Research report
An animal model of antipsychotic-induced weight gain
Anibal A. Arjona, Sandy X. Zhang, Brittany Adamson, Richard J. Wurtman

Abstract

We have established an animal model for olanzapine-induced body weight gain, and used it to explore the relation between this weight gain, excessive food consumption, gross motor activity, and macronutrient choice. Female Sprague-Dawley rats received olanzapine (OLAN) or saline (1.2 mg/kg per day) via gavage for 10 days. Rats receiving OLAN exhibited significant increases in body weight when compared with control rats. Body weight returned to control levels once OLAN treatment was discontinued. Food consumption among the OLAN-treated group was significantly greater than among control rats between 6 and 10 days of treatment. Between 4 and 10 days of treatment, feed efficiency (grams of weight gained/grams of food consumed) was also significantly greater among animals receiving OLAN. In contrast, chronic administration of haloperidol (0.04 mg/kg; q.d.; gavage) did not influence body weight or food consumption of treated rats. Gross motor activity was significantly reduced by OLAN between 1 and 10 days of treatment, also returning to control levels when treatment was discontinued. No significant changes were observed in brain DA, DOPAC, HVA or 5-HIAA among animals receiving OLAN daily for 30 days; however, 5-HT levels were significantly elevated. In contrast, acute (1.2 mg/kg; 2 h, i.p.) administration of OLAN significantly increased brain DOPAC and HVA levels without affecting those of 5-HT or 5-HIAA. OLAN (1.2 mg/kg; q.d.; 10 days) administration did not alter macronutrient choice (carbohydrate:protein ratio) of rats. These data show that an animal model of OLAN-induced weight gain is readily generated, and suggest that the weight gain results at least in part from increased food intake, reduced gross motor activity, and enhanced feed efficiency.

Keywords: Olanzapine; Haloperidol; Body weight gain; Antipsychotics; Female rats; Sprague-Dawley; Gross motor activity; Serotonin

1. Introduction

Atypical antipsychotic drugs such as olanzapine (OLAN) and clozapine can cause patients to develop clinically relevant increases in body weight [1,11,14,17,23]. These increases may lead to critical problems in compliance and to other medical complications including diabetes and cardiovascular disease [19]. The slow progress in understanding the mechanism of this side-effect can be traced in part to the absence of reliable animal models which mimic changes occurring in individuals who receive the antipsychotic drugs.

A few publications have described attempts at establishing an animal model for antipsychotic-induced obesity [2,4,16,25,31]. For example, Baptista et al. [2] reported that chronic administration of the racemic mixture of sulphiride (20 mg/kg; q.d.) induced significant increases in body weight and food consumption among female but not male Wistar rats, with greatest increases taking place after 10 days of treatment. In humans, sulpiride causes significant increases in body weight in males as well as females [1]. Recently Goudie et al. [16] showed that female Wistar rats receiving daily injections of olanzapine (4 mg/kg; b.i.d.; 4.5 h apart) exhibited significant increases in body weight after 1 day and up to 10 days of treatment. Baptista et al. [4] reported that female but not male Wistar rats receiving risperidone (0.125, 0.25, or 0.5 mg/kg; s.c.; q.d.; 16 days) exhibited significant increases in weight gain at all dosages tested. Using a different rat strain, Ota et al. [25] showed that male Sprague-Dawley rats treated with a low dose of risperidone (0.005 mg/kg; b.i.d.; s.c.) developed significant increases in body weight, while higher concentrations of risperidone (0.5 mg/kg) significantly decreased weight. These studies show that, under certain conditions, rats treated with atypical antipsychotics can develop increases in body weight; however the effects differ from model to model, and existing models may not mirror human responses to these compounds.
Atypical antipsychotic agents such as olanzapine differ from the older antipsychotic agents (e.g. chlorpromazine; haloperidol) in that they block brain serotonin, histamine, and muscarinic acetylcholine receptors as well as dopamine receptors [8,9,28]. Since activation of serotonin 2A, 2B and 2C receptors has been shown [33,37] to promote satiety and to decrease the proportion of carbohydrate to protein that rats choose to eat, it seemed possible that some of the obesity-promoting actions of olanzapine could result from excessive consumption of carbohydrates.

