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Olanzapine causes hypothermia, inactivity, a deranged feeding pattern and weight gain in female Wistar rats

S.S. Evers *, F. Calcagnoli, G. van Dijk, A.J.W. Scheurink

Department of Neuroendocrinology, University of Groningen, The Netherlands

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ABSTRACT

Olanzapine is an a-typical antipsychotic drug antagonizing predominantly 5-HT and dopamine, but also histamine, muscarin, and α-adrenergic receptors. In humans, Olanzapine induces weight gain and increases the risk of type 2 diabetes. The underlying mechanisms of Olanzapine-induced weight gain are unclear. To study this we administered Olanzapine (5 mg/kg) in female Wistar rats on a medium fat diet for 14 days via a permanent gastric catheter twice a day, just prior to the onset and at the middle of dark phase. Food and water intake, locomotor activity and body temperature were measured. Olanzapine acutely induced hypothermia, markedly decreased locomotor activity and increased body weight during 14 days of treatment. Olanzapine treatment did not result in an alteration of 24 h food intake, but diurnal patterns of feeding behavior and body temperature were dramatically changed. We conclude that in female Wistar rats Olanzapine has an acute hypothermic effect, that the effect of Olanzapine on feeding behavior is secondary to the effect on activity, and that Olanzapine-induced weight gain is primarily the result of reduction in locomotor activity.

1. Introduction

Over the recent years, considerable attention has been paid to the metabolic side effects of the a-typical antipsychotic drug (APD) Olanzapine. Olanzapine is primarily designed to be antagonistic on 5-$HT_{2A/C}$ and dopamine receptors (Bymaster et al., 1996a,b) for treatment of schizophrenia and bipolar disorder. However, besides its effect on psychotic illnesses, Olanzapine in humans causes body weight gain and increases the risk of developing type 2 diabetes (Baptista et al., 2002; Ananth et al., 2002; Caballero, 2003).

The underlying mechanisms are still unclear, as several contradictions with respect to Olanzapine's actions on metabolic pathways have been reported in humans or animals (Pouzet et al., 2003; Cohen and Perel, 2004; Aichhorn et al., 2006; Choi et al., 2007). Olanzapine does not only act on serotonin or dopamine receptors, but has antagonistic properties on histaminergic, muscarinic, and α-adrenergic receptors as well (Bymaster et al., 1996a,b, 1999). Receptors targeted by Olanzapine are located in CNS neuronal networks involved in energy homeostasis (Sawchenko et al., 1983; Zubieta and Frey, 1993; Richtand et al., 1995; Tavares et al., 1996; Yoshimatsu, 2008), but can also be found throughout the digestive tract (Bymaster et al., 2001), in skeletal muscle (Hajduch et al., 1999) and adipose tissue (Yang et al., 2009). The wide-spread distribution of putative action site for Olanzapine explains the multitude of mechanisms and various time–dose relationships that have been reported with Olanzapine treatment in humans.

Experimental studies in animals on the mechanisms underlying Olanzapine's metabolic effects also provide confusing data. Female rats appear to increase body weight more profoundly than male rats (Cooper et al., 2005, 2007) and this increase in body weight, predominantly adipose tissue, may be related to a decreased level of physical activity (the sedative effect of Olanzapine), or by an increase in food intake, although again contradictory results have been found (Lee and Clifton, 2002; Victoriano et al., 2009; Davoodi et al., 2009). Furthermore, Olanzapine has also been shown to induce hypothermia (Oerther and Ahlenius, 2000) and to block orexin-A induced hyperthermia (Monda et al., 2008), but these effects have not been investigated in the face of Olanzapine's effect on body weight gain.

One of the gaps between the pre-clinical rodent studies and human clinical studies is the huge discrepancy between dosing. The main cause is that Olanzapine's half life time in rats is about 2.5 h compared to 21–54 h in human (Kapur et al., 2003). Therapeutic doses in human are aimed to reach 65–80% D2-receptor occupancy (Farde et al., 1988; Kapur et al., 2003; Naiker et al., 2006), to reach such levels in male Sprague–Dawley rats (250–275 g) Kapur et al. show that Olanzapine needs to be administered continuously using an osmotic minipump at 7.5 mg/kg/day (Kapur et al., 2003). However, Van der Zwaal et al. showed that Olanzapine is vulnerable to degradation at body temperature therefore long term infusion of

* Corresponding author. Department of Neuroendocrinology, University of Groningen, Kerklaan 30, 9751 NN Haren, The Netherlands. Tel.: +31 50 363 2333.
E-mail address: s.s.evers@rug.nl (S.S. Evers).

