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ORIGINAL PAPER

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Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD

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Abstract In this study, we investigated whether availability of striatal dopamine transporter (DAT) may have an influence on the response of adult patients with attention deficit hyperactivity disorder (ADHD) on methylphenidate (MPH). In 18 non-smoking and non-medicated adult patients with ADHD, availability of DAT was measured with [^{99m}Tc] TRODAT-1 SPECT. Then, the patients received methylphenidate (MPH), individually titrated up to 60 mg per day. Ten weeks later, clinical improvement was rated by Clinical Global Impressions scale. In all, 6 patients were classified as non-responders, and 12 responded to MPH. From the non-responders, 5 presented with a DAT availability below that of normal controls of the same age, whereas in the group of responders all patients had elevated DAT availability. There was a significant negative correlation between values for global clinical improvement and striatal DAT availability. In conclusion, ADHD patients with low DAT availability seem not to respond to therapy with MPH.

Key words attention deficit hyperactivity disorder (ADHD) · brain imaging techniques · dopamine transporter · methylphenidate · TRODAT-1 SPECT

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Introduction

ADHD is the most common psychiatric disorder of childhood, affecting 8–12 % of schoolchildren worldwide [8]. In the last years, growing evidence showed that in many patients the disorder persists into adulthood; meanwhile, adult ADHD has been recognized in the literature as a valid clinical entity, affecting as many as 2–4 % of adults [18]. Very high prevalence rates for ADHD have been found for young male prison inmates [15, 16]. Like in childhood, methylphenidate (MPH) is the mainstay of treatment for adult ADHD, reflecting that abnormalities of the dopamine system seem to play an important role in the pathophysiology of ADHD [3]. In some investigations, an elevation of striatal dopamine transporter (DAT) availability has been found with single photon emission computed tomography (SPECT) using specific ligands such as [^{123}I] altropane, [^{99m}Tc] TRODAT-1 and [^{123}I]IPT in children and adults with ADHD [5–7, 10]; only in a study using beta-CIT, which labels also the serotonine transporter, has no elevation of DAT in ADHD been found [19]. It has been shown that striatal DAT availability is lowered very effectively in children and adults with ADHD by methylphenidate (MPH), even in doses as low as 5 mg three times a day [1, 7, 10]. However, some patients presented with a lower binding of TRODAT-1 to the DAT as compared to the controls. In these cases, it remains unclear whether the patients with low DAT availability generally do not respond to stimulants as well as patients presenting with elevated DAT. We hypothesized that generally non-response to MPH, which is known to occur in approximately 30 % of patients with ADHD, may be caused by lower baseline DAT availability in these patients. In this investigation, we, therefore, compare striatal DAT availability in MPH responders and non-responders with ADHD. Only non-smoking patients were included in

this study because earlier results had shown that nicotine, which is frequently abused by patients with ADHD, may have an influence on DAT similar to that of stimulants [11].

Methods

The study was approved by the ethics committee of the University of Munich and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki; all subjects gave informed consent to be included. In 18 non-smoking patients with ADHD (10 males, 8 females, age 21–57 years, mean ± s.d. 39.5 ± 11.1), striatal DAT binding was assessed using [^{99m}Tc] TRODAT-1 SPECT [6, 8]. Diagnosis of ADHD was made by semi-structured interviews according to DSM-IV criteria [2]. No patient had ever been treated with stimulants. Exclusion criteria were a known history of alcohol or drug abuse, or past or current history of psychosis, bipolar disorder, anxiety disorder, major depression or dysthymia. Severity of illness was estimated using the Clinical Global Impressions (CGI-S) scale, with ranges from 1 (normal) to 7 (among the most extremely ill patients) [9]. For evaluation of the DAT, SPECT images were acquired using a triple-headed gamma camera (Philips, former Picker Prism 3000 XP). All subjects were injected with 740 MBq [^{99m}TC]TRODAT-1 three hours before scanning. Images were acquired in a 128 × 128 matrix with a pixel width of 2.11 mm in the projection domain. After reconstruction and attenuation correction, the final slice thickness was 3.56 mm. In each patient, data were evaluated in the two consecutive transverse slices, which showed the highest tracer accumulation in the basal ganglia. Templates were used for defining the striatal regions of interest. The size and shape of the templates were established and optimized using the data of a control group. The templates were adjusted to fit individuals and corrected for anatomical differences in angle, size and distance between the interesting structures. For semi-quantitative evaluation of the DAT, specific binding [(STR-BKG)/BKG] was calculated in the striatum (STR) with the cerebellum used as background (BKG) [7]. The observer was blinded to the clinical data. Because the striatal availability of DAT declines with age by a rate of approximately 6–7 % per decade [14, 20], the value of specific DAT binding was expressed as the percentage of deviation from the value obtained by control groups (20–40, and over 40 years) of the same age without ADHD; this percentage value could be positive (DAT availability above controls) or negative (DAT availability below controls). After SPECT investigation, the patients received MPH with an initial dose of 5 mg, followed by a titration in relation to the clinical improvement up to 60 mg per day. After 10 weeks, global improvement was rated for each patient by the Clinical Global Improvement (CGI-I) scale [9], ranging from 1 (very much improved) to 7 (very much worse). As non-responders, patients with a value of ≥ 4 in the CGI-I scale were defined (no change or worse). DAT availability in the group of non-responders was compared with that of responders (< 4 in CGI-I), using Student's t-test. Severity of illness, assessed with the CGI-S scale [9], was compared between the groups of patients with DAT availability below that of controls and those with a value over that of the controls. A linear regression analysis was employed between DAT availability and values of global improvement in CGI-I. Differences were considered to be statistically significant when $p < 0.05$, and highly significant when $p < 0.01$.

