Impulsivity related to brain serotonin transporter binding capacity in suicide attempters

Mats B. Lindström a,*, Erik Ryding b, Peter Bosson a, Jan-Anders Ahnlide b, Ingmar Rosén b, Lil Träskman-Bendz a

*Section of Psychiatry, Department of Clinical Neuroscience, University Hospital of Lund, SE 221 85 Lund, Sweden
bSection of Clinical Neurophysiology, Department of Clinical Neuroscience, University Hospital of Lund, Lund, Sweden

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Abstract

Altered monoaminergic activity has earlier been associated with violent suicidal behaviour. In this study whole brain binding potential of the serotonin transporter (5HTT) and dopamine transporter (DAT) was measured by single photon emission computerised tomography (SPECT) in 12 patients after a serious suicide attempt and in 12 age, sex and season matched healthy controls. Clinical and temperamental assessments were analysed for possible associations with 5HTT and DAT.

We found no significant 5HTT or DAT differences between patients and controls. In patients, but not in controls, there was a significant correlation between whole brain 5HTT and DAT. Impulsiveness according to the Marke Nyman Temperament (MNT) was significantly correlated to 5HTT in suicide attempters, but not in controls.

Neither of the transporters could be regarded as a marker for serious suicidal behaviour. A previously discussed connection between serotonin and dopamine was replicated in this study. In suicide attempters, low 5HTT was associated with impulsivity and to some extent with depressive disorder—key factors for suicidal behaviour.

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1. Introduction

Many studies of different body fluids of patients and controls have shown that impulsive violent and suicidal behaviour is associated with central serotonin and/or dopamine deficits.

The findings have so far been mainly in depressed patients or in patients with alcoholism (for an overview, see e.g. Träskman-Bendz and Mann, 2000).

The monoamine systems are to a large extent interconnected and modulate each other. An early study by Ågren et al. (1986) showed a significant correlation between the serotonin and dopamine metabolites in lumbar cerebrospinal fluid, which was replicated by ourselves in suicide attempt patients (Engström et al., 1999). The CSF metabolite correlations prompted Roy et al. (1986) to use the ratios of the monoamine metabolites homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA) in their calculations of cerebrospinal fluid findings, rather than each metabolite per se. The Agren et al. (1986) findings were mainly explained by a functional serotonergic influence on dopamine turnover. Similar theories on variations of interdependencies between serotonin and catecholamines during depression and recovery have been put forward by Geracioti et al. (1997).

Recently developed brain imaging techniques have the advantage of offering studies of central monoamine metabolism in vivo.

Audenart et al. (2001) studied serotonin-2a (5HT-2a)-receptors of male deliberate self-harm patients and healthy controls by use of single photon emission computed tomography (SPECT). They found an age-dependent 5HT-2a binding index. After correction for age the most prominent decrease of frontal 5HT-2a binding was found in patients who attempted suicide by violent means.

SPECT can also be used to study monoamine transporters by use of the cocaine analogue 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane, labelled with 123-iodine, (123I-β-...
CIT) (Laruelle et al., 1994). In a Finnish study, brain monoamine transporters were studied in this way in impulsive violent individuals (Tiihonen et al., 1997). The analysis then showed that the serotonin transporter (5HTT) density in the midbrain of violent offenders was significantly lower than that in the healthy control subjects or the non-violent alcoholics. Reduced hypothalamic and thalamic 5HTT availability was found in bulimia patients by another research group (Tauscher et al., 2001). 123I-β-CIT SPECT has also been studied in drug-free depressed patients with (Willeit et al., 2000) or without (Laasonen-Balk et al., 1999; Malison et al., 1998) seasonal affective disorder (SAD). The results of these studies showed that both non-SAD patients and SAD-patients had significantly lower 123I-β-CIT binding (here reflecting availability of the 5HTT) in thalamus–hypothalamus or in brainstem than in healthy subjects, while the β-CIT uptake [in this case reflecting the dopamine transporter (DAT)] was significantly higher on both sides of the basal ganglia in non-SAD patients than healthy controls. A study of depressive drug-naïve children and adolescents showed that they had significantly higher 5HTT availability in the hypothalamic/midbrain area than non-depressed subjects (Dahlstrom et al., 2000). A reduced brain 5HTT availability was seen in healthy controls during winter as compared to the summer season (Neumeister et al., 2001).

The aim of the present study was to study brain serotonin and dopamine transporters of suicide attempters, not exposed to antidepressants or antipsychotics during 6 months before the attempt, in vivo. We expected to find a reduced 5HTT (reflecting a changed serotonin activity), especially in violent suicide attempters, and possibly a significant association between DAT and/or 5HTT and depressive disorder.

