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ORIGINAL INVESTIGATION

A model for antipsychotic-induced obesity in the male rat

Julie Minet-Ringuet · Patrick C. Even · Magali Lacroix · Daniel Tomé · Renaud de Beaurepaire

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Abstract
Introduction Weight gain is a common and severe side effect of antipsychotic drugs. A usual tool to study the side effects of psychotropic drugs is animal models. However, attempts to create an animal model of antipsychotic-induced weight gain were not successful so far. Female rodents are sensitive to the effects of antipsychotics, but not males. This does not match the human clinical situation. Antipsychotics have different pharmacokinetic properties in rats and humans, and rats and humans have different spontaneous diets.
Materials and methods In the present study, we tested the hypothesis that the insensitivity of male rats to the weight-promoting effects of antipsychotics could be related to the mode of administration of antipsychotics and to the animals' diet. Antipsychotics were mixed with the food, and rats were fed a diet resembling the human diet. Rats were treated with 0.01, 0.1, 0.5, and 2 mg/kg of olanzapine or with a control solution for 6 weeks. Their weight and food intake were recorded, and their body composition were analyzed. The effects on weight and food intake of olanzapine (1 mg/kg), haloperidol (1 mg/kg), and ziprasidone (10 mg/kg) were also compared in a 3-week treatment experiment.
Results The results showed that 0.5 and 2 mg of olanzapine, but not lower doses, increase body weight and subcutaneous fat deposition. After the 3-week treatment, olanzapine-treated rats, but not haloperidol- or ziprasidone-treated rats, had significantly increased their weight.
Conclusion This study shows that a rat model of obesity induced by antipsychotics can be created under specific conditions of drug administration, diet, and dose.

Keywords Olanzapine · Antipsychotic · Adiposity · Weight gain · Food intake · Diet

J. Minet-Ringuet · R. de Beaurepaire (✉)
Laboratoire de Psychopharmacologie,
Centre Hospitalier Paul Guiraud,
54 Avenue de la République,
94806 Villejuif, France
e-mail: debeaurepaire@wanadoo.fr

J. Minet-Ringuet · P. C. Even · M. Lacroix · D. Tomé
UMR Physiologie de la Nutrition
et du Comportement Alimentaire,
Institut National Agronomique Paris-Grignon,
16 rue Claude Bernard,
75231 Paris, Cedex 05, France

R. de Beaurepaire
Institut National de la Santé et de la Recherche Médicale,
513, 94010 Créteil, France

Introduction

Weight gain is a serious and frequently reported side effect of antipsychotic treatments. Antipsychotics also often produce metabolic disturbances, including hyperlipidemia, glucose dysregulation, and type II diabetes mellitus, which increase the risk of cardiovascular diseases and mortality in treated patients (Wirshing et al. 1999, 2002). These side effects are particularly marked with clozapine and olanzapine (Allison et al. 1999; Meyer 2001). Studies indicate that antipsychotic-induced weight gain is a common cause of noncompliance and discontinuation of treatment, resulting in the relapse of psychotic symptoms (Myers and Rosen 1999, Silverstone et al. 1988). The mechanisms by which antipsychotics increase weight and produce metabolic disturbances are not known. Animal models are commonly used to investigate the mechanisms of action antipsy-

chotics. However, attempts to create an animal model of antipsychotic-induced weight gain were so far not successful. Female, but not male, rodents appear to be sensitive to the weight-promoting effects of antipsychotics. After chronic antipsychotic treatments, female mice and rats (Arjona et al. 2004; Baptista et al. 2002; Fell et al. 2004a,b; Goudie et al. 2002; Kaur and Kulkarni 2002; Pouzet et al. 2003; Cooper et al. 2005) increase their weight, but male rats do not (Baptista et al. 1993; Pouzet et al. 2003; Minet-Ringuet et al. 2005). Weight gain in female rats seems to result from hyperphagia, while no change in food intake was reported in males (Arjona et al. 2004; Minet-Ringuet et al. 2005). The weight- and food intake-promoting effects of antipsychotics in female rats were attributed to an interaction with female hormones (Baptista et al. 1998, 1999). These observations do not match the clinical situation in humans in which antipsychotic treatments induce a weight gain and an increase in food intake in both males and females (Allison et al. 1999; Baptista et al. 1999; Ganguli et al. 2001).

