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The investigation of leptin and hypothalamic neuropeptides role in first attack psychotic male patients: Olanzapine monotherapy

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Summary The mechanism underlying the weight gain due to treatment with olanzapine and other second generation antipsychotics has not been fully understood. To examine olanzapine's weight gain effects, we accepted first attack psychotic patients with no medication (pre-treatment) (n = 22) and the healthy control group (n = 26) in this study. After patientś diagnosis, they were hospitalized and then treated for four weeks with olanzapine (post-treatment). We used case-control association design to test body mass index (BMI) and biochemical changes in each group. We also investigated peripheral leptin and neuropeptides/hormones namely, pro-opiomelanocortin (POMC), cocaine and amphetaime regulated transcript (CART), and neuropeptide Y (NPY) levels. These neuropeptides which are synthesized/secreted from arcuate nucleus of hypothalamus affect food intake and therefore, body weight. After 4 weeks of olanzapine treatment; BMI (body mass index), waist circumference, blood triglyceride, total cholesterol, and very low density lipoprotein (VLDL) levels were increased significantly in patients compared to their pre-treatment baseline. In pre-treatment, patients' NPY levels were significantly lower while α-MSH, the anorexigenic product of POMC levels were significantly higher vs. control. Both leptin and NPY levels were significantly increased in patients after the treatment but the NPY levels were also significantly lower in post-treatment vs. the control group. The CART levels did not change after the treatment. We may presume that the antagonist effect of olanzapine on the serotonin (5HT2CR and 5HT1BR) receptors of the arcuate hypothalamic neurons may be a basis for a deregulation of the neurohormones secretion.

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1. Introduction

The discovery of antipsychotics was a breakthrough in the treatment of schizophrenia and other psychotic disorders. Compared to the first generation antipsychotics, second generation antipsychotic drugs (SGAs) are superior in ameliorating negative symptoms and cognitive function deficits in schizophrenia patients (Wagner et al., 2005; Purdon et al., 2001). SGAs rarely result in extrapyramidal effects such as dystonia, Parkinsonism and akathisia but commonly cause weight gain and metabolic syndrome which create serious contradiction to clinical use of these drugs (Allison et al., 1999; Goldstein, 2000). The weight gain caused by SGAs leads not only to diminished commitment to the treatment but also creates medical complications such as hypertension, type II diabetes, coronary artery diseases, stroke, dislipidemia and respiratory problems (Parsons et al., 2009; Kirk et al., 2004). Therefore, the mechanism underlying the weight gain due to SGAs needs to be investigated (Wagner et al., 2005; Purdon et al., 2001; Kroeze et al., 2003; Yazici and Yazici, 2008). It is now known that young patients with normal BMI values (BMI = 20—25) and non-Caucasian respond well to the SGA treatment but exhibit an increase in their body weight in the first few weeks of the treatment (Sengul and Herken, 2009; Sengul et al., 2010; Reynolds and Kirk, 2010; Jin et al., 2008; Goldstein, 2000). Among SGAs, olanzapine is reported to have the greatest effects on weight gain (De Hert et al., 2011; Tandon, 2002). Parsons et al. (2009) indicated that 57% of the patients treated with olanzapine gain more than 7% of their initial weight at the end of one year (Parsons et al., 2009). Olanzapine have antagonistic effects on several neurotransmitter receptors specifically for serotonin (5-HT_2) and dopamine (D2) and lower affinities for M1, H1, 5-HT2c, 5-HT3, 5-HT6, α-1, α-2 and D4 (Bhana et al., 2001; Tandon, 2002).

