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ORIGINAL PAPER

Adrenergic α2A receptor gene is not associated with methylphenidate response in adults with ADHD

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Abstract Adrenergic α2A receptor gene (*ADRA2A*) is one of the most promising candidate genes for ADHD pharmacogenetics. Thus far, three studies have investigated the association between the *ADRA2A* −1291 C>G polymorphism and the therapeutic response to methylphenidate (MPH) in children with ADHD, all of them with positive results. The aim of this study is to investigate, for the first time, the association between three *ADRA2A* polymorphisms (−1291 C>G, −262 G>A, and 1780 C>T) and the response to MPH in adults with ADHD. The sample comprises 165 Brazilians of European descent evaluated in the adult ADHD outpatient clinic of the Hospital de Clínicas de Porto Alegre. The diagnostic procedures followed the DSM-IV criteria. Drug response was assessed by both categorical and dimensional approaches, through the scales Swanson, Nolan, and Pelham Rating scale version IV and the Clinical Global Impression-Severity Scale, applied at the beginning and after the 30th day of treatment. We found no evidence of association between the three *ADRA2A* polymorphisms and the therapeutic response to MPH treatment. Our findings do not support a significant role for the *ADRA2A* gene in ADHD pharmacogenetics, at least among adult patients.

Keywords Attention deficit/hyperactivity disorder · Pharmacogenetics · *ADRA2A* gene · Methylphenidate

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly heritable psychiatric disorder characterized by impairments in attention, inhibitory control, and increased motor activity [1]. The core symptoms of the disorder arise during the childhood and are accompanied by high rates of comorbidities and significant social, emotional, and occupational impairments [6, 7, 55]. The worldwide prevalence of ADHD is estimated in 5.3% in children and adolescents [42] and 2.5% in adults [50].

Although the precise mechanisms of ADHD development are not completely understood, converging evidence from genetic and neurobiology studies strongly suggest that dysfunctions in the catecholamine neurotransmission play a crucial role in the pathophysiology of the disorder [4, 45]. In accordance, the clinical experience has demonstrated that stimulant drugs, which potentiate the catecholamine neurotransmission, are the most effective ADHD treatment [24, 59]. Methylphenidate hydrochloride (MPH) is the most prescribed psychostimulant for children and adults with ADHD and several controlled clinical trials have proven the effectiveness and safety of the treatment [8, 15, 24, 28]. However, many patients still do not show an appropriate clinical response to the MPH treatment [29, 51, 52]. Additionally, there is a considerable variability in dosage, tolerability, and adherence among responders [9, 20].

Taking into account this scenario, several efforts to identify genetic factors associated with the variability in the therapeutic response to MPH treatment have focused on catecholaminergic genes, but most loci have not revealed robust findings across replications. Likewise, the results of the first genome-wide association study for the response to MPH did not reveal any markers that met criteria for statistical significance genome wide [38]. Among the most promising pharmacogenetic findings revealed is the adrenergic α2A receptor gene (*ADRA2A*) [17, 27]. In fact, *ADRA2A* is also a candidate gene in ADHD etiology. A meta-analysis revealed substantial heterogeneity in effect sizes of an *ADRA2A* polymorphism (1780 C>T) across studies, suggesting that more studies are warranted to explain these findings [19]. Adrenergic α2A receptors are important modulators of the prefrontal cortex (PFC) function, which is highly relevant to ADHD [3, 4], and there is evidence that α2A receptors mediate directly the therapeutic effects of MPH in the PFC [2].

Some studies have already shown an effect of the *ADRA2A* −1291 C>G polymorphism in the response to treatment in psychiatric disorders, such as depression [33, 57] and schizophrenia [40]. In ADHD, three studies have investigated the association between the −1291 C>G polymorphism and the therapeutic response to MPH in children samples [10, 12, 43]. In all studies, the presence of the G-allele was associated with improvement in ADHD symptoms after MPH treatment, providing additional evidence for the involvement of the noradrenergic system in the modulation of MPH action. Interestingly, the influence of the *ADRA2A* −1291 C>G polymorphism in the response to MPH treatment seems to be more specific for the symptoms of inattention [12, 43], which is in accordance with previous reports of an effect of the G-allele in the inattentive dimension of ADHD [41, 46, 47, 49].

