Increased serum nesfatin-1 levels among adolescents diagnosed with major depressive disorder

S. Burak Acikel[1]
https://orcid.org/0000-0002-8964-9513

Esra Hosoglu[2]
https://orcid.org/0000-0003-0090-1389

Abdulbaki Artik[3]
https://orcid.org/0000-0001-7909-9944

Fatma Humeyra Yerlikaya Aydemir[4]

https://orcid.org/0000-0002-4107-5389

[1]*Department of Child and Adolescent Psychiatry, Konya City Hospital, Konya, Turkey*
[2]*Department of Child and Adolescent Psychiatry, Giresun University, School of Medicine, Giresun Turkey*
[3]*Department of Child and Adolescent Psychiatry, Kayseri City Hospital, Kayseri Turkey*
[4]*Department of Biochemistry, School of Medicine, Selcuk University, Konya, Turkey*

Received: 11-06-2020– **Accepted:** 10-09-2020

DOI: 10.15761/0101-60830000000272

ABSTRACT

Background: Nesfatin-1 is an anorexigenic protein expressed in the hypothalamus. Besides the effect on appetite, nesfatin-1 has some effect on mood. In this study, we aimed to investigate the relationship between serum nesfatin-1 levels and major depressive disorder in adolescents diagnosed as major depressive disorder.
Methods: A total of 30 patients between the ages of 12 and 18 with primary diagnosis of major depressive disorder have been included. Depressive scores of both groups were measured by the Children's Depression Inventory. Serum nesfatin-1 concentrations were measured by a commercially available kit based on the enzyme-linked immunosorbent assay (ELISA) method.
Results: The mean serum nesfatin-1 levels in patients with MDD was 40.11±1.62 pg/ml, whereas it was 37.51±5.10 pg/ml in healthy controls. Mean serum nesfatin-1 levels difference between groups was statistically significant. There is a positive correlation between serum nesfatin-1 levels and CDI scores in the whole sample.
Discussion: This is the first study to examine the relationship between major depressive disorder and serum nesfatin-1 levels in adolescents diagnosed as major depressive disorder. Further studies are needed to clarify this relationship.

Burak Acikel S / Arch Clin Psychiatry. 2021;48(1):16-19

Keywords: depression; adolescent; nesfatin-1; depressive disorder

Introduction

Nesfatin-1 is an anorexigenic protein expressed in the hypothalamus which was discovered in 2006. Its name is an abbreviation of NEFA/nucleobindin 2 encoded satiety-and fat-influencing protein[1]. Nesfatin-1 was previously discovered in the hypothalamus, which is in the central nervous system, but it also exists in peripheral tissue. Specifically, it is secreted by peripheral adipose tissue, gastric mucosa, pancreatic endocrine beta cells, and testis tissue[2]. In terms of appetite, nesfatin-1 has an anorexigenic effect and reduces food intake[3]. In addition to the effect on appetite, the effect of nesfatin-1 on mood is also remarkable. It has been shown that the intracerebroventricular administration of nesfatin-1 can stimulate the HPA axis[4] and increases anxiety, depression-like behavior, and anhedonia in normal-weight rats[5]. The relationship between the nesfatin-1 levels and major depressive disorder, especially among the adult population, has been mentioned in several studies[6].

Depressive disorders in childhood and adolescence have been characterized by persistent and pervasive anhedonia, sadness, boredom, or irritability that cause functional impairment[7]. The prevalence of depressive disorders is 3-8% in adolescents[8]. In Turkey, the prevalence of any mood disorders reported as 2.5%, and the prevalence of major depressive disorder was reported as 1.7% in a relatively young sample[9]. In addition to being a psychiatric disorder, there has been a lot of evidence that emphasizes the relationship between major depressive disorder and metabolic system. The effects of some peptide hormones that affect the hypothalamus have been studied in recent years. Hypothalamus is an important target because the areas which are related to mood (i.e. raphe and arcuate nucleus) exist in the hypothalamus and the HPA axis is an important factor for depression and anxiety. Leptin is one of the most studied hormone derived from adipose tissue and it has effects both on mood and appetite[11].

There is a relationship between appetite-related peptide hormones and major depressive disorder among adolescents. Nesfatin-1 is a novel candidate molecule in this area. In this study, we aimed to investigate the relationship between serum nesfatin-1 levels and major depressive disorder among adolescents diagnosed with major depressive disorder. We hypothesized that there could be an association between nesfatin-1 and major depressive disorder among adolescents like adults.

