DOI: 10.5455/bcp.20110627110925

Increased Plasma Nesfatin-1 Levels in Patients with Obsessive Compulsive Disorder

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ÖZET:

Obsessif kompulsif bozukluk hastalarında artmış plazma nesfatin-1 düzeyi

Amaç: Bu yazıda, obsesif kompulsif bozukluk (OKB) tanısı olan hastalarda ve sağlıklı kontrollerde plazma nesfatin-1 (bir tokluk peptidi) düzeylerinin tespit edilmesi ve karşılaştırılması amaçlanmıştır.

Yöntem: OKB tanısı olan 31 hastanın (18 kadın, 13 erkek) ve ağırlık, yaş ve cinsiyet açısından benzer nitelikte 28 sağlıklı bireyin (16 kadın, 12 erkek) plazma nesfatin-1 düzeyi ölçülmüştür. OKB hasta grubunda ve kontrol grubunda obsesyon ve kompulsiyonların şiddeti Yale-Brown Obsesyon Kompulsiyon Ölçeği (Y-BOKÖ) kullanılarak elde edilmiştir. Plazma nesfatin-1 düzeyi ölçümü için ELİSA yöntemi kullanılmıştır.

Bulgular: OKB tanısı olan hastalarda ve kontrol grubunda ortanca plazma nesfatin-1 düzeylerinin sırasıyla 4.61 ng/ml (min-max: 1.28-8.11) ve 2.0 ng/ml (min-max: 0.11-4.98) olduğu bulunmuştur. Gruplar arasında plazma nesfatin-1 düzeyi açısından gözlemlenen fark istatistiksel olarak anlamlı düzeydedir ($p<0.001$). Hem hasta grubunda hem de kontrol grubunda Y-BOCS skorları ve plazma nesfatin-1 düzeyleri arasında anlamlı bir korelasyon saptanmamıştır (sırasıyla $r=0.205$, $p=0.27$ ve $r=0.335$, $p=0.071$).

Sonuç: OKB tanısı olan hastalarda gözlenen plazma nesfatin-1 düzeyi yüksekliği, bu peptidin önceden bilinen anoreksijenik etkilerinin yanı sıra anksiyete durumlarında da potansiyel bir rolünün olabileceğini düşündürmektedir.

Anahtar sözcükler: Nesfatin-1, obsesif kompulsif bozukluk, anksiyete, tokluk peptidi, iştah

Klinik Psikofarmakoloji Bülteni 2012;22(1):5-9

ABSTRACT:

Increased plasma nesfatin-1 levels in patients with obsessive compulsive disorder

Objective: To determine and compare the plasma nesfatin-1 (a satiety peptide) levels of patients with obsessive compulsive disorder (OCD) and healthy control subjects.

Method: Plasma nesfatin-1 levels of 31 patients with OCD (18 females, 13 males) and 28 healthy control subjects (16 females and 12 males) similar to the study group in terms of weight, age, and gender were measured in this study. Severity of obsessions and compulsions both in OCD patients and control subjects were determined by using Yale-Brown Obsessive Compulsive Scale (Y-BOCS). ELISA method was used to measure plasma nesfatin-1 levels.

Results: Median plasma nesfatin-1 levels in patients with OCD and healthy control subjects were 4.61 ng/ml (min-max: 1.28-8.11) and 2.0 ng/ml (min-max: 0.11-4.98) respectively. The observed difference in plasma nesfatin-1 levels between two groups was statistically significant ($p<0.001$). No statistically significant correlation was observed between Y-BOCS scores and plasma nesfatin-1 levels either in the study group ($r=0.205$, $p=0.27$) or in the control group ($r=0.335$, $p=0.071$).

Conclusion: Increased plasma nesfatin-1 levels observed in patients with OCD suggest a potential role to nesfatin-1 in anxiety states besides its previosly known anorexigenic effects.

Key words: Nesfatin-1, obsessive compulsive disorder, anxiety, satiety peptide, appetite

Bulletin of Clinical Psychopharmacology 2012;22(1):5-9

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Gönderme tarihi / Date of submission: 24 Nisan 2011 / April 24, 2011

Kabul tarihi / Date of acceptance: 27 Haziran 2011 / June 27, 2011

Bağıntı beyanı:
Y.B., M.A., O.H.O., S.O., Y.C.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
Y.B., M.A., O.H.O., S.O., Y.C.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Altering of food intake is known to affect stress sensitivity of hypothalamo-pituitary-adrenal axis, as well (1,2). Irregularities in the process of food intake may lead to activation of stress-related systems and at the same time emotional changes can alter food intake (3-5). This may suggest some common mediators of both conditions. Supporting this suggestion some studies have shown that peptides like CRF, leptin, ghrelin, orexin, neuropeptide Y (NPY), melanocortin, and cholecystokinin regulate both appetite and affect and responses to stressful situations (4,6-12). As a consequence, one may think that some other peptides involved in regulation of appetite like nesfatin-1, may play role in regulation of affect and response to stressful situations, as well.

