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Short-Communication

Oren-gedoku-to suppresses hypothalamic adenosine 5′-monophosphate-activated protein kinase activity and olanzapine-induced hyperglycemia

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Abstract

Objective: Atypical antipsychotics such as olanzapine (OLZ) are associated with elevated blood glucose levels. Owing to serious cases of diabetic ketoacidosis and diabetic coma in Japan, OLZ is contraindicated in patients with diabetes, and blood glucose monitoring is advised even in non-diabetic cases. However, the precise mechanism of antipsychotic-induced hyperglycemia remains unclear; therefore, we investigated the role of hypothalamic adenosine 5′-monophosphate-activated protein kinase (AMPK) activity and adrenaline secretion in hyperglycemia induced by long-term OLZ administration. Additionally, we examined the potential effects of Oren-gedoku-to (OGT), a traditional Chinese medicine that suppresses hypothalamic AMPK activation, on hyperglycemia induced by chronic OLZ administration.

Materials and Methods: Female Wistar rats were divided into three treatment groups: saline (control), OLZ (20 mg/kg/d), and OLZ (20 mg/kg/d)/OGT (500 mg/kg/d). Each treatment was orally administered twice daily for 2 weeks. Blood glucose and adrenaline concentrations, as well as hypothalamic AMPK alpha and phosphorylated AMPK alpha activities, were measured and compared using the Tukey–Kramer multiple comparison test.

Results: Serum glucose and adrenaline levels were elevated in the OLZ group but not in the OLZ/OGT group. Furthermore, an increase in hypothalamic AMPK activity was observed in OLZ rats but not in OLZ/OGT rats.

Conclusion: Our results suggest that OGT administration inhibits hyperglycemia induced by chronic OLZ administration by suppressing increased AMPK activity and adrenaline secretion.

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Introduction

Atypical (second-generation) antipsychotics currently represent the first-line treatment for psychotic disorders because they exhibit fewer extrapyramidal side effects and are indicated for a wider range of psychotic disorders than typical (first-generation) antipsychotics (Solmi et al., 2017). However, atypical antipsychotics including olanzapine (OLZ) (Seabury et al, 2001; Varma et al., 2007; Kohen et al., 2008; Nakamura and Nagamine, 2010), quetiapine (Nanasawa et al., 2017; Roth et al., 2023), and paliperidone (De Hert et al., 2012), are associated with elevated blood glucose levels. In 2002, emergency safety information was issued in Japan for OLZ and quetiapine following reports of serious cases of diabetic ketoacidosis and diabetic coma caused by elevated blood glucose levels during treatment. Thereafter, the use of these drugs in patients with diabetes has been contraindicated. Moreover, blood glucose monitoring is necessary during treatment, even in healthy individuals, as hyperglycemia induced by atypical antipsychotics has also been reported in patients without diabetes (Seabury et al, 2001; Varma et al., 2007).

Hyperglycemia has been reported with both acute and chronic administration of OLZ which is used to treat schizophrenia and bipolar disorder (Kohen et al., 2008; Nakamura and Nagamine, 2010). In previous studies, we demonstrated that adrenaline is involved in the increase of blood glucose induced by a single dose of OLZ (Nagata et al., 2016). Furthermore, a single dose of paliperidone, a drug of the same family, can activate hypothalamic adenosine 5'-monophosphate-activated protein kinase (AMPK) which is correlated with adrenaline secretion and blood glucose elevation (Xue et al., 2022). However, despite several reports addressing the mechanisms underlying hyperglycemia associated with long-term OLZ administration (Ma et al., 2015; Li et al., 2021; Yang et al., 2019; Chintoh et al., 2008), the impacts of these factors on hyperglycemia induced by chronic OLZ treatment remain unclear.

In this study, we investigated hypothalamic AMPK activity, blood adrenaline concentration, and blood glucose levels after long-term OLZ administration to elucidate the mechanism underlying hyperglycemia. We also investigated the use of Oren-gedoku-to (OGT), a traditional Chinese medicine that contains berberine and suppresses hypothalamic AMPK activation (Zhang et al., 2014), as a prophylactic agent against atypical antipsychotic-induced hyperglycemia by examining its effect on blood glucose levels in combination with OLZ.

