Methylphenidate down-regulates the dopamine receptor and transporter system in children with attention deficit hyperkinetic disorder (ADHD).

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Methylphenidate Down-Regulates the Dopamine Receptor and Transporter System in Children with Attention Deficit Hyperkinetic Disorder (ADHD)

Abstract

Adults suffering from Attention Deficit Hyperactivity Disorder (ADHD) are known to have disturbed central dopaminergic transmission. With Single Photon Emission Computed Tomography (SPECT) we studied brain dopamine transporter and receptor activity in six boys with ADHD. Three months after initiation of treatment with methylphenidate we found a down-regulation of the post-synaptic dopamine receptor with a maximum of 20% and a down-regulation of the dopamine transporter with a maximum of 74.7% in the striatal system. This corresponded to a positive clinical response evaluated by neuropsychological questionnaires and tests. We suggest that dopamine transporter imaging by SPECT might be used to monitor psychostimulant treatment in children suffering from ADHD.

Key words
ADHD · SPECT · methylphenidate

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood disorder characterised by impaired attention, excessive motor activity, and impulsivity. Although its exact cause is unknown, dopamine pathways in the brain are hypothesized to play an important role [7]. The dopamine system is the main target of the commonly used stimulant medications, e.g. methylphenidate [8]. The increasing frequency with which ADHD is diagnosed has led to a considerable rise in the prescription of these drugs. Long-term use of stimulant medication may adversely affect the maturing brain. Therefore, additional instruments are needed to monitor medical treatments in ADHD more precisely.

Dougherty et al recently showed that Single Photon Emission Computed Tomography (SPECT) may be used to visualise an increased dopamine transporter activity in adult ADHD patients [2,3]. Krause et al [5] demonstrated using SPECT with [Tc-99 m]TRODAT, a ligand specifically binding to the dopamine transporter, that after 4 weeks of methylphenidate treatment, the increased striatal DAT availability becomes lower in adults suffering from ADHD.

Following this line of thought we studied dopamine pathways in six boys with ADHD, before and after methylphenidate treatment.

Patients and Methods

Children (six boys: aged 6 – 10 yrs) included fulfilled the criteria for diagnosis of ADHD, made through a clinical interview, according to DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders). Apart from the ADHD diagnosis additional inclusion criteria were: no additional psychiatric disorders, no seizure disorders, normal EEG examination results, and no current or previous psychopharmacological treatment. On neurological examination all children were normal.

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All boys showed inappropriate behavior within the classroom with severe consequences for their academic and social functioning. The Child Behaviour Check List, an instrument to detect the presence of problem behaviour in children aged 4 – 18 years commonly encountered in ADHD children, was used. Furthermore, an extensive neuropsychological examination (Continuous Performance Task, Kaufman Assessment Battery for Children, developmental test of visual motor integration task, a digit repetition task and gestalt closure task) was performed. After informed consent we measured baseline dopamine transporter and post-synaptic dopamine D_2-receptor integrity in the brain with ^{123}I-Ioflupane (FP-CIT, Nycomed, Amersham, UK) SPECT, and ^{123}I-benzamide (IBZM, Amersham, Cygne, Netherlands) respectively. SPECT was performed with a triple head camera (MultiSPECT3, Siemens) equipped with fan-beam collimators. A semi-automatic template model programme 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 Butterworth clinical filter with a cut-off value of: 0.500.6 and an order of 0.4 – 0.5. A division between the caudate nucleus and putamen was made. The ratios were corrected using Alderson's brain phantom (striatum/occipital cortex for the ^{123}I-IBZM and putamen/occipital cortex and the caudate nucleus/occipital cortex in case of ^{123}FP-CIT, respectively). After baseline SPECT studies, the boys received methylphenidate at 0.25 – 0.6 mg/kg/day. After 3 – 4 months we repeated SPECT studies and a child-neurologist and a neuropsychologist saw all children. The neuropsychologist re-evaluated the boys with the instruments mentioned above.

Results

The baseline and follow-up for IBZM SPECT and FP-CIT SPECT ratios (mean values + S.D.) are shown in Table **1 a** and **1 b** respectively.

Base line IBZM SPECT values in the six boys varied from 3.47 to 4.84 in the left striatum and 3.49 to 5.05 in the right striatum respectively. In the six patients D_2-receptor availability in basal ganglia changed within a range of +4 to – 44% (Table **1 a**) after three months of methylphenidate treatment. We observed no consistent left-right asymmetry of receptor integrity before and after treatment with methylphenidate.