Recently, weight gain due to olanzapine and other SGAs have been studied intensively but the exact mechanism remains to be elucidated. The weight gain mechanism/s of SGAs may also be related to their receptor binding profiles which also need to be clarified (Kroeze et al., 2003; Reynolds and Kirk, 2010; Jin et al., 2008). Although the energy balance and body weight regulation mechanisms are under the control of many systems in humans (Karen et al., 2006; Jequier, 2002), they are mainly controlled by the arcuate nucleus of hypothalamus in the brain. Food intake is negatively controlled by the hypothalamic anorexigenic neurohormones which include pro-opiomelanocortin (POMC) along with the cocaine and amphetamine regulated transcript (CART) and positively controlled by the hypothalamic orexigenic peptides, neuropeptide Y (NPY) and agouti related transcript (AgRP) (Konturek et al., 2005). The synthesis and secretion of these neurohormones are modulated by pancreatic insulin and the adipose tissue derived hormone leptin (Beck, 2000; Schwartz et al., 1992a,b; Schwartz et al., 1992a,b; Benoit et al., 2002; Air et al., 2002). At satiety leptin, like insulin, passes the blood—brain—barrier (BBB) and binds to its receptors (leptA and leptB) leading to a reduction of orexigenic peptides, NPY and AgRP while inducing synthesis of the anorexigenic peptides POMC and CART (Jequier, 2002). It has been speculated that olanzapine itself causes a disruption in the neurons regulating the eating mechanisms and thus leads to weight gain (Jin et al., 2008; Parsons et al., 2009; Schwartz et al., 1992a,b) by affecting the serotonergic and GABAergic receptors found on those neurons (Jin et al., 2008; Schwartz et al., 1992a,b).

In this study, the weight gain development in the first attack psychotic disorder patients who were treated for 4 weeks with olanzapine was investigated. The objective of this study was to determine the change of plasma lipid profile and arcuate nucleus neurohormone levels in the study group. There are several neuropeptides/hormones that affect body weight and appetite regulation peripherally such as peptide YY (PYY), ghreline, adiponection, resistin (Gail et al., 2004), glucagon like peptide-1 (GLP-1) (Blundell and Finlayson, 2004) and endocannabinoids (Chen et al., 2004); yet, we were interested in neurohormones that are expressed in the CNS since olanzapine exerts its effects centrally. Since NPY, α-MSH, the anorexigenic product of POMC may reflect hypothalamic activity; we analyzed plasma NPY and α-MSH along with CART and leptin concentrations. Due to the antagonistic effect of olanzapine on the $5HT_{2C}$ receptors, POMC and NPY production may be affected, hence the body weight; therefore, we hypothesized that circulating levels of leptin, NPY and α-MSH may significantly change with the drug treatment even in a short-time usage.

2. Materials and methods

2.1. Study group

The study group was consisted of a control group (n = 26) and a patient group (n = 22) whose blood samples were taken before (pre-treatment) and after (post-treatment) the treatment. Young male patients, mean age 21.46 $\pm$ 1.1, who had applied to Gulhane Medical School (GMS), Ankara, Turkey and diagnosed as having the first attack psychotic disorder were included in the study and immediately hospitalized for 4 weeks. Subjects included in the study were not using any antipsychotics or drugs leading to the metabolic side effects at least for one year and had no co-morbid psychiatric disorder history. The severity and change of psychotic symptoms were analyzed by Scale for Assessment of Negative Symptoms (SANS) Scale for Assessment of Positive Symptoms (SAPS) and Brief Psychiatric Rating Scale (BPRS). After the patients' diagnosis, their height and weight were documented and blood samples were collected for both biochemical and hormone tests; which created data of pre-treatment. Patients received an average calorie value of 2500 calorie/day from hospital meals; however they were not prevented from obtaining extra food from the hospital facilities. The patients had claimed hyperphagic behavior, which was increase in their appetite and craving for food even they were full, as observed by the clinicians in their daily psychiatric examination. During their hospitalization, they received daily antipsychotic treatment, olanzapine. At the beginning of the study, olanzapine was administered orally at a dose of 5—10 mg/day and the dose change was applied according to the response of the patient. The final dose was 10—20 mg/day, with the mean value of 12.08 $\pm$ 3.8 mg/day. At the end of the 4th week, the weights of the patients were again measured and blood samples were collected into EDTA tubes for the measurements; which created data of post-treatment. The control group was consisted of 26 healthy