Early effects of olanzapine on serum levels of ghrelin, adiponectin and leptin in patients with schizophrenia

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Abstract

Although treatment with antipsychotics, particularly olanzapine and clozapine, has been implicated in weight gain and higher incidence of diabetes, the mechanism of these adverse reactions remains unclear. The purposes of this study were to explore the early effects of olanzapine on serum levels of ghrelin, adiponectin and leptin, three recently identified hormones that play crucial roles in the regulation of energy balance and glucose metabolism. Thirteen patients with schizophrenia who had not received any medication in the 4 weeks prior to this study were included. The patients received olanzapine at an average dose of 14.5 mg/day. Serum levels of ghrelin, adiponectin, leptin and insulin, as well as weight and fasting glucose, were investigated at the baseline and at 4 weeks. Serum ghrelin levels had decreased ($p = 0.03$) and leptin had increased ($p = 0.02$), while adiponectin and insulin levels had not significantly changed at Week 4 ($p = 0.29$ and $p = 0.25$, respectively). Weight had increased ($p = 0.01$), while fasting glucose had not significantly changed ($p = 0.46$). These findings suggest that ghrelin levels decrease and leptin levels increase after initiation of olanzapine therapy. Weight gain is also considered to be an early change, while change in insulin sensitivity is not an early change of treatment with olanzapine. Further large-scale and longitudinal studies are warranted to elucidate metabolic changes involving ghrelin, adiponectin, leptin and insulin and their impact on weight and glucose metabolism during treatment with olanzapine and other antipsychotics.

Keywords
olanzapine, schizophrenia, weight gain, diabetes, ghrelin, adiponectin, leptin

Introduction

Enhanced appetite and weight gain are potential side effects of treatment with antipsychotic agents. Interest in this subject has increased considerably as a result of reports that two atypical antipsychotics, olanzapine and clozapine, are associated with a higher risk of excessive weight gain than other drugs (Allison et al., 1999; Wetterling, 2001). On the other hand, abnormalities in glucose regulation have also been associated especially with the use of olanzapine and clozapine (McIntyre et al., 2001; Sernyak et al.,
2002). Weight gain is a robust risk factor for type 2 diabetes in general. However, this cannot be the only explanation for diabetes arising from the use of these agents, since an accumulating body of evidence suggests that patients receiving these agents may present with new-onset diabetes or even diabetic ketoacidosis in the absence of weight gain, or any familial or individual risk factor (Jin et al., 2002). The mechanisms of weight gain and diabetes related to olanzapine and clozapine are not fully understood, and various parts of the endocrine system are presumably involved in these side effects (Newcomer et al., 2002; Henderson et al., 2005).

Leptin, an adipocyte-derived hormone, is considered one of the main peripheral signals that affects food intake and body weight (Prolo et al., 1998). Leptin also directly influences insulin secretion, and could be involved in the development of diabetes in obese subjects with insulin resistance (Janecekova, 2001). Leptin levels have been shown to increase in patients receiving clozapine or olanzapine (Bromel et al., 1998; Kraus et al., 1999; Herran et al., 2001; Atmaca et al., 2003), suggesting an association between leptin, weight gain and diabetes induced by clozapine or olanzapine.

In recent publications, we have shown that serum ghrelin and adiponectin concentrations are significantly different in patients receiving olanzapine or risperidone in comparison with healthy subjects (Togo et al., 2004a, 2004b). These are recently identified hormones, which have been revealed to play crucial roles in the regulation of energy balance and glucose metabolism in combination with leptin. Ghrelin, which is produced mainly in the stomach and is involved in the regulation of growth hormone (GH) secretion by the central nervous system, controls energy balance, enhancing fat mass deposition and food intake through the activation of the hypothalamic nuclei (Kojima et al., 1999; Tschop et al., 1999). In addition, ghrelin levels were significant between patients receiving olanzapine and clozapine (Bromel et al., 1998; Kraus et al., 1999; Herran et al., 2001; Atmaca et al., 2003), suggesting an association between ghrelin, weight gain and diabetes induced by clozapine or olanzapine.

