GIPR Gene Polymorphism and Weight Gain in Patients With Schizophrenia Treated With Olanzapine

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Association between gastric inhibitory polypeptide receptor polymorphism, rs10423928, and body mass index in olanzapine-treated schizophrenia was examined. Body mass index change for the A/T+A/A genotypes was significantly higher than that for the T/T genotype. rs10423928 may predict weight gain in schizophrenia.

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Patients with schizophrenia have a 20% shorter lifespan than the general population and a 50% increased risk of death from medical causes.[1] Patients with schizophrenia also have an increased prevalence of cardiometabolic risk factors such as obesity, hyperglycemia, and lipid abnormalities compared with the general population.[2–4] There is growing interest in the effects of antipsychotic treatment on metabolism, based on evidence that treatment with specific antipsychotics is associated with changes in weight, plasma lipids, insulin resistance, and glucose tolerance.[5–9]

Incretin gastrointestinal hormones affect insulin secretion from pancreatic β cells. Gastric inhibitory polypeptide (GIP) is one of two incretin hormones that stimulate insulin responses after oral glucose challenge. A recent meta-analysis found a relationship between a GIP receptor (GIPR) gene polymorphism, rs10423928 (A/T), and insulin secretion.[10] In addition to pancreatic β cells, GIP contributes to obesity by incorporating glucose into adipocytes.[11]

Olanzapine and clozapine appear to induce more weight gain compared with other antipsychotics.[12] From these studies, we hypothesized that the *GIPR* polymorphism, rs10423928, influences weight gain induced by olanzapine administration. In this study, we examined the association between *GIPR* rs10423928 and body mass index (BMI) change in Japanese patients with schizophrenia treated with olanzapine.

METHODS

Study Participants

Thirty-two patients 18–65 years of age were included in this study who fulfilled the diagnostic criteria for schizophrenia according to the DSM-IV. Other inclusion criteria were as follows: all patients were required to have received no treatment with antipsychotics for more than 2 months before study entry, and all patients were recruited among outpatients of Niigata University Medical and Dental hospital. Exclusion criteria included patients with diabetes mellitus, either diagnosed in prior assessments using fasting glucose levels or having a history of diabetes mellitus, and a history of recognized cardiovascular and respiratory conditions with hemodynamic compromise or hypoxia, malignancy, epilepsy, endocrine disease (excluding corrected stable thyroid abnormalities), fever, dehydration, nausea, pregnancy or high-dose estrogen therapy, narcotic use, oral corticosteroid or spironolactone therapy, sedative hypnotic withdrawal, or treatment with either glucose- or lipid-lowering medications. Among the total sample, 23 patients had not previously received any antipsychotic drug, five patients had received oral risperidone, two patients had received oral perospirone, one patient had received aripiprazole, and one patient had received haloperidol.

The study was conducted with the approval of the Gene Ethics Committee of Niigata University Graduate School of Medical and Dental Sciences. Subjects participated in this study after providing written informed consent. All subjects began oral administration of olanzapine after baseline assessment. Changes in BMI were measured 4 weeks after the start of olanzapine administration.

Genotyping

The *GIPR* polymorphism, rs10423928 (T/A), was genotyped by TaqMan allelic discrimination assays using an ABI PRISM 7900 sequence detector (Applied Biosystems, Foster City, CA).

Assessments

At baseline, patients were evaluated using the Brief Psychiatric Rating Scale (BPRS), and blood samples were drawn

after overnight fasting to examine glucose, insulin, and triglyceride levels. Demographic assessment of age, sex, and BMI was also conducted at baseline. Serum analyses were performed by standard methods (SRL Inc., Tokyo, Japan). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance, which was calculated as follows: homeostasis model assessment of insulin resistance = fasting plasma insulin (μIU/mL) × fasting plasma glucose (mg/dL)/405.[13] The trial was conducted over 4 weeks and allowed flexible olanzapine dosing. Another assessment, using the same parameters as at baseline, was conducted 4 weeks after beginning olanzapine treatment.

TABLE 1. Relationship Between *GIPR* rs10423928 Polymorphism and Body Mass Index (BMI), Brief Psychiatric Rating Scale (BPRS) score, and Other Parameters[a]

	Baseline			Week 4		
Variable	A/T+A/A	T/T	p	A/T+A/A	T/T	p
BMI	20.3±2.0	21.3±3.2	NS	21.5±2.2	21.8±3.3	NS
Change in BMI	NA	NA	—	1.2±0.9	0.5±0.6	0.016
Mean dosage of olanzapine (mg)	NA	NA	—	8.2±2.4	8.3±3.3	NS
BPRS score	35.1±5.4	31.9±7.1	NS	28.4±6.6	29.5±5.8	NS
Triglyceride (mg/dL)	98.6±30.0	121.3±97.7	NS	131.9±55.6	150.5±82.1	NS
Fasting glucose (mg/dL)	89.6±9.4	94.4±10.5	NS	91.5±9.4	95.0±9.2	NS
Fasting insulin (IU/mL)	6.7±2.9	6.9±4.8	NS	10.7±7.0	8.8±4.8	NS
HOMA-IR	1.4±0.7	1.6±1.3	NS	2.4±1.6	2.0±1.2	NS

[a] Change in BMI was compared by *t*-test between A/T+A/A and T/T groups at week 4. BMI, BPRS, triglyceride, fasting glucose, fasting insulin, and HOMA-IR were compared between A/T+A/A and T/T groups at baseline and week 4. All values represent the mean ± standard deviation or number of subjects. BMI: body mass index; BPRS: Brief Psychiatric Rating Scale; HOMA-IR: homeostasis model assessment of insulin resistance; NA: not available; NS: not significant.