Materials and Methods

Animals

Nine-week-old female Wistar rats were obtained from Japan SLC Corporation (Hamamatsu, Japan). Rats were housed in a controlled environment and acclimatized for one week prior to oral OLZ administration. All animal experiments were approved by the Institutional Animal Care and Use Committee of Tokyo Medical and Dental University (Approval No. A2023-126A) and were carried out in accordance with the National Institutes of Health guidelines on animal care.

Materials

OLZ was purchased from Wako Pure Chemical Industries (Osaka, Japan). OGT is composed of crude ingredients obtained by extraction with boiling water from four medicinal herbs in the following proportions: *Scutellariae* Radix (3.0), *Coptidis* Rhizome (2.0), *Gardeniae* Fructus (2.0), and *Phellodendri* Cortex (1.5). Spray-dried extract powder of OGT was provided by Tsumura Co. (Tokyo, Japan). OLZ solution was prepared by dissolving 20 mg OLZ in 2.4 ml of 0.1 M HCl, then adding saline to achieve a total volume of 5 ml, and finally adjusting with distilled water to

obtain a final concentration of 2.0 mg/ml. For the OLZ/OGT solution, 20 mg of OLZ was dissolved in 2.4 ml of 0.1 M HCl, which was then adjusted to 5 ml with saline; after adding 500 mg of OGT, the mixture was diluted with distilled water to a total volume of 10 ml. (R)-(-)-Epinephrine and isoproterenol hydrochloride, internal standards for adrenaline measurement, were purchased from Fujifilm Wako Pure Chemical Industries (Osaka, Japan). Potassium ferricyanide (III) was purchased from Sigma-Aldrich (St. Louis, MO, USA). All chemicals were of analytical grade.

Experimental procedure

The rats (n = 24) were divided into three treatment groups: Saline group (control, n = 7), OLZ group (20 mg/kg/day, n = 9), and OLZ (20 mg/kg/day)/OGT (500 mg/kg/day) group (n = 8). OGT dosage was based on a previous report (Ohta et al.,2004). Concerning OLZ dosage, we initially administered 10 mg/kg/day for 2 weeks in a preliminary study, but observed no significant difference in blood glucose levels between the OLZ-treated and control groups, we thus increased the dose to 20 mg/kg/day. Each treatment was administered orally twice daily for two weeks. Rats were fasted overnight after the final day of administration before blood samples and hypothalamic tissue were collected under isoflurane anesthesia. Blood was centrifuged at 2,000 × *g* for 10 min to obtain serum. Hypothalamic tissues were immediately flash-frozen with liquid nitrogen. The samples were then stored at −80°C until analysis.

Analysis

Blood glucose and adrenaline concentrations were measured as previously reported (Nagata et al., 2016; Xue et al., 2022).

The amounts of AMPK alpha and phosphorylated AMPK alpha in hypothalamic tissue were measured by western blotting, as described in a previous report (Xue et al., 2022). Briefly, tissue lysates were prepared with RIPA buffer (Nacalai Tesque, Japan), and equal amounts of protein were separated by SDS–PAGE and transferred to PVDF membranes. Membranes were incubated with rabbit antibodies against AMPKα (1:2500; Cell Signaling Technology) and phosphorylated AMPKα (Thr172) (1:2500; Cell Signaling Technology) at 4 °C for 16h, followed by Anti-Rabbit IgG (1:10,000; Cell Signaling Technology). After washing, membranes were immersed in Clarity Western ECL substrate (Bio-Rad) for 5 min, and signals were detected using the ChemiDoc MP Imaging System (Bio-Rad). Band intensities were normalized to β-actin (1:10,000; Cell Signaling Technology) with Anti-mouse IgG (1:10,000; Cell Signaling Technology).

Statistical analysis

Data are presented as the mean and standard deviation. The Tukey–Kramer multiple comparison test was used to compare blood glucose levels, blood adrenaline levels, and hypothalamic AMPK activity among the three groups. Statistical significance was set to $p < 0.05$.

Results

Effects of OGT on body weight, blood glucose and adrenaline levels

After 2 weeks of treatment, the average body weight increased from 154, 159, and 158 g to 168, 164, and 160 g in the control, OLZ, and OLZ/OGT groups, respectively. Although the OLZ and OLZ/OGT groups gained slightly less weight compared to the control, the differences remained statistically non-significant.

