INTRODUCTION

Schizophrenia is a devastating emotional, physical and mental disorder. One percent of the US population is afflicted with schizophrenia, and antipsychotics have become the first-line treatment for schizophrenia as well as for other psychotic disorders (1). Recently developed antipsychotics generally possess a similar efficacy compared to older antipsychotics, but they have a better side-effect profile, especially with regard to extrapyramidal symptoms and tardive dyskinesia (2). The increased use of second-generation antipsychotics over the last decade has raised concerns about their metabolic side effects, such as weight gain, diabetes and dyslipidemia (3, 4).

Obesity, dyslipidemia and diabetes have serious implications for overall health and survival because they are associated with an increased risk for cardiovascular and malignant disorders (5). In addition, medication-induced weight gain has been associated with a lower quality of life (6) and noncompliance (7), which increases the risk for relapse (8). Among the atypical antipsychotics, significantly more weight gain occurred during treatment with olanzapine than with other antipsychotics (9). However, the mechanisms of weight gain and dyslipidemia are poorly understood, and various parts of the endocrine system are presumably involved in these side effects.

The hypothalamus has been recognized as a major site of energy homeostasis in the central nervous system (10). Recent studies have shown that the hormones leptin and ghrelin are crucial elements of the hypothalamic neurocircuitry. Leptin is one of a number of cytokine-like molecules synthesized in adipose tissue. It is actively transported into the hypothalamus, where it acts to limit food intake (11). It also directly influences insulin secretion (12). Thus, leptin has been intensively investigated with respect to its association with changes in weight and glucose metabolism during treatment with various antipsychotics (13). Ghrelin is a recently discovered orexigenic hormone that is primarily secreted by the stomach and duodenum, and it has been implicated in both mealtime hunger and the long-term regulation of body weight (14). Ghrelin is associated with metabolic changes, in combination with leptin, during olanzapine treatment. However, further large-scale and longitudinal studies are warranted to elucidate the metabolic changes involving ghrelin, leptin and insulin during treatment with antipsychotics.

Body Weight and Plasma Levels of Ghrelin and Leptin during Treatment with Olanzapine

Although enhanced appetite and weight gain are potential side effects of treatment with antipsychotic agents, particularly olanzapine and clozapine, the mechanisms underlying these side effects are poorly understood. Leptin and ghrelin were recently identified as hormones that play crucial roles in the regulation of energy balance and glucose metabolism. To elucidate relationships between weight change and plasma levels of ghrelin and leptin, we investigated the circulating ghrelin and leptin levels and body weight during olanzapine treatment. Twenty-four patients with schizophrenia were examined during 6-month administration of olanzapine. Ghrelin, leptin, weight and body mass index (BMI) were measured before and after 2, 4, 8, 12, 16, and 24 weeks of olanzapine treatment. The concentration of glucose and various lipid metabolic parameters were measured at baseline and at 24 weeks. Significant increases in weight, BMI and leptin were observed at week 24. On the other hand, the serum levels of ghrelin decreased significantly after olanzapine treatment. In addition, the level of ghrelin was negatively correlated with the leptin level, BMI and weight. The leptin level was positively correlated with both BMI and weight. Ghrelin is associated with metabolic changes, in combination with leptin, during olanzapine treatment. However, further large-scale and longitudinal studies are warranted to elucidate the metabolic changes involving ghrelin, leptin and insulin during treatment with antipsychotics.

Key Words: Olanzapine; Weight Gain; Ghrelin; Leptin; Schizophrenia
ghrelin are increased under conditions of starvation and in anorexia nervosa, but decreased under conditions of feeding and in obesity (16, 17). Ghrelin has been shown to play crucial roles in the regulation of energy balance and glucose metabolism in combination with leptin. Ghrelin and leptin may have opposite actions in the regulation of body weight (18).

