

Plasma Neurotrophic Factor Levels are not Associated with the Severity of Depression: Prospective Pilot Study

Содержание нейротрофических факторов в плазме крови не ассоциировано с тяжестью депрессии: проспективное пилотное исследование

doi: 10.17816/CP110

Original article

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ABSTRACT

INTRODUCTION: Depression is one of the most common mental illnesses. Impaired neurogenesis is observed in depression. Biomarkers of impaired neurogenesis in depression can act as a useful objective and diagnostic and prognostic tool to determine the severity of depression.

AIM: To study the concentration of biochemical indicators in the blood that may be involved in the pathogenesis of depression and their intercorrelations, and to determine any associations between the concentrations of biochemical indicators and severity of depressive symptoms.

METHODS: We determined the plasma concentrations of serotonin, dopamine, and neurotrophic factors involved in neurogenesis (BDNF, CDNF and neuropeptide Y) using enzyme immunoassay and mass spectrometry in depressed patients ($n=22$) and healthy controls ($n=16$) matched by socio-demographic parameters. All participants were assessed using the Hamilton Depression Scale (HAMD), the Generalized Anxiety Disorder Questionnaire (GAD-7), and the Center

for Epidemiologic Studies Depression Scale (CES-D) to enter the study. The standard cut-offs for the CES-D and GAD-7 scales were used to confirm the presence or absence of depression and anxiety.

RESULTS: The concentrations of serotonin, dopamine, BDNF, CDNF, and neuropeptide Y in plasma did not differ between the groups and was not found to be associated with the scores on the scales. Positive correlations were found between the concentration of neuropeptide Y and serotonin, BDNF, and CDNF in blood plasma.

CONCLUSIONS: Plasma concentrations of biomarkers related to the pathophysiology of depression did not correlate with the severity of its symptoms.

АННОТАЦИЯ

АКТУАЛЬНОСТЬ: Изучение концентрации биохимических показателей в крови, принимающих возможное участие в патогенезе депрессии, поиск ассоциаций с тяжестью депрессивной симптоматики может быть полезным в качестве объективной диагностики заболевания и прогнозирования тяжести течения патологии.

ЦЕЛЬ: Изучение биохимических показателей крови, которые могут быть связаны с депрессией. Определения корреляционной взаимосвязи этих показателей при депрессивных расстройствах.

МАТЕРИАЛ И МЕТОДЫ: В работе определяли концентрацию в плазме крови моноаминовых нейромедиаторов серотонина и дофамина, и нейротрофических факторов, участвующих в нейрогенезе (BDNF, CDNF и нейропептид Y) у пациентов с депрессией и здоровых добровольцев с одинаковыми социо-демографическими параметрами, используя методы иммуноферментного анализа и масс-спектрометрии. Все участники исследования были опрошены по шкале депрессии Гамильтона (HAMD), опроснику генерализованного тревожного расстройства (GAD-7) и опроснику депрессии центра эпидемиологических исследований (CES-D). Показатели шкал CES-D и GAD-7 использовались для подтверждения наличия или отсутствия депрессии и тревоги у участников исследования.

РЕЗУЛЬТАТЫ: Суммарный балл по трем исследованным шкалам у пациентов с депрессией существенно выше, чем в контрольной группе. Содержание серотонина, дофамина, BDNF, CDNF и нейропептида Y в плазме крови не отличалось в группах испытуемых и не было ассоциировано с баллами по шкалам. Обнаружены положительные корреляции содержания нейропептида Y с серотонином, и BDNF с CDNF в плазме крови.

ВЫВОДЫ: Исследованные маркеры хоть и связаны с патофизиологией депрессии, не коррелируют с тяжестью симптоматики и содержание их в плазме крови не отражает процессы, происходящие в мозге.

