Pharmacology, Biochemistry and Behavior 97 (2010) 130–137

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Olanzapine affects locomotor activity and meal size in male rats

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ARTICLE INFO

Available online 15 May 2010

Keywords:
Olanzapine
Adiposity
Locomotor activity
Meal size
Food preference
Rat

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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doi:10.1016/j.pbb.2010.05.009

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