INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Research Article

THE EFFECT OF RESVERATROL ON WEIGHT GAIN ASSOCIATED WITH OLANZAPINE TREATMENT

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Article Received on: 02/05/12 Revised on: 20/05/12 Approved for publication: 09/06/12

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ABSTARCT
The use of antipsychotic medication has consistently been associated with serious side effects including weight gain and metabolic abnormalities. Strategies for mitigating these side effects have been tested, yet effective interventions have not been identified. Present study tested effect of resveratrol, a natural phytoalexin with on weight gain induced by the antipsychotic olanzapine. Male Sprague–Dawley rats fed a normal chow diet were randomized (n=6 per group) to receive one of the following for 18 days: vehicle plus vehicle, olanzapine plus vehicle (2.4 mg/kg, i.p.), olanzapine plus resveratrol (10 mg/kg, i.p.), Rats receiving olanzapine plus resveratrol (10 mg/kg i.p.), gained significantly less weight than rats receiving only olanzapine. Differences in weight gain were not attributable to decreased food intake.
Keyword: Trans-resveratrol, olanzapine, weight gain

INTRODUCTION

Resveratrol is a naturally occurring polyphenolic compound that can be found in a variety of plants[1,2]. Resveratrol belongs to a group of substances known as phytoalexins, which are low molecular weight secondary metabolites produced by plants as a defensive response to microbial injury, fungal infection, or abiotic (i.e., environmental) stress[3]. Resveratrol is found in nature as both cis and trans isomers, however, the trans-isomer is believed to be the most abundant and biologically active form[4]. Humans ingest trans-resveratrol by consuming foods or plants that contain it naturally or via resveratrol-containing dietary supplements. Trans-Resveratrol can be found in over 300 edible plants, with significant dietary amounts found in grape skin, and it is subsequently present in red wine and may be related to the ‘‘French Paradox” (a reduced risk of coronary heart disease and cancer, associated with the consumption of red wine)[2,5]. Trans-Resveratrol can also be found to lesser extents in peanuts, cranberries and mulberries, as well as several inedible plants[6,7]. Trans-Resveratrol has been suggested to possess cancer chemopreventive, antioxidative, antiplatelet, antifungal and cardioprotective properties[4]. Resveratrol has also been shown to act as a calorie restriction mimetic, enhancing vitality and extending life-span in several species including yeast cells[8]. Treatment with many antipsychotics is temporally associated with weight gain[9,10,11]. Excessive weight gain during antipsychotic therapy is undesirable for many reasons. Obesity is associated with increased rates of morbidity due to hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and respiratory problems; and also endometrial, breast, prostate, and colon cancers[12]. Furthermore, weight gain temporally associated with antipsychotic treatment in patients with mental illness can lead to decreased quality of life[13]. Most atypical antipsychotics appear to have greater association with weight gain than the majority of the conventional antipsychotics[9]. Olanzapine is an atypical antipsychotic approved for the treatment of schizophrenia (Sch) and acute bipolar (BP) mania; similar to treatment with several other antipsychotics, olanzapine treatment is associated with metabolic side-effects, including weight gain, impaired glucose tolerance and insulin resistance, which increase the risk of developing cardiometabolic disorders, future research is needed to develop targeted, mechanistically based strategies for managing these metabolic side effects[14]. Consistent with these needs, the current animal study tested resveratrol to attenuate weight gain caused by olanzapine.

MATERIAL AND METHODS

Drug preparation

Olanzapine is an antipsychotic medication lyophilised injection [Sun Pharma, baroda] was purchased commercially. For this experiment, olanzapine was prepared daily with sterile water for injection and resveratrol was purchased from Cayman Chemicals, USA dissolved in 10 % v/v of ethanol in sterile water for injection. All other reagents used were of analytical grades.

Animals

Adult female Sprague–Dawley rats weighing 200-250 g (n=18) were fed a normal chow fed *ad libitum*. Tap water was available *ad libitum*. Animals were individually housed in suspended stainless steel wire-mesh cages in an environmentally controlled room. Temperature and humidity were monitored and controlled, 12 hours light dark cycle was maintained. Prior to the experiment there was a 2-day acclimation period to habituate the animals to the housing environment. Animals were observed daily with respect to general health and signs of disease.

Procedure

Animals were randomly assigned (n=6 per group) to receive 18 days of one of the following treatments: vehicle plus vehicle, olanzapine (2.4 mg/kg/day) plus vehicle, olanzapine (2.4 mg/kg/day) plus resveratrol (10 mg/kg/day), All treatments were administered via intraperetonial route in divided doses, twice daily, for 18 consecutive days. The dose for olanzapine was determined from previous publications that described animal models of olanzapine-induced weight gain[15,16]. Measurement of the primary endpoint, body weight, was conducted on every day. Food consumption was measured daily. Clinical observations for morbidity,

mortality, injury, general health, and the availability of food and water were conducted twice daily. The study, conducted at MIBP Gondia (Maharashtra), was approved by their Institutional animal ethics committee in compliance with the CPCSEA, Govt. of India.

