Psychiatry and Clinical Neurosciences (2005), **59**, 736–738

Short Communication

High serum leptin levels in depressive disorders with atypical features

OMER GECICI, MD,[1] MURAT KULOGLU, MD,[2] MURAD ATMACA, MD,[2] A. ERTAN TEZCAN, MD,[2] HIKMET TUNCKOL, MD,[2] H. MURAT EMÜL, MD[1] AND BILAL USTUNDAG, MD[3]

[1]*Department of Psychiatry, Medical Faculty, Kocatepe University, Afyon,* [2]*Department of Psychiatry and* [3]*Biochemistry, Medical Faculty, Firat University, Elazig, Turkey*

Abstract Leptin is thought to be related to vegetative symptoms of depression such as alterations in food intake and weight. Fifty-seven drug-free patients and 26 healthy controls were enrolled in this study. We have found that the serum leptin levels were higher in patients with atypical depressive disorder than in controls, but not in patients with nonatypical depressive disorder, however, body mass index, age, and gender were not significantly different between these groups. Probably, these findings seem to be associated with some features of the atypical depressive disorders such as weight gain, a result of hyperphagia.

Key words atypical feature, body mass index, depression, leptin, weight gain.

INTRODUCTION

Leptin is an adiposity hormone that regulates food intake and energy balance, provides information on the amount of body fat to hypothalamus, as the product of the ob gene, and was discovered by Zhang *et al*.[1] Murck reported that a decrease in the hypothalamus–pituitary–adrenocortical (HPA) axis activity seems to exist in atypical depression,[2] although hyperactivity of HPA axis has been reported in 30–50% of patients with depressive disorders.[3] Leptin exerts its central nervous system anorexigenic effects through several neuroendocrine systems, including the HPA axis.[4] Some of the activities of neuropeptide-Y (NPY) having anxiolytic feature could be antagonized by leptin.[5] This reflects probable anxiogenic effect of leptin. Likewise leptin is thought to play an important role in symptoms of depression such as change of food intake and weight.[6] Depression is one of the most prevalent reasons of weight loss. However atypical depression refers to fatigue superimposed on history of somatic anxiety and phobias, together with reverse vegetative signs (mood worsening in the evening, hypersomnia, tendency to oversleep or overeat).

To explore pathophysiology of the food intake and weight changes in depression, we decided to measure body mass index (BMI), leptin, insulin, cortisol and growth hormone (GH) levels, and we hypothesized that the patients with atypical depressive disorder might have higher serum leptin levels than healthy controls.

MATERIALS AND METHODS

The study included 26 healthy controls and 57 drug-free outpatients who were divided into two groups: depressive disorder with (ADD) or without (DD-NA) the atypical features. The criteria for ADD were mood reactivity and two (or more) of the following features, present for most of the time, for at least 2 weeks: significant weight gain or increased appetite, hypersomnia, leaden paralysis and long-standing pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment. All patients were evaluated by a semistructured questionnaire form and Hamilton Depression Rating Scale (HDRS). All subjects had been thoroughly informed about the research details and written informed consent to participate in the study was obtained from the subjects.

Correspondence address: Omer Gecici, MD, Afyon Kocatepe Universitesi, Ahmet Necdet Sezer Uygulama ve Arastirma Hastanesi, Psikiyatri Klinigi (Pembe Hastane), Afyon, Turkey.

Email: drogecici@yahoo.com or ogecici@aku.edu.tr

Received 8 November 2004; revised 25 April 2005; accepted 22 May 2005.

The research protocol was approved by the Local Ethics Committee. Exclusion criteria were presence of history of severe physical illness such as hypertension, diabetes, or other endocrinopathy; abnormal physical or laboratory findings; a history of alcohol and substance abuse or dependence; a previous history of cholesterol lowering treatment.

After fasting overnight, venous blood samples were drawn from all patients and controls, from the antecubital vein in the morning between 08.00 and 09.00 hours. The samples were immediately centrifuged and stored at –25°C until assayed for leptin. The leptin levels were measured using the ELISA kit (Cayman Chemical Co., Ann Arbor, MI, USA). Serum insulin, GH and cortisol levels were assayed in the Immulite Immunoanalyzer using DPC kits (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistical analysis was performed using the statistical package for social sciences (SPSS/PC 9.05 version, 1998; SPSS Inc., Chicago, IL, USA). One-way ANOVA post-hoc Tukey HSD test and Student's *t*-test were used to compare the mean levels of nominal parameters. We then used the General Linear Model command of SPSS when controlling for covariates. The χ^2 test was used to compare the sex between groups. Correlation analysis was performed by Pearson's correlation test. Differences were considered significant at $P < 0.05$ for all these tests.

