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# The Elucidation of the Mechanism of Weight Gain and Glucose Tolerance Abnormalities Induced by Chlorpromazine

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**Abstract.** Antipsychotic drugs induce weight gain and metabolic abnormalities. Recently, the role of adipocytokines secreted from adipocytes in the development of metabolic syndrome has received attention. The aim of this study was to investigate the effects of chlorpromazine (Cp) on body weight, glucose, lipid metabolism, and adipocytokine secretion in rats fed sucrose. Wistar rats received 15% sucrose (Suc group), 15% sucrose and Cp at 7.5 mg/kg per day (Suc + Cp group), or Cp alone (Cp group) in water for 10 weeks. Fasting glucose levels in the Suc and Suc + Cp groups were significantly higher than in the control (Cont) group. Fasting insulin levels in the Suc, Suc + Cp, and Cp groups were also significantly higher than in the Cont group. The adiponectin level in the Suc group was significantly higher than in the Cont group, although the adiponectin level in the Suc + Cp group was not. Furthermore, the plasma tumor necrosis factor (TNF)-$\alpha$ level in the Suc + Cp group was significantly higher than in the Suc group. These data suggest that Cp inhibits the compensatory response of adiponectin with respect to obesity due to increased expression of plasma TNF-$\alpha$ level. Cp may exert more harmful effects on the glucose level and insulin resistance than on other factors, which may be one of the mechanisms responsible for the metabolic syndrome induced by antipsychotic agents.

***Keywords***: chlorpromazine, metabolic syndrome, adiponectin, tumor necrosis factor-$\alpha$, visceral fat

## Introduction

Weight gain and hyperglycemia are reported frequently in schizophrenia patients even when they are not receiving antipsychotic drug therapy (1 – 4), and treatment with antipsychotic agents increases their incidence (5 – 7). Moreover, after treatment with atypical antipsychotic agents, ketoacidosis may occur due to rapid abnormal glucose metabolism and deaths among patients have been reported (8, 9). These adverse events are important in clinical practice. However, the detailed mechanism of weight gain and hyperglycemia has not yet been elucidated, although various candidate factors have been suggested. Recently, the combination of obesity, abnormal glucose metabolism, hyperlipidemia, and hypertension has been defined as the metabolic syndrome, which is thought to be related to the accumulation of visceral fat (10). Visceral fat tissue stresses endocrine organs, which not only process nutrients but also secrete various physiologically active substances (adipocytokines) (11). It is thought that excessive visceral fat results in an imbalance in adipocytokine secretion and is one of the causes of metabolic syndrome. It was reported that the frequency of metabolic syndrome is higher in patients with schizophrenia than in the general population (12). Changes not only in weight, blood glucose levels, and blood lipid levels but also in adipocytokine secretion have been reported in patients with schizophrenia (13). Although there have been numerous reports on leptin secretion (14 – 17), few on other adipocytokines are available. We therefore investigated the influence of the antipsychotic drug chlorpromazine (Cp) on body weight, glucose and lipid levels, and adipocytokine (e.g., leptin, adiponectin, tumor necrosis factor (TNF)-$\alpha$, and interleukin (IL)-6) secretion in rats at risk of developing metabolic

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syndrome due to sucrose administration. Generally, although leptin and adiponectin improve the symptoms of metabolic syndrome, TNF-$\alpha$ and IL-6 tend to worsen them (18 – 21). We used chlorpromazine, a phenothiazine derivative, because antipsychotics in the phenothiazine class are known to increase the risk of weight gain and hyperglycemia (22). Allison et al. (23) reported that conventional and newer antipsychotics, including chlorpromazine, were associated with weight gain after 10 weeks of treatment at a standard dose. Furthermore, Thonnard-Neumann (24) reported that the phenothiazine derivative increased the rate of patients becoming diabetic and called this phenomenon "phenothiazine diabetes". In addition, Erle et al. (25) report that higher acute doses of the drug may induce hyperglycaemia and can inhibit insulin secretion both in normal individuals and in patients with latent diabetes mellitus.