The goal of the present study was to develop a reliable method for producing enhanced weight gain in rats using olanzapine, a drug that also clearly increases weight in humans. A secondary goal was to determine whether this increase was associated with increased food consumption, increased food efficiency, decreased gross motor activity, or changes in macronutrient choice (protein:carbohydrate ratio).

2. Materials and methods

2.1. Animals

Female Sprague-Dawley rats (250 g) (Charles River Laboratories, Wilmington, MA, USA) were maintained under standard husbandry conditions. Animals were exposed to a 12:00 h light/12:00 h dark cycle with food and water provided ad libitum. Unless otherwise stated, animals were fed standard rat chow (Prolab® RMH 3000, PMI® Nutrition International, St. Louis, MO, USA; 22% protein; 60% carbohydrate; 3.2 kcal/g metabolizable energy).

2.2. Chronic studies

Olanzapine, dissolved in acidified water (pH 5.5 with citric acid) to a final concentration of 2 mg/ml, was given daily via gavage 1 h before the beginning of the dark-phase, at the ED30 dosage needed to reduce amphetamine-induced hyperactivity (1.2 mg/kg) [21]. Controls received an equivalent volume of the diluent. All animals were sham gavaged with water for 2 weeks prior to the start of the study. Body weight and food consumption were measured every 2 days. In some studies, olanzapine was administered for periods of 10 or 30 days; in others it was administered for 10 days, followed by a washout period of 15 days, and then given again for 10 days.

In other studies, the effects of chronic administration of haloperidol on body weight and food consumption were determined. Haloperidol, dissolved in acidified water (pH 5.5 with citric acid) to a final concentration of 1 mg/ml, was given daily via gavage 1 h before the beginning of the dark-phase, at the ED30 dosage needed to reduce amphetamine-induced hyperactivity (0.04 mg/kg). Controls received an equivalent volume of the diluent. At the end of each experiment, animals were sacrificed and their brains quickly removed and frozen in liquid nitrogen. Tissues were stored at –80°C until analysis.

2.3. Acute studies

To compare the acute effects of olanzapine (1.2 mg/kg) and haloperidol (2 mg/kg) (Sigma, St. Louis, MO, USA) on brain levels of dopamine, serotonin, and their metabolites of female Sprague-Dawley rats (250 g), the compounds were dissolved in dimethylsulfoxide (DMSO) and administered as a single intraperitoneal injection while control animals received DMSO. After 2 h, the animals were sacrificed and their brains quickly removed and frozen in liquid nitrogen. Tissues were stored at –80°C until analysis.

2.4. Gross motor activity

Gross motor activities of olanzapine-treated (1.2 mg/kg; q.d.; p.o.) and control rats, housed singly, were monitored continuously using the Vital-View system (MiniMitter Company Inc., Bend, OR, USA) for 2 weeks prior to and throughout the duration of the study. This system uses infrared motion detectors to monitor the motion of the animal by counting the number of motion-induced switch closures. Changes are scored as activity counts, and the total number of counts during a sampling period interval is recorded by the system. There is no quantification of magnitude or direction of movement.

2.5. Macronutrient choice

For macronutrient choice experiments, rats were presented concurrently with a choice of a high carbohydrate (80%)-no protein (0%) diet, and a high protein (20%)-carbohydrate (60%) diet (standard rat chow) (Harlan Teklad, Teklad Mills, Madison, WI, USA) (see Table 1 for diet composition). Both diets had a metabolizable energy content