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Olanzapine using minipumps is not recommended (van der Zwaal et al., 2008). Rat studies show the most pronounced effects on food intake and body weight gain when Olanzapine is administered at 1–2 mg/kg twice a day (Cooper et al., 2005; Davoodi et al., 2009). Whereas studies focusing on central receptor activity in specific brain areas (Robertson and Fibiger, 1996; Bymaster et al., 1996b; Li et al., 1998; Rollema et al., 2000; Lacroix et al., 2003; Angelucci et al., 2005) or Olanzapine's effect on thermogenesis (Oerther and Ahlenius, 2000; Monda et al., 2008; Stefanidis et al., 2009) use often a single administration up to 10 mg/kg.

In this study, we re-evaluated a number of potential mechanisms, i.e. food intake patterning, locomotor activity, body temperature, by which Olanzapine may induce weight gain in female rats subjected to a high-fat diet. To amplify Olanzapine's effect on locomotor activity and thermogenesis we decided to administer a dose of 5 mg/kg b.i.d. of Olanzapine. The main outcome of this study paradigm is that weight gain by Olanzapine treatment is predominantly caused by reduced locomotor activity combined with dramatic derangements of several circadian behavioral and physiological patterns.

2. Materials and methods

2.1. Animals

All procedures involving animal care and experimental procedures have been approved by the Animal Experimentation Committee of the University of Groningen. Female Wistar rats (232 ± 3.5 g; on arrival), obtained from Harlan (Horst, NL) were individually housed in clear Plexiglass cages (25*25*30 cm) on a plastic floor with wood chip bedding. Female rats were chosen based on the results of Cooper et al. (2005, 2007). Room temperature was controlled at 22 ± 2 °C, under a 12:12 h light–dark cycle (lights off at 11:00 AM). Animals had one week to adapt to the new environment before undergoing surgery, the baseline measurements started one week after surgery when all animals had surpassed their pre-surgical body weight. Prior to drug treatment, animals had ad libitum access to standard chow (3.8 kcal/g) and water. From day 0 (the start of drug treatment) a medium fat diet with lard (4.7 kcal/g; 45% fat, Arie Blok Diets, Woerden, NL) was given to all animals to stimulate weight gain.

2.2. Drugs

Olanzapine (as powder) was kindly provided by Solvay Pharmaceuticals (Fournier Laboratory, France). To obtain a daily administration of 10 mg/kg Olanzapine was diluted to 1.5 mg/ml in 0.9% NaCl saline. Olanzapine was first dissolved in saline using 1 M HCl and adjusted to pH 6.5 using 1 M NaOH. Animals were administered Olanzapine or saline twice a day, prior to the dark phase and 6 h after lights went off.

2.3. Surgical procedure

Animals were equipped with a permanent gastric catheter for stress-free intragastric drug administration and a telemetry transmitter (model TA10TA-F40, Data Sciences, St. Paul, MN) in the abdominal cavity for continuous temperature and activity registration (Meerlo et al., 1996). Surgical procedures were performed by using isoflurane-O_2/N_2O gas-anesthesia. A silicon catheter (1.40-mm OD, 0.80-mm ID) was inserted through the gastric wall at the level of the corpus, extending 0.5 cm into the gastric lumen. The catheter was drawn subcutaneous towards the head where it was fixed to the skull with dental cement (Wielinga et al., 2005). Animals were given 0.1 ml Finadine s.c. for analgesia and 0.25 ml penicillin s.c. to prevent infection.

2.4. Circadian registration

Core body temperature and activity were recorded throughout the duration of the experiment using radiotelemetry. Telemetry signals were received by separate responder plates (model RA1010, Data Sciences) underneath each cage. Data was collected every 5 min by a PC and analyzed by using specialized recording and analyses software (Dataquest IV, Data Sciences) (Meerlo et al., 1996).

2.5. Experimental set-up

Data was collected starting at 7 days before the start of drug administration (day 0). Olanzapine was administered intragastric twice a day at CT 11.5 (CT 12 = lights off at 11 AM) and at CT 18. From day 0 all animals were switched from the standard lab chow diet to the medium fat diet. Body weight, food intake and water intake was measured every day at CT 11.5 for 14 days. At day 17 the animals were individually housed in a specialized cage for continuous registration of food intake and locomotor activity for 3 days (TSE Systems GmbH, Bad Homburg, Germany) to monitor circadian feeding patterns, meal sizes and meal numbers. Circadian food intake patterns were calculated as an average of the last two consecutive days, the first day was used for adaptation. These plexiglass cages (40*23*15 cm) consist of a sensitive weight balanced food station (stainless steel food container for standard size food pellets); water bottles were weighed once a day prior to dark phase. Olanzapine administration was continued all the time twice a day at the above mentioned time points. At the end of the experiment rats had ad lib access to two bottles with either a 10% (g/vol) sucrose solution or a water bottle for 24 h in a two-bottle-preference test. The bottles were presented at CT 12 and intake was measured at time point 6 and 24 h after presentation.