Statistical Analyses

The Student t test or the chi-square test was used for comparisons between two groups sorted by genotype for the demographic data. Repeated-measures two-way analysis of variance (ANOVA) was performed for changes of BMI, with treatment (two groups) and time (baseline and week 4) as factors and weight at baseline as covariant. All statistical analyses were performed using SPSS statistical software package 19.0 (IBM Japan Ltd., Tokyo, Japan).

RESULTS

Thirty-two subjects completed this study (mean age: 27.6± 10.5 years; 16 womean and 16 men). BPRS score was significantly decreased at 4 weeks compared with that at baseline (33.3±6.5 at baseline; 29.0±6.1 at 4 weeks; $p<0.001$). BMI was significantly increased at 4 weeks compared with that at baseline (20.9±2.8 at baseline; 21.7±2.8 at 4 weeks; $p<0.001$). The genotype frequencies of the *GIPR* gene polymorphism were T/T (N=18), A/T (N=12), and A/A (N=2). The genetic variation was in Hardy-Weinberg equilibrium. The change in BMI between the baseline value and after 4 weeks of treatment in the A/T+A/A group was significantly higher than that in the T/T group (p=0.016; Table 1). A two-way ANOVA repeated-measures test suggested a significant gene × time interaction effect, but a weight at baseline × time interaction effect was not observed.

The mean ages of the A/T+A/A and T/T groups were 26.1±7.6 and 28.6±12.5 years, respectively. The mean age, dosage of olanzapine at baseline, and sex distribution were not significantly different between the A/T+A/A and T/T groups. BMI, BPRS, triglyceride, fasting glucose, fasting insulin, and homeostasis model assessment of insulin resistance at baseline did not differ between the A/T+A/A and T/T groups. BMI, BPRS, triglyceride, fasting glucose, fasting insulin, and homeostasis model assessment of insulin resistance at 4 weeks were not different between the A/T+A/A and T/T groups.

DISCUSSION

This study suggests that the *GIPR* gene rs10423928 polymorphism is associated with weight gain in olanzapine-treated patients with schizophrenia. The schizophrenia group with the rs10423928 A allele showed significantly higher weight gain compared with the group without the rs10423928 A allele.

A meta-analysis of nine genome-wide association studies found a relationship between the *GIPR* rs10423928 (A/T) polymorphism and insulin secretion measured with an oral glucose tolerance test in healthy subjects.[10] The A allele of *GIPR* rs10423928 was associated with reduced insulin secretion, which could potentially increase the risk of type 2 diabetes. In addition, weight gain can increase the risk of developing diabetes; therefore, the A allele of rs10423928 may be a diabetes susceptibility allele. In an animal study, mice with disrupted *Gipr* were resistant to diet-induced obesity.[14] The association of a *GIPR* variant that associates with a significant change in BMI suggests a link between incretins, insulin secretion, and body weight regulation in humans.

The A allele of rs10423928 was previously associated with a decrease in BMI and lean body mass.[15] In addition, the *GIPR* genotype was associated with a lower BMI for each additional A allele in a cohort study.[16] Although the A allele groups in our study showed significantly higher weight gain compared with the group without the A allele, there was no significant difference in BMI at baseline between groups with or without the A allele. This result is inconsistent with the results of studies by Sonestedt et al.[16] and Lyssenko et al.[15] Interestingly, our findings for patients with schizophrenia receiving olanzapine treatment differ from previous findings regarding nonpsychiatric patients with no olanzapine treatment

regarding the impact of the *GIPR* rs10423928 polymorphism on weight gain.

Our study has several limitations. First, the sample size was relatively small. Although we found significant differences, there is the possibility of a type I error because of a small sample size. Second, we have no clear explanation for how the GIP and GIPR pathways result in weight gain after treatment with olanzapine. Thus, future studies are required to take accurate measurements of plasma GIP concentrations. Finally, the lack of comparison with a direct control group was a major limitation. Unfortunately, we were not able to directly compare schizophrenic and nonschizophrenic individuals in this study. It will be necessary to analyze a group of patients treated with another class of medication that does not interfere with weight gain to prove our hypothesis that olanzapine medication and/or schizophrenia itself in synergy with the *GIPR* genotype contributes to weight gain.

CONCLUSIONS

This study demonstrated that patients with schizophrenia with the A allele of the *GIPR* rs10423928 polymorphism treated with olanzapine experienced increased weight gain. These observations should be replicated in a larger and independent sample set.

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