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# Olanzapine affects locomotor activity and meal size in male rats

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ABSTRACT

Olanzapine is an antipsychotic drug that frequently induces weight gain accompanied by increased fat deposition as a side effect. To investigate how olanzapine affects different aspects of energy balance, we used male rats to determine effects on meal patterns, food preference, locomotor activity and body temperature. In two short-term experiments olanzapine was administered via osmotic minipumps. In the first experiment, we offered rats standard lab chow only. In the second experiment, we offered rats free choice between chow, sucrose and saturated fat. In a third experiment, olanzapine was chronically administered via the drinking water to determine effects on body composition. In each experiment olanzapine decreased locomotor activity and altered meal patterns. Olanzapine caused an increase in average meal size accompanied by reduced meal frequency, without clearly affecting food preference. In the chronic experiment body composition was altered, favoring adipose tissue over lean muscle mass, despite reductions in overall body weight gain. The increase in average meal size implies that the primary effect of olanzapine on feeding is an impairment of the normal satiation process. Furthermore, energy balance is clearly affected by a reduction in locomotor activity. Thus, the effects of olanzapine on adiposity do not depend solely on the presence of hyperphagia.



## 1. Introduction

Over recent years, olanzapine has become one of the most commonly prescribed atypical antipsychotic drugs due to its high therapeutic efficacy in the treatment of both schizophrenia and bipolar disorder (Leucht et al., 2009a;Leucht et al., 2009b; Scherk et al., 2007; Smith et al., 2007). However, similar to several other atypical antipsychotics, such as clozapine and quetiapine, significant weight gain is a common side effect (Parsons et al., 2009). This weight gain is associated with increased fat deposition, especially abdominal fat (Eder et al., 2001; Graham et al., 2005; Zhang et al., 2004), and often accompanied by deleterious effects on glucose and lipoprotein metabolism, leading to an increased cardiovascular risk (Hennekens, 2007; Ryan and Thakore, 2002) . Moreover, weight gain is an important cause of non-compliance, thereby increasing the risk of relapse and rehospitalization (Lieberman et al., 2005).

In order to investigate the mechanisms underlying olanzapine-induced weight gain, attempts have been made to model the metabolic side effects in rats. However, these have led to conflicting reports in both males and females. In most studies administering olanzapine once or twice daily to female rats, weight gain was readily observed, and in many cases accompanied by hyperphagia (Albaugh et al., 2006; Arjona et al., 2004; Cooper et al., 2005; Fell et al., 2004; Fell et al., 2005b; Goudie et al., 2002; Hillebrand et al., 2005; Kalinichev et al., 2005; Kalinichev et al., 2006; Pouzet et al., 2003; Stefanidis et al., 2009). However, sometimes these effects were only temporary and not all studies investigated whether weight gain was accompanied by an increase in adipose tissue. Conversely, most studies using similar dosing-schedules in male rats failed to induce any weight gain (Albaugh et al., 2006; Minet-Ringuet et al., 2005; Pouzet et al., 2003). Some studies did find a significant increase in adipose tissue in male rats treated with olanzapine, although this was not always accompanied by overall body weight gain or hyperphagia (Cooper et al., 2007; Minet-Ringuet et al., 2006b; Minet-Ringuet et al., 2006a; Victoriano et al., 2009).

Regarding the investigation of underlying mechanisms, most studies have focused on demonstrating increased energy intake, whereas changes in energy expenditure can equally play a role in generating positive energy balance. We, therefore, simultaneously investigated the effects of olanzapine on different aspects of energy balance, including food intake, meal patterns, food preference, locomotor activity and body temperature. Because feeding behavior and body weight regulation in female rats is subject to larger variability due to their estrous cycle (Blaustein and Wade, 1976; ter Haar, 1972), we preferred to use male rats.

One of the challenges of administering olanzapine to rodents is the large inter-species difference in drug-metabolism. The half-life of olanzapine in male rats is only 2½ h (Aravagiri et al., 1999), where it is

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approximately 30 h in humans (Callaghan et al., 1999; Kassahun et al., 1997). Due to the different pharmacokinetics, single or twice daily injections of olanzapine in rats, therefore, lead to fluctuations in plasma levels that are not comparable to the human situation. Interestingly, the only studies that reported increased adiposity levels in male rats were those that administered olanzapine by twice daily injections or mixed with the food (Cooper et al., 2007; Minet-Ringuet et al., 2006b; Minet-Ringuet et al., 2006a). This led us to hypothesize that circumventing the problem of rapid drug-metabolism would provide a better model for olanzapine-induced weight gain. The first aim of our study, therefore, was to examine the effects of continuous infusion of olanzapine by osmotic minipump on different aspects of energy balance in male rats in two short-term experiments. In the first experiment, rats had access only to standard lab chow. Because it has been suggested that antipsychotic treatment may increase the desire for sugary or fatty foods (Bromel et al., 1998; Kluge et al., 2007), we examined whether olanzapine has additional effects on food preference in the second experiment, by offering rats a cafeteria style diet with free choice between standard lab chow, saturated fat and a sucrose solution.

