In Vivo Neuroreceptor Imaging in Attention-Deficit/Hyperactivity Disorder: A Focus on The Dopamine Transporter

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There is converging evidence of the role of catecholamine dysregulation in the underlying pathophysiology of attention-deficit/hyperactivity disorder (ADHD). The dopamine transporter (DAT) is known to be a key regulator of dopamine, and recent genetic, treatment, and imaging studies have highlighted the role of DAT in ADHD. There is an emerging literature on in vivo neuroreceptor imaging of DAT in ADHD and control subjects reported by a number of groups internationally. A comprehensive review of existing imaging studies of DAT binding in ADHD shows that six of eight independent studies by six different groups have reported increased DAT binding in (mostly) treatment-naïve children and adults with ADHD. Although there is fair agreement regarding the presence and direction of abnormal DAT binding, there remains disagreement as to the magnitude of the finding and the importance of many potentially confounding variables, including clinical characteristics and imaging methodology. Three studies by three different groups have reported decreased DAT binding after methylphenidate treatment. Interpretation of the latter finding awaits clarification of the issue of timing of drug administration and imaging to disentangle receptor occupancy from downregulation.

Key Words: ADHD, neuroimaging, dopamine transporter, methylphenidate

Attention deficit-hyperactivity disorder (ADHD) is one of the major clinical and public health problems in the United States in terms of morbidity and disability in children and adolescents. It is estimated to affect 5%–10% of school-aged children and 3%–5% of adults (Kessler et al, in press). Its impact on society is enormous in terms of financial cost, the stress to families, the impact on schools, and the damaging effects on self-esteem. In adults, it is associated with unemployment and under-employment, as well as social, legal, and marital difficulties (Kessler et al, in press). Although its etiology remains unclear, there is very strong evidence supporting the role of genes in the disorder. An emerging neuropsychological and neuroimaging literature provides compelling support for the hypothesis that abnormalities in frontal networks or fronto–striatal dysfunction are the disorder's underlying neural substrate and that catecholamine dysregulation is its underlying pathophysiologic substrate.

The Role of the Dopamine Transporter

Because dopamine has a central role in the regulation of psychomotor activity and reward-seeking behavior, and the dopamine transporter (DAT) is the main target for anti-ADHD stimulant medications, initial molecular genetic (Faraone et al 2005) and imaging studies have focused on the DAT. Using a family-based association study, Cook et al (1995) first reported an association between ADHD and the 480-base-pair (bp) allele of a DAT VNTR (variable number of tandem repeats) polymorphism located in the 3′ untranslated region. Waldman's pooled analysis of all family-based studies showed a statistically significant effect (Waldman, unpublished data), whereas the several ensuing studies of this gene were individually inconclusive. A recent pooled analysis of association-based studies of the DAT1 VNTR polymorphism reveals a significant but small effect of the polymorphism on ADHD, with a pooled odds ratio of 1.13 (Faraone et al 2005). In nuclear families with an ADHD proband, Barr et al (2001) found significant biased transmission of a haplotype of three polymorphisms that included the 480-bp VNTR allele.

In mice, eliminating DAT gene function through the knockout procedure leads to two features suggestive of ADHD: hyperactivity and deficits in inhibitory behavior. Moreover, the DAT knockout mouse shows reductions in hyperactivity with stimulant treatment (Gainetdinov et al 1999; Giros et al 1996). Similar findings were seen in a DAT knockdown model, in which DAT activity was reduced to 10% of normal (Zhuang et al 2001). These mouse models show the potential complexities of gene–disease associations. The loss of the DAT gene has many biological effects: increased extracellular dopamine, a doubling of the rate of dopamine synthesis (Gainetdinov et al 1998), decreased dopamine and tyrosine hydroxylase in striatum (Jaber et al 1999), and a nearly complete loss of functioning of dopamine autoreceptors (Jones et al 1999). Because ADHD is believed to be a disorder of altered dopamine regulation, it is the decreased striatal dopamine that might be most relevant to the disorder. The mechanism by which stimulants decrease hyperactivity in the knockout mouse is unclear; however, it might be relevant that methylphenidate (MPH) also increases levels of norepinephrine (NE), possibly through the NE transporter (Bymaster et al 2002; Kuczenski and Segal 1997, 2002).

Because of the postulated hypothesis that DAT abnormalities might be involved in the pathophysiology of ADHD, imaging studies in ADHD have also focused on the DAT. In the course of developing ligands for single photon emission computed tomography (SPECT) imaging of DAT sites, an optical (E) isomer of ^{123}I-2β-carbomethoxy-3β-(4-fluorophenyl)-N-(1-iodoprop-1-en-3-yl)nortropane (E-IACFT, designated as Altropane [Boston Life Sciences, Boston, Massachusetts]) was developed (Elmaleh et al

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1996). On the basis of in vitro binding studies with ^{3}H CFT and ^{3}H citalopram (a high-affinity and selective ligand for 5-hydroxytryptamine [5-HT, serotonin] transporter sites [D'Amato et al 1987]), E-IACFT was shown to have high affinity (inhibitory concentration of 50% = 6.62 ± .78 nmol) and selectivity (DA/5-HT = 25:1) for DAT sites. In addition, autoradiographic and SPECT studies in monkeys demonstrated rapid and extremely high levels of accumulation in the striatum and minimal activity in other brain regions (Fischman et al 1997). Recently, dynamic SPECT studies in healthy volunteers and patients with Parkinson's disease confirmed these findings (Fischman et al 1998). Thus, with the highly selective radiopharmaceutical ^{123}I-labelled Altropane, DAT density by SPECT could be measured.

