Brief report

Increased orexin levels in the cerebrospinal fluid the first year after a suicide attempt

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Abstract

Background: The orexins (hypocretins) and cocaine and amphetamine regulated transcript (CART) are hypothalamic peptides involved in the regulation of sleep and appetite. We have previously shown that levels of both orexin-A and CART in the cerebrospinal fluid (CSF) are related to specific psychiatric symptoms.

Methods: Ten patients took part in lumbar punctures and psychiatric evaluations in conjunction to a suicide attempt and after 6 and 12 months. We measured CSF-orexin and CART using radioimmunoassays.

Results: Mean CSF-orexin was significantly higher at the first and second follow-up than at the suicide attempt. In contrast, mean CSF-CART did not differ over time. Total SUAS scores, as well as ratings of CPRS item 66 (global illness) were significantly lower at follow-up. At one year, there was a significant negative correlation between the change in CSF-orexin and the change in total SUAS score.

Limitations: The number of patients who participated was relatively small.

Conclusions: Our results support the hypothesis that orexin is involved in psychiatric symptomatology.

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Keywords: Orexin; Hypocretin; Suicide; CART; Cerebrospinal fluid; Hypothalamus

1. Introduction

The orexins (A and B) are neuropeptides, secreted from the lateral hypothalamus, that have an important role in the regulation of wakefulness (de Lecea et al., 1998; Sakurai et al., 1998; Sakurai, 2007). Cocaine and amphetamine regulated transcript (CART) is another hypothalamic neuropeptide, which is also expressed in the nucleus accumbens and amygdala. It plays a role in addictive behaviour and anxiety, and has been suggested to be a novel target for treating depression (Kuhar and Dall Vechia, 1999; Pae et al., 2006).

We have previously found that suicide attempters with major depressive disorder (MDD) have lower CSF-orexin than other patient groups (Brundin et al., 2007a), and that low orexin is associated with severe symptoms of lassitude and decreased motor function. Furthermore, patients who were perceived as more globally ill by the responsible psychiatrists displayed the lowest CSF-orexin (Brundin et al., 2007b). In contrast, CSF-CART did not
differ between diagnostic groups. There was an association with ability to concentrate, but not with symptoms of depression or anxiety (Brundin et al., 2008).

In the current study, we measured CSF-levels of CART and orexin in patients who came for follow-up during the year after a suicide attempt. We hypothesized that CSF-orexin would increase with clinical improvement, as measured using the Suicide assessment scale (SUAS) and the Comprehensive psychiatric rating scale (CPRS). For CART, we hypothesized that there could be a change over time related to clinical improvement.

2. Methods

2.1. Overall design of the study

This study was approved by the Lund University Medical Ethics Committee. Patients admitted to Lund University Hospital after a suicide attempt between 1987 and 2001 were asked to participate. After a medication-free period of 14 days, a spinal tap and psychiatric evaluation took place. After completion of the first part of the study during hospitalization, ten patients agreed to participate in the follow-up. The first follow-up spinal tap occurred at a mean of six months (range four to ten) and the second at 12 months (11–13) after the suicide attempt. Five of the original ten patients chose to undergo lumbar puncture at the second follow-up. Some patients had started medication at follow-up and therefore blood samples were assayed for anxiolytic-, neuroleptic- and antidepressive drugs.

2.2. Patients

Patients consisted of four males and six females, 41 ± 9 years old (mean ± SD). They were diagnosed according to DSM-III-R (American Psychiatric Association, 1987) with MDD (DSM-code 296.20, n = 4), substance abuse (305.90, n = 2), dysthymia (300.40, n = 2), depressive syndrome (311.00, n = 1) and psychotic syndrome (298.90, n = 1). On the day of the lumbar puncture, patients were evaluated using SUAS (Stanley et al., 1986) and CPRS (Åsberg et al., 1978). SUAS is an interview-based scale, assessing suicidality, consisting of 20 items. CPRS is a 67 item-scale rating a broad spectrum of psychiatric symptoms.

