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ORIGINAL ARTICLE

Energy metabolism, leptin, and biochemical parameters are altered in rats subjected to the chronic administration of olanzapine

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DESCRIPTORS

Schizophrenia;
Olanzapine;
Cafeteria diet;
Energy metabolism;
Leptin.

Abstract

Objectives: Olanzapine, an atypical antipsychotic drug with affinities for dopamine, serotonin, and histamine binding sites appears to be associated with substantial weight gain and metabolic alterations. The aim of this study was to evaluate weight gain and metabolic alterations in rats treated with olanzapine on a hypercaloric diet. **Methods:** We used 40 rats divided into 4 groups: Group 1, standard food and water conditions (control); Group 2, standard diet plus olanzapine; Group 3, cafeteria diet (hypercaloric); and Group 4, olanzapine plus cafeteria diet. Olanzapine was administered by gavage at a dose of 3 mg/kg for 9 weeks. **Results:** There were no significant changes in the cholesterol levels in any group. Glucose levels increased in Group 3 by the fourth week. Triglyceride levels were altered in group 2 toward the end of the experiment. Leptin levels decreased in Groups 2 and 4. Complex II activity in the muscles and liver was altered in Group 2 (muscle), and Groups 2, 3, and 4 (liver). Complex IV activity was altered only in the liver in Group 2, without significant alterations within the muscles. **Conclusion:** These results suggest that olanzapine is correlated with weight gain and the risks associated with obesity.

DESCRITORES:

Esquizofrenia;
Olanzapina;
Dieta da lanchonete;
Metabolismo calórico;
Leptina.

Metabolismo calórico, leptina e parâmetros bioquímicos se alteram em ratos submetidos à administração crônica de olanzapina**Resumo**

Objetivos: A olanzapina, uma droga antipsicótica atípica com afinidade por locais de ligação de dopamina, serotonina e histamina, parece se associar a um ganho de peso e a alterações metabólicas consideráveis. O objetivo desse estudo foi avaliar o ganho de peso e as alterações metabólicas em ratos tratados com olanzapina numa dieta hipercalórica. **Métodos:** Usamos 40 ratos divididos em 4 grupos: Grupo 1, condições padrão de alimento e água (controle); Grupo 2, dieta padrão mais olanzapina; Grupo 3, dieta hipercalórica; e Grupo 4, olanzapina mais dieta hipercalórica. Olanzapina foi administrada por gavagem a uma dose de 3 mg/kg por 9 semanas. **Resultados:** Não houve alterações significativas nos níveis de colesterol em qualquer um dos grupos. Os níveis de glicose aumentaram no Grupo 3 por volta da quarta semana. Os níveis de triglicerídeos estavam alterados no Grupo 2 ao final do experimento. Os níveis de leptina diminuíram nos Grupos 2 e 4. A atividade do complexo II nos músculos e no fígado se alterou no Grupo 2 (músculos) e nos Grupos 2, 3 e 4 (fígado). A atividade do complexo IV se alterou apenas no fígado no Grupo 2, sem alterações significativas nos músculos. **Conclusão:** Esses resultados sugerem que olanzapina se correlaciona ao ganho de peso e aos riscos associados à obesidade.

Introduction

Schizophrenia is one of the most intriguing and widely studied mental diseases. Cognitive impairment related to schizophrenia produces neuropsychological deficits in various functions, including attention, working memory, verbal learning, and problem-solving/executive functions. Such deficits are directly related to functional changes in social behavior, occupational performance, and daily activities.¹ According to Harrison,² schizophrenia patients' brains show abnormalities, including ventricular enlargement and decreased cerebral (cortical and hippocampal) volume (which triggers the initial symptoms), as well as an absence of gliosis and other neurodegenerative features.