Materials and methods

Subjects

Patients with schizophrenia fulfilling the DSM-IV diagnostic criteria for schizophrenia were recruited through outpatient clinics at the Psychiatric Center, Yokohama City University Medical Center and the Department of Psychiatry, Yokohama Maioka Hospital. In advance of the present study, body mass index (BMI: kg/m²) and fasting blood glucose levels were examined; subjects suffering from obesity (BMI > 30), or diabetes (fasting glucose ≥ 126) (American Diabetes Association, 2004) were excluded from the study. Patients who had a substance-related disorder or other physical illness, including hypertension or hyperlipidaemia, that might affect appetite or glucose metabolism were also excluded. Patients were also excluded if they had received any medications in the 4 weeks prior to the study to exclude the influence of previous medications including antipsychotics. In addition, patients included in previous publications (Togo et al., 2004a, 2004b) were excluded from the present study. Altogether, 13 patients (nine male and four female) participated in this study; seven patients (three male and four female) were antipsychotic-naive first-episode patients, and six male patients were of recurrent episode and had a history of antipsychotic medication. The mean age of the patients was 37 years (range: 20–56 years). Five patients, out of 13 patients, had smoked before and through the study period. This study was approved by the Ethics Committee of Yokohama City University Medical Center and Yokohama Maioka Hospital. All patients were able and willing to give written consent after the study procedure was fully explained.

Procedure

Seven inpatients (six males and one female), including two patients of first episode and five patients of recurrent episode, received treatment with olanzapine and were hospitalized throughout the study; the other patients were treated as outpatients. Patients with schizophrenia received only olanzapine as an antipsychotic agent during the observation period (4 weeks). Benzodiazepines were permitted as a concomitant medication. Olanzapine was started at 5–20 mg once a day. The dose was incremented at weekly intervals, guided by clinical improvement, to a final dose between 10 mg/day and 20 mg/day. The mean daily dose of olanzapine was 14.5 mg/day (range: 7.5–20) for 4 weeks in patients with schizophrenia. In the present study, blood samples were collected and physical and psychopathological conditions were evaluated at two points: Week 0 (baseline) and Week 4. All blood samples were obtained between 8.00 AM and 10.00 AM after overnight fasting. Therefore, the first collection was conducted in a medication-free state (Week 0), while the last antipsychotic medication was given 10–14 h before blood withdrawal at Week 4. At both points, the following variables were assessed: BMI (kg/m²), serum levels of ghrelin (pg/ml), adiponectin (pg/ml), leptin (ng/ml), glucose (mg/dl) and insulin (µU/ml). Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) originally described by Matthews et al. (1985). HOMA-IR was calculated using the following formula: HOMA-IR (mmol/L × µU/ml) = fasting glucose (mg/dl) × fasting insulin (µU/ml)/405. In addition, psychopathological assessment was performed by means of the expanded Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986). A paired t-test was used to evaluate the changes in all measurements between the baseline and Week 4. The differences of variables between patients with
Effects of olanzapine on ghrelin, adiponectin and leptin

Table 1  Ghrelin, adiponectin and leptin serum levels, weight, body mass index, fasting glucose and BPRS scores of 13 patients with schizophrenia treated with olanzapine over 4 weeks

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Ghrelin serum level (pg/ml)</td>
<td>92.6</td>
<td>62.6</td>
<td>61.2</td>
</tr>
<tr>
<td>Adiponectin serum level (µg/ml)</td>
<td>11.9</td>
<td>4.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Leptin serum level (ng/ml)</td>
<td>3.2</td>
<td>2.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>94.2</td>
<td>12.5</td>
<td>90.5</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>5.80</td>
<td>2.11</td>
<td>5.10</td>
</tr>
<tr>
<td>Insulin resistance (HOMA-R)</td>
<td>1.39</td>
<td>0.61</td>
<td>1.15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.0</td>
<td>14.0</td>
<td>58.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.3</td>
<td>3.7</td>
<td>20.9</td>
</tr>
<tr>
<td>Total BPRS score</td>
<td>50.3</td>
<td>11.4</td>
<td>33.8</td>
</tr>
</tbody>
</table>

and without smoking were investigated by t-test. The data was analysed using SPSS for Windows Version 11.0J (SPSS Inc., Chicago, USA), and significance levels were set at \( p < 0.05 \).