2.3. CSF-neuropeptide assays

Lumbar punctures were performed as previously described (Brundin et al., 2007a), and samples stored in −80°. CSF-CART and orexin-A were measured using commercially available125I radioimmunoassay (RIA) kits (CART 55–102 and orexin-A; Phoenix Pharmaceuticals, Belmont, CA, USA). Duplicate samples were assayed and levels were determined against a known standard.

2.4. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) program version 13.00 for Windows was used. One-tailed, paired T-tests were used to detect differences in CSF-orexin levels between the suicide attempt and the follow-up occasions. For analyses of pairwise differences in CSF-CART two-tailed Wilcoxon matched pairs signed rank sum tests were used. Psychiatric ratings were compared using one-tailed Wilcoxon matched pairs signed rank sum tests. Analyses of correlation were performed using Spearman’s rho.

3. Results

3.1. Neuropeptide levels

CSF-orexin increased significantly between the suicide attempt and the first follow-up, from 161.3 ±

<table>
<thead>
<tr>
<th>Variable</th>
<th>Suicide attempt n = 10</th>
<th>1st follow-up n = 10</th>
<th>Statistical significance</th>
<th>2nd follow-up n = 5</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF-Orexin pg/ml</td>
<td>161.3 (±19)</td>
<td>182.6 (±30)</td>
<td>p=0.021*</td>
<td>183.3 pg/ml (±19)</td>
<td>p=0.026*</td>
</tr>
<tr>
<td>CSF-CART pg/ml</td>
<td>575 pg/ml (2892)</td>
<td>541 pg/ml (398)</td>
<td>NS</td>
<td>540 pg/ml (579)</td>
<td>NS</td>
</tr>
<tr>
<td>SUAS</td>
<td>26 (42)</td>
<td>20.5 (36)</td>
<td>p=0.031*</td>
<td>14 (45)</td>
<td>p=0.031*</td>
</tr>
<tr>
<td>CPRS 66</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>z=−1.9</td>
<td>0 (2)</td>
<td>z=−2.0</td>
</tr>
<tr>
<td>CPRS</td>
<td>18.5 (21)</td>
<td>15.5 (31)</td>
<td>z=−1.9</td>
<td>13.5 (32.5)</td>
<td>NS</td>
</tr>
<tr>
<td>HS</td>
<td>15.5 (17)</td>
<td>12 (19)</td>
<td>NS</td>
<td>7 (19)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The rating scales were the Suicide assessment scale (SUAS), the comprehensive psychiatric rating scale (CPRS) and Beck hopelessness scale (HS). CPRS item 66 is the rating of global illness. The statistical significance values are based on the pairwise comparisons between the suicide attempt and the first follow-up and between the suicide attempt and the second follow-up. NS = non significant. * Statistical significance.
19.0 pg/ml to 182.6±30.0 pg/ml (p=0.021, paired T-test, ±1SD, n=10) (Table 1). Orexin was higher in all patients but one, and the mean pairwise increase was 28.5±9.0 pg/ml (Table 2). At the second follow-up after one year, mean CSF-orexin was still significantly higher than at the suicide attempt, 183.3±19.0 pg/ml (p=0.026, paired T-test, ±1SD, n=5). Four patients had begun antidepressive medication at the follow-up. Mean change in CSF-orexin in patients receiving the respective drugs are shown in Table 2.

There was no difference in CSF-CART between the suicide attempt and the first follow-up (NS, Wilcoxon signed ranks test, n=10) (Table 1). One patient with main diagnosis psychotic syndrome (DSM-code 298.90) had an extremely high CART value at the suicide attempt, 3352 pg/ml. In total, CART levels had increased in three patients and decreased in seven patients at the first follow-up. Neither at one year could any significant changes in CSF-CART be detected (n=5).

3.2. Psychiatric symptoms

The SUAS scores decreased significantly between the suicide attempt and the first follow-up (exact p=0.03, Z=-1.9, Wilcoxon signed ranks test, n=10) (Table 1), indicative of a clinical improvement. SUAS scores were also significantly lower at the second follow-up than at the initial suicide attempt (exact p=0.03, Z=-2.0, n=5). The total CPRS-scores displayed a non-significant trend towards a decrease both at the first and the second follow-up (NS, Wilcoxon signed ranks tests) (Table 1).

