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Corticotropin-releasing hormone induces depression-like changes of sleep electroencephalogram in healthy women

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ABSTRACT

We reported previously that repetitive intravenous injections of corticotropin-releasing hormone (CRH) around sleep onset prompt depression-like changes in certain sleep and endocrine activity parameters (e.g. decrease of slow-wave sleep during the second half of the night, blunted growth hormone peak, elevated cortisol concentration during the first half of the night). Furthermore a sexual dimorphism of the sleep-endocrine effects of the hormones growth hormone-releasing hormone and ghrelin was observed. In the present placebo-controlled study we investigated the effect of pulsatile administration of 4 × 50 μg CRH on sleep electroencephalogram (EEG) and nocturnal cortisol and GH concentration in young healthy women. After CRH compared to placebo, intermittent wakefulness increased during the total night and the sleep efficiency index decreased. During the first third of the night, REM sleep and stage 2 sleep increased and sleep stage 3 decreased. Cortisol concentration was elevated throughout the night and during the first and second third of the night. GH secretion remained unchanged. Our data suggest that after CRH some sleep and endocrine activity parameters show also depression-like changes in healthy women. These changes are more distinct in women than in men.

1. Introduction

Corticotropin-releasing hormone (CRH) has an active role in sleep regulation as shown by various preclinical and human studies. However, previous studies were restricted to male laboratory animals and male human subjects, providing no evidence for the effects of CRH on sleep in women. In this report we address this issue.

Previous studies in both humans and rats have shown that CRH administration leads to a decrease in slow-wave sleep (SWS) and increase in rapid eye movement (REM) sleep. After intracerebroventricular (icv) administration of CRH, SWS was decreased in rats (Ehlers et al., 1986). Even after 72 h of sleep deprivation, SWS is decreased by CRH in rats. In addition sleep latency and REM sleep increase (Marrosu et al., 1990). The synthesis and the release of CRH are reduced due to hypothalamic gene defect in the Lewis rat. In comparison to intact strains Lewis rats spend more time in SWS and less time awake (Opp, 1997). Vice versa spontaneous wakefulness is diminished by a CRH antisense oligodeoxynucleotide in rats (Chang and Opp, 2004). In mice overexpressing CRH in the central nervous system, REM sleep is elevated throughout 24 h when compared to the wildtype (Kimura et al., 2010). In young healthy male volunteers given pulsatile intravenous CRH injections around sleep onset, SWS in the second half of the night and REM sleep were reduced, the growth hormone (GH) surge was blunted and cortisol was elevated during the first half of the night (Holsboer et al., 1988). After a low dosage of CRH which did not affect sleep in young healthy men, middle −aged healthy men showed prolonged wakefulness and reduced SWS (Vgontzas et al., 2001). Most of the reported sleep-endocrine effects of CRH are similar to characteristic changes of sleep EEG and nocturnal hormone secretion (disinhibition of REM sleep, elevated wakefulness, decrease of SWS, hypercortisolism and blunted GH secretion) which can be found in patients with depression (review: Dresler et al., 2014; Waters et al., 2015). This observation is in line with the view that CRH overactivity plays a key role in the pathophysiology of depression (review: Holsboer and Ising, 2010). Vice versa after treatment of depressed patients with a CRH-1 receptor antagonist their characteristic sleep EEG changes were counteracted. The number of awakenings and

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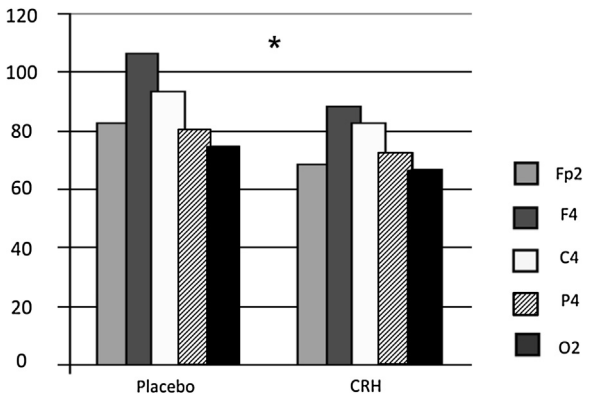

Fig. 1. EEG theta activity (μV^2) of the right hemisphere during the first third of the night. * – indicates significant differences in the theta activity between the two treatments at each electrode position (main effect over all electrodes).

REM density, which is a measure for the amount of rapid eye movements during REM sleep, both decreased and SWS increased (Held et al., 2004).

A sexual dimorphism in the effects of peptides on sleep EEG and nocturnal hormone secretion was found after administration of GH-releasing hormone (GHRH) and ghrelin. In male laboratory animals (review: Obál and Krueger, 2004) and young healthy men (Steiger et al., 1992) the effects of GHRH on sleep are opposite to those of CRH, as GHRH promotes non-REM sleep and GH in animals and humans and inhibits cortisol secretion in male human subjects. In women, however,sleep is impaired after GHRH (Antonijevic et al., 2000a; Mathias et al., 2007) and cortisol and ACTH are stimulated (Antonijevic et al., 2000b) or remain unchanged (Mathias et al., 2007). Ghrelin promotes sleep in young (Weikel et al., 2003; Kluge et al., 2008) and elderly (Kluge et al., 2010) healthy men but not in young (Kluge et al., 2007) and in elderly healthy (Kluge et al., 2010) women.