RESULTS

The patients and controls did not differ with respect to age, sex and BMI. There was no significant difference among the patient groups for HDRS scores. In the ADD group, mean serum leptin level was significantly higher than in the control group (respectively, 16.57 ± 12.66 ng/mL; 9.52 ± 7.69 ng/mL, $P = 0.037$). By contrast there was no significant difference among leptin levels between ADD, DD-NA (11.51 ± 9.45 ng/mL), and DD-NA, controls (respectively, $P = 0.15$, $P = 0.74$). Due to well-known gender and BMI differences in leptin secretion, we also found a significant difference in the serum leptin levels among ADD, DD-NA and control groups with gender and BMI as covariates ($F = 80.48$, $P = 0.000$; $F = 38.40$, $P = 0.000$, respectively). There was no significant difference among all groups for the mean serum insulin, GH and cortisol levels (Table 1).

There was a positive correlation between leptin and BMI for ADD, DD-NA and control groups ($P = 0.000$, $P = 0.022$, $P = 0.001$, respectively). Likewise, serum leptin levels showed a positive correlation in ADD with insulin levels ($P = 0.027$); and a positive correlation with GH and insulin levels and a negative correlation with HDRS scores in DD-NA ($P = 0.047$, $P = 0.045$, $P = 0.029$, respectively). No significant correlation was found between serum leptin levels and cortisol or age for all groups.

DISCUSSION

To our knowledge, this is the first study on leptin levels in depressive disorder with atypical features in which the major finding was higher serum leptin levels in patients with ADD but not in controls. However, in DD-NA we have found no significant difference for serum leptin levels compared with control group. Kraus *et al*. have demonstrated that plasma leptin levels were significantly lower in both female and male depressive patients than controls.[6] Likewise in our pre-

Table 1. Comparison of general characteristics and biochemical data in patient and control groups

	I-DD-NA ($n = 31$)	II-ADD ($n = 26$)	III-Controls ($n = 26$)	General statistical analysis
Age (years)†	36.74 ± 10.17	34.96 ± 8.46	36.38 ± 8.89	$F = 0.283$, d.f. = 2, $P = 0.76$
Sex (F/M)‡	20/11	16/10	16/10	$\chi^2 = 0.074$, d.f. = 2, $P = 0.96$
Hamilton Depression Rating Scale§	25.61 ± 4.64	24.27 ± 4.35	–	$t = 1.120$, $P = 0.27$
Body mass index†	24.41 ± 3.43	26.36 ± 4.17	25.61 ± 3.50	$F = 1.94$, d.f. = 2, $P = 0.14$
Leptin†	11.51 ± 9.45	16.57 ± 12.66	9.52 ± 7.69	$F = 3.39$, d.f. = 2, $P = 0.04$*
Insulin†	8.05 ± 3.67	8.12 ± 3.51	7.63 ± 2.67	$F = 0.16$, d.f. = 2, $P = 0.85$
Growth hormone†	0.44 ± 0.76	0.54 ± 0.75	0.64 ± 0.86	$F = 0.50$, d.f. = 2, $P = 0.61$
Cortisol†	12.25 ± 4.23	12.43 ± 4.14	10.90 ± 4.41	$F = 1.02$, d.f. = 2, $P = 0.37$

*$P < 0.05$

†One-way ANOVA post hoc Tukey HSD test was used.

‡The χ^2 test was used.

§Student's *t*-test was used.

ADD, depressive disorder with atypical features; DD-NA, depressive disorder without atypical features.

vious study[7] we have found that leptin levels did not differ in depressive patients; supporting results of Deuschle *et al*.[3]

It has been reported that leptin administration reduced food intake and weight,[5] suggesting its role on weight regulation. One of the physiologic roles of leptin is to limit food intake and leptin deficiency leads to hyperphagia. In contrast, it has also induced hypophagia when administered to lean mice.[8] The weight gain induced by atypical antipsychotics, clozapine and olanzapine, has been reported to be associated with an increase in leptin levels.[9] In addition, it is well known that leptin shows a positive correlation with BMI and percentage body fat. In this study, we also found a positive correlation between leptin and BMI in both patients and control groups. The high serum leptin level in ADD is thought to be related to primarily weight gain rather than increased food intake, and it seems to be a result of weight gain, not a cause of hyperphagia and weight gain. This finding is supported by clinical observations that atypical depression increases the appetite in terms of gaining fat and carbohydrate intake but not protein, which leads to increase fat body mass.

