

Yu.R. Akhmeldinova, L.S. Evert, T.V. Potupchik

BRAIN NEUROTROPHIC BDNF LEVEL AT TEENAGERS WITH SYNCOPAL CONDITIONS

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The aim of the study was to assess the level of cerebral neurotrophic factor BDNF in the blood plasma of adolescents with syncopal conditions.

Materials and methods: 225 people (boys and girls) aged 12-17 years were examined, of which 63 adolescents with a history of neurogenic syncope (main group) and 162 without syncope (control group). The plasma BDNF content (in pg / ml) was determined on a Multiscan FC apparatus (Finland) using the Quantikine® ELISA ELISA using the R&D systems® reagent kit (USA). The obtained data were processed in the program "Statistica 12".

Results: lower levels of BDNF in the blood plasma of adolescents with neurogenic syncopal conditions were detected. A large number of individuals with slightly and significantly reduced BDNF levels among adolescents with syncope episodes were found.

Discussion: taking into account the significant role of BDNF in modulating neuroplastic processes, the decrease in its level detected by us can probably be regarded as a metabolic marker of the risk of the occurrence and presence of neurodegenerative processes in the brain tissue of adolescents with recurrent syncope. This assumption can be confirmed by further studies.

Conclusions: syncope in adolescents is associated with lower levels of cerebral neurotrophic factor BDNF. Among adolescents with syncope, there are more individuals with slightly- and significantly reduced BDNF levels compared to the group without syncope.

Keywords: adolescents, syncope, cerebral neurotrophic factor BDNF.

Introduction. Syncope (fainting) is an episode of sudden short-term loss of consciousness associated with a sharp weakening of postural muscle tone and characterized by a spontaneous restoration of cerebral functions. The main signs of a syncope are sudden development, short duration and reversibility. The problem of neurogenic syncope states related to psychosomatic disorders is currently an urgent medical problem [2]. An equally important task is the timely diagnosis and effective correction of these disorders, taking into account the peculiarities of metabolic processes in the brain tissue and affecting the functioning of the central nervous system [6,7,10,13].

According to the results of large population studies, the frequency of syncope in children is 126 per 100,000 children and adolescents [16,18,19]. According to epidemiological data, 15-20% of adolescents experience at least a single episode of syncope before reaching the age of 18 years [3]. The frequency of occurrence of episodes of syncopal conditions in schoolchildren of the city of Krasnoyarsk according to a questionnaire survey is 7.6%, with a predominance in girls, compared with boys, and in older students, compared with children of primary school age [5]. The most frequent and significant types of syncope in children and adolescents include: vasovagal syncope (up to 90% of all cases of syncope); orthostatic syncope (8-10%); respiratory affective seizures (only in children from 6 months to 2 years old); toxic / medicinal syncope (poisoning, side effects of drugs, are rare); cardiogenic syncope (about 5% of all cases of syncope).

There are many reasons that can provoke attacks of loss of consciousness. In most cases, syncopal conditions are primarily neurogenic in nature and are mediated by conditioned or unconditionally reflex mechanisms of regulation of the cardiovascular system, causing the body to respond to external influences. However, they can occur during decompensation of severe somatic diseases and cerebral pathological processes that threaten the life of the child (brain tumor, cerebral aneurysm, etc.).

The immediate cause of syncope is a sharp and sudden decrease in blood supply to the brain below the level necessary to maintain adequate brain tissue metabolism. The consequence of repeat-

ed episodes of cerebral hypovolemia in children with syncopal conditions and neuron hypoxia arising from it may lead to the development of degenerative processes in the substance of the brain.

A special role in the modulation of neuroplastic processes is played by neurotrophic germ factors (NTF). To date, the most studied is the brain neurotrophic factor - brain-derived-neurotrophic-factor (BDNF). It refers to physiologically active polypeptides that regulate the growth and differentiation of neurons during phylogenesis, contribute to the formation of new synaptic connections in the postnatal period. BDNF plays a crucial role in the pathogenesis of neurodegenerative diseases, in the restoration of functions in traumatic and vascular lesions of the nervous system. BDNF is a protein with a molecular weight of 27 kDa and is expressed in fibroblasts, astrocytes, neurons, platelets, as well as in lemmocytes [17]. During the development of the nervous system, BDNF is involved in the differentiation of neurons, in synaptogenesis, and plays a role in long-term potentiation and synaptic plasticity. It is believed that it can play a role in the formation of memory.