SPECT Imaging Studies in ADHD

Table 1 lists the published DAT binding studies in ADHD patients and control subjects. The first SPECT study taking advantage of Altropane was performed by Dougherty et al (1999) in a sample of 6 adults with ADHD and compared with a database of 30 control subjects. Subjects were injected with 5–7 mCi of ^{123}I Altropane, serial SPECT images were acquired over 1.5 hours, and time–activity curves were constructed for regions of interest with high concentrations of DAT in the striatum (Str) and reference tissue (Ref) with low concentrations of DAT. The expression $Str_{TAC} - Ref_{TAC}$ was fitted to a gamma variate function, with division of the maximum by the value Ref_{TAC} at the same time yielding an equilibrium estimate of binding potential. High count density images showed intense concentration of radioligand in the striatum and minimal accumulation in other areas of the brain (Figure 1). Binding potential (defined in this study as k3/k4) estimates (Figure 2) clearly indicate that DAT density was consistently raised in patients with ADHD. The binding potential for patients with ADHD exceeded the mean values of the control group by at least 2 SD. In fact, DAT binding potential was elevated by approximately 70% compared with healthy control subjects.

Dresel et al (2000) investigated DAT binding in 17 treatment-naïve adults with ADHD compared with 10 age- and gender-matched control subjects. These 17 patients (7 men, 10 women, aged 21–64 years) had no history of drug or alcohol abuse and no psychiatric comorbidity. All subjects were injected with 800 MBq [99mTc]TRODAT-1 and imaged. Single-photon emission tomography scans were acquired with a triple-headed gamma camera. Transverse slices were used to calculate specific binding in the striatum, with the cerebellum used as background [(Str–Bkg)/Bkg]. Data were compared with those of an age-matched control group. It was found that untreated patients presented with a significantly increased (average 17%) specific binding of [99mTc]TRODAT-1 to the DAT as compared with normal control subjects ($p < .001$). After treatment with MPH (5 mg t.i.d.), specific binding decreased (average 29%) significantly in all patients ($p < .001$). The last dose of MPH was administered 90 min before the scan. The decrease in available DAT binding sites under treatment with MPH correlated with the improvement in clinical symptoms. The investigators concluded that the number of DAT binding sites is higher in drug-naïve patients suffering from ADHD than in normal control subjects.

In a more recent report of an expanded sample of the Dresel data, Krause et al (2003) reported DAT binding of adults with ADHD ($n = 31$) and control subjects ($n = 15$). They replicated their earlier findings of greater DAT binding in adults with ADHD and were able to examine subpopulations. Dopamine transporter binding was only slightly greater in the group with childhood hyperactivity compared with the pure inattentives. In this new study, however, the increased DAT binding was restricted to nonsmokers. Smokers with ADHD had DAT binding equal to or less than that in control subjects.

Van Dyke et al (2002) investigated DAT binding in nine adults with ADHD and nine age- and gender-matched control subjects. Eight of the nine adults were treatment naïve. The investigators used the radioligand ^{123}I B-CIT. They found no difference in striatal DAT binding between the two groups. Eight of the adults with ADHD were openly treated after the scan with MPH, with robust reduction of ADHD symptoms. Dopamine transporter binding was not correlated with severity ratings of symptoms of ADHD at baseline or with symptom improvement after open treatment with MPH.

In a multisite ($n = 4$) study, investigators examined striatal DAT density in 8 adults with ADHD and 16 age-matched control adults, using SPECT with ^{123}I Altropane (McGough, unpublished data). Adults with ADHD had no comorbid psychiatric or substance use disorders and no recent stimulant use. A 30% greater DAT density was found in the ADHD adults than in control adults ($p < .0011$), replicating prior research with this imaging agent and technology. Binding potential was significantly related to level of inattentive ($p < .008$) and hyperactive–impulsive symptoms ($p < .014$) but not to comorbid levels of anxiety, depression, or academic achievement skills. The findings are consistent with prior research implicating abnormal dopamine pathway activity as one contributing factor to ADHD.

Cheon et al (2003) investigated DAT density in children with ADHD using ^{123}I IPT SPECT. Nine drug-naïve children with combined-type ADHD and six normal children (aged 6–12 years) were studied. Children with ADHD showed a significantly increased specific/nonspecific DAT binding ratio in the basal ganglia. The children with ADHD had 40% greater DAT binding in the left striatum and 51% greater DAT binding in the right striatum. Although the correlation between the severity scores of ADHD symptoms and the DAT binding did not reach the level of statistical significance (.05), there was a trend ($p < .06$) for a correlation between parent ratings of inattention and DAT binding.

In a further preliminary report, Cheon et al (unpublished data) reported on DAT density in children with ADHD before and after treatment with MPH. Seven drug-naïve children with ADHD were treated with .7 mg/kg/day of MPH for 8 weeks. All achieved a clinical response. Dopamine transporter densities decreased to within the normal range after MPH treatment (reductions of 38% and 44.2% in left and right striatum, respectively).

Vles et al (2003) examined DAT binding in six drug-naïve boys with ADHD (aged 6–10 years), using ^{123}I-loflupane. Three months after treatment with MPH, they found a 28%–75% decrease of DAT binding in the striatum. The decreased DAT binding corresponded to a positive response to treatment on neuropsychological testing.

Positron Emission Tomography Imaging Studies in ADHD

Positron emission tomography (PET) has many clear and important advantages relative to SPECT for making quantitative physiologic measurements. First, dynamic tomographic measurements are far more precise with PET. "Dynamic tomographic measurement" refers to collecting imaging data from multiple angles over time (as opposed to static imaging like a chest X-ray,