Dopamine transporter in attention-deficit hyperactivity disorder normalizes after cessation of methylphenidate

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Dopamine Transporter in Attention-Deficit Hyperactivity Disorder Normalizes After Cessation of Methylphenidate

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Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder of childhood, which is frequently treated with methylphenidate. The short-term response to treatment with methylphenidate is a substantial decrease in dopamine transporter density, with improvement in neuropsychological tests. In this study, single-photon emission computed tomography was used to investigate possible long-term alterations in the cerebral dopamine system after cessation of treatment with methylphenidate in five children with ADHD. Three months after initiation of treatment with methylphenidate, a reduction of the dopamine transporter in the striatal system was observed. Methylphenidate was administered for a period of 9 to 20 months. Follow-up with single-photon emission computed tomography after withdrawal of methylphenidate medication disclosed an increase of dopamine transporter activity comparable with pretreatment values. The observed upregulation of dopamine transporter activity might support the assumption that methylphenidate does not lead to permanent damage of the nigrostriatal dopaminergic pathways. © 2005 by Elsevier Inc. All rights reserved.

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Introduction

Attention-deficit hyperactivity disorder (ADHD), a common neurodevelopmental disorder of childhood, is a clinically heterogeneous syndrome, with core symptoms of inattention, excessive motor activity, and impulsivity. The therapeutic use of methylphenidate for the management of children with ADHD is increasing on a large scale, as its short-term efficacy in modifying motor, cognitive, and affective responses is well documented [1-4]. Trials with 14 to 24 months of follow-up suggested that consistent use of stimulant medication was associated with maintenance of effectiveness [5,6].

However, as ADHD can persist into adulthood, concern has been raised about the possible negative effects of long-term exposure of developing brains to methylphenidate [3,4,7]. Data on chronic methylphenidate use and abuse are scarce. In addition, the possibility that methylphenidate, like other psychostimulant amphetamine derivatives, might produce toxic effects on central monoamine-containing neurons has received relatively little attention [8]. Extrapolating experimental animal data, methylphenidate is probably safer than amphetamine, because it lacks the dopamine neurotoxic potential that has been well documented for amphetamine [8]. However, data in children related to this topic are unavailable.

Recent research suggests that the cerebral dopamine transporter is the primary target for methylphenidate in ADHD patients [4]. Both adults and children with ADHD appear to have increased dopamine transporter binding

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Table 1. FP-CIT SPECT: Baseline (=T0), after 3 months methylphenidate (=T1), and after withdrawal methylphenidate (=T2) in 5 males with ADHD

Patient	Age (yr)	Baseline ^{T0}				3 Months Methylphenidate ^{T1}				Follow-Up ^{T2}			
		Left		Right		Left		Right		Left		Right	
		Caudatus	Putamen	Caudatus	Putamen	Caudatus	Putamen	Caudatus	Putamen	Caudatus	Putamen	Caudatus	Putamen
1	8	10.47	11.22	11.96	11.07	7.55	8.67	6.95	7.97	17.12	15.51	16.72	16.31
2	9	11.70	14.10	12.66	11.68	4.80	4.02	6.09	4.16	15.87	13.94	14.99	13.74
3	8	11.78	11.91	11.78	12.50	5.70	7.25	5.18	6.96	12.13	13.16	11.46	14.66
4	9	11.50	14.10	17.00	15.80	4.14	4.02	4.34	3.84	14.65	21.37	16.22	15.94
5	10	12.63	11.13	14.05	14.16	5.67	4.33	5.10	5.08	13.14	12.32	14.69	16.40

Longitudinal FP-CIT SPECT data with: T0 = baseline (drug naïve); T1 = after 3 months of treatment methylphenidate; T2 = 4-6 weeks after withdrawal of methylphenidate treatment.

Duration of treatment: 9-12 months in five males with ADHD.

Abbreviations:

ADHD = Attention deficit-hyperactivity disorder

FP-CIT = ¹²³I-ioflupane

SPECT = Single-photon emission computed tomography

ratios in the basal ganglia compared with normal subjects [9,10]. We recently found that imaging of the cerebral dopamine system using single-photon emission computed tomography is a useful instrument to monitor psychostimulant treatment in children with ADHD: a reduction of dopamine transporter activity during methylphenidate treatment was observed [11]. In order to be informed about the potential long-term effects of chronic methylphenidate treatment, in the present study, single-photon emission computed tomography was used to monitor the dopamine system in five males with ADHD after cessation of methylphenidate treatment.