This study was designed to investigate the relationships between weight gain and plasma levels of ghrelin and leptin because the correlation between olanzapine-induced weight gain and changes in plasma levels of ghrelin and leptin was not fully described in previous studies.

MATERIALS AND METHODS

Subjects

The subjects of this study were 24 male in-patients in the Department of Psychiatry at Hadong Wooridle Hospital in Korea who fulfilled the DSM-IV diagnostic criteria for schizophrenia. We chose to study only males because gender differences in the effects of antipsychotic drugs on weight have not been fully investigated. The exclusion criteria were: 1) patients who had a substance-related disorder or other physical illness, including hypertension or hyperlipidemia, that might affect their appetite or glucose metabolism; 2) significant weight loss/gain ± 1 kg in the past 8 weeks. The patients underwent a screening evaluation followed by a washout period of up to 2 weeks if they had received any antipsychotic medication. Each subject was informed of the purpose, procedures, and potential risks of participation in the study before signing an informed consent form.

Procedure

Olanzapine was initially administered at a dose of 5-20 mg once daily. The dose was increased at weekly intervals based on clinical improvement. Benzodiazepines were permitted to control nonpsychotic symptoms like anxiety. Body weight, body mass index (BMI) and plasma levels of ghrelin and leptin were assessed at baseline and after 2, 4, 8, 12, 16, and 24 weeks. Glucose, total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol and triglyceride levels were assessed at baseline and at 24 weeks. All meals were prepared and provided by the kitchen staff at Wooridle Hospital.

Blood samples

The author collected 10-12 mL venous blood samples between 7:00 am and 8:00 am after overnight fasting. The samples were immediately analyzed for glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides. The samples to be analyzed for ghrelin and leptin were immediately centrifuged and stored at -80°C until thawing for analysis. Plasma concentrations of ghrelin and leptin were determined using a commercially available radioimmunoassay system at Gyeongsang National University (ghrelin: LINCOResearch Inc., Mo, U.S.A.; Leptin: LINCOResearch, Mo, U.S.A.).

Statistics

Analysis of variance (ANOVA) with repeated measure was used to evaluate ghrelin, leptin, weight and BMI at the medication-free stage and after treatment in those subjects who had data for all of the time points. Differences in glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels before and after olanzapine treatment were compared using the paired t-test. Pearson correlation coefficient analyses were used to examine the correlation between changes in weight, BMI, ghrelin and leptin levels following treatment with olanzapine. p<0.05 was considered statistically significant in all analyses. All statistical analyses were performed using SPSS software (version 11.0).

RESULTS

A total of 24 patients with schizophrenia met our inclusion criteria. Most of the patients were diagnosed with paranoid schizophrenia according to DSM-IV diagnostic criteria for subtypes of schizophrenia. The only other subtype observed in our patients was undifferentiated schizophrenia. All patients completed the full 24-week study. The mean age of

| Measure                  | Mean (SD)          | Statistics* |
|-------------------------|--------------------|-------------|
|                         | Baseline | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 24 | F   | p      |
| Weight (kg)             | 62.5 (7.8) | 63.2 (8.1) | 64.0 (7.9) | 65.1 (7.9) | 65.6 (8.4) | 67.0 (8.9) | 68.0 (10.1) | 14.0 | <0.01  |
| BMI (kg/m²)             | 21.3 (2.0) | 21.6 (2.1) | 21.8 (2.0) | 22.2 (2.0) | 22.4 (2.0) | 22.8 (2.2) | 23.2 (2.5) | 16.5 | <0.01  |
| Leptin (ng/mL)          | 3.0 (1.3) | 3.3 (1.5) | 3.6 (1.5) | 3.8 (1.6) | 4.0 (1.7) | 4.1 (1.7) | 4.1 (1.8) | 11.5 | <0.01  |
| Ghrelin (pg/mL)         | 45.3 (10.1) | 40.9 (10.2) | 41.4 (9.9) | 38.2 (10.9) | 37.1 (11.0) | 34.8 (9.5) | 32.7 (10.1) | 17.8 | <0.01  |

*, ANOVA with repeated measures. BMI, body mass index.
The mean age of the patients treated with olanzapine was 34.3 ± 6.5 yr. The mean daily dose used by the patients at week 24 was 11.7 ± 3.1 mg.