Address for correspondence: S. Burak Acikel MD, Department of Child and Adolescent Psychiatry, Dr. Sami Ulus Maternity and Child Health Hospital, Babur Street No: 44 Altindag Ankara, Turkey, Tel: +90 544 860 23 16; Fax: +90 312 305 62 36; E-mail: acikel42@gmail.com

Methods

Sample

This study has been conducted at Necmettin Erbakan University, Meram School of Medicine, Child and Adolescent Psychiatry Department outpatient unit. The diagnostic evaluation has been made according to the DSM 5 diagnostic criteria with the K-SADS-PL Turkish version[12] formed by a child and adolescent psychiatrist (BA and EH). A total of 30 patients between the ages of 12 and 18 with primary diagnosis of major depressive disorder have been included in the study. All the patients were at the first depressive episode when they were included in the study. The following conditions have been considered as exclusion criteria because of the potential confounding effect of medical treatment on the nesfatin-1 levels; having psychiatric treatment in the last 3 months; an additional medical condition (disorders that affect the hormonal system such as diabetes mellitus, thyroid disorders, adrenal system disorders, long-term medical follow-up, and treatment); diagnosed with neurodevelopmental disorders such as autism, schizophrenia, bipolar disorder, and intellectual disability; and any other psychiatric disorders and treatment. The control group (n=30) consists of age and sex equalized adolescents and families, without any psychiatric disorder. They were included in the research as the study group that applied to the Department of Pediatrics Outpatient Unit at Necmettin Erbakan University and they have no psychiatric comorbidity. Also, the diagnostic evaluation has been made with the K-SADS-PL Turkish version to a healthy control group formed by a child and adolescent psychiatrist. Informed consent was provided with both the patient and the control groups. This study has also been approved by Necmettin Erbakan University Ethical Committee (Protocol number: 2016/753).

Tools

Depressive scores of both groups were measured by the Children's Depression Inventory (CDI). CDI is a self-assessment scale applicable to children between the ages of 6 and 17. For this study, the scale has been filled in by the child him/herself. There were three different options for each item on the 27-point scale. The child is asked to choose the most appropriate sentence for the last two weeks. Each item takes 0, 1, or 2 points according to the severity of the indication. The highest score is 54. The higher the score, the greater the depression is[13]. The validity and reliability of the inventory in Turkish have also been formed[14]. The cut point is recommended as 19.

Physical measurement (weight and height measurements and calculation of body mass indexes (BMI)) of all participants were done studiously by the same measure and digital scales.

Biochemical Measurements

Blood samples for nesfatin-1 were obtained in the morning around 9 a.m. from a forearm vein of the participants at the end of an overnight 10 hours fasting period at least. Then the blood was carefully and immediately (in a few seconds) transferred from the blood tubes to centrifuge tubes. After the centrifuge process, the separated serum was stored at −80°C, in a freezer until the time of assay. Serum nesfatin-1 concentrations were measured by a commercially available kit based on the enzyme-linked immunosorbent assay (ELISA) method (Human Nesfatin 1 ELISA Kit, Uscn Life Science, Wuhan, PR China). The assay uses a two-side sandwich technique with two selected polyclonal antibodies that bind to different epitopes of human nesfatin-1. The minimum detectable dose (sensitivity) of nesfatin-1 with ELISA kit is typically less than 234.2pg/mL. This assay has high sensitivity and excellent specificity for detection of nesfatin-1. The detection range of kit is 617.3-50,000pg/mL. The standard curve concentrations used for the ELISA's were 50,000pg/mL, 16,666.7pg/mL, 5,555.6pg/mL, 1,851.9pg/mL, 617.3pg/mL. Samples were assayed in duplicate. The serum nesfatin-1 concentration values are reported in picogram per milliliter (pg/mL). Blood samples were obtained in empty vacuum tubes after overnight fasting. Serum samples were obtained after suitable centrifugation and samples were stored at -80°C in a freezer until the day of serum nesfatin-1 analysis.