![Table 1: Composition of test diets](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Diet composition (g/kg)</th>
<th>20% protein</th>
<th>20% carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein (high protein)</td>
<td>230.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D,L-Methionine</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sucrose</td>
<td>431.7</td>
<td>631.8</td>
<td>-</td>
</tr>
<tr>
<td>Corn starch</td>
<td>200.0</td>
<td>200.0</td>
<td>-</td>
</tr>
<tr>
<td>corn oil</td>
<td>52.3</td>
<td>54.6</td>
<td>-</td>
</tr>
<tr>
<td>Cellulose</td>
<td>37.86</td>
<td>66.46</td>
<td>-</td>
</tr>
<tr>
<td>40060 vitamin mix</td>
<td>10.0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Ethoxyquinox (antioxidant)</td>
<td>0.01</td>
<td>0.01</td>
<td>-</td>
</tr>
<tr>
<td>TD 79055 mineral mix, Ca-P Def.</td>
<td>13.37</td>
<td>13.37</td>
<td>-</td>
</tr>
<tr>
<td>Calcium phosphite, dibasic (CaHPO4)</td>
<td>16.66</td>
<td>23.72</td>
<td>-</td>
</tr>
<tr>
<td>Calcium carbonate (CaCO3)</td>
<td>5.1</td>
<td>0.038</td>
<td>-</td>
</tr>
</tbody>
</table>

a Harlan Teklad.

b High protein diet TD93328; high carbohydrate diet TD91352.

c Both diets have equal metabolizable energy content (0.67 kcal/g).
of 3.67 kcal/g. OLAN (1.2 mg/kg; q.d.; p.o.) was freshly mixed and administered as described above. Body weight and food consumption were determined every 2 days.

2.6. HPLC-EC analysis

Brain concentrations of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) were determined using high performance liquid chromatography with electrochemical detection. Brains were homogenized in 0.02 M acetic acid (5.1 buffer:brain wet weight), sonicated (4°C), and sedimented (14,000 rpm/15 min/4°C). The supernatant fluid (1 ml) was lyophilized and resuspended in 1 ml of HPLC-grade water. Epinephrine (Sigma) was added to the brain samples prior to homogenization to serve as the internal standard.

Brain levels of catecholamines and indolamines were determined using an ESA Coul orthochron II 5100A detector (E1 = −175 mV; E2 = +325 mV; Guard Cell 350 mV) with an ESA Microdialysis Cell model 3014B (ESA Inc., North Chelmsford, MA, USA). The mobile phase consisted of 90 mM sodium dihydrogen phosphate, 50 mM citric acid, 1.7 mM 1-octanesulfonic acid, 50 μM EDTA, 10% acetonitrile, pH 3.0 (adjusted with phosphoric acid). The column (ESA MD 150 mm × 3.2 mm, particle size 3 μm; pore size 120 Å (ESA Inc.) (flow rate 0.4 ml/min)) was maintained at 40°C. Peak heights were determined manually from the chromatograms, and values were corrected using the internal standard.

2.7. Data analysis

Repeated Measurements Analysis of Variance (ANOVA) was used to determine differences among groups (significance level, P ≤ 0.05), with drug treatments serving as the independent variables. Brain neurotransmitter levels were normalized against those of controls. When differences were present, means were separated using Duncan's Multiple Range Test. Data are presented as mean ± S.E.M.

3. Results

OLAN significantly increased body weight after 8 days of treatment (P < 0.05) (Fig. 1A). Food consumption in the OLAN-treated group was greater than that of control rats (P < 0.05) (Figs. 1A and 4B). It also increased feed efficiency (grams of weight gain/grams of food consumed) between 4 and 8 days of treatment (Fig. 1C). When OLAN treatment was discontinued for 2 weeks, body weight and food consumption of treated animals returned to control levels (data not shown). Chronic administration of haloperidol, on the other hand, did not influence body weight or food consumption of treated rats (Fig. 5A and B). Chronic administration of OLAN (1.2 mg/kg; q.d.; 10 days) significantly reduced dark-phase and total gross motor activity counts (1212 ± 26 versus 804 ± 30 and 1815 ± 81 versus 1489 ± 15, control versus olanzapine-treated, respectively); dark-phase and total activity counts returned to control levels during the 15-day washout period (1136 ± 36 versus 1075 ± 45 and 1730 ± 72 versus 1750 ± 53, control versus olanzapine-treated, respectively) (Fig. 2). We did not observe any evidence of tolerance development in response to chronic daily olanzapine administration.
Fig. 2. Effect of chronic administration of olanzapine (1.2 mg/kg; q.d.; 10 days) and clonazapine-free periods on gross motor activity of 250 g female Sprague-Dawley rats. During treatment periods 1 and 2, animals received the drug, during post-treatment periods 1 and 2 they received its diluent. Data represent the average motor activity during each treatment and post-treatment period. Olanzapine significantly decreased gross motor activity during the dark phase without affecting activity during the light phase. Gross motor activity returned to control levels upon discontinuation of olanzapine administration. Gross motor activity was monitored continuously using the vital-view system for a week prior to and throughout the study (E: initial value; C: control group; O: olanzapine group). Values represent mean ± S.E.M.; n = 11, 9 (**P ≤ 0.01).