The changes in ghrelin, leptin, weight and BMI are shown in Table 1. The BMI (F=16.5, p<0.001) and weight (F=14.0, p<0.001) of the patients increased significantly during the period of treatment with olanzapine. The patients were an average 5.5 kg heavier at week 24 than they were at baseline. Plasma leptin levels also increased significantly (F=11.5, p<0.001). However, plasma ghrelin levels decreased significantly (F=17.8, p<0.001).

The change in plasma ghrelin levels was significantly correlated with the changes in BMI (r=-0.481, p=0.017) and weight (r=-0.411, p=0.046) (Fig. 1A), while the change in plasma leptin levels was significantly correlated with the changes in BMI (r=0.784, p<0.001) and weight (r=0.773, p<0.001) (Fig. 1B). The level of ghrelin (r=-0.724, p<0.001) correlated negatively with the level of leptin (Fig. 2).

The level of glucose and lipid metabolic parameters in patients with schizophrenia during olanzapine treatment are

| Parameter               | Fasting glucose (mg/dL) | Total cholesterol (mg/dL) | Triglyceride (mg/dL) | LDL-cholesterol (mg/dL) | HDL-cholesterol (mg/dL) |
|-------------------------|-------------------------|---------------------------|----------------------|------------------------|-------------------------|
| Baseline, mean (SD)     | 89.2 (7.8)              | 172.2 (10.8)              | 116.8 (10.4)         | 112.1 (14.0)           | 50.4 (8.7)              |
| Week 24, mean (SD)      | 91.1 (9.0)              | 192.3 (19.9)              | 123.8 (7.7)          | 119.0 (12.9)           | 47.7 (9.5)              |
| t                       | -0.91                   | -4.29                     | -2.42                | -1.67                  | 2.28                    |
| df                      | 23                      | 23                        | 23                   | 23                     | 23                      |
| p                       | 0.373                   | <0.001                    | 0.024                | 0.024                  | 0.033                   |

Table 2. The levels of glucose and lipid metabolic parameters in patients with schizophrenia during olanzapine treatment

*, paired t-test. LDL, low density lipoprotein; HDL, high density lipoprotein; SD, standard deviation.
shown in Table 2. The concentrations of glucose ($t=-0.91$, $df=23$, $p=0.373$) and LDL-cholesterol ($t=-1.67$, $df=23$, $p=0.109$) did not change significantly from the baseline values after 24 weeks. However, the concentrations of total cholesterol ($t=-4.293$, $df=23$, $p<0.001$), HDL-cholesterol ($t=2.28$, $df=23$, $p=0.033$) and triglycerides ($t=-2.42$, $df=23$, $p=0.024$) changed significantly.

**DISCUSSION**

Many reports have suggested that olanzapine induces weight gain (19). However, the mechanism behind this weight gain remains unclear. It was recently found that appetite and body weight are controlled by complex hypothalamic neurocircuitry, and that the hormones leptin and ghrelin are crucial elements of this control system. The circulating concentration of leptin is directly proportional to adiposity and functions within the hypothalamus to limit food intake, while ghrelin is synthesized in the stomach and functions within the hypothalamus to stimulate food intake (20-22). A few studies investigated the association of leptin and ghrelin with weight changes and glucose metabolism during treatment with antipsychotics. Previous studies have reported an increase in circulating leptin in patients treated with olanzapine (23, 24). However, Hosojima et al. reported that ghrelin levels decreased after the initiation of olanzapine therapy and suggested that ghrelin is associated with metabolic changes in combination with leptin, during treatment with olanzapine (25). Potential limitations of previous studies include the relatively short duration of exposure and the evaluation of a relatively small number of subjects. Thus, we conducted a prospective study using the changes in plasma levels of ghrelin, leptin and body weight to elucidate the relations with each other behind the weight gain observed in 24 patients with schizophrenia after 24 weeks of treatment with therapeutic doses of olanzapine.