Keywords: *depression; HAMD; CES-D; GAD7; BDNF; CDNF; neuropeptide Y*

Ключевые слова: *депрессия; HAMD; CES-D; GAD7; BDNF; CDNF; нейропептид Y*

INTRODUCTION

Depression is a common mental disorder with multifactorial etiology. There is a need for the search for biomarkers that correlate with depression that will allow for timely diagnostics of at-risk individuals and to assess treatment efficacy for those who develop depression.^{1,2} Depression is known to be accompanied by biochemical changes in the blood that could potentially serve as appropriate biomarkers.²

Although there are many hypotheses on how depression actually develops, the pathophysiology of the disease is still not fully understood. The monoaminergic hypothesis was one of the earliest on the development of depression, which attributes the depressive symptomatology to the dysfunction of monoamine neurotransmitter systems.¹ Serotonin is a key neurotransmitter for emotional responses, whose metabolism and reuptake

from the synaptic cleft are impaired in depression. Dopamine is the main neurotransmitter supporting the reward pathway.³ Depression is associated with a decrease in activity of the dopaminergic system.³⁻⁵ Although the main functions of monoamine neurotransmitters are in brain tissue, their concentrations in blood may reflect certain neurochemical changes, and identifying such associations is promising in terms of finding potential biomarkers of depression.⁵

Depression is associated with structural and cellular changes in the corticolimbic brain areas that control mood and emotions, such as neuronal loss and synaptic dysfunction.⁶⁻⁹ The loss or reduction of neurogenesis in the hippocampal dentate gyrus and subventricular zone of the lateral ventricles in adults may cause depression. Impaired growth factor signaling is associated with manifestations of depression.^{7,10} The brain-derived neurotrophic factor (BDNF) is a well-researched protein that has multiple functions and is involved in the processes of neurogenesis, neuroplasticity, and memory formation.¹¹ The BDNF has been found not only in the brain but also in blood and saliva.^{12,13} Numerous studies have shown that the BDNF in blood is involved in certain depression-associated mechanisms.¹⁴⁻¹⁷ Cerebral dopamine neurotrophic factor (CDNF) shows neuroprotective and neurorestorative activity. Among the known growth factors, CDNF is the least studied.^{19,20} Neuropeptides function as neuromodulators in the brain. Neuropeptide Y (NPY) is widely distributed in the central nervous system and is involved in physiological and behavioral regulation, and in neurogenesis modulation.^{21,22} NPY is associated with anxious behavior in animals and humans and affects cognitive function.²³⁻²⁵ Several studies have shown that NPY concentrations may alter in cerebrospinal fluid and blood during depression and antidepressant therapy.²⁶⁻³⁰

Thus, specific growth factors, neuropeptides, and neurotransmitters in the blood may potentially act as biomarkers for depressive disorders. To confirm this assumption, we conducted a study to examine blood concentrations of factors related to the regulation of neuroplasticity and neurogenesis (BDNF, CDNF, and neuropeptide Y) and monoamine neuromediators (serotonin and dopamine), and to determine the connections between these factors and the severity of depressive symptoms. Another aim was to determine possible correlations between the levels of neurotrophic

factors in plasma and the relationships between these parameters with each other in depressive disorders.

This study is a part of the study "Metagenomic analysis of the gut microbiota in people with depressive disorders to identify marker gene compositions. A single center non-interventional observational exploratory study" (study code "PKB1-2020-01").

MATERIAL AND METHODS

STUDY POPULATION

The study includes twenty-two patients with depression (13 males and nine females, aged 18–59 years old) and sixteen healthy volunteers (seven males and nine females, aged 18–45 years old). The patients were continuously selected from inpatients of Mental Health Clinic No. 1, named after N.A. Alexeev, of the Moscow Healthcare Department with diagnoses of depression.

Inclusion criteria:

Patients with moderate to severe depressive episodes with or without psychotic symptoms within bipolar disorder, depressive episodes, recurrent depression (ICD-10 F31.3; F31.4, F31.5; F32.1; F32.2; F32.3; and F32.8, F32.9, F33.1, F33.2, F33.3), aged 18–60 years old were enrolled in the study. Additionally, patients underwent evaluation using the Generalized Anxiety Disorder Questionnaire (GAD-7)³³, and the Center for Epidemiological Studies (CES-D)³². Following scales cut-offs were used to confirm the presence of depression and absence of anxiety: The patients had total scores of HAMD ≥ 14 , CES-D ≥ 27 , and GAD-7 < 10 .