Statistical Analysis

The analysis of the data has been performed by using a Statistical Package programmer for Social Sciences (SPSS) 20.0 statistical software (Chicago, IL, USA). The normal distribution of the data was evaluated with the skewness and kurtosis value[15]. The Student's t-test was used in analyzing the differences of psychiatric test scores between groups because the normality of the distribution of variables is acceptable. Pearson correlation analysis has been used in investigating the relationship between serum nesfatin-1 levels and depressive scores. A two-tailed p-value of 0.05 is considered to be statistically significant.

Results

The study sample consists of 60 adolescents. 30 (4 male, 26 female) of them have been diagnosed with major depressive disorders and 30 (7 male, 23 female) of them are healthy controls. There are no significant differences between the patient and the control groups in terms of gender, age, and body-mass index. The mean BMI is 21.38±4.89 in patient groups and 21.15±4.37 in the control group *(t=0.192, p=0.848)*. The comparisons of sex, age, and body-mass index are given in Table 1.

The mean CDI scores (30.40±6.91 in the patient group, and 11.03±6.60 in the control group) were statistically higher in the patients with MDD than in the control group *(t=10.998, p<0.001)* (Table 2) The mean serum nesfatin-1 levels in the patients with MDD was 40.11±1.62 pg/ml, whereas it was 37.51±5.10 pg/ml in healthy controls. The difference of mean serum nesfatin-1 levels between groups was statistically significant *(t=2.66, p=0.04, cohen's d=0.538)*. The serum nesfatin-1 levels values are given in Table 2.

In the patient group, there is a positive correlation between serum nesfatin-1 levels and CDI scores, and this relationship is nearly statistically significant *(p=0.05, r=0.349)*.

Table 1. Comparison of sex, age and body-mass index

Demographics	Patient		Control		Statistics	
	N	%	N	%	x^2	p
Sex (Male/Female)	4/26	13.3/86.7	7/23	23.3/76.7	1.002	0.317
	Mean	SD	Mean	SD	t	p
Age	15.63	1.51	15.30	1.66	0.810	0.421
BMI	21.38	4.89	21.15	4.37	0.192	0.848
BMI: Body mass index						

Table 2. Comparison of depressive scores and serum Nesfatin 1 Level

	Patient		Control		Statistics		
	Mean	SD	Mean	SD	t	p	Cohen's d
CDI Scores	30.40	6.91	11.03	6.60	10.998	<0.001**	2.867
Nesfatin-1 Levels (pg/ml)	40.11	1.62	37.51	5.10	2.076	0.04*	0.538

Discussion

Our study has been the first that investigates the relationship between serum nesfatin-1 levels and major depressive disorder among adolescents. It has been found that serum nesfatin-1 levels are significantly higher in patients than in healthy controls. In the patient group, there is a nearly statistically significant positive correlation between serum nesfatin-1 levels and depressive symptoms.

There have been several studies that investigate the relationship between nesfatin-1 levels and major depressive disorder among adults. In these studies, higher mean plasma levels of nesfatin-1 were found in depressed patients[16,17]. In addition to these findings, it has been found that plasma nesfatin-1 levels were associated with depression severity. Moreover, it was an independent indicator of severe depression[18]. Consistent with these findings, we have found a higher serum nesfatin-1 levels in patients and a positive correlation between serum nesfatin-1 levels and depressive symptoms. This has been the first finding about the relationship between serum nesfatin-1 levels and major depressive disorder among adolescents. In the literature, there have also been some animal studies investigating the relationship between nesfatin-1 and major depressive disorder. Among rats, intraperitoneal injection of nesfatin-1 increased the depressive behaviors. For instance; it increased the immobility in the forced swim test and decreased the swimming time[19]. In addition to this, plasma interleukin 6 and CRP levels which are important cytokines for depression[20] increased the dose-dependently[19]. In a recent study, nesfatin-1, corticosterone, interleukin 6, and CRP levels have been found significantly higher in patients with the major depressive disorder than controls. A positive correlation has been found between nesfatin-1, interleukin 6, and CRP concentrations[21]. So, it could be mentioned that nesfatin-1 might activate the immune system and cytokines and might trigger depression. In our sample, we have found a higher serum nesfatin-1 levels in the patient group and a positive correlation between serum nesfatin-1 levels and depressive symptoms.