The second aim of our study was to develop a chronic model to investigate effects on body weight and composition. However, osmotic minipumps are not suitable for long-term administration of olanzapine, as this drug is not stable in solution at body temperature and degradation gradually takes place within the minipump reservoir (van der Zwaal et al., 2008). Therefore, in the third experiment, olanzapine was administered chronically via the drinking water. Effects on the same aspects of energy balance were determined as in the experiments where olanzapine was continuously infused via minipumps, making it possible to determine whether energy balance was affected in the same way, which would support the validity of this chronic model.

## 2. Methods

### 2.1. Animals

Male Wistar rats, weighing 275–300 g, were purchased from Charles River Laboratories (Crl-Wu, Germany). They were individually housed in a temperature and humidity controlled room (21 ± 2 °C) under a 12 h/12 h light/dark cycle (lights on at 0700 h). All experimental procedures were approved by the Committee for Animal Experimentation of Utrecht University.

### 2.2. Procedures

A week after arrival, all rats received a transmitter (TA10TA-F40, Data Science International, St. Paul, Minnesota, USA) in the abdominal cavity, to continuously monitor body core temperature and locomotor activity. Surgery was performed under fentanyl/fluanisone (Hypnorm®, Janssen Pharmaceutica, Beerse, Belgium, 0.1 ml/100 g i.m.) and midazolam (Dormicum®, Roche, Woerden, The Netherlands, 0.05 ml/100 g i.p.) anesthesia. Carprofen (Rimadyl®, Pfizer Animal Health, Capelle a/d Ijssel, the Netherlands, 0.01 ml/100 g s.c.) was administered as pain medication pre-operatively and once daily post-operatively for 2 days. Animals were allowed to recover for 2 weeks before baseline recording started.

Osmotic minipumps were implanted under brief isoflurane anesthesia (experiments 1 and 2). After filling of the minipumps with drug- or control-solution, and priming in saline at 37 ºC overnight, these were inserted through a small incision on the back of the rat, closing the incision with surgical staples.

On the final day of each experiment, animals were decapitated and wet weights of mesenteric, perirenal, epididymal and subcutaneous (inguinal) white adipose tissue were determined. The gastrocnemius–plantaris muscle complex was also dissected and weighed, as a measure of lean muscle mass.

### 2.3. Experimental designs

#### 2.3.1. Experiment 1: Short-term minipump administration with standard diet

Throughout this experiment, rats had free access to standard lab chow (CRM(E), Special Diet Services, Witham, Essex, United Kingdom) and tap water only. After 1 week of baseline recording, olanzapine (1 ($n=5$), 2.75 ($n=5$) or 7.5 mg/kg/day ($n=6$)) or a saline ($n=6$) was administered for 9 days via osmotic minipump (Alzet®, model 2ML4, Durect Corp., Cupertino, California, USA). This dose-range was chosen to obtain D2 receptor occupancy levels comparable to humans (Kapur et al., 2003).

#### 2.3.2. Experiment 2: Short-term minipump administration with choice diet

In this experiment, animals were offered a choice diet with continuous access to standard lab chow, tap water and two palatable food sources: a 30% sucrose solution (w/v), provided in a separate drinking bottle, and saturated fat (Ossewit/Blanc de Boeuf, Vandemoortele, Roosendaal, the Netherlands), provided in a separate food hopper. Sucrose and fat were made available from 1 week before implantation of the minipumps. Because rats need a few days to adjust to the choice diet, average intake of each food source during the last 5 days before surgery was used as baseline measurement. Osmotic minipumps (Alzet®, model 2ML2, Durect Corp., Cupertino, California, USA) delivered olanzapine (1, 2.75 or 7.5 mg/kg/day) or a control solution for 9 days ($n=6$ per group). Care was taken to match rats over treatment groups for both food preference and total caloric intake.

#### 2.3.3. Experiment 3A: Chronic administration via drinking water with standard diet

To circumvent the problem of degradation of olanzapine in minipumps (van der Zwaal et al., 2008), the drug was administered via the drinking water in this long-term experiment. As rats will drink water throughout the day, addition of olanzapine to the drinking water results in drug exposure that is more comparable to the human situation than after daily injections, albeit not as constant as with continuous infusion (Perez-Costas et al., 2008). Furthermore, because olanzapine in solution is more stable at room temperature than 37 °C (unpublished data) and water bottles were refreshed at least once a week, degradation of olanzapine was unlikely to interfere with drug delivery in this paradigm.

Rats had access to standard lab chow and drinking water only. After a week of baseline recording, olanzapine was administered for 30 days via the drinking water of 1 group of rats ($n=8$). The control group received regular tap water ($n=7$). Based on the results of experiment 1, we aimed to administer olanzapine via the drinking water at a dose of 7.5 mg/kg/day, adjusting the concentration of the drug-solution based on individual water intake. However, the addition of olanzapine to the drinking water dose-dependently reduced total water intake. We therefore limited the dose of administered olanzapine to ~6.5 mg/kg/day, which resulted in an acceptable reduction in water intake of approximately 30%. As we did not see any reduction in water intake in the experiments in which olanzapine was administered via osmotic minipumps, this effect was most likely secondary to the bitter flavor of olanzapine. To determine whether any other effects in this experiment were secondary to reduced water intake or flavor of the drinking water, we performed a control experiment using quinine, which has previously been used to examine flavor effects on feeding behavior (Ishii et al., 2003; Thornton-Jones et al., 2007).