Contrary to typically depression, in ADD with hypersomnia and hyperphagia plasma cortisol in the morning has been reported to have no change.[10] In this study, we also found no difference in serum cortisol levels among groups. However, delayed and reduced adrenocorticotropic hormone response to corticotropin-releasing hormone (CRH) despite normal cortisol has been reported in some forms of ADD.[11] Similarly in a study examining cerebrospinal fluid (CSF)-CRH levels in patients with atypical features, a decrease in CSF-CRH compared with controls has been reported.[12] We can conclude that despite normal plasma cortisol levels in the morning, a decrease in CRH-activity may be suggested to be associated with clinical features of ADD. In this study we have also evaluated serum GH and insulin levels in patients with ADD, and found no difference among groups.

Several limitations should be taken into consideration when interpreting these results. First, leptin secretion has diurnal variation, but the leptin level was measured only once. However all samples were obtained between 08.00 and 09.00 hours after a 12-h fasting. Another limitation of this study was that we could not assay the correlation between leptin levels and features of depression. Likewise, the female and male individuals were not divided into different groups, but matched for all groups.

In conclusion, among sex-, age- and BMI-matched groups, patients with ADD seem to have increased serum leptin levels, but not those with DD-NA. Probably this finding is primarily associated with weight gain, a feature of ADD. However, this is obviously only a suggestion and our results need to be confirmed by more comprehensive and detailed further studies to decipher the roles of leptin in atypical features.

REFERENCES

1. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; **372**: 425–432.
2. Murck H. Atypical depression spectrum disorder–neurobiology and treatment. *Acta Neuropsychiatr.* 2003; **15**: 227–241.
3. Deuschle M, Blum WF, Englaro P *et al.* Plasma leptin in depressed patients and healthy controls. *Horm. Metab. Res.* 1996; **28**: 714–717.
4. Uehara Y, Shimizu H, Ohtani K, Sato N, Mori M. Hypothalamic corticotropin-releasing hormone is a mediator of the anorexigenic effect of leptin. *Diabetes* 1998; **47**: 890–893.
5. Suomalainen M, Mannistö PT. Lack of effect of leptin on the behavior of mice predicting the level of anxiety and depression. *Pharmacol. Toxicol.* 1998; **83**: 139–142.
6. Kraus T, Haack M, Schuld A, Hinze-Selch D, Pollmacher T. Low leptin levels but normal body mass indices in patients with depression or schizophrenia. *Neuroendocrinology* 2001; **73**: 243–247.
7. Atmaca M, Kuloglu M, Tezcan E, Gecici O, Ustundag B. Serum cholesterol and leptin levels in patients with borderline personality disorder. *Neuropsychobiology* 2002; **45**: 167–171.
8. Mantzoros CS. The role of leptin in human obesity and disease: a review of current evidence. *Ann. Intern. Med.* 1999; **130**: 671.
9. Kraus T, Haack M, Schuld A *et al.* Body weight and leptin plasma levels during treatment with antipsychotic drugs. *Am. J. Psychiatry* 1999; **156**: 312–314.
10. Casper RC, Kocsis J, Dysken M *et al.* Cortisol measures in primary major depressive disorder with hypersomnia or appetite increase. *J. Affect. Disord.* 1988; **15**: 131–140.
11. Joseph-Vanderpool JR, Rosenthal NE, Chrousos GP *et al.* Abnormal pituitary-adrenal responses to corticotropin-releasing hormone in patients with seasonal affective disorder: clinical and pathophysiological implications. *J. Clin. Endocrinol. Metab.* 1991; **72**: 1382–1387.
12. Geracioti TDJ, Loosen PT, Orth DN. Low cerebrospinal fluid corticotropin-releasing hormone concentrations in eucortisolemic depression. *Biol. Psychiatry* 1997; **42**: 165–174.