Analysis of blood samples

The blood samples were immediately centrifuged and the serum samples were stored at \(-80^\circ\text{C}\) until thawing for analysis. With regard to ghrelin, we measured bioactive ghrelin, which is acylated by \(n\)-octanoic acid at its third serine, since this acylation is thought to be critical in enabling the drug to cross the blood-brain barrier and is also essential for GH release and other endocrine activities related to appetite (Kojima et al., 1999; Matsumoto et al., 2001). Serum concentrations of bioactive ghrelin (with an \(n\)-octanoyl modification at its third serine) were determined in triplicate by a commercially available radioimmunoassay (RIA) system, according to the manufacturer’s instructions (GHRA-88HK-Rev. 08/20/02; LINCO Research Inc., MO, USA). Adiponectin was measured in serum by the ELISA method, using a commercial ELISA kit (Otsuka Inc., Tokyo, Japan). Serum leptin levels were determined by the RIA method, using a commercial RIA kit (LINCO Research Inc., MO, USA). Insulin levels were also measured by the RIA method (SRL Inc., Tokyo, Japan).

Results

Descriptive information for changes in ghrelin, adiponectin and leptin, as well as changes in glucose levels, insulin (µU/ml), insulin resistance (HOMA-R), weight and BMI is shown in Table 1. The patients showed a significant improvement in psychiatric symptoms after treatment with olanzapine as indicated by change in BPRS score \((t = 7.07, \ df = 12, \ p < 0.001)\). Serum ghrelin levels had decreased significantly from the baseline at Week 4 \((t = 2.48, \ df = 12, \ p = 0.03)\), while serum leptin levels had increased \((t = -2.70, \ df = 12, \ p = 0.02)\). On the other hand, serum adiponectin levels had not significantly changed at Week 4 \((t = 1.11, \ df = 12, \ p = 0.29)\). Likewise, fasting glucose levels \((t = 1.22, \ df = 12, \ p = 0.46)\) and insulin resistance \((t = 1.53, \ df = 12, \ p = 0.15)\) had not significantly changed at Week 4, and no patients developed diabetes during the study period. The patients had gained 1.7 kg (3.2%, SD = 4.1%) of their baseline weight at Week 4, and this change was considered significant \((t = -3.03, \ df = 12, \ p = 0.01)\). No differences were observed between patients with and without smoking in weight and serum levels of ghrelin, leptin, adiponectin, insulin and fasting glucose at baseline \((p = 0.78, \ p = 0.90, \ p = 0.70, \ p = 0.81, \ p = 0.44, \ p = 0.19, \) respectively) as well as at Week 4 \((p = 0.95, \ p = 0.69, \ p = 0.99, \ p = 0.84, \ p = 0.17, \ p = 0.16, \) respectively). No patients developed hypertension or hyperlipidaemia during the study period.

Discussion

In the present study, we have demonstrated that ghrelin and leptin are associated with metabolic change during treatment with olanzapine. These recently identified hormones are involved with energy homeostasis and glucose metabolism. Among them, leptin has been intensively investigated with respect to its association with change in weight and glucose metabolism during treatment with antipsychotics. Previous studies have reported an increase in circulating leptin in patients treated with olanzapine (Kraus et al., 1999) and this was corroborated by the present study. Furthermore, olanzapine was associated with a significant increase in weight in this study, which is also in line with previous reports (Allison et al., 1999); however, no significant change was found in glucose levels, possibly due to the short observation period and the small sample size.