## Materials and Methods

*Animals*

All experiments were performed using 8-week-old male Wistar rats (SLC, Hamamatsu). All studies were performed in accordance with the "Guiding Principles for the Care and Use of Laboratory Animals" of The Japanese Pharmacological Society. The rats were housed in a room with temperature controlled to 21 ± 3°C, humidity of 55 ± 5%, and a dark/light cycle of 12:12 h.

*Drug treatment*

The rats were divided into four groups; the numbers in each group for the various investigations are given in the figure legends. Solid chow (CE2; Japan CLEA, Tokyo) was available to all groups ad libitum. Fifteen percent sucrose (Suc) and Cp at 7.5 mg/kg per day were administered in drinking water. This dose of Cp was converted from the maximum dosage in patients (750 mg/60 kg per day) clinically. The concentration of 15% sucrose was decided referring to reported by Yang et al. (26). All groups received the study diets for 10 weeks. Total food intake in each group was recorded during the experimental period.

After 10 weeks of treatment, all groups were fasted overnight for the measurement of fasting blood glucose levels. After weighing, the rats were killed by decapitation under light ether anesthesia, and the trunk blood and visceral fat tissue were collected. The visceral fat tissue was taken from abdominal fat which excluded testicle surrounding fat under the diaphragm. The weight of visceral fat tissue (mg)/body weight (g) was determined. Trunk blood was placed in EDTA-coated tubes and centrifuged at 3,000 × $g$ for 20 min at 4°C to obtain plasma.

*Plasma biochemical parameters*

Plasma glucose levels were measured using a combination of the mutarotase and glucose oxidase method (Glucose C2 test, Sensitivity: 10 – 700 mg/dl; Wako, Osaka) and plasma total cholesterol levels were measured using the cholesterol oxidase-DAOS method (Cholesterol E-Test, sensitivity: 10 – 1,000 mg/dl; Wako), which each used 20 $\mu$l of plasma. Plasma insulin, leptin, adiponectin, TNF-$\alpha$, and IL-6 levels were each determined by enzyme-linked immunosorbent assay (ELISA); the following kits were employed: Lebis Insulin Kit (sensitivity: 156 – 10,000 pg/ml; Shibayagi, Gunma) using a plasma volume of 10 $\mu$l. Rat Leptin ELISA Kit (sensitivity: 312.5 – 20,000 pg/ml, Wako) using a plasma volume of 20 $\mu$l. Mouse/rat adiponectin ELISA Kit (sensitivity: 0.25 – 8.0 ng/ml; Otsuka, Tokyo) using a plasma volume of 10 $\mu$l diluted to 1111-fold. Rat TNF-$\alpha$ ELISA kit (sensitivity: 15.6 – 1,000 pg/ml; Bio Source, Camarillo, CA, USA) using a plasma volume of 50 $\mu$l diluted to 2-fold. Rat IL-6 ELISA (sensitivity: 1.0 – 2,000 pg/ml, Bio Source) using a plasma volume of 50 $\mu$l diluted to 2-fold.

All absorbances were measured with a microplate reader (Multiskan JX; Thermo Labsystems, Helsinki, Finland) with Ascent Software (Ver. 2.6, Thermo Labsystems).

*Statistical analyses*

Statistical analysis was performed using Stat View (Ver. 4.58; Abacus, Berkeley, CA, USA). Differences between the groups were analyzed by ANOVA, followed by Scheffe's method. A $P$ value of less than 0.05 was considered to represent a statistically significant difference. Results are expressed as the mean ± S.E.M.

## Results

The body weights of each group at the end of the study were not different significantly (Fig. 1). Suc intake did not significantly affect body weight in the Suc and Suc + Cp group.

The weight of visceral fat in the Suc, Suc + Cp, and Cp groups was significantly greater than that in the Cont group (Fig. 2). The levels of fasting plasma glucose at the end of the study in the Suc group and Suc + Cp groups were significantly higher than in the Cont group. Although the blood glucose level in the Cp group was higher than that in the Cont group, the difference was not

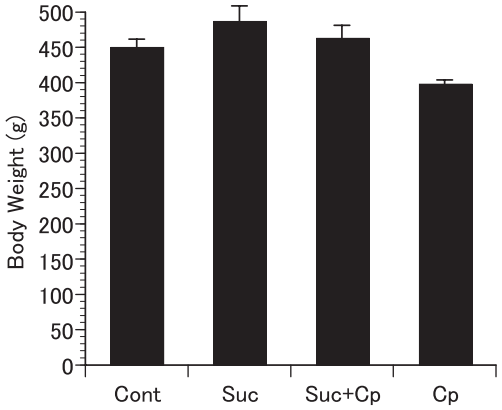


**Fig. 1.** Effects of 15% sucrose and chlorpromazine administration on the body weight (g) of rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). Bars represent the mean ± S.E.M.