Blood glucose levels in rats administered with OLZ for 2 weeks were significantly higher than those in the control group (Figure 1). The blood adrenaline level of the OLZ group was also significantly higher than that of the control group (Figure 2). However, neither blood glucose nor blood adrenaline levels were significantly increased in the OLZ/OGT

group compared to those in the control group (Figure 1 and 2).

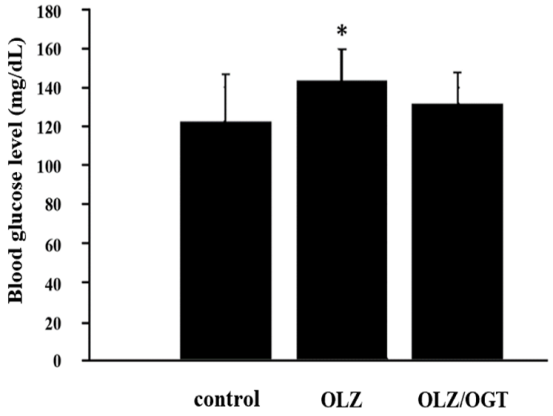

Figure 1. Effects of long-term OLZ and OGT administration on fasting blood glucose levels in rats. Saline group (control, n = 7), OLZ group (20 mg/kg/day, n = 9), and OLZ (20 mg/kg/day)/OGT (500 mg/kg/day) group (n = 8). Each column represents the mean ± SD. *p < 0.05 vs. the control group (Tukey–Kramer).

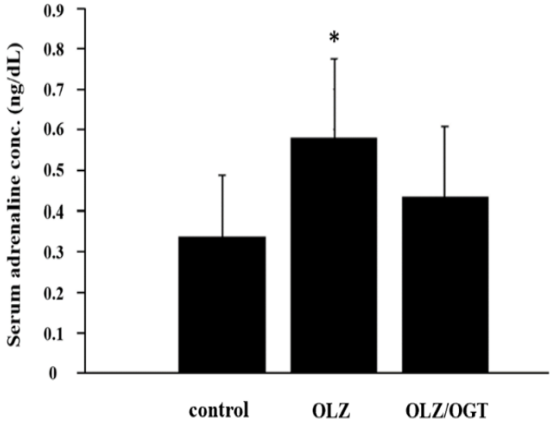

Figure 2. Effects of long-term OLZ and OGT administration on serum adrenaline concentrations in rats. Saline group (control, n = 7), OLZ group (20 mg/kg/day, n = 9), and OLZ (20 mg/kg/day)/OGT (500 mg/kg/day) group (n = 8). Each column represents the mean ± SD. *p < 0.05 vs. control group (Tukey–Kramer).

Effects of OGT on hypothalamic AMPK activity

In rats administered with OLZ for 2 weeks, AMPK activity in the hypothalamus was significantly higher than that in the control group. However, no significant increase in hypothalamic AMPK activity from the control group was observed in the OLZ/OGT group (Figure 3).

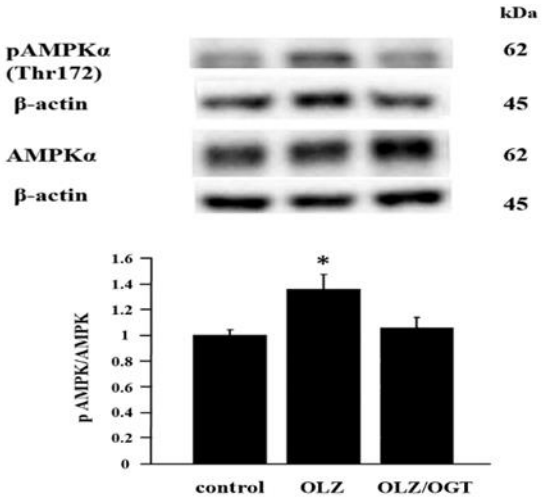

Figure 3. Effects of long-term OLZ and OGT administration on the amount of AMPKα phosphorylated at threonine 172 and total AMPKα in rats. Saline group (control, n = 7), OLZ group (20 mg/kg/day, n = 9), and OLZ (20 mg/kg/day)/OGT (500 mg/kg/day) group (n=8). Top panel: immunoblots of hypothalamus pAMPK, β-actin, and AMPKα in each group. Bottom panel: semiquantitative analysis of pAMPKα and AMPKα band intensity, normalized by β-actin. Each column represents the mean ± SD for each group. *p<0.05 vs. control group (Tukey–Kramer).

