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Absence of Association with DAT1 Polymorphism and Response to Methylphenidate in a Sample of Adults with ADHD

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Abstract

Objective—A polymorphism in the dopamine transporter gene (DAT1) has been previously associated with ADHD and methylphenidate has been hypothesized to block the dopamine transporter. The goal of this study was to examine whether a 40-bp variable number of tandem repeats (VNTR) of DAT1 moderate response and adverse effects associated with methylphenidate treatment of adults with ADHD.

Methods—Subjects were 106 adults with ADHD enrolled in six-week randomized placebo-controlled parallel design trials of methylphenidate (OROS and immediate release preparations).

Results—There was no evidence of an association between DAT1 VNTR and response to methylphenidate ($F(2,100)=0.04$, $p=0.9$). Similarly, there was no pattern of statistically significant association with DAT1 VNTR and cardiovascular or spontaneously reported adverse effects.

Conclusions—We failed to identify an association with DAT1 and the response or tolerability of methylphenidate in adults with ADHD.

Keywords

dopamine transporter (DAT1); methylphenidate; attention-deficit/hyperactivity disorder (ADHD); medication response; adults

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a highly heritable condition (Faraone et al. 2005) that is now estimated to effect 3%–5% of adults in the US population (Kessler et al. 2005). ADHD in adults is associated with similar emotional and functional impairments (Biederman et al. 2004) as observed in children with the disorder and a similar response to treatment with methylphenidate when equipotent doses are used (i.e. 1.0 mg/kg) (Biederman et al. in press; Spencer et al. 2005).

Dysregulation of dopamine has been implicated in the pathophysiology of ADHD. Methylphenidate, which has been shown to have therapeutic effects on ADHD symptoms, blocks the dopamine transporter (Madras et al. 2005). There is mounting evidence that individuals with ADHD have increased dopamine transporter activity than non-ADHD individuals (Spencer et al. 2006). Emerging data from meta analyses have identified a small

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but statistically significant association between ADHD and the 10-repeat allele of a variable number tandem repeat (VNTR) in the 3'-unstranslated region (3'-UTR) of the DAT gene (DAT1) in both case control and family-based studies (Faraone et al. 2005). A recent *in vitro* study found that the 10-repeat variant was associated with a 50% increase in DAT binding density over that of the 9-repeat variant (Vanness et al. 2005). Thus, although this VNTR falls outside the gene's coding region, it may have functional implications via modulatory influences on DAT density (Vanness et al. 2005).

Although this evidence would suggest that DAT1 genotype moderates treatment response to MPH in individuals with ADHD, results from the few pharmacogenomic studies examining this issue have been equivocal (McGough 2005). While early studies indicated that the homozygous 10/10 genotype was associated with decreased response to methylphenidate (Roman et al. 2002; Winsberg and Comings 1999), subsequent studies have found either an increased response with the presence of a 10-repeat allele (see (McGough 2005; Stein et al. 2005)), or no association (Langley et al. 2005). Recently, Joober et al (2005) presented findings in which heterozygous 9/10 individuals showed the most positive response to methylphenidate, while homozygous individuals of either type were more responsive to placebo.

Thus, the main goal of this study was to evaluate the whether DAT1 genotype moderates response and adverse effects associated with treatment with methylphenidate in adults with ADHD. To this end we used data from two randomized, double blind, placebo controlled 6-week clinical trials of OROS and immediate release methylphenidate. Based on the pediatric literature we hypothesized that DAT1 would moderate response to methylphenidate treatment in adults with ADHD.

Materials and Methods

SUBJECTS

Subjects were outpatient adults with ADHD between 19 and 60 years of age. To be included subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview. We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, I.Q. <80, dementia, other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis, suicidal), drug or alcohol abuse or dependence within the six months preceding the study, or previous adequate trial of methylphenidate. We also excluded pregnant or nursing females. The human research committee approved this study, and all subjects completed a written informed consent.

