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The stress hormone system in various sleep disorders

Zuzana Lattova [a,b,1], Marietta Keckeis [a,b,1], Eszter Maurovich-Horvat [a,b], Thomas C. Wetter [b,c], Johanna Wilde-Frenz [a], Andreas Schuld [a], Thomas Pollmächer [a,b,*]

[a] Centre of Mental Health, Klinikum Ingolstadt, Ingolstadt, Germany
[b] Max Planck Institute of Psychiatry, Munich, Germany
[c] Sleep Medicine Department, University Hospital of Psychiatry, University of Zurich, Zurich, Switzerland

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ABSTRACT

Hypothalamic-pituitary-adrenal (HPA)-system activity is regulated by the suprachiasmatic nucleus, the primary endogenous circadian pacemaker. In addition, sleep plays an important modulatory role. However, data on HPA-system activity in sleep disorders are quite conflicting. A sensitive challenge test to assess negative feedback sensitivity of the HPA-system like the dexamethasone/corticotropin-releasing-hormone (DEX/CRH)-test has never been used so far in sleep disorders. Therefore we studied 25 obstructive sleep apnea (OSA) patients, 18 restless legs syndrome (RLS) patients, 21 patients with primary insomnia and compared them to 33 healthy controls. The dynamic response of the HPA-system was assessed by the DEX/CRH-test which combines suppression (dexamethasone) and stimulation (CRH) of the stress hormone system. After HPA-axis suppression the number of non-suppressors did not differ among groups indicating normal negative feedback sensitivity. In RLS patients ACTH levels were slightly lower compared to controls while cortisol levels were similar between groups. Following CRH stimulation we did not detect differences in ACTH- or cortisol levels and adrenocortical responsitivity to ACTH was comparable between groups. These results for the first time document normal HPA-system feedback sensitivity in various sleep disorders and suggest that abnormalities of the stress hormone system in affective disorders are unlikely due to concomitant sleep problems.

1. Introduction

Neuroendocrine systems, in particular the hypothalamo-pituitary-aderenal (HPA)-system, play a pivotal role during the response of the organism to external and internal challenges, generally referred to as stress (Kudielka and Wüst, 2010). The HPA-system represents a feedback loop regulating the release of cortisol. It is internally controlled mainly by circadian signals derived from connections between the hypothalamic nucleus paraventricularis (PVN) and the nucleus suprachiasmaticus (SCN). The PVN secretes corticotropin-releasing hormone (CRH), which acts on CRH receptors in the anterior pituitary to cause the release of the adrenocorticotropic hormone (ACTH) into the bloodstream (Hauger and Datzenberg, 2000). ACTH then induces the release of cortisol from the adrenal cortex. In turn cortisol feeds back onto the PVN and the pituitary to control CRH or ACTH synthesis and release. Whether feedback onto the PVN and pituitary is inhibitory or excitatory depends on the type of receptor activated (high affinity mineralcorticoid receptors, MR's, type I; low affinity glucocorticoid receptors, GR's, type II) and on its location within the brain (Buckley and Schatzberg, 2005).

There is long-standing evidence of reciprocal interactions between the HPA-system and sleep regulation (Steiger, 2007). Exogenous CRH has been shown to increase EEG frequency, light sleep and wakefulness (Ehlers et al., 1986; Chang and Opp, 2001) to enhance REM sleep (Kimura et al., 2010) and to decrease the amount of slow-wave sleep (SWS; Holsboer et al., 1988). Studies focusing on the direct effects of glucocorticoids have shown dose dependent actions. Low doses of glucocorticoids decrease wakefulness and increase SWS amount by MR mediated PVN inhibition, particularly via the hippocampus (Born et al., 1989; Friess et al., 1994, 2004). Furthermore, low doses of the synthetic glucocorticoid dexamethasone, which selectively bind to GR's at the level of the pituitary, produce direct negative feedback on subsequent ACTH and reduce both SWS and REM sleep (Born et al., 1991). In contrast higher cortisol doses increase wakefulness and decrease SWS (Vazquez-Palacios et al., 2001) which may reflect GR activation in the amygdala and may exert a positive feedback effect on PVN CRH (Reul and Holsboer, 2002).