2. Experimental procedures

2.1. Subjects

The patients were recruited from the medical emergency room after having been admitted after a suicide attempt. The pace of the study was very slow, as the subjects were supposed not to have taken antidepressants or antipsychotic drugs at any time during a period of 6 months or less before, or at the suicide attempt. Screening for plasma-levels of psychotropic drugs was performed on the same day as the SPECT-study and was found to be blank.

The patients were also rated according to the Suicidal Intent Scale (Beck et al., 1974) by an independent consultant psychiatrist. Patients who were rated 18 or more were included in the study.

For each patient an age-, gender- and season of the year matched healthy person was recruited, mainly from hospital staff.

The method of suicide attempt was noted as well as potential previous suicide attempts. Immediately prior to the SPECT, the patients were diagnosed according to the International Classification of Diseases, 10th version (ICD 10, World Health Organisation, 1993), which was transformed into the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV; American Psychiatric Association, 1994).

Both patients and controls filled in the Marke Nyman Temperament (MNT) scale (Engström et al., 1996a,b), based on the Sjöbring theories of solidity, stability and validity (Sjöbring, 1973).

The study was approved by the Lund Medical Faculty Ethics Committee.

2.2. 123I-β-CIT SPECT

123I-β-CIT is a potent ligand for both dopamine and serotonin reuptake sites, and it can be used for SPECT camera measurements of its three-dimensional regional brain distribution.

SPECT recordings of the distribution of brain radioactivity were made on a Ceraspect (DSI, Waltham, MA, USA) camera for 30 min, beginning 1, 6 and 22 h after 300 MBq 123I-β-CIT was administered. The 5HTT uptake is expected to be maximal at the 1-h recording, and the DAT uptake at the 22-h recording (Kuikka et al., 1995). Immediately after the recording at 1 h, 20 mg citalopram, was given orally in order to block the 5HTT.

Each SPECT recording gave a three dimensional 128 × 128 × 64 matrix of cubic voxels with 1.667 mm side. The SPECT measurement result was scatter and attenuation corrected, and had a resolution of about 9 mm (FWHM).

The regions of interest (ROI) were identified by rotating the three-dimensional SPECT data set to the orbitomeatal (OM) plane, summing the data set into ten one cm thick slices, which were analysed with an Amersham ROI analysis program, with identical ROI-size at each measurement-time.

The predefined sets of ROIs (whole brain ROI and included regional anatomical structures) were positioned on the recorded SPECT slice and semi-automatically scaled to the actual external brain dimensions (automatic scaling with manual minor corrections) at the 1-h measurement, and an identical ROI-size was then used at each later measurement time. The ROIs from each slice were compounded into three-dimensional regions. In this study, only the values from the three-dimensional whole brain and cerebellum ROIs were used.

Since the cerebellum has little or no dopaminergic innervation, the cerebellum SPECT recordings (after correction for 5HTT uptake; Rydning, manuscript in preparation) was used as reference to calculate a measure of the 5HTT (at the 1-h recording) and DAT (at the 22-h recording) binding potential (BP*)=(reference 123I-β-CIT concentration – reference concentration)/reference concentration for each region).
2.3. Statistical methods

The contrasts between the results from the patients with suicide attempt and those from the paired control subjects were calculated with the Wilcoxon signed rank test for non-parametric data. We also used ranking correlations (Spearman rho, ρ).

3. Results

Twelve patients (10 men and two women) and their matched controls were recruited (Table 1). Their mean ± S.D. age was 38.8 ± 14.0 years; range 23–67 years.

Five of the patients (all men) made violent suicide attempts. Two patients had previously made a suicide attempt. No patient has so far committed suicide.

Six patients had a mood disorder, one a social phobia, and three had an adjustment disorder, while two patients did not have an axis I, DSM IV-disorder. One patient with a major depressive disorder had a co-morbidity of alcoholism. Half of the patients received a diagnosis of personality disorder (DSM IV, Axis II).

3.1. β-CIT SPECT-results

3.1.1. Differences between suicide attempters and control subjects

There were no significant whole brain 5HTT or DAT BP differences between patients and controls Table 2. Violent suicide attempters (N=5) did not differ significantly from their matched controls or from non-violent suicide attempters (N=7).
eters (Table 3). There were no significant DAT differences between patients with depressive episodes \( (N=5) \) and other patients \( (N=7) \). Patients with a depressive disorder had 5HTT in the low range compared to non-depressed patients or matched healthy controls but in all, the findings turned out to be non-significant (Table 4).

### 3.1.2. Correlations between 5HTT and DAT

Among patients (Spearman \( r = 0.65; P = 0.018; \) Fig. 1), but not among controls, there was a significant correlation between 5HTT and DAT.