Statistical Analyses

All data are expressed as Mean ± SEM. Statistical analyses were performed using one way analysis of variance (ANNOVA) followed by Newmanns Keuls test comparing each group versus the vehicle reference group and each group versus the olanzapine reference group.P≤ 0.05 was considered significant.

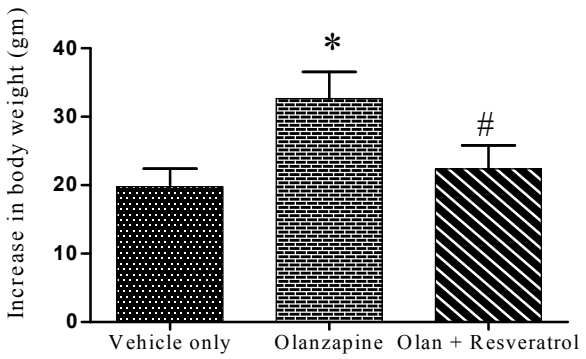
RESULTS

Body weight

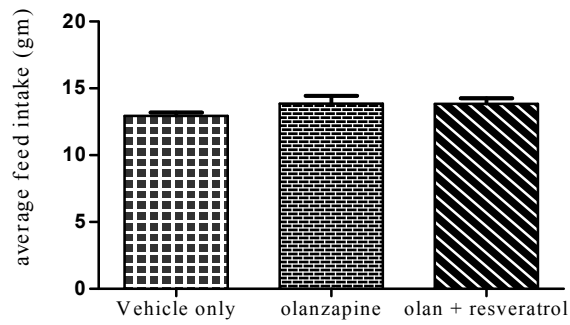
Graph 1 provides the mean changes in weight gain from baseline to endpoint for each treatment group. Rats receiving olanzapine plus resveratrol (10 mg/kg/day) gained significantly less weight than rats receiving only olanzapine ($P \leq 0.05$). Mean weight gain observed in the groups receiving 10 mg/kg doses of the resveratrol did not differ statistically from the mean weight gain observed in the group receiving only vehicle ($P \leq 0.05$).

Food consumption

Average food intake for all treatment groups and significance tests from planned statistical comparisons are shown in Graph 2. Mean daily food consumption was greater in the group treated with only olanzapine compared to the group treated with only vehicle (no significance). The other groups receiving resveratrol in conjunction with olanzapine did not differ in food consumption compared to the olanzapine group.



Graph 1: Mean changes from baseline in body weight by treatment (n=06 per group).



Graph 2: average food intake (n=06 per group).

DISCUSSION

Following administration for 18 days, olanzapine caused significant weight gain in rats. Rats that received olanzapine and concomitant treatment with resveratrol gained significantly less weight than rats given olanzapine alone and was comparable with the weight gain observed in the young adult rats receiving vehicle only (see Graph1). Although rats receiving olanzapine plus resveratrol gained less weight than rats receiving olanzapine only, they ingested comparable amounts of food. The observation that weight gain prevention was not mediated by a decrease in food consumption suggests that these compounds may mechanistically operate on metabolic processes rather than by controlling appetite.

The expected mechanism of reduction in olanzapine induced weight gain by resveratrol is not yet elucidated. However, several lines of previous research suggest that changes in insulin sensitivity may be involved in antipsychotic induced weight gain. Increased glucocorticoid activity (cortisol in humans and corticosterone in rats) causes resistance to insulin[17] also adipocytokines may involve in weight gain. It is common for patients with Cushing's syndrome to be insulin insensitive, hyperglycemic, and frankly diabetic[18]. Glucocorticoid receptor antagonists cause increased sensitivity to insulin in both animal and human models[19]. Perhaps this increased insulin sensitivity leads to more efficient metabolism and less weight gain in a system perturbed by antipsychotic medication. Role of resveratrol over many of above condition is already proved.

From the above result it is concluded that resveratrol mitigate the antipsychotic olanzapine induced adverse side effect of weight gain in rodents. Moreover, as the prevalence of prescribing atypical antipsychotics for multiple psychiatric conditions increases, the issue of weight gain will reach new levels of importance. It appears warranted to do human studies to evaluate the utility of resveratrol rich diet suppliment in reducing and preventing the weight gain associated with atypical antipsychotic use.

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Source of support: Nil, Conflict of interest: None Declared