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Blood levels of agouti-related peptide (AgRP), obestatin, corticosteroid-binding globulin (CBG), and cortisol in patients with bipolar disorder (BD): a case–control study

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ABSTRACT

OBJECTIVES: Bipolar disorder (BD) is a chronic psychiatric disorder with a high prevalence of obesity. There are a number of hypotheses regarding the association between obesity and BD. One involves common neurobiological abnormalities, such as dysfunction in the hypothalamic pituitary adrenal axis and changes in secretions of orexigenic and anorectic peptides. The purpose of this study was to evaluate the blood levels of agouti-related peptide (AgRP), obestatin, cortisol, and corticosteroid-binding globulin (CBG) and metabolic parameters in patients with euthymic BD, and to compare these to those of healthy controls.

METHODS: Twenty-nine outpatients with BD type I admitted to the psychiatric clinic were consecutively enrolled and compared with 25 sex- and body mass index (BMI)-matched controls.

RESULTS: There was a significant difference in AgRP, cortisol, and CBG levels between patients and the controls ($p = .005, .021, \text{ and } .034$, respectively). AgRP and CBG did not correlate with any parameter in BD patients, but cortisol correlated with BMI.

CONCLUSIONS: We conclude that BD patients have higher levels of AgRP, cortisol, and CBG than healthy controls with similar BMIs. This may represent a new insight into the neurobiology of BD.

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KEYWORDS

Bipolar disorder; agouti-related protein; hydrocortisone; corticosteroid-binding globulin; obesity

Introduction

Bipolar disorder (BD) is a widespread, chronic psychiatric condition that can result in high levels of dysfunction [1]. It is associated with cardio- and cerebrovascular disease, and with metabolic and endocrine disorders [2]. Obesity, a metabolic disorder, is reported to be significantly more prevalent in patients with BD than in subjects without BD [3]. Association of BD with obesity includes several convergent findings. Explanations for this association are several and includes dietary and lifestyle factors, treatment variables, medical disorders, and socio-demographic variables [4,5]. One study suggested that disinhibition and perception of hunger may be linked to the disproportionately high rate of obesity in BD [6]. Another opinion discriminates obesity from metabolic syndrome (MeS) in BD [7]. In this case, MeS is supposed to result from adipokines levels independently from obesity [8]. Biological explanations are also present. Human obesity, especially abdominal obesity, is accompanied by elevated glucocorticoids and hyperactivation of the hypothalamic pituitary adrenal (HPA)

axis [9]. Elevation in cortisol levels, when exposed to stressors, promotes increased food intake and leads to obesity. In addition, diet-induced obesity is associated with insulin resistance and impaired feedback control of HPA axis [10].

Agouti-related peptide (AgRP), which is synthesized in the arcuate nucleus of the hypothalamus, is a powerful orexigenic peptide that increases food intake and has been considered a gene potentially involved in human obesity [11]. The role of AgRP in schizophrenia obesity treated with antipsychotics has been investigated in a few studies [12,13]. However, its role in BD obesity has not previously been investigated but it is implicated to have a role in impaired energy homeostasis during manic episode [14]. Since during manic episode AgRP levels are reported to be higher than euthymic patients and controls, AgRP is suggested to be a state marker for manic episodes. AgRP's orexigenic effect derives primarily from opposing the anorexic actions of pro-opiomelanocortin [13,15,16]. It has long-lasting orexigenic properties [17]. It increases appetite and reduces metabolism, induces obesity by

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antagonism of the melanocortin receptors, and stimulates adrenocorticotrophic hormone and cortisol [17,18]. Glucocorticoids, on the other hand, affect feeding behaviour, mainly via the modulation of orexigenic and anorexigenic neuropeptides [19]. Obestatin is a peptide derived from the ghrelin gene has still unclear metabolic actions. But it is known that obestatin levels are decreased in obesity and seem to be negatively correlated with body mass index (BMI) [20]. Obestatin levels have not been studied in BD, but recently ghrelin which is encoded from the same gene with obestatin was found higher in euthymic period of BD than the manic episode [8].

To the best of our knowledge, there are studies present that relate adipokine levels with BD, but only one study is present with regard to AgRP levels in BD [14]. This study was designed to investigate various socio-demographic characteristics and biochemical parameters including serum levels of AgRP, obestatin, CBG, and total cortisol in patients with BD. Additionally, the results were compared to those of healthy controls with similar BMIs in order to contribute to the understanding of the neurobiology of BD that can overlap with obesity.

