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Sleep-endocrine effects of growth hormone-releasing hormone (GHRH) in patients with schizophrenia

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ABSTRACT

Changes in sleep-EEG after endocrine stimulation tests in patients with schizophrenia include reduced sleep efficiency, prolonged sleep latency and increased awaking after sleep onset Findings on sleep associated growth hormone (GH) secretion were ambiguous. The aim of this study was to elucidate the sleep-endocrine activity especially in the GH system of patients with schizophrenia after repeated administration of GHRH. The effect of repetitive injections of 4 × 50 µg GHRH between 22.00 and 01.00 h on sleep endocrine parameters was investigated in 9 patients diagnosed for schizophrenia. Patients did not receive any medication for one week. Concentrations of ACTH, cortisol, prolactin and GH were determined. Patients spent three consecutive nights in the sleep laboratory. Blood was taken every 20min. Results were compared with matched healthy controls.

A non-significant prolonged sleep onset latency and increased time awake was found in patients compared to controls. Sleep stage 2 was significantly reduced in patients. No significant difference in ACTH and cortisol was detected, whereas the GH secretion in patients following GHRH stimulation was significantly elevated compared to controls.

Our results in drug free patients confirm already known changes in sleep-EEG in these patients. The GH response to GHRH-stimulation indicates a different regulatory sensitivity of the system between daytime and night-time.

1. Introduction

The hormones growth hormone releasing hormone (GHRH) and corticotropin releasing hormone (CRH) play a key role in sleep regulation (Obal and Krueger, 2004; Steiger, 2007). Their balance is supposed to be disturbed in depression. We showed previously, that in young, male, normal subjects after repeated injection of 4 × 50 µg GHRH around sleep onset slow wave sleep (SWS) and growth hormone (GH) increased whereas cortisol decreased (Steiger et al., 1992). Similarly we found in male patients with depression a promotion of sleep after GHRH administration (Antonijevic et al., 2000).

Patients with schizophrenia show distinct changes in their sleep architecture. Former studies found a delayed sleep onset and an elevated sleep stage 1 in these patients (Kempenaers et al., 1988). Poulin et al. (2003) described in neuroleptic naive patients with schizophrenia compared to controls difficulties in sleep initiation, a decrease in stage 4 duration, shortened rapid eye movement (REM) sleep latency, normal sleep spindles and REM densities. Furthermore these authors found an association between sleep disturbances and positive symptoms. In their meta-analysis Chouinard et al. (2004) found reduced sleep efficiency, prolonged sleep latency and increased awaking after sleep onset to be mostly reported. Wilson and Argyropoulos (2012) discuss changes in circadian rhythm and sleep spindles to be associated to cognitive function in patients with schizophrenia. Only small knowledge exists about sleep-endocrine activity in schizophrenia. Growth hormone (GH) secretion is under complex control of various neurotransmitters as acetylcholine, norepinephrine, serotonin, and histamine stimulate GH secretion, whereas y-aminobutyric acid (GABA) and dopamine have

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inhibitory effects on GH (Peabody et al., 1990). Hints for a disturbance of the GH system have already been submitted by Vigneri et al. (1974), who found an impaired sleep related GH secretion in patients with schizophrenia, whereas Van Cauter et al. (1991) reported increased cortisol and prolactin and unchanged GH secretion during the night compared to normal controls. Belvederi Murri et al. (2012) reported the HPA axis activity to be associated with different clinical symptoms in patients with a first-episode psychosis. Several groups reported decreased GH response to stimulation with different dopaminergic substances and GHRH in patients with schizophrenia (Peabody et al., 1990; Ettigi et al., 1976; Rotrosen et al., 1976; Meltzer et al., 1984; Whalley et al., 1984; Brown et al., 1988).

The aim of our study was to elucidate sleep-endocrine activity in drug-free patients with schizophrenia after GHRH stimulation compared to healthy subjects.

2. Methods

2.1. Subjects

The effect of repetitive administration of 4 × 50 µg GHRH between 22.00 and 01.00 h on sleep-endocrine parameters in 9 in-patients with a diagnosed schizophrenia compared to healthy matched controls was investigated. 6 males (age 32.5 ± 9.3 years) and 3 females (age 31.0 ± 10.6 years) were enclosed into the study after a wash out period for any medication of 1 week. Only patients receiving medication with a short half-life period were enclosed. They were matched to 9 healthy controls 6 males (age 32.3 ± 8.6) and 3 females (age 30.1 ± 11.7). Mean BPRS was 54.5 ± 9.65. All patients and controls gave their written informed consent.