In the present study, we demonstrated that plasma ghrelin levels decreased significantly during olanzapine treatment, while plasma leptin levels and BMI increased significantly during treatment with olanzapine. Leptin has been intensively investigated with respect to association with obesity induced antipsychotics. Previous studies have reported an increase in leptin in subjects treated with olanzapine (23). And this was corroborated by our results. Results of the present study correspond with the results of earlier studies which indicated that the circulating concentration of leptin is directly proportional to adiposity and functions within the hypothalamus to limit food intake, while ghrelin is synthesized in the stomach and functions within the hypothalamus to stimulate food intake (20-22). A few studies investigated the association of leptin and ghrelin with weight changes and glucose metabolism during treatment with antipsychotics. Previous studies have reported an increase in circulating leptin in patients treated with olanzapine (23, 24). However, Hosojima et al. reported that ghrelin levels decreased after the initiation of olanzapine therapy and suggested that ghrelin is associated with metabolic changes in combination with leptin, during treatment with olanzapine (25).

In this study, no significant changes in the levels of glucose and LDL-cholesterol were observed. However, serum levels of HDL-cholesterol, total cholesterol and triglycerides changed significantly. In a previous study, Huang et al. reported that triglyceride levels increased significantly 3 weeks after treatment with olanzapine (33). Furthermore, Brown and Estoup reported that olanzapine-treated patients showed adverse changes in all measured metabolic parameters, with increases in total cholesterol and triglycerides reaching a statistical significance (34). In addition, several previous studies have emphasized that individuals most at risk for the development of coronary heart disease are those with combined dyslipidemia (35). The results of our study and previous studies indicate that regular health screenings are needed in patients with schizophrenia. These findings also suggest that psychiatrists should discuss the potentially serious side effects of olanzapine with patients prior to initiating treatment and provide psychoeducation concerning the management of the metabolic side effects of olanzapine.

A possible first limitation of this study is that only male patients were included. Second limitation of this study is that all of the subjects in this study were within the normal weight range, although the patients with schizophrenia tended to have higher body weights than the healthy individuals. Therefore, the generalization of these results to all schizophrenia is limited. Third limitation is that benzodiazepines were permitted to control the nonpsychotic symptoms. Even though these are not known to affect appetite and glucose metabolism definitely, there are some possibilities of risk to increase appetite (36) and might affect the result of this study. Additionally, feeding behavior is extremely complicated because it involves many factors, including emo-
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during treatment with olanzapine and other antipsychotics. 
evaluate the many processes involving ghrelin and leptin 
ed in the effect of antipsychotics on weight gain. Therefore, 
However, the generalization of the study results to all patients 
tion with weight gain and BMI during olanzapine treat-
ment. Leptin, on the other hand, shows a positive correla-
tively with weight gain and BMI during olanzapine treat-
weight gain and increases in BMI. Ghrelin correlates nega-
tively with weight gain and BMI during olanzapine treatment. 
Thus, further long-term studies must 
be conducted taking these factors into consideration.

In summary, treatment with olanzapine is associated with weight gain and increases in BMI. Ghrelin correlates negatively with weight gain and BMI during olanzapine treatment. Leptin, on the other hand, shows a positive correlation with weight gain and BMI during olanzapine treatment. However, the generalization of the study results to all patients with schizophrenia is limited because various parts of the endocrine system and genetic factors are presumably involved in the effect of antipsychotics on weight gain. Therefore, further large-scale and longitudinal studies are warranted to evaluate the many processes involving ghrelin and leptin during treatment with olanzapine and other antipsychotics.

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