The symptoms of this highly debilitating psychiatric disorder are traditionally divided into 3 primary clusters: positive (hallucinations, delusions, and catatonia), negative (social and affective withdrawal) and disorganized (bizarre behavior, thought disorganization, and inappropriately affected). Due to the symptoms frequency and severity, schizophrenia is a heterogeneous disease that is difficult to treat.³

Atypical antipsychotic drugs are prescribed as a first-line intervention and represent a great advance in schizophrenia drug treatment.⁴ According to Reinke et al.,⁵ atypical antipsychotic drugs such as olanzapine seem to confer a lower risk of extra-pyramidal side effects compared to typical antipsychotics, and provide good antipsychotic properties. Olanzapine is an atypical thienobenzodiazepine-class antipsychotic with an affinity for dopamine binding sites D_1 and D_4 , as well as serotonin 5-HT_{2,3,6} muscarin (subtypes 1-5), adrenergic (α_1), and histamine (H_1) binding sites. The drug possesses weak D_2 receptor blockade properties, and its serotonin receptor 5-HT_{2A} blockage is about 8 times more intense than that of dopamine receptor D_2 .⁶ Clinical assay suggests that olanzapine decreases both positive and negative symptoms, and that it is associated with a low incidence of extra-pyramidal side effects.⁷

Despite the advantages of atypical antipsychotics over typical ones, their use, especially olanzapine, is related to significant weight gain and metabolic alterations such as dyslipidemias, diabetes, and other problems involving the metabolic syndrome.⁷ These metabolic alterations significantly increase the risk of death from cardiovascular disease, which is already the major cause of mortality in patients with schizophrenia.⁸ Furthermore, according to Jacob et al.,⁷ even without treatment, patients with schizophrenia have a higher risk for obesity, type 2 diabetes mellitus (DM), hypertension, and dyslipidemia compared to the general population. Weight gain is a common and severe side effect of atypical antipsychotic drugs; therefore, animal models are used to elucidate the mechanisms that lead to such alterations.⁹ Although most cases of antipsychotic-induced hyperglycemia and type 2 DM are associated with substantial weight gain, a significant number of cases occur among non-obese patients. Some studies indicate that first-episode drug-naïve patients with schizophrenia have 3 times the visceral adiposity, a lower glucose tolerance and stronger insulin resistance when compared to matched control groups.^{10,11}

Atypical antipsychotic drug-induced weight gain has multiple causes. Many of these drugs stimulate the appetite, generating a preference for sweet or greasy foods, which suggests a direct action on the metabolic systems and the centers of the brain associated with satiety and weight control.¹¹ Bear et al.¹¹ reported the important role of the dopaminergic system in regulating motivation, including feeding behavior. Thus, when dopaminergic neurons are destroyed or their receptors are blocked by drugs, electrical stimulation is much less effective in triggering feeding behavior. Antipsychotic-induced weight gain occurs even in the presence of high levels of leptin. Therefore, it is postulated that such drugs can reduce the sensitivity of the hypothalamus to the action of leptin.¹²

Molecular mechanisms for leptin and insulin signaling in the hypothalamus are responsible for neural appetite regulation.¹³ Leptin is an adipocyte-secreted, negative-feedback

hormone that acts on the hypothalamus to regulate both food intake and energy expenditure.¹³ There are at least two distinct neuronal groups that both possess leptin receptors in the arcuate nucleus: orexigenic neurons, which produce neuropeptide Y (NPY) and agouti-related protein (AGRP) and anorexigenic neurons, which produce proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Thus, leptin acts in catabolic and anabolic pathways via POMC and NPY, respectively.¹⁴ Data shows that antipsychotic-induced weight gain may be related to a dysfunction in leptin levels.¹⁵ In addition, abnormalities in glucose metabolism are described among atypical antipsychotic-treated patients with schizophrenia.¹⁶

Strategies to prevent alterations to the metabolic system are important in understanding the mechanisms underlying lipid metabolism, their association with changes in energy metabolism, and the control of reactive oxygen species formation.¹⁷ *In vitro* experiments have been developed to study how the use of atypical antipsychotic drugs affects lipid metabolism in adipocytes;¹⁸ a study suggests that these mechanisms can be modulated through mitochondrial activity,¹⁹ mainly by the inhibition of complex I.²⁰

In addition, the use of atypical antipsychotics not only alters the metabolism responsible for the homeostasis of the metabolic system, but also alters the energetic metabolism of the brain.^{21,22} Ji et al.²² demonstrated that olanzapine acts by inhibiting the enzymatic activity of complex I of the mitochondrial respiratory chain in some brain areas, such as the cerebral cortex and hippocampus, in addition to inhibiting subunits of complex V or adenosine triphosphate (ATP) synthase.²² Since antipsychotics act directly on the dopamine and serotonin pathways, the interaction leads to dopamine's modulation of the electron transport chain functioning by diminishing complex I activity, ATP synthesis, and membrane potential.^{23,24}

Considering schizophrenia is a complex and incurable disease and that drugs currently used for its management have potential side effects that make the maintenance of treatment difficult, the aim of our study is to evaluate metabolic alterations as well as the weight gain in animals treated with olanzapine and cafeteria diets.