The group of healthy volunteers met the following criteria: (1) absence of current psychiatric disorders; (2) total CES-D score under 18 and GAD-7 score under 5. Exclusion criteria were:

- acute infectious and chronic autoimmune diseases, somatic diseases that may affect biochemical analysis (for instance, cancer, HIV, diabetes, mellitus);
- concurrent eating disorders, posttraumatic stress disorder, or psychoactive substance use disorder, including alcohol dependence;
- concomitant neurological diseases, or a history of severe craniocerebral trauma.

INSTRUMENTS

Medical examination and medical history investigation were carried out in accordance with routine clinical

practice, including anthropometric parameter evaluation (height, weight), collecting information about smoking or alcohol use, and any family history of mental disorders.

17-item Hamilton Depression Rating Scale (HAMD-17) scores³¹ and CES-D³² were used to assess symptoms severity in patients with depression.

Fasting blood samples were collected from the cubital vein in the morning on the second or third day after admission. Plasma was separated by centrifugation immediately after blood sampling (3,000 rpm for 10 minutes) at 4°C and was stored at -80°C.

Healthy volunteers were blood sampled using the same protocol.

Before the analysis, the plasma samples were thawed and BDNF, CDNF, and neuropeptide Y plasma concentrations were determined using an enzyme immunoassay kit (Abcam) according to the manufacturer's protocols. Monoamines were determined using an Agilent 6490A mass spectrometer combined with an Agilent 1290 liquid chromatograph.

STATISTICAL ANALYSIS

Given the small sample size, all statistical analyses were performed using nonparametric statistical methods, regardless of the variables' distribution patterns. Continuous variables were presented as medians with indication of quartiles 1 (Q1) and 3 (Q3), and categorical variables were presented as absolute and relative frequencies. The Kruskal-Wallis test was used to compare continuous variables between the groups. The differences between the frequencies were analyzed using Fisher's exact test. Relationships between quantitative variables were measured using the Spearman's rank correlation method. All statistical tests were performed at a statistical significance level of 5%. Statistical analysis was performed using the freeware R (RStudio, Version 1.3.1073, 2020) and Jamovi software suites (Jamovi, Version 1.6, 2021).

All study participants signed voluntary informed consent forms. The study was approved by the Research Clinical Institute of Otorhinolaryngology of L.I. Svelzhevsky (Protocol No. 2 dated May 20, 2020).

RESULTS

Overall and clinical characteristics of the study sample are shown in Table 1. Among the 22 patients, 11 were diagnosed with a first depressive episode, six patients had had a second episode, and five patients had had three or more

episodes. Five patients had family histories of psychiatric disorders, whilst in the group of healthy volunteers no one had family history of mental disorders. Five patients showed a moderate severity of depression (total HAMD score of 14 to 18), 14 patients had severe depression (score of 19 to 24), and three had extreme depression (score >24).

Study groups were comparable in age, gender, anthropometric parameters, smoking or alcohol use status, and family histories of mental disorders (Table 1).

No differences were found in blood biomarker concentrations between patients with depression and healthy volunteers (Table 2).

The correlation analysis showed no relationship between biomarker concentrations and the total score in the CES-D, GAD-7, and HAMD scales (Tables 3 and 4). Positive correlations between NPY and serotonin in the depressed patient group, and between CDNF and BDNF in the healthy volunteer group, were revealed.

DISCUSSION

In our study we did not find differences in the blood concentrations of the examined biochemical indicators (biomarkers) for depression between the patient and healthy volunteers groups. In the patients group, we did not find any correlations between biomarker concentrations and HAMD and CES-D scales scores.

Quantitative serotonin and dopamine levels seem to be very useful indicators of depression,^{4,26} although our study has not revealed any links between plasma concentrations of neurotransmitters and depression, other studies show mixed results.³⁴⁻³⁶ Plasma serotonin levels have been investigated as biomarkers, even though the relationship between plasma serotonin and brain serotonin is uncertain.³⁵ Plasma levels of serotonin have been shown to be very low or undetectable in patients with monopolar depression.³⁷ However, there is evidence that plasma levels of serotonin do not change in depression,³⁵ which is similar to the results of our study. Some authors have concluded that plasma serotonin levels do not correlate with the amount of serotonin in the brain; in a similar manner, serotonin levels in the blood do not depend on the depressive disorder stage, and it thus cannot be used as a quality marker for treatment.³⁴ In terms of dopamine, some researchers revealed an increase,⁵ some a decrease,³⁸ and some did not find any changes in the blood in depression.