We hypothesized that differences in medication pharmacokinetics and macronutrient preferences between humans and laboratory animals could explain the difficulties involved in creating a reliable animal model of antipsychotic-induced weight gain. In rodent studies published in the literature, antipsychotics were almost always administered by using daily gavage (Arjona et al. 2004; Minet-Ringuet et al. 2005; Pouzet et al. 2003), intraperitoneal injections (Baptista et al. 1993; Fell et al. 2004b; Kaur and Kulkarni 2002), or subcutaneous injections (Baptista et al. 2002, 2004). However, the plasma half-life of antipsychotics is much longer in humans than in rodents. Haloperidol's half-life in humans is 24 h, while it is 1.5 h in rats (Cheng and Paalzow 1992), and olanzapine's half-life of is 33 h in humans and 2.5 h in rats (Aravagiri et al. 1999). We previously undertook an experiment in which antipsychotics were mixed with food. We supposed that this would allow the maintenance of relatively constant antipsychotic blood levels throughout the 24-h period. We observed that animals treated by mixing olanzapine with food for 6 weeks did not gain weight, but that they significantly increased their adipose tissue deposition (Minet-Ringuet et al. 2006), while animals treated by once-daily gavage did not gain weight and did not significantly increase fat tissue deposition (Minet-Ringuet et al. 2005). In a recently published study Albaugh et al. (2006) also used the technique of mixing the treatment (olanzapine or clozapine) with the food, and they found no increase in weight in male rats, similar to our observations, but the authors did not measure fat tissue deposition.

Rats and humans also differ in their spontaneous macronutrient intake. Humans have a high carbohydrate intake (approximately 50% of daily energy), a low protein intake (less than 20% daily energy), and an intermediate lipid intake (approximately 30–40% of daily energy) (Volatier and Verger 1999). Unlike humans, rats have high protein intake (35%), high lipid intake (50%), and low carbohydrate intake (15%). We have recently shown that the interaction between carbohydrates and lipids is essential in the induction of obesity in rats fed with high-fat diets (Marsset-Baglieri et al. 2004).

We therefore undertook experiments where treatments were mixed with the food and where rats were fed with a diet resembling a human macronutrient diet. In the first series of experiments, we measured the weight gain of male rats chronically treated with different doses of olanzapine and we analyzed the body composition of the animals at the end of the experiment. In a second series of experiments, we compared the effects on weight gain of olanzapine to those of two other antipsychotics, haloperidol and ziprasidone. Olanzapine is an atypical antipsychotic known to increase weight in humans (Allison et al. 1999), haloperidol is a classical antipsychotic, which has a moderate effect on weight (Ascher-Svanum et al. 2005), and ziprasidone is an atypical antipsychotic, which has a very low impact on weight (Allison et al. 1999). During the last week of this experiment, we analyzed the feeding patterns of the animals to further compare and characterize the effects of the three antipsychotics on food intake.

Materials and methods

Experiment 1: dose-dependent effects of olanzapine on body weight and body composition

Animals Thirty male Sprague-Dawley rats (Harlan, Gannat, France) initially weighing 175–200 g were housed in individual Plexiglas cages with an artificial 12:12-h light-dark cycle (lights on at 08:00 h) in a room maintained at 24±1°C and 55±5% humidity. Food and water were available ad libitum throughout. All rats were fed with a medium fat diet (metabolizable energy 17.50 kJ/g) (INRA, Jouy-en-Josas, France) composed of 140 g/kg of whole milk protein, 538.1 g/kg of cornstarch, 87.6 g/kg of sucrose, and 137 g/kg of soya bean oil, and this diet was supplemented with minerals and vitamins according to the AIN-93M requirements (mineral salts 35 g/kg, vitamins 10 g/kg, cellulose 50 g/kg, and choline 2.3 g/kg) (Reeves et al. 1993). This food, named P14-L, which resembles the usual human diet (14% proteins, 31% lipids, and 54% carbohydrates) was prepared in our laboratory in the form of a powder. All experiments were performed under an approved protocol according to the Declaration of Helsinki and the guidelines of the French Ministry of Agriculture on the use and care of laboratory animals.