Methods

Subjects and Procedure

In the present study, single-photon emission computed tomography was used to monitor the dopamine system in five children with ADHD before (= T0), during methylphenidate treatment (= T1), and after withdrawal methylphenidate (= T2) after a duration of 9-20 months treatment. The study included five children, all right-handed males, mean age 8.54 years; S.D. = 0.88 years, range 7.3-9.6 years. Mean intelligence level as measured with the Kaufman Assessment Battery for Children [12] was in the average to low-average range: mean score 88.8; S.D. = 8.3. Written informed consent was obtained from the parents of all children after the procedures had been explained to the parents and children in detail. The study protocol was approved by an institutional clinical audit. On ethical considerations it was not possible to include in this study the effects of methylphenidate in a matched control sample.

The diagnosis of ADHD included medical, developmental, school, psychosocial data, and family histories obtained by the youth health care practitioner as well as input from parents and teachers, using the Child Behavior Check List and Teachers Report Form, examination by a child neurologist, and neuropsychological assessment to cover the presenting symptoms, differential diagnosis, and possible comorbid conditions [13]. Children included fulfilled the criteria for diagnosis of ADHD, made through a clinical interview, according to criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [14-16].

Apart from the ADHD diagnosis, additional inclusion criteria were: no additional psychiatric disorders, no seizures disorders, no history of tics, normal electrocardiographic and electroencephalographic examination results, and no current or previous psychopharmacologic treatment. The males included manifested inappropriate behavior within the classroom, with

severe consequences for their academic and social functioning. On neurologic examination, all children were normal. The child neurologist who examined the subjects also prescribed the methylphenidate medication. The subjects had not received any psychotropic medication whatsoever and were not using any other medication after methylphenidate cessation.

Neuropsychological Instruments

In addition to single-photon emission computed tomography, medication monitoring was performed by means of neuropsychological testing and assessment of behavioral functioning in the home situation, using the Child Behavior Checklist [17,18] and Teachers Report Form before methylphenidate medication (= T0), after 3 months of medication (= T1), and after withdrawal of medication (= T2). Furthermore, a comprehensive neuropsychological examination was performed at T0, T1 and T2. To test information processing in the children, the Kaufman Assessment Battery for Children [12] was used. This battery is designed for testing children aged 2.5 to 12.5 years, and includes eight subtests (mean score = 10; S.D. = 3). Based on these eight subscales, two total scales for information processing can be derived: the Sequential information processing scale and the Simultaneous information processing scale (mean score = 100; S.D. = 15) [12,19]. Sequential processing refers to solving problems in which the emphasis is on the serial or temporal order of the stimuli [12] and to measuring the child's ability to tackle and solve problems in turn and with logical consistency. Simultaneous processing is defined as "using a gestalt-like or holistic approach to integrate many stimuli to solve problems" [12,19]. A Continuous Performance Task was used to measure sustained visual attention (Bourdon-Vos test for children [20]). Standard scores can be calculated measuring speed of working and accuracy of working (mean score = 0; S.D. = 1). The Developmental Test of Visual-Motor Integration (VMI Beery) [21] was used to measure the visuomotor integration abilities. The child must copy geometric forms that become progressively more difficult and which are presented simultaneously with three forms on one page (mean score = 100; S.D. = 15).

Procedure

Neuropsychological medication monitoring was performed by using a Continuous Performance Task (speed and accuracy of working), the Developmental Test of Visual-Motor Integration (VMI Beery), and two subtests of the Kaufman Assessment Battery for Children (auditory working memory and Gestalt closure) [12]. To assess short-term auditory working memory, the Number Recall subtest of the Kaufman Assessment Battery for Children was used. During methylphenidate treatment (T1 = after 3 months of methylphenidate medication), and following with-

drawal methylphenidate (= T2) after a duration of 9-20 months treatment neuropsychological testing was repeated.

With ^{123}I -ioflupane (FP-CIT; Nycomed, Amersham, U.K.) single-photon emission computed tomography, baseline dopamine transporter integrity in the brain was measured. Single-photon emission computed tomography was performed with a triple head camera (MultiSPECT3, Siemens) equipped with fan-beam collimators. A semi-automatic template model program was used to calculate the ratios between left striatal and right striatal and occipital regions, respectively. Total time of acquisition was 30 minutes (45 seconds per frame for 40 views per detector). Zoom factor used was 1.23, and the matrix size was 128×128 . Filtered back-projection acquisition was performed. Images were filtered using a Butterworth filter with a cutoff value of 0.4-0.5 and an order of 5. A division between the caudate nucleus and putamen was made. The ratios were corrected using Alderson's brain phantom, with known activities in the caudate nucleus and putamen. Scans were not reviewed in a blinded fashion, because we believed that the use of regions of interest led to an acceptable interrater reliability [22].