Table 1. Clinical and demographic characteristics of the study population

Parameter	Main group (n=22)	Control group (n=16)	Statistical significance rates
Age ^a - Median (Q1, Q3)	29.0 (21.0, 38.0)	25.0 (24.0, 30.0)	KW=0.00 p=0.951
Gender ^b			
- Females	9 (40.9%)	9 (56.2%)	p=0,512
- Males	13 (59.1%)	7 (43.8%)	
Weight, kg ^a - Median (Q1, Q3)	58.5 (54.2, 76.8)	62.0 (57.0, 79.5)	KW=0.13 p=0.722
Height, cm ^a - Median (Q1, Q3)	171.5 (169.2, 177.8)	172.0 (164.5, 178.0)	KW=0.087 p=0.768
Smoking status ^b			
- Negative	13 (59.1%)	9 (56.3%)	p=1.000
- Positive	9 (40.9%)	7 (43.7%)	
Alcohol use status ^b			
- Negative	12 (54.5%)	8 (50.0%)	p=0.743
- Positive	10 (45.5%)	8 (50.0%)	
Depression in past medical history ^b			
- Positive	11 (50%)	0 (0%)	p=0.005
- Negative	11 (50%)	16 (100%)	
Family history of psychiatric disorders ^b			
- Negative	17 (77.3%)	16 (100.0%)	p=0.067
- Positive	5 (22.7%)	0 (0.0%)	
HAMD, total score ^a - Median (Q1, Q3)	20.0 (19.0, 22.0)	2.0 (0.0, 3.5)	KW=26.3 p <0.001
GAD7, total score ^a - Median (Q1, Q3)	7.5 (5.0, 8.8)	2.0 (0.8, 3.0)	KW=22.0 p <0.001
CES-D, total score ^a - Median (Q1, Q3)	28.0 (28.0, 30.5)	3.0 (0.0, 8.2)	KW=27.5 p <0.001

^a Kruskal-Wallis test

^b Fisher's exact test

Table 2. Comparison of serotonin, dopamine, neuropeptide Y, BDNF, and CDNF values in plasma of patients with depression and healthy volunteers

Biomarkers	Depression (n=22)	Volunteers (n=16)	Statistical significance rates
Serotonin (ng/ml) - Median (Q1, Q3)	4.4 (1.7, 11.0)	7.2 (2.9, 31.2)	KW=0.423 p=0.284
Dopamine (pg/ml) - Median (Q1, Q3)	3.4 (1.9, 5.9)	3.7 (2.4, 6.8)	KW=0.013 p=0.908
NPY (pg/ml) - Median (Q1, Q3)	408.1 (148.6, 618.2)	492.4 (186.2, 571.9)	KW=0.014 p=0.906
BDNF (pg/ml) - Median (Q1, Q3)	312.1 (293.4, 458.3)	313.3 (165.8, 406.9)	KW=0.423 p=0.515
CDNF (ng/ml) - Median (Q1, Q3)	82.9 (68.3, 152.7)	55.8 (43.3, 97.5)	KW=1.773 p=0.183

Table 3. The correlation analysis of serotonin, dopamine, neuropeptide Y, BDNF, and CDNF content in the plasma of patients with depression and healthy volunteers. The table also shows the associated p-values