Since embryonic development of platelets and neurons comes from the same precursor in the scallop, the concentration of BDNF in the blood may reflect the level of synthesis of BDNF in the central nervous system. To date, 2 types of BDNF receptors are known: the first are low-affinity NGF receptors with a molecular weight of 75 kDaltons (LNGFR), the second are high-affinity receptors for tropomyosine kinase-B with a molecular weight of 145 kDaltons (TrkB) [15]. These

AKHMEL'DINOVA Yuliya Rinatovna - 6th year student of the pediatric faculty of KrasGMU; Russia, 660022, Krasnoyarsk, ul. Partizan Zheleznyak, 1, e-mail: axmeldinova@mail.ru; **EVERT LIDIYA Semenovna** - Doctor of Medical Sciences, Chief Researcher at the Clinical Department of Somatic and Mental Health of Children, Research Institute of the Ministry of Railways, FIC KSC SB RAS; Russia, 660022, Krasnoyarsk, ul. Partizan Zheleznyak, d. 3G; Professor of the Department of General Professional Disciplines FSBEI of HE "KSU named after N.F. Katanova"; Russia, 665000, Abakan, ul. Khakasskaya, 68; <https://orcid.org/0000-0003-0665-7428>; e-mail: lidiya_evert@mail.ru; **POTUPCHIK Tat'yana Vital'evna** - candidate of medical sciences, associate professor of the Department of Pharmacology and Pharmaceutical Consulting with a course at FSBEI HE "KrasGMU named after prof. V.F. Voyno-Yasenetsky" Ministry of Health of the Russian Federation; Russia, 660022, Krasnoyarsk, st. Partizan Zheleznyak, d.1; <https://orcid.org/0000-0003-1133-4447>; e-mail: potupchik_tatyana@mail.ru

receptors determine the specificity of the action of BDNF. The functional activity of neurotrophic factors (including BDNF) is quite high. During the development of the nervous system, they participate in the differentiation, maturation of neurons and the formation of synapses. In the adult body, they play a neuroprotective role, protect brain neurons from hypoxia and ischemia [14]. BDNF and the serotonergic system, interacting with each other in the central nervous system and modulating brain processes together, are involved in the pathogenesis of anxiety, depression and impaired cognitive processes in humans.

Antidepressant therapy increases the production of BDNF, which leads to the restoration of processes of neurogenesis and neuronal plasticity. In recent years, the possibility of using a serum BDNF concentration indicator and / or BDNF gene polymorphisms to predict or evaluate the effectiveness of a response to therapy has been widely studied. The identification of the significant role of NTF and, in particular, BDNF in stimulating neuroplasticity is promising in the treatment of vascular, traumatic and neurodegenerative diseases of the nervous system.

The aim of our study was to assess the level of cerebral neurotrophic factor BDNF in adolescents with neurogenic syncopal conditions.

Materials and research methods.

The object of the study was adolescents 12-17 years old (boys and girls) in the amount of 225 people, the subject of the study was the neurotrophic factor BDNF. The main group consisted of 63 adolescents with neurogenic syncope, and 162 adolescents without a history of syncope were included in the control group. Information about the presence of syncope was obtained by questioning.

The level of neurotrophic factor BDNF in the blood plasma was determined on a Multiscan FC apparatus (Finland, 2009) using the Quantikine® ELISA ELISA using the R&D systems® reagent kit (USA). The BDNF content in the analyzed plasma samples was expressed in PG / ml.

The survey was carried out after obtaining written informed consent to participate in the study of parents of adolescents under 15 years old or the adolescents themselves over the age of 15 years. The study was approved by the Ethics Committee of the Federal State Budgetary Institution of Science and Technology of the Federal Research Center of the Kola Scientific Center of the SB RAS (Minutes No. 1 dated March 16, 2020).

Statistical processing of the obtained data was carried out by non-parametric statistics methods in the program "Statistika 12" [8]. The results of the analysis of quantitative traits are presented as the median (Me) and interquartile range (Q25 – Q75). Binary features are presented as % share and boundaries of the confidence interval estimated by the Wilson method. The achieved level of significance of differences (p) for quantitative indicators was determined by the Mann – Whitney U-test, for binary characters, by the Pearson χ^2 criterion. Differences between groups were considered statistically significant at a achieved level of $p \leq 0.05$.

Results and discussion. To assess the level of BDNF in the blood plasma of the examined adolescents at the first stage, we developed internal standards for this indicator: the percentile values of the cerebral neurotrophic factor in adolescents in the control group were determined. The 5 % values in adolescents in the control group were 256 pg / ml, 10 % - 321 pg / ml, 15 39 - 394 pg / ml, 25 52 - 527 pg / ml, 50 % - 823 pg / ml, 75 % - 1122 pg / ml, 85 % - 1420 pg / ml, 90 % - 1660 pg / ml and 95 % - 1990 pg / ml. Criteria for assessing BDNF levels are presented in tables 1 and 2.