Olanzapine doses and preparation Four doses of olanzapine (Zyprexa Velotab, Lilly, France) were tested: 0.01, 0.1, 0.5, and 2 mg/kg, in addition to the control solution. Olanzapine was solubilized in water and then incorporated into the diet [addition of the olanzapine solution (as well as addition of other antipsychotics in experiment 2) did not change the powdered texture of the food]. The basal food intake was recorded during the adaptation period and determined the daily quantity of olanzapine incorporated into food. The olanzapine solutions were mixed into the food in the laboratory with a blender.

Procedure After 1 week of adaptation to the laboratory conditions, the rats were separated into five groups (n=6 per group) with homogenous weight and received the olanzapine treatments in their food during 6 weeks. Weight was recorded three times per week.

Body composition Body composition was measured at the end of the study by dissection and by weighing the main organs and tissues as previously described (Rolland et al. 2002). In summary, rats were deeply anesthetized by an intraperitoneal injection of an overdose of anesthetic (sodium pentobarbital 48 mg/kg, Sanofi santé animale, France) and heparinized (100 U heparin/100 g body weight). They were bled (to avoid coagulation in tissues) by sectioning the vena cava and abdominal aorta before removal and weighing of the main fresh organs (liver, spleen, kidneys, and pancreas) and tissues (perirenal and scapular brown adipose tissue, epididymal, retroperitoneal, visceral, and subcutaneous white adipose tissues (WATs), and carcass defined by muscles and skeleton).

Experiment 2: weight gain and food intake in olanzapine treated rats compared to two other antipsychotics: haloperidol and ziprasidone

Animals Twenty-four male Sprague-Dawley rats (Harlan) initially weighing 200–220 g were housed in individual cages with an artificial 12:12-h light-dark cycle (lights on at 08:00 h) in a room maintained at 24±1°C and 55±5% humidity. Food and water were available ad libitum throughout. All the rats were fed with the P14-L diet described in experiment 1.

Antipsychotic solutions Haloperidol (Sigma-Aldrich, France) (1 mg/kg) and olanzapine (1 mg/kg) were solubilized,whereas ziprasidone (Pfizer, NY, USA) (10 mg/kg) was suspended in 10% ethanol solution. The doses used corresponded to 50% of the maximal physiologic human dose (Food and Drug Administration) and were the same as those used in a previous work (Minet-Ringuet et al. 2006). The antipsychotic solutions were incorporated into the diet as described in experiment 1. The basal food intake was determined during the adaptation period.

Procedure During the third week of treatment, the rats were placed into a cylindric cage containing a recorder bowl. To prevent spillage and to precisely measure food intake, rats were fed liquid food: P14-L was dissolved in water (50% P14-L and 50% water). Drugs were incorporated into the liquid diet. Food intake was recorded as the amount of liquid food consumed.

Food intake recording and analysis Food intake was recorded by means of food cups placed on a strain-gauge (Entran SA, Les Clayes-sous-Bois, France; accuracy of 0.1 g) connected to a 34970A data acquisition/switch unit (Agilent Technology, Les Ulis, France) and to a personal computer programmed to record data every 10 s via the Dac Express software (Agilent Technology). The cumulative food intake was recorded during 23 h (18:00 to 17:00 h) over 4 days (Monday to Friday, that is to say, 4 days × 23 h). Only the last two 23-h recordings were kept for analyses. These two recordings are considered as the most stable because during the first recording days animals were sometimes disturbed by the noise of the computer.

Statistical procedures

All results were expressed as means±SEM. Statistical analyses were performed using the SAS statistical package (SAS/STAT version 6.12 for Windows 95; SAS Institute, Cary, NC, USA). Repeated measures within time were compared using mixed linear model analysis (PROC MIXED), whereas data related to body composition and biochemical assays was analyzed using generalized linear model analysis (PROC GLM). Data subsets were compared using contrast computed within each analysis. Statistical significance was set at $p<0.05$.

Results

Experiment 1: olanzapine dose-dependent effects on body weight, and body composition

At the end of the control period, there were no differences in body weight between rats. During olanzapine treatments, the changes in body weight differed dose-dependently (Fig. 1). The autoregressive covariance structure analysis showed the following: group effect p=0.07, day effect $p<0.0001$, and group/day effect p=0.03. At the beginning of the treatment, each group had a similar body weight. The lowest doses of olanzapine (0.01 and 0.1 mg/kg) produced no effect on the evolution of body weight. The largest doses (0.5 and 2 mg/kg) accelerated the daily weight gain, and the rats in these treatment groups had a significantly higher body weight at the end of experiment (0 vs 0.5 mg/kg p=0.02; 0 vs 2 mg/kg p=0.03).

