Research report

The efficacy of mifepristone in the reduction and prevention of olanzapine-induced weight gain in rats

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Abstract

Atypical antipsychotics, such as olanzapine, have been associated with clinically significant weight gain. Changes to the hypothalamic pituitary adrenal axis may partially mediate this weight increase. Two experiments were conducted to test the effects of mifepristone on both mitigating and preventing olanzapine-induced weight gain. In the first experiment, adult female Sprague–Dawley rats gained significantly more weight on average when administered olanzapine for 35 days compared to vehicle controls. Subsequently, the olanzapine-treated rats were randomized to three dose levels of mifepristone (20, 60, and 200 mg/kg) in conjunction with olanzapine. Weight measurements were taken for 21 additional days. Rats receiving olanzapine plus mifepristone rapidly lost a significant portion of the weight gained during the olanzapine only phase ($p = 0.0001$). Rats in the 200 mg/kg dose group had significantly less abdominal fat compared to controls ($p < 0.001$) at study end. In the second experiment, daily mifepristone (20, 60, 200 mg/kg) initiated concomitantly with olanzapine was compared with olanzapine alone to determine if mifepristone prevented olanzapine-induced weight gain. After 21 days of treatment, mifepristone treated rats gained significantly less weight and had significantly less abdominal fat than rats administered olanzapine alone ($p = 0.0002$). Results suggest that mifepristone, a potent glucocorticoid antagonist, may both reduce and prevent olanzapine-induced weight gain in rats.

1. Introduction

Atypical antipsychotics have provided significant benefit to patients with schizophrenia [1], bipolar disorder [2] and other major psychiatric conditions. In current psychiatric practice, atypical antipsychotics are favored over conventional antipsychotics because of better tolerability and medication compliance [3]. However, significant side effects associated with atypical antipsychotics have emerged in recent years, namely the propensity to induce significant weight gain [4], contribution to metabolic syndrome [5] and an increased risk of diabetes mellitus and hyperglycemia. The FDA recently implemented a mandatory class warning for all atypical antipsychotics related to the risk of 'Hyperglycemia and Diabetes Mellitus'. Weight gain

is among the most common reasons that a patient might discontinue an effective antipsychotic [6]. Little is known about the etiology and the effective management of antipsychotic induced weight gain.

Clozapine was the first atypical antipsychotic shown to induce substantially more weight gain than conventional antipsychotics [7]. The weight gain exceeded 10% of initial body weight within 12 weeks in more than one third of patients [8,9]. Subsequently, olanzapine was found to have a similar weight gain profile to clozapine. Olanzapine is widely prescribed for the treatment of many psychiatric conditions including schizophrenia, schizoaffective disorder, bipolar disorder and as antidepressant augmentation therapy for refractory major depressive disorder [10]. In a meta-analysis of antipsychotic trials involving over 30,000 patients, olanzapine and clozapine were the atypical agents associated with the greatest weight gain [4]. Some long-term studies indicate that the weight gain associated with olanzapine may not plateau for 30 weeks or longer [11].

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The medical consequences of atypical antipsychotic induced weight gain are significant, including an increased risk of type II diabetes, hypertension, obstructive sleep apnea and other serious obesity-related medical problems [10]. In addition, antipsychotic induced obesity has been implicated in increasing triglyceride levels, decreased HDL cholesterol, and increasing LDL cholesterol [12]. These lipid abnormalities may contribute to a higher risk for coronary artery disease.

It is not clear by what mechanism antipsychotics induce weight gain. One possible mechanism is through antagonism of the H-1 receptor [5]. Olanzapine has a greater affinity for the H-1 receptor than other atypical agents, perhaps correlating to its greater risk of weight gain. Another proposed mechanism includes antagonism of the 5HT2c receptor subtypes [13]. Olanzapine and clozapine are both potent antagonists of the 5HT2c receptor, while aripiprazole and ziprasidone are both weak 5HT2c antagonists and have a more weight neutral profile. Other possible mechanisms for antipsychotic induced weight gain include endocrine factors such as greater insulin resistance, effects on glucocorticoids, and hyperprolactinemia [14]. Strategies for controlling antipsychotic induced weight gain have been of limited success, highlighting the need to further understand the physiology and treatment of antipsychotic induced weight gain [15,16].