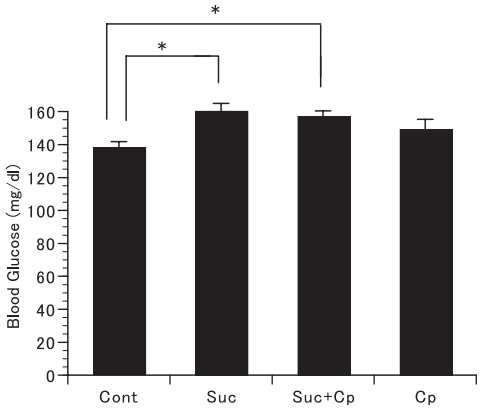


**Fig. 3.** Effects of 15% sucrose and chlorpromazine administration on plasma fasting glucose levels (mg/dl) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* Cont group. Bars represent the mean ± S.E.M.

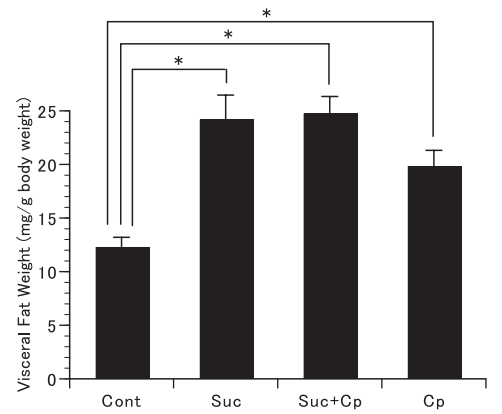


**Fig. 2.** Effects of 15% sucrose and chlorpromazine administration on the visceral fat weight/body weight (mg/g) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* Cont group. Bars represent the mean ± S.E.M.

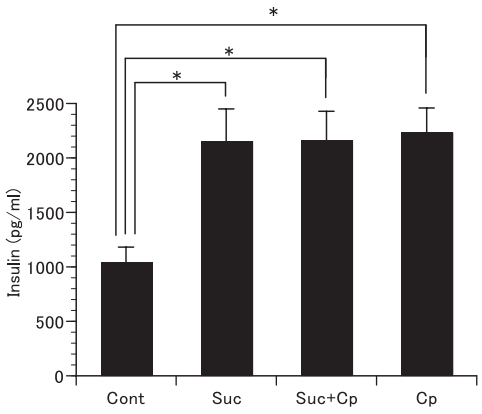


**Fig. 4.** Effects of 15% sucrose and chlorpromazine administration on plasma fasting insulin levels (pg/ml) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* Cont group. Bars represent the mean ± S.E.M.

significant (Fig. 3). The levels of plasma insulin at the end of the study period in the Suc, Suc + Cp, and Cp groups were significantly higher than that in the Cont group (Fig. 4). The level of plasma cholesterol at the end of the study period in the Suc + Cp group was significantly higher than that in the Cont group (Fig. 5).

The levels of plasma leptin at the end of the study period were significantly higher in the Suc and Suc + Cp groups compared with those in the Cont and Cp groups (Fig. 6). Plasma adiponectin levels at the end of the study period were significantly higher in the Suc group compared with the Cont, Suc + Cp, and Cp groups (Fig. 7).

Plasma TNF-$\alpha$ levels at the end of the study period in the Suc + Cp group was significantly higher than those in the Cont, Suc, and Cp groups (Fig. 8). There were no significant differences among groups in the plasma IL-6 levels in this study (Fig. 9).

The total food intake in each group up to 10 weeks was measured. The total food intake in the Suc and Suc + Cp groups were significantly lower than those in the Cont group. There were no significant differences between the Cont and Cp groups or the Suc and Suc + Cp groups (Fig. 10).

