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Weight Gain Associated With the α_{2a}-Adrenergic Receptor −1291 C/G Polymorphism and Olanzapine Treatment

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Weight gain can be an adverse effect of antipsychotics and is an important factor for long-term health and treatment compliance. Many reports have shown that the α_2-adrenergic receptor may be related to eating behaviors or lipolytic activities, both associated with body weight change. We hypothesized that there might be a relationship between the α_{2a}-adrenergic receptor −1291 C/G polymorphism and olanzapine-induced weight gain. A group of 62 Korean schizophrenic patients participated in a study; weight and height measurements were obtained prior to starting olanzapine and measured again after long-term treatment. Genotyping for the −1291 C/G polymorphism was performed on all participants. Body weight changes from baseline to endpoint were significantly associated with genotypes ($P = 0.028$). The frequency of the G allele was significantly higher in subjects who had severe weight gain (defined as a more than 10% weight gain from baseline) compared to subjects who did not have extreme weight gain (less than 10% weight gain from baseline) ($X^2 = 6.120$, $P = 0.013$; OR = 2.58, 95% CI = 1.21–5.51). Therefore, the findings from this study support a relationship between the −1291 C/G polymorphism of the α_{2a}-adrenergic receptor and weight gain in Korean schizophrenic patients receiving olanzapine treatment.

KEY WORDS: olanzapine; weight gain; α_{2a}-adrenergic receptor; polymorphisms; schizophrenia

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INTRODUCTION

Atypical antipsychotic-induced weight gain is well recognized and has important physical and psychological consequences. Weight gain is a major reason for discontinuation or noncompliance with atypical antipsychotics. Obesity and weight gain in adulthood have been associated with significant health complications such as type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and some types of cancer [Allison et al., 1999]. Substantial weight gain may also adversely affect self-esteem, social functioning, and physical activity [Taylor and McAskill, 2000]. Clozapine and olanzapine, in particular, may induce profound weight gain, although among other classical and atypical antipsychotics, few are free of this effect [Allison et al., 1999]. Olanzapine is associated with significant weight gain comparable to that produced by clozapine [Jibson and Tandon, 1998]. Most weight gain occurs during the first 6–8 weeks of olanzapine therapy and reaches a plateau by the end of the first year of treatment [Nasrallah, 2003].

The underlying mechanisms by which these medications cause weight gain remain unclear. However, there are some pharmacological clues, such as those proposed to involve the histamine, serotonin (5-HT), and adrenergic receptors [Casey and Zorn, 2001]. Direct injections of selective α_1-adrenergic receptor agonists into the paraventricular nucleus (PVN) of rats have resulted in reduction in food intake. By contrast, intra-PVN injection of the selective α_2-adrenergic receptor agonist stimulates feeding [Wellman et al., 1993]. Catecholamines have been shown to play a major role by acting through α_2- and β-adrenergic receptors and with pronounced lipolytic action in man [Arner, 1999]. They control metabolic effects such as lipolysis through regulation of adenylyl-cyclase activity and cAMP levels under the balanced control of positive β_1-, β_2-, and β_3-adrenergic receptor-dependent stimulation; as well as α_2-adrenergic receptor-mediated inhibition [Lafontan and Berlan, 1993]. Indeed, catecholamine stimulates lipolysis in internal fat depots (omental, pericolonic) whereas they inhibit lipolysis in subcutaneous fat pads where α_2-adrenergic receptors largely outnumber β-adrenergic receptors [Mauriege et al., 1987; Castan et al., 1993]. Moreover, it has recently been shown, using in situ microdialysis, that the physiological activation of α_2-adrenergic receptors represents an important inhibitory factor for epinephrine-induced lipid mobilization during exercise [Stich et al., 1999]. This impairment of lipolysis is enhanced in obese subjects [Stich et al., 2000]. On the other hand, rapid weight loss as a result of very low-calorie diets due to decreased α_2-adrenergic receptor sensitivity in turn may promote lipid mobilization. Therefore, it appears that variation in α_2-adrenergic receptor sensitivity in adipocytes may be predictive of weight loss during very low-calorie diets [Hellstrom et al., 1997]. Recently, Wang et al. [2005] reported that clozapine-induced weight gain was related to the −1291 C/G single nucleotide polymorphism (SNP) of the α_{2a}-adrenergic

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receptor gene. In this study, we investigated the possible association between the α_{2a}-adrenergic receptor −1291 C/G SNP and olanzapine-induced weight gain.

MATERIALS AND METHODS

Subjects

The study subjects were 82 schizophrenic patients who agreed to olanzapine treatment. All enrolled patients were chronic psychiatric inpatients from Eumsung Mental Hospital and Korea University Hospital in Korea. All subjects were examined by trained psychiatrists using the Korean version of the Structured Clinical Interview for DSM-IV [Han and Hong, 2000], leading to a diagnosis based on DSM-IV criteria [American Psychiatric Association, 1994]. Exclusion criteria included evidence of other medical or neurological illness, family history of diabetes or eating disorder, and age over 65 or under 18. According to these criteria, 20 patients were excluded. All the patients were ethnic Korean. Written informed consents were obtained and the study protocol was approved by the Ethics Committee of the Korea University Medical Center.