Nesfatin-1, a recently discovered satiety peptide, contains 82 amino acids and is derived from NEFA/nucleobindin-2 (NUCB2) (13). It was claimed to be extensively responsible for provision of appetite and

metabolic regulation in hypothalamus (13,14). Its intracerebroventricular administration was shown to reduce food intake, whereas antibody injection against it was related with increase in food consumption (13).

According to a recent study nesfatin-1 peptide may also play role in generation of anxiety and fear-related behavior besides its well-known action on regulation of food intake (15). In that study, Merali et al. (2008) showed that intracerebroventricular (ICV) nesfatin-1 injection to rats led to anxiety and fear-related behaviors. Thus, they concluded that nesfatin-1 might also play role in the process of emotional states like anxiety and stress. Two recent studies have shown increased levels of plasma nesfatin-1 in patients with major depression and panic disorder (16,17). However, these findings still need replication and most importantly need to be supported by studies on real patients with anxiety disorders.

In an attempt to fill this gap in the literature, we decided to investigate plasma nesfatin-1 (a satiety peptide) levels and its clinical and demographical correlates in patients with obsessive compulsive disorder (OCD), which possesses anxiety as one of its major components.

METHOD

A total of 33 patients (19 females, 14 males) diagnosed with OCD according to Diagnostic and Statistical Manual for Psychiatric Disorders – fourth version (DSM-IV) provided written informed consent and was included in the study. The OCD diagnosis was confirmed and depression diagnosis was excluded by a detailed psychiatric interview including anxiety disorders and depression sections of Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID). Two patients withdrew their informed consents at the day of blood analysis and were excluded from the study. The remaining 31 patients (18 females and 13 males) diagnosed only with OCD formed the study group. On the other hand, control group consisted of 28 healthy volunteers (16 females and 12 males), who were similar to the study group in terms of weight, BMI, age, and sex. In the control group the diagnoses of OCD and depression were excluded with a detailed psychiatric interview including anxiety disorders and depression sections of SCID. All participants included in the study were not currently under the effect of any medical treatment.

In addition to complete blood count and electrocardiogram, routine biochemical evaluations were conducted on all subjects. Any endocrine pathology, infectious disease, neoplasm, autoimmune disorder, gestation, obesity, abnormal lipid profile, history of alcohol or substance abuse or dependence, and presence of any co-morbid axis I disorder other than OCD were accepted as exclusion criteria. All female subjects reported that they were not mensturating when their bloods were collected to exclude possible confounding effects of hormonal changes during mensturation. Yale-Brown Obsession Compulsion Scale (Y-BOCS) was applied to all participants (18). The weight and height measurements and calculation of body mass indexes (BMI) of all subjects were done meticulously.

The blood samples for nesfatin-1 were drawn in the morning around 8 AM from a forearm vein of the participants at the end of an overnight fasting period of at least 8 hours. Tubes with 2 milliliters capacity and containing EDTA were used for collecting blood. Then the blood was carefully and immediately (in a few seconds) transferred from these tubes to centrifuge tubes which contain aprotinin (0.6 TIU/ml of blood) inside. Tubes were stored on ice immediately and gently rocked several times to inhibit the activity of proteinases until the centrifuge process. After the centrifuge process at 1,600 x g rate for 15 minutes at 4°C the plasma was obtained. The separated plasma was stored in -80°C freezer until the time of assay. Plasma nesfatin-1 levels were measured using a commercial ELISA kit (Uscn Life Science, Wuhan, P.R.China). Some previous studies in the literature have used ELISA method for measuring nesfatin-1 peptide level (19-20).

This study was approved by the local Ethics Committee of Gaziantep University and all participants gave written informed consent before their enrollment in the study.

Statistics

One-sample Kolmogorov-Smirnov test showed normal distribution of age, BMI, and fasting blood glucose, whereas abnormal distribution of plasma nesfatin-1 level and Y-BOCS scores both in the study group and the control group. Student t test and Mann-Whitney U test were used to evaluate differences between groups accordingly. In order to analyze gender difference between groups the χ^2 test was used. The association between the nesfatin-1 levels and Y-BOCS scores in both groups were analyzed by using Spearman's rank correlation test. P value <0.05 was considered to be statistically significant.

RESULTS

Both the study and control groups were statistically similar in terms of demographic variables. The demographic and biochemical variables are shown in Table 1. In terms of BMI and fasting plasma glucose levels differences between the groups were not statistically significant (Table 1). The median of Y-BOCS scores in patient group was statistically higher than that of the healthy control subjects ($z=-6.6$, $p<0.001$) (Table1). The median of plasma nesfatin-1 level in patients with OCD was 4.61 ng/ml (min-max: 1.28-8.11), whereas, it was 2.0 ng/ml (min-max: 0.11-4.98) in control group. Difference in plasma nesfatin-1 level between groups reached statistically significant level ($z=-4.8$, $p<0.001$). There were positive correlations, which did not show statistical significance, between plasma nesfatin-1 levels and plasma Y-BOCS scores both in the patient group ($r=0.205$, $p=0.27$) and the control group ($r=0.335$, $p=0.071$). The median plasma nesfatin-1 levels were 5.12 ng/ml (min-max: 2.16-7.33) in male and 4.19 ng/ml (min-max: 1.28-8.11) in female patients with OCD. It was 2.37 ng/ml (min-max: 0.11-4.98) in male and 2.02 ng/ml (min-max: 0.28-4.89) in female control subjects. There was no statistically significant gender difference within both groups in terms of mean plasma nesfatin-1 levels.