## Discussion

Although the mean values of body weight in the Suc

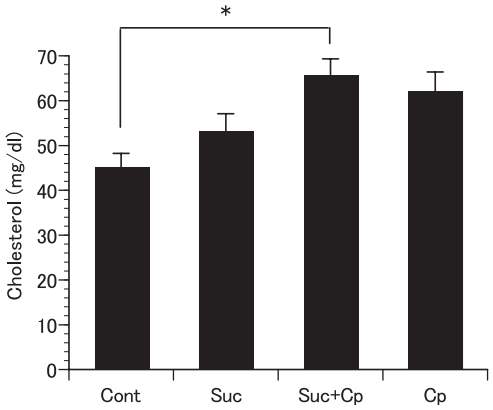


**Fig. 5.** Effects of 15% sucrose and chlorpromazine administration on plasma total cholesterol levels (mg/dl) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* Cont group. Bars represent the mean ± S.E.M.

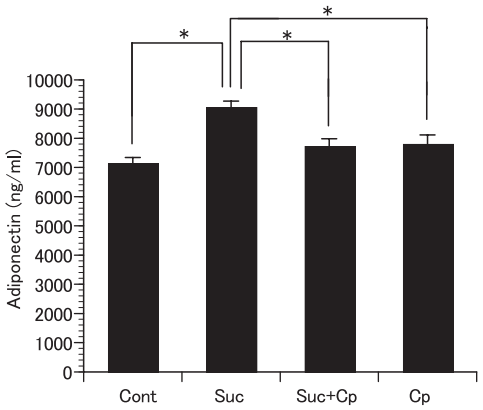


**Fig. 7.** Effects of 15% sucrose and chlorpromazine administration on plasma adiponectin levels (ng/ml) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* multiple other groups. Bars represent the mean ± S.E.M.

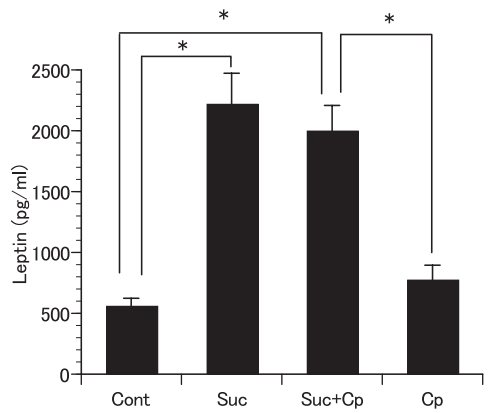


**Fig. 6.** Effects of 15% sucrose and chlorpromazine administration on plasma leptin levels (pg/ml) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* multiple other groups. Bars represent the mean ± S.E.M.

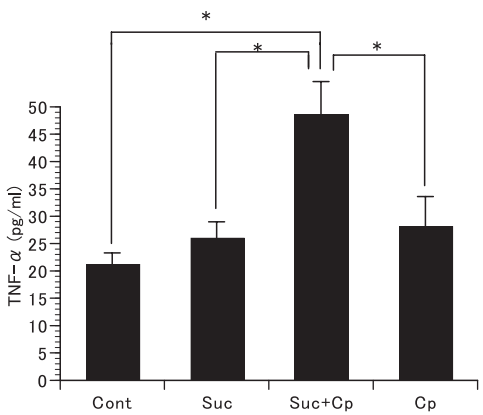


**Fig. 8.** Effects of 15% sucrose and chlorpromazine administration on plasma TNF-$\alpha$ levels (pg/ml) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). **P*<0.05 *vs* multiple other groups. Bars represent the mean ± S.E.M.

and Suc + Cp groups were higher than those in the Cont and Cp groups, the difference was not significant.