Women suffer more often from depression than men (Kessler 2003; Collins et al., 2011). Preclinical data suggest sex differences in CRH sensitivity (Waters et al., 2015). Specifically CRH 1 receptor binding is greater in female than in male rats in brain regions implicated in depression (Weathington et al., 2014). Furthermore CRH 1 receptors are differentially affected by stressor exposure or excessive CRH release in males compared to females (review: Waters et al., 2015). Enhanced CRH sensitivity may contribute to the elevated prevalence of depression in women.The effect of CRH on sleep in healthy women is unknown so far. We investigated sleep EEG and the nocturnal secretion of cortisol and GH after pulsatile injections of CRH around sleep onset, in accordance to our previous protocol in healthy young men (Holsboer et al., 1988). Since sleep shows topographic differences between brain regions (Werth et al., 1996) which are not addressed in most pharmacologic and neuroendocrine sleep EEG studies our assessment included topographic quantitative sleep EEG analysis.

2. Subjects and methods

2.1. Subjects

8 healthy women, aged 22–30 (25.4 ± 3.6) yrs. (body mass index (BMI) 23.0 ± 2.7) were recruited for the study. Exclusion criteria included a lifetime or family history of psychiatric disorders, any current diseases or drug-intake, smoking, sleep disturbances and shift work or transmeridian flights within 3 months prior to study entry. Study eligibility was assessed by taking the past and current medical history and performing a rigid physical examination and a screening test (electroencephalogram [EEG], electrocardiogram [ECG], routine laboratory parameters, drug screening). To rule out the influence of gonadal hormone activity (Driver et al., 1996) procedural steps of the study were adapted to the phase of the menstrual cycle, with sessions at the fourth to sixth day of the menstrual cycle. All procedures followed the guidelines of the Declaration of Helsinki. Written informed consent was obtained and approval was given by the Ethics Committee of the Medical Faculty of the University of Munich.

2.2. Study design

This single-blind placebo-controlled, randomized, crossover study comprised 2 sessions separated by at least 28 days, each consisting of 2 consecutive nights in the sleep laboratory. Sleep EEG was recorded during the second night only, with the first night serving for adaptation to the laboratory setting. During recording nights, 5 ml saline which contained 50 μg CRH (CRH-Ferring, Ferring, Kiel, Germany) or 5 ml saline as placebo were administered at hourly intervals between 22:00 and 01:00 h through an indwelling intravenous catheter connected to a plastic tubing running through a sound proof lock into the adjacent room. Lights were turned off between 23:00 and 07:00 h at the next morning. Blood samples were collected every 30 min between 20:00 and 22:00 h and every 20 min between 22:00 and 07:00 h. The specimens collected between 20:00 and 22:00 h were used to exclude stress effects and did not enter into analysis.

2.3. Polysomnography

Polysomnography consisted of two EEGs, vertical and horizontal electrooculograms, and ECG (Comlab 32 Digital Sleep Lab, Schwarzer GmbH, Munich, Germany). Sleep stages were visually scored per 30-s epoch according to conventional criteria (Rechtschaffen and Kales, 1968) by experienced raters, who were unaware of the aim of the study. Conventional sleep-EEG variables included sleep period time (SPT, interval from sleep onset [first episode of stage 2 sleep] until final awakening, minutes) and sleep efficiency index (SEI, quotient of SPT minus intermittent time spent awake and time in bed [480 min]). SWS consists auf stages 3 and 4 of Non REM sleep. Sleep EEG data was additionally analyzed quantitatively. A Fast Fourier Transform routine including a rectangular window for consecutive, non-overlapping 2-s mini epochs was applied (Weikel et al., 2003). EEG frequency bands were defined after excluding epochs of awake or stage 1 as follows: delta: 0.5–4 Hz; theta: 4.5–8.0 Hz; alpha: 8.5–12.0 Hz; sigma: 12.5–16.0 Hz; beta: 16.0–20.0 Hz. For topographic EEG analysis spectral power of each electrode (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2) on each hemisphere was assessed.

2.4. Hormone analysis

Blood samples were centrifuged immediately and plasma was frozen at −25 °C. GH was measured by chemiluminescence method in an automatic analyzer (Immulite 2500 hGH L5KGH2; Siemens Health Care Diagnostics, Derfield, USA). Intra- and interassay coefficients were below 7%. Cortisol was determined using a commercially available radio immunoassay (DRG Diagnostics, Marburg, Germany). Intra- and inter assay coefficients of variance were below 9%.

For statistical evaluations of the hormone concentrations during the various intervals of the night, two indicators were defined and considered in each of these intervals: mean concentration (mean) and area under the curve (AUC).