We think that it is important to state the pathophysiological meaning of the change of nesfatin-1 levels in depression. There have been few studies that indicate the interaction between nesfatin-1 and the serotoninergic system which has an important role on depression pathophysiology. 5HT 1B/2C agonism results in anorexigenic effect by upregulating NUCB2 expression in the hypothalamus. Besides that, the activation of 5HT 2C receptors might play a role in regulating NUCB2 expression and feeding behavior[22]. It is shown that inverse agonism of 5HT 2C receptor via olanzapine decreases the NUCB2/nesfatin-1 expression in hypothalamic feeding-related areas of rats. This effect results in increased food intake and weight gain[23]. So, it could be mentioned that the serotonin 5HT2C receptor has an important effect on nesfatin-1 expression. It is also known that 5-HT2C receptor blockade has a reducing effect on depressive and anxious states[24]. Therefore, it could be suggested that 5-HT2C antagonism decreases the nesfatin-1 levels and at the same time it has an antidepressant effect. This relationship could explain the inverse relationship between nesfatin-1 levels and depression. Longitudinal studies are needed to examine whether increased nesfatin-1 levels are the cause or the effect of mood disorders.

There is a close relationship between depression and obesity. Obesity and being overweight are positively associated with depression in adolescents[25]. Furthermore, the psychological and social difficulties (i.e decreased self-esteem, problems in social interaction, social rejection, and bullying) in obesity could increase the depressive mood[26]. It can be stated that there has been a bi-directional relationship between obesity and depression. In obese adolescents, serum nesfatin-1 levels have been found higher compared to non-obese adolescents. In this study, it has been suggested that the efficiency of nesfatin-1 is reduced in obese individuals due to the saturation of transporters that transport nesfatin-1 from blood to cerebrospinal fluid. (CSF)[27]. When we consider the bi-directional relationship between obesity and depression, it might be mentioned that the reduced nesfatin-1 efficiency in the central nervous system might result in both obesity and depression. Nesfatin-1 could be a biological junction in the depression and obesity relationship.

This study has certain limitations. The small sample size is the main limitation of our study. It is not clear whether the measure of nesfatin-1 levels from peripheral blood reflects its levels in the brain or not. Serum nesfatin-1 levels were measured by only the ELISA method but not confirmed through any other method (Western blot, etc). This should be mentioned as a methodological limitation. We haven't been able to establish causality between nesfatin-1 levels and depression because of the cross-sectional design of our study. Several confounding factors that change in depression such as BMI or eating behaviors couldn't be analyzed in this cross-sectional study. Future longitudinal studies are going to be useful to clarify the variability of nesfatin-1 levels according to the variability of symptoms and related behaviors.

As a conclusion, this is the first study to examine the relationship between major depressive disorder and serum nesfatin-1 levels among ciladolescents diagnosed with major depressive disorder.

Conflict of interest statement: There is no conflict of interest to declare

Funding: There is no funding source for this research. All materials required for the study were provided by the authors.

This study was conducted in Necmettin Erbakan University, Meram School of Medicine Department of Child and Adolescent Psychiatry, Konya TURKEY

References

1. Oh-I S, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K, et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature. 2006;443(7112):709–12.
2. Ayada C, Toru Ü, Korkut Y. Nesfatin-1 and its effects on different systems. Hippokratia. 2015;19(1):4–10.
3. Stengel A, Taché Y. Nesfatin-1. In: Handbook of Biologically Active Peptides. Second Edi. Elsevier Inc.; 2013. p. 850–5.
4. Stengel A, Goebel M, Wang L, Rivier J, Kobelt P, Mönnikes H, et al. Central nesfatin-1 reduces dark-phase food intake and gastric emptying in rats: differential role of corticotropin-releasing factor2 receptor. Endocrinology. 2009;150(11):4911–9.
5. Kühne S, Schalla M, Friedrich T, Kobelt P, Goebel-Stengel M, Long M, et al. Nesfatin-130-59 Injected Intracerebroventricularly Increases Anxiety, Depression-Like Behavior, and Anhedonia in Normal Weight Rats. Nutrients. 2018;10(12):1889.
6. Caroleo M, Carbone EA, Primerano A, Foti D, Brunetti A, Segura-Garcia C. The role of hormonal, metabolic and inflammatory biomarkers on sleep and appetite in drug free patients with major depression: A systematic review. J Affect Disord. 2019;250:249–59.
7. Birmaher B, Brent D. Depressive and Disruptive Mood Dysregulation Disorders. In: Dulcan's Textbook of Child and Adolescent Psychiatry. American Psychiatric Association Publishing; 2016.
8. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence. Arch Gen Psychiatry. 2003;60(8):837.

