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Effects of antidepressant treatment and of gender on serum leptin levels in patients with major depression

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Abstract

Leptin is a product of the obese gene and plays an important role in the regulation of body weight and food intake. Weight and appetite are frequently altered in depression. So far, inconsistent results have been reported in terms of leptin levels in depression. Therefore, the authors investigated serum leptin levels in patients with depression and in healthy controls, and whether there was any alteration throughout antidepressant treatment. Female patients showed significantly higher leptin levels than those of the control females both before and after the response to antidepressant treatment, whereas no difference was found between the male patients and the male controls. The improvement from depression with antidepressant treatment caused a further elevation on the leptin levels, in both female and male patients. These findings confirm an increase in leptin levels in depressive patients and presence of a sexual dimorphism. Moreover, clinical response to antidepressant treatment seems to have an additional increasing effect on leptin levels.

Keywords: Antidepressant treatment; Gender; Leptin; Major depression

1. Introduction

Leptin is a protein synthesised in the adipose tissue and is the product of obese (*ob*) gene. Studies show that leptin levels can be predicted with four independent parameters: body mass index, percent body fat, gender and glycerol concentration in blood (Hennessey, 2003). Leptin is believed to be a messenger from adipose tissue to the brain, which acts by binding to specific receptors in the hypothalamus, and decreases food intake and increases energy expenditure (Jequier, 2002). It exerts its anorexigenic effects via activation of several neuroendocrine systems, including the hypothalamic–pituitary–adrenal axis (Ahima et al., 2000), or via inhibition of some hypothalamic neuropeptides such as neuropeptide Y (Stephens et al., 1995; Hennessey, 2003).

Since appetite is affected in psychiatric diseases in general, leptin has been investigated in psychiatric illnesses in recent years. Leptin levels have been found to be altered in patients with depression (Antonijevic et al., 1998; Kraus et al., 2001), bipolar disorder (Atmaca et al., 2002a), and suicide attempt (Atmaca et al., 2002b).

Interactions between leptin and serotonergic system (Leibowitz and Alexander, 1998; Yamada et al., 1999), glucocorticoids (Bjorntorp, 2001), NPY (Stephens et al., 1995), and cytokines (Hosoi et al., 2003), all of which are suggested to be involved in the pathophysiology of depression, have been reported. Since weight loss and reduced appetite are typical symptoms of depression, leptin

Abbreviations: BMI, body mass index; CRH, corticotropin releasing hormone; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; MADRS, Montgomery–Asberg Depression Rating Scale; NPY, neuropeptide Y.

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may show some alterations in depression, which may be in some way related to the endocrinologic dysregulations in the disorder. In depressed patients, the results of the studies concerning leptin levels have so far been inconsistent. Unaltered (Deuschle et al., 1996), increased (Antonijevic et al., 1998), decreased (Kraus et al., 2001) or increased only in women (Rubin et al., 2002) leptin levels have been reported in depressed patients. Moreover, it is not known how antidepressant treatment affects leptin levels in depression because there are few studies on this issue reporting inconsistent results. A slight rise in leptin levels with mirtazapine (Kraus et al., 2002), no effect with venlafaxine, paroxetine or tricyclic agents (Kraus et al., 2002; Hinze-Selch et al., 2000), or a decrease with short-term fluoxetine (Dryden et al., 1999) have been reported. Thus, the aim of the present study was to investigate leptin levels in depressive patients and whether antidepressant treatment has any effect on the levels of this protein.

2. Methods

2.1. Subjects

Thirty-six inpatients who fully met the fourth Diagnostic and Statistical Manual of Mental Disorders criteria for major depressive disorder (recurrent) (DSM-IV; American Psychiatric Association, 1994) and who were all reported to have a decrease in appetite during the present depressive episode were included in the study (mean age±SD: 39.81±11.15, range: 18–55). Two independent specialists in Psychiatry (EE, SS) diagnosed the patients. They were selected from those who were refereed to the inpatient setting from the psychiatric outpatient clinic. The patients had been drug-free for at least 2 weeks. Exclusion criteria for patients were: having taken electroconvulsive therapy or lithium within the previous 6 months, having a physical or psychiatric disease other than depression as judged from their clinical and biochemical examinations, having alcohol or drug abuse, or endocrine disorder history, being above or below 15% of their ideal body weight (i.e., BMI is 20–25), and taking oral contraceptives for female patients. The severity of clinical symptomatology was assessed by Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979), and all patients had 25 or more scores in MADRS before the treatment. The patients were treated by various antidepressant drugs in standard antidepressant doses for 6 to 10 weeks (5 of them were treated with amitriptyline, 15 with venlafaxine, 7 with paroxetine, and 9 with fluoxetine) in the psychiatric inpatient clinic by the two of the authors (EE, SO), and a decrease of more than 50% in MADRS scores was accepted as the response to the treatment. They remained hospitalised for the full duration of the study and the same authors made the follow-up examinations (EE, SO). The patients did not take any additional drug or non-drug therapies such as physiotherapy or sport, which may have an influence on leptin or on body weight. Thirty-two of the patients responded to antidepressant treatment and only those who responded to the treatment were taken into account in the statistical analyses.

Twenty-three physically and mentally healthy subjects who were recruited from volunteers and hospital staff members composed the control group (mean age±SD: 36.65±10.78, range: 18–55). The same specialists examined them.

This study was carried out in Psychiatry Department of Erciyes University School of Medicine and was approved by the local Ethics Committee. Written informed consent was obtained from each patient after the description of the study.

2.2. Procedures

The BMI was calculated by dividing the weight (kilogram) by the squared height (meter). Serum levels of leptin were measured before the initiation of the treatment in all patients, and after the clinical response to the treatment in those who responded to the treatment, and only once in the control subjects. Blood samples for leptin measurement were taken with a catheter inserted into antecubital vein at 08:00 after an overnight fast. Separated serum was stored at −70 °C until analysed. Serum leptin levels were determined by using immunoradiometric assay kits (Diagnostic Systems Laboratories, INC, USA). The sensitivity was 0.10 ng/ml and the intra- and inter-assay coefficients of variation were 4.9% and 5.3%, respectively.

2.3. Statistical analysis

The distributions of the all variables were checked by Kolmogorov–Smirnov test and all showed normal distribution. Ages and BMIs of the patients and those of the controls were compared by using *t*-test for independent groups. Two-way ANCOVA was performed in order to compare the baseline leptin levels of the patients and those of the controls and to investigate the gender effect on the leptin levels by taking the presence of disorder and gender as between-subject factors, and age and BMI as covariates. Since a considerable effect of gender on the leptin levels was observed, the differences between the patients and the controls were separately investigated in women and men by ANCOVA, taking the leptin levels as dependent factor, the presence of disorder as fixed factor and the age and BMI as covariates. The comparison of the leptin levels of all the patients before the treatment and after the clinical response was carried out by repeated measures ANCOVA (gender×time) followed by Greenhouse–Geisser correction, controlling for age and BMI. Pearson's correlation test was carried out to seek the relation between BMI and leptin levels, and partial correlation test was performed in assessing the relationships among the age, MADRS score