#### 2.3.3. Experiment 3B: Control experiment administering quinine via drinking water

This experiment was identical to experiment 3A, with the exception that, instead of olanzapine, quinine was added to the drinking water of half of the rats ($n=5$). In the first week, the concentration of quinine was titrated to a concentration of 0.3 mM, which resulted in reductions

of water intake comparable to experiment 3A. Due to the light-sensitivity of quinine, water bottles were wrapped in aluminum foil.

### 2.4. Drugs

Olanzapine (Chempacific Corp., Baltimore, USA) was dissolved in a minimum quantity of 1 M hydrochloric acid and then diluted to the required concentration with purified water (experiments 1 and 2). If necessary, 1 M sodium hydroxide was used to adjust the pH of this solution to ~5.5 For experiment 3A, a stock solution of 3 mg/ml was made at the start of the experiment, using the same method, but adding tap water instead of purified water. This solution was aliquoted, stored at −20 ºC and used during the experiment to prepare fresh solutions by diluting with tap water as needed (1–2 times per week). In experiment 3B, a fresh solution of quinine hemisulphate (Sigma-Aldrich, Steinheim, Germany) in tap water was made at least once a week.

### 2.5. Data analysis

The intra-abdominal transmitters sent digitized data of body core temperature (°C) and locomotor activity (arbitrary units) to a receiver plate present below the home cage via radio frequency signals. These data were automatically recorded every 10 min using DSI software (Data Science International, St. Paul, Minnesota, USA). Measurements were taken from each rat for at least 2 consecutive days in each experimental week. Due to technical difficulties in experiment 3A, telemetry data of 1 control rat had to be excluded from analysis in all 4 weeks, and for a different control rat in the last week.

Body weight, food and water intake were measured daily. Meal patterns were determined from 2 consecutive days in each experimental week, using data collected by Scales (Department Biomedical Engineering, UMC Utrecht, the Netherlands). This program records the weight of food hoppers in the home cage automatically every 12 s, as well as the amount of licks from water or sucrose bottles. A meal was defined as an episode of food intake with a minimal consumption of 1 kcal (0.3 g chow/0.05 g lard/0.83 ml sucrose solution or a combination) and a minimal intermeal interval of 5 min. Ingestion rate was calculated as kcal/min. Due to technical difficulties in experiment 2, meal patterns of three rats had to be excluded from analysis.

Because of the variability in feeding behavior, locomotor activity and body temperature, it was difficult to match individual rats over the different treatment groups for all measured parameters. For this reason, changes in average food and water intake, locomotor activity and meal patterns are all expressed as percentage of baseline. Effects on body temperature are expressed in degrees centigrade change from baseline. To allow comparison with other studies, baseline values of each experiment are also provided. Adipose tissue and gastrocnemius–plantaris muscle weights are expressed as percentage of body weight. Abdominal fat was calculated as the sum of epididymal, perirenal and mesenteric fat pad weights.

Statistical significance between treatment groups in experiments 1 and 2 was calculated by a one-way analysis of variance (ANOVA), followed by Dunnett's *t* test, if appropriate. For experiment 3 repeated measures analysis was performed, using treatment as between-subjects factor. Where appropriate, independent samples *t*-tests or repeated measures for each group were performed. If the condition of sphericity was not met, Greenhouse–Geisser correction was used. Analysis was performed using SPSS 15.0 for Windows software.

## Results

### 3.1. Experiment 1: Short-term minipump administration with standard diet

Average food intake during 9 days of minipump administration was higher in olanzapine-treated rats than in controls (Fig. 1). This effect was dose-dependent and significant in the highest dose group (ANOVA: $F(3,18)=3.30$, $P=0.044$, Dunnett's: $P=0.019$; baseline 72.9 kcal ± 1.60). Analysis of meal patterns (Fig. 2) revealed a dose-dependent increase in average meal size (ANOVA: $F(3,18)=4.33$, $P=0.018$, Dunnett's: $P=0.009$; baseline 5.0 kcal ± 0.15) and a decrease in average meal frequency (ANOVA: $F(3,18)=3.29$, $P=0.045$, Dunnett's: $P=0.017$; baseline 14.2 ± 0.40), which were both significant in the highest dose group. In each dose group, this was accompanied by reduced ingestion rates, although this effect was not significant. Water intake was unaffected.

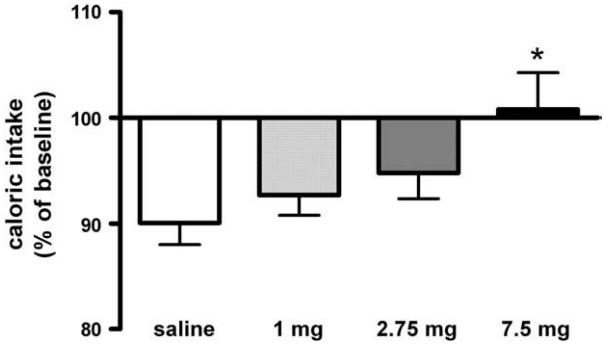


**Fig. 1.** Changes in average caloric intake during 9 days of olanzapine treatment in experiment 1. Data is expressed as percentage of baseline (Mean ± SEM). *$P<0.05$ vs control.

