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CSF-hypocretin-1 levels in patients with major depressive disorder compared to healthy controls

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ABSTRACT

Depressive patients exhibit symptoms of impaired regulation of wakefulness with hyperarousal and agitation as well as difficulties to falling asleep and preserving sleep continuity. Changes in hypocretin (hcrt) levels as polypeptides with impact on arousal and sleep–wake-regulation have been discussed in affective disorders but have not been investigated in patients with solely unipolar depression in comparison to healthy controls. In the present study, cerebrospinal fluid (CSF) levels of hcrt-1 for the first time were analyzed in patients with major depressive disorder (MDD) without psychiatric comorbidities and compared with levels in healthy controls. In 17 inpatients with MDD (mean Hamilton Depression Rating Scale 13.9 ± 7.4) and 10 healthy controls, CSF-hcrt-1 levels were measured using a fluorescence immunoassay (FIA). The mean hcrt-1 CSF levels in patients with MDD (74.3 ± 17.8 pg/ml) did not differ compared to that of healthy controls (82.8 ± 22.1 pg/ml). Hcrt-1 levels did not correlate with the severity of depressive episode, the symptoms of depression or the number of episodes. Although autonomic and neurohumoral signs of hyperarousal are common in MDD, hcrt-1 levels in CSF were not found to be altered in MDD compared to healthy controls. Whether hcrt-1 levels are altered in depressive patients exhibiting impaired vigilance regulation has to be investigated in further studies combining measures of CSF-hcrt-1 with electroencephalography.

1. Introduction

Hypocretins are polypeptides originating from the lateral hypothalamus (LH) and involved in arousal, opposition of the sleep drive and sleep–wake transition in humans (Nishino, 2007; Bonnavion and de Lecea, 2010; Sakurai et al., 2010). Hypocretin (hcrt) neurons have widespread projections to the entire neuroaxis (Carter et al., 2009) providing interactions throughout the central nervous system (CNS), among other means by activating the hypothalamic-pituitary-adrenal (HPA) axis (Kuru et al., 2000; Russell et al., 2001; Spinazzi et al., 2006). Disturbance of stress response with hyperactivity of the HPA axis is a thoroughly investigated finding in depression (Swaab et al., 2005). Another area of projection for hcrt is the locus coeruleus (LC), which is modulated by corticotrophin-releasing hormone (CRH) linking the stress-related activity of the HPA axis to LC activity (reviewed by Valentino and Van Bockstaele, 2008). Accordingly, the firing rate of the LC is broadly reflected in the firing rate of the hcrt-containing neurons of the LH (Hagan et al., 1999; Lee et al., 2005). Studies demonstrated a hyperactivity of the LC in depression (for references see West et al., 2010) with elevated cerebrospinal fluid (CSF)-levels of norepinephrine and changes in firing rates under antidepressant medication (West et al., 2009). Recent resting-state electroencephalography (EEG) studies showing smaller and delayed declines into lower vigilance stages under resting conditions (Hegerl et al., submitted) indicated a hyperstable vigilance regulation in patients with major depressive disorder (MDD) (Hegerl et al., 2009).

Characteristic clinical findings of patients with MDD such as hyperarousal and agitation, the effects of hcrt-1 on sleep–wake rhythmicity and arousal as well as the interactions of hcrt-1 with areas involved in stress response indicate a pathogenetic role of hcrt-1 in the disorder.

The aim of the study was to investigate exploratively CSF-hcrt-1 levels for the first time in patients with unipolar depression without comorbidities compared to controls without psychiatric or neurological disturbances. Within the MDD group CSF-hcrt-1 levels were compared between patients with mild, moderate and severe episodes. Moreover, associations between CSF-hcrt-1 levels and depressive symptoms such as sleep disturbances and agitation as indicated by the Hamilton Depression Rating Scale (HDRS) were investigated.

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2. Methods

2.1. Subjects

Between 2007 and 2009, we consecutively recruited subjects and included 17 patients with mild to severe depressive episodes (10 male, 7 female; mean age 51.3 ± 16.3 S.D.) and 10 healthy controls (4 male, 6 female; mean age 36.4 ± 11.8) in the study. The mean score on the 17-item HDRS (Hamilton, 1960) in the patient group was 13.9 ± 7.4. Patient's characteristics such as age, gender and psychotropic medication are depicted in Table 1. While 15 patients were suffering from a recurrent depressive disorder, two patients were suffering from a first depressive episode. All patients were admitted to hospital as inpatients. They provided formal consent for appropriation in this clinical study. Patients showing any indication of limitation to provide full consent were excluded from the study. Patients were diagnosed with a major depressive disorder by a senior specialist in psychiatry according to DSM IV criteria and only included when no psychiatric comorbidities and neurological disorders were diagnosed by clinical and laboratory investigation.

Healthy controls did not show any neurological or psychiatric disorder in clinical and laboratory investigation. All patients were admitted to hospital as inpatients. They provided formal consent to their inclusion in this clinical study. To standardize clinical investigation and to exclude any psychiatric symptomatology, cognitive impairment or dementia, the Structured Clinical Interview Axis I Disorder (SCID) and the neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) were performed. A neurological disorder was excluded by a specialist in neurology, Department of Neurology, University Hospital Leipzig. This study was approved by the Leipzig University Medical Ethics Committee.

2.2. Neuropeptide assays

After lumbar puncture performed between 00:30 pm and 01:30 pm, samples were immediately aliquoted in non-absorbing polypropylen-tubes of 300 µl. Probes were shock-frozen in fluid N2 of −80 °C and stored in freezers at −80 °C until further measurements. The storage time of the samples ranged from 12 to 21 months. CSF-hcrt-1 levels of five depressed patients and five healthy controls have been compared with levels of manic patients as described previously by our group (Schmidt et al., 2010).