Ghrelin is the only known orexigenic hormone (Zigman and Elmquist, 2003); its levels increase preprandially and decrease after meals, suggesting a role in meal initiation (Cummings et al., 2001; Tschop et al., 2001; Wren et al., 2001). Contrary to our preliminary expectation and in accordance with the findings of our previous cross-sectional study (Togo et al., 2004a), serum ghrelin...
levels decreased after olanzapine therapy. This finding supports the view that ghrelin is not a direct cause of increased food intake and weight gain with the use of olanzapine. It may be also reasonable to speculate that ghrelin levels decrease after olanzapine therapy, showing a normalizing effect on energy homeostasis and metabolic change induced by olanzapine. Weight gain and elevation of glucose levels during treatment with olanzapine may be associated with disorders in the regulation of ghrelin secretion. Recently, Murashita et al. (2005) investigated change in plasma ghrelin levels 6 months after switching to olanzapine from other antipsychotics in seven patients with schizophrenia. Interestingly, plasma ghrelin levels had increased significantly 6 months after switching to olanzapine. Change in ghrelin levels during olanzapine treatment needs to be clarified by future studies. It is also possible that other antipsychotics affect ghrelin levels, showing a discrepancy between their findings and the results of the present study.

Changes in adiponectin levels were not significant 4 weeks after the initiation of olanzapine therapy in this study, although our previous cross-sectional study indicated increased levels of serum adiponectin in schizophrenic patients receiving olanzapine over a long period of time in comparison with healthy subjects (Togo et al., 2004b). Recently, weight and metabolic changes were investigated in rats, indicating that olanzapine-induced hyperphagia acts as an initial stimulus which leads to weight gain, enhanced visceral adiposity and subsequent insulin resistance, although the latter may be ameliorated by compensatory responses in adiponectin levels (Cooper et al., 2005). Taken these results together, elevated adiponectin levels may well be a delayed response associated with drug-induced weight gain.

Olanzapine has been reported to be associated with abnormality in insulin levels and insulin sensitivity, although the implications of previous reports are somewhat conflicting. Newcomer et al. (2002) reported increased insulin resistance in patients treated with olanzapine over 3 months, while Henderson et al. (2005) described increased insulin resistance during treatment with olanzapine with a mean duration of 29.5 months, using an oral glucose tolerance test. Melkersson and Dahl (2003) described elevated insulin levels in patients treated with olanzapine with a median duration of 1.2 years (Melkersson and Dahl, 2003). Another recent study demonstrated an increased insulin level over approximately 12 weeks of olanzapine treatment (Graham et al., 2005). On the other hand, significant changes in insulin sensitivity were not observed after 3 weeks of treatment with olanzapine (Sowell et al., 2003). In the present study, insulin levels and insulin resistance, as evaluated by HOMA-IR, did not change significantly over 4 weeks of olanzapine treatment. Increased insulin resistance, inducing elevated insulin levels, may be secondary to the olanzapine-induced weight gain which was observed after a few months of treatment with olanzapine.

Several limitations in this study deserve mention. Most importantly, this study included both inpatients and outpatients, and their eating behaviour was not assessed; therefore, caloric intake was not fixed during the study period, particularly among outpatients. Furthermore, some of the patients were admitted to the hospital at the time of the study, which may have caused dietary change after initiation of this study. The small number of subjects must also be taken into account. Although this study focused on the change in ghrelin, adiponectin, leptin and insulin, a number of other hormones are reasonably involved in the metabolic change during olanzapine therapy. These limit our ability to define the mechanistic pathways that led to the olanzapine-associated weight gain and change in glucose metabolism.

In conclusion, ghrelin decreases after the initiation of olanzapine therapy, possibly indicating its normalizing effect on the abnormality in energy homeostasis and metabolic change. Ghrelin is associated with metabolic change, in combination with leptin, during treatment with olanzapine. On the other hand, the overall change in adiponectin levels was not significant during the short observation period. Future large-scale and longitudinal studies, as well as studies of the hormonal responses to food intake, are warranted to elucidate metabolic changes involving ghrelin, adiponectin, leptin and insulin, and their impact on weight and glucose metabolism during treatment with olanzapine and other antipsychotics.

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