2.6. Data analyses

Activity data was analyzed as a percentual change of activity relative to baseline per individual. Baseline was calculated as the average activity per day during one week prior to day 0 per individual, this average was set as 100%. All activity data were then expressed as percentage of this baseline value.

All data are expressed as averages ± SEM. Statistical analyses were performed using repeated measures (rm)ANOVA between-subjects for time dependent analyses. A multivariate (m)ANOVA between-subjects test was used to calculate significance at different time points during time related treatment. Activity and body temperature data were analyzed from baseline average to day 14 of treatment. Because average daily activity and body temperature data consist of a too large amount of data points, rmANOVA was performed for four consecutive 6 h time frames. All data expressed without a time dependent factor are analyzed using One-way ANOVA test. All statistical analyses were performed in SPSS16, outcomes were regarded significantly different when $P<0.05$.

3. Results

3.1. Chronic treatment

Fig. 1 presents 24 h food intake, activity, body temperature and the changes in body weight in the Olanzapine-treated animals and controls before and during treatment. Olanzapine treatment (5 mg/kg b.i.d.) stimulated body weight gain (Fig. 1a) which was significant after 6 days (mANOVA: $P<0.05$) and persisted during the rest of treatment (rmANOVA: $F_{14,112}=3.893$, $P<0.01$). The increase of body weight was not accompanied by changes in 24 h food intake (Fig. 1b) or average 24 h body temperature (Fig. 1d). Olanzapine decreased the activity of the animals during 14 days of treatment (Fig. 1c), this was