The study was performed in March 2002 to November 2004. Weights were checked prior to starting olanzapine and measured again after long-term treatment of at least 3 months. We controlled the use of drugs other than olanzapine. Medications such as antipsychotics, mood stabilizers, and antidepressants were avoided during the study, because of the potential effect on weight change. However, we combined the use of benzodiazepines or anticholinergics as needed. No subject had received olanzapine or clozapine prior to the current study. The mean dose of olanzapine at the endpoint examination was 14.3 mg (SD = 4.87).

Other clinical variables that were measured in the study were gender, age, olanzapine treatment duration and dosages, and previous antipsychotics dosages (chlorpromazine equivalents). Changes in body weight and BMI during the treatment were also calculated.

Genotyping

Genotyping of the α_{2a}-adrenergic promoter −1291 C/G SNP was carried out as described by Lario et al. [1997] protocol with some modifications. Using PCR, a 522 bp fragment of the α_{2a}-adrenergic receptor gene promoter was amplified. Genotyping for the C/G polymorphism at position −1291 of the α_{2a}-adrenergic receptor gene promoter was performed by digestion with the restriction enzyme *Msp*I, followed by agarose gel electrophoresis. This resulted in the predicted fragment sizes of 174, 165, 116, 62, and 5 bp for the C allele and the 165, 121, 116, 62, 53, and 5 bp for the G allele. All genotyping procedures were conducted after each subject completed the study. Investigators who were involved in rating the data were blinded to genotype status.

Statistical Analyses

Differences in allele frequencies between cohorts with different body weight change were evaluated by a Chi-square analysis. The association of genotype to weight gain and change in BMI, was tested with univariate analysis of variance (ANOVA). Post hoc pair wise analysis by the LSD method was performed if an overall significant ANOVA was obtained. All of the analyses were performed using standard software (SPSS for Windows), and *P*-values smaller than 0.05 were considered statistically significant.

RESULTS

Table I shows the demographic and clinical variables of our sample. There were no differences in socio-demographics, initial body weight, initial BMI, olanzapine dosage, previous antipsychotics dosage, and treatment duration between the groups of subjects when compared with various genotypes at baseline (Table I). The body weight change from baseline to the endpoint after olanzapine treatment was significantly different across genotypes ($P = 0.028$). A post hoc analysis with the LSD test showed significant differences in body weight change between CC and GG genotypes ($P = 0.021$) and between CG and GG genotypes ($P = 0.030$). The C and G alleles for the whole group were 39% and 61%, respectively. The G allele frequency was significantly higher in subjects with severe weight gain (more than 10%) compared to subjects with minimal weight gain (less than 10%) ($X^2 = 6.120$, $P = 0.013$). The odds ratio for excessive weight gain was 2.58 (95% CI, 1.21–5.51) for subjects with the G allele (Table II). These findings show that patients with the G allele were more frequently associated with body weight gain during olanzapine treatment.

DISCUSSION

Our results show that −1291 C/G SNP of the α_{2a}-adrenergic receptor promoter region is associated with weight gain after olanzapine treatment. The exact mechanisms involved in weight gain associated with olanzapine treatment and other

TABLE I. Demographic and Clinical Variables of 62 Schizophrenia Patients in the Three Genotype Groups

	CC (n = 8)	CG (n = 32)	GG (n = 22)	*P*-value
Age	52.9 ± 13.2	44.9 ± 8.8	46.6 ± 13.0	0.199
Sex (M/F)	3/5	25/7	16/6	0.075
Previous antipsychotics (mg/day)[a]	612.5 ± 264.2	688.7 ± 436.2	673.5 ± 462.7	0.903
Baseline body weight (kg)	68.0 ± 17.3	63.3 ± 11.8	66.5 ± 11.3	0.508
Baseline BMI (kg/m^2)	29.7 ± 5.2	27.3 ± 4.1	28.4 ± 4.2	0.360
Treatment duration (day)	599.5 ± 433.7	517.6 ± 283.5	496.3 ± 373.9	0.760
Olanzapine dosage (mg/day)	14.8 ± 2.5	15.3 ± 4.0	12.6 ± 6.2	0.134
Weight change (kg)	3.3 ± 2.7*	5.2 ± 5.7**	8.5 ± 5.2*,**	0.028
Weight change (%)[b]	5.3 ± 3.9	8.9 ± 9.9	14.4 ± 10.4	0.037
BMI Change (kg/m^2)	1.5 ± 1.2	2.3 ± 2.5	3.6 ± 2.6	0.062
Baseline BPRS	30.3 ± 6.4	28.4 ± 6.0	26.9 ± 5.4	0.283
3BPRS change	21.8 ± 4.8	19.8 ± 4.2	19.6 ± 3.6	0.427

The values are mean ± SD.