We also analyzed changes in ratings of four individual CPRS items, based on our previous observations (Brundin et al., 2007b). Wilcoxon signed ranks test did not detect any significant changes in CPRS item 14 (fatigue), 15 (lassitude) or 60 (slowness of movement) either at the first or second follow-up. For CPRS item no 66 (global rating of illness), scores were significantly lower at both the first and the second follow-up than at the suicide attempt (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>No of patients</th>
<th>Change in CSF-orexin pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>10</td>
<td>29 (±9)</td>
</tr>
<tr>
<td>No treatment</td>
<td>3</td>
<td>29 (±20)</td>
</tr>
<tr>
<td>Tranquilizer</td>
<td>3</td>
<td>35 (±10)</td>
</tr>
<tr>
<td>Antidepressive drug</td>
<td>3</td>
<td>24 (±11)</td>
</tr>
<tr>
<td>Triple-drug regimen</td>
<td>1</td>
<td>-51</td>
</tr>
</tbody>
</table>

We also investigated the relationship between the pairwise changes in orexin and CART levels and the pairwise change in total CPRS and SUAS scores at the follow-up occasions compared with the suicide attempt. There was a significant correlation between the magnitude of change in total SUAS and CSF-orexin at one year (p=0.019, Spearman’s rho -0.9, n=5) (data not shown).

4. Discussion

We show that CSF-orexin increases significantly during the first year after a suicide attempt. The increase in orexin was accompanied by an improvement (reduction) of the SUAS scores. It is not possible using the current experimental setting to determine whether this relationship is direct or indirect. However, the fact that we found a strong correlation between the magnitude of change in CSF-orexin levels and SUAS scores support the hypothesis that there may be a causative relation between these two parameters. As for CSF-CART, we did not find any evidence for a role in suicidal or depressive symptomatology.

A limitation of this study is the small number of subjects (ten). In previous studies, we found that CSF-orexin levels correlated significantly with specific psychiatric symptoms such as lassitude and motor function (Brundin et al., 2007b). The fact that these parameters did not fall out significant in the current study may be due to the smaller sample size. Furthermore, the number of patients in the group receiving antidepressive medication was too small for any conclusions to be drawn regarding its effect on CSF-orexin.

Other groups have investigated orexin levels in different groups of psychiatric patients. Salomon et al (2003) found a reduced diurnal orexin variation in depressed patients. In that study, which excluded suicidal patients, there was no relation between orexin levels and clinical improvement of the patients. CSF-orexin has also been analyzed in schizophrenic patients. No difference was found between patients and controls, although the orexin level was related to sleep latency in the schizophrenic patients (Nishino et al., 2002). Furthermore, CSF-orexin was significantly lower in patients treated with haloperidol compared to unmedicated subjects (Dalal et al., 2003). Taken together, the studies suggest that CSF-orexin levels may be related to individual symptoms and features of several psychiatric disorders.

Patients with MDD often display an activated hypothalamic–pituitary adrenal (HPA) axis (Bao et al., 2008). Studies investigating suicide attempters are less
Role of funding source

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Conflict of interest

All authors of the paper declare that they have no conflict of interest.

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References


Abundant, although reduced levels of e.g. corticotropin releasing hormone (CRH) in CSF has been reported (Geracioti et al., 1992; Träskman-Bendz et al., 1992; Westrin et al., 1999). The results in our current study are in line with our previous findings that low orexin is related to depressive symptoms and with low CRH levels in suicide attempters (Brundin et al., 2007a,b). We therefore find it likely that a process involving changes in CSF-orexin and other hypothalamic peptides plays a role in the generation of specific psychiatric symptoms. As orexin levels had increased significantly at the first follow-up consultation after the suicide attempt, we speculate that this reflects a recovery of a previously overstressed hypothalamus.