Material and methods

Subjects

Twenty-nine patients with BD type I admitted to the outpatient psychiatric clinic of the Karadeniz Technical University Faculty of Medicine were consecutively enrolled if they had been in the euthymic period for at least two months. Euthymia was defined as scoring 12 or less on the Young Mania Rating Scale (YMRS), less than 7 on the Hamilton Depression Rating Scale (HDRS), and less than 12 on the Montgomery–Asberg Depression Rating Scale (MADRS) using the structured clinical interview for DSM-IV (SCID) [21–28]. Patients are classified as chronic and non-chronic user of antipsychotic. Chronic antipsychotic or mood stabilizer use was defined as the cases including taking the same drug for at least one year. Bipolarity Index (BI) is a five-item clinical scale rated by clinicians. The cardinal features of the disorder across five domains including signs and symptoms, age of onset, course of illness, response to treatment, and family were rated. Each of the five scales contribute up to 20 points with a maximum score of 100. Twenty-nine sex- and BMI-matched volunteers were included as controls. The control group was enrolled among hospital staff, including secretaries, nurses, and support personnel.

Approval for the study protocol was given by the Local Ethics Committee of the Karadeniz Technical University Medical School at April 25, 2013, with a decision number 17522305\282. All subjects gave

informed consent, and patient anonymity was preserved. Financial support was granted by the institutional Research Projects Coordination Unit of the Karadeniz Technical University at March 11, 2014, with the project code 9850.

Determination of the biochemical parameters

Sampling

Blood samples were collected without any anticoagulant for serum and with ethylenediaminetetraacetic acid (EDTA)–anticoagulant tubes following 12 h overnight fasting, at 8:00–09:00 am. Samples were centrifuged at 3000 rpm for 10 min to obtain plasma and serum. The plasma and serum samples were then stored at -80°C until biochemical analyses.

Determination of the levels of glucose, insulin, and HOMAIR

Fasting serum glucose was measured using an enzymatic (glucose oxidase) colorimetric method, performed with an autoanalyzer (Beckman Coulter AU5800, Japan). Insulin levels were determined by the chemiluminescent immunometric method using an Immulite 2000 XPi autoanalyzer (USA). Homeostatic model assessment of insulin resistance (HOMAIR) was then calculated using the below formula:

$$\text{HOMA - IR} = \frac{\text{serum glucose}(\text{mg/dL}) \times \text{plasma insulin}(\mu\text{U/mL})}{405}.$$

Determination of human obestatin and AgRP

Human obestatin levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Wuhan EIAab Science Co. Ltd., China, Cat. No. E2039h, Lot No. 3E215C), and human AGRP using an ELISA kit (Wuhan EIAabScience Co. Ltd., China, Cat. No. E1302h, Lot No. 3E215C) according to the manufacturer's instructions. Absorbance of the samples was measured at 450 nm using a VERSA max tunable microplate reader (designed by Molecular Devices in California, USA). The results of both parameters were expressed in pg/L.

Determination of the free cortisol index (FCI)

Levels of human corticosteroid-binding globulin (CBG) were determined using an ELISA kit (Wuhan EIAabScience Co. Ltd., China, Cat. No. E0191h, Lot No. 3H055C), and human total cortisol using an ELISA kit (Labs™ Inc. Biotechnology, Canada, Cat. No. EN1007-1, Lot No. EN10011), according to the manufacturer's instructions. The absorbance of samples was measured at 450 nm using a VERSA max tunable microplate reader (designed by Molecular Devices in California, USA). The results for CBG were

calculated in nmol/L and for cortisol in µg/dL, and were then converted to nmol/L (1 µg/dL = 27.59 nmol/L). FCI was then calculated using the below formula:

$$\text{FCI} = \frac{\text{cortisol (nmol/L)}}{\text{CBG (nmol/L)}}.$$

Statistical analysis

Normality of the measured data was assessed using the Kolmogorov–Smirnov test. Comparison of quantitative data for patients and controls was performed using Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for data without normal distribution. Comparison of qualitative data was performed using the χ^2 test. Yates and/or Fisher corrections were not used in chi-square analyses. Two-tailed analysis was used to compare the data. Quantitative data were presented as mean \pm standard deviation and qualitative data as percentages. Significance was set at $p < .05$ with two-tailed analysis. Pearson's correlation coefficient was used to examine relations between variables. Age was regarded as a covariate. Once means had been corrected, the difference between patients and healthy controls was evaluated using analysis of covariance (ANCOVA).