Thus, considering the possible effect of the *ADRA2A* gene in therapeutic response to MPH treatment, the aim of this investigation is to evaluate the association between three *ADRA2A* polymorphisms and the clinical response to MPH in a sample of adults with ADHD. In addition to the most investigated *ADRA2A* polymorphism, −1291 C>G, we selected two other (−262 G>A and 1780 C>T), since there is evidence that the main haplotype families of the gene can be characterized by these 3 markers [30].

Materials and methods

Subjects

The sample comprised 165 adults with ADHD from the ADHD Outpatient Program at the Hospital de Clinicas de Porto Alegre. The inclusion criteria were as follows: (a) Native-Brazilian of European descent; (b) age 18 years or older; (c) fulfillment of DSM-IV diagnostic criteria for ADHD [1], both currently and during childhood; and (d) eligibility to immediate-release methylphenidate (IR-MPH) treatment. Exclusion criteria were the presence of: (a) clinical contra-indication to IR-MPH; (b) any significant neurological disease (e.g., delirium, dementia, epilepsy, head trauma, multiple sclerosis); (c) current or past history of psychosis; (d) intelligence quotient (IQ) <70, and (e) current clinically significant comorbid disorders (excluding tobacco dependence, oppositional defiant disorder (ODD), and antisocial personality disorder). The project was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the hospital (IRB # 00000921). All patients signed an informed consent. This protocol is part of a larger study on predictors of MPH treatment response, including phenotypic characteristics [56].

The diagnostic procedures in our unit have been described elsewhere [16, 22, 25]. Briefly, diagnoses of ADHD and comorbidities were achieved through the following semi-structured interviews: (1) K-SADS-E (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version), adapted to adults as described in Grevet et al. [21] and Karam et al. [26], for ADHD and ODD; (2) SCID-IV-R (Structured Clinical Interview for DSM-IV) for the Axis I psychiatric comorbidities, and (3) M.I.N.I (Mini-international Psychiatric Interview) for the diagnoses of conduct and antisocial personality disorder. The estimated IQ scores were obtained from the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) [58] administrated by a trained psychologist.

Pharmacological intervention and drug response

Patients were treated with weekly increases in IR-MPH dose until symptom control or occurrence of limiting adverse effects. All patients took at least the minimum MPH dose of 0.3 mg/kg/day. Although this dose is considered low, there is evidence that it may be effective [48]. IR-MPH was administered twice or three times a day according to the patient's daily activities. Patients were usually reassessed one or two times in a period of 30 days after initiation and titration of IR-MPH. The final measurements were taken after the 30th day of treatment.

The outcome measures of MPH treatment were the Portuguese version of the Swanson, Nolan, and Pelham Rating Scale version IV (SNAP-IV) [54] and the Clinical Global Impression-Severity scale (CGI-S) [23]. Stimulants side effects were assessed with the Barkley Side Effect Rating Scale (SERS) [5]. All scales were applied at the beginning of the treatment (baseline levels) and after the

30th day of treatment. A detailed description of the application of these scales in MPH pharmacogenetics is in accordance with Contini et al. [11].

Drug response was assessed by both categorical and dimensional approaches. The a priori categorical definition of response was a 30% or greater symptom reduction in SNAP-IV and a CGI-S score of two points or less. The dimensional evaluation of drug response was measured by the variation in SNAP-IV scores.

Laboratory methods

DNA was extracted from whole blood by an adaptation of Lahiri and Nurnberger [31]. The *ADRA2A* −1291 C>G (rs1800544) polymorphism was amplified using the polymerase chain reaction (PCR) conditions adapted from Lario et al. [32] and Lima et al. [34]. The −262 G>A (rs1800545) and the 1780 C>T (rs553668) polymorphisms were genotyped using the Taqman SNP genotyping assays (Applied Biosystems), according to the manufacture's recommended protocol.

Statistical analysis

Responders and non-responders were compared regarding demographic characteristics, IQ, baseline SNAP-IV, CGI-S and SERS scores, ADHD subtype, comorbidities, use of concomitant medication, and MPH dose. The chi-square test was used for categorical variables and the ANOVA test for continuous variables. The characterization of the linkage disequilibrium and the estimation of the haplotypes comprising the three *ADRA2A* polymorphisms were performed with the MLOCUS program [35, 36].