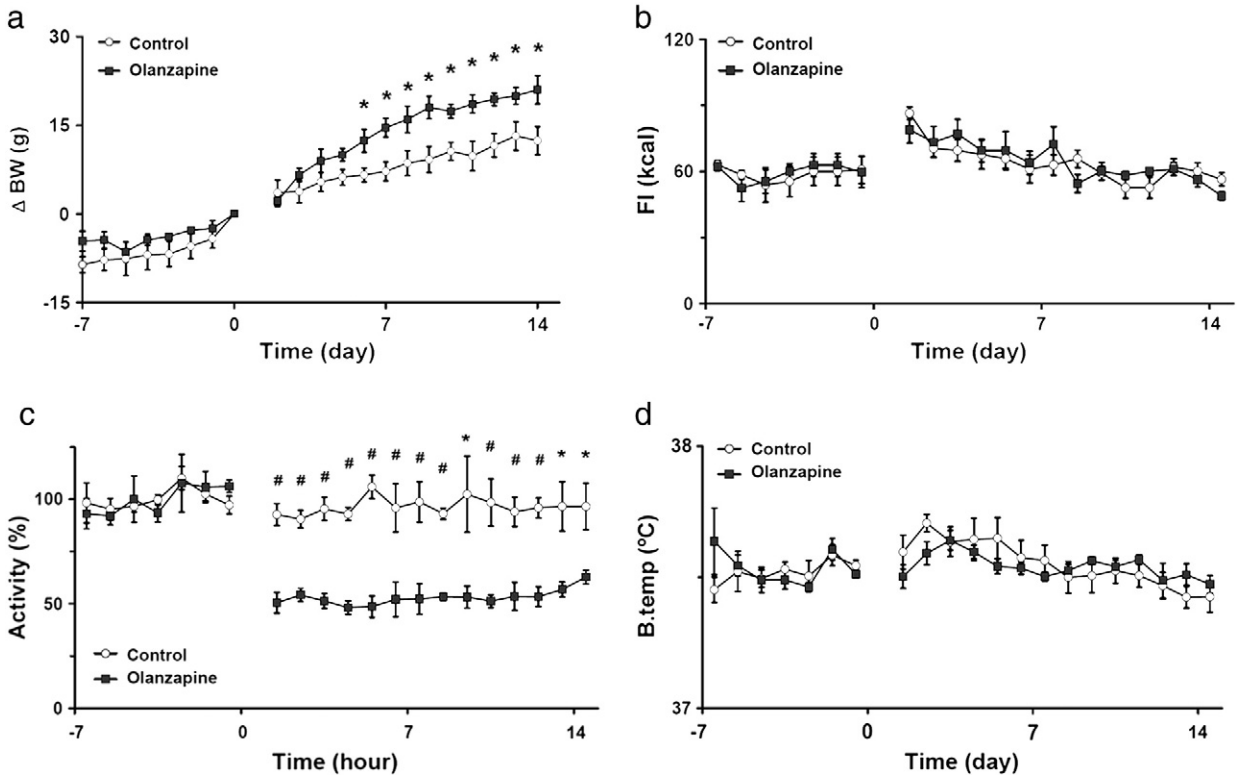

Fig. 1. a) Effects of intragastric administration of Olanzapine (n = 5) or saline (n = 5) on body weight gain in grams, expressed as changes from day 0, the start of drug administration. b) The effect of Olanzapine (n = 5) and saline (n = 5) on 24 h food intake, expressed as kcal. Day −7 to −1 show standard chow intake, days 1 to 14 show medium fat diet intake. c) The effect of Olanzapine (n = 4) and saline (n = 4) on 24 h activity expressed as a percentage of baseline activity. d) The effect of Olanzapine (n = 5) and saline (n = 5) on average 24 h body temperature. In all graphs, Olanzapine is presented as filled squares and saline controls as open circles. Significance is presented as * $P<0.05$, and # $P<0.01$.

significant when compared with both baseline activity and the values in the control rats (rmANOVA: $F_{15,90} = 2.914$, $P<0.01$; mANOVA: $P<0.05$ and $P<0.01$).

Fig. 2 presents both the 24 water intake and the cumulative intake over days 0–14 during Olanzapine or saline treatment. The switch from the standard lab chow to the medium fat diet led to a reduction in water intake in the controls but not in Olanzapine-treated animals (Fig. 2). Both the water intake per day ($F_{1,8} = 8.304$, *$P<0.05$; One-way ANOVA) and 14 day cumulative water intake (rmANOVA: $F_{15,120} = 2.703$, $P<0.01$) were significantly increased in the Olanzapine-treated animals in comparison to the control animals.

3.2. Telemetry data

The average activity and body temperature over both the 12 h dark and 12 h light phase were calculated to investigate the diurnal rhythms in activity, food intake and body temperature. Dark and light phase activities are expressed as percentage of average 24 h activity in the baseline measurements in the week before day 0. Fig. 3a–b shows that Olanzapine significantly reduced the activity in the dark period (Fig. 3a, rmANOVA: $F_{15,90} = 5.558$, $P<0.01$), while light phase activity was unaffected (Fig. 3b).

Fig. 3c–d shows that Olanzapine treatment led to a significant reduction in body temperature in the dark phase (Fig. 3c, rmANOVA: $F_{15,120} = 8.630$, $P<0.01$), and a significant increase in the light phase (Fig. 3d, rmANOVA: $F_{15,120} = 4.231$, $P<0.01$). Fig. 4 provides more detailed information (every 5 min) on body temperature and activity. Drug administration (indicated by arrows) caused an acute significant drop of both body temperature (rmANOVA CT 12–18: $F_{71,568} = 12.144$, $P<0.01$; and CT 18–0: $F_{71,426} = 2.13$, $P<0.01$) and locomotor activity (CT 12–18; rmANOVA: $F_{71,426} = 1.778$, $P<0.01$; and CT 18–0: $F_{71,426} = 2.13$, $P<0.01$), which persisted throughout the dark period. In the light period Olanzapine treatment caused an increase in body temperature (Fig. 4b, rmANOVA CT 0–6: $F_{71,568} = 9.184$ $P<0.01$, and CT 6–12: $F_{71,568} = 11.664$, $P<0.01$) with no significant changes in activity (Fig. 4a). Fig. 4 also shows a diurnal rhythm in the control

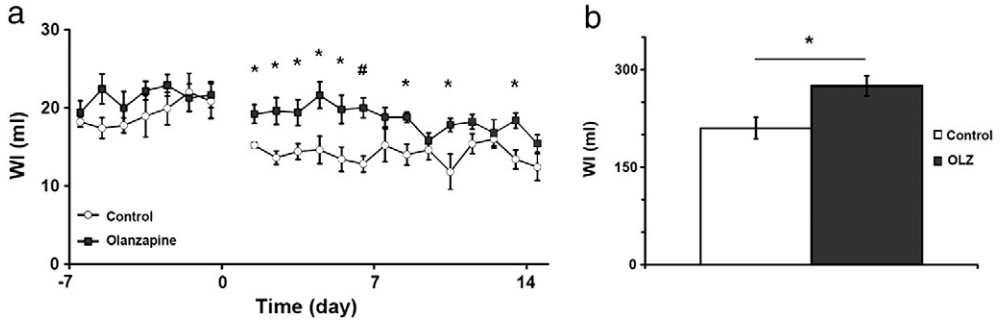

Fig. 2. a) The effect of Olanzapine (n = 5) and saline (n = 5) treatment on 24 h water intake (WI), expressed as ml. b) Cumulative water intake after 14 days of Olanzapine or saline treatment. Olanzapine is presented as filled squares, control as open circles. Significance is presented as * $P<0.05$, and # $P<0.01$.

