

Dex/CRH-test response and sleep in depressed patients and healthy controls with and without vulnerability for affective disorders

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Abstract

Sleep electroencephalographic (EEG) abnormalities and increased hypothalamo–pituitary–adrenal (HPA) axis activity are the most prominent neurobiological findings in depression and were suggested as potential biomarker for depression. In particular, increased rapid eye movement sleep (REM) density, deficit in slow wave sleep and excessive stress hormone response are associated with an unfavorable long-term outcome of depression. Recent studies indicate that the sleep and endocrine parameters are related to each other. This study investigated the association of sleep structure including a quantitative EEG analysis with the results of the combined dexamethasone (Dex)/corticotropin-releasing hormone (CRH)-test in 14 patients with a severe major depression, 21 healthy probands with a positive family history of depression (HRPs) and 12 healthy control subjects without personal and family history for psychiatric disorders. As expected patients with depression showed an overactivity of the HPA axis, disturbed sleep continuity and prolonged latency until slow wave sleep in the first sleep cycle. Differences in microarchitecture of sleep were less prominent and restricted to a higher NonREM sigma power in the HRP group. Dexamethasone suppressed cortisol levels were positively associated with higher NonREM sigma power after merging the three groups. We also observed an inverse association between the ACTH response to the Dex/CRH-test and rapid eye movement sleep (REM) density in HRPs, with suggestive evidence also in patients, but not in controls. This contra-intuitive finding might be a result of the subject selection (unaffected HRPs, severely depressed patients) and the complementarity of the two markers. HRPs and patients with high disease vulnerability, indicated by an elevated REM density, seem to have a lower threshold until an actual disease process affecting the HPA axis translates into depression, and vice versa. To summarize, our findings provide further evidence that the HPA axis is involved in the sleep regulation in depression. These associations, however, are not unidimensional, but dependent on the kind of sleep parameters as well as on the selection of the subjects.

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1. Introduction

Disturbed sleep electroencephalographic (EEG) patterns are one of the most prominent neurobiological findings in depression and were suggested as potential biomarker for depression. In detail, slow wave sleep deficit in the first

sleep cycle, decreased sleep continuity, short latency to rapid eye movement (REM) sleep and increase in its phasic components, i.e., the density of the REMs, have been repeatedly described (Reynolds and Kupfer, 1987; Lauer et al., 1992; Steiger et al., 1989; Wichniak et al., 2000). Interestingly, phasic and tonic REM sleep parameters differ in their neurophysiological regulation and have been characterized as distinct functional substates within REM sleep (Holsboer-Trachslers et al., 1993; Quattrochi and Hobson, 1999; Wehrle et al., 2007). There is good evidence that phasic REM sleep parameters play a significant role in memory consolidation (Fogel et al., 2007) in particular with respect

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to avoidance task learning (Datta, 2000; Mavanji and Datta, 2003). The increase in REM density was demonstrated not only as one of the most significant and stable abnormalities of sleep in patients with depression but also in individuals who are at a high familial risk to develop the disease (high-risk probands, HRP; “Munich Vulnerability Study on Affective Disorders”). Therefore, this parameter has been suggested as vulnerability marker for affective disorders (Modell et al., 2002, 2005). In view of the ontogeny of REM sleep a deficit in postnatal REM sleep inhibition was proposed to account for the life-long REM sleep abnormalities in humans predisposed to the disease (Vogel et al., 2000). On the other hand, there is compelling evidence that the excessive increase in hypothalamo–pituitary–adrenal (HPA) axis activity is one of the most relevant endocrine abnormalities in depression resulting from an impaired corticosteroid receptor function as the key mechanism in the pathogenesis of the disease (Holsboer, 2000; DeKloet et al., 2005). The function of the HPA axis can be most sensitively assessed by the combined dexamethasone (Dex)/corticotropin-releasing hormone (CRH) test (Heuser et al., 1994). Recent studies on the course and treatment response suggest this test as a potential biomarker in depression (Ising et al., 2005a). HRPs for affective disorders demonstrated moderately abnormal hormone response in the Dex/CRH-test lying inbetween the levels of healthy controls and patients with depression (Holsboer et al., 1995; Modell et al., 1998), which, however, was not predictive for the development of an affective disorders in HRPs (Ising et al., 2005b).