PROCEDURE

Randomized Trial of IR-MPH(tid) (Spencer et al. 2005)—This was a double-blind, randomized, 6 week, placebo-controlled, parallel design study of MPH in the treatment of adult ADHD. Patients were randomized to MPH or placebo at a ratio of 2.5:1. Weekly supplies of MPH or placebo were dispensed by the pharmacy in identically appearing 5 and 10 mg capsules. Study physicians prescribed medication under double blind conditions in three times a day dosing (7:30 am, noon and 5 pm). Compliance was monitored by pill counts at each physician visit. Study medication was titrated (forced titration) up to 0.5 mg/kg/day by week one, 0.75 mg/kg/day by week two and 1.0 mg/kg/day by week three, in TID dosing, unless adverse effects emerged. The dose could be increased to a maximum of 1.3 mg/kg by weeks 5 and 6 if efficacy was partial and treatment was well tolerated.

Randomized Trial of OROS-MPH (Biederman et al. in press)—This was a double-blind, randomized, 6-week, placebo-controlled, parallel design study of OROS-MPH. Patients were randomized to OROS-MPH or placebo at a ratio of 1:1. Medication was titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal response, dose was increased by 36 mg/day but only for subjects who failed to attain an *a priori* definition of improvement (CGI-Improvement of 1 or 2 or a reduction in the AISRS score larger than 30%) and who did not experience adverse effects. All doses of OROS-MPH and placebo were delivered in identically appearing tablets.

Comparability of the Original Studies (Biederman (unpublished)—Three groups created from the 2 clinical trials: Placebo, IR-methylphenidate (tid) and OROS-methylphenidate. Eight-five percent (N=98) of placebo treated subjects, 75% (N=76) of the IR-methylphenidate (tid) treated subjects, and 81% (N=54) of the OROS- methylphenidate treated subjects completed the 6-week trial (p=0.3). In placebo, IR- methylphenidate (tid) and OROS-methylphenidate subjects the reasons for dropout were: adverse effects (N=5, N=14, and N=9, respectively), lost to follow-up (N=3, N=3, and N=4, respectively) procedure/lack of compliance (N=6, N=9 and N=0, respectively), and lack of effect (N=4, N=0, and N=0, respectively). There were no differences in dose at endpoint between IR-methylphenidate (tid) and OROS-methylphenidate (0.97±0.21 mg/kg versus 0.99±0.32 mg/kg; p=0.09) but both were statistically significantly lower than placebo (1.15±0.21 mg/kg; p≤0.001). At endpoint, 66% (N=44) of subjects receiving OROS- methylphenidate and 70% (N=71) of subjects receiving IR-methylphenidate (tid) were considered responders compared with 31% (N=36) on placebo (p<0.001), using our *a priori* definition of response of much or very much improved on the CGI *plus* more than a 30% reduction in symptoms on the AISRS. Both active medication groups were statistically significantly more likely to demonstrate this level of improvement compared with placebo (p<0.001) but not when compared to one another (p=0.6).

ASSESSMENT

To assess inclusion and exclusion criteria, subjects underwent a comprehensive clinical assessment which included a psychiatric evaluation by a board certified psychiatrist, structured diagnostic interview, medical history, vital signs, and laboratory assessments (liver function tests, complete blood count, weight, vital signs, and electrocardiogram). The structured diagnostic interview used was the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1997), supplemented for childhood disorders by modules (DSM-IV ADHD and conduct disorder) from the Kiddie SADS-E (Epidemiologic Version). (Orvaschel 1994). This interview was selected because it diagnoses both lifetime and current month psychopathology and has been used extensively in clinical and research settings (Biederman et al. 2004; Spencer et al. 2005).