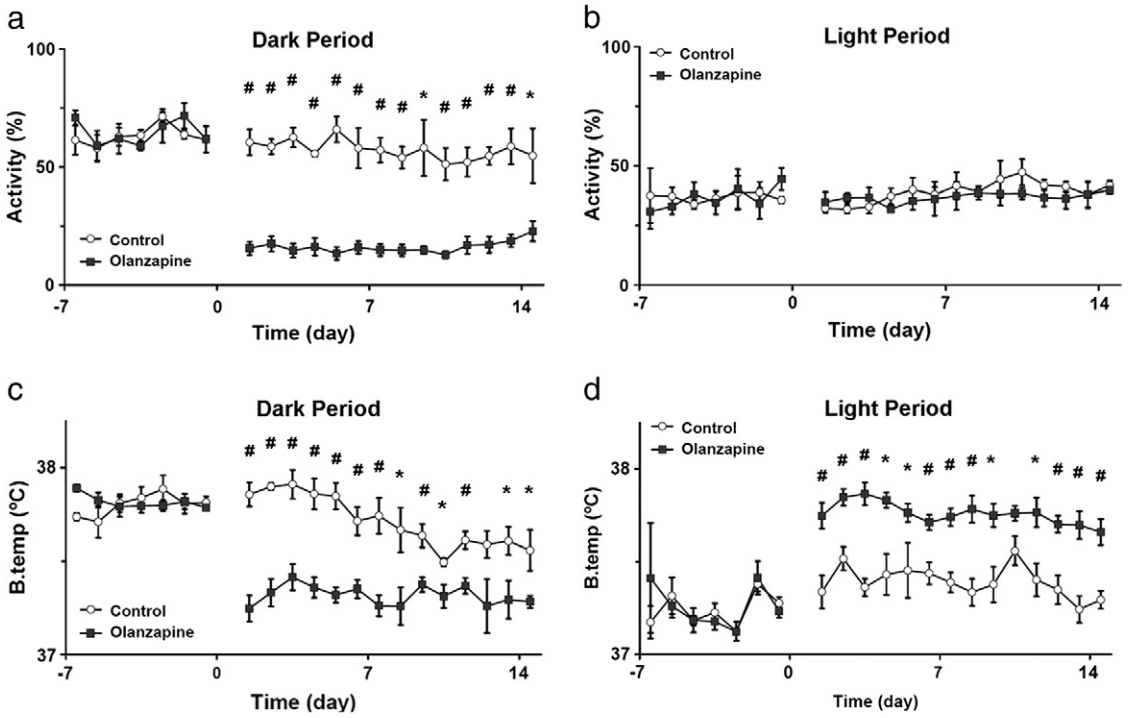

Fig. 3. a and b) The effect of Olanzapine and saline on locomotor activity in the dark (a) and light (b) period. Activity is expressed as a percentage of total 24 h activity during the baseline period. c and d) The effect of Olanzapine and saline on body temperature in the dark (c) and light (d) period. In all graphs, Olanzapine is presented as filled squares, controls as open circles. Significance is presented as * $P<0.05$, and # $P<0.01$.

group, by which activity and body temperature are higher during the dark phase (11:00 h–23:00 h) compared to the light phase, This daily rhythm is disturbed by the administration of Olanzapine.

3.3. Food registration data

At days 17 and 18, feeding behavior was continuously monitored during two consecutive days. Fig. 5a gives the average intake over these two days is per hour. There were marked differences in feeding patterns between both groups (rmANOVA: $F_{23,414}=3.864$, $P<0.01$). Fig. 5b shows the cumulative food intake over 24 h and reveals that there is a decrease of food intake during the second half of dark phase, while food intake during the light period is increased when compared to control values. The 24 h cumulative data (Fig. 5b) shows that Olanzapine reduced food intake during the dark (Controls: 45.45 ± 3.22 kcal; Olanzapine: 28.72 ± 2.14 kcal; One-way ANOVA: $F_{1,18}=18.739$, $P<0.01$). During the light period Olanzapine increased food intake relative to control treatment (Controls: 19.74 ± 2.80 kcal; Olanzapine: 27.45 ± 1.69 kcal. ANOVA: $F_{1,18}=5.546$, $P<0.05$). During the dark period meal size (Fig. 5c) was decreased by Olanzapine (One-way ANOVA: $F_{1,18}=4.606$, $P<0.05$), without significant effects on meal number (Fig. 5d).

