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Original article

Protective effects of green tea on olanzapine-induced-metabolic syndrome in rats

Bibi Marjan Razavi[a], Fariba Lookian[b], Hossein Hosseinzadeh[c,*]

[a] Targeted Drug Delivery Research Center, Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[b] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Pharmaceutical Research Center, Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Atypical antipsychotics particularly olanzapine are associated with obesity and serious metabolic disturbances. As green tea (*Camellia sinensis*) is generally associated with beneficial effects on obesity and other metabolic disturbances, this study was undertaken to evaluate the effect of green tea aqueous extract (GTAE) on olanzapine induced weight gain and metabolic abnormalities in rats. Male Wistar rats were divided into eight groups: control, olanzapine (5 mg/kg/day, IP.), GTAE (25, 50 and 100 mg/kg/day, IP.) plus olanzapine and GTAE (25, 50 and 100 mg/kg/day, IP.). Treatments were continued for 11 days. Body weight gain, average food and water intake were measured during the experiment. Plasma lipid, glucose and leptin levels, mean systolic blood pressure and total locomotion were evaluated at the end of experiment. Olanzapine induced significant weight gain at the end of treatment (10.38% of body weight) when compared to control (3.13% of body weight) in male Wistar rats. Average food and water intake were increased by olanzapine treatment. 11 days olanzapine administration led to hyperleptinemia, hyperglycemia and dyslipidemia. Olanzapine also increased mean systolic blood pressure and decreased total locomotion. GTAE decreased significantly body weight gain and average food and water intake, improved the changes in lipid profile as well as fasting blood glucose, and finally decreased hyperleptinemia and hypertension induced by olanzapine. Results of this study demonstrated that GTAE could exert protective effects against olanzapine induced obesity partially due to its lowering effect on leptin. GTAE improved other metabolic abnormalities including dyslipidemia, hyperglycemia and hypertension induced by olanzapine in rats.

1. Introduction

Atypical antipsychotics are the first line medications for acute and maintenance therapy of schizophrenia, because of better tolerability and medication compliance when compared with conventional antipsychotics [1]. However, accumulating evidence suggests that many atypical antipsychotics particularly olanzapine and clozapine are associated with serious metabolic disturbances, such as weight gain, insulin resistance, blood glucose abnormalities and hyperlipidemia which can increase risks for developing metabolic and cardiovascular diseases in patients with schizophrenia and can lead to decreased quality of life in patients with mental illness [2,3]. The incidence of metabolic syndrome after atypical antipsychotic treatment was reported to be 20–60%, which is at least twofold the incidence rate in the general population [4].

Although exact mechanisms of antipsychotic–induced weight gain and metabolic disturbances are not yet fully elucidated, however, the proposed mechanisms underlying antipsychotic-induced weight gain include D_2 receptor antagonism, H_1 receptor antagonism, muscarinic (M_3) receptor antagonism, 5-HT_{2C} receptor antagonism or inverse agonist [5,6] and HTR2C and HTR2A gene polymorphisms [7]. Moreover, a reduction of physical activity [8], an increase in food intake, increased appetite and insulin resistance seem to be associated with the occurrence of metabolic abnormalities induced by olanzapine [9].

Green tea, produced from the unfermented dried leaves of the plant *Camellia sinensis*, has been consumed by humans worldwide, especially in East Asian countries [10]. Green tea contains caffeine and polyphenolic compounds known as catechins. Catechins are a

* Corresponding author.
E-mail address: hosseinzadehh@mums.ac.ir (H. Hosseinzadeh).

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class of low molecular weight polyphenols which consist mainly of flavan-3-ol monomers [11].

The most important catechins are (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG) and (−)-epicatechin (EC). Among them, EGCG is the most abundant catechin found in green tea and has been suggested to be responsible for many of the potential health effects of green tea particularly antioxidant properties [11,12]. Regular drinking of green tea has been associated with many health benefits on lipid profile, blood glucose levels, cancer, hypertension and weight loss [11,13]. Protective effects of green tea and its main constituents against natural and chemical toxins have been shown [14]. In addition, tea consumption reduces the risk of cardiovascular diseases and metabolic syndrome [15].

Strategies for management antipsychotic induced weight gain have been of limited success, emphasizing the need to further investigation [16]. Several plants and their active components such as *Vitis vinifera* [17], *Nigella sativa* [18], *Allium sativum* [19], *Rosmarinus officinalis* [20], *Crocus sativus* [21], *Persea americana* [22], *Cinnamomum verum* [23], thymoquinone [18] and rutin [24] are being used for the therapy of different disorders including metabolic syndrome due to their safety, efficacy, cultural acceptability and lesser side effects. As green tea is generally associated with beneficial effects on obesity and other metabolic disturbances, the attraction of using green tea extract as therapeutic agents in olanzapine induced weight gain and metabolic abnormalities is considerable.