Multiple animal models of obesity have been designed to help further understand the physiological factors of obesity, including genetic models (fa/fa rats), induction of obesity through high fat diets, and through administration of atypical antipsychotics. Adrenal glucocorticoids appear to be important in the etiology of many types of obesity including dietary, hypothalamic and genetic forms of obesity [17]. Adrenalectomy prevents hyperphagia and reduces fat synthesis in animal models of obesity [18]. Preliminary work indicates that blocking the type II glucocorticoid receptor with mifepristone reverses genetic obesity in young fa/fa Zucker rats [19]. After 15 days of treatment with mifepristone, 5-week old obese Zucker rats resembled lean vehicle rats in terms of body composition. In addition, dietary obesity in Osborn–Mendel rats also appears to be reversed by mifepristone [20].

Mifepristone Mifeprex is both a potent type II glucocorticoid receptor antagonist and a progesterone receptor antagonist. Given the evidence from prior studies that mifepristone may reverse genetic and dietary obesity in rodent models, there may be a role for mifepristone in preventing or reversing antipsychotic induced weight gain as well. The objectives of these experiments were to test a reproducible model of atypical antipsychotic induced weight gain in rodents, and to demonstrate that mifepristone may mitigate and also prevent the weight gain associated with administration of olanzapine.

2. Materials and methods

2.1. Animals

A total of 48 adult female Sprague–Dawley rats, age 8–11 weeks (CD®, Charles River Laboratories, Wilmington, MA, USA) were maintained under standard husbandry conditions following a 2–4 week acclimation period. Animals were exposed to a 12 h light/12 h dark cycle and food and water were provided ad libitum. The basal diet was standard rat chow (Lab Diet® Certified Rodent Diet #5002, PMI Nutrition International, Inc., St. Louis, MA, USA)

2.2. Experimental methods

Two separate experiments were conducted. In the first experiment, the effects of mifepristone on reducing olanzapine-induced weight gain were evaluated by administering mifepristone concomitantly with the olanzapine after weight gain had been established using olanzapine alone. In the second experiment, the effect of mifepristone in preventing weight gain was examined by co-administering olanzapine with mifepristone from the onset.

The first experiment was conducted in two phases. Over an initial 35-day weight induction phase, either olanzapine or vehicle was administered. Olanzapine was administered at 12 h intervals (7 a.m. and 7 p.m.) at a dose of 1.2 mg/kg. The olanzapine was dissolved in sterile water and administered by oral gavage. Controls received an equivalent volume of vehicle (0.25% carboxymethylcellulose and 0.2% Tween 80 dissolved in Sterile Water) on a similar 12 h dosing schedule. On days 0 (baseline) and 7, animals were fasted overnight to obtain blood glucose and insulin measurements. This procedure was discontinued after day 7 due to the confounding effect of overnight fasting on the animals' body weight.

On day 35, animals in the olanzapine treatment group were randomized to receive one of three dose levels of mifepristone (10, 30, or 100 mg/kg, dosed twice a day.). The mifepristone was dissolved in sterile water and administered by oral gavage. Olanzapine plus mifepristone were administered twice daily for the subsequent 21 days. Controls received vehicle as described above.

Body weight was measured every 2–3 days and food consumption was measured daily over the course of the 55-day study. All animals were observed twice daily for morbidity, mortality, injury, and availability of food and water. A detailed clinical examination of each animal was performed weekly.

In the second experiment, animals were randomized to receive olanzapine 1.2 mg/kg twice daily or olanzapine 1.2 mg/kg twice daily plus one of three doses of mifepristone (10, 30, or 100 mg/kg, dosed twice a day) for 22 days. As in the first experiment, body weight was measured every 2–3 days and food consumption was measured daily. The administration and preparation of olanzapine and mifepristone were identical to procedures used in experiment 1, and animals were observed twice daily for morbidity, mortality, injury and the availability of food and water.

3. Data analysis

Changes in body weight were compared across groups using repeated-measures analysis of variance models. These models included treatment group as a between-subjects factor and time as a within-subjects factor. When models were statistically significant (<0.05), one-way analyses of variance were conducted to compare groups. When no differences were observed between the three experimental groups (i.e., dose level was not a significant source of variance), they were combined for subsequent comparisons with control. Effect sizes were calculated using Cohen's delta, or the difference in mean weight change divided by the pooled standard deviation. In addition to the body weight analyses, secondary analyses compared groups on mean abdominal fat and mean daily food consumption.

4. Results

4.1. Experiment 1

4.1.1. Weight gain induction: baseline—day 35
At baseline, the mean body weight for all 48 animals was 249.5 g ($m = 249.5 \pm 13.3$). Between baseline and day 35, repeated-measures ANOVA indicated a statistically sig-