* Corresponding author. Klinikum Ingolstadt, Centre of Mental Health, Krumenauerstrasse 25, D-85049 Ingolstadt, Germany. Tel.: +49 841 880 2201; fax: +49 841 880 2209.
E-mail address: thomas.pollmaecher@klinikum-ingolstadt.de (T. Pollmächer).
[1] These authors contributed equally to this study.

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In turn, sleep and experimental sleep deprivation have modulatory effects on the HPA-system. Several studies reported an inhibitory effect of sleep on cortisol secretion and slightly higher plasma cortisol levels during total sleep deprivation (Weitzman et al., 1974, 1983; Weibel et al., 1995, von Treuer et al., 1996). Leproult et al. (1997) documented enhanced HPA-system activity coupled with a delayed onset of the quiescent secretory phase of cortisol in the evening following a sleep deprivation night. Hence, sleep loss seems to alter negative glucocorticoid feedback regulation. Furthermore, nocturnal awakening is associated with a pulsatile release of cortisol. These arousals are followed by temporary inhibition of cortisol secretion indicating that wakefulness may help to increase the negative feedback sensitivity of the HPA-system. However, sustained sleep disruption does not enhance cortisol secretion (Späth-Schwalbe et al., 1991). Nevertheless, there are some studies which have reported either no change (Moldofsky et al., 1989; Scheen et al., 1996; Brun et al., 1998) or a decrease in the secretion of cortisol (Vgontzas et al., 1999) after experimentally induced sleep disruption.

Results obtained from studies in sleep disorders are quite inconsistent. In patients with an obstructive sleep apnea syndrome (OSAS) some studies reported enhanced cortisol secretion (Bratel et al., 1999; Vgontzas et al., 2007; Schmoller et al., 2009) while other studies did not find alterations in HPA-system activity (Grunstein et al., 1989; Meston et al., 2003; Entzian et al., 1996; Dadoun et al., 2007). Noteworthy, several of these studies were limited in that cortisol was measured at a single time point. Primary insomnia is thought to be a disorder of hyperarousals which is present throughout the 24-h sleep/wake cycle. Insomnia patients with objectively fragmented night time sleep show elevated 24-h plasma ACTH and cortisol levels (Rodenbeck and Hajak, 2001) with greatest elevations in the evening and the first half of the night (Vgontzas et al., 2001). However, insomnia patients showing only minor alterations of sleep exhibited normal cortisol secretion levels (Riemann et al., 2002). Finally, four studies assessed HPA-axis activity in patients with a restless legs syndrome (RLS). Wetter et al. (2002) as well as Garcia-Borreguero et al. reported normal cortisol profiles and no differences in feedback inhibition has been reported by Hornyak et al. (2008). However, the most recent study focusing on HPA-system activity in RLS patients reported enhanced nocturnal cortisol secretion levels (Schilling et al., 2010).

One specific approach to dynamically test HPA-system activity is the dexamethasone suppression/corticotropin-releasing-hormon stimulation test (DEX/CRH-test), described in detail by Heuser et al. (1994). The DEX/CRH-test has been developed to study neuroendocrine abnormalities in psychiatric disorders. This test has been shown to be sensitive in documenting HPA-system overactivity in affective disorders (Heuser et al., 1994) and diminished activity in post traumatic stress disorder (Yehuda, 2009). So far, the DEX/CRH-test has not been performed in sleep disorders. Due to its high sensitivity we used this test to assess HPA-system functioning in the framework of a larger metabolic study in sleep disorders (Keckeis et al., 2010) including patients suffering from the obstructive sleep apnea syndrome, restless legs syndrome and primary insomnia and healthy controls.