The weight of visceral fat in the Suc and Suc + Cp groups was greater than that in the Cont group, but no significant difference was seen between the Suc and Suc + Cp groups in this study. There have been a number of reports (27, 28) that antipsychotic agents induce obesity via their inhibitory effects on $H_1$, 5-$HT_{1A}$, and 5-$HT_{2C}$ receptors in the hypothalamus, thus increasing appetite. Cp inhibits 5-$HT_{2C}$ receptors (29, 30), although in the present experiment, there was no significant difference between the Cont and Cp groups or the Suc and Suc + Cp groups in the amount of food consumed. On the other hand, plasma insulin levels were significantly higher in the Suc, Suc + Cp, and Cp groups compared with those in the Cont group. Insulin stimulates glucose uptake by adipose tissue (31), and an imbalance between the uptake of energy-rich substrates (e.g., glucose) leads to hyperinsulinemia. Defects in the metabolism of glucose in hyperinsulinemia are closely associated with disturbances in the metabolism of lipids (32). Laviola et al. (33) reported that insulin signaling in human visceral adipose tissue is significantly higher than that in subcutaneous adipose tissue. Therefore, the increases in visceral fat tissue seen in the Suc, Suc + Cp, and Cp groups may be related to increases in plasma insulin and glucose levels. The results of the present study showed that concomitant Suc and Cp administra-

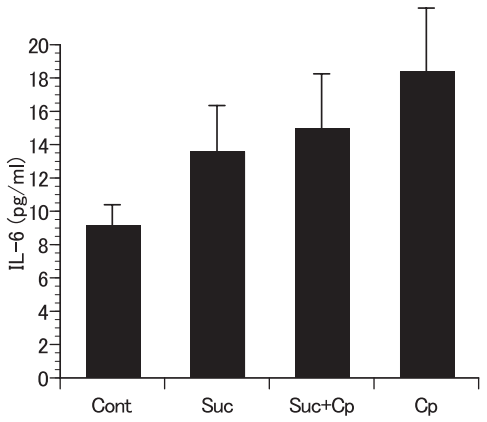


**Fig. 9.** Effects of 15% sucrose and chlorpromazine administration on plasma IL-6 levels (pg/ml) in rats. Cont: control group (n = 23), Suc: 15% sucrose group (n = 16), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 18), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9). Bars represent the mean ± S.E.M.

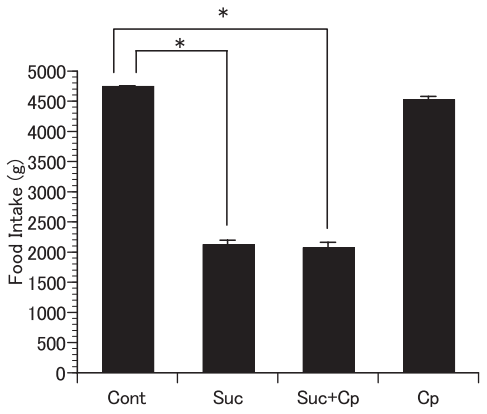


**Fig. 10.** Effects of 15% sucrose and chlorpromazine administration on total food intake (g) up to 10 weeks in rats. Cont: control group (n = 3), Suc: 15% sucrose group (n = 9), Suc + Cp: 15% sucrose + chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 9), Cp: chlorpromazine 7.5 mg/kg per day for 10 weeks group (n = 6). *$P$<0.05 *vs* Cont group. Bars represent the mean ± S.E.M.

tion affects the weight gain of visceral fat.

Plasma glucose and insulin levels in the Suc and Suc + Cp groups were significantly increased compared with those in the Cont group. Interestingly, the plasma insulin level in the Cp group also significantly increased compared with that in the Cont group. The plasma glucose level in the Cp group showed a tendency to increase compared with that in the Cont group, but the difference was not significant. Suc administration induces hyperglycemia in some experimental models (34). Therefore, the increases in plasma glucose and insulin levels in the present study may have been due to Suc administration. On the other hand, plasma insulin and glucose levels in the Cp group were higher than those in the Cont group. Dwyer et al. (35) reported that atypical antipsychotics increased insulin resistance in PC12 cells by inhibiting the cellular uptake of glucose. Those results suggest that the increases in plasma insulin and glucose levels in the Cp group may be related to the mechanism of action of Cp. Furthermore, it is possible that the increases in insulin and glucose levels in the Suc + Cp group are related to the combined effects of Suc and Cp. However, the levels of insulin and glucose in the Suc + Cp group did not increase additively compared with those in the Suc and Cp groups. Therefore, the detailed mechanism of the increases in insulin and glucose levels cannot be explained based on our results.