2. Materials and methods

2.1. Chemicals

Olanzapine (Hetero drugs limited, India), Folin reagent (Fluka, Germany), sodium carbonate (Sigma, Germany) and galic Acid (Sigma, Germany) were obtained.

2.2. Preparation of green tea aqueous extracts (GTAE)

Green tea leaves were collected from North of Iran. The leaves were powdered using a milling machine. 100 g of green tea powder was macerated in 1000 mL of boiling water for 15 min. Then the extract was centrifuged at 3000 × *g* for 7 min after filtration and the supernatants were pooled and then lyophilized [25].

2.3. Determination of total polyphenol content of green tea extract

Total amount of phenolic compounds has been estimated by Folin-Ciocalteu reagent using the standard gallic acid calibration curve. The method was based on the reduction of phosphotungstic acid in alkaline solution to phosphotungstic blue [26]. Briefly, 0.5 mL of GTAE was mixed with 4.5 mL distilled water. Then 0.2 mL Folin-Ciocalteu phenol reagent and 0.5 mL of 20% sodium carbonate solution was added to the mixture, which was then shaken thoroughly and diluted to 10 mL by adding distilled water. The mixture was incubated for 60 min and blue color formed was measured at 725 nm using a spectrophotometer. A calibration curve of gallic acid was prepared and the results were expressed as mg gallic acid equivalents per gram of dried weight of the tea.

2.4. Animals

Adult male Wistar rats, weighing 230 ± 20 g, were provided by Animal House, School of Pharmacy, Mashhad University of Medical Sciences, Iran. Rats were housed singly in standard plastic cages in the colony room under 12-h light/dark cycle, 22 ± 2 °C and 40–50% humidity and had free access to food and water. This study was approved by the ethical committee (No:920801) of Mashhad University of Medical Sciences. Rats were randomly divided into eight groups. Control (distilled water, IP.), olanzapine (5 mg/kg/day, IP.), GTAE (25, 50 and 100 mg/kg/day, IP.) plus olanzapine, and GTAE (25, 50 and 100 mg/kg/day, IP.) groups. Treatments were continued for 11 days. The dose for olanzapine was determined from previous studies with some modifications [27]. Food consumption and body weights were measured daily. Daily food intake was calculated as the difference in the amount of food placed in the hopper and that remaining 24 h later, less the amount recovered as spillage. To evaluate the effect of olanzapine on motor activity and mean systolic blood pressure open field test [9] and non-invasive tail cuff method [28] were used respectively at the end of experiment. After 11 days, all rats were killed by decapitation, and trunk blood collected and serum was separated. Total cholesterol, LDL-C, HDL-C, TG and glucose levels were determined using enzymatic kits. Serum leptin level (Leptin Rat ELISA Kit; ab100773, United States) was also measured at the end of experiment.

2.5. Statistical analysis

Data are expressed as mean ± SEM. One way and two-way ANOVA followed by Tukey–Kramer and Bonferroni post hoc tests, respectively, were performed to compare means. P values less than 0.05 were considered as significant.

3. Results

3.1. Total polyphenol content of green tea

The total phenolic content was 50 mg/g of dry weight of extract, expressed as gallic acid equivalents.

3.2. Body weight

In male Wistar rats, olanzapine treatment induced significant weight gain. As shown in Fig. 1, olanzapine induced significant weight gain at the end of treatment (10.38% of body weight, 24 g) when compared to vehicle treatment (3.13% of body weight, 7 g).

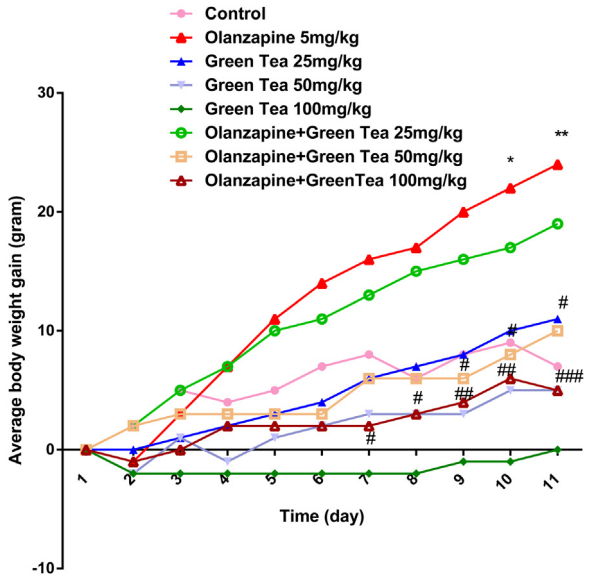

Fig. 1. Effect of olanzapine and green tea on body weight gain during treatment. *P < 0.05 and ** P < 0.01 vs control group, # P < 0.05, ## P < 0.01 and ### P < 0.001 vs olanzapine group. Two-way ANOVA followed by Bonferroni post-hoc test for multiple comparisons. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)