2. Materials and methods

2.1. Participants

The study protocol was approved by the ethics committee of the Bavarian Medical Council, Munich, Germany. All subjects provided written informed consent prior to entering the study. Of 97 subjects investigated, 25 suffered from OSAS, 21 from primary insomnia, 18 from RLS and 33 were healthy controls. Subjects were recruited through advertisements in local newspapers. All subjects had normal findings on medical examination; they did not suffer from any psychiatric disorder and had a regular sleep-wake cycle. Pregnant women, shift workers, and persons who had travelled across multiple time zones within 3 months prior to the study were excluded. Similarly, subjects exhibiting other sleep disorders were excluded. All subjects showed normal results in numerous blood tests (see Keckeis et al., 2010). All subjects showed normal EEG findings during waking.

RLS patients met the diagnostic criteria defined by the International Restless Legs Syndrome Study Group (Allen et al., 2003) and did not suffer from any severe somatic condition such as polyneuropathy or secondary RLS. The severity of RLS was assessed using the International Restless Legs Syndrome Study Group Rating Scale (IRLS; Walters et al., 2003). In patients suffering from primary insomnia as well as in patients suffering from OSAS, diagnosis was based on the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2005). OSAS patients with an apnea-hypopnea-index (AHI) above 15 (moderate sleep apnea) were included. Controls did not suffer from any sleep disturbances, and sleep related breathing disorder was excluded (AHI $>$ 5) by an ambulatory sleep apnea screening (Weinmann Somnocheck, Hamburg, Germany).

2.2. Procedure and measurements

Subjects underwent a detailed check-up including a physical examination, anthropometric measurements, a survey of sleep history and a detailed medical and psychiatric interview including the Becks Depression Inventory (BDI; Beck et al., 1961), Hamilton Depression Scale (HAMD; Hamilton, 1960) and Hamilton Anxiety Scale (HAMA; Hamilton, 1959). In addition, sleep quality was evaluated by means of the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and daytime sleepiness using the Epworth Sleepiness Scale (ESS; Johns, 1991). To verify regular sleep-wake patterns, participants were asked to wear a wrist activity monitor (Cambridge Neurotechnology, Cambridge, UK; Actiwatch Activity Analysis, Version 5.06) for 8 days prior to the study. In all patients standard nocturnal polysomnography (PSG) was conducted for two nights. Polysomnographic recordings were performed from 23:00 to 06:00 h. Sleep stages were scored according to Rechtschaffen and Kales (1968). Sleep stages 3 and 4 were summed up to slow-wave sleep (SWS). Arousals (American Sleep Disorder Association, 1992) PLMS (American Sleep Disorders Association, 1993), and apneas/hypopneas were scored and the number of both PLMS and apneas/hypopneas per hour of total sleep time (PLMS-index and AHI, respectively) calculated. Additionally, we calculated the number of both PLMS and apneas/hypopneas associated with arousals (PLMS-arousal-index and apnea-arousal-index, respectively). Sleep stages and associated parameters were scored by two experienced scorers in each individual.

Ten days before the PSG nights took place subjects underwent the dexamethasone suppression/corticotropin-releasing-hormone stimulation test (DEX/CRH-test). The DEX/CRH-test is a dynamic test which combines suppression and stimulation of the HPA-system. At 23:00 subjects received 1.5 mg dexamethasone (Fortecortin, Merck Pharma GmbH, Darmstadt, Germany). On the following day, at 15:02, 100 μg human CRH (Ferring Inc., Kiel, Germany) reconstituted in 1 ml 0.02% HCl in 0.9% saline solution was infused within 30s. After hCRH infusion four blood samples were taken at 15:30; 15:45; 16:00 and at 16:15. Cortisol plasma concentrations were analysed using a radioimmunoassay kit with a coated tube technique. For ACTH measurements a dual antibody immunoradiometric assay without extraction was used. The baseline sample, which represents the suppressive effects of dexamethasone, was drawn at 15:00. It was used to identify non-suppressors, defined as subjects showing