References


BRIEF REPORTS

Unaltered Dopamine Transporter Availability in Adult Attention Deficit Hyperactivity Disorder

Christopher H. van Dyck, M.D.
Donald M. Quinlan, Ph.D.
Lisa M. Cretella, M.A.
Julie K. Staley, Ph.D.
Robert T. Malison, M.D.
Ronald M. Baldwin, Ph.D.
John P. Seibyl, M.D.
Robert B. Innis, M.D., Ph.D.

Objective: The authors examined whether patients with attention deficit hyperactivity disorder (ADHD) have altered striatal dopamine transporter levels, which may explain psychostimulant effects in this disorder.

Method: Single photon emission computed tomography and [123I]2-β-carbomethoxy-3-β-(4-iodophenyl)tropane ([123I]β-CIT) were used to assess dopamine transporter availability in nine adult patients with ADHD (eight of whom were stimulant naive) and nine age- and gender-matched healthy comparison subjects.

Results: Striatal [123I]β-CIT binding did not differ significantly between the ADHD and comparison subjects.

Conclusions: The findings suggest that a hypothesized dysregulation of dopamine function in ADHD does not entail altered dopamine transporter levels.

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In the study group included nine patients with ADHD (six men, three women) who ranged in age from 25 to 56 years (mean=41 years, SD=11). All patients were recruited from the Yale Clinic for Attention Disorders in Adults where they were actively seeking evaluation and treatment. Patients were evaluated by a psychologist (D.M.Q.) and psychiatrist (C.H.V.D.) to establish the diagnosis of ADHD according to the DSM-IV criteria and to exclude current neurological or psychiatric diseases, including substance abuse. The diagnoses were made by using contemporary information, including patients’ recollections of childhood behavior. Eight patients met the DSM-IV criteria for ADHD, combined type, and one for the predominantly inattentive type. Eight patients were stimulant naive; one had received methylphenidate intermittently for the predominantly inattentive type. Eight ADHD patients elected open-label treatment with methylphenidate after the SPECT scan. Methylphenidate was administered twice daily and titrated to a dose of 1.0 mg/kg per day until limiting side effects occurred. The ADHD Rating Scale and the Clinical Global Impression of change (7-point Likert-type scale) were administered when the patients attained maximal dosages.

Results

Striatal $^{[123]}\beta$-CIT SPECT data are displayed in Figure 1. Mean values of striatal $V_3''$ did not differ between the healthy group (mean=6.27, SD=1.12) and the ADHD group (mean=6.25, SD=0.54) (t=0.04, df=16, p=0.97, two-sample t test; t=0.04, df=8, p=0.97, paired t test). Mean values of $V_3''$ did not differ between groups for the diencephalon (healthy subjects: mean=1.77, SD=0.33; ADHD subjects: mean=1.83, SD=0.27) (t=0.43, df=16, p=0.67, two-sample t test; t=0.47, df=16, p=0.65, paired t test) or the brainstem (healthy subjects: mean=1.13, SD=0.11; ADHD subjects: mean=1.14, SD=0.20) (t=0.11, df=16, p=0.92, two-sample t test; t=0.10, df=16, p=0.92, paired t test).

When age was considered as a covariate, there was still no difference between groups in $V_3''$ for the striatum and behavioral measures within the ADHD group was examined with Pearson’s product-moment correlation.

Eight ADHD patients elected open-label treatment with methylphenidate after the SPECT scan. Methylphenidate was administered twice daily and titrated to a dose of 1.0 mg/kg per day until limiting side effects occurred. The ADHD Rating Scale and the Clinical Global Impression of change (7-point Likert-type scale ranging from –3, very much worse, to 3, very much improved) were administered when the patients attained maximal dosages.

An comparison group was selected from a database of healthy subjects who had recently received $^{[123]}\beta$-CIT SPECT imaging. The comparison subjects were individually matched with the ADHD patients for age (±5 years, actual range=25–57 years, mean=41, SD=11), gender, hormone status (one female patient and one comparison subject—age 56 and 57 years, respectively—were postmenopausal and were not receiving hormone replacement therapy), and smoking status (all patients and comparison subjects were nonsmokers). Additional screening procedures for all patients and comparison subjects included evaluation with the SCID-I/P: physical and neurological examinations, ECG, routine blood and urine tests, and brain MRI. No subject was taking medication known to affect the central dopamine or serotonin systems. All subjects gave written informed consent for the study procedures. Subjects received 0.6 g of saturated potassium iodide oral solution (SSKI, Upsher-Smith Laboratories, Minneapolis) in the 24 hours before the scan.

All subjects received an injection of $^{[123]}\beta$-CIT (mean=5.9 mCi, SD=0.3), followed by SPECT scanning the next day (mean=23.0 hours after injection, SD=2.2). SPECT data acquisition and image analysis were performed as previously described (6). Briefly, simultaneous transmission and emission scans were acquired on a PRISM 3000 XP SPECT camera (Picker, Cleveland, Ohio). MRI scans of 3-mm contiguous transaxial slices were obtained with a 1.5-T Signa device (General Electric, Milwaukee). Image analysis was conducted by an operator (L.M.C.) who was unaware of the subject’s information. Nonuniform attenuation correction was performed by using the transmission scan, and MRI surface co-registration was performed in MEDx (Sensor Systems, Sterling, Va.) to guide the placement of standardized region-of-interest templates (for the striatum, diencephalon, brainstem, and cerebellum) on the corresponding SPECT slices.

