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Dopamine transporter imaging in adult patients with attention-deficit/hyperactivity disorder

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Abstract

The aim of this study was to provide *in vivo* evidence for the hypothesis that dopaminergic neurotransmission is altered in adult patients with attention-deficit/hyperactivity disorder (ADHD). We used high-resolution brain-dedicated single-photon emission computed tomography and the dopamine transporter (DAT) marker [^{123}I]FP-CIT in 17 adult treatment-naïve ADHD patients and 14 age-matched controls. Magnetic resonance imaging-based region of interest analysis was performed to quantify the DAT availability (expressed as a ratio of specific to non-displaceable binding, V_3'') in the striatum. Additionally, the specific radiotracer binding was assessed in the thalamus and the midbrain/brainstem regions (reflecting also the availability of the serotonin transporter to which [^{123}I]FP-CIT binds with moderate affinity). In the striatal areas of the ADHD patients, a significantly reduced specific tracer binding was found (V_3'': 5.18±0.98; controls 6.36±1.34). In contrast, the specific [^{123}I]FP-CIT binding did not differ from controls in the thalamus and midbrain/brainstem areas. These data indicate a reduced dopaminergic but not serotonergic transmitter reuptake function in adult ADHD. Further studies will have to deal with the question of whether these findings have the potential to influence treatment decisions in this complex disorder.

Keywords: ADHD; SPECT; Serotonin

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous clinical disorder defined by the occurrence of hyperactivity, impulsivity and inattention with a childhood onset. The involvement of dopamine dysfunction in ADHD has been proposed on the basis of abnormal dopaminergic metabolism determined by measurements of the homovanillic acid levels in the cerebrospinal fluid (Castellanos et al., 1996), abnormal (reduced) brain decarboxylase activity using either [^{18}F]dopa (Ernst et al., 1998) or L-[^{11}C]dopa (Forssberg et al., 2006) positron emission tomography (PET), and altered dopamine D_2 receptor binding using [^{11}C]raclopride PET (Rosa-Neto et al., 2005). The current hypothesis that the brain dopamine transporter (DAT) is involved in the pathogenesis of ADHD is based on the effectiveness of treatment with stimulants (i.e., methylphenidate) that block the

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DAT (Volkow et al., 2002), and the association of a polymorphism of the DAT-encoding gene (DAT1) with the occurrence of this disorder (Heiser et al., 2004).

Recent single-photon emission computed tomography (SPECT) and PET imaging studies of the DAT in children, adolescents and adults with ADHD revealed either higher DAT availability (Krause et al., 2000; Dresel et al., 2000; Cheon et al., 2003; Spencer et al., 2005), ranging from a 70% increase in the initial report (Dougherty et al., 1999) to a less pronounced increase most recently (Larisch et al., 2006), unaltered level (van Dyck et al., 2002a), or reduced *in vivo* DAT availability (Jucaite et al., 2005; Volkow et al., 2007). Thus, the findings are not consistent across studies, but it is currently assumed that an elevated striatal DAT activity is of patho-physiological importance in ADHD. The prevailing studies differ in methodology, applied radiotracers, outcome measures, pretreatment with stimulants and clinical definition of ADHD (compiled by Krause et al., 2003; Madras et al., 2005). Studies that were initiated by the cited groups with the goal of replicating these findings failed in part, e.g., when correcting for confounders like nicotine smoking. Krause et al. (2002) replicated increased DAT availability in non-smokers but not in smokers with ADHD. La Fougère et al. (2006) found higher striatal DAT availability in 17 out of 22 adult ADHD patients, but reduced striatal DAT availability in further five study participants who did not respond well to subsequent methylphenidate treatment. This led to the hypothesis that the subgroup of ADHD patients with low DAT activity may have a poor response to drug therapy (Krause et al., 2005). As a result, there is a need to clarify the status of DAT availability in adults with ADHD who have never been treated with stimulants. Therefore, the aim of our study was to elucidate DAT availability in drug-naïve adult patients with strictly defined ADHD who had no other psychological problems or co-morbidities.

In addition, the present study is the first one in which central serotonin transporter (SERT) availability was assessed *in vivo* in patients with ADHD. Altered serotonin levels were associated with both impulsivity/aggression (Krakowski, 2003) and hyperactivity (Gainetdinov et al., 1999). Moreover, venlafaxine [a combined norepinephrine transporter (NET) and SERT inhibitor] shows beneficial effects on core ADHD components in children and adolescents (Findling et al., 2007). Given that SERT specificity (to a moderate degree) of both thalamic and midbrain/brainstem [^{123}I] FP-CIT binding was recently successfully detected (Booij et al., 2007), we sought to study the specific uptake in these regions, too.

2. Methods

2.1. Patients

We included 17 treatment-naïve adult patients fulfilling the DSM-IV criteria (American Psychiatric Association, 1994) for ADHD (9 females, age: 32±8 years) and 14 age-matched normal controls from our database of [^{123}I]FP-CIT SPECT studies [6 females, not significant (n.s.) *vs.* ADHD patients (χ^2-test); age: 32±9 years, n.s. *vs*. ADHD patients (unpaired two-tailed *t*-test)]. Patients were recruited from a specialized ADHD outpatient center with a highly selective patient group with limited co-morbidity. The diagnosis was based upon an extensive guideline-based symptom-oriented clinical interview. Also, the patients were rated by applying the Adult ADHD Self-Report Scale (ASRS; cut-off 23 points) (Kessler et al., 2005) and the Wender Utah Rating Scale (WURS; cut-off 90 points) (Ward et al., 1993; Groß et al., 1999). Furthermore, patients had to retroactively fulfill the criteria of the German SBB-HKS (*Selbst-Beurteilungs-Bogen-Hyperkinetische-Störung*) and FBB-HKS (*Fremd-Beurteilungs-Bogen-Hyperkinetische-Störung*) forms of DISYPS-KJ (*Diagnostik-System für psychische Störungen im Kindes- und Jugendalter nach ICD-10 und DSM-IV*), which is an established diagnostic system in Germany for registering psychiatric disorders in childhood and adolescence that was developed by an expert panel in accordance with the ICD-10 and DSM-IV (Döpfner et al., 2000). This includes self- and external rating scales and checklists for an operational categorical diagnostic and differential dimensional description of psychiatric abnormalities. ADHD-typical formulations in the assessment of school certificates were also taken into account. Finally, all patients had to complete a personality questionnaire of the International Personality Disorder Examination (IPDE) (Mombour et al., 1996), and we also used ratings such as the Beck Depression Inventory (BDI, Hautzinger et al., 1995) to exclude relevant depressive symptomatology.

The study cohort comprises all subtypes of the disorder, i.e., hyperactive/impulsive, combined and inattentive forms. Subtype differentiation was performed by applying the DSM-IV classification with regard to the dominant symptomatology. There was no history of illicit drug use, antidepressants (at least not over the last 3 months) or other psychoactive medication/medication affecting DAT (such as buproprion) in either patients or controls. The use of illicit drugs was also excluded by means of urine testing for amphetamine, methamphetamine, cannabinoids and their derivatives. Records of the controls were checked for alcohol non-abuse and