3.4. First day of treatment

The data of day 0, the day that all animals switched to the new diet and received their first injection of saline or Olanzapine, are presented in Table 1. The switch from lab chow to medium fat diet led to a significant increase in food intake in the control group (chow $=58.35\pm3.55$ kcal, medium fat diet $=100.58\pm3.82$ kcal; One-way ANOVA: $F_{1,8}=64.150$, $P<0.01$) but not in the Olanzapine group (chow $=59.39\pm4.57$ kcal, medium fat diet $=75.20\pm5.56$ kcal; One-way ANOVA: $F_{1,8}=4.826$, $P=0.06$). Water intake was lower compared to baseline levels, with no difference between groups. Locomotor activity and body temperature were decreased by Olanzapine when compared to control. This amount of activity within the Olanzapine group during the light phase was significantly lower ($F_{1,6}=10.569$,

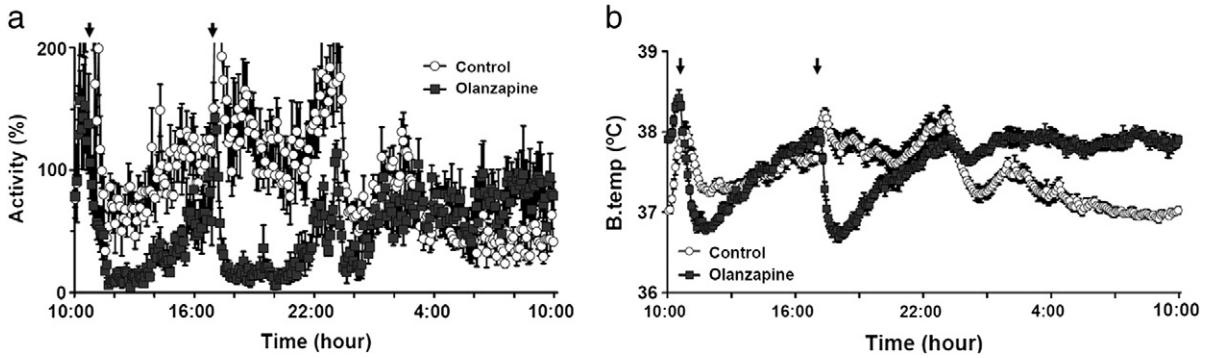

Fig. 4. a) The effect of Olanzapine and saline administration on locomotor activity expressed as average of 14 days of treatment. Activity is expressed as the percentage of average baseline activity per 5 min per 24 h. b) The effect of Olanzapine and saline administration on body temperature (°C) expressed as the average body temperature over 14 days of treatment. Arrows indicate the time of drug administration. Lights turned off at 11:00 h. Olanzapine is presented as filled squares, controls as open circles.