Results

Six patients were classified as non-responders, 12 responded to therapy with MPH (Fig. 1). Severity of illness in the CGI-S scale did not differ significantly in the responders (mean ± s.d. 4.8 ± 0.9) and non-responders (4.5 ± 0.8, non-significant in t-test) (see Table 1). The mean value ± s.d. for DAT availability for responders was 1.52 ± 0.18 and for non-responders 1.10 ± 0.25 [for healthy controls DAT value was 1.22 ± 0.06 (see 7)]. The DAT availability score as percentage of normals of the same age group (mean ± s.d.) was –8.2 % ± 17.1 in the non-responders compared with 22.2 ± 12.5 in the responders ($p < 0.001$). Five patients showed a DAT availability below that of controls of the same age group; all of these patients were non-responders; one of these five patients worsened with MPH, the others were unchanged. The value for global clinical improvement in the CGI-I scale for these five patients was 4.2 ± 0.4 compared with 1.9 ± 0.8 in the 13 patients with DAT values above the controls ($p < 0.001$). Regression analysis showed a highly significant negative regression between DAT availability and the result of global clinical improvement, according to the CGI-I scale ($r = -0.70$, $p < 0.001$).

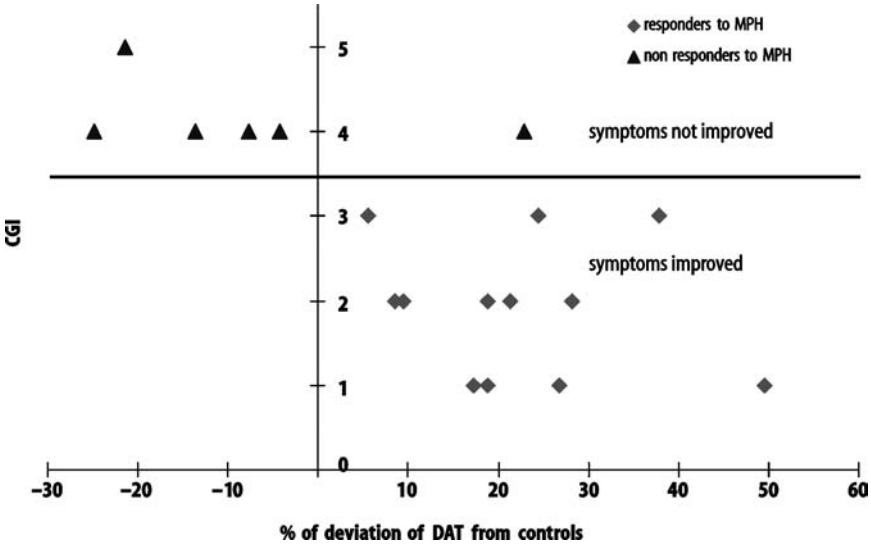

Fig. 1 Specific binding of striatal dopamine transporter (DAT), measured with [^{99m}Tc]TRODAT-1 SPECT, in 18 non-smoking and non-medicated adults with ADHD, expressed as percentage of deviation from values of controls of the same age group, in relation to the values of global improvement in Clinical Global Improvement (CGI) scale after 10 weeks of intake of methylphenidate (MPH)