Patients with depression					
Parameter	BDNF (pg/ml)	Serotonin (ng/ml)	NPY (pg/ml)	Dopamine (pg/ml)	CDNF (ng/ml)
BDNF	1	0.074	0.906	0.396	0.763
Serotonin	0.074	1	0.024	0.333	0.744
NPY	0.906	0.024	1	0.354	0.617
Dopamine	0.396	0.333	0.354	1	0.662
CDNF	0.763	0.744	0.617	0.662	1
CES	0.871	0.508	0.900	0.783	0.281
GAD7	0.389	0.512	0.139	0.267	0.263
HAMD	0.091	0.056	0.639	0.783	0.480
Healthy volunteers					
Parameter	BDNF (pg/ml)	Serotonin (ng/ml)	NPY (pg/ml)	Dopamine (pg/ml)	CDNF (ng/ml)
BDNF	1	0.356	0.299	0.536	0.008
Serotonin	0.356	1	0.462	1.000	0.200
NPY	0.299	0.462	1	0.132	0.880
Dopamine	0.536	1.000	0.132	1	0.136
CDNF	0.008	0.200	0.880	0.136	1
CES	0.409	0.613	0.774	0.115	0.076
GAD7	0.281	0.553	0.955	0.389	0.843
HAMD	0.539	0.883	0.695	0.096	0.744

Chronic stress has a negative impact on hippocampal neurogenesis in adults. Preclinical studies show that exposure to stress leads to atrophy and cell loss in the hippocampus, as well as to decreased expression of neurotrophic growth factors.¹⁰ Therefore, the focus of this study has concentrated on identifying the substances in blood that affect neurogenesis and the neuroplasticity of the brain.

Some authors suggest that depression develops due to dysfunctional neurogenesis in the regions of the brain responsible for emotion and cognition.³⁹ This hypothesis is based on the revealed correlation between lower BDNF levels and a higher incidence of depressive symptoms. If we review the existing research on the relationship between BDNF blood concentrations and depression, we may find sufficient evidence to support this pattern. Patients with depression have lower serum and plasma BDNF levels than healthy controls.¹⁴⁻¹⁷ Thus, many studies have identified BDNF as a possible biomarker for depression. Our study showed no apparent differences in plasma

BDNF concentrations of the patients with depression and healthy volunteers, as well as the absence of associations of their levels with depression scale scores. Such studies should be interpreted with caution as they show mixed results, have small sample sizes, systematic publication errors, and different patterns of BDNF measurement, where these studies mostly ignore the different sampling factors that affect BDNF, which is problematic when interpreting the relationship between peripheral blood BDNF and depression. The question of the relationship between peripheral BDNF and depression has many unresolved issues and requires further careful validation, and at this stage the blood BDNF value is not recommended for use as a biomarker in clinical practice.¹²

CDNF has a unique mode of action associated with the prevention of cell death,²⁰ therefore it was useful to investigate whether the CDNF concentration in blood can be related to depressive state. In our study, we found no apparent connection between this factor and diagnosed depression and its severity. However, we have

Table 4. The correlation analysis of serotonin, dopamine, neuropeptide Y, BDNF, and CDNF content in the plasma of patients with depression and healthy volunteers. The table shows the correlation factor values

Patients with depression					
Parameter	BDNF (pg/ml)	Serotonin (ng/ml)	NPY (pg/ml)	Dopamine (pg/ml)	CDNF (ng/ml)
BDNF	1	-0.516	-0.032	-0.393	-0.082
Serotonin	-0.516	1	-0.721	0.800	0.133
NPY	-0.032	-0.721	1	-0.429	0.135
Dopamine	-0.393	0.800	-0.429	1	0.214
CDNF	-0.082	0.133	0.135	0.214	1
CES	0.037	0.202	-0.034	-0.111	0.287
GAD7	0.192	-0.200	0.375	-0.491	0.297
HAMD	-0.370	0.549	-0.122	-0.108	-0.190
Healthy volunteers					
Parameter	BDNF (pg/ml)	Serotonin (ng/ml)	NPY (pg/ml)	Dopamine (pg/ml)	CDNF (ng/ml)
BDNF	1	0.309	-0.345	-0.262	0.840
Serotonin	0.309	1	-0.310	0.000	0.595
NPY	-0.345	-0.310	1	0.595	-0.050
Dopamine	-0.262	0.000	0.595	1	-0.667
CDNF	0.840	0.595	-0.050	-0.667	1
CES	0.221	0.173	-0.101	-0.610	0.641
GAD7	0.287	0.202	-0.023	-0.346	0.084
HAMD	0.172	-0.058	0.136	-0.630	0.141

revealed that CDNF levels are correlated with plasma BDNF levels in the group of healthy volunteers. This pattern requires further investigation, as CDNF has only recently been discovered and is thus a poorly studied growth factor.