Brain DA, DOPAC, and HVA levels were unaffected after 30 days administration of olanzapine; however, 5-HT levels were slightly but significantly increased (1.22 ± 0.09-fold basal; P < 0.05) (Fig. 3B). Acute administration of OLAN (1.2 mg/kg; 2 h; i.p.) significantly increased brain DOPAC (4.23 ± 0.41-fold basal; P < 0.05) and HVA (3.07 ± 0.40-fold basal) levels (Fig. 3A) without affecting brain DA, 5-HT, or 5-HIAA. Although OLAN (1.2 mg/kg; q.d.; 10 days) administration significantly increased body weight (6.26 ± 1.91 g versus 19.10 ± 3.30 g, control versus olanzapine-treated) (Fig. 4A), it did not alter macronutrient choice (carbohydrate:protein ratio) of treated animals (3.84 ± 0.38 versus 3.2 ± 0.2, carbohydrate:protein ratio, control versus olanzapine-treated) (Fig. 4B).

4. Discussion

These data show that an animal model of olanzapine-induced weight gain is readily generated by giving rats the drug via gavage, and suggest that this weight gain results at least in part from increased food intake (Fig. 1B), increased feed efficiency (Fig. 1C), and reduced gross motor activity (Fig. 2). Olanzapine administration significantly increased body weight after 8–10 days of treatment, and this increase persisted for at least 30 days if treatment was continued (Fig. 1A). When treatment was discontinued after 10 days, body weights gradually returned to control levels after 2 weeks. A similar decline in weight gain following olanzapine withdrawal has also been observed in humans receiving this medication [32].

Other recent studies have also described effects of olanzapine administration on weight gain by rats [16,26]. Goudie
Fig. 4. Effect of chronic administration of OLAN (1.2 mg/kg; q.d.) on body weight gain and macronutrients choice. Daily administration of OLAN (1.2 mg/kg; gavage; q.d.) (solid line) significantly increased the body weight of rats compared with those of control (hatched line) (A), but failed to affect the proportions of carbohydrate and protein which animals chose to eat (B). Values represent mean ± S.E.M.; N = 5, 5(*) P ≤ 0.05.

et al. [16] showed that female Wistar rats receiving daily injections of olanzapine (4 mg/kg; b.i.d.; 4.5 h apart) exhibited significant increases in body weight after 1 day, and up to 10 days of treatment. Pouzet et al. [25] showed that administration of olanzapine (5 or 20 mg/kg; q.d.; gavage) or haloperidol (0.08 or 0.31 mg/kg; q.d.; gavage) did not influence body weight gain of male Wistar rats, but did induce significant increases among female rats. The doses chosen in the study by Pouzet et al. are reported to induce an antipsychotic-like effect in rat models of schizophrenia. The findings in these papers, and of other attempts to generate an animal model of antipsychotic-induced weight gain, suggest the notion that failure to develop a reliable model might be related to the pronounced differences in dosages used or the strains, routes and times of administration. The dose of OLAN that we used to enhance weight gain (1.2 mg/kg) equals the drug’s ED50 dosage that results in a 50% reduction in amphetamine-induced hyperactivity. This may allow this model to be used to test the effectiveness of various interventions in reducing OLAN-induced body weight gain while preserving the drug’s therapeutic efficacy.