All subjects fulfilled the following Inclusion criteria: Medical history without major or chronic diseases (e.g. diabetes, heart failure, hepatitis etc.), patients had to be diagnosed with a schizophrenia according to ICD-10 and DSM-IV, control subjects were not allowed to have a history of previous psychiatric disorder, no chronic physical disorder, normal physical examination including a complete neurological examination, standard electrocardiogram (ECG), laboratory results, electroencephalogram (EEG) and a written informed consent.

Subjects with a personal or family history of sleep disorders, shift workers and persons who had made a transmeridian flight during the last 3 months were excluded. Abuse of drugs, or alcohol also resulted in exclusion as described in Murck et al. (2001).

2.2. Protocol

Subjects had to spend three nights in the sleep laboratory. The first night served for adaptation to the laboratory setting. Sleep-EEG was recorded between 23:00 and 07:00, and blood samples were collected by long catheter every 20 min for analysing ACTH, cortisol and GH between 22:00 and 07:00 during the 2nd and the 3rd night. During these nights between 22:00 and 01:00 hourly iv injections of physiological NaCl solution serving as placebo in the 2nd night and of 50 µg GHRH (Ferring, Kiel, Germany) in the 3rd night were injected. Electrodes were attached for recording the sleep EEG and spectral analysis at 21.00 h. Lights were switched off at 23.00 h. Sleeping was not permitted before this time. The examination ended at 07.00 h the next morning. The first examination period took place before initiation of neuroleptic treatment. Only chloralhydrate up to 1000 mg was allowed as concomitant medication, but not on the days of sleep-EEG investigation.

Polysomnographic sleep-EEG recordings consisted of two EEGs (C3-A2, C4-A1; time constant 0.3 s, low-pass filtering 70 Hz), vertical and horizontal electrooculograms (EOG), an electromyogram (EMG) and an electrocardiogram. EOG, EMG and EEG signals were filtered and transmitted by an optical fibre system to polygraph (Schwarzer, Munich, Germany), recording the sleep-EEG for visual scoring.

Sleep-EEG was visually scored for sleep stages I, II, III, IV and REM sleep according to the conventional criteria of Rechtschaffen and Kales (1968) by independent analysts who were blind to treatment.

The study was performed in accordance with the Declaration of Helsinki and with the “Note for Guidance on Good Clinical Practice for Studies on Medical Products in the European Community, July 11, 1990”. The study was approved by the ethical committee of the University of Munich.

2.3. Hormone analysis

Blood samples were centrifuged immediately and plasma was frozen at −20°C, GH (Advantage; Nichols Institute, San Juan Capistrano, Calif., USA; intra- and interassay coefficients of variation 10%) concentrations were determined by chemiluminescence. Plasma ACTH (Ria Kit J 125; Nichols Institute, San Juan Capistrano, Calif., USA; intra- and interassay coefficients of variation 8%) and cortisol (Ria Kit J 125; ICN Biomedicals, Carson, Calif., USA; intra- and interassay coefficients of variation 7%) and were measured by radioimmunoassay.

2.4. Statistical analysis

Differences in the sleep-EEG variables and hormone secretion between the baseline and nights during treatment were assessed for significance with the Wilcoxon paired-rank test (two-tailed). Endocrine parameters (22.00–07.00 h) were calculated by computing the area under the curve (AUC) according to the trapezoid rule for distinct intervals (Held et al., 2005).

3. Results

3.1. Sleep-EEG

Patients spent less time in sleep stage 2 than healthy subjects after

Table 1
Group difference sleep EEG.

Sleep parameters	Controls		Patients		Level of significance
	Placebo	GHRH	Placebo	GHRH	
Sleep onset latecy	32.2 ± 18.4	25.7 ± 18.6	58.2 ± 43.5	71.0 ± 83.5	n.s.
REM latency	84.2 ± 42.2	78.4 ± 33.3	77.2 ± 57.3	64.2 ± 13.6	n.s
Awake	24.4 ± 15.3	26.6 ± 14.2	49.1 ± 44.3	39.2 ± 29.1	n.s
REM	71.2 ± 19.7	80.3 ± 23.6	87.7 ± 27.8	89.2 ± 26.1	n.s
Sleep stage II	255.1 ± 36.4	258.6 ± 34.3	190.1 ± 19.8	199.2 ± 73.3	Placebo 0.000/ GHRH0.043
SWS	42.2 ± 34.1	36.2 ± 26.5	45.8 ± 34.1	40.5 ± 29.0	n.s
REM density	4.6 ± 1.7	4.4 ± 1.0	4.9 ± 2.1	5.3 ± 2.5	n.s

Values corresponding to TIB (23.00–07.00 h), mean ± SD, min.

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