Methods

Male 60-day-old Wistar rats were obtained from the Central Animal House of the Universidade do Extremo Sul Catarinense. They were caged in groups of 5, given free access to food and water and maintained in a 12-h light/dark cycle (lights on 7:00 am) at 22 (1)°C. All experimental procedures were carried out in accordance with the National Institute of Health's 'Guide for the Care and Use of Laboratory Animals' and the Brazilian Society for Neuroscience and Behavior's (SBNeC) Recommendations for Animal Care with the approval of the Ethics Committee of the *Universidade do Extremo Sul Catarinense*.

Animals were randomly divided into 4 groups: Group 1 (sham animals) received a standard diet plus saline administration, Group 2 received the standard diet plus olanzapine administration, Group 3 received a cafeteria (hypercaloric) diet plus saline administration, and Group 4 received the cafeteria diet plus olanzapine administration.

Olanzapine treatment consisted of one gavage administration (3 mg/kg olanzapine) per day for 9 weeks. Sham animals and group 3 received saline by gavage. The animals were weighed weekly during the 9 weeks of treatment.

The hypercaloric diet - designated *cafeteria* (Table 1) - consisted of food that was changed daily. All food was processed, mashed, and mixed with standard food for rats (1:1, cafeteria diet food: normal ration).

Determination of glucose, cholesterol, and triglycerides: these parameters were determined by Laboratório Búrgio. Blood was collected at the beginning of treatment, on the fourth week, and at the end of the treatment period.

Determination of leptin blood levels: leptin blood levels were determined using an ELISA Millipore Rat Leptin® commercial kit. The measurements were performed using blood collected at the end of the treatment period.

At the end of the treatment period, the animals were sacrificed by decapitation without anesthesia; the liver and muscles were removed to evaluate the activity of respiratory chain complexes II and IV. The livers and skeletal muscles were homogenized (1:20, w/v) in SETH buffer (pH 7.4; 250 mM sucrose, 2.0 mM EDTA, 10 mM Trizma base, and 50 UI/mL heparin). The homogenates were centrifuged at 800 × g for 10 min, and the supernatants were kept at -70°C until they were used for enzyme activity determination. The period between tissue preparation and enzyme analysis was always less than 5 days.

The activities of succinate-2,6-dichloroindophenol (DCIP)-oxidoreductase (complex II) and succinate:cytochrome c oxidoreductase (complex II-III) were determined in homogenates of the cerebral cortex as described previously.²⁵ The activity of cytochrome c oxidase (complex IV) was assayed in cerebral cortex homogenates.²⁵ The activities of the respiratory chain complexes were calculated as nmol·min⁻¹·mg⁻¹ protein.

Protein was measured using the method described by Lowry et al.²⁶ using bovine serum albumin as standard.

Statistical analysis

We performed Shapiro-Wilk and Levene median tests to assess normality and equal variance, respectively. If $p > 0.05$ was reached for both tests, we compared means using repeated measures ANOVA or one/two way analysis of variance (ANOVA) (both identified by F values). Otherwise, the non-parametric equivalent tests were performed (Friedman Repeated Measures ANOVA on Ranks or Kruskal Wallis ANOVA; both identified by H values). Friedman Repeated Measures ANOVA on Ranks was followed by Dunnett's test.

Results

Weight

All groups have gained weight throughout the nine week period (control group $\chi^2 = 70.47$, $p < 0.001$; olanzapine $\chi^2 = 70.94$, $p < 0.001$; hypercaloric diet $\chi^2 = 68.90$, $p < 0.001$; olanzapine + hypercaloric diet $\chi^2 = 68.90$, $p < 0.001$). The group treated with olanzapine + hypercaloric diet showed a significant weight difference starting from the fourth week while it took five weeks for all other groups (Table 2). Weight change throughout the nine weeks showed normal distribution but no significant difference between the four groups

Table 1 Hypercaloric diet (cafeteria diet). This diet was used in the hypercaloric diet and hypercaloric diet plus olanzapine groups for 10 weeks