Numerous studies revealed that both sleep and endocrine alterations are associated with an unfavorable long-term outcome of depression (Kupfer et al., 1993; Thase et al., 1998; Buysse et al., 1997; Clark et al., 2000; Zobel et al., 1999, 2001). In addition, a recent study by Hatzinger et al. (2004) found that sleep variables unfavorable for long-term outcome were related to excessive stress hormone response. It has been suggested that underlying mechanisms may affect both sleep regulation and long-term course of depression.

The aim of this study was to examine the association between the microstructure of sleep and stress hormone regulation. For this purpose, we analyzed the associations between spectral sleep EEG parameters and the neuroendocrine response to the Dex/CRH-test in patients suffering from Major Depression, in a subgroup of HRPs from the “Munich Vulnerability Study on Affective Disorders”, and in healthy control subjects without personal or familial history for psychiatric disorders.

2. Methods

2.1. Study samples

Twenty-one non-obese inpatients suffering from severe major depression (ICD10 F32.2, F33.2) who participated in a previous study investigating acute cortisol administra-

tion on sleep and growth hormone secretion were recruited (Schmid et al., 2008). Patients underwent a careful clinical evaluation to exclude concomitant severe somatic, neurological or endocrinological diseases or substance abuse. They were free of any psychotropic medication in 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. There was a total number of $n = 6$ drop-out cases ($n = 1$ diagnosed as rapid cycling, $n = 2$ withdrew consent, $n = 3$ refused to participate until the end of the protocol, $n = 1$ refused to participate in blood sampling). Due to technical reasons the sleep recordings of $n = 1$ patient in the baseline night could not be analyzed. Therefore, the data of $n = 14$ patients (8 men, 6 women; age $M = 47.2$, $SD = 11.6$; Hamilton Depression Rating Scale (HDRS), $M = 19.1$, $SD = 6.4$, ranging from 18 to 38) were examined with respect to sleep profile and HPA system function.

Additionally, 21 healthy subjects (high-risk probands, HRPs) with at least one first-degree relative suffering from an affective disorder participated, who were a subgroup of participants in the “Munich Vulnerability Study on Affective Disorders”. During two study periods of the “Munich Vulnerability Study on Affective Disorders” 740 psychiatric inpatients with a diagnosis of major depression, bipolar disorder, or “bipolar II” disorder (bipolar disorder not otherwise specified) were screened. We looked for patients who had at least one first-degree relative with an affective disorder or schizophrenia and at least one first-degree relative with no current of lifetime diagnosis of a psychiatric disorder, the latter verified by the Structured Clinical Interview for DSM-III-R (SCID I, German Version, Wittchen et al., 1990). This relative was then identified as HRP. The inclusion criteria mentioned above were fulfilled by 136 patients, and 50 patients of this group agreed to participate in the study (index patients). These patients led to 101 HRPs. Out of this group, quantitative analysis of sleep EEG was established in $n = 21$ HRPs (12 men, 9 women; age $M = 27.1$, $SD = 6.1$). These 21 HRPs belonged to 12 families. Thus, our study group consisted of several siblings since one family provided four HRPs, one family three HRPs, 4 families two HRPs, and 6 families one HRPs. None of the index patients or the HRPs participating in the “Munich Vulnerability Study on Affective Disorders” was related to the patients with depression examined in the present study.

The sleep–endocrine data of the HRPs and patients with depression were compared to the data of 12 healthy control subject without personal (SCID I) or family history (semi-structured clinical interview) of psychiatric disorders (CPs; 3 men, 9 women; age $M = 28.0$, $SD = 5.9$) recruited in the “Munich Vulnerability Study on Affective Disorders”.

2.2. Experimental Protocol

Before entering the study, patients, HRPs and CPs underwent extensive physical, psychiatric, and laboratory

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