Olanzapine treatment dose-dependently decreased locomotor activity (Fig. 3). This effect was significant in all dose groups (ANOVA: $F(3,18)=13.47$, $P<0.001$, Dunnett's: $P<0.01$; baseline 2.6 ± 0.23) and most prominent during the dark phase (ANOVA: $F(3,18)=15.277$, $P<0.001$, Dunnett's: $P<0.01$) but similarly present in the light phase (ANOVA: $F(3,18)=10.825$, $P<0.001$, Dunnett's: $P<0.05$). Average body core temperature was not significantly affected. Short-term administration of olanzapine in this paradigm did not significantly affect body weight gain or measures of adiposity, although there was a trend

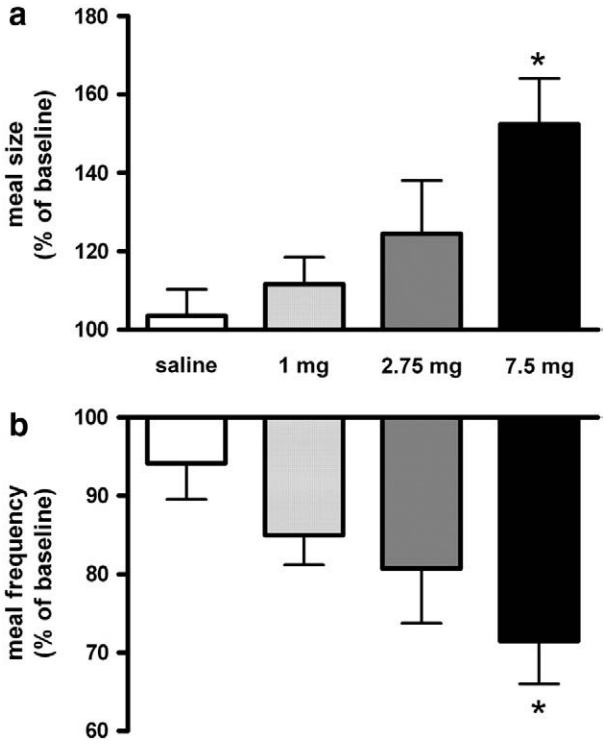


**Fig. 2.** Changes in meal patterns during 9 days of olanzapine treatment in experiment 1. a. Average meal size. b. Average meal frequency. Data is expressed as percentage of baseline (Mean ± SEM). *$P<0.05$ vs control.

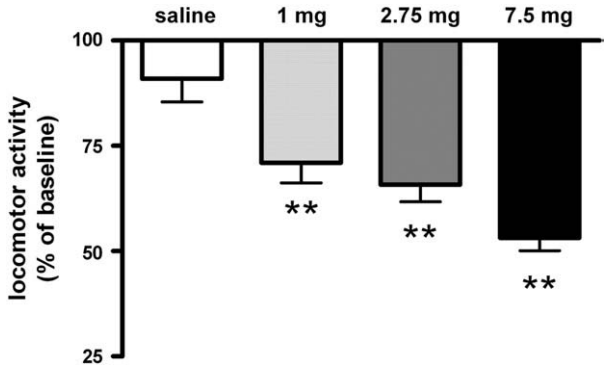


**Fig. 3.** Changes in average locomotor activity during 9 days of olanzapine treatment in experiment 1. Data is expressed as percentage of baseline (Mean ± SEM). $^{**}P<0.01$ vs control.


**Fig. 4.** Changes in average caloric intake during 30 days of olanzapine treatment in experiment 3A. Data is expressed as percentage of baseline (Mean ± SEM).

towards a reduction in gastrocnemius–plantaris muscle weight in all olanzapine-treated groups (data not shown).