To have been given a full diagnosis of adult ADHD, the subject must have: a) met full DSM-IV-TR criteria (at least 6 of 9 symptoms) for inattentive and/or hyperactive/impulsive subtypes (American Psychiatric Association 2000) by the age of seven as well within the past month (i.e. ADHD-IA, ADHD-HI and ADHD-C subjects were enrolled); b) described a chronic course of ADHD symptomatology from childhood to adulthood and c) endorsed a moderate or severe level of impairment attributed to the ADHD symptoms.

The Adult ADHD Investigator System Report Scale (AISRS), shown to be sensitive to drug effects in pediatric and adult populations (Spencer and Adler 2004), assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0=not present; 3=severe; overall minimum score=0; maximum score=54). Adverse events were elicited by spontaneous reports through open-ended questions at each visit. Weight and vital signs were

obtained at each visit and an ECG was performed at baseline and endpoint. Raters and subjects were blind to treatment assignment.

MICROSATELLITE GENOTYPING FOR DAT1

All genotyping was conducted at the Psychiatric and Neurodevelopmental Genetics Unit of the Massachusetts General Hospital. Lab technicians were not aware of the source of the samples and all genotyping was performed in duplicate. DNA was extracted from blood and the completion rate was 100%. Genomic DNA (1.4 ng) was amplified in a of 7 μl reaction using KlenTaq DNA Polymerase (0.2 U), the proprietary KlenTaq Buffer (1X), dNTPs (200 μM each), Mg (2.5 mM), Betaine (0.5M) and the marker specific primers (0.2μM). Primers were ordered from Applied BioSystems and are as follows: DAT1-F 6FAM-TGTGGTGTAGGGAACGGCCTGAG, DAT1-R CCTCCTGGAGGTCACGGCTCAAGG. The DAT1-R primer also contains a proprietary tail that helps stabilize the amplified product. Amplification is performed with the following basic protocol. Samples are heated at 92°C for 9 minutes to activate the KlenTaq Polymerase. This is followed by twelve cycles of denaturation for 30 seconds at 93°C, annealing for 30 seconds beginning at 6.5°C above the ideal temperature and dropped 0.5°C every cycle until the ideal temperature is reached, and primer extension at 72°C for 45 seconds. A subsequent 36 cycles are performed at the ideal annealing temperature followed by a final extension at 72°C for 1 hour. The ideal temperature was determined empirically and was 65°C for DAT1. Amplified products are pooled and combined with size standard (LIZ-250) before being analyzed on an ABI-3730. GeneMapper v3.5 is used to analyze the raw results from the ABI3730, however, a genotype is not considered final until two laboratory personnel (blinded to phenotype) have independently checked (and corrected) the GeneMapper results and both individuals are in agreement.

STATISTICAL ANALYSIS

All analyses were intention to treat (ITT) with the last observation carried forward (LOCF) for subjects who did not complete the full study schedule. Analysis of variance was used to analyze continuous variables (AISRS score, cardiac measures) and Pearson's chi-square test or Fisher's exact test (in the event of sparse data) was used to analyze categorical variables (adverse effects). The impact of DAT1 genotype on the response to methylphenidate was tested with drug by genotype interactions. Effect sizes were calculated as the difference in the mean change divided by the pooled standard deviations (Cohen 1988). Differences were considered statistically significant if two-sided p-values were less than 0.05.

Results

Two hundred eighty five adults with ADHD were randomized to immediate-release methylphenidate or placebo (N=102 and N=42, respectively) in Spencer et al (2005) and to OROS-methylphenidate or placebo (N=67 and N=74, respectively) in Biederman et al (in press). DAT1 genotypes were available in 66 (32 OROS- and 34 immediate-release) methylphenidate subjects and 40 (30 OROS and 10 immediate) placebo subjects. The change in AISRS scores was numerically, but not statistically significantly larger ($F(1,281)=0.25$, $p=0.6$) in those subjects providing DNA than in those not providing DNA (-18.4 ± 9.2 vs. -17.0 ± 11.2 in the methylphenidate arm and -11.1 ± 11.9 vs -8.2 ± 10.8 in the placebo arm). The effect size in both the group that provided (0.75) and did not provide (0.67) DNA was in the moderate range (Cohen 1988).