The total cholesterol level in the Suc + Cp group was significantly higher than that in the Cont group. Although that in the Cp group was higher than that in the Cont group, the difference was not significant. Clark et al. (36) reported that Cp increases both triglycerides and total cholesterol. Gupta and Rudney (37) found that Cp inhibits sphingomyelinase, which inhibits HMG-CoA reductase in cultured cells. On the other hand, Houtia et al. (38) reported that Cp inhibits low-density lipoprotein catabolism in J774 monocyte-like cells. It is thus possible that the increases in plasma cholesterol levels in the Suc + Cp and Cp groups in the present study may be related to those mechanisms, since our results suggest that Cp affects total cholesterol metabolism.

Plasma leptin levels in the Suc and Suc + Cp groups were significantly higher than in the Cont group. The correlation between leptin and antipsychotic-induced obesity has attracted attention (39). At present, it is thought that the increase in leptin levels is the result of increased visceral fat or Suc intake, and it is thought that antipsychotics do not directly affect leptin levels (40). This study indicated that leptin levels changed with the increase in visceral fat weight, suggesting that sucrose affects the plasma leptin level.

The plasma adiponectin level in the Suc group was significantly higher than that in the Cont group. Moreover, although no significant difference in visceral fat weight was seen between the Suc and Suc + Cp groups, the level of adiponectin was significantly lower in the Suc + Cp group than that in the Suc group. Levels of the most abundant adipocytokine, adiponectin, decrease in conditions such as obesity, diabetes, and coronary heart disease (41 – 43). Cooper et al. (44) reported that when olanzapine was administered to female rats for 20 days, although body weight and insulin resistance increased, there was a compensatory increase in adiponectin. However, we found a compensatory increase in the adiponectin level in the Suc group

but that increase in adiponectin was inhibited in the Suc + Cp group. These results suggest that Cp inhibits the Suc-induced increase in the plasma adiponectin level. Adiponectin levels have a negative correlation with adiposity, insulin sensitivity, diabetes, and atherosclerosis (45). Therefore, the inhibition of compensatory increases in the adiponectin level in the Suc + Cp group may explain antipsychotic drug-induced weight gain and hyperglycemia.

The level of TNF-$\alpha$ was significantly higher in the Suc + Cp group than in the Suc-alone group, suggesting that Cp increased TNF-$\alpha$ levels with Suc administration. Baptista and Beaulieu (46) reported that the increase in TNF-$\alpha$ levels in patients receiving antipsychotic agents is due to obesity as well as to changes in leptin levels. However, the difference in TNF-$\alpha$ levels in this study between the Suc and Suc + Cp groups suggests that Cp affects the production of TNF-$\alpha$ with Suc administration. Krogh-Madsen et al. (47) reported that insulin stimulates *TNF-α* gene expression in adipose tissue. These results of our study combined with those in previous reports indicate that Cp may enhance the stimulation of insulin and *TNF-α* gene expression in adipose tissue. On the other hand, TNF-$\alpha$ is essentially a cytokine secreted by monocytes or macrophages of inflammatory cells. In addition, in recent years, it has been reported that an increase in the number of fat cells due to obesity increases the number of macrophages in fat tissues (48, 49). Therefore, the synergistic effects of Suc and Cp may not only affect adipose tissue but also peripheral macrophages. Furthermore, Brustolim et al. (50) reported that the antidepressant bupropion, which is a norepinephrine and dopamine weak reuptake inhibitor, may suppress TNF-$\alpha$ synthesis by mediating increased signaling $\beta$-adrenoreceptors and dopamine type 1 receptors, resulting in increased cAMP that inhibits TNF-$\alpha$ synthesis. In addition, Cloëz-Tayarani et al. (51) reported that serotonin inhibited TNF-$\alpha$ production human peripheral blood mononuclear cells. These findings and our present data suggested that Cp may increase TNF-$\alpha$ production because of its blocking effects on dopamine and serotonin in adipose tissue. Further studies are necessary.

The results of this study suggest that Suc increases plasma glucose and insulin levels. In addition, in rats, Cp appears to inhibit the compensatory increase in adiponectin due to increased expression of TNF-$\alpha$ with Suc intake and has an enhanced injurious effect on the glucose level and insulin resistance. These effects may be one risk factor for the development of metabolic syndrome induced by antipsychotic drugs.

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