Diet	Components of Diet	Weight	Days
1	Chocolate cookie Chantilly Corn salted Peanut sweet	5 g of each component every day	3 consecutive days
2	Chocolate Chocolate cookie Peanut	5 g of each component every day	3 consecutive days
3	Bacon salted Chantilly Corn salted	5 g of each component every day	3 consecutive days
4	Thread of Milk Peanut Peanut	5 g of each component every day	3 consecutive days
5	Chocolate cookie Bacon salted Thread of Milk	5 g of each component every day	3 consecutive days
6	Bacon salted Peanut Supplied cookies	5 g of each component every day	3 consecutive days
7	French fries Peanut Chocolate	5 g of each component every day	3 consecutive days
8	Cheese Peanut Sweet Supplied cookies	5 g of each component every day	3 consecutive days
9	Peanut sweet Cheese Cheese	5 g of each component every day	3 consecutive days
10	Thread of Mil Supplied cookies	5 g of each component every day	3 consecutive days

It was added 15 g of normal ration to complement the diet.

Table 2 Weight gain evaluations of the group undergoing chronic administration of olanzapine while receiving the hypercaloric diet for 9 weeks. Data is expressed as median (25, 75 percentiles).

Group	Control	Olanzapine	Hypercaloric diet	Olanzapine + Hypercaloric diet
P1	277 (250, 290)	260.5 (257, 274)	272 (259.5, 296.5)	273 (252.5, 280.5)
P2	297.5 (269, 309.5)	281 (271.5, 296.5)	283 (271, 302)	285 (260.5, 292)
P3	316 (287, 330)	307.5 (296, 314.5)	312 (299.5, 345)	306 (280.5, 317)
P4	325 (297.5, 344)	325.5 (309, 331.5)	335 (318, 356.5)	327.5 (301, 340)
P5	346.5 (322, 357)	332.5 (324, 339)	350 (343.5, 381)	341.5 (311, 357.5)*
P6	354.5 (331.5, 369)*	344 (331.5, 354)*	363 (349.5, 394.5)*	352.5 (320, 369.5)*
P7	357 (343, 377)*	354 (351, 366.5)*	367 (348.5, 407)*	350 (314.5, 371)*
P8	366.5 (341.5, 388.5)*	365 (357.5, 377.5)*	390.5 (371, 414)*	367.5 (330.5, 384.5)*
P9	372 (354.5, 384.5)*	374 (362, 380)*	402.5 (386, 428.5)*	387.5 (344, 398.5)*
P10	383 (362.5, 398)*	379.5 (360.5, 386.5)*	414 (388.5, 431)*	391 (347, 404)*

Data is present as median (0.25, 0.75 percentile). *p < 0.05 compared to P1.

was observed ($F = 1.69$, $p = 0.189$). Furthermore, we did not observe an interaction between a hypercaloric diet and olanzapine treatment ($F = 1.75$, $p = 0.196$).

Serum analysis

Serum cholesterol was measured at the baseline on the fourth and ninth week. We observed a statistical trend for an increased cholesterol level in the olanzapine and olanzapine + hypercaloric diet groups (control group $\chi^2 = 5.33$, $p = 0.072$; olanzapine $\chi^2 = 6.33$, $p = 0.052$; hypercaloric diet $\chi^2 = 3.50$, $p = 0.273$; olanzapine + hypercaloric diet $\chi^2 = 6.00$, $p = 0.500$). There was no significant difference in the cholesterol changes between groups (fourth week $H = 1.35$, $p = 0.716$; ninth week $F = 1.01$, $p = 0.405$). Moreover, we did not observe an interaction between the hypercaloric diet and olanzapine treatment (fourth week $F = 0.01$, $p = 0.998$; ninth week $F = 2.45$, $p = 0.130$).

Glucose serum levels were measured on the baseline on the fourth and ninth week. We observed lower glucose levels after both olanzapine treatment and/or a hypercaloric diet in all groups (control group $\chi^2 = 12.07$, $p = 0.0003$; olanzapine $\chi^2 = 11.14$, $p = 0.001$; hypercaloric diet $\chi^2 = 12.28$, $p = 0.0003$; olanzapine + hypercaloric diet $\chi^2 = 10.33$, $p = 0.002$). We found a lower glucose change in the hypercaloric diet group when compared to the control group after four weeks ($F = 3.31$, $p = 0.03$, post hoc $p = 0.005$). Results showed no interaction between treatments (fourth week $F = 2.19$, $p = 0.151$; ninth week $F = 0.02$, $p = 0.871$).