Discussion

To elucidate the mechanism of hyperglycemia induced by long-term OLZ administration, we measured blood glucose levels, blood adrenaline concentration, and AMPK activity in the hypothalamus of female Wistar rats after two weeks of OLZ treatment. Fasting blood glucose levels, serum adrenaline concentrations, and AMPK activity in the hypothalamic tissue were elevated after OLZ administration (Figures 1-3). OLZ and OGT combination treatment suppressed AMPK activation in the hypothalamus, with no significant increase in blood adrenaline or glucose levels (Figures 1-3). These findings suggest that increased hypothalamic AMPK activity and elevated serum adrenaline concentrations are involved in the induction of hyperglycemia during long-term OLZ administration. Additionally, suppressing AMPK activity in the hypothalamus through concomitant OGT administration may prevent OLZ-induced hyperglycemia.

OGT is a traditional Chinese herbal medicine comprising four herbal ingredients, *Coptidis* Rhizoma, *Scutellariae* Radix, *Phellodendri* Cortex, and *Gradeniae* Fructus (Qi et al., 2019), and is used for its antipyretic effects to treat skin diseases, insomnia associated with high blood pressure, neurosis, and psychiatric symptoms. Furthermore, OGT is used in China as an adjunctive treatment for type 2 diabetes, although conclusive evidence for its effects has not yet been provided (Hu et al., 2021). *Coptidis* Rhizoma and *Phellodendri* Cortex contain berberine, which suppresses increased hypothalamic AMPK activity (Zhang et al., 2014). As berberine can prevent hyperglycemia induced by atypical antipsychotics (Xue et al., 2022; Al-Naimi et al., 2019), we investigated OGT as a prophylactic agent for atypical antipsychotic-induced hyperglycemia. Our results suggest that elevated hypothalamic AMPK activity contributes to hyperglycemia induced by long-term OLZ administration, whereas combined treatment with OGT may prevent hyperglycemia by suppressing the increase in hypothalamic AMPK activity. This suggests that OGT may also be effective in treating hyperglycemia caused by other atypical antipsychotics such as clozapine, which affects hypothalamic AMPK (Kim et al., 2007). Furthermore, other herbal medicines containing berberine, such as Unseiin, Orento, and Sano-shashin-to, may prevent OLZ-induced hyperglycemia.

OGT improves insulin resistance and blood glucose levels in rats with type 2 diabetes by increasing GLUT4 protein expression in adipose tissues and skeletal muscles (Chen et al., 2007). Berberine also affects insulin resistance (Mi et al., 2019). As previous studies have suggested that long-term OLZ administration increases insulin resistance in adipose tissue (Li et al., 2021; Wang et al., 2022), various factors in addition to hypothalamic AMPK may be involved in suppressing long-term OLZ administration-induced hyperglycemia by OGT. However, this requires further investigation.

This study has some potential limitations. First, the mechanism of OLZ-induced hyperglycemia may be complex and involve a variety of pathways; for example, lipid abnormalities and sugar uptake in skeletal and adipose muscle tissues are also involved. Second, sex-related differences may exist in the effects of OLZ, but only female rats were used in this study. However, female rats are more prone to weight gain and metabolic changes than male rats (Choi et al., 2007). Similarly, OLZ side effects such as weight gain occur more frequently in women than in men (Seeman, 2020). Third, no fingerprinting or detailed characterization of OGT was conducted, which may limit the reproducibility and generalizability of the findings.

In conclusion, both AMPK activation in the hypothalamus induced by long-term OLZ administration and the accompanying adrenaline secretion are involved in elevating blood glucose levels, suggesting that combination therapy with OGT can prevent the OLZ-induced elevation of blood glucose levels.

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Conflicts of interest

The authors declare no conflict of interest.

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