Table 1: Comparison of study variables of patients with obsessive compulsive disorder and control group

Variables	OCD group (n=31) Mean±SD	Control group (n= 28) Mean±SD	Statistics t or χ^2	p
Age	28.34±4.51	27.61±4.42	0.28	0.65
Gender (female/male)	18/13	16/12	0.04*	0.84
BMI (kg/m^2)	22.32±1.39	22.06±2.05	0.57	0.57
Glucose (mg/dl)	92.09±4.62	93.40±4.59	1.10	0.27
	Median (min-max)	**Median (min-max)**	**Z**	**p**
Y-BOCS	21.0 (12.0-29.0)	3.5 (0-7.0)	-6.6	<0.001
Nesfatin-1 (ng/ml)	4.61 (1.28-8.11)	2.0 (0.11-4.98)	-4.8	<0.001

SD: Standard deviation; BMI:Body mass index; Y-BOCS:Yale Brown Obsession and Compulsion Scale; (*) shows χ^2 value.

DISCUSSION

High levels of plasma nesfatin-1 found in our patients with OCD support the idea that nesfatin-1 might be taking part in stress and anxiety states in addition to its previously shown role in decreasing food intake. Support for this suggestion comes from the study of Merali and colleagues (15). They raised a presumption that ICV injection of nesfatin-1 to rats caused anxiety and fear reactions which were more prominent in higher doses. Although it did not reach statistically significant level, a positive correlation between Y-BOCS scores and plasma nesfatin-1 level in OCD patients shown in our study was also consistent with their presumption. In a recently published animal study comparing rats under stress and without stress, higher numbers of cells immunolabeled with nesfatin-1 were found in raphe nucleus and locus ceruleous of rats which were under stress (21). At the end of this study, authors argued in favor of the idea that nesfatin-1 level in hypotalamus and hindbrain might be one of the neuromediators of anxiety states. This suggestion finds an indirect support also from a recent study that showed inhibition of NPY neurons, previously shown to have anxioloytic and antidepressant effects, by nesfatin-1 (22).

Although the exact mechanism of appetide is still unclear to some extend, impaired appetite is accepted as a common feature in anxiety states. The central regulation of appetide usually involves complex relations between neuropeptides and monoamines (23). The CRF, leptin, ghrelin, orexin, NPY, melanocortin, and cholecystokinin are among those neuropeptides and monoamines. Currently, it is believed that they do not only take part in regulation of food intake, but they are also proposed to play role in mechanisms related to development of stress and anxiety states (2-4,6-12). Although they are preliminary our findings may suggest a similar role for nesfatin-1.

Nesfatin-1 levels were also shown to be increased in some neurological diseases like epilepsy and some psychiatric disorders such as depression and panic disorder

(16,17,19). In their study Ari and his colleagues shown that patients with major depressive disorder had higher levels of mean plasma nesfatin-1 concentration than that of healthy control subjects (16). In another study plasma nesfatin-1 levels of panic disorder patients were found to be positively correlated with disease severity as well. Consistent with them, we found that plasma nesfatin-1 level of patients with OCD was higher than healthy control subjects (16,17). Thus it looks as if any role played by nesfatin-1 in anxiety is not specific to a psychiatric condition.

Small sample size and cross sectional design of our study and comprising collection of the blood samples at only one time point make interpretation and generalization of the study findings difficult. Additionally, if performed a Western Blot analysis would have strengthen the study findings. Since nesfatin-1 is known to be related with cortisol and adrenocorticotropic hormone, measurement of them would help us to better understand its role in human body. On the other hand, it should also be kept in mind that there is still an ongoing obscurity about how much of the peripheral nesfatin-1 account for its central effects, although nesfatin-1 has been shown to cross blood brain barrier. However, perhaps it is important to note at this point that the permeability of blood brain barrier to circulating nesfatin-1 peptide was previously shown in the literature (24,25).

Consequently, high levels of plasma nesfatin-1 in patients with OCD bring mind its potential role in anxiety states besides its previosly known effects on food intake. Findings of this study was consistent with the results of previous animal studies showing anxiogenic effect of it. Future studies with larger sample sizes investigating alterations in plasma nesfatin-1 levels associated with succesful treatment of psychiatric conditions are needed to understand the complex relationship between food intake and anxiety states and how nesftain-1 hormone fits into this picture.

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