As a result of the study, it was found that among the examined with syncopal conditions there was a greater number of adolescents with a slightly reduced level of BDNF (14.3%, CI = 7.9-24.3%) compared with the control group (6.6%, CI = 3.9-10.9%, $\chi^2 = 3.93$, $p = 0.0475$). The proportion of adolescents with a significantly reduced level of the analyzed factor was also significantly larger in the group with a history of syncope (10.0%, CI = 4.9-19.2%) than in the group without syncope (1.5%, CI = 0.5-4.4%, $\chi^2 = 10.36$, $p = 0.0013$). Relative to other gradations of blood plasma BDNF level, there were no statistically significant differences in the compared groups, but there was a clear tendency for a greater number of individuals with BDNF levels below the normative values among adolescents with syncopal conditions. At the same time, the results of our comparative analysis revealed a tendency toward a higher incidence of adolescents with normal and elevated levels of BDNF in the group without a history of syncope.

A comparative analysis of the quantitative values of the level of BDNF in the blood plasma of adolescents with syncope and without syncope in the history is illustrated in table 3.

As can be seen from the table above, adolescents with syncopal conditions had

a statistically significantly lower content of cerebral neurotrophic factor BDNF in plasma compared to the level of a similar indicator in adolescents without syncope in history.

Numerous studies in recent years have shown that BDNF plays a significant role in the pathophysiology of a large number of diseases and pathological conditions. A decrease in the content of this neurotrophic factor has been established in a number of diseases and syndromes, with impaired memory and cognitive functions. Thus, a decrease in the level of BDNF was detected in adult patients with chronic tension headache [11] and those with memory impairment and cognitive dysfunction [1].

It has been established that there are fewer individuals with normal plasma concentrations of BDNF and a greater proportion of individuals with a low content of this indicator in adolescents with connective tissue dysplasia syndrome, dorsopathy, autonomic dysfunction syndrome, arterial hypertension, recurrent cephalgia and asthenic syndrome. Adolescents with a violation of psychoemotional status are characterized by a lower content of BDNF in plasma, a tendency to a decrease in the concentration of BDNF was revealed as the severity of distress, depression, anxiety, somatization and asthenia increased [12].

A relationship was found between the level of serum concentration of cerebral neurotrophic factor in children with hypoxic-ischemic brain lesions in which the serum concentration of BDNF was 1.3-1.6 times lower [4]. T.V. Samsonova (2013) found a decrease in the adaptive capabilities of the apparatus of autoregulation of cerebral circulation and autonomic regulation in adolescent children who underwent perinatal hypoxic brain lesions of moderate severity, associated with a decrease in the production of neuropeptide P substance 10-14 years old and brain neurotrophic factor BDNF - at the age of 15-17 [9].

Our data confirm the identified T.V. Samsonova (2013) direction of changes in the level of BDNF in adolescents with a history of PPCNS and the subsequent development of autonomic dysfunction. In our study, syncopal conditions in the examined adolescents had a neurogenic etiology due to the presence of autonomic dysfunction syndrome predominantly of the vagotonic type, and in patients with hypertension, the sympathicotonic type. In the history of most of the examined there were indications of a perinatal lesion of the central nervous system.

To date, the important role of BDNF

Table 1

Criteria for assessing normal and elevated plasma BDNF levels

Percentile range		BDNF percentile range		Plasma BDNF
≥ 25	≤ 75	≥ 527	≤ 1122	normal
> 75	≤ 85	> 1122	≤ 1420	slightly increased
> 85	≤ 90	> 1420	≤ 1660	moderately elevated
> 90	≤ 95	> 1660	≤ 1990	significantly upgraded
> 95		> 1990		high

Table 2

Criteria for evaluating a reduced level of BDNF in plasma

Percentile range		BDNF percentile range		Plasma BDNF
< 25	≥ 15	< 527	≥ 394	slightly reduced
< 15	≥ 10	< 394	≥ 321	moderately reduced
< 10	≥ 5	< 321	≥ 256	significantly reduced
< 5		< 256		lower

in modulating neuroplastic processes, in the regeneration of brain neurons and the restoration of their functions, is well known. In our opinion, a decrease in plasma levels of BDNF can be regarded as a metabolic marker for the presence and risk of neurodegenerative processes in the brain of adolescents with repeated episodes of neurogenic syncope.

Conclusions:

1. The presence of syncope in adolescents is associated with a lower level of cerebral neurotrophic factor BDNF in blood plasma.

2. Among adolescents with syncope, there are more individuals with a slightly and significantly reduced level of BDNF compared to the group without a history of syncope.

3. The assessment of the significance of a reduced level of BDNF in blood plasma as a metabolic marker for the presence and risk of neurodegenerative processes in the brain tissue of adolescents with syncopal conditions is relevant and requires further study.