<table>
<thead>
<tr>
<th></th>
<th>Depressed mean, S.D.; range</th>
<th>Controls mean, S.D.; range</th>
<th>Non-depressed mean, S.D.; range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HTT</td>
<td>0.16 ± 0.11; 0–0.3</td>
<td>0.34 ± 0.20; 0–0.5</td>
<td>0.40 ± 0.18*; 0.1–0.6</td>
</tr>
<tr>
<td>DAT</td>
<td>1.12 ± 0.41; 1.1–1.8</td>
<td>1.24 ± 0.30; 1.0–1.7</td>
<td>1.29 ± 0.23; 1.1–1.7</td>
</tr>
</tbody>
</table>

Comparisons were N.S. *\( P = 0.04 \) between depressed and non-depressed patients, but N.S. after Bonferroni correction.

### 3.1.3. Temperament results

There were no significant differences between patients and their matched controls concerning MNT validity (mean ± S.D.: 10.8 ± 5.6 vs. 14.8 ± 3.5) and solidity (9.4 ± 3.4 vs. 10.3 ± 3.3). Our patients had significantly higher MNT stability than their controls \( (8.0 ± 2.9 \text{ vs. } 4.7 ± 3.5; P = 0.028) \).

### 3.1.4. Correlations between temperament and 5HTT or DAT in suicide attempters or control subjects, respectively

In the control subjects there was no significant correlation between the MNT (MNT stability, MNT solidity, MNT validity) scores and DAT or 5HTT. In the suicide attempters, there was a significant positive correlation between whole brain 5HTT and MNT solidity (Spearman \( r = 0.63; P = 0.028 \) (Fig. 2).

### 4. Discussion

Based on many previous studies on the relationship between monoamines and suicidal behaviour, and assum-
ing that previously used monoamine measures reflect 5HTT and DAT estimated by SPECT, we had in this study expected to find significantly lower 5HTT in violent suicide attempters than in other suicide attempters or matched controls. Our findings, however, turned out to be non-significant. One explanation could be that the postsynaptic serotonergic receptor 5HT2 is of specific importance for violent behaviour rather than the 5HTT, as has been shown in numerous previous studies (Träskman-Bendz and Mann, 2000), and recently in a SPECT-study by Audenart et al. (2001).

Our results indicate differences between patients and controls, as we found significant associations between whole brain 5HTT and DAT in patients but not in the control group. This finding is not only in line with previous CSF studies of suicide attempters showing a significant correlation between CSF 5-HIAA and HVA (Engström et al., 1999), but is also of interest when compared to findings by Malison et al. (1998), who found a significant positive correlation between β-CIT binding potentials in brainstem (reflecting 5HTT) and striatum (reflecting DAT) in depressed patients and healthy controls taken together. The fact that this significant correlation was seen only in patients in the present study could indicate that among patients, the serotonin and dopamine systems are more intertwined and in need of interactive processes than among healthy individuals. Such theories have previously been put forward by Geracioti et al. (1997). A significant correlation in patients, but not in controls also indicates that the correlational pattern is not a result of the SPECT methodology, but rather shows a sufficient validity of the measurement of 5HTT and DAT by the SPECT-method.

In the present study, suicide attempters suffering from mood disorders had lower 5HTT than non-depressed patients, but not significantly lower than matched controls. However, the risk of creating a type 2 error ought to be pointed out, since repeated statistical analyses result in a risk of mass-significance. Our results are probably in accordance with those of previous studies (Laasonen-Balk et al., 1999; Malison et al., 1998; Willeit et al., 2000).

We were also able to replicate findings by ourselves and others of low 5HT-function, reflected as low whole brain 5HTT in “subsolid” (impulsive) patients. Interestingly, there were no significant differences in MNT solidity between our patients and matched controls. In our previous studies of suicide attempters, we were only able to find a significant association between serotonergic markers and impulsivity in patients with alcoholism (Engström et al., 1996a,b). Similarly, Virkkunen et al. (1994) have discussed the importance of serotonin dysfunction and alcohol dependence for impulse dyscontrol. The significant β-CIT findings in violent individuals, reported by Laruelle et al. (1994); Tiihonen et al. (1997) were observed in patients with alcoholism. Among the patients belonging to the present study, there is only one patient suffering from alcohol dependence, which means that alcoholism per se could not explain our significant findings.

In this study we have presented whole brain serotonin and dopamine transporter findings. We are in the process of treating data from different brain regions, which will hopefully reveal the mere site of action of the significant associations reported here.

It also remains to be clarified whether low whole brain 5HTT binding potential is correlated to few 5HT-neurons in the brain or less 5HTT-protein per neuron, or both.

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