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Amino acids in cardiology, gastroenterology and neurology

Aim. To determine the role of amino acids in cardiology, gastroenterology and neurology.

Materials and methods. The material of the article was the literature data on the use of amino acids in cardiology, gastroenterology and neurology, which were processed by methods of generalization and systematization.

Results and discussion. Data on the role of leucine, isoleucine, and valine in the pathogenesis of heart failure and the effect on their metabolism for prophylactic and therapeutic purposes are provided. The antiatherogenic role of glycine and leucine, taurine and arginine in the metabolic syndrome has been highlighted. The neuroprotective and cardioprotective values of L-arginine, and the neurotransmitter value of glutamate have been indicated. The attention is focused on the role of amino acids in the implementation of hepatoprotection.

Conclusions. In the pathogenesis of cardiovascular, gastroenterological, neurological diseases a significant role is given to amino acids. The analysis of the literature data confirms the rationality of the introduction of drugs containing branched-chain amino acids in order to achieve cardioprotective, neuroprotective and hepatoprotective effects.

Key words: *amino acids; pathogenesis; cardiology; gastroenterology; neurology*

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Амінокислоти в кардіології, гастроентерології та неврології

Мета дослідження. Визначення ролі амінокислот у кардіології, гастроентерології та неврології.

Матеріали та методи. Матеріалом статті слугували літературні дані щодо застосування амінокислот у кардіології, гастроентерології та неврології, які були опрацьовані методами узагальнення та систематизації.

Результати та їх обговорення. Надані дані щодо ролі лейцину, ізолейцину, валіну в патогенезі серцевої недостатності і впливі на їхній обмін з профілактичною і лікувальною метою. Виділена антиатерогенна роль гліцину і лейцину, таурину і аргініну при метаболічному синдромі. Вказано нейропротекторне та кардіопротекторне значення L-аргініну, нейротрансміттерне – глутамату. Акцентовано увагу на ролі амінокислот у реалізації гепатопротекції.

Висновки. У патогенезі серцево-судинних, гастроентерологічних, неврологічних захворювань важливе місце відведене амінокислотам. Проведений аналіз літературних даних підтверджує раціональність введення препаратів, що містять амінокислоти із розгалуженими ланцюгами задля досягнення кардіопротекторної, нейропротекторної та гепатопротекторної дії.

Ключові слова: *амінокислоти; патогенез; кардіологія; гастроентерологія; неврологія*

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Цель исследования. Установление роли аминокислот в кардиологии, гастроэнтерологии и неврологии.

Материалы и методы. Материалом статьи служили литературные данные относительно использования аминокислот в кардиологии, гастроэнтерологии и неврологии, которые обрабатывали методами обобщения и систематизации.

Результаты и их обсуждение. Предоставлены данные относительно роли лейцина, изолейцина, валина в патогенезе сердечной недостаточности и влиянии на их обмен с профилактической и лечебной целью. Выделена антиатерогенная роль глицина и лