Brief report

Lower cerebrospinal fluid homovanillic acid levels in depressed suicide attempters

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Abstract

Background: Studies suggest that the dopaminergic system is involved in the pathogenesis of major depression, Axis II disorders, and suicidal behavior. Depressed suicide attempters constitute a heterogenous group and important differences may exist between depressed suicide attempters with or without Axis II disorders. Therefore, we compared demographic and clinical parameters, and cerebrospinal fluid (CSF) homovanillic acid (HVA) levels in depressed suicide attempters without comorbid Axis II disorders, depressed non-attempters without comorbid Axis II disorders, and normal controls.

Methods: Thirty-one depressed subjects with a history of a suicide attempt, 27 depressed subjects without a history of a suicide attempt, and 50 healthy controls were included in the study. Subjects with comorbid Axis II disorders were excluded. Demographic and clinical parameters, and CSF HVA levels were examined.

Results: The two depressed groups did not differ with regard to depression, aggression, hopelessness, and total hostility scale scores. Depressed suicide attempters had higher current suicidal ideation scores compared to depressed non-attempters. Depressed suicide attempters had lower CSF HVA levels compared to depressed non-attempters (t = 4.4, df = 56, p < 0.0001) and to controls (t = −4.09, df = 79, p < 0.0001). There was no difference in CSF HVA levels between depressed non-attempters and controls (t < 1, df = 75, NS).

Conclusions: Dopaminergic abnormalities are associated with suicidality but not with depression. The variability in the rates of comorbid Axis II disorders and in the prevalence of suicide attempters in different patient populations may affect both clinical and biological results of studies of mood disorders.

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1. Introduction

Low serotonergic activity is associated with suicidal behavior independently of psychiatric diagnosis (Mann, 2003; Sher and Mann, 2003). A possible role of altered dopaminergic function in suicidal behavior independently of depression has not been extensively studied.
Cerebrospinal fluid (CSF) homovanillic acid (HVA), a metabolite of dopamine, reflects functional activity of the dopamine-containing neurons localized mainly in the substantia nigra pars compacta, the ventral tegmental area and the hypothalamus (Papeschi et al., 1971; Stanley et al., 1985; Blennow et al., 1993). The majority of dopamine cells, which synthesize approximately three-fourth of all of the dopamine in the brain, are located in the anterior midbrain or mesencephalon (Melchitzky et al., 2000). Whereas 5-hydroxyindolacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) concentrations in lumbar CSF are thought to include some contributions from spinal cord and peripheral nervous system sources, lumbar CSF HVA exclusively reflects brain metabolism of dopamine (Post and Goodwin, 1978). It is important to note, however, that the results of CSF HVA studies may be affected by some non-specific factors such as the motor activity of the patient or the size of the sample (Asberg et al., 1984; Degrell and Nagy, 1990).

An association between CSF HVA levels and suicidality was found by Traskman et al. (1981), Montgomery and Montgomery (1982), Agren (1983), Roy et al. (1986), Roy et al. (1989), Jones et al. (1990), Engström et al. (1999) but not by Berrettini et al. (1986) and Cremniter et al. (1999). Post-mortem studies of suicides have also provided conflicting results reporting higher HVA concentrations in the hippocampus (Crow et al., 1984) and prefrontal cortex (Ohmori et al., 1992), lower dihydroxyphenylacetic acid (DOPA) in the basal ganglia (Bowden et al., 1997) and no change in cortex (Crow et al., 1984; Arranz et al., 1997).

The dopaminergic system also plays a role in the neurobiology of Axis II disorders. Dopamine abnormalities are reported in borderline personality disorder (Schulz et al., 1985; Szegethy and Schulz, 1997; Coccaro, 1998; Chotai et al., 1998; Chengappa et al., 1999; Rocca et al., 2002; Friedel, 2004), antisocial traits (Gabel et al., 1995; van Goozen et al., 1999; Vanyukov et al., 2000; Soderstrom et al., 2001; Gerra et al., 2003) and schizoid personality disorder (Blum et al., 1997; Rosmond et al., 2001), schizotypal personality disorder (Siever et al., 1991, 1993; Siever and Davis, 2004; Abi-Dargham et al., 2004), and paranoid personality disorder (Rosmond et al., 2001).

Depressed suicide attempters frequently have comorbid Axis II disorders. Including both Axis II and non-Axis II subjects in prior studies could obscure the relationship between dopamine and suicidal behavior in patients with major depression. Indeed, depressed suicide attempters constitute a heterogeneous group and important differences may exist in attempt behavior between depressed suicide attempters with or without Axis II disorders. Therefore, to determine the relationship of dopaminergic function to major depression and to suicidal behavior, we compared CSF HVA levels in depressed suicide attempters without comorbid Axis II disorders, depressed non-attempters without comorbid Axis II disorders, and normal controls.

2. Methods

2.1. Subjects

Thirty-one depressed subjects with a history of a suicide attempt, 27 depressed subjects without a history of a suicide attempt, and 50 healthy controls participated in the study after giving written informed consent. The study was approved by the Institutional Review Board. All patients had a DSM-III-R diagnosis of major depressive disorder. Exclusion criteria included presence of any Axis II disorders; current substance use disorders; a cognitive disorder which interfered with the patient’s ability to answer clinician-administered and self report rating scales; a history of head trauma resulting in coma; and more than mild mental retardation. The depressed subjects were divided into two groups according to the presence or absence of a history of a suicide attempt. A suicide attempt was defined as a self-destructive act committed with some intent to end one’s life.

2.2. Diagnostic assessment

Patients were assigned DSM-III-R diagnoses following a structured clinical interview. Interrater reliability for the primary diagnosis was high (κ = 0.90). Current severity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Beck Depression Inventory (BDI) (Beck et al., 1961). Lifetime aggression was assessed with the Brown–Goodwin Aggression History Scale (Brown and Goodwin, 1986). Hostility was rated on the Buss–Durkee Hostility Inventory (Buss and Durkee et al., 1957), which includes subscales of assault, irritability, resentment, indirect hostility, negativism, suspiciousness, verbal hostility, and guilt. Current hopelessness was measured with the Beck Hopelessness Scale (Beck et al., 1974a). A lifetime history of all suicide attempts was recorded. The degree of suicide intent at the time of the most lethal suicide attempt was rated with the Suicide Intent Scale (Beck et al., 1974b). The Scale for Suicide Ideation (Beck et al., 1979) was used to measure the severity of suicidal ideation during the week prior to index hospitalization. The Recent Life
Changes Questionnaire was used to document and quantify events in the two years prior to assessment (Rahe, 1975). Psychometric evaluation also included the Brief Psychiatric Rating Scale (Overall and Gorham, 1962).

2.3. Lumbar puncture

The lumbar puncture was performed between 8:00 a.m. and 10:00 a.m., following a night of supervised bed rest and a fast of at least 8 h. Before the lumbar puncture, patients were in bed in a prone position. The lumbar puncture was carried out under sterile conditions by a research psychiatrist using a fine-gauge (20 G) spinal needle, with the patient lying in a left lateral knee–chest position. CSF samples were obtained from the space between the third and fourth lumbar vertebrae. Eighteen milliliters of CSF were collected in three aliquots of 2, 15, and 1 ml. The 15-ml aliquot was centrifuged (750 \( \times g \) for 5 min) and divided into 1-ml aliquots. All aliquots were stored at \(-80^\circ C\) until assayed. CSF HV A was assayed by high-performance liquid chromatography with electrochemical detection (Scheinin et al., 1983).

2.4. Data analysis

The three groups were compared on demographic parameters using Analysis of Variance and Chi-square Analysis, as appropriate. The CSF HVA levels in the three groups were compared using Analysis of Variance. The two depressed groups were compared on psychiatric measures using two-tailed Student’s \( t \)-tests for continuous variables, and Chi-square Analysis for categorical variables. In addition, correlations were computed to examine relationships between psychiatric measures and CSF HVA levels. These data were collected in 1985–2000. These analyses have not been published before.

3. Results

Demographic and clinical characteristics of subjects in the three groups are presented in Tables 1 and 2. No

<p>| Table 1 | Demographic characteristics of controls and depressed groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Variable name</th>
<th>Healthy volunteers ((n=50))</th>
<th>Depressed subjects without a history of a suicide attempt ((n=27))</th>
<th>Depressed subjects with a history of a suicide attempt ((n=31))</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean or ((N)) SD or (%)</td>
<td>Mean or ((N)) SD or (%)</td>
<td>Mean or ((N)) SD or (%)</td>
<td>(F/\chi^2) df (P)</td>
</tr>
<tr>
<td>Gender (% males)</td>
<td>38.2 18.3</td>
<td>43.5 15.4</td>
<td>41.3 14.6</td>
<td>0.9 2 n.s.</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>25 (50%)</td>
<td>13 (48%)</td>
<td>15 (48%)</td>
<td>0.2 2 n.s.</td>
</tr>
<tr>
<td>Marital status (% married)</td>
<td>18 (53%)</td>
<td>18 (75%)</td>
<td>22 (71%)</td>
<td>8.5 2 n.s.</td>
</tr>
<tr>
<td>Education (% some college or more)</td>
<td>29 (85%)</td>
<td>12 (52%)</td>
<td>17 (55%)</td>
<td>9.3 2 0.01*</td>
</tr>
</tbody>
</table>

* Healthy volunteers are different from depressed subjects without a history of suicide attempt and depressed subjects with a history of suicide attempt at \(p<0.05\).

<p>| Table 2 | Clinical characteristics of depressed subjects with or without a history of a suicide attempt |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Measure</th>
<th>Depressed subjects without a history of a suicide attempt ((n=27))</th>
<th>Depressed subjects with a history of a suicide attempt ((n=31))</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous psychiatric hospitalizations</td>
<td>1.0 2.2</td>
<td>2.2 3.4</td>
<td>(-1.4) 50 n.s.</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>22.9 9.2</td>
<td>26.2 10.3</td>
<td>(-1.2) 52 n.s.</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>23.3 11.2</td>
<td>21.1 10.8</td>
<td>0.5 25 n.s.</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale</td>
<td>39.8 7.2</td>
<td>39.2 9.2</td>
<td>0.3 45 n.s.</td>
</tr>
<tr>
<td>Aggression History Scale</td>
<td>15.3 4.5</td>
<td>16.2 4.1</td>
<td>(-0.7) 47 n.s.</td>
</tr>
<tr>
<td>Buss–Durke Hostility Scale</td>
<td>30.6 11.5</td>
<td>35.7 12.1</td>
<td>(-1.5) 46 n.s.</td>
</tr>
<tr>
<td>Beck Hopelessness Scale</td>
<td>7.3 6.0</td>
<td>8.9 6.3</td>
<td>(-0.9) 45 n.s.</td>
</tr>
<tr>
<td>Suicide Ideation Scale</td>
<td>N/A 4.8</td>
<td>12.8 10.8</td>
<td>(-3.5) 45 0.001</td>
</tr>
<tr>
<td>Suicide Intent Scale</td>
<td>N/A 17.8</td>
<td>16.5 N/A N/A N/A</td>
<td></td>
</tr>
<tr>
<td>Life changes 0–6 months</td>
<td>3.4 4.0</td>
<td>3.7 3.6</td>
<td>(-0.2) 33 n.s.</td>
</tr>
</tbody>
</table>
Table 3

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (pmol/ml)</th>
<th>SD</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>50</td>
<td>196.9</td>
<td>76.3</td>
<td>10.02, 2 &lt;0.0001*</td>
</tr>
<tr>
<td>Depressed subjects without a history of a suicide attempt</td>
<td>27</td>
<td>210.7</td>
<td>86.1</td>
<td></td>
</tr>
<tr>
<td>Depressed subjects with a history of a suicide attempt</td>
<td>31</td>
<td>133.4</td>
<td>50.9</td>
<td></td>
</tr>
</tbody>
</table>

* Depressed subjects with a history of suicide attempt are different from depressed subjects without a history of suicide attempt and healthy volunteers at p<0.0001.

Our results may help to clarify the inconsistent findings regarding suicidal behavior and CSF HVA and underscore the importance of taking Axis II diagnosis into account in biological studies. Our findings are in agreement with several previous studies. Indeed, Traskman et al. (1981) found lower levels of CSF HVA in patients with a history of either violent or nonviolent suicide attempts than in normal controls. Roy et al. (1986) and Jones et al. (1990) found that depressed suicide attempters had lower CSF HVA levels compared to depressed non-attempters. Lower levels of CSF HVA have been found in depressed patients with a history of either violent or nonviolent suicide attempts than in controls (Engström et al., 1999). Other studies that did not find an association between CSF HVA and suicidal behavior (Berrettini et al., 1986; Creminiter et al., 1999) may have included Axis II diagnosis which may have an independent association with the dopaminergic system and, thus, have obscured the potential findings.