Serum triglyceride levels were measured on the fourth and ninth week. We observed increased triglycerides in the olanzapine group after treatment for nine weeks (control group $\chi^2 = 3.50$, $p = 0.273$; olanzapine $\chi^2 = 7.00$, $p = 0.029$; hypercaloric diet $\chi^2 = 3.71$, $p = 0.192$; olanzapine + hypercaloric diet $\chi^2 = 2.00$, $p = 0.486$) (Table 3). There was a significant triglyceride change after nine weeks of clozapine treatment when compared to control (fourth week $H = 3.58$, $p = 0.310$; 9th week $F = 5.35$, $p = 0.005$, control x olanzapine $p = 0.004$). We have also found statistically significant results for the

interaction between hypercaloric diet and olanzapine treatment after nine weeks (fourth week $F = 0.174$, $p = 0.681$; ninth week $F = 9.47$, $p = 0.005$).

Leptin serum level was measured after nine weeks of treatment. Our results indicate that the olanzapine + hypercaloric diet group showed statistically significant lower leptin levels than the control group after nine weeks of treatment ($H = 17.36$, $p = 0.0005$, post hoc olanzapine + hypercaloric diet x control $p = 0.001$).

Respiratory chain complex II and IV, present in the skeletal muscles and livers of rats subjected to olanzapine administration in the absence or presence of the hypercaloric diet, were also measured.

We observed an increase in muscle complex II activity in the olanzapine-administered group ($F = 4.45$, $p = 0.02$, control x olanzapine $p = 0.02$). Similarly, the hepatic complex II activity increased ($F = 11.23$, $p < 0.01$) in the olanzapine ($p = 0.011$), cafeteria diet ($p = 0.001$), and olanzapine plus cafeteria diet ($p = 0.001$) groups (Figure 1). Furthermore, hepatic complex IV activity increased in the olanzapine group ($F = 9.83$, $p = 0.001$, control x olanzapine $p = 0.002$) (Figure 2).

Discussion

Cholesterol levels

In the present study, we did not observe significant alterations in blood cholesterol levels after treatment with olanzapine or the hypercaloric diet. Teixeira et al.²⁷ report that most of the studies concerning dyslipidemia and psychopharmaceuticals highlight antipsychotic drugs, particularly clozapine and olanzapine, as presenting an increased risk of general cholesterol increase. Koro et al.²⁸ analyzed a database containing over 18,000 patients with schizophrenia and concluded that olanzapine treatment is related to a nearly 5-fold increase in the incidence of dyslipidemia compared to the general population and an over 3-fold increase in typical antipsychotic-treated

Table 3 Cholesterol, glucose and triglyceride evaluation in the baseline, at the 4th and 9th week of the experiment. Leptin was evaluated only at the end of the experiment. Data is expressed as median (25, 75 percentiles).

Group		Control	Olanzapine	Hypercaloric diet	Olanzapine + Hypercaloric diet
Chol.	Baseline	52.5 (45.5, 58.5)	54.5 (51.5, 62)	54 (47.75, 59.25)	55.5 (50.5, 58)
	4 th week	65 (62, 75)	72 (64, 80)	74.5 (69, 86)	85.5 (67.25, 87.75)
	9 th week	62 (54, 71)	73 (66.5, 75.5)	69 (61.25, 75.5)	57 (55.5, 70.5)
Gluc.	Baseline	226 (207.5, 315)	255 (221, 295.75)	210 (197.25, 233.5)	221 (202, 257)
	4 th week	157 (124.25, 163.5)*	164 (147, 169.75)*	187 (173.75, 201.75)	165 (161, 169)
	9 th week	136.5 (126.5, 143.5)*	136 (113, 137.75)*	134 (129, 147.5)*	141.5 (128, 146)*
Triglyc.	Baseline	92(75, 114)	98 (68.5, 118)	107 (63, 113.75)	107.5 (87, 129)
	4 th week	161 (139, 180)	111.5 (109, 129)	112 (90, 245.5)	119 (91, 143.75)
	9 th week	136.5 (132, 154)	316 (224, 403)*	182 (109, 249.5)	133 (118, 167.5)
Leptin	9 th week	0.372 (0.278, 0.436)	0.243 (0.164, 0.294)	0.414 (0.326, 0.506)	0.224 (0.114, 0.267)

Chol: Cholesterol; Gluc: Glucose; Triglyc: Triglycerides. Data is present as median (0.25, 0.75 percentile). * $p < 0.05$ compared to baseline.