### 3.2. Experiment 2: Short-term minipump administration with choice diet

In the second paradigm, where animals had access to fat and sucrose in addition to their standard lab chow and water, olanzapine did not significantly affect total caloric intake, food preference or water intake (Table 1). However, similar to experiment 1, analysis of meal patterns revealed an increase in average meal size in the two highest dose groups (121.2% ± 8.7 and 109.3% ± 5.7 for 2.75 and 7.5 mg/kg) compared to the saline group (89.9% ± 6.2). This effect was significant in the middle dose group, (ANOVA: $F(3,17)=5.46$, $P=0.008$, Dunnett's: $P=0.02$; baseline 4.5 kcal ± 0.18) and was accompanied by a decrease in average meal frequency (77.0% ± 3.3 and 82.0% ± 3.5 for 2.75 and 7.5 mg/kg groups vs 95.4% ± 7.6 for the saline group) which was also significant in the middle dose group (ANOVA: $F(3,17)=3.43$, $P=0.041$, Dunnett's: $P=0.045$; baseline 19.8 ± 0.44). Ingestion rate was not significantly affected. Locomotor activity was significantly decreased in each dose group to levels comparable to experiment 1 (ANOVA: $F(3,20)=29.50$, $P<0.001$, Dunnett's: $P<0.05$; baseline 1.8 ± 0.10) (data not shown). Body core temperature in the dark phase was significantly reduced in the two highest dose groups (−0.14° ± 0.03 and −0.11° ± 0.02 for 2.75 mg/kg and 7.5 mg/kg) compared to controls (0.00° ± 0.02) (ANOVA: $F(3,20)=6.92$, $P=0.002$, Dunnett's: $P<0.01$; baseline 37.9° ± 0.02), whereas body core temperature in the light phase was slightly increased in the highest dose group (+0.08° ± 0.02) compared to controls (0.00° ± 0.02) (ANOVA: $F(3,20)=3.21$, $P=0.045$, Dunnett's: $P=0.026$; baseline 37.1° ± 0.02 ). Although body weight gain was unaffected, there was a dose-dependent increase in all fat pad weights, accompanied by a dose-dependent decrease in gastrocnemius–plantaris muscle weight; however these effects did not reach significance (data not shown).

### 3.3. Experiment 3A: Chronic administration via drinking water with standard diet

Throughout this experiment olanzapine-treated rats had significantly lower relative water intake compared to controls (64.9% ± 2.8 vs 99.3% ± 3.0; treatment: $F(1,13)=71.29$, $P<0.001$; baseline 22.7 ± 0.89 ml). Although food intake seemed to increase compared to baseline (70.5 kcal ± 1.33) in the first week, it seemed to gradually decline in the last two weeks (Fig. 4). Repeated measures analysis did not reveal a main effect of treatment, but there was a time × treatment interaction ($F(3,39)=3.98$, $P=0.014$), which was due to a significant effect of time in olanzapine-treated rats ($F(1.53,21)=13.32$, $P=0.002$), indicating that food intake significantly changed over time in olanzapine-treated rats. However, *t*-tests between groups failed to reach significance. Analysis of meal patterns (Fig. 5) revealed a significant increase in average meal size (treatment: $F(1,13)=47.28$, $P<0.001$; baseline 5.5 kcal ± 0.07) that was accompanied by a decrease in average meal frequency in olanzapine-treated rats (treatment: $F(1,13)=50.31$, $P<0.001$; baseline 13.1 ± 0.26). Additionally, ingestion rate was lower than in controls (87.7% ± 5.5 vs 103.3% ± 3.9; treatment: $F(1,13)=6.23$, $P=0.027$; baseline 0.73 kcal/min ± 0.02). None of the effects on meal patterns showed any time × treatment interaction, indicating that these effects did not change significantly over the course of the experiment. A reduction in

**Table 1**
Average caloric intake of olanzapine-treated rats offered a choice diet in experiment 2.

| | Controls | 1 mg/kg | 2.75 mg/kg | 7.5 mg/kg |
|---|---|---|---|---|
| Chow | 42.4 ± 1.5 | 40.0 ± 3.2 | 43.1 ± 3.9 | 45.9 ± 2.3 |
| Fat | 20.9 ± 1.3 | 22.5 ± 3.8 | 27.4 ± 2.8 | 19.3 ± 3.9 |
| Sucrose | 15.0 ± 3.1 | 17.0 ± 5.3 | 16.1 ± 5.7 | 15.0 ± 2.3 |
| Total | 78.4 ± 3.7 | 79.5 ± 3.6 | 86.6 ± 3.5 | 80.1 ± 3.1 |

Data is expressed as kilocalories (Mean ± SEM) consumed during 9 days of olanzapine treatment.

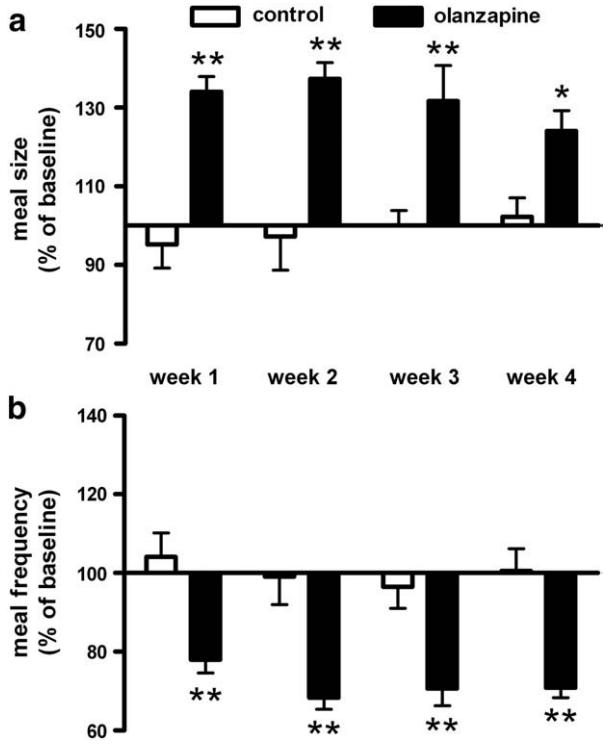


**Fig. 5.** Changes in meal patterns during 30 days of olanzapine treatment in experiment 3A. a. Average meal size. b. Average meal frequency. Data is expressed as percentage of baseline (Mean ± SEM). $^{*}P<0.05$, $^{**}P<0.01$ vs control.