After baseline single-photon emission computed tomography studies (= T0), the males received methylphenidate at 0.25-0.6 mg/kg/day. After 3-4 months, single-photon emission computed tomography studies (= T1) were repeated, and a child neurologist and a neuropsychologist saw all children again. The neuropsychologist reevaluated the subjects with the instruments mentioned above. It is our policy to withdraw medication during summer holidays. After a drug-free period of at least 4 weeks (mean 5.6; S.D. = 0.54), a third FP-CIT single-photon emission computed tomography (= T2) was performed. Scans at T0, T1, and T2 were taken under the same conditions. Furthermore, the subjects were again reevaluated by the neuropsychologist.

Data were analyzed with SPSS version 12.0 (SPSS Inc., Chicago, IL). A General Linear Model [23] repeated measures design was used to perform analysis of variance of the FP-CIT single-photon emission computed tomography uptake values before (= T0), during methylphenidate treatment (= T1), and after withdrawal methylphenidate (= T2). To compare the results of two subsequent moments, a paired *t* test was employed.

Table 2. Longitudinal FP-CIT SPECT data: analysis of variance

	TYPE III Sum of Squares	DF	Mean Square	F	Significance
Left caudate	210.845	2	105.423	44.521	0.000
Error (left caudate)	18.934	8	2.368		
Left putamen	244.273	2	122.136	17.863	0.001
Error (left putamen)	54.699	8	6.837		
Right caudate	252.134	2	126.067	41.900	0.000
Error (right caudate)	24.070	8	3.009		
Right putamen	261.930	2	130.965	42.981	0.000
Error (right putamen)	24.376	8	3.047		

General linear model; repeated measures at T0, T1, and T2: tests of within-subjects effects.

Abbreviations:

DF = Degrees of freedom

FP-CIT = ^{123}I -ioflupane

SPECT = Single-photon emission computed tomography

Table 3. Paired samples *t*-test: differences in FP-CIT SPECT uptake values in left and right caudate nucleus, respectively, left and right putamen before (=T0), during methylphenidate treatment (=T1), and after withdrawal of methylphenidate (=T2)

	Pair	T	DF	P Value
Left caudate	T0-T1	7.478	4	0.002
	T1-T2	-10.126	4	0.001
	T0-T2	-2.510	4	0.066
Left putamen	T0-T1	4.599	4	0.010
	T1-T2	-4.686	4	0.009
	T0-T2	-2.065	4	0.108
Right caudate	T0-T1	5.969	4	0.004
	T1-T2	-10.303	4	0.001
	T0-T2	-1.312	4	0.260
Right putamen	T0-T1	4.929	4	0.008
	T1-T2	-11.644	4	<0.0005
	T0-T2	-2.897	4	0.044

Abbreviations as in Table 2.

Results

Baseline FP-CIT single-photon emission computed tomography uptake values in the five subjects varied from 11.78 to 17.00 in the right caudate nucleus and from 10.47 to 12.63 in the left caudate nucleus (normal range: 8.23 ± 2.36) and were 11.07-15.80 in the right putamen and 11.13-14.10 in the left putamen (normal range: 9.18 ± 3.71) (Table 1). Follow-up FP-CIT single-photon emission computed tomography in the five males after using methylphenidate for 3 months revealed a reduction of dopamine transporter activity in the right and left caudate nucleus within a range of 42-74% and 28-64%, respectively. Dopamine transporter activity in the right and left putamen decreased in a range of 28-76% and 23-71%, respectively. The five males manifested a positive clinical response evaluated by neuropsychological questionnaires and tests during methylphenidate treatment. The period in which medication was used before the third drug-naïve FP-CIT single-photon emission computed tomography was carried out varied from 9 to 20 months.

Dopamine transporter activity in the right and left caudate nucleus varied within a range of 11.46-16.72 and 12.13-17.12, respectively. Dopamine transporter activity in the right and left putamen varied within a range of 14.66-16.40 and 12.32-21.37, respectively. Seventeen of these 20 calculated ratios for dopamine transporter activity were above pretreatment values. The increase of dopamine transporter activity above pretreatment values varied within a range of 3-64% (mean: 17%) (Table 2).