In a 5-year longitudinal study, Roy et al. (1989) observed that patients who reattempted suicide during the follow-up had lower CSF HVA levels compared to controls. This predictive value of low CSF HVA concentrations has been confirmed in another longitudinal study over a period of 2 years (Träskman-Bendz et al., 1993). Montgomery and Montgomery (1982) and Agren (1983) also showed a highly significant relationship between low CSF HVA levels and suicidal behavior. According to Montgomery and Montgomery (1982) and Agren (1983), who studied both CSF HVA and 5-HIAA in depressed patients, low CSF HVA levels could be a more reliable index of suicidal behavior than low CSF 5-HIAA concentrations. Roy et al. (1986) also lend support to the hypothesis that low CSF HVA levels could be a more potent predictive index of suicide than low CSF 5-HIAA concentrations.

Several studies using measures other than CSF HVA have also implicated the dopaminergic system in suicidal behavior. The growth hormone (GH) response to apomorphine, a selective dopaminergic agonist, in depressed patients with a history of suicide attempts is low compared to patients who never attempted suicide (Pitchot et al., 1992; Pitchot et al., 2001; Pitchot et al., 2003). Bergquist et al. (2002) found high CSF DA-IgG in suicide attempters compared with control subjects undergoing neurological investigation. This result indicates that an autoimmune mechanism may affect the dopaminergic neurotransmitter system and may play a role in the pathophysiology of suicidal behavior. Subsets of gamma-aminobutyric acid interneurons and pyramidal glutamatergic neurons in the prefrontal cortex

differences were found in age, gender, ethnicity, and marital status. Healthy volunteers were more educated than depressed patients in the both groups.

There was no difference between the two depressed groups with regard to Hamilton Depression Rating Scale, Beck Depression Inventory, Brief Psychiatric Rating Scale, Aggression History Scale, Buss–Durke Hostility Scale, Beck Hopelessness Scale, and Recent Life Changes Questionnaire scores, and number of previous psychiatric hospitalizations (Table 2). Depressed suicide attempters had higher current suicide ideation score compared to non-attempters (Table 2), and higher hostility subscales scores on negativism (2.7 ± 1.6 vs. 1.7 ± 1.6, t = –2.3, df=46, p<0.03) and guilt (5.6 ± 2.4 vs. 3.2 ± 1.8, t = –3.8, df=46, p<0.0001) compared with depressed non-attempters. Psychiatric measures did not correlate with CSF HVA levels (data not shown).

Depressed suicide attempters had lower CSF HVA compared with depressed non-attempters and controls (Table 3). There was no difference in CSF HVA levels between depressed non-attempters and controls. We found no correlations between CSF HVA levels and the number of previous suicide attempts (data not shown).

4. Discussion

Depressed suicide attempters without Axis II disorders have lower CSF HVA levels compared to depressed non-attempters without Axis II disorders and healthy controls. Depressed nonattempters have CSF HVA levels comparable to healthy controls. These results suggest that the dopaminergic system is involved in the pathophysiology of the diathesis for suicidality but not in the mood disorder in major depression.
which receives significant dopaminergic input, contain cholecystokinin. Cholecystokinin mRNA levels are elevated in the prefrontal cortex in suicide victims (Bachus et al., 1997).

We observed no significant difference in CSF HVA levels between depressed non-attempters and controls which is consistent with findings by Koslow et al. (1983) and Westenberg and Verhoeven (1988). Vestergaard et al. (1978) reported higher and Reddy et al. (1992) reported lower CSF HVA levels in depressed patients compared to controls. Possibly, the variability in the rates of comorbid Axis II disorders and prevalence of suicide attempters in different patient populations play a role in the inconsistency of findings regarding CSF HVA levels in depressed subjects.

Studies have demonstrated that the dopamine metabolite HVA and the serotonin metabolite 5-HIAA are correlated in human CSF (Reddy et al., 1992; Sher et al., 2003, 2005; Stuerenburg et al., 2004). Therefore, 5-HIAA data from the same patients might have reflected the same association with suicidal behavior, independent of the diagnosis of depression.

CSF HVA appears to be a biologic marker of suicidal behavior in depressed patients. Axis II diagnoses having dopaminergic abnormalities may obscure relationships of the dopaminergic system to other frequently comorbid psychopathologies such as mood disorders and suicidal behavior.

Future studies of dopaminergic function in depression and suicidal behavior should include neuroimaging techniques. Functional imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) can provide more valuable information than CSF HVA measurements and significantly help in understanding the pathophysiology of mood disorders and suicide. These techniques can also provide a better understanding of the effects of different treatments.

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