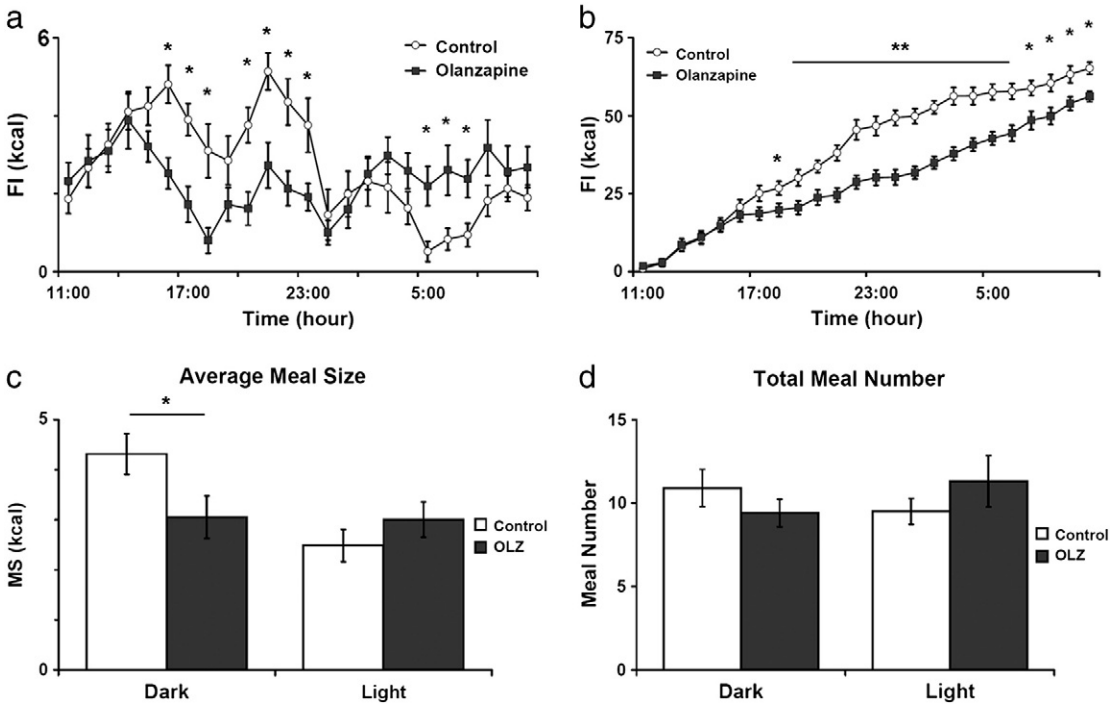

Fig. 5. a and b) The effect of Olanzapine and saline treatment on circadian food intake (kcal) per hour (a) or 24 h cumulative food intake (kcal). Lights turned off at 11:00 h and turned on at 23:00 h. Significance is presented as *P<0.05. c) and d) The effect of Olanzapine and saline on average meal size (a) and meal number (d) in the dark and light period, expressed as an average of two consecutive days. Significance is presented as *P<0.05. All Olanzapine data is presented as filled squares/bars, controls as open circles/bars.

P<0.05; One-way ANOVA) the first day of treatment compared to the average light phase activity of 14 day Olanzapine treatment. 24 h body temperature is significantly decreased ($F1,8 = 83.175$, P<0.05; One-way ANOVA) in the first day of Olanzapine treatment compared to the average of 14 day treatment.

3.5. Sucrose preference

At the end of experiment a two bottle preference test for 10% (g/vol) sucrose solution was performed. Table 2 shows that sucrose intake was significantly higher in the controls (6 h = 17.52 ± 2.51 ml; 24 h = 53.52 ± 9.18 ml) when compared to Olanzapine (6 h = 4.24 ± 1.61 ml; 24 h = 21.76 ± 4.22 ml) treated animals, both after 6 ($F_{1,8} = 19.851$, P<0.01, One-way ANOVA) and 24 h ($F_{1,8} = 9.879$, P<0.05, One-way ANOVA).

4. Discussion and conclusions

In this study in female Wistar rats we found that chronic Olanzapine treatment led to a significant weight gain without changes in 24 h food intake. Olanzapine dramatically reduced locomotor activity, caused an acute hypothermia and completely deranged the circadian patterns in food intake.

Since there were no changes in 24 h food intake, one may argue that the Olanzapine-induced weight gain might be secondary to the marked reduction in locomotor activity, previously described as the sedative effect of Olanzapine (Ahnaou et al., 2003). Fig. 4 shows in detail the acute reduction of locomotor activity after Olanzapine administration, which persisted throughout the duration of the experiment. Comparable results of reduction in activity by Olanzapine have been reported before in both rats (Hillebrand et al., 2005; Stefanidis et al., 2009) and humans (Callaghan et al., 1997; Putzhammer et al., 2005; Roerig et al., 2005).

Olanzapine did not affect 24 h food intake in this study, but we observed marked differences between dark and light period feeding patterns by Olanzapine. Food intake was markedly reduced in the dark phase and was increased in the light phase. It is tenable to assume that the reduction in dark phase food intake is mainly caused by the sedative effect of Olanzapine. The increased food intake in the normally inactive light phase could then be considered as a compensatory homeostatic response to compensate controlling total 24 h food intake. These marked derangements in day/night food intake support previous observations by Lee and Clifton (2002) who found that Olanzapine failed to affect 22 h food intake but also noticed that the size of the first meal as well as the latency to eat was reduced after Olanzapine administration. In the present study we found that Olanzapine during the dark phase reduced meal size, with a small but not significant reduction in meal frequency.

The effects of Olanzapine on body temperature were remarkably similar to the effects on feeding: there was no effect on average 24 h body temperature but there were marked derangements of the dark and light phase patterns. As shown is Fig. 4 in detail, Olanzapine induced a dramatic hypothermic response immediately after

Table 1
Responses at first day of treatment. The effect of Olanzapine or Control treatment on 24 h food and water intake, average 24 h activity, and average 24 h body temperature at the first day of treatment (day 0).