Table 1 Age, sex, severity of illness [according to Clinical Global Impression Scale (CGI-S)], response to medication with methylphenidate [according to Clinical Global Improvement Scale (CGI-I)] after 10 weeks of therapy, striatal dopamine transporter availability (DAT), expressed as [STR (specific binding in striatum) – BKG (specific binding in the cerebellum as background)]/BKG, and percentage of deviation of the DAT (DAT%) from controls of the age group of 20–40 years (1.27, n = 6) and > 40 years (1.17, n = 8) in 18 adult patients with ADHD

Age	Sex	CGI-S	CGI-I	DAT	DAT%
21	f	6	1	1.90	+50
22	m	4	3	1.75	+38
29	f	6	1	1.61	+23
30	m	4	1	1.49	+17
31	m	5	2	1.39	+9
31	f	5	2	1.54	+21
35	f	5	4	1.56	+23
39	f	5	3	1.58	+24
40	m	5	3	1.34	+6
41	f	6	1	1.51	+19
42	m	5	5	0.92	–21
43	m	4	4	0.88	–25
45	f	5	4	1.12	–4
47	m	5	4	1.01	–14
48	m	5	2	1.27	+9
51	m	3	4	1.08	–8
54	m	4	2	1.50	+28
55	f	3	2	1.39	+19

Discussion

The results obtained in this study seem to indicate that adult ADHD patients with high striatal DAT availability respond better to therapy with MPH than those with low DAT availability; for theoretical reasons, this should be expected because MPH is known to interact directly with the DAT by lowering their availability with the consequence of higher dopamine level in the synaptic cleft. If our preliminary results are confirmed, measurement of DAT could be an important prognostic predictor for therapy with stimulants in ADHD; own experiences show that most of the MPH non-responders benefited from a therapy with amphetamines, which are known to influence the catecholamines in a more complex way than MPH. It should be emphasized that, even when a patient with ADHD has elevated DAT, therapy with MPH does not necessarily result in good clinical improvement: one of our patients was a non-responder despite high DAT availability. On the other hand, most of the patients with high DAT availability showed good clinical improvement after intake of MPH, whereas none of the patients with lowered DAT availability did so. In non-medicated smokers with ADHD, we found that despite low DAT levels the response to MPH was good (unpublished data). Thus, in studies with DAT measurement in adults with ADHD, who are frequently smokers, patients with and without nicotine abuse should be considered separately. Recently, Cheon et al. [4] investigated the correlation between homozygosity for 10-repeat allele at DAT1 gene and response to MPH in 11 children with ADHD, who were also measured for DAT availability using [^{123}I]IPT SPECT. They found that the seven children with 10–10 homozygosity had higher DAT binding ratio than the others; the response to treatment was better in the four children without homozygosity, who all responded well to MPH, whereas only two of the seven children with homozygosity were responders. The finding of better response to MPH in patients without homozygosity is in accordance with the results of Winsberg and Comings [21] and Roman et al. [17]. In our study, no genetic investigation has been carried out. Generally, the influence of 10–10 homozygosity on striatal DAT availability is far from clear: increase, decrease and no influence have been found in earlier studies in normal controls and patients with psychiatric disorders other than ADHD [12, 13]. Unpublished own data in 29 adults with ADHD showed a statistically not significant tendency towards lower DAT availability in patients with 10–10 homozygosity [Krause et al. (2004), Relations between striatal dopamine transporter density and DAT-1 gene in adults with ADHD (Abstract) World J Biol Psychiatry 5(Suppl 1):36]. The results of Cheon et al. [4] are in contrast with our findings, which showed better response in patients with higher DAT availability. Cheon et al. [4] suggest that ADHD children with 10–10 homozygosity possibly need higher doses of MPH than those used in their study because of their higher DAT availability. Furthermore, they noted the fact that the ADHD children without 10–10 homozygosity in their study had a significantly higher degree of severity of ADHD symptoms; thus, the change in symptoms after treatment with MPH could be more pronounced than those in the children with 10–10 homozygosity, who were not affected so severely. Differences between the two studies could also result from the different radiopharmaceuticals used with possibly other kinetics or specificity. Another possibility is that there are differences between children and adults, concerning influence of DAT availability on response to MPH. In our study, it was remarkable that five of the six non-responders were aged above 40 years; this is possibly due to a lower response rate in elderly patients with ADHD. Generally, in both studies the number of patients is too small to come to a final conclusion. Studies with greater collectives of children and adults with ADHD with respect to correlations between DAT availability, response to medication and genetic status should be carried out. An interesting point will be whether, in non-responders to MPH, substances like atomoxetine, which influence the frontal dopamine status by blocking the norepinephrine transporter [13], may be a useful alternative treatment, and whether the effect of different medications will be predictable by summarizing clinical, genetic and radiologic factors.

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