Analysis of variance, using General Linear Model-repeated measures, documented significant effects: left caudate nucleus ($F_{(2,8)} = 44.521$, $P < 0.0005$); right caudate nucleus ($F_{(2,8)} = 17.863$, $P = 0.001$); left putamen ($F_{(2,8)} = 41.900$, $P < 0.0005$), and right putamen ($F_{(2,8)} = 42.981$, $P < 0.0005$).

Paired samples *t* test yielded significant differences of the FP-CIT single-photon emission computed tomography

Table 4. Transformed z-scores (mean = 0; S.D. = 1)

	T0	T1	T2	Chi-Square	Significance
CPT speed of working	-1.00 (0.71)	0.75 (1.25)	0.60 (1.14)	6.50	0.039
CPT accuracy of working	-0.20 (1.10)	0.25 (0.96)	0.00 (0.71)	0.13	0.936
Auditory working memory	-0.86 (0.38)	-0.18 (0.81)	-0.66 (0.46)	1.50	0.472
Gestalt closure	0.06 (0.51)	1.10 (0.62)	0.86 (1.12)	6.16	0.037
Visuomotor integration	-0.60 (0.87)	-0.53 (0.78)	-1.22 (0.44)	1.50	0.472

Differences between mean scores before medication (T0), after 3 months of medication (T1) and after withdrawal of medication (T2) were analyzed using Friedman nonparametric test ($n = 5$).

Abbreviation:

CPT = Continuous Performance Task

uptake values in left and right caudate nucleus, respectively, left and right putamen before (= T0), during methylphenidate treatment (= T1), and after withdrawal methylphenidate (= T2) (Table 3). Neuropsychological questionnaires and test results were comparable with pretreatment data (Table 4).

Wilcoxon signed rank test was used to test the significance of the effect between T0 and T1 on the one hand and the difference between T1 and T2 on the other. As the group of children was small ($n = 5$), differences were not significant. We saw a clear tendency of better scores in T1 compared with T0 especially for speed of working and Gestalt closure, which could be expected as medication was initiated. When comparing T2 with T1, we saw a tendency to diminished scores, especially in Gestalt closure and visuomotor integration, which is again in accordance with our expectations.

Discussion

To study possible long-term alterations in the cerebral dopamine system by methylphenidate, single-photon emission computed tomography imaging was used in five males with ADHD after cessation of treatment with methylphenidate. Methylphenidate reduced dopamine transporter activity in the caudate nucleus and putamen in males with ADHD, and after withdrawal of methylphenidate medication an increase of dopamine transporter activity was observed in 17 of the 20 calculated ratios compared with baseline values. Although these data seem to point in one direction, one should be cautious to draw firm conclusions from this, as the numbers are small. We would nevertheless like to make a few points.

Whether this is a simple rebound phenomenon or an active upregulation after treatment with methylphenidate is unclear. To study this phenomenon precisely, more sequential single-photon emission computed tomography scans during treatment would have to be performed. In our small pilot study, we chose a drug-free period of at least 4 weeks, because animal studies demonstrate that, despite the relatively short half-life of methylphenidate, pharmacologic effects on dopamine systems can persist for several days [8].

Little is known of possible consequences of long-term exposure to methylphenidate [24-28]. One study in rats concluded that there is no abuse liability associated with therapeutic methylphenidate treatment [29]. These authors found no increase in dopamine levels in the nucleus accumbens and no sensitized locomotor responses in adolescent rats treated with methylphenidate. Our data after withdrawal of methylphenidate might accord with their observation that methylphenidate does not lead to definite damage of the nigrostriatal dopaminergic pathways [29,30]. However, our data, albeit from a small group of patients, do indicate an increased dopamine transporter activity after cessation of methylphenidate. If one assumes that increased dopamine transporter activity is associated with clinical severity of ADHD, then our observation should be followed up on, to assess whether this rebound phenomenon is temporary or more permanent. It is generally assumed that outgrowth of the disorder ADHD is associated with a decrease per decade of life in striatal dopamine transporters [31].

Taken together, the data presented here seem to support the hypothesis that the dopamine transporter is a primary target for methylphenidate in ADHD [10,31-33]; this seems in contrast with the observation that dopamine transporter gene knockout mice do respond clinically to methylphenidate [34], but others have pointed out that this model does not necessarily represent human ADHD [35]. Although labeled dihydrotetrabenazine appears to be a superior marker for dopaminergic hyperinnervation [36], we believe that the ease of use of single-photon emission computed tomography to assess dopamine transporter activity makes it a superior tool in the clinical setting [32,33,37,38].

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