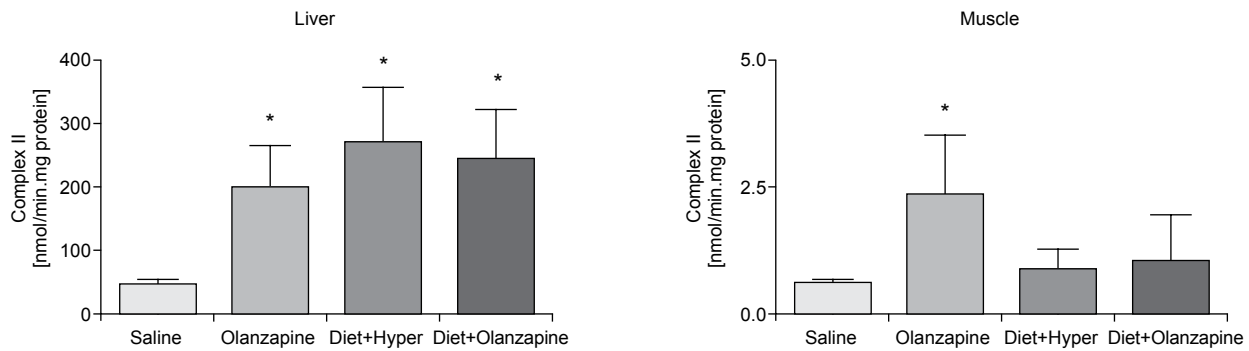


Figure 1 Effects of olanzapine and hypercaloric diet administration on the activity of complex II of the respiratory chain in rat liver and muscles. Data is expressed as mean \pm SD (n = 10).

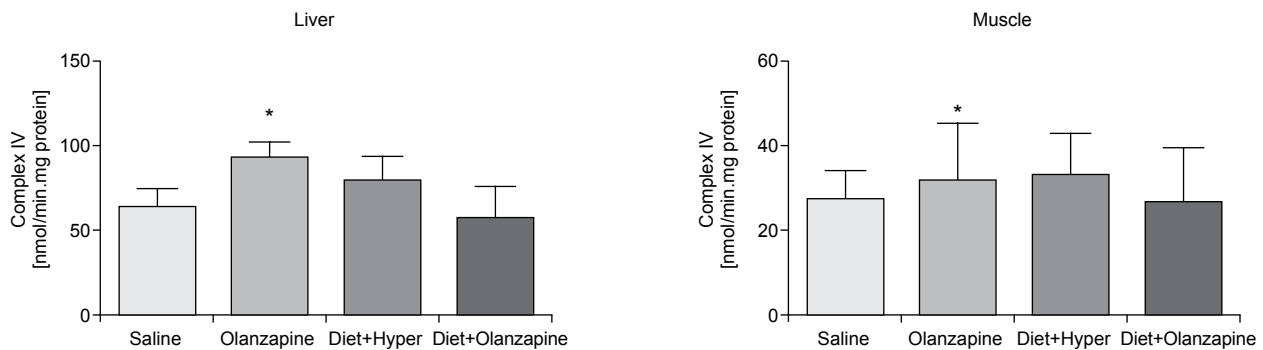


Figure 2 Effects of olanzapine and hypercaloric diet administration on complex IV of the respiratory chain in rat liver and muscles. Data is expressed as mean \pm SD (n = 10).

patients. Although data from the literature remain controversial, in the present study, 3 mg/kg doses of olanzapine did not significantly affect cholesterol levels; this can be explained due to the short duration of treatment considering that the references cited above utilized longer periods of treatment. Nevertheless, another study corroborates our findings, indicating either small or non-significant increases in lipid levels as a result of olanzapine administration.²⁹

Triglyceride levels

Triglyceride levels increased in Group 2 (treated with olanzapine only) at the end of treatment. Previous studies indicate a more significant increase in triglyceride levels compared to cholesterol levels.^{29,30} The first published study comparing treatment with atypical (e.g., olanzapine) and typical (e.g., haloperidol) antipsychotics indicates a significant increase in triglyceride levels among patients treated with olanzapine.³¹