Although our study demonstrated no alterations in plasma NPY concentrations in depression, the correlation between NPY concentrations in the central nervous system and depression has been shown in a number of studies.²⁶ In cases of depression, NPY expression is reduced in the hippocampus, amygdala, and cerebrospinal fluid, but is increased in the hypothalamus. However, the scientific literature provides us with mixed results on blood NPY levels in people with major depressive disorder (MDD). It has been shown that in cases of MDD, blood NPY concentrations can remain unchanged,²⁶ can increase,²⁷ or decrease.⁴⁰ However, a meta-analysis of studies³⁵ has revealed that NPY levels are lower in patients with depression compared to healthy controls,²⁹ and there is evidence that NPY levels increase (become normal)

with antidepressant medication.³⁰ It is also worth noting that psychotropic drug use and the female gender are associated with higher NPY levels.²⁹

In our study, we found no association between NPY and the presence of depression and its severity, but we have found a positive correlation between plasma NPY and serotonin concentrations in the group of patients with depression. This association is an interesting finding because there are indications in animal studies that certain mechanisms of interaction between serotonin and NPY exist in the brain. In animal studies, it has been shown that serotonin neurons and NPY-synthesizing neurons in the hypothalamus, which inhibit and stimulate food intake, respectively, can interact with fluoxetine (a serotonin reuptake inhibitor) to control energy homeostasis, significantly reducing NPY levels in the paraventricular nucleus, the main area of NPY release.⁴¹ Also, intracerebroventricular administration of NPY increases serotonin release in the hypothalamus.⁴² The results reported in these studies

show an association between serotonin and NPY in the central nervous system and its possible association with depression; however, this does not exclude possible peripheral associations of these factors, and which thus require further research.

Our study was limited by the small sample size, clinical heterogeneity of the depressive episode (bipolar and unipolar depression, half of the patients having had their first episode), and also because the medications used in therapy were not considered.

CONCLUSIVE STATEMENT

Contrary to our expectations, we have found no apparent association between the concentration of the studied biochemical parameters and the severity of depressive symptoms. At the same time, our work has shown definite connections between concentrations of biochemical indicators in plasma. A positive correlation between serotonin and NPY levels in the plasma of patients with depression, and between CDNF and BDNF in the plasma of healthy volunteers has been shown. These findings require closer attention in future studies.

Article history:

Submitted: 26.10.2021

Accepted: 15.11.2021

Published: 20.12.2021

Funding: This work was supported by the Russian Science Foundation, grant 20-14-00132.

Conflict of interests: The authors report no conflicts of interest.

Acknowledgements: The authors would like to express their gratitude to all the patients and volunteers who agreed to participate in this study.

Authors' contributions: O.A. Karpenko, V.N. Danilenko, O.I. Gurina, G.P. Kostyuk, A.U. Morozova — research design development; D.A. Susloparova, E.B. Khobta, A.V. Pavlichenko, D.S. Andreyuk — obtaining data, working with patients; R.A. Yunes, T.S. Syunyakov — obtaining data for analysis, analysis of received data; Y.A. Zorkina, O.V. Abramova — manuscript writing; Y.A. Zorkina, O.V. Abramova, T.S. Syunyakov, G.Y. Tsarapkin, K.A. Pavlov — conception of the paper, setting of research

objectives, discussion of results and formation of conclusions; O.I. Gurina, G.P. Kostyuk, A.U. Morozova — review of publications on the topic of the article.

For citation:

Zorkina YaA, Syunyakov TS, Abramova OV, Yunes RA, Pavlichenko AV, Pavlov KA, Khobta EB, Susloparova DA, Tsarapkin GY, Karpenko OA, Andreyuk DS, Danilenko VN, Gurina OI, Kostyuk GP, Morozova AY. Plasma Neurotrophic Factor Levels are not Associated with the Severity of Depression: Prospective Pilot Study. *Consortium Psychiatricum*. 2021;2(4):15–24. doi: 10.17816/CP110

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