific improvement of SWS deficiency and REM-density increase through CRH 1 receptor antagonism may be of great importance in preventing a further recurrence of depression.

In all, our data suggest that the CRH 1 receptor antagonist R121919 improves the sleep of patients with depression. The cluster of effects (increase of SWS, decrease of the number of awakenings and REM density) corresponds to a normalization of sleep-EEG changes. This differs from the pattern of sleep-EEG changes following treatment with the vast majority of conventional antidepressants (Vogel et al., 1990) which frequently impair sleep by suppressing REM sleep and SWS (Dorsey et al., 1996; Künzel et al., 2000). Our data suggest that R121919 facilitates the restoration of physiological sleep in patients with depression. The same mechanism of action may also be useful for the treatment of disturbed sleep in other stress-related clinical conditions such as anxiety, posttraumatic stress disorder (PTSD) or withdrawal from alcohol (Steiger, 2002). Further placebo controlled studies in normal controls are necessary to delineate.

References