Glucose levels

We found increased glucose levels in Group 3 (cafeteria diet without olanzapine) during the fourth week (the middle of treatment). We suggest that this alteration, which was verified only at the fourth week and disappeared following treatment,³² is an adaptation to the hypercaloric diet. An

experimental study with rats conducted by Coccorello et al.³² found increased glucose levels, even in the presence of high insulin levels, when olanzapine was administered at 3 mg/kg. This suggests that the outcome is attributable to insulin resistance.³² Sena et al.³⁰ reported that glucose metabolic alterations are more common in patients with schizophrenia than in the general population. They concluded that hyperglycemia is not dose-dependent in most cases, that it is reversible with treatment cessation and reappears once the antipsychotic is re-administered. In addition, some reports suggest that atypical antipsychotic drugs like olanzapine have a strong affinity for serotonergic receptors (i.e., 5HT_{1A} and 5HT₂), resulting in the reduction of pancreatic cell activity.³³

Leptin levels

Decreased levels of blood leptin were found in Groups 2 and 4 (treatment with olanzapine plus cafeteria diet and olanzapine alone, respectively). Findings related to the association of leptin action and the use of atypical antipsychotic drugs remain limited and controversial. Treatment with atypical antipsychotics increase body weight by 20%, and leptin appears to be responsible for such results.²⁴ Another study indicates that leptin receptor levels are not altered, suggesting leptin resistance to its own receptors in patients treated with olanzapine³⁴ or a leptin blockade caused by olanzapine that results in weight gains.³⁵

The olanzapine-induced blockade of neurotransmitters in the hypothalamus has been studied in rats. Since it appears that this drug is involved in the blockade of receptors 5HT_{2C}, D₂ and H₁, satiety signaling does not occur, which consequently increases food intake and body weight³⁶ Danaci et al.³⁷ observed weight gain within an olanzapine-treated group, although low leptin levels were maintained at the end of the experiment. Studies suggest that low leptin levels slow down satiety signaling to the hypothalamus, resulting in increased appetite and subsequent weight gain.³⁷ Our findings are corroborated by the data from these studies, indicating that leptin levels are lower than normal, thus, inducing weight gain via the inhibition of the satiety sensation. This can result in obesity and subsequent health problems from continuous use of the medication.

Mitochondrial respiratory chain

A previous study on patients with schizophrenia found membrane alterations and mitochondrial dysfunction.³⁸ We evaluated the activity of complexes II and IV of the mitochondrial respiratory chain within the muscles and liver. In muscle tissue, we observed a significant increase in complex II activity within the olanzapine-treated group compared to the saline group. In the liver, we found increased complex II activity in groups treated with olanzapine, olanzapine plus cafeteria diet, and cafeteria diet alone. Regarding complex IV activity, we found no significant alteration among the groups within muscle tissue. Nevertheless, in the liver, complex IV activity increased in olanzapine-treated groups compared to saline-treated ones. Data from literature demonstrate that the effects of leptin are mediated by the liver.³⁹ Thus, our results suggest increased oxygen consumption, which consequently increases the basal metabolic level and the activities of complexes II and IV.

Streck et al.⁴⁰ showed that chronic administration of antipsychotics, including olanzapine, does not alter complex IV activity in rat brains. The same study showed reduced complex II activity in rat cerebellums with olanzapine treatment. Oxidative stress was also assessed with the use of antipsychotics; lipid peroxidation is observed in different brain regions, leading to the formation of free radicals, which results in neuronal injury.³²

Conclusion

Schizophrenia is a highly debilitating mental disease that features chronic cognitive deficits that significantly affect the lives of patients and their guardians. Our research indicates that adverse metabolic effects are still important challenges that should be overcome by psychopharmacology.

We believe that the discrepancies found in the metabolic profiles of these animals could be attributed to the dosage of olanzapine that was used, or because of the short duration of the experiment. Olanzapine is a drug that is used chronically and its side effects such as metabolic alterations and weight gain can be observed after a few weeks of use. In our study, the duration of the experiment was much shorter, so we could not observe the alterations expected.

Interestingly, during the course of this study, we observed leptin reduction in both groups which were on olanzapine and alterations of mitochondrial complex II and complex IV. These findings suggest a possible link between metabolic deficits and mitochondrial dysfunction following olanzapine

treatment. Furthermore, the association between mental illness and cardiometabolic risks suggests that psychiatrists must play an important role in evaluating and monitoring such risks coupled with the use of antipsychotic drugs.

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* Modest

** Significant

*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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