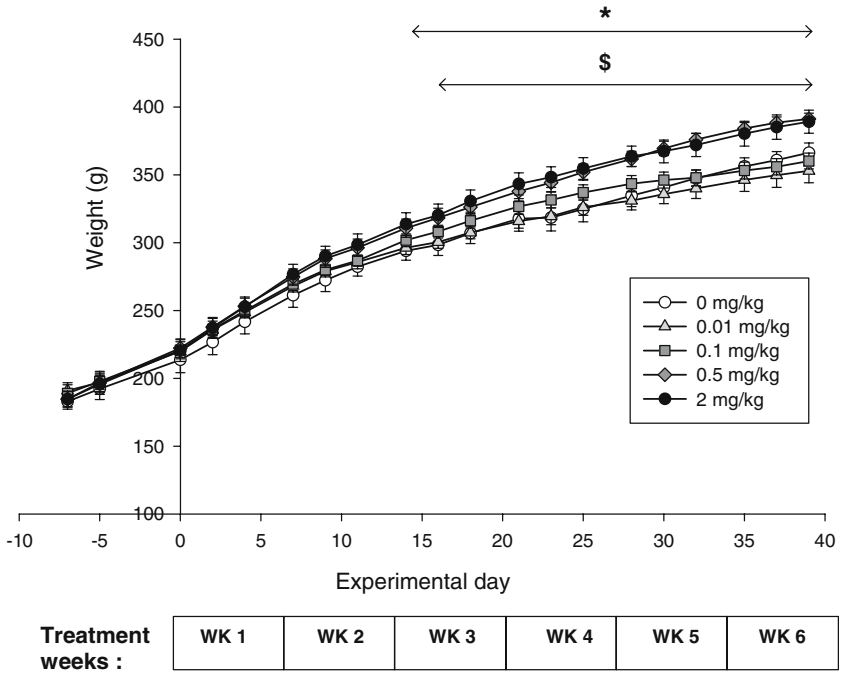

Fig. 1 Body weight of olanzapine-treated rats under different treatment doses (0.01, 0.1, 0.5, and 2 mg/kg) during 6 weeks. Experimental day-0 indicates start of treatment. Values are means±SEM, n=6 per group. Significant differences at p<0.05 are indicated: *Dollar symbol* between 0 and 0.5 mg/kg, *asterisk* between 0 and 2 mg/kg

Body composition analyses showed that significant increases in body weight were associated with increased WAT weight (group effect p<0.01) (Table 1). Although all WAT compartments tended to increase weight in a dose-dependent manner (group effect p=0.03), the increase was only significant for subcutaneous adipose tissue.

Analysis of the organs showed that the spleen was smaller in the 0.01 mg/kg group and the pancreas was bigger in the 2 mg/kg group. However, when the results were expressed in percentage of body weight the effects on organs were no longer significant (data not shown).

Table 1 Body composition of rats treated with different doses of olanzapine after a 6-week treatment period

Olanzapine doses (mg/kg)		0	0.01	0.1	0.5	2
Body weight		371.90±5.66^{ab}	357.24±10.39^{a}	363.46±6.39^{a}	393.23±5.23^{bc}	393.81±8.96^{c}
Organs	Livers	11.17±0.37	10.48±0.55	10.60±0.47	11.69±0.33	11.37±0.60
	Kidney	1.95±0.05^{ab}	1.89±0.06^{a}	1.88±0.07^{a}	2.08±0.05^{b}	2.08±0.05^{b}
	Spleen	0.81±0.04^{a}	0.73±0.03^{b}	0.74±0.02^{ab}	0.81±0.02^{a}	0.77±0.02^{a}
	Pancreas	1.52±0.05^{a}	1.55±0.08^{ab}	1.61±0.03^{ab}	1.59±0.05^{ab}	1.76±0.12^{b}
	Epididymal	6.58±0.40^{abc}	5.76±0.27^{ab}	5.59±0.28^{a}	6.93±0.30^{bc}	7.15±0.76^{c}
	Retroperitoneal	8.24±0.50^{ab}	7.19±0.63^{a}	7.54±0.36^{ac}	9.26±0.58^{b}	9.09±0.62^{bc}
	Subcutaneous	20.44±1.27^{a}	19.29±1.65^{a}	19.56±1.05^{a}	26.06±1.14^{b}	24.58±0.83^{b}
	Visceral	5.42±0.26^{ab}	4.72±0.28^{a}	4.55±0.27^{a}	5.59±0.50^{ab}	5.93±0.43^{b}
BAT	Total	1.34±0.13^{ab}	1.04±0.14^{a}	1.34±0.15^{ab}	1.41±0.04^{b}	1.23±0.07^{ab}
	Retroperitoneal	0.70±0.12^{ab}	0.48±0.11^{a}	0.59±0.10^{ab}	0.77±0.06^{b}	0.58±0.08^{ab}
	Interscapular	0.64±0.05^{ab}	0.56±0.04^{a}	0.75±0.08^{b}	0.65±0.05^{ab}	0.65±0.04^{ab}
Adrenals		0.04±0.00	0.06±0.00	0.06±0.01	0.06±0.01	0.05±0.01
Carcass (muscle and skeleton)		167.52±2.23^{ab}	159.89±4.61^{a}	165.30±3.35^{ab}	174.45±3.81^{b}	176.26±4.46^{b}

