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Reduced brain serotonin transporter binding in patients with panic disorder

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Abstract

There is strong evidence for the importance of the serotonin (5-HT) system in the neurobiology of panic disorder (PD); however, the exact role of this system remains unclear. The 5-HT transporter (5-HTT) is a key element in 5-HT neurotransmission. The current study aimed to investigate the binding of 5-HTT in the brain of patients with PD. We used single-photon emission computed tomography with a radioligand that specifically labels the 5-HTT, [^{123}I]nor-β-CIT. Subjects comprised eight patients with current PD, eight patients with PD in remission, and eight healthy control subjects. The patients with current PD showed a significant decrease in 5-HTT binding in the midbrain, in the temporal lobes and in the thalamus in comparison to the controls. The binding of 5-HTT in patients with PD in remission was similar to findings in the control group in the midbrain and in the temporal lobes, but lower in the thalamus. Regional 5-HTT binding significantly and negatively correlated with the severity of panic symptoms. These findings point to a dysregulation of the 5-HT system in PD patients. Altered function of 5-HTT appears to be related to the clinical status of patients. Clinical improvement in the patients in remission is associated with normalization of 5-HTT binding.
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Keywords: Panic disorder; Serotonin transporter; Brain imaging; SPECT; Nor-β-CIT

1. Introduction

Panic disorder (PD) is a prevalent and potentially disabling condition characterized by recurrent panic attacks, anticipatory fear and avoidance. There is strong evidence for the involvement of the brain serotonin [5-hydroxytryptamine (5-HT)] system in the

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pathophysiology of PD. The impact of this system in PD is substantiated by the established clinical efficacy of the selective 5-HT reuptake inhibitors (SSRI) in the treatment of PD (Kent et al., 1998). The mechanism of action of the SSRIs supports the involvement of the 5-HT transporter (5-HTT) in PD, but the exact role of the 5-HTT is unclear. Genetic studies have failed to demonstrate an association between a functional polymorphism in the 5-HTT gene promoter region and PD (Deckert et al., 1997; Hamilton et al., 1999; Ishiguro et al., 1997). There is some evidence for decreased 5-HTT binding in platelets of patients with PD (Faludi et al., 1994; Marazziti et al., 1999), an abnormality that is normalized after successful treatment with antidepressants (Marazziti et al., 1999). However, other studies have not found differences in platelet 5-HTT binding between patients with PD and normal controls (Maguire et al., 1995; Stein et al., 1995). Moreover, a study of Malison et al. (1998), which demonstrated a lack of correlation between the binding of 5-HTT in platelets and in the brain in patients with depression, raises doubts on the validity of the platelet binding model. To our knowledge, so far there have been no brain-imaging studies of the function of 5-HTT in PD. Therefore, we investigated brain 5-HTT binding potential in patients with PD in comparison to healthy subjects. The aims of this study were to detect whether there are quantitative alterations in 5-HT re-uptake sites in brain regions that are involved in the neurobiology of PD, and whether the 5-HTT binding characteristics are related to the symptomatic status of the patients.

2. Methods

2.1. Subjects

In total, 16 patients with PD and 8 healthy control subjects participated in this study. The PD group consisted of 8 (1 male and 7 females) patients with current PD, 6 of them with agoraphobia, and 8 (1 males and 7 females) patients with PD in remission. The healthy controls (1 male and 7 females) were matched by sex and age. The mean age (standard deviation) in the three groups was similar: 34.8 (15.8), 32.0 (13.9) and 33.6 (6.5) years, respectively. The patients were selected from the outpatients at the Clinic of Psychiatry of the Tartu University Clinics and by newspaper advertisement in Tartu, Estonia. The control subjects were recruited in Kuopio, Finland. The institutional ethics committees at the University of Tartu and at the Kuopio University Hospital approved the study protocol, and all subjects gave written informed consent before participation. All subjects were right-handed, in good physical health, and not pregnant. The patients with current PD and healthy controls were nonsmokers; there were three smokers among the remitted patients (fewer than six cigarettes per day). All participants had been free of alcohol and benzodiazepines for at least 2 weeks as confirmed by questioning and medical records, and none of them had current or lifetime alcohol dependence or abuse. None of the subjects had received any antidepressant or other medication known to affect 5-HTT binding for at least 4 months before the study. Two (25%) patients with current PD and six (75%) patients in remission had previously received treatment with antidepressants. One female patient with current PD used hormonal contraceptives, one female patient in remission used substitutive treatment with thyroxin, and one male patient with current PD occasionally used atenolol.

2.2. Assessment

The Mini International Neuropsychiatric Interview (MINI) 5.0.0. (Sheehan et al., 1998) was used to confirm the DSM-IV diagnosis of PD and exclude other types of psychiatric morbidity. The clinical status of PD was defined as remission if a patient had not met the DSM-IV diagnostic criteria for PD in the past month. According to the MINI, none of the patients had a lifetime diagnosis of major depression, bipolar disorder, or psychotic disorder or a history of suicidal attempts, with the exception of one remitted female patient who had a history of a single depressive episode. None of the patients had current axis I psychiatric comorbidity, except for both male patients, who had current mild depressive episode secondary to PD. On the study day, the patients were assessed with the Panic Disorder Severity Scale (PDSS; score range=0–28; Shear et al., 1997, 2001) and with the Hamilton Anxiety Scale (HAM-A; score range=0–42; Hamilton, 1959). Before the first scan, the patients evaluated themselves on a Visual Analogue Scale of

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