**Fig. 6.** Changes in average locomotor activity during 30 days of olanzapine treatment in experiment 3A. Data is expressed as percentage of baseline (Mean ± SEM). $^{**}P<0.01$ vs control.

locomotor activity (Fig. 6) was observed at all time points (treatment: $F(1,12)=10.09$, $P=0.008$; baseline 1.6 ± 0.09) without any time × treatment interaction. Conversely, body core temperature in the dark phase gradually decreased over the course of the experiment in olanzapine-treated rats, with a significant effect of treatment ($F(1,12)=8.8$, $P=0.012$; baseline 37.7° ± 0.05) and time x treatment interaction ($F(3,36)=6.47$, $P=0.001$). The difference from controls reached significance in week 3 (−0.28° ± 0.04 vs −0.07° ± 0.04, $P=0.004$) and week 4 (−0.36° ± 0.05 vs −0.09° ± 0.05 for treatment vs controls, $P=0.004$). In the light phase, no significant effects of treatment were present although a non-significant decrease in body core temperature was observed in olanzapine-treated rats in week 4 (−0.15° ± 0.05 vs −0.05° ± 0.02 in controls, $P=0.08$; baseline 37.05° ± 0.05). At the end of this experiment, olanzapine-treated rats showed reduced body weight gain compared to control rats (4.0% ± 1.3 vs 14.7% ± 0.93, $P<0.001$). However, analysis of body composition (Table 2) revealed a numerical increase in all fat pad weights, which was significant for perirenal fat ($P<0.01$) with a trend towards increased abdominal fat pad weight ($P=0.096$). Conversely, weight of the gastrocnemius–plantaris muscle complex was significantly decreased ($P=0.025$).

### 3.4. Experiment 3B: Control experiment administering quinine via drinking water

To determine whether reduced water intake was responsible for any of the effects observed in experiment 3A, quinine was administered to the drinking water in this experiment to mimic the bitter flavor of olanzapine. This resulted in reduced water intake (67% ± 4.1) that was comparable to that of the olanzapine-treated rats (treatment: $F(1,8)=49.16$, $P<0.001$; baseline 26.3 ml ± 1.27). Remarkably, the reduction in water intake in this experiment was accompanied by a slight hypophagia compared to controls (95.0% ± 2.2 vs 106.1% ± 5.3; treatment: $F(1,8)=18.13$, $P<0.01$; baseline 68.1 kcal ± 1.50). This hypophagia was significant in each experimental week ($P<0.02$) and due to minor, non-significant reductions in both meal size and meal frequency (data not shown). Locomotor activity was unaffected, but there was a trend towards reduced body weight gain in quinine-treated rats versus controls (10.8% ± 1.1 vs 15.5% ± 1.8; $P=0.055$). Body composition revealed non-significantly reduced fat pad weights and increased muscle mass in quinine-treated rats. In summary, reduced water intake in this experiment only affected total food intake and body weight gain.

**Table 2**
Body composition of rats treated with olanzapine for 30 days in experiment 3A.

| | Controls | Olanzapine |
|---|---|---|
| Gastrocnemius–plantaris muscle | 0.61 ± 0.008[a] | 0.58 ± 0.002[b]* |
| White adipose tissue (WAT) | | |
| Mesenteric | 0.71 ± 0.06 | 0.84 ± 0.05 |
| Epididymal | 0.64 ± 0.06 | 0.67 ± 0.05 |
| Perirenal | 0.58 ± 0.05 | 0.79 ± 0.05** |
| Subcutaneous | 0.72 ± 0.05 | 0.83 ± 0.04 |
| Abdominal | 1.93 ± 0.16 | 2.30 ± 0.13^ |
| Total | 2.66 ± 0.20 | 3.21 ± 0.16 |

All values are expressed as percentage of body weight (Mean ± SEM ). Abdominal refers to the sum of mesenteric, epidydimal and perirenal WAT. Total refers to the sum of abdominal and subcutaneous WAT. $^{*}P<0.05$, $^{**}P<0.01$, ^$P=0.096$.
[a] $n=5$.
[b] $n=4$.

## 4. Discussion

To our knowledge, this is the first study to simultaneously investigate the effects of olanzapine on multiple aspects of energy balance in male rats in their homecage environment. These effects were determined with either continuous infusion or multiple dosing of the drug via the drinking water, to mimic drug exposure in humans (Perez-Costas et al., 2008). The results show that olanzapine has a prominent effect on locomotor activity, an effect that has received little attention in previous models of olanzapine-induced weight gain, but was present in each of our experiments. Additionally, analysis of meal patterns indicates that the increase in average meal size caused by olanzapine is an effect that is independent of total food intake. Finally, our study confirms that olanzapine alters body composition by increasing adipose tissue while reducing lean muscle mass. Therefore, under appropriate dosing conditions, male rats are a useful model to study the disruptions in energy balance that lead to increased fat deposition by olanzapine.

