



Olanzapine depot exposure in male rats: Dose-dependent lipogenic effects without concomitant weight gain



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Abstract

Treatment with second-generation antipsychotic agents such as olanzapine frequently results in metabolic adverse effects, e.g. hyperphagia, weight gain and dyslipidaemia in patients of both genders. The molecular mechanisms underlying metabolic adverse effects are still largely unknown, and studies in rodents represent an important approach in their exploration. However, the validity of the rodent model is hampered by the fact that antipsychotics induce weight gain in female, but not male, rats. When administered orally, the short half-life of olanzapine in rats prevents stable plasma concentrations of the drug. We recently showed that a single intramuscular injection of long-acting olanzapine formulation yields clinically relevant plasma concentrations accompanied by several dysmetabolic features in the female rat. In the current study, we show that depot injections of 100–250 mg/kg olanzapine yielded clinically relevant plasma olanzapine concentrations also in male rats. In spite of transient hyperphagia, however, olanzapine resulted in weight loss rather than weight gain. The resultant negative feed efficiency was accompanied by a slight elevation of thermogenesis markers in brown adipose tissue for the highest olanzapine dose, but the olanzapine-related reduction in weight gain remains to be explained. In spite of the absence of weight gain, an olanzapine dose of 200 mg/kg or above induced significantly elevated plasma cholesterol levels and pronounced

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activation of lipogenic gene expression in the liver. These results confirm that olanzapine stimulates lipogenic effects, independent of weight gain, and raise the possibility that endocrine factors may influence gender specificity of metabolic effects of antipsychotics in the rat.

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1. Introduction

In patients suffering from serious mental disorders, morbidity and mortality due to cardiovascular disease is increased 2–3-fold relative to the general population (Brown et al., 2010; Laursen et al., 2009; Nordentoft et al., 2013; Osborn et al., 2007). This is partly due to lifestyle issues, but antipsychotic-induced metabolic adverse effects also contribute significantly (Brown et al., 2010; Foley and Morley, 2011; Osborn et al., 2007). The so-called *atypical* or *second-generation* antipsychotic agents (SGAs), particularly olanzapine and clozapine, are well known for their propensity to induce metabolic disturbances, i.e. weight gain, dyslipidaemia and diabetes (Daumit et al., 2008; Leucht et al., 2013; Newcomer et al., 2008; Rummel-Kluge et al., 2010). The mechanisms underlying these metabolic adverse effects remain largely unknown, but data from clinical and preclinical studies have demonstrated that antipsychotic-induced weight gain is mainly caused by stimulation of appetite (hyperphagia), presumably mediated through antagonistic effects on serotonin 5HT_{2C} and/or histamine H₁ receptors in the hypothalamus (Kroeze et al., 2003). However, antipsychotic-induced metabolic adverse effects may also occur independent of weight gain (Albaugh et al., 2011b; Birkenaes et al., 2008; Teff et al., 2013). In order to further improve our understanding of the underlying molecular mechanisms, model systems that enable detailed molecular analysis are required. Rodent models of antipsychotic-induced metabolic adverse effects are essential in these ongoing efforts. However, these models have several important shortcomings, both with respect to gender-specific effects, with antipsychotic-induced weight gain observed in female rats only, and with regard to the highly accelerated metabolism of these drugs in rats than in humans, which makes it difficult to obtain steady-state levels of olanzapine in the rat (Aravagiri et al., 1999).

While women may be at a slightly higher risk for antipsychotic-induced metabolic adverse effects than men (Coccurello and Moles, 2010; Gebhardt et al., 2009), gender differences are by no means as pronounced in patients as in rodents (Boyda et al., 2010; Komossa et al., 2010; McEvoy et al., 2007). Numerous experiments have demonstrated that in the female rat, olanzapine exposure results in hyperphagia and increased body weight due to adiposity (Albaugh et al., 2006; Goudie et al., 2002; Skrede et al., 2012). Olanzapine also increases plasma triglyceride levels, an effect that can occur independent of weight gain (Skrede et al., 2012). In male rats, the picture is more complicated. Most experiments in male rats have failed to demonstrate convincing weight gain during treatment with antipsychotics (Albaugh et al., 2006, 2011a; Cooper et al., 2007; Minet-Ringuet et al., 2006a; Pouzet et al., 2003; Shobo et al., 2011a), with the exception of one group reporting significant olanzapine-induced weight

gain (Minet-Ringuet et al., 2006b). With regard to food intake, some studies have reported increased energy intake in male rats during the treatment with olanzapine (Guesdon et al., 2010; Hartfield et al., 2003, 2006; Shobo et al., 2011b), while others did not (Albaugh et al., 2011a; Cooper et al., 2007; Davoodi et al., 2008; McNamara et al., 2011; Minet-Ringuet et al., 2006a; Shobo et al., 2011a). Notably, the studies reporting hyperphagia or weight gain all include rats receiving chow with a higher fat content than standard laboratory chow (Guesdon et al., 2010; Hartfield et al., 2003, 2006; Minet-Ringuet et al., 2006a). Of note, increased white adipose tissue mass has consistently been reported in male rats treated with olanzapine, in spite of the lack of weight gain (Albaugh et al., 2006, 2011a; Guesdon et al., 2010; Minet-Ringuet et al., 2006a; Shobo et al., 2011a).

We recently showed that in the female rat, a single injection of the long-acting (depot) formulation of olanzapine results in sustained, clinically relevant plasma concentrations of olanzapine, with concomitant hyperphagia, weight gain, plasma triglyceride increase, and increased transcription of lipogenic genes in liver and white adipose tissue (Skrede et al., 2014). In the present study, we examined whether high plasma olanzapine concentrations could also be obtained in male rats following such depot injection and whether olanzapine affects metabolic parameters in a dose-dependent manner. In addition, we investigated whether dietary fat content affects olanzapine plasma levels and metabolic phenotype. We hypothesized that depot injection would result in high, stable plasma concentrations of olanzapine in the male rat, possibly leading to more pronounced metabolic disturbances than previously observed. Our results show that olanzapine long-acting injections enable the replication of some, but not all, of the molecular alterations observed in female rats, indicating that the gender differences observed in rat are not solely an issue of drug administration and pharmacokinetic effects.

2. Experimental procedures

2.1. Animals

All experiments were approved by and carried out in accordance with the guidelines of the Norwegian Committee for Experiments on Animals (Forsøksdyrutvalget, FDU) through standardized applications to the animal facility at Haukeland University Hospital (ID 20124231). Rats were kept under standard conditions with an artificial 12:12-hour light/dark cycle (lights on: 08:00) and constant 48% humidity. Animals were housed individually and allowed access to tap water and free (*ad libitum*) access to standard laboratory chow (SC; 3% fat, 3.5 kcal/g) or a high-fat diet (HFD, 60% lipids, 5.1 kcal/g), both from Special Diets Services (SDS, Witham, UK) during the experimental period.

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