Values are expressed in grams (means±SEM, n=6 per group). Means in a row without a common letter differ significantly at p<0.05. No superscript indicates no significant difference on the same horizontal line

BAT Brown adipose tissue

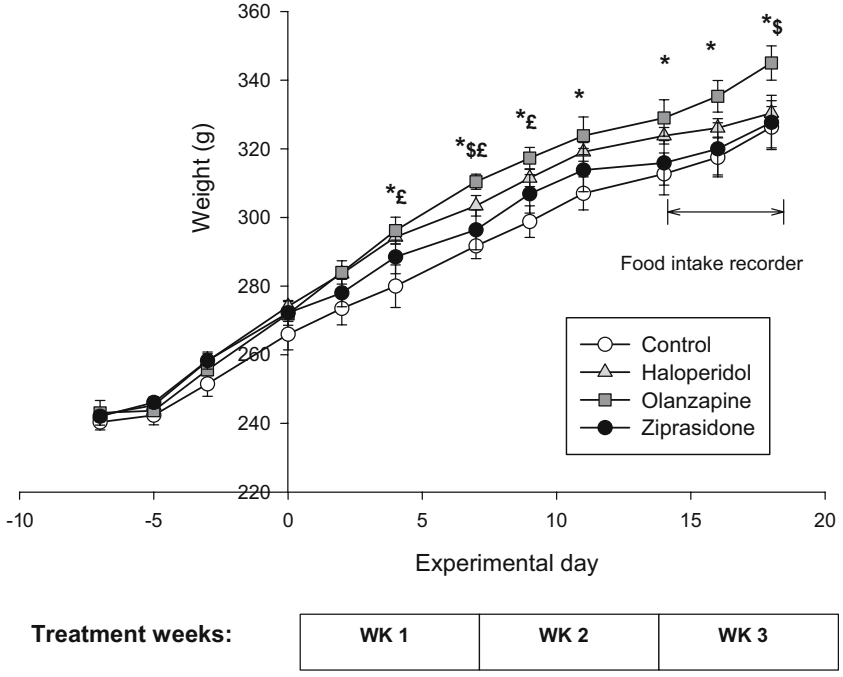

Fig. 2 Body weight of antipsychotic-treated rats during 3 weeks. Values are means±SEM, n=6 per group. Experimental day-0 indicates start of treatment. Significant differences at $p<0.05$ are indicated: *Asterisk* olanzapine vs control, *pound symbol* haloperidol vs control, and *dollar symbol* olanzapine vs ziprasidone

Experiment 2: effects of olanzapine, haloperidol, and ziprasidone on food intake

From the second week of treatment until the end of the experiment the weight of olanzapine-treated rats was significantly higher than that of the control group (Fig. 2). At the end of the experiment, the weight of the olanzapine group was also significantly higher than that of the ziprasidone group. The weight of the haloperidol group was not different from that of the control group at the end of the experiment, but the weight of the haloperidol group was significantly higher than that of the control group during the second week of treatment. It is also worth noting that the weight of olanzapine-treated rats in this experiment (1 mg/kg) significantly increased compared to the controls at the same time (week 2) than in the previous experiment using 0.5 and 2 mg/kg of olanzapine. At the beginning of the third week, the texture of the food was changed (powder to liquid food) and the weight gain in the haloperidol, ziprasidone, and control groups clearly slowed, but the weight gain in the olanzapine group did not.

