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Psychiatry Research: Neuroimaging 140 (2005) 63–72
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Serotonin and dopamine transporter imaging in patients with obsessive–compulsive disorder

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Received 11 August 2003; received in revised form 16 February 2005; accepted 24 July 2005

Abstract

In obsessive–compulsive disorder (OCD), the success of pharmacological treatment with serotonin re-uptake inhibitors and atypical antipsychotic drugs suggests that both the central serotonergic and dopaminergic systems are involved in the pathophysiology of the disorder. We applied [^{123}I]-2β-carbomethoxy-3β-(4-idiophenyl)tropane (β-CIT) and a brain-dedicated high-resolution single photon emission computed tomography (SPECT) system to quantify dopamine transporter (DAT) and serotonin transporter (SERT) availability. By comparing 15 drug-naïve patients with OCD and 10 controls, we found a significantly reduced availability (corrected for age) of striatal DAT and of thalamic/hypothalamic, midbrain and brainstem SERT in OCD patients. Severity of OCD symptoms showed a significant negative correlation with thalamic/hypothalamic SERT availability, corrected for age and duration of symptoms. Our data provide evidence for imbalanced monoaminergic neurotransmitter modulation in OCD. Further studies with more selective DAT and SERT radiotracers are needed.

Keywords: Obsessive–compulsive disorder; Dopamine; Serotonin; [^{123}I]β-CIT; Single photon emission tomography; SPECT

1. Introduction

There is strong evidence for the involvement of neurobiological factors in the pathogenesis of obsessive–compulsive disorder (OCD). This evidence is derived from the success of pharmacological treat-

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doi:10.1016/j.pscychresns.2005.07.002

ments, i.e., with selective serotonin re-uptake inhibitors (SSRIs), which target central serotonin transporters (SERT; Cartwright and Hollander, 1998), and with atypical neuroleptics, which can enhance the effect of SSRIs (Marek et al., 2003), especially in cases refractory to therapy (McDougle et al., 2000; Hollander et al., 2002; Dougherty et al., 2004). Most regimens combine drug treatment with cognitive behavioral psychotherapy (Petty et al., 1996; Hohagen et al., 1998; Stein, 2002). Furthermore, atypical neuroleptics are also capable of precipitating obsessive–compulsive symptoms in patients with schizophrenia (Khullar et al., 2001). Apart from these therapeutic implications, data from genetic investigations provide information about the possible roles of dopamine and serotonin in the pathogenesis of OCD (Pato et al., 2002; Hemmings et al., 2003). However, both the pathophysiology of potential drug-transporter interactions that may be involved in clinical response and the underlying functional deficits of the disorder remain unclear (Denys et al., 2004; Zohar et al., 2004).

Neuroimaging techniques such as positron emission tomography (PET) studies using [^{18}F]fluoro-2-deoxy-D-glucose (FDG) as a marker of metabolic activity and single photon emission computed tomography (SPECT) with perfusion markers, respectively (Saxena and Rauch, 2001), have provided in vivo evidence for disturbed cortico-basal ganglia-thalamic-cortical brain circuits in OCD. These network imbalances might be connected to or influenced by monoaminergic cortico-striatal, midbrain-basal ganglia, or midbrain-thalamus projections, which consist of serotonergic fibers (Heinz, 1999; Micallef and Blin, 2001). It has also been speculated that autoimmune processes induced by streptococcal infection are capable of altering basal ganglia functionality (Stein, 2002).

For in vivo registration of serotonin and dopamine transporter (SERT and DAT, respectively) availability, PET and SPECT have been used in various neuropsychiatric disorders and behavioral abnormalities, mostly applying the cocaine congener [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyltropane ([^{123}I]β-CIT) as a sensitive DAT and SERT marker for SPECT (for review, see Kasper et al., 2002; Hesse et al., 2004). Despite high affinity to SERT and DAT (Okada et al., 1998), differential pharmacokinetics (Fujita et al., 1996; Pirker et al., 2000) and brain distributions (Olivier et al., 2000) of the two transporter types permit them to be investigated within one [^{123}I]β-CIT SPECT examination. As shown recently by our group, exact anatomical alignment, i.e., co-registration of functional and morphological (MR) imaging data, seems to be advantageous for that purpose (Murai et al., 2001).

This SPECT technique has been used in patients with Tourette's syndrome, a disorder within the OCD spectrum. A negative association between SERT availability and the severity of tics was found (Heinz et al., 1998). Although some authors reported increased availability of DAT in Tourette's patients (Krause et al., 2002; Müller-Vahl et al., 2000), others found no changes (Stamenkovic et al., 2001) or a reduction of DAT (Malison et al., 1995) availability. In OCD itself, early SERT imaging studies showed inconclusive results (Simpson et al., 2003; Pogarell et al., 2003; Stengler-Wenzke et al., 2004).

The present study was therefore initiated to examine in vivo whether there is a dysfunction of the serotoninergic and/or dopaminergic neurotransmission in OCD. We hypothesized that SERT availability in SERT-rich regions—the thalamus/hypothalamus, brainstem and midbrain—would be impaired in OCD patients compared with healthy controls.

2. Methods

2.1. Patients and clinical investigations

Fifteen drug-naïve patients (7 females, 8 males; mean age = 32.1 ± 11.7 years, S.D. = 11.7, range = 19–64 years) with OCD (ICD-10 diagnosis F42.2; World Health Organization, 1992) were prospectively included in this study. Severity of OCD was rated using the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS; Goodman et al., 1989a,b), and that of depression was evaluated using the Beck Depression Inventory (BDI; Hautzinger, 1991). Presence of clinical depression was defined as a BDI score >17 points. Patients compared with 10 healthy controls (mean age = 40, S.D. = 13.2, range = 19–63 years) recruited from our database of normal subjects, which has been published elsewhere (Müller et al., 2000; Hesse et al., 2003b). Due to limited availability of control subjects, we were not able to match the control group for gender (3 females, 7 males, $P < 0.05$,