Results

Twenty-nine patients with BD and 25 healthy subjects were enrolled. Mean BI of the BD patients was 78.00 ± 7.76 , and mean duration of the disease was 10.26 ± 6.25 years. Females comprised 66.7% ($n = 36$) of the entire sample and males 33.3% ($n = 18$). There were no significant differences between the groups in terms of sex or marital status. However, statistically significant differences were determined in mean age, education level, and employment status ($p = .015$, $p = .006$, and $p = .004$, respectively). Mean BMI of the patients was 28.61 ± 4.90 kg/m² compared to 27.89 ± 5.7 kg/m² in the control group. The difference was not significant. Patients with BD were between overweight and obese according to the WHO classification [29]. The rate of overweight in BD was 31% ($n = 9$) and the rate of obese patients was 37.9% ($n = 11$). There were also no significant differences in height or weight between the patient and control groups (Table 1). Of the patient group, 62.1% ($n = 18$) and 82.8% ($n = 24$) are on chronic treatment of mood stabilizer and antipsychotics respectively. Twenty-five (46.3%) patients were on both chronic antipsychotic and mood stabilizer treatment. The mean length of last treatment period was 48.14 ± 44.52 months (min: 3; max: 180 months). Due to wide range of treatment duration, the trimmed mean, median, and interquartile range were calculated and reported as 4.1, 36, and 45 months, respectively.

Table 1. Socio-demographic features of BD patients and control.

| | BD patients ($n = 29$) <i>n</i> (%) | Control ($n = 25$) <i>n</i> (%) | <i>p</i> -value |
|--------------------|--|--------------------------------------|-----------------|
| Mean age, years | 38.48 \pm 11.37 | 31.52 \pm 8.48 | .015 |
| Education, (years) | 10.21 \pm 3.24 | 13.04 \pm 4.09 | .006 |
| BMI | 28.61 \pm 4.90 | 27.89 \pm 5.73 | .620 |
| Sex | | | .629 |
| Male | 11 (62) | 7 (28) | |
| Female | 18 (38) | 18 (72) | |
| Marital status | | | .782 |
| Married | 20 (69) | 15 (60) | |
| Single | 9 (31) | 10 (40) | |
| Occupation | | | .004 |
| Employed | 11 (38) | 20 (80) | |
| Unemployed | 18 (62) | 5 (20) | |

Note: *p*-value, from ANOVA for age and education duration and from chi-square test for marital status and occupation, significant if < 0.05

AgRP, CBG, and cortisol levels were significantly higher in the patient group ($p = .005$, $p = .021$, and $p = .034$, respectively). The effect sizes of AgRP, CBG, and cortisol are 0.81, 0.67, and 0.62, respectively. However, there were no differences in the levels of obestatin, FCI, glucose, insulin, and HOMAIR between the two groups (Table 2). Coefficient of variation of obestatin, FCI, glucose, insulin, and HOMAIR was also demonstrated in Table 2. Since the mean age of the patient group was significantly higher than that of the healthy controls, ANCOVA was performed with the aim of eliminating the effect of age. After covariance analysis, significant differences in AgRP, cortisol, and CBG persisted. AgRP was significantly positively correlated with obestatin in the control group ($p = .0005$, $r = 0.75$), but not in the BD patients (Figure 1). Linearity was tested with linear regression analysis for the relationship between obestatin and AgRP levels suggesting for non-linearity in control group. The standardized coefficient beta was 0.752, *t* was 5.472, and $p \leq .001$. AgRP was not correlated with any parameters in the patient group. Cortisol was positively correlated with obestatin levels and BMI in the patient group, but not in the control group. CBG was positively correlated only with BMI in the control group and with none of the parameters in the patient group. In the patient group, FCI was negatively correlated with CBG, disease duration, and number of depressive episodes and

Table 2. Plasma levels of biochemical parameters.

| | BD patients ($n = 29$) | | Control ($n = 25$) | | <i>p</i> |
|---------------------------|-----------------------------|------|-------------------------|------|----------|
| | Mean \pm SD | CV | Mean \pm SD | CV | |
| Glucose (mg/dL) | 93 \pm 6 | 0.88 | 91 \pm 7 | 0.86 | .315 |
| Insulin (mU/mL) | 7.95 \pm 5.52 | 0.18 | 7.70 \pm 6.93 | 0.05 | .883 |
| HOMAIR | 1.88 \pm 1.40 | 0.15 | 1.74 \pm 1.61 | 0.04 | .744 |
| Cortisol (nmol/L) | 494 \pm 172 | 0.48 | 403 \pm 127 | 0.52 | .034 |
| CBG ^a (nmol/L) | 464 \pm 108 | 0.62 | 349 \pm 215 | 0.24 | .021 |
| FCI ^b | 1.18 \pm 0.70 | 0.26 | 4.52 \pm 8.60 | 0.31 | .597 |
| AgRP ^c | 359 \pm 224 | 0.23 | 181 \pm 224 | 0.11 | .005 |
| Obestatin | 64 \pm 62 | 0.01 | 48 \pm 63 | 0.14 | .352 |

^aCorticosteroid-binding globulin.