Baseline FP-CIT SPECT values in the six boys varied from 9.28 to 17.0 in the nucleus caudatus (normal range: 8.23 ± 2.36) and were 10.52 – 15.09 in the putamen (normal range: 9.18 ± 3.71). In all six boys a left-right asymmetry (Le < Ri) in DAT activity in the caudate nucleus in the drug naive boys was observed. No left-right consistent asymmetry in DAT activity before treatment was observed in the putamen. Follow-up FP-CIT SPECT in the six boys showed reduction of dopamine transporter (DAT) activity in the left and right caudate nucleus within a range of 27.8 – 64% and 41.9 – 74.5%, respectively. It is of interest that the left-right asymmetry disappeared. DAT activity in the left and right putamen decreased within a range of 22.7 – 71.5% and 32.5 – 74.7%, respectively (Table **1 b**). Behaviour problems, accuracy of working, continuous performance and visuo-motor integration improved according to the tests used (Table **2**).

In one child (no. 3), methylphenidate treatment was withdrawn after one year, to initiate a drug holiday. One month afterwards IBZM SPECT and FP-CIT SPECT were performed. Post-synaptic striatal dopamine receptor density returned to pre-treatment values. On FP-CIT SPECT the right nucleus caudatus and right pu-

Table **1 a** Baseline and follow-up IBZM SPECT ratios (striatum/occipital) in 6 boys with ADHD, treated with methylphenidate

Pat.	*Age (yrs)*	*Baseline striatum*		*Follow-up striatum*	
		Left	*Right*	*Left*	*Right*
1	7	3.83	3.96	4.02	4.60
2	9	4.84	5.05	3.82	3.27
3	9	4.52	4.12	3.77	4.17
4	9	4.57	3.81	2.60	3.30
5	8	4.57	4.63	3.84	3.22
6	10	3.47	3.49	3.29	3.71
Mean (sd)		4.3 (0.52)	4.17 (0.56)	3.55 (0.52)	3.71 (0.56)

Table **1 b** Baseline and follow up FP-CIT SPECT values (ratios) in six boys with ADHD, treated with methylphenidate

Pat.	*Age (yrs)*	*Baseline*				*Follow-up*			
		Left		*Right*		*Left*		*Right*	
		Caudatus	*Putamen*	*Caudatus*	*Putamen*	*Caudatus*	*Putamen*	*Caudatus*	*Putamen*
1	7	9.28	11.57	10.98	10.52	3.56	4.49	4.30	4.62
2	9	11.50	14.10	17.00	15.80	4.14	4.02	4.34	3.84
3	9	13.06	14.25	13.50	15.09	4.72	4.44	5.18	5.23
4	9	12.36	12.06	14.25	11.85	7.19	7.34	5.53	5.89
5	8	10.47	11.22	11.96	11.07	7.55	8.67	6.95	7.47
6	10	12.63	11.13	14.05	14.16	5.67	4.33	5.10	5.08
Mean (sd)		11.60 (1.4)	12.40 (1.4)	13.60 (2.1)	13.10 (2.2)	5.50 (1.6)	5.50 (2.0)	5.20 (1.0)	5.40 (1.2)

Table **2** Baseline and follow-up neuropsychological findings in 6 boys with ADHD, treated with methylphenidate

	Mean before	*Mean after*	*Z*	*P*
Neuropsychological testing				
– *CPT: speed of working*	– 0.80	– 0,25	– 1.633	0.102
– *CPT: accuracy of working*	– 1.00	0.75	– 1.841	0.066
– *Auditory working memory*	– 0.78	– 0.34	– 1.490	0.136
– *Gestalt closure*	– 0.12	0.56	– 1.841	0.066
– *Visuomotor integration*	– 0.64	– 0.15	– 1.826	0.068
Behaviour self report (CBCL)				
– *Externalising behaviour problems*	2.28	1.20	– 1.826	0.68
– *Internalising behaviour problems*	1.72	0.92	– 1.826	0.68
– *Attentional problems*	2.73	1.35	– 1.826	0.68
– *Aggressive behaviour*	2.68	1.43	– 1.826	0.68

Transformed z-scores (mean = 0; standard-deviation = 1); differences between mean scores before and after medication started were analysed using Wilcoxon signed rank test.

tamen ratios returned to pre-treatment values. However, in the left nucleus caudatus and putamen the obtained ratios after withdrawal of methylphenidate were increased by 30% (left nucleus caudatus: pre-treatment 11.50, after withdrawal 14.65; left putamen: pre-treatment ratio 14.10, after withdrawal 21.37) and 50% compared to pre-treatment values, respectively. There were no complications during SPECT investigations. The well known complaints/side effects of methylphenidate were mostly dose-dependent and disappeared over time or with lowering of the daily dose.