Over the 23-h periods, olanzapine-treated rats ingested more energy than haloperidol, ziprasidone, and control rats (Table 2). Analysis of food intake during the 23-h recording periods indicated an important group effect for the cumulative energy intake ($p<0.0001$) (Fig. 3). The olanzapine group was largely responsible for this effect, and was significantly different from the other groups for all cumulative energy intake measures. The olanzapine group was significantly different from the three other groups (which did not differ from one to the other).

Table 2 Energy intake by antipsychotic-treated rats during the third treatment week

		Controls	Haloperidol	Olanzapine	Ziprasidone
Energy intake (kJ)	Total on 22 h	347.45±10.98^{a}	323.86±13.67^{a}	381.81±11.20^{b}	330.97±12.02^{a}
	Dark period	308.87±10.18^{a}	298.33±12.04^{a}	369.64±12.31^{b}	304.54±10.26^{a}
	Light period	38.58±9.68^{a}	25.53±9.30^{ab}	12.17±6.03^{b}	26.43±12.61^{ab}

Values are the mean±SEM of 12 determinations (six rats per group, two 23-h recordings). Means in a row without a common letter differ significantly at $p<0.05$

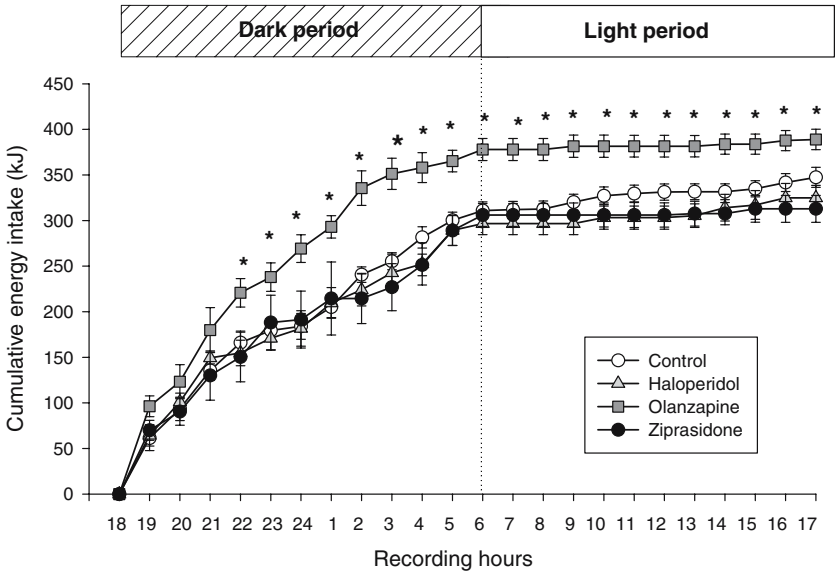

Fig. 3 Cumulative energy intake of antipsychotic-treated rats during the third treatment week. Food is given at 18:00 h and withdrawn at 17:00 h the next day. Dark period begins at 18:00 h and finishes at 06:00 h. Each *point* represents the mean±SEM of 12 determinations (two energy intake recordings × six rats per group). Significant difference at $p<0.05$ is indicated: *asterisk* olanzapine vs control

Discussion

The results of the present study show for the first time that an animal model of antipsychotic-induced weight gain can be created in the male rat under certain experimental conditions. These experimental conditions were that the antipsychotic treatment was mixed with the food and that the diet of the animals resembled that of humans. The present study also shows that olanzapine-induced weight gain is accompanied by an increase in food intake and subcutaneous fat deposition, and that the feeding pattern of olanzapine-treated rats is different from that of haloperidol- and ziprasidone-treated rats.

Mixing treatment with the food may not be the only usable experimental procedure and other ways of administration can be proposed. For instance slow delivery through micropumps could be useful, but dissolving antipsychotics in drinking water may be more problematic because many antipsychotics are not soluble in water. However, it is likely that maintenance of a durable or constant blood level of treatment throughout the experiment is essential. Constant drug delivery is not sufficient to obtain a model of antipsychotic-induced weight gain in the male rat; in a previous study we showed that mixing olanzapine with food increases body fat deposition in the male rat, but is not enough to produce significant increases in food intake and body weight over 6 weeks (Minet-Ringuet et al. 2006).