The association between specific alleles or haplotypes with the categorical response to MPH treatment was analyzed by logistic regression analyses. Genetic effects in the dimensional variation in SNAP-IV scores after the MPH treatment were analyzed by ANCOVA considering baseline scores as covariates. Potential confounders (demographic characteristics, IQ, ADHD subtype, comorbidities, use of concomitant medication, and MPH dose) were included as covariates using a statistical definition (association with both the study factor and outcome for a $P \leq 0.20$) [37].

Results

The sample comprised 90 men and 75 women. The mean age of the subjects was 35 years (±11). Ninety-three percent of patients were currently employed, and the average number of years of schooling was 13.9 (±3.6). The average estimated full scale IQ of the sample is 101.6 (±9.5). Mean baseline scores for the overall symptoms of ADHD according to the SNAP-IV and CGI-S were 1.7 (±0.5) and 4.5 (±0.7), respectively. The most frequent comedications were antidepressants and mood stabilizers, with no significant evidence for pharmacointeractions.

To confirm the general efficacy of MPH treatment in this sample, we explored effects of its use over SNAP-IV total scores during the first month of treatment. A significant reduction in total scores was detected during the follow-up period ($t = 22.90$; $P < 0.001$). One hundred and thirty-seven patients (83%) responded to treatment (responders), as defined by a 30% or greater symptom reduction in SNAP-IV plus a CGI-S score of two points or less. Twenty-eight participants (17%) failed to show a clinical response to MPH. The characteristics of both groups (responders and non-responders) are given in Table 1.

The estimated allele frequencies for the *ADRA2A* polymorphisms were (1) 0.67 (C) and 0.33 (G) for the −1291 C>G; (2) 0.88 (G) and 0.12 (A) for the −262 G>A and (3) 0.80 (C) and 0.20 (T) for the 1780 C>T. Genotype frequencies in all polymorphisms did not reveal a significant deviation from expected values for the Hardy–Weinberg equilibrium (all $P > 0.20$). The haplotype analysis revealed that the polymorphisms are in strong linkage disequilibrium. The pairwise linkage disequilibrium was as follows: −1291/−262: $D' = 1.00$, $r^2 = 0.28$, $P < 0.001$; −1291/1780: $D' = 0.95$, $r^2 = 0.46$, $P < 0.001$; −262/1780: $D' = 1.00$, $r^2 = 0.034$, $P < 0.001$. The most frequent haplotypes observed in our sample and respective frequencies were C-1291/G-262/C1780 (0.67); G-1291/G-262/T1780 (0.19), and G-1291/A-262/C1780 (0.12).

Considering the low frequency of homozygous genotypes for the less frequent alleles, the statistical analyses for the MPH response were performed between carries (homozygous plus heterozygous) and non-carriers of the rare alleles. In the haplotype analysis, we focused on the risk haplotype for ADHD (G-1291/G-262/T1780) (carries vs. non-carries), as suggested by Park et al. [41]. The results of the stratified analysis of response to MPH are presented in Tables 2 and 3. There were no significant differences in genotype or haplotype frequencies between MPH responders and non-responders in any *ADRA2A* polymorphisms (Table 2). Likewise, there are no significant effects of the *ADRA2A* polymorphisms on the response to MPH evaluated through the variation between pre- and post-treatment SNAP-IV scores (Table 3).

Discussion

This is the first pharmacogenetic investigation into *ADRA2A* polymorphisms in adults with ADHD, a gene with promising findings in previous studies of children

Table 1 Demographic and clinical characteristics of the sample according to MPH response