For the measurement of hcrt-1 we used a fluorescence immunoassay (FIA) with a measuring range of 29.9–10000 pg/ml and a linear interval until approximately 400 pg/ml (Phoenix Pharmaceuticals, Burlingame, CA, US). The intra-assay coefficient of variation was found to be in average 5.4%. The measurements were performed by the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital of Leipzig.

2.3. Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS) program version 18.0 for Windows was used for all statistical analyses. The significance level was set at $p<0.05$ for all statistical analysis. *T* test was performed for mean differences of hcrt-1 in MDD and healthy groups as well as mean differences of hcrt-1 in gender explorations. *T*-test were performed to analyze mean differences in hcrt-1 levels and number of episodes, discriminating first and recurrent (≥2) episodes. One-way ANOVA and post-hoc Multiple Comparisons Scheffe's and Duncan's test were performed for mean differences of hcrt-1 in groups with differing severity of MDD episode. For bivariate correlation of hcrt-1 levels and scores HDRS, Body-mass index and age, two- tailed analyses were performed using Pearson's correlation.

3. Results

As shown in Fig. 1, mean hcrt-1 levels in CSF did not differ significantly between depressive patients (74.32 ± 17.81 pg/ml) and controls (82.82 ± 22.06 pg/ml) (*t* test, $p=0.28$). A sub-group analysis of sex- and age-matched depressive patients (4 male, 6 female; mean age 39.9 ± 9.28) compared to the control group showed no significant differences in mean hcrt-1 CSF levels (73.77 ± 18.46 pg/ml) (*t* test, $p=0.33$).

Analyses showed neither significant correlations between hcrt-1 and total scores on the HDRS on the day of puncture ($r=0.01$, $p=0.68$) (Fig. 2) nor specific items concerning sleep onset ($r=0.29$, $p=0.29$), sleep continuity ($r=0.01$, $p=0.98$), preterm awakening ($r=0.21$, $p=0.464$), work and activities ($r=0.11$, $p=0.71$) and agitation ($r=0.12$, $p=0.69$) (items 4–7, 9). The hcrt-1 levels did not differ within groups according to clinically diagnosed severity on the day of admission (mild = 67.35 pg/ml (S.D. = 2.41), moderate = 77.18 pg/ml (S.D. = 24.16), severe = 74.57 pg/ml (S.D. = 18.73); one-way ANOVA, $p=0.31$, Fig. 3) nor in the number of depressive episodes (first = 83.30 pg/ml (S.D. = 13.58); recurrent = 71.30 pg/ml (S.D. = 17.57); *t* test, $p=0.38$. Pearson's correlation analyses of age, sex, body mass index and hcrt-1 levels among patients and controls showed no significant correlations and did not appear to interfere with the results from above (data not shown).

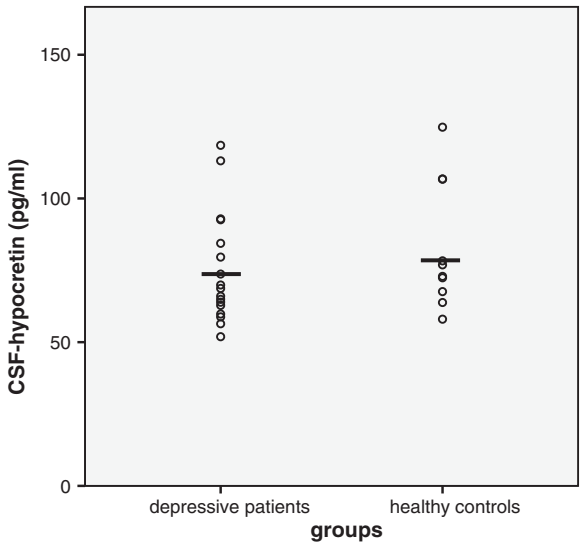

Fig. 1. Mean hypocretin-1 level (mean ± S.D.) in depressive patients was 74.32 ± 17.81 pg/ml; 82.82 ± 22.06 pg/ml in healthy controls.

Table 1
Subject characteristics.

	Major dipressive disorder (MDD)	Healthy controls
Number	17	10
Age (means ± S.D.)	51.3 (± 16.2)	36.4 (± 11.8)
Males	10	4
Females	7	6
Psychotropic medication	17	0
Tranquilizer	5	0
Antidepressants	17	0
Neuroleptics	5	0
Others	0	0

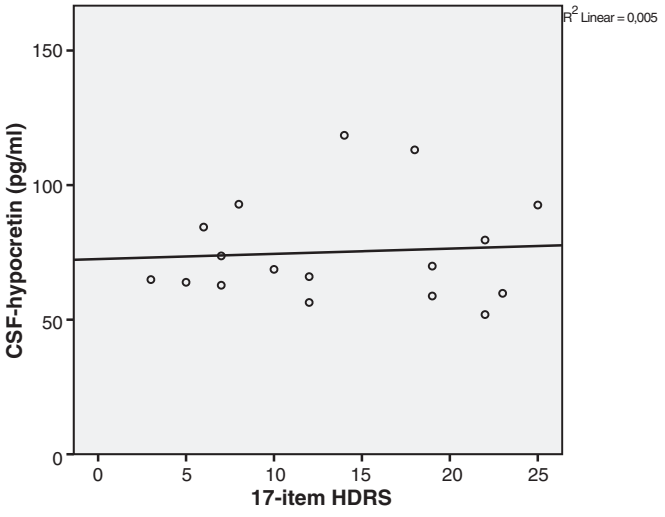

Fig. 2. Correlations between hcrt—levels and scores on the Hamilton Depressive Rating Scale (n.s.).