	Control	Olanzapine	$F_{1,8(*1,6)}$	P-value
Food intake (kcal)	100.58±3.82	75.20±5.56	14.155	<0.01
Water intake (ml)	13.20±0.92	15.40±1.29	1.936	
Activity (%)	105.11±10.22	42.26±4.72	*31.191	<0.01
Body temperature (°C)	37.59±0.03	37.23±0.03	115.852	<0.001

Table 2
Sucrose preference. The effect of Olanzapine and Control treatment on 6 and 24 h sucrose intake during a two-bottle preference test.

		Control	Olanzapine	$F_{1,8}$	P-value
Sucrose intake (ml)	6 h	17.52±2.51	4.24±1.61	19.851	<0.01
	24 h	53.52±9.18	21.76±4.22	9.879	<0.05

administration. The dynamics of this response make it unlikely that this reduction in body temperature was secondary to the sedative and hypophagic effects of Olanzapine (i.e., leading to reduced activity- and diet-induced thermogenesis). Instead, data from literature suggest that the hypothermia may be explained by a direct inhibitory effect of Olanzapine on sympathetic outflow and brown adipose tissue (BAT) thermogenesis (Oerther and Ahlenius, 2000). Indeed, Olanzapine decreases uncoupling protein 1 (UCP1) expression in BAT and increases Fos expression in orexin-A positive neurons in perifornical region (PeF) of the lateral hypothalamic area (LHA) projecting to the BAT (Stefanidis et al., 2009). Likewise, Olanzapine inhibits the increase in sympathetic activity after icv orexin-A administration (Monda et al., 2008). Taken together, these data suggest that the Olanzapine-induced hypothermia has, at least in part, a centrally regulated origin, directly related to the orexin-A system at the level of the lateral hypothalamus (LHA).

Body temperature was significantly increased during the light period (Figs. 3 and 4). This increase was probably the result of an increased diet-induced thermogenesis caused by the elevated food intake in the light period in the Olanzapine-treated animals.

Olanzapine treatment reduced the intake of sucrose in a two-bottle-preference test, suggesting a reduced motivation for palatable foods (Table 2). Likewise, Olanzapine prevented the normal increase in food intake (as seen in the control animals) on day 0, the first day that the animals were confronted with the palatable medium fat diet (Table 1) These findings might be explained by Olanzapine's antagonist action on the dopaminergic system, because D2-receptor antagonism has been shown to reduce sucrose preference (Yu et al., 2000). Since Olanzapine has been shown to increase swimming activity in a forced swim test (Molina-Hernandez et al., 2009), one may conclude that Olanzapine does not inhibit activity per se, but may predominantly inhibit the motivation to be active.

In this study we used a relatively high dose of Olanzapine (5 mg/kg b.i.d). Studies performed by Cooper et al. (2005) and Davoodi et al. (2009) revealed that lower dose (2–4 mg/kg/day) might lead to a higher increase in body weight, partly the result of increased food intake. Oerther et al. show that Olanzapine-induced hypothermia is dose dependent (Oerther and Ahlenius, 2000), which probably accounts also for the reduction of activity when compared to our data. As seen in Fig. 4 control animals increase their activity and body temperature at the time of administration, after which there is a significant drop in temperature and activity. Preliminary studies in our lab revealed that lower doses of Olanzapine will not result in a significant drop of activity and body temperature compared to control treated animals. In addition, we also noticed that there are remarkable differences in the effect of olanzapine on metabolism in, male and female rats, we are currently investigating this. During this study we have not measured if Olanzapine may decrease both basal metabolic rate and locomotor activity, Future studies should reveal if Olanzapine affects both these parameters of energy expenditure.

Based on the data above, we conclude that, in female Wistar rats, Olanzapine-induced weight gain in this paradigm is primarily the result of a major reduction in locomotor activity without changes in 24 h daily food intake. These findings are in line with the data from human literature in which the sedative effect of Olanzapine is well-documented (Callaghan et al., 1997; Putzhammer et al., 2005; Roerig et al., 2005). Evidence in humans for an effect of Olanzapine on food intake is less consistent (Eder et al., 2001; Gothelf et al., 2002; Roerig et al., 2005; Stauffer et al., 2009). We also found that Olanzapine has a dramatic acute effect on body temperature. Data in literature suggests that this Olanzapine-induced hypothermia is mainly the result of decreased BAT sympathetic activity, involving the orexin-A system at the level of the PeF in the LHA. Future studies are needed to unravel the possible effects of Olanzapine-induced locomotor inactivity and hypothermia on meal size, meal frequency and feeding patterns.

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