Previous studies have demonstrated that $^{[123]}\beta$-CIT reaches equilibrium binding in the brain by 18–24 hours after injection (9), yielding the following simple unitless ratio of regional radioactivities in estimating the maximum number of dopamine transporter or serotonin transporter binding sites (i.e., $B_{max}$):

$$V_3'' = [(cpm/pixel)_{\text{region}} - (cpm/pixel)_{\text{cerebellum}}]/(cpm/pixel)_{\text{cerebellum}},$$

where “$V_3''$” refers to the specific binding/nondisplaceable binding ratio, and “cpm” refers to counts per minute. Values of $V_3''$ for the striatum, diencephalon, and brainstem for the two diagnostic groups were compared with both two-sample and paired t tests as well as with analysis of covariance (ANCOVA), with age controlled. The relationship between $V_3''$ and behavioral measures within the ADHD group was examined with Pearson’s product-moment correlation.

FIGURE 1. Striatal $^{[123]}\beta$-CIT Availability ($V_3''$) in Healthy Comparison Subjects (N=9) and Adults With Attention Deficit Hyperactivity Disorder (ADHD) (N=9), Individually Matched for Age and Gender

Striatal $V_3''$ did not differ between healthy and ADHD groups (t=0.04, df=16, p=0.97, two-sample t test; t=0.04, df=8, p=0.97, paired t test).
For the eight patients who elected open-label methylphenidate treatment after SPECT imaging, a maximal daily dose of 0.60 mg/kg (SD=0.16, range=0.41–0.86) was achieved by a mean of 37 days (SD=22, range=11–74). During treatment, the mean ADHD Rating Scale score fell from 35.5 (SD=5.7, range=29–36) at baseline to 19.0 (SD=7.4, range=8–32) at maximal dose, with a mean reduction of 16.5 (SD=10.8, range=6–36). The mean Clinical Global Impression of change score was 1.9 (SD=0.8, range=1–3). One patient discontinued methylphenidate after 11 days because of side effects; another after 2 months because of noncompliance. Six patients continued to take methylphenidate or other stimulants at the time this report was written, 17–25 months later.

Within the ADHD patients, striatal $V_3$ was uncorrelated with either baseline symptom severity as measured by the ADHD Rating Scale (mean=34.1, SD=6.8, range=23–44; r=0.11, N=9, p=0.77) or with symptom improvement (reduction in the ADHD Rating Scale score) during open-label methylphenidate treatment (r=0.17, N=8, p=0.68).

Discussion

The SPECT measures of $[123I]\beta$-CIT availability in adults with ADHD did not differ from those of matched comparison subjects. It is difficult to explain the striking discrepancy between our results and those of Dougherty et al. (3), who found a 70% higher age-corrected dopamine transporter density in six adult ADHD patients than in healthy comparison subjects. All but one of the patients in our study were stimulant naive, whereas Dougherty and colleagues subsequently disclosed that four of the six patients in their study had been previously treated with psychostimulants, although not within 1 month of study participation (12). Abstinence from stimulants might be associated with higher dopamine transporter levels, as has been observed in some neuroimaging studies of acute abstinence from cocaine (13). However, it is unlikely that this explanation could account for the 70% difference reported by Dougherty et al. (3). Moreover, stimulant effects cannot account for the difference between our results and those of Dresel et al. (4), who found that reportedly drug-naive adult ADHD patients (N=17) had a 17% higher level of dopamine transporter specific binding than healthy comparison subjects; the binding level for the patients decreased by 43% with methylphenidate treatment (4). Radioligand differences are also implausible sources of divergence. Although $[123I]altropane and $[99mTc]TRODAT-1, used in the studies by Dougherty et al. (3) and Dresel et al. (4), respectively, both possess greater selectivity for the dopamine transporter than for the serotonin transporter, $[123I]\beta$-CIT uptake in the striatum is associated almost exclusively with the dopamine transporter (5).

We cannot exclude the possibility that our study group was too small to detect a significant difference between diagnostic groups. However, on the basis of the mean value and standard deviation for striatal $V_3$ in our pooled study group (mean=6.26, SD=0.86), our study had >99% power to detect a 70% difference between subject groups (the result reported by Dougherty et al. [3]), and approximately 80% power to detect even the 17% difference between groups reported by Dresel et al. (4) (alpha=0.05, two-tailed t test). Nonetheless, additional investigations are warranted with larger groups of stimulant-naive patients to clarify the discrepancy among these three preliminary studies.

This negative result does not rule out the possibility of an alteration of the brain’s dopamine system in ADHD. The absence of a difference in dopamine transporter availability does not preclude differences in dopamine transmission or dopamine receptors. Previous studies from our group have demonstrated differences in amphetamine-induced dopamine transmission (14) in patient populations (patients with schizophrenia) in which dopamine transporter availability did not differ (15). Additional studies should be conducted to examine stimulant-induced displacement of dopamine receptors in adults with ADHD.

References

Empirical studies suggest that sexually abused children may deny or only reluctantly disclose their experiences (1, 2); the explanation for this is currently subject to controversy (3, 4).

The aim of this study was to investigate to what extent children who were sexually abused would disclose in information about their experiences as well as to describe obstacles to such disclosure. We observed police interviews of 10 children who had been sexually abused by the same man on a total of 102 occasions. Videotapes of the abuse were found by police in the home of the suspect. The man was known to the victims either by being related or by working at their day care centers. The perpetrator was detained, and two of the children (stepchildren of the perpetrator) were placed in foster care during the investigation. No child had disclosed abuse before the police investigation.

The perpetrator was 13–14 years old at the time of the first incident and 18–21 years old during the remaining ones. Abuse ranged in severity from exposing children's