Consistent with large population studies (Doucette-Stamm et al. 1995), the 10-repeat allele frequency was 74% and deviation from Hardy-Weinberg equilibrium was not significant in either the methylphenidate ($\chi2(1)=0.08$, $p=0.8$) or placebo groups ($\chi2(1)=0.2$, $p=0.7$).

Demographic and baseline clinical characteristics stratified by DAT1 genotypes are presented in Table 1. There were no statistically significant differences in age, sex, ADHD age at onset, number of symptoms and clinical ratings of severity (all drug by genotype interactions were statistically insignificant, Table 1).

At baseline there was no statistically significant difference in AISRS scores at baseline (Table 2). The interaction of drug status with DAT1 genotype was also not statistically significant for the change from baseline in the AISRS. The methylphenidate effect size was similar in each group of subjects: 0.59 in 10/10 subjects, 0.71 in 9/10 subjects, and 0.59 in 9/9 subjects. There was no statically significant difference ($F(2,63)=1.0$, $p=0.4$) in the final dose (endpoint) amongst methylphenidate responders with 10/10- repeat (0.97±0.28 mg/kg), 9/10-repeat (0.91±0.28 mg/kg) and the 9/9-repeat (0.81±0.32 mg/kg) variant.

Cardiovascular data are presented in Table 3. With one exception there was no difference in the relative change from baseline to endpoint in methylphenidate and placebo treated subjects stratified by DAT1 genotype (Table 3). The one statistically significant drug by genotype interaction of change scores was in the QT interval accounted for by the 9/10-repeat group (methylphenidate subjects decreased while the placebo subjects increased, p-0.004).

The rates of adverse effects are presented in table 4. Because there were several instances with sparse data, we could not model drug/genotype interactions. Nonetheless, DAT1 genotype did not statistically significantly affect the rate of any adverse effect in the methylphenidate and placebo subjects tested separately (Table 4). There was no statistically significant difference in the proportion of completers in the 10/10-repeat (N=34, 87%), 9/10-repeat (N=21, 87%) and the 9/9-repeat (N=3, 100%) variant groups.

Discussion

In this report we evaluated the putative impact of DAT1 on the efficacy and tolerability of methylphenidate in adults with ADHD. Subjects homozygous for the 10-repeat DAT1 allele were not distinguishable from heterozygous 9/10 or homozygous 9-repeat allele subjects in level of symptom reduction, dose required for response, cardiac side effects, or spontaneously reported adverse effects. Although tempered by the small size, these results fail to support a role of the DAT1 VNTR in the 3'-UTR as a moderator of efficacy or tolerability of methylphenidate treatment for adults with ADHD.

The potential of pharmacogenomic research is to identify genetic markers that will enable genotype based clinical algorithms that optimize response and tolerability for individual patients (McGough 2005). The literature on DAT1 highlights the current challenges to achieving this goal, however. Although methylphenidate may exert a therapeutic effect on ADHD via blockade of the dopamine transporter and there is indication that the 10-repeat DAT1 allele is associated with ADHD, the literature examining modification of treatment response has been mixed and inconclusive.

The current report is the second to demonstrate no difference in response based upon DAT1 genotype (Langley et al. 2005). As discussed by Langley et al (2005) the lack of consistency in the literature could be due to etiological heterogeneity or, more likely, due to small sample sizes that lead to reduced power or false positive findings. In a recent literature review, it was shown that an equal number of studies indicate either a reduced or enhanced response to methylphenidate in subjects with the 10-repeat allele (McGough 2005). Taking together, the literature converges on a pattern of results that seem to be consistent with chance findings (i.e. Type I or Type II errors).