^bFree cortisol Index.

^cAgouti-related peptide.

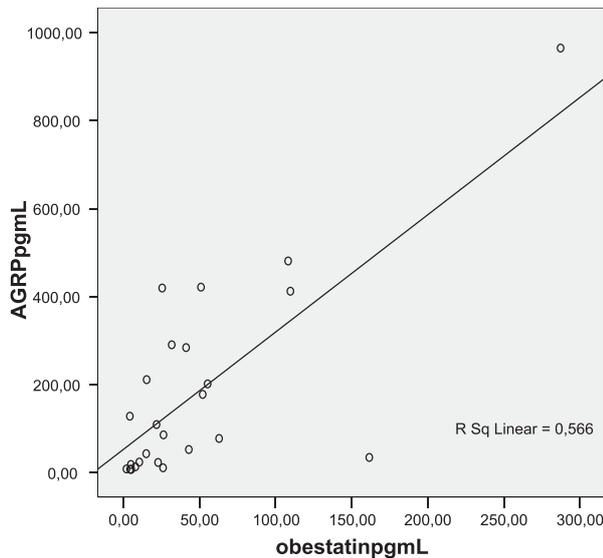


Figure 1. Correlation between AgRP and obestatin in control group

positively correlated with cortisol levels, while in the control group it was positively correlated with cortisol levels and negatively correlated with CBG, obestatin, and AgRP. BMI was positively correlated with duration of disease, glucose, insulin, and HOMAIR and negatively correlated with cortisol levels in the BD patients, and negatively correlated with CBG and positively correlated with insulin and HOMAIR in the control group.

When we compare the patients on chronic treatment of antipsychotic ($n = 18$) with the patients without chronic treatment of antipsychotic ($n = 11$), the levels of AgRP, CBG, cortisol, obestatin, FCI, glucose, insulin, and HOMAIR did not differ. But the patients with BD who were not on chronic treatment of antipsychotic ($n = 11$) had significantly higher AgRP and CBG than the healthy control ($p = .021$ and $p = .003$, respectively).

Discussion

This study was performed with overweight to obese patients with BD and healthy controls with similar socio-demographic variables to find out whether serum levels of AgRP, cortisol, or CBG differ between the patients and healthy controls. We have found significantly higher level of AgRP, cortisol, and CBG in BD patients. Although the patients were older than the controls, age did not affect AgRP, cortisol, or CBG. The control group had higher levels of education and employment. This might be explained by sampling method of the control group.

AgRP is a powerful orexigenic neuropeptide, elevation in which leads to hyperphagia and obesity [11], but its role in the development of obesity in BD is undefined. Parlak et al. reported a significant lower AgRP levels in manic patients, and linked it to

impaired homeostasis [14]. In addition to its orexigenic effect, it is defined as a powerful modulator of energy balance. In this study, there is a significant difference in serum levels of AgRP between patients with BD and healthy control which might indicate a modulator role of AgRP on energy balance in BD. The high level of AgRP in BD may be linked with one of the peripheral action which remains unresolved yet. Ilnytska and Argyropoulos presented a fresh idea concerning peripheral function of AgRP implying that AgRP levels do not always correlate with obesity [11]. In this study, AgRP levels do not correlate with the BMI and average of BMI did not differ between the two groups; so the higher level of AgRP may therefore be linked with higher energy expenditure of the BD patients other than orexigenic effect. This may be the reason for the difference in correlations of AgRP and obestatin between the patient and the control group, also related with the pathophysiology of BD. This may also give some clues about the physiological act of AgRP in BD patients, in which the higher level of AgRP might modulate disease-related food intake and regulate the energy balance. Although overweight or obesity is strongly associated with psychopharmacological treatments in bipolar patients in previous studies [30,4], the use of antipsychotics did not have any effect on blood levels of AgRP among patients in this study. This might be explained by documented data about indifference in AgRP levels between obese and non-obese schizophrenic patients [17,31]. In contrast to our results, Parlak et al. reported significant lower serum levels of AgRP in manic non-obese patients than euthymic and control group, and attributed it to impaired energy homeostasis [14]. The different results may be attributed to the weight status of the patients and actual period of the disease. In this study the sample includes overweight to obese euthymic BD patients distinct from previous study and the previous study excluded obese participants.