### 4.1. Energy balance

In all three experiments olanzapine caused a reduction in voluntary locomotor activity, that was dose-dependent with a maximum reduction of approximately 40%. This effect has been previously observed in rat models after once or twice daily administration of olanzapine, however the effect appeared limited to the dark phase (Arjona et al., 2004; Fell et al., 2007; Stefanidis et al., 2009). This is in contrast with our finding that the effect of olanzapine on locomotor activity is sustained throughout the day with continued delivery of the drug. Most likely this is due to the fact that, in these earlier studies, olanzapine was administered just before or in the dark phase and plasma levels had declined significantly at the beginning of the light phase.

Spontaneous physical activity has been shown to account for up to 50% of total energy expenditure and to be an important predictor of weight gain (Levine et al., 1999; Rising et al., 1994). Therefore, even though we did not use metabolic cages, it seems fair to assume that energy expenditure in olanzapine-treated rats was significantly reduced. Because one would expect rats to compensate for a reduction in energy expenditure by reducing their energy intake, we speculate that, even in the absence of absolute hyperphagia, olanzapine does exert orexigenic effects that prevent compensatory reductions in food intake. The prominent effect on activity levels may, therefore, explain why hyperphagia is not always observed in rat models of olanzapine-induced weight gain. A recent pair-feeding study suggested that hyperphagia is a necessary requirement for olanzapine-induced weight gain (Davoodi et al., 2009). However, this study did not determine effects on body composition, which might have revealed increased adiposity levels in the paired group that were independent of total body weight gain. Furthermore, this experiment was performed using female rats that exhibited hyperphagia and weight gain in the unpaired group. As mentioned previously, male rats frequently fail to exhibit hyperphagia and weight gain, although they do increase adiposity levels. The models may therefore not be comparable.

The reduction in body core temperature, observed in experiments 2 and 3A, seems to be an independent effect of olanzapine, as in experiment 3A effects on body temperature increased over time, whereas effects on

locomotor activity were similar throughout the experiment. Furthermore, previous studies in rats have reported acute hypothermia (Goudie et al., 2007; Ninan and Kulkarni, 1999), and a decrease in brown-adipose tissue temperature after olanzapine treatment (Stefanidis et al., 2009). Together, this indicates that olanzapine can further decrease energy expenditure through independent effects on thermoregulation.

Regarding the effects on feeding behavior of olanzapine-treated rats, an increase in average meal size was present in all three experiments, that was accompanied by a compensatory decrease in meal frequency, which limited effects on total caloric intake. Interestingly, average meal size remained increased over the course of our chronic experiment, despite the slight decrease in total food intake, indicating that the primary effect of olanzapine on feeding behavior is a disruption of the normal satiation process which is independent of total food intake. A number of previous studies using both male and female rats have also suggested that olanzapine impairs satiation (Cooper et al., 2009; Davoodi et al., 2009; Hartfield et al., 2003; Thornton-Jones et al., 2002), although one study using males failed to see any effect on meal size (Lee and Clifton, 2002). This discrepancy could be due to methodological differences (single injection of doses varying from 0.3 to 3 mg/kg, use of 45 mg pellets and an intermeal interval of 2 min), however, a more recent study using the same method in female rats receiving olanzapine 1 mg/kg twice daily for 7 days by oral gavage, did report an increased meal size and decreased meal frequency, similar to our findings (Davoodi et al., 2009). In marked contrast, a recent study using male rats reported a decrease in meal size and an increase in meal frequency (Victoriano et al., 2009). Several methodological differences could account for this discrepancy. Meal patterning was performed using a mash consisting of a powdered medium-fat diet and water with an intermeal interval of 10 min. Furthermore, meal patterns were determined on 2 consecutive days in test chambers, after olanzapine (2 mg/kg/day) had been administered mixed with a powdered diet in the homecage for 21 days. Although we administered 6.5 mg/kg/day in our chronic experiment, minipump administration of 2.75 mg/kg/day in the present study also increased meal size, making it unlikely that difference in dose explains this discrepancy. Interestingly, Victoriano et al (2009) did report a decrease in ingestion rate, similar to what was observed in the present study, as well as in other studies that suggest olanzapine-induced impairment of satiation (Davoodi et al., 2009; Hartfield et al., 2003), implying independent effects on meal size and ingestion rate.

Our finding that olanzapine does not affect food preference is in line with several other studies that failed to observe any effects of olanzapine on macronutrient diet choice in both male and female rats (Arjona et al., 2004; Minet-Ringuet et al., 2005; Minet-Ringuet et al., 2006a), although one study reported increased preference for protein over fat in female rats (Fell et al., 2007). Taken together, our findings seem in line with most, but not all, previous studies examining effects of olanzapine on meal patterns and food intake in rats.