Characteristic	Total $N = 165$	Responders $N = 137$	Non-responders $N = 28$	P*
Age, median (±SD)	35 (±11)	34 (±11)	37 (±11)	0.18
Sex: Male, *N* (%)	90 (54.5)	71 (51.8)	19 (67.9)	0.12
IQ, median (±SD)[a]	101.6 (9.5)	101.7 (9.9)	101.4 (8.1)	0.91
ADHD subtype, *N* (%)[b]				
Combined	92 (56.1)	79 (57.7)	13 (48.2)	0.60
Inattentive	64 (39.0)	52 (37.9)	12 (44.4)	
Hyperactive	8 (4.9)	6 (4.4)	2 (7.4)	
Lifetime comorbid conditions, *N* (%)[b]				
Any bipolar disorder	18 (11.0)	15 (11.0)	3 (10.7)	1.00
Major depression	50 (30.5)	46 (33.8)	4 (14.3)	0.04
Generalized anxiety disorder	19 (11.6)	16 (11.8)	3 (10.7)	1.00
Oppositional defiant disorder	57 (43.8)	48 (35.3)	9 (32.1)	0.75
Antisocial personality disorder	13 (7.9)	11 (8.1)	2 (7.1)	0.87
Alcohol dependence	9 (5.5)	6 (4.4)	3 (10.7)	0.18
Nicotine use	72 (43.9)	62 (45.6)	10 (35.7)	0.34
SNAP-IV baseline scores, median (±SD)				
Total	1.71 (±0.52)	1.73 (±0.51)	1.61 (±0.52)	0.26
Inattentive	1.86 (±0.54)	1.87 (±0.53)	1.81 (±0.62)	0.57
Hyperactivity-impulsivity	1.56 (±0.71)	1.59 (±0.70)	1.41 (±0.73)	0.22
Oppositional	0.85 (±0.63)	0.85 (±0.64)	0.85 (±0.58)	0.98
CGI-S baseline scores, median (±SD)	4.50 (±0.72)	4.56 (±0.74)	4.21 (±0.57)	0.02
Concomitant use of medication, *N* (%)	22 (13.3)	17 (12.4)	5 (17.9)	0.54
MPH dose, mg/kg median (±SD)				
At baseline	0.15 (±0.06)	0.15 (±0.06)	0.14 (±0.06)	0.69
At endpoint	0.52 (±0.20)	0.51 (±0.21)	0.53 (±0.16)	0.69
SERS baseline score, median (±SD)[c]	38.37 (±23.55)	36.75 (±22.91)	45.83 (±25.68)	0.14

MPH methylphenidate hydrochloride, *SD* standard deviation, *IQ* intelligence coefficient, *ADHD* attention/deficit hyperactivity disorder, *SNAP-IV* Swanson, Nolan, and Pelham scale version IV, *CGI-S* clinical global impression, severity scale, *SERS* Barkley effect rating scale

* Responders and non-responders were compared using the chi-square (categorical variables) or the ANOVA test (continuous variables)

[a] Total $N = 140$; responders $N = 115$, non-responders $N = 25$

[b] One patient with missing information

[c] Total $N = 101$; responders $N = 83$, non-responders $N = 1$

Table 2 Association of *ADRA2A* polymorphisms with categorical response to MPH

ADRA2A polymorphism	Genotype (*N*)	Responders *N* (%)	Non-responders *N* (%)	P*	OR (CI)
−1291 C>G	CC (64)	53 (44.2)	11 (45.8)	1.00[a]	1.00 (0.41–2.45)
	CG+GG (80)	67 (55.8)	13 (54.2)		
−262 G>A	GG (125)	106 (78.5)	19 (70.4)	0.55[b,c]	0.75 (0.29–1.94)
	GA+AA (37)	29 (21.5)	8 (29.6)		
1780 C>T	CC (100)	85 (63.4)	16 (59.3)	0.34[a,b]	0.65 (0.26–1.57)
	CT+TT (60)	49 (36.6)	11 (40.7)		
Haplotype	−1291G/−262G/1780T (59)	49 (36.3)	10 (37.0)	0.73[a]	0.86 (0.36–2.06)
	Others (103)	86 (63.7)	17 (63.0)		

ADRA2A adrenergic α2A receptor gene, *MPH* methylphenidate hydrochloride, *OR* odds ratio, *CI* confidence interval

* Calculated by logistic regression analyses. Potential confounders considered in analyses: [a] age; [b] sex; [c] alcohol dependence (lifetime)

Table 3 Association of *ADRA2A* polymorphisms with response to MPH according to SNAP-IV scores

ADRA2A Polymorphism	Genotype (*N*)	Hyperactivity		Inattention		Total ADHD		Opposition	
		Δ SNAP-IV	*P**	Δ SNAP-IV	*P**	Δ SNAP-IV	*P**	Δ SNAP-IV	*P**
−1291 C>G	CC (64)	0.87	0.59[a]	1.00	0.33[b]	0.93	0.85[c]	0.50	0.63[d]
	CG+GG (80)	0.89		1.17		1.03		0.46	
−262 G>A	GG (125)	0.88	0.42[a]	1.07	0.86[b,e,f]	0.97	0.58[c]	0.49	0.24[d,f]
	GA+AA (37)	0.92		1.23		1.07		0.48	
1780 C>T	CC (101)	0.94	0.20[a,g]	1.12	0.62[b,e,h]	1.03	0.54[c]	0.53	0.60[d,g,h,i]
	CT+TT (60)	0.79		1.09		0.94		0.41	
Haplotype	−1291G/−262G/1780T (59)	0.82	0.20[a,g]	1.11	0.81[b]	0.96	0.69[c]	0.41	0.54[d,g,i]
	Others (103)	0.93		1.10		1.01		0.52	

ADRA2A adrenergic α2A receptor gene, *MPH* methylphenidate hydrochloride, *SNAP-IV* Swanson, Nolan, and Pelham scale version IV, *SD* standard deviation, *Δ SNAP-IV* baseline—endpoint SNAP-IV scores (mean ± SD)

* Calculated by ANCOVA. Potential confounders considered in analyses: [a] hyperactivity baseline SNAP-IV scores; [b] inattention baseline SNAP-IV scores; [c] total baseline SNAP-IV scores; [d] opposition baseline SNAP-IV scores; [e] sex; [f] MPH dose (at endpoint); [g] nicotine use; [h] age; [i] concomitant use of medication

with ADHD. However, we found no evidence of association between three *ADRA2A* polymorphisms (−1291 C>G, −262 G>A, and 1780 C>T) or haplotypes and the response to MPH treatment. Although there are three previous *ADRA2A* pharmacogenetic studies, all of them with positive findings, none of them included adults. Furthermore, we assessed two additional *ADRA2A* polymorphisms, which were never investigated in ADHD pharmacogenetic studies, and performed a haplotype analysis.

The therapeutic response to MPH, similarly to other drugs, is the result of a complex matrix of factors in which several genes may play a part [53]. The fact that we did not find a putative association is consistent with the complex effect of the *ADRA2A* gene in ADHD etiology [19]. Considering the significant heterogeneity found in the meta-analysis of association studies [19], we cannot rule out the possibility of heterogeneity in pharmacogenetic studies as well. The effect of *ADRA2A* polymorphisms may be related to other phenotypes, such as tobacco smoking [44] and personality [13], which could mediate the response to the treatment.

Of special interest is the fact that the all positive results for the *ADRA2A* gene in ADHD pharmacogenetic studies were found in pediatric samples, where the male/female ratio is approximately 3:1. In our sample, however, this proportion is near 1:1. This is consistent with the reported differences in male/female ratios between children and adults with ADHD [14, 18, 22, 39]. Thus, this gender difference in the sample composition of ADHD children and adults might influence pharmacogenetic results. This hypothesis is supported by a post-hoc finding that the subsample of men carrying the G-allele of the *ADRA2A* −1291C>G polymorphism tended to show lower inattentive scores after MPH treatment than subjects without the G-allele ($P = 0.08$, data not shown).

Our study should be understood in the context of some limitations. This is not a controlled, but a naturalistic design; we did not have a placebo arm in this trial, so we did not have an internal control to correct for any effect of time. The rate of improvement in ADHD symptoms, however, was similar to those generally found in placebo-controlled studies. In addition, this limitation would be more severe if the placebo response was related to the *ADRA2A* polymorphisms assessed, which is unlikely. The lack of a strictly standardized medication titration is another limitation of our study. However, the fact that all patients were treated in a comparable manner by the same experienced psychiatrist trained in our protocol minimizes, to some extent, the limitations of the approach. Negative findings are not surprising in pharmacogenetic studies of ADHD. Currently, there is no known genetic polymorphism with substantial evidence for involvement in MPH treatment response, notably in adults [17, 27]. Another issue, considering the small effect of *ADRA2A* in ADHD, is the risk of a type II error. Our sample size, however, is similar to previous studies and analyses one of the largest samples of adults with ADHD ever presented in pharmacogenetic investigations. Therefore, if this gene plays a role in the response to MPH in ADHD patients, we propose that the effect would be small and of limited clinical relevance or limited to a subset of patients (e.g., men). In conclusion, our findings fail to support a significant role of three relevant *ADRA2A* polymorphisms in the clinical response to MPH treatment in ADHD, at least among Brazilian adults.

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