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Table 3

The content of BDNF in the blood plasma of adolescents with syncope and without syncope (in pg / ml)

Groups	M	N	Me	25%	75%	Std. Dev.	P ₁₋₂
1 gr. - without syncope	999.53	162	892.00	590.00	1190.00	643.31	0.0135
2 gr. - with syncopal conditions	814.12	63	705.00	471.00	1009.00	453.10	

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E.V. Ferubko

INVESTIGATION OF THE ROLE OF PHENOLIC COMPOUNDS IN THE MECHANISM OF ACTION OF THE NEW AGENT FOR PREVENTION AND TREATMENT OF DIGESTIVE DISEASES

The article presents a study on pharmacological activity of phenolic compound complex isolated from the polycomponent extract "Hexaphyte", which has choleretic activity.

The aim of the study was to determine the role of the phenolic compound complex in the mechanism of action of hexaphyte.

The results of successive series of experiments to determine the role of phenolic compounds in the mechanism of action of "Hexaphyte" extract, including in the manifestation of choleretic activity, concluded that the phenolic compound complex isolated from hexaphyte had a positive effect on the manifestation of choleretic, antioxidant and membrane-stabilizing activity of extract "Hexaphyte".

Keywords: polycomponent plant extract, phenolic compound complex, choleretic action.

Introduction. Digestive diseases occupy a leading place in the general structure of human diseases, and they have a recurrent course, a functional nature of the disorders, and the organic nature of the pathology [14, 9].

The use of plant-derived choleretics is indicated for chronic diseases of the liver, gall bladder, and biliary tract [11]. The range of herbal medicines with choleretic activity is small and is represented by plant composition (species), as well as purified extracts in the form of tablets (flamin, caleflon and hofitol), a solution for oral administration (hofitol), tablets of allochol, etc. [4].

In this regard, the expansion of the range of drugs with choleretic activity is promising. Given this circumstance, the creation of new and effective drugs based on a rational herbal composition is appropriate [5, 12, 13].

Based on information-analytical analysis of the literature and preliminary phytochemical study of raw plant materials, the authors developed the dry extract under the code name "Hexaphyte" that has

choleretic activity due to the presence of biologically active substances, mainly of phenolic nature [8].

In this regard, the aim of our study was clarifying the role of the phenolic compound complex isolated from hexaphyte for interpretation its action mechanism, in particular, its choleretic activity.

Materials and methods. The object of the research is the phenolic compound complex isolated from extract "Hexaphyte".

The dry extract under the code name "Hexaphyte" was obtained from the following species of medicine plant raw materials: flowers of dwarf everlast (*Helichrysum arenarium* L.) – 300g, flowers of tansy (*Tanacetum vulgare* L.) – 100g, rose hips (*Rosa* sp.) – 100g, leaves of common nettle (*Urtica dioica* L.) – 100g, leaves of peppermint (*Mentha piperita* L.) – 50g, roots of liquorice (*Glycyrrhiza glabra* L.) – 50g.

The hexaphyte was obtained during simultaneously component extraction with hot water (75-85o C). It contains polysaccharides, flavonoids, carotenoids, organic acids, vitamins, macro- and micronutrients, essential oils and other natural compounds. Extract "Hexaphyte" was standardized according to a complex of flavonoids in terms of luteolin standard and isosalipurposide standard, while the content of flavonoids is regulated at least 4% in the first case and at least 15% in the second case [8].

The phenolic compound complex of hexaphyte was obtained by eluting with an alcohol-water mixture in increasing concentration on a polyamide sorbent produced by the WOEL company.

This work was carried out in accordance with the Federal Law "On Medicinal Products" and the "Guidelines for Conducting Preclinical Studies of Medicines". The experiments were performed on 120 outbred male rats with an initial weight of 180-200 g. The animals were obtained from the Federal State Budgetary Scientific Institution Biomedical Technology Research Center of the Federal Medical and Biological Agency of Russia; they lived in the vivarium having free access to food and water. Pharmacological studies were carried out according to the Order of the Ministry of Health of the Russian Federation No. 199n dated 04/01/2016 "On the approval of the rules of good laboratory practice", according to the norms of good laboratory practice (GLP). The research was approved by the Institute's Bioethical Commission (protocol No. 7 of October 1, 2018).

We studied the effect of phenolic compound complex isolated from hexaphyte on the liver choleretic function in intact rats with a single dose of 100 mg/kg or 500 mg/kg.

Bile of rats anesthetized with sodium thiopental, 45 mg/kg, was obtained according to the standard procedure [7] using a polyethylene cannula inserted

FERUBKO Ekaterina Vladimirovna – PhD (candidate of medical sciences), head of the department of experimental and clinical pharmacology; Federal State Budgetary Scientific Institution "All-Russian Scientific Research Institute of Medicinal and Aromatic Plants" Address: Greene St., 7. Moscow, 117216, Russian Federation, e-mail eferubko@yandex.ru.