There were significant differences in body weight change in *CC compared to GG genotypes ($P = 0.021$) as well as in **CG compared to GG genotypes ($P = 0.030$).

[a]Chlorpromazine equivalents.

[b]Weight change from baseline in percentage.

TABLE II. Comparison of The α_{2a}-Adrenergic Receptor Genotypes and Allele Frequencies Between Higher Weight Gain >10% and Lower Weight Gain <10%

	Genotypes				Allele frequencies		
	CC	CG	GG		C	G	
Weight gain >10%	1	13	14	$X^2 = 6.74$,	0.27	0.73	$X^2 = 6.12$[a],
Weight gain <10%	7	19	8	$P = 0.034$	0.49	0.51	$P = 0.013$

[a]OR = 2.58, 95%CI = 1.21–5.51.

second-generation antipsychotics remain unclear. It has been suggested that the interactions of these drugs with several neurotransmitter receptors, including $5HT_{2A}$ and $5HT_{2C}$ serotonin receptors, H_1-histamine receptors, α_1- and α_2-adrenergic receptors, and m_3-muscarinic receptors, may play a significant role [Kroeze et al., 2003].

Several studies [Basile et al., 2002; Reynolds et al., 2002, 2003; Ellingrod et al., 2005; Miller et al., 2005] have reported a significant relationship between the 759 C/T polymorphism of the $5HT_{2C}$ receptor and clozapine (or olanzapine) induced weight gain. By contrast, Tsai et al. [2002] did not confirm these findings in an Asian population. Therefore, their relationship is still controversial.

The adrenergic system has been reported to play a key role in regulating energy balance through the stimulation of both thermogenesis and lipid mobilization in adipose tissue [Loos and Rankinen, 2005]. DNA sequence variations in the adrenergic receptor genes have been extensively studied for their association with obesity and body composition [Snyder et al., 2003]. Variants in α_{2a}-adrenergic receptor could alter lipolytic activity in adipose tissue, making the α_{2a}-adrenergic receptor an attractive candidate gene for the dysregulation of energy balance [Hamann et al., 2001]. Besides their local effects in adipose tissue, α_{2a}-adrenergic receptors play an important role in the regulation of the sympathetic tone and could thereby influence energy balance [Heinonen et al., 1999]. A polymorphism in the promoter of the α_{2a}-adrenergic receptor gene could, depending on its effect on gene transcription, predispose to either underweight conditions and/or obesity [Hamann et al., 2001]. Recently, Wang et al. [2005] reported that α_{2a} receptor −1291C/G SNP may be related to clozapine-induced weight gain; the investigators suggested that the CC homozygote may be associated with a reduced weight gain whereas, the GG homozygote may be associated with greater weight gain. These findings are similar to ours.

Although the present study showed the association between the α_{2a}-adrenergic receptor and olanzapine-induced weight gain, it is difficult to explain the biological mechanism by which this might occur. Furthermore, there is a low affinity for the α_{2a}-adrenergic receptor for olanzapine.

Obesity is a complex trait characterized by multifactorial inheritance in which numerous genes most likely to interact with environmental factors (diet, exercise, and drugs, etc). Genetic influences which contribute to olanzapine-induced weigh gain are presumably affected by the interaction of multiple genes of different size(s) and olanzapine-induced metabolic changes such as hyperlipidemia [Meyer, 2001; Koro et al., 2002; Lambert et al., 2003]. We hypothesize that the −1291 C/G SNP in the promoter of the α_{2a}-adrenergic receptor gene is one of the multiple contributing factors to the complex interaction.

This study has several limitations. First, due to the nature of this natural long-term study, we did not control the use of drugs completely. Therefore, we cannot exclude the effects of the different medications (including dosage and combined medications), although there was no significant difference in the drugs used (regarding olanzapine dosage and combined medications) among genotype groups. Furthermore, most patients had received other antipsychotics before olanzapine treatment. Therefore, we cannot exclude the effects of prior medication. However, we observed no significant difference in the chlorpromazine equivalent doses of the previous antipsychotics when compared to genotypes. Second, the duration of medication was not the same in our sample. This fact could influence our results. However, if this did have an effect we do not believe it would be a significant effect; because there was no difference in duration of olanzapine treatment in the genotype groups and we checked the final body weight at least 3 months later in all patients. Previous studies have reported that most weight gain occurred during the first 6–8 weeks of olanzapine therapy [Nasrallah, 2003]. Third, we did not assess and control caloric intake (caloric counts, meal refusal, etc.) because of nature of long-term study, which is one of limitations of this study. Fourth, the relatively small sample size limits the generalizability of our findings.

Therefore, additional study with a larger sample size and medication control and use is needed. In addition, it is necessary to evaluate the possible involvement of as-yet-uncovered gene(s) that influence susceptibility to olanzapine-induced weight gain as well as the possibility of gene–gene and gene–environment interaction.

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