Since there is widespread evidence supporting a pathological predisposition to MeS in psychotic patients taking antipsychotic treatment in both humans and animal models, data concerning the co-occurrence of obesity or overweight in drug-naive patients may imply mediating factors rather than pharmacological causes of overweight in bipolar patients. Since Wysokiński et al. also could not describe any difference in AgRP levels between patients taking clozapine and healthy control group [17]. In this study, patients without chronic treatment for psychotropics had higher levels orexigenic peptide than healthy control; then AgRP can be a candidate for being a mediating factor for obesity and metabolic problems in BD patients independent from antipsychotic use. Since it may be demonstrated more reliably in a longitudinal studies, medications are supposed to influence the adipokine levels of BD in a follow-up study [32].

The higher level of AgRP in the patient group may also be related with its neuroendocrine role which is implicated in relation with neuroendocrine regulatory role other than orexigenic effect which acts in case of which higher food intake is essential [18]. A common neurobiological pathway between obesity and BD can be suggested since overlap of obesity and BD has many theoretical and clinical implications [33]. In a longitudinal study, adipokines are supposed to be potential mood-regulating molecules that represent a novel pathophysiological mechanism linking elevated BMI and mood disorders [32].

In this study, BD patients in the euthymic period had higher levels of cortisol and CBG than healthy controls. This may be related to HPA axis dysfunction which is reported to be a trait marker in BD patients [34,35]. High CBG and cortisol levels may result from feedback mechanism in the event of excess expression or from CBG release triggering compensatory activation of the HPA axis, and thus to high levels of adrenal cortisol production [36]. This effect is overtly manifested in patients with BD, reflecting chronic activation of the HPA axis. HPA axis activation might also be related to overweight or obesity of the patient group, because it is known that the glucocorticoid action has a central role in the development of obesity, as demonstrated in human and animal studies [37]. Obesity may therefore be linked with unidentified chronic low-grade inflammation and unique typical and atypical pathways contributing to the neurobiology of BD [38]. In this study, plasma levels of obestatin which is an anorectic peptide did not differ between the groups. Data concerning the physiology of obestatin are scarce, and the role of obestatin in pathophysiology of BD is obscure. It functions as an anorectic peptide hormone, plasma levels of which are significantly lower in obese patients. However, conflicting results which do not support the modulation of food intake or energy balance have been reported in recent studies [39–41]. Furthermore, obestatin correlated with cortisol levels in the patient group, but not in the control group. The data about obestatin relation with cortisol is still unclear but ghrelin to which obestatin is derived from increases and has opposite metabolic actions increase the release of a number of different systems including cortisol [42]. An opposite finding was cited in a study concerning the feeding behaviour of rats, which reported that obestatin does not modify the secretion of glucocorticoids [40]. So, further clinical and experimental studies are required to clarify the physiological effects of obestatin in BD patients.

There are some limitations to this study. The cross-sectional design hindered the exploration of impact of the biochemical parameters on the neurobiology of BD. Since in a longitudinal study adipokines are supposed to be a represent a pathophysiological link between

BMI and mood disorders [33], the relation between the parameters might be addressed further by longitudinal follow-up studies. BD patients exhibited increased obestatin, insulin, and glucose levels, but these differences did not achieve statistical significance. They may potentially be significant, however, in larger samples. We also analysed the blood levels of hypothalamic neuropeptides, instead of the levels in the hypothalamus, and this may represent another limitation. There is postulated hypothesis about the rate of obesity in different sexes, but there is no significant difference in sex distribution between the groups in this study, so we could not address the effect of sex, and this may be a limitation. It is known that the MeS is greater in BD patients taking antipsychotic medication and the adipokines levels are affected by antipsychotic doses [43]. Third limitation is about the issue of the lack of the effect of cumulative antipsychotic doses on parameters for this study; additionally we could not have pre-treatment levels of any parameter due to the cross-sectional design of the study. Another limitation is that we do not have any data regarding the life styles of the participants including eating or exercise habits since many lifestyle factors may increase the risk of MeS in BD [44]. Furthermore, we do not measure low-grade inflammation course which is known to interact with adipokines action, so this may be another confusing limitation. For overcoming the limitations, further studies with larger samples are required.

In conclusion, our results are consistent with the view that AgRP, obestatin, CBG, and cortisol may add a new perspective on the neurobiology of BD. Further studies are now required to confirm these findings.

Disclosure statement

No potential conflict of interest was reported by the authors.

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