Discussion

The signs of underarousal and underfocussed attention in ADHD might be due to a decreased dopamine (DA) and serotonin (5 HT) activity in the fronto-striatal and fronto-mesolimbic areas and/or an increased norepinephrine (NE) activity in the locus coeruleus. The dopamine system consists of two primary ascending systems: a) the nigrostriatal system originating in the substantia nigra and terminating in the striatum, which consists of the caudate nucleus and putamen; and b) the mesocorticolimbic pathway in which several limbic structures receive their dopaminergic input from the midbrain. Both systems are thought to play an important role in the two main characteristics of ADHD, namely, attention and motor behaviour. The association of the dopamine transporter gene (DAT1) with ADHD is of particular importance. Over-expression of DAT results in lower concentrations of dopamine in the synaptic cleft. This relative dopamine deficiency is postulated to be one of the causes of ADHD and is the main target for medication. Different specialised medications have been used in infants with ADHD in order to stimulate DA and HT activity (methylphenidate) or to antagonize NE activity (clonidine). Because of the different neurometabolic action of these above mentioned drugs, it is of interest to study these drug-induced metabolic changes related to neuropsychological functioning in infants with ADHD.

Our results extend those of Dougherty [2] and Krause et al [5], showing an increase of dopamine transporter density in basal ganglia of untreated adult ADHD patients, to the child ADHD population. As a result, a selective deficiency in the availability of dopamine at the synaptic cleft may be the cause of this disorder characterized by impaired attention, excessive motor activity and impulsivity. It is assumed that methylphenidate increases the synaptic concentration of dopamine by blocking the dopamine transporter. SPECT ratios of DAT during treatment in the six boys under study are in accordance with this hypothesis. Our results in six boys indicate that dopamine transporter metabolism is an important primary target of methylphenidate treatment. Dopamine transporter imaging by FP-CIT SPECT may be useful to monitor psychostimulant treatment in ADHD in children.

Recently Ilgin and co-workers [4] were able to show a decrease of midbrain dopamine receptors in ADHD patients as a result of methylphenidate treatment [6]. We found a dopamine receptor down-regulation of the same magnitude, but this was much smaller than the one we observed for the dopamine transporter. The smaller decrease in D_2 dopamine receptor studied by IBZM SPECT is probably secondary to the down-regulation of the dopamine transporter system. An alternative explanation for the dopamine 2 receptor density decrease is an increase in dopamine concentration in the synaptic cleft competing with a tracer for binding sites.

The left-right asymmetry (Ri > Le) in DAT activity in the caudate nucleus, not found in the putamen in the drug naive boys, is consistent with the findings of Castellanos et al [7] and accords with the hypothesis of ADHD as a right hemispheral disorder. Whether asymmetry is physiological in this age group, or is a sign of abnormal function, is still a matter of debate. The studies related to this topic of asymmetry are very inconsistent (Spalletta et al [6]). Moreover, to decide which side is the pathological one is difficult to answer without studying a control sample of normal children. The observation in one boy that after stopping medication, the obtained ratios returned to pre-treatment values on the right side, and above pre-treatment values on the left side, is suggestive of a functional, and not a structural disorder in the dopamine metabolism. This is in accordance with the observation that in all neuroimaging studies performed in ADHD no evidence of brain damage was found. Whether long-term methylphenidate prevents the natural down-regulation in DAT activity with aging and even gives rise to an up-regulation of DAT activity in the left hemisphere is of clinical importance and needs further study.

Conclusion

Dopamine transporter imaging by FP-CIT SPECT may be useful in the pathophysiological clinical research of ADHD as well as in evaluating different treatment approaches.

References

[1] Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1996; 53: 607 – 616

[2] Dougherty DD, Bonab AA, Spencer TJ, Rauch L, Madras BK, Fischmann AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 1999; 354: 2132 – 2133

[3] Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with ADHD. Lancet 2000; 355: 1461 – 1462

[4] Ilgin N, Senol S, Gucuyener K, Gokcora N, Atavci S, Sener S. Is increased D2 receptor availability associated with response to stimulant medication in ADHD. Dev Med Child Neurol 2001; 43: 755 – 760

[5] Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neuroscience Letters 2000; 285; 107 – 110

[6] Spalletta G, Pasini A, Pau F, Guido G, Menghini L, Caltagirone C. Prefrontal blood flow dysregulation in drug naive ADHD children without structural abnormalities. J Neural Transm 2001; 108: 1203 – 1216

[7] Swanson JM, Flodman P, Kennedy J, Spence MA, Moyzis R, Schue S et al. Dopamine genes and ADHD. Neuroscience Biobehavior Rev 2000; 24: 21 – 25

[8] Swanson JM. Dopamine-transporter density in patients with ADHD. Lancet 2000; 355: 1461