The ability of olanzapine to increase body weight could result from its ability to antagonize brain serotonergic, histaminergic, and/or dopaminergic receptors, among others [1,29,33]; 5-HT2A, 5-HT2C receptors, histamine H1 receptors and dopamine receptors are all affected by the drug, and all have been shown to influence food intake [5,13,20,22,37] as well as gross motor activity [10,24,30].

Fig. 5. Effect of chronic administration of haloperidol (0.04 mg/kg; q.d.) on body weight gain and food consumption. (A) Daily administration of haloperidol (0.04 mg/kg; gavage; q.d.) (hatched line) did not influence body weight gain of rats compared with those of control (solid line). (B) Food consumption in the haloperidol-treated group (hatched line) was not significantly different from that of the control group (solid line). Values represent mean ± S.E.M.; N = 5, 5(*) P ≤ 0.05.

In our study, we focused on the possible involvement of serotonergic neurotransmission because of serotonin’s well-recognized role in the control of food intake (i.e. its role in satiety [6] and in macronutrient selection [37]). Since olanzapine antagonizes 5-HT2A and 2C receptors, we hypothesized that the obesity-promoting actions of olanzapine would be associated with an increase in carbohydrate craving [37]. Our results show that rats which developed increased weight gain when given OLAN failed to exhibit a selective increase in carbohydrate consumption (Fig. 4). Furthermore, the increase in body weight gain and food consumption was not influenced by giving the rats two diets, one of which contained only carbohydrate and no protein (Fig. 4). Similarly, patients receiving atypical antipsychotics may not exhibit carbohydrate craving [14]. This lack of effect on macronutrient selection is compatible with the failure of acute OLAN treatment to affect brain levels of 5-HT or 5-HIAA, and the small rise in 5-HT seen with chronic OLAN treatment (Figs. 3 and 5).

Attempts to reduce or eliminate antipsychotic-induced weight gain by enhancing intrasynaptic serotonin levels have
met with mixed results. Wurtman et al. [36] demonstrated that a treatment program which included daily consumption of carbohydrate rich drinks, which increased the plasma tryptophan/LNAAs ratio and presumably brain 5-1T levels [12,38], caused significant weight loss in patients with psychotropic drug-induced obesity. Other studies have found various serotoninergic-active compounds (e.g. fluoxetine, fenfluramine) to be ineffective [7,27] or significant [15,34].

In toto, these studies suggest that serotoninergic neurons may play some role in antipsychotic-induced weight gain, however, the consequences of attempting to treat this weight gain by modifying serotoninergic function are highly variable. Histaminergic synapses may be a better target; Kroese et al. [18] examined the affinity of various typical and atypical antipsychotics for various serotoninergic, adrenergic, muscarinic, and histaminergic receptors, and noted that affinity for H1 histamine receptors was the best predictor of short-term weight gain. Histaminergic neurons have also been implicated in the regulation of gross motor activity [10,24,30]. In our study, the increase in body weight of OLAN-treated rats was associated with increased food intake and with an even greater increase in weight gain per gram of food eaten. This enhancement in food efficiency was probably related in part to the drug-induced decrease in gross motor activity, inasmuch as body weight gain and gross motor activity returned to control levels concurrently, once olanzapine administration had been discontinued. A similar decrease in gross motor activity occurs in humans undergoing atypical antipsychotic therapy [14]. The enhanced weight gain of rats given olanzapine could also result from activity-independent changes in metabolic rate. A full range of studies aiming at establishing energy expenditure will be necessary in order to understand the effect of olanzapine on energy metabolism.

In conclusion, we describe a convenient and reliable animal model for antipsychotic-induced body weight gain, which uses female Sprague–Dawley rats. Data obtained using this model suggest that this weight gain results at least in part from increased food intake increased feed efficiency, as well as a reduced gross motor activity.

Acknowledgements

This work was supported by grants from the National Institute of Health (MH-28783) and the Center for Brain Sciences and Metabolism Charitable Trust.

References

[24] Oncedora K, Yamadama A, Watanabe T. Effects of alpha-fluoromethylation of leuciner in locomotor activity, brain histamine and cate-