Unfortunately, only a limited amount of clinical studies have thoroughly investigated effects of olanzapine on ingestive behavior in humans. To our knowledge, there is only one study that actually confirmed an increased caloric intake in olanzapine- versus haldol-treated patients (Gothelf et al., 2002). A different study, using healthy subjects, reported an increase in caloric intake at a buffet-style dinner (Roerig et al., 2005) and a study with patients taking second-generation antipsychotics reported a decrease in the satiating effect of a standardized breakfast (Blouin et al., 2008). Interestingly, olanzapine and clozapine have been associated with binge eating episodes, defined as eating a larger amount of food than normal during a short period of time, accompanied by the feeling one cannot stop eating (Gebhardt et al., 2007; Kluge et al., 2007; Theisen et al., 2003). Finally, several clinical studies failed to observe any effects of treatment with atypical antipsychotics on food choice (Gothelf et al., 2002; Henderson et al., 2006; Strassnig et al., 2003), which is in line with our finding that olanzapine did not clearly affect food preference. Taken together, the increase in average meal size observed in olanzapine-treated rats seems to reflect the impairment of satiation observed in patients, although further clinical research is required to validate this.

The reduction in voluntary locomotor activity in olanzapine-treated rats seems to reflect the sedative side effects of olanzapine observed in humans (Costa e Silva et al., 2001; Gao et al., 2008; Lehman et al., 2004). Regarding the reduction in body temperature, several case-reports described patients with hypothermia induced by olanzapine treatment (Blass and Chuen, 2004; Fukunishi et al., 2003; Hung et al., 2009). Suitable clinical studies are lacking, however, and therefore it remains unclear to what extent antipsychotic medication affects physical activity levels and body temperature in patients.

### 4.2. Body composition

In experiment 3A, chronic olanzapine treatment resulted in an increase in adipose tissue mass, accompanied by a reduction in lean muscle mass and total body weight gain. A similar effect on body weight was observed when water intake was reduced with quinine treatment, although less pronounced, indicating that reduced water intake was partly responsible for the reduction in body weight gain in olanzapine-treated rats. Conversely, effects on body composition were clearly specific for olanzapine and independent of water intake, as we observed no significant effects on body composition in quinine-treated rats. The reduced muscle mass observed is most likely secondary to the marked reduction in voluntary locomotor activity caused by olanzapine treatment, as it is well-known that immobility results in a reduction of muscle mass (Bloomfield, 1997; Musacchia et al., 1988). The reduction in total body weight gain might seem remarkable at first, especially since adiposity levels were increased in olanzapine-treated rats. However, fat tissue weighs less, but is more energy dense than lean muscle mass. Therefore the exchange of lean muscle mass for adipose tissue can lead to a decrease in body weight, despite increases in energy content.

The effects of olanzapine on body composition that we observed are in line with previous findings in both male and female rats (Cooper et al., 2007; Kalinichev et al., 2005). However, as mentioned previously, an increase in total body weight was generally not reported in male rats, whereas weight gain has been frequently observed in females. The reasons for this discrepancy are not clearly understood, yet it has been suggested to make female rats most suitable to study olanzapine-induced weight gain. It is noteworthy, in this respect, that weight gain has also been reported in female rats treated with antipsychotics that do not induce weight gain in humans, such as aripiprazole and ziprasidone (Fell et al., 2005a; Kalinichev et al., 2005; Kalinichev et al., 2006). Conversely, weight loss has been reported in female rats treated with clozapine (known to induce weight gain in patients), although this was accompanied by enhanced adiposity, similar to our study (Cooper et al., 2008). This implies that total body weight gain in female rats lacks predictive validity for weight gain induced by antipsychotics in general. Similar to previous authors (Cooper et al., 2008; Kalinichev et al., 2005) we suggest that future studies consider adiposity as primary outcome measure instead of total body weight. Male rats may then prove to be a more accurate model of antipsychotic-induced weight gain than female rats.

Studies investigating the effects of olanzapine treatment on body composition in humans have not yet described the effect on lean muscle mass observed in rats (Eder et al., 2001; Graham et al., 2005). This discrepancy may be due to the fact that schizophrenic patients already exhibit highly sedentary lifestyles due to their illness (Gothelf et al., 2002; Jolley et al., 2006). Lean muscle mass may therefore already be reduced before initiation of antipsychotic medication in patients, contrary to the rats used in our experiments, that show normal baseline activity levels. Nevertheless, antipsychotic-induced weight gain in humans has been attributed mainly to an increase in body fat, especially abdominal fat deposition (Eder et al., 2001; Graham et al., 2005; Zhang

et al., 2004), and a similar pattern was observed in our experiment, indicating that the effects of olanzapine on fat deposition were effectively modeled in this paradigm.

### 4.3. Conclusions

In this study we were able to directly compare effects of olanzapine on energy balance between two different modes of administration, both aimed to achieve drug exposure comparable to humans: continuous infusion using osmotic minipumps for 9 days versus administration via the drinking water for 30 days. The short-term experiments indicate that reduced locomotor activity is an important effect of olanzapine on energy balance. In addition, the increase in average meal size indicates that olanzapine interferes with normal satiation. Moreover, administration of olanzapine via the drinking water elicited identical effects that persisted throughout the chronic experiment, and were accompanied by an increase in adiposity. This confirms that metabolic side effects of olanzapine can be accurately modeled in male rats, provided that appropriate dosing conditions are met.

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