In the event that DAT1 genotypes do not modify the rate of response to methylphenidate, it is possible that they could impact the doses required to achieve a therapeutic effect. Our studies were designed to determine optimal dose after either a 3-week forced titration (Spencer et al. 2005) or a flexible dosing protocol (Biederman et al. in press). Among responders we did not find a statistically significant difference in dose between DAT1 genotypes. However, the lowest dose (0.8 mg/kg) was used in subjects with the 9/9-repeat genotype. Considering the *in vitro* findings that the 10/10 variant may be associated with an increased DAT binding density (Vanness et al. 2005), larger studies specifically designed to address genotype differences in the dose-response relationship in adults with ADHD are needed.

We also examined cardiovascular and adverse effects in these data. Although we found no consistent statistical evidence of any association with DAT1 genotypes on these variables, qualitative differences in the 9/9-repeat subjects raises a few questions. In particular, we found a 16-point increase in systolic blood pressure in these subjects that, coupled with the qualitatively lower dose in this group, may indicate that individuals with the 9/9-repeat genotype are at greatest risk for adverse cardiovascular effects and can only tolerate lower doses. However, the number of subjects with the 9/9-repeat (N=6) was very small resulting in reduced power to detect differences with this group and imprecise point estimates. While the difference between groups on AISRS scores was so small that very large sample sizes would be needed to detect them, differences in blood pressure and dose were large enough that moderately larger studies would have the power to follow-up on these findings.

This study is also limited in that we only examined a single marker that does not provide adequate information about other variants across this rather large gene. Thus, we can only comment on the role of the VNTR in the 3'-UTR with these data. Langley et al (2005) did examine three additional single nucleotide polymorphisms (SNPs) in the promoter region of the gene and failed to find any association with response to methylphenidate. Considering the strong theoretical basis indicating a role of DAT in the etiology and treatment of ADHD a more rigorous examination of this gene is warranted.

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Table 1

Demographic and Clinical Characteristics at Baseline

	DAT1 Genotype						
	10/10		9/10		9/9		
	MPH N=39	Placebo N=20	MPH N=24	Placebo N=17	MPH N=3	Placebo N=3	
Age (years)	36.9±9.1	37.9±8.3	35.1±6.9	38.7±8.8	33.3±6.7	39.8±7.6	F(2,100)=0.5, p=0.6
Sex (male)	23 (39)	11 (55)	13 (54)	10 (59)	2 (67)	1 (33)	$\chi^2_{(2)}$=0.7, p=0.7
ADHD							
Onset	4.4±3.1	4.6±2.7	5.4±2.7	4.4±2.5	2.7±2.9	5.0±1.0	F(2,91)=1.1, p=0.3
Symptoms (Lifetime)	14.1±3.4	14.2±2.9	14.4±3.2	14.2±2.4	15.0±2.7	11.7±3.5	F(2,91)=0.8, p=0.4
Symptoms (Current)	11.6±3.5	11.7±4.8	12.2±4.5	12.4±2.6	9.0±2.0	14.0±3.6	F(2,91)=1.1, p=0.3
CGI Severity	4.7±0.6	4.5±0.7	4.7±0.6	4.8±0.7	4.7±0.6	4.7±0.6	F(2,100)=0.4, p=0.7

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Table 2

Improvement in ADHD symptoms

	DAT1 Genotype						
	10/10		9/10		9/9		
	MPH N=39	Placebo N=20	MPH N=24	Placebo N=17	MPH N=3	Placebo N=3	
AISRS Scores							
Baseline	32.3±7.1	31.8±8.8	30.8±8.2	31.4±8.8	28.3±6.4	31.3±3.5	F(2,100) = 0.16, p=0.8
Change Score	−16.5±11.2	−12.1±12.4	−18.5±13.0	−10.5±9.7	−13.7±8.0	−7.0±6.6	F(2,100) = 0.04, p=0.9