Two factors, olanzapine dose and diet, induced weight gain in male rats

There were many attempts to create an animal model of obesity induced by antipsychotics. Studies showed that female, but not male, rodents are sensitive to antipsychotics. A study by Ota et al. (2002) showed that subcutaneous injections of a very low dose of risperidone (0.005 mg/kg) increase body weight in male rats, while a higher dose (0.5 mg/kg) decreases weight. These results may be considered at variance with our results, which show that very low doses of olanzapine do not increase weight. Another study of the dose-dependent effects of risperidone in male rats (subcutaneous injections) found no effects (Baptista et al. 2002).

Several authors have raised the question of the relationship between antipsychotic treatments and macronutrient intake in rats. It was shown that rats given macronutrient selection choice during antipsychotic treatments do not change their feeding behavior: Treated rats eat the same proportions of proteins, lipids, and carbohydrates as controls (Baptista et al. 2004; Minet-Ringuet et al. 2005, 2006). It was also shown that chronic antipsychotic treatments in male rats given high-fat diets do not result in body weight alterations (Baptista et al. 1993). These diets are rich in carbohydrates and poor in proteins, while rats spontaneously ingest diets rich in proteins and poor in carbohy-

drates. These results are in accordance with previous works from our laboratory, which showed that the interaction between carbohydrates and lipids is essential to induce obesity in rats (Marsset-Baglieri et al. 2004). Following Marsset-Baglieri et al. (2004), our hypothesis is that lipid-rich diets determine an increase in food intake and weight only if they are associated to a substantial increase in carbohydrate intake. The association of high amounts of lipids and carbohydrates may increase insulin secretion and consequently increase the storage of lipids in adipocytes. Further work is necessary to determine whether feeding humans treated with antipsychotics with diets containing low contents of carbohydrates and high contents of proteins could slow weight gain. However, we found in a previous experiment that rats treated with antipsychotics mixed with their food and given usual rat diet (rats self-selected their diet) did not significantly increase their weight over a 6-week treatment period, but rats did accumulate body fat (so it is likely that a longer treatment would have lead to a significant gain of weight) (Minet-Ringuet et al. 2006). Therefore, insofar as animal experimental conditions can be extended to humans, it is unlikely that a simple change in diet in humans would prevent the long-term antipsychotic-induced fat accumulation and weight gain.

Feeding patterns

Olanzapine-treated rats differed from haloperidol- and ziprasidone-treated rats in their feeding behavior and weight gain. At the end of the study, olanzapine-, but not haloperidol- or ziprasidone-treated rats, had a significant increase in weight, which is in accordance with clinical studies (Allison et al. 1999; Ascher-Svanum et al. 2005). The weight of ziprasidone-treated rats was similar to the weight of the controls throughout the study. In a recent study, Fell et al. (2005) showed that a chronic ziprasidone treatment does not change body weight in female rats; therefore, our study and the Fell et al. (2005) study are in agreement, and both studies are in agreement with clinical observations. Haloperidol-treated animals had a significant increase in weight during the second week of treatment, and this weight gain disappeared when the experimental procedures were changed. Further work is necessary to determine whether haloperidol-treated animals would have remained overweight in the absence of environmental and feeding method changes, and why such changes modified their feeding behavior.

The present study also showed that the feeding behavior of rats treated by olanzapine was different from that of the other groups of treatment. Olanzapine-treated animals had increased energy intake during the 23 h of the experiment. This increase occurred exclusively during the dark period, while the food intake was almost nil during the light period. We made a detailed analysis of the feeding behavior of the rats during the dark period (data not shown) and found that during this period olanzapine-treated animals demonstrated behavior similar to that previously described by Lee and Clifton (2002) (single injection experiments): The animals displayed increased meal size, ingestion rate and meal duration, and decreased intermeal intervals. As far as we know, particularities of feeding behavior induced by antipsychotic treatments during the light and dark periods have never been reported before in rodents and humans.

In conclusion, this study shows that a male rat model of obesity induced by antipsychotics can be created under specific conditions of drug administration, diet, and dose. The balance between carbohydrate and lipids may be an important factor for inducing weight gain in the male rat. This model should facilitate further investigations into the mechanisms by which antipsychotics produce undesirable metabolic side effects. However, because of the small size of groups of animals tested in the present study, our results should be considered as preliminary.

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