9. Karacetin G, Arman AR, Fis NP, Demirci E, Ozmen S, Hesapcioglu ST, et al. Prevalence of Childhood Affective disorders in Turkey: An epidemiological study. J Affect Disord. 2018;238:513–21.
10. Hryhorczuk C, Sharma S, Fulton SE. Metabolic disturbances connecting obesity and depression. Front Neurosci. 2013;7.
11. Carvalho-Ferreira JP de, Masquio DCL, Campos RM da S, Netto BDM, Corgosinho FC, Sanches PL, et al. Is there a role for leptin in the reduction of depression symptoms during weight loss therapy in obese adolescent girls and boys? Peptides. 2015 Mar;65:20–8.
12. Ünal F, Öktem F, Çuhadaroğlu FÇ, Kültür SEÇ, Akdemİr D, Özdemİr DF, et al. Reliability and Validity of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, DSM-5 November 2016-Turkish Adaptation (K-SADS-PL-DSM-5-T). 2019;30(1):42–50.
13. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull. 1985;21(4):995–8.
14. Öy B. Çocuklar için depresyon ölçeği: Geçerlilik ve güvenirlik çalışması [The validity and reliability study of the Turkish version of children's depression inventory]. Turkish J Psychiatry. 1991;2(2):132–6.
15. George D, Mallery P. Descriptive Statistics: Measures of central tendency, variability, deviation from normality, size, and stability. In: SPSS for Windows Step by Step: A Simple Guide and Reference. 11th ed. 2003. p. 95–105.
16. Algul S, Ozcelik O. Evaluating the Levels of Nesfatin-1 and Ghrelin Hormones in Patients with Moderate and Severe Major Depressive Disorders. Psychiatry Investig. 2018 Feb 25;15(2):214–8.
17. Ari M, Ozturk OH, Bez Y, Oktar S, Erduran D. High plasma nesfatin-1 level in patients with major depressive disorder. Prog Neuro-Psychopharmacology Biol Psychiatry. 2011;35(2):497–500.
18. Xiao M-M, Li J-B, Jiang L-L, Shao H, Wang B-L. Plasma nesfatin-1 level is associated with severity of depression in Chinese depressive patients. BMC Psychiatry. 2018;18(1):88.
19. Ge J-F, Xu Y-Y, Qin G, Peng Y-N, Zhang C-F, Liu X-R, et al. Depression-like Behavior Induced by Nesfatin-1 in Rats: Involvement of Increased Immune Activation and Imbalance of Synaptic Vesicle Proteins. Front Neurosci. 2015;9:429.
20. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150(3):736–44.
21. Xia Q-R, Liang J, Cao Y, Shan F, Liu Y, Xu Y-Y. Increased plasma nesfatin-1 levels may be associated with corticosterone, IL-6, and CRP levels in patients with major depressive disorder. Clin Chim Acta. 2018;480:107–11.
22. Nonogaki K, Ohba Y, Sumii M, Oka Y. Serotonin systems upregulate the expression of hypothalamic NUCB2 via 5-HT2C receptors and induce anorexia via a leptin-independent pathway in mice. Biochem Biophys Res Commun. 2008;372(1):186–90.
23. Rojczyk E, Pałasz A, Wiaderkiewicz R. Effect of short and long-term treatment with antipsychotics on orexigenic/anorexigenic neuropeptides expression in the rat hypothalamus. Neuropeptides. 2015;51:31–42.
24. Millan MJ. Serotonin 5-HT2C receptors as a target for the treatment of depressive and anxious states: focus on novel therapeutic strategies. Therapie. 2015;60(5):441–60.
25. Quek Y-H, Tam WWS, Zhang MWB, Ho RCM. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. Obes Rev. 2017;18(7):742–54.
26. Djalalinia S, Qorbani M, Peykari N, Kelishadi R. Health impacts of Obesity. Pakistan J Med Sci. 2015;31(1):239–42.
27. Anwar GM, Yamamah G, Ibrahim A, El-Lebedy D, Farid TM, Mahmoud R. Nesfatin-1 in childhood and adolescent obesity and its association with food intake, body composition and insulin resistance. Regul Pept. 2014;188:21–4.