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Table 3

Cardiac Parameters and Baseline and Endpoint

	DAT1 Genotype						
	10/10		9/10		9/9		
	MPH N=39	Placebo N=20	MPH N=24	Placebo N=17	MPH N=3	Placebo N=3	
Systolic Blood Pressure							
Baseline	124.5±12.9	121.9±15.1	119.1±12.7	123.6±9.8	122.7±16.9	115.0±9.0	F(2,100)=1.1, p=0.3
Change	0.6±12.5	−3.7±11.0	4.6±12.0	2.1±11.7	16.3±11.1	−3.0±16.6	F(2,100)=1.3, p=0.3
Diastolic Blood Pressure							
Baseline	73.3±10.1	71.7±11.0	70.0±9.1	73.8±8.9	71.0±7.0	68.0±7.0	F(2,100)=1.0, p=0.4
Change	3.1±7.3	−2.8±10.3	5.2±9.0	−2.8±6.9	−2.7±5.8	1.7±12.0	F(2,100)=1.4, p=0.3
Pulse							
Baseline	75.5±13.2	75.8±10.7	77.5±11.0	76.9±13.2	72.3±20.1	75.3±14.0	F(2,100)=0.06, p=0.9
Change	4.0±12.3	−4.3±9.5	0.4±10.5	−6.8±11.2	−3.3±5.9	−7.7±19.1	F(2,100)=0.09, p=0.9
PR Interval							
Baseline	156.6±26.6	152.2±13.5	139.0±20.1	158.7±20.9	160.0±14.1	139.0±1.4	F(2,94)=4.0, p=0.03
Change	−5.1±11.0	−3.2±9.4	3.2±13.3	−1.3±8.8	4.0±8.5	−2.0±2.8	F(2,84)=1.0, p=0.4
QRS Interval							
Baseline	92.0±13.2	87.6±11.2	89.6±9.4	89.8±11.0	98.0±2.8	91.3±1.2	F(2,94)=0.5, p=0.6
Change	1.0±8.3	−1.8±5.9	−2.5±8.2	−2.1±7.5	0.0±0.0	−0.7±4.6	F(2,84)=0.4, p=0.6
QT Interval							
Baseline	393.9±26.1	400.0±29.1	398.5±33.9	391.3±36.8	405.0±35.4	436.0±33.6	F(2,94)=1.1, p=0.3
Change	−12.9±26.2	−0.1±28.2	−15.5±28.0	14.4±28.5	20.0±14.1	−22.0±40.4	F(2,84)=3.7, p=0.03
QTC Interval							
Baseline	411.6±15.4	412.8±16.9	409.4±17.5	410.1±11.7	402.0±2.8	424.3±11.0	F(2,94)=1.1, p=0.3
Change	3.7±14.8	−0.1±13.7	4.3±15.9	2.3±15.2	14.0±8.5	−16.3±15.1	(F2,84)=2.0, p=0.1

Table 4

Adverse Effects

	DAT1 Genotype						Fisher's Exact Test	
	10/10		9/10		9/9			
	MPH N=39	Placebo N=20	MPH N=24	Placebo N=17	MPH N=3	Placebo N=3	MPH p-value	Placebo p-value
Dry Mouth	14 (36)	1 (5)	7 (29)	1 (6)	0 (0)	1 (33)	0.3	0.6
Headache	15 (38)	4 (20)	9 (38)	6 (35)	0 (0)	2 (67)	0.2	0.6
Decreased Appetite	14 (36)	1 (5)	3 (12)	0 (0)	0 (0)	0 (0)	0.9	0.08
GI Complaints	7 (18)	2 (10)	7 (29)	2 (12)	0 (0)	2 (67)	0.08	0.4
Sleep Problems	7 (18)	2 (10)	2 (8)	1 (6)	0 (0)	0 (0)	0.9	0.7
Moodiness	7 (18)	1 (5)	3 (13)	3 (18)	0 (0)	0 (0)	0.8	0.5

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