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Impulsivity related to brain serotonin transporter binding capacity in suicide attempters

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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.

Keywords: Serotonin transporter; Dopamine transporter; SPECT; Suicide attempt; Impulsivity

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 Agren 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, (^{123}I-β-

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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). ^{123}I-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 ^{123}I-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. ^{123}I-β-CIT SPECT

^{123}I-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 ^{123}I-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 $128 \times 128 \times 64$ 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; Ryding, 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*)=(regional ^{123}I-β-CIT concentration − reference concentration)/reference concentration for each region).