Psychoneuroendocrinology (2016) 1–185

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Olanzapine-depot administration induces time-dependent changes in adipose tissue endocrine function in rats

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ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 23 June 2016
Accepted 26 July 2016

Keywords:
Adipokine
Adipose tissue
Dyslipidemia
Leptin
Olanzapine
Sprague-Dawley rats

ABSTRACT

Objective: Metabolic adverse effects of atypical antipsychotics (AAP) contribute significantly to increased risk of cardiovascular morbidity and mortality in patients suffering from schizophrenia. Extensive preclinical research has addressed this issue over the past years, though mechanisms underlying these adverse effects of AAP are still not understood completely. Recently, attention is drawn towards the role of adipose tissue metabolism and neurohormonal regulations.
Methods: The aim of this study was to evaluate the time-dependent effects of olanzapine depot administration at clinically relevant dosing on the regulation of energy homeostasis, glucose and lipid metabolism, gastrointestinal and adipose tissue-derived hormones involved in energy balance regulations in female Sprague-Dawley rats. The study lasted 8 weeks and the markers were assayed at day 8, 15, 29, 43 and 57.
Results: The results indicate that in the absence of hyperphagia, olanzapine chronic exposure induced weight gain from the beginning of the study. In the later time-point, increased adiposity was also observed. In the initial phase of the study, lipid profile was altered by an early increase in triglyceride level and highly elevated leptin level was observed. Clear bi-phasic time-dependent effect of olanzapine on leptin serum concentration was demonstrated. Olanzapine treatment did not lead to changes in serum levels of ghrelin, FGF-21 and pro-inflammatory markers IL-1a, IL-6 and TNF-α at any time-point of the study.
Conclusion: This study provides data suggesting early alteration in adipose tissue endocrine function as a factor involved in mechanisms underlying metabolic adverse effects of antipsychotics.

1. Introduction

The benefits of atypical antipsychotics (AAP) in the treatment of schizophrenia and other disorders not limited to psychotic spectrum are indisputable in general. One of the great advantages of AAP in the treatment of psychotic disorders is their low propensity to induce extrapyramidal symptoms, though the neurological side effects are 'replaced' by adverse metabolic effects (Nasrallah, 2008; Newcomer, 2007). These metabolic alterations, including weight gain, dyslipidemia, increased adiposity, glucose intolerance and insulin resistance which correspond to the cluster of metabolic syndrome (MetS) symptoms further increase the risks for development of obesity, type-2 diabetes, cardiovascular morbidity, and the overall mortality of patients with schizophrenia (De Hert et al., 2012; Leucht et al., 2007). The overall rate of MetS was 32.5% in patients with schizophrenia and related disorders according to a recent meta-analysis (Mitchell et al., 2013).

The propensity to induce metabolic alterations substantially differs among the antipsychotic drugs. This can be partially explained by their unique receptor binding profiles (Nasrallah, 2008). The highest potential to induce weight gain, increased adiposity, dyslipidemia and to impair glucose tolerance has been reported in the context of treatment with multi-acting receptor targeted agents (MARTA) antipsychotics, especially olanzapine and clozapine. Olanzapine seems to be the drug most associated with the symptoms of metabolic syndrome (De Hert et al., 2012; Leucht et al., 2013; Mitchell et al., 2013). The exact pharmacological

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http://dx.doi.org/10.1016/j.psyneuen.2016.07.218
0306-4530/

molecular mechanisms underlying metabolic adverse effects of AAP are poorly understood; however, there is increasing evidence suggesting metabolic dysregulations as an antecedent factor of obesity development (Correll et al., 2010; De Hert et al., 2012).

Extensive preclinical research has addressed this issue over the past years. Nevertheless, findings from preclinical studies are frequently inconsistent due to methodological issues such as use of different animal strains and gender, drug dose, route of administration and duration of treatment (Boyda et al., 2010; van der Zwaal et al., 2014). Above all, one of the important challenges has been represented by possibly inadequate dosing of AAP in animal studies not corresponding to the clinical condition, which arises from incomparable pharmacokinetic profiles of AAP in rodents and humans, because rodents have a much shorter half-life of AAP (Kapur et al., 2003). Recently the availability of AAP in the form of long-acting injections has enabled researchers to optimize the dosing regimens of AAP in preclinical studies, ensuring stable drug exposure. In humans there is evidence supporting the assumption that adverse metabolic effects of AAP may be associated to serum concentration, since olanzapine and clozapine induced metabolic abnormalities appear to show concentration-dependent relationship (Simon et al., 2009). This was clearly observed with regard to weight gain in patients receiving different doses of long-acting injectable olanzapine (Kane et al., 2010).

Despite the lack of definite evidence of gender-specific effects of AAP on weight changes or other metabolic parameters in humans (Correll et al., 2010; Mitchell et al., 2013), female rats were shown to be more suitable for modeling AAP-induced weight gain than males (Albaugh et al., 2006; Boyda et al., 2010; Davey et al., 2012; van der Zwaal et al., 2014). Furthermore, the AAPs with the least liability to metabolic dysregulation in humans, such as aripiprazole or ziprasidone (Leucht et al., 2013), were also associated with weight gain in rodent experiments (Boyda et al., 2010; Skrede et al., 2012; van der Zwaal et al., 2014).

Lately, with regard to metabolic alterations induced by AAP, attention has been paid to dysregulation of adipose tissue metabolism and its endocrine/paracrine function in human studies and animal experiments (Potvin et al., 2015; Skrede et al., 2012; Zhang et al., 2013). Particularly, the research has been focused on the potential effects of AAP on adipokines, as well as proteins released by adipose tissue and neurohormonal regulations. The intricacy of interplay of modulators of food intake and energy balance and gastrointestinal hormones in general is also being investigated intensively (Perry and Wang, 2012) but these variables were incompletely explored in context of AAP-induced metabolic adverse effects in animal models. Furthermore, specific biochemical marker which enables the identification of patients at a high risk of AAP-induced MetS has not yet been proposed, and the underlying molecular mechanisms of AAP-induced metabolic effects remain to be elucidated.

Therefore, the aim of this study was to evaluate the time-dependent effects of olanzapine depot administration on the regulation of energy homeostasis, specifically feeding behavior, lipid profile, alterations of adipose tissue endocrine/paracrine functions and hormonal regulations in order to elucidate their interrelationships in the mechanisms of AAP-induced metabolic alterations. Apart from basic biochemical analysis (lipid spectrum, glucose serum level), serum levels of leptin, ghrelin, glucagon-like peptide-1 (GLP-1) and glucagon, fibroblast growth factor-21 (FGF-21) were assessed to describe alterations in adipose tissue endocrine functions and in neurohumoral regulation. Spectrum of adipokines and hormones was selected for the analysis, in order to explore their possible interrelationships and roles in the mechanisms of AAP-induced metabolic alterations, since eg. leptin and ghrelin are suggested to have opposite an/orexigenic effects in appetite and energy homeostasis regulation (Klok et al., 2007; Muller et al., 2015). These two factors have been studied most extensively with inconsistent findings in both preclinical and human studies (Potvin et al., 2015; Skrede et al., 2012; Zhang et al., 2013). However, the regulations are more complex, thus GLP-1 and adipokine FGF-21 were included as there is evidence confirming physiological role of GLP-1 in the complex regulation of appetite (Ronveaux et al., 2015), and FGF-21 is known regulator of glucose and lipid homeostasis, which possesses functions of endocrine hormones (Kharitonenkov, 2009). We also assessed pro-inflammatory cytokines (interleukin 1a and 6, tumor necrosis factor-α), which are known to be elevated in MetS (Kucerova et al., 2015).

2. Material and methods

2.1. Animals

Forty female 8 weeks old albino Sprague-Dawley rats weighing 200–225 g at the beginning of the study were purchased from Charles River (Germany) and housed individually in standard housing cages. Environmental conditions during the whole study were constant: relative humidity 50–60%, temperature 23 °C ± 1 °C, normal 12-h light-dark cycle (6 a.m.–6 p.m. light). Standard rodent chow and water were available *ad libitum*. All experiments were conducted in accordance with all relevant laws and regulations of animal care and welfare. The experimental protocol was approved by the Animal Care Committee of the Masaryk University, Faculty of Medicine, Czech Republic, and carried out under the European Community guidelines for the use of experimental animals.

2.2. Drugs and treatments

Olanzapine (OLA) was administered in a depot formulation for human use (ZypAdhera®) by an intramuscular injection at dose 100 mg/kg every 14 days in the evening hours (administration on day 1, 15, 29 and 43). The solvent vehicle was injected to the control group. The food was removed from the cages and all rats were subjected to overnight fasting in order to prevent weight gain differences induced by sedation in the OLA-treated group as we observed in our previous experiments (unpublished data) and was also already recently validated (Skrede et al., 2014).

2.3. Food consumption and body weight recording

Body weight (BW) and food consumption were recorded daily in all animals. Feeders in all cages were filled with 50 g of the rodent chow, the consumption was recorded after 24 h and then filled to 50 g again. On the days of drug administration when the chow was removed overnight the food consumption data were not recorded (day 1, 15, 29 and 43).

2.4. Treatment groups and sample collection

Rats were randomly assigned to 2 treatment groups: vehicle (VEH) treated (n = 17) and olanzapine (OLA) treated (n = 23). Two subgroups of animals, vehicle (n = 7) and olanzapine-treated rats (n = 8), were sacrificed by decapitation under short isoflurane anesthesia to collect blood (for serum), liver and visceral fat tissue 8 days after the first administration. The dissection was performed after decapitation by wide laparotomy, the liver was excised and weighted and abdominal fat tissue was collected and weighed. Other two subgroups of rats, vehicle (n = 10) and olanzapine-treated (n = 15), were kept until the day 57 (8 weeks of treatment) and then sacrificed and dissected in the same manner. Furthermore, 1.5–2 ml of blood for serum was collected under short isoflurane anesthesia every 2 weeks (day 1, 15, 29 and 43) by retro-orbital puncture and the same amount of liquid was supplied by the