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Research Report

Association of the adrenergic alpha 2a receptor −1291C/G polymorphism with weight change and treatment response to mirtazapine in patients with major depressive disorder

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ABSTRACT

Background: Adrenergic α2a receptors (ADRA2A) are expressed in the central nervous system and peripheral tissues. The primary mechanism of action of mirtazapine is the antagonism of central presynaptic α2 receptors. Mirtazapine is reportedly associated with weight gain. Our objective was to determine whether the ADRA2A −1291C/G polymorphism is associated with weight gain and treatment response to mirtazapine in patients with major depressive disorder (MDD). **Methods**: The ADRA2A −1291C/G polymorphism was analyzed in 314 MDD patients and 162 control subjects. All patients were evaluated using the 21-item Hamilton Depression Rating Scale at the beginning of the study and at 1, 2, 4, and 8 weeks of mirtazapine treatment. **Results**: No relationship was observed between the ADRA2A −1291C/G polymorphism and MDD. No significant difference was found between responder and non-responder groups when comparing the ADRA2A genotype distribution with treatment response to mirtazapine. Repeated measures ANOVA with the last observation carry-forward test indicated that after adjusting for baseline body weight, age, and gender, the subjects with the C/C genotype exhibited a greater mean body weight gain than the subjects with the C/G or G/G genotype after 8 weeks of mirtazapine treatment ($p=0.052$). **Conclusions**: The ADRA2A −1291C/G polymorphism does not appear to be a predictor of treatment response to mirtazapine. This polymorphism was weakly associated with weight change after 8 weeks of mirtazapine treatment. Further investigation is required to determine whether other polymorphisms of this gene influence treatment response and weight change in patients receiving mirtazapine.

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1. Introduction

The neurobiological mechanisms of responses to various drugs involve alterations in the functions of neurotransmitter systems and reinforce the importance of changes in both the serotonergic and noradrenergic systems for successful antidepressant therapy (Blier and de Montigny, 1994; Delgado et al., 1993). The latest development has been the introduction of the noradrenergic and specific serotonergic antidepressant mirtazapine. Its antidepressant effect appears to be related to the dual enhancement of central noradrenergic and serotonergic neurotransmission via the blockade of adrenergic α2 receptors (Herman, 1999; Kasper, 1997; Preskorn, 1997). Several antidepressants such as mianserin and its structural analogs exhibit adrenergic α2 receptor antagonism (Charney et al., 1984).

Previous studies have outlined the functional aspects of α_2 receptors in depression, reporting reduced α2 inhibition of platelet adenylate cyclase activity (Siever et al., 1984) and increased adrenergic α2 agonist-induced platelet aggregation in depressed patients (Garcia-Sevilla et al., 1990).

Three genes that encode human adrenergic α2 receptors have been cloned: *α2A*, *α2B*, and *α2C* (Bylund et al., 1994). The adrenergic α2a receptor (ADRA2A) subtype is expressed in the central nervous system and peripheral tissues. The α2B receptor is expressed in the liver and kidneys, and the α2C receptor is expressed exclusively in the brain (Lorenz et al., 1990). According to this classification, the classic α2 receptor studied in mood disorders is the α2a receptor. Although information is available regarding the normal function of these receptors, polymorphism in the promoter or enhancer region may result in altered gene expression and receptor density. A transversion from C to G at position −1291, upstream of the putative origin of transcription, has been described for the ADRA2A gene (Lario et al., 1997). Many psychiatric diseases, including attention deficit hyperactivity disorder (Deupree et al., 2006), weight gain after olanzapine medication (Park et al., 2006), suicide (Fukutake et al., 2008; Sequeira et al., 2004), and the treatment response to milnacipran (Wakeno et al., 2008), have been associated with this polymorphism.

The adrenergic α2 receptor plays an important role in the mechanism of action of mirtazapine. A few studies on the association between the ADRA2A −1291C/G polymorphism and major depressive disorder (MDD) have been reported. Based on this evidence, we hypothesized that the α2a receptor gene is involved in the pathophysiology of MDD and the treatment response to mirtazapine. Our aim was to determine whether the ADRA2A −1291C/G polymorphism is associated with susceptibility to MDD, weight change after mirtazapine administration, and treatment response to mirtazapine in MDD patients.

2. Results

2.1. *Demographic data and clinical characteristics*

The gender distribution did not differ significantly between control subjects (47 males/114 females) and MDD patients (93 males/279 females; $\chi^2=1.02$, $df=1$, $p=0.31$). There was no significant difference in age distribution between control subjects and MDD patients (48.5±18.0 vs. 50.8±14.4 years, respectively; $t=-1.58$, $df=524$, $p=0.12$). Age, gender, age at onset, and family history did not differ among the three potential ADRA2A −1291C/G genotypes in MDD patients (Table 1).

2.2. *Genetic predisposition to MDD among adrenergic α2a −1291C/G genotypes*

The ADRA2A −1291C/G genotype distributions showed Hardy–Weinberg equilibrium for both the normal controls and MDD patients ($p=0.33$ and 0.87, respectively) and did not differ significantly between the two groups (Table 2).

2.3. *Predicted response to mirtazapine treatment according to genotype*

The ADRA2A −1291C/G genotype distributions did not differ significantly between mirtazapine responders and non-responders (Table 2). The Hamilton Depression Rating Scale (HAMD) scores at baseline and 8 weeks did not differ significantly according to genotype in MDD patients (Table 1). Based on a repeated measures ANOVA for HAMD scores against the ADRA2A −1291C/G genotypes, we observed a significant change in HAMD scores over the treatment period, but this change was not dependent upon genotype (data not shown).

Table 1 – Demographic data and clinical characteristics

Characteristic	C/C genotype	C/G genotype	G/G genotype	P-value
Age (years)	48.4±13.8	50.3±14.6	50.8±14.4	0.26
Gender (M/F)	12/31	44/120	37/128	0.59
HAMD, baseline	22.5±4.8	22.3±4.9	23.2±5.0	0.22
HAMD, 8 weeks	11.6±4.9	12.2±6.1	12.2±6.7	0.89
Weight, baseline (kg)	59.9±11.9	59.6±10.1	59.0±9.5	0.86
Weight, 8 weeks (kg)	67.2±13.8	60.8±9.8	61.6±9.4	0.09
Age of onset	45.6±18.95	46.2±15.4	46.4±14.4	0.98
Family history	7.5%	15.9%	14.6%	0.40

Data are the means±8 SD or the percentage of *n*, where appropriate.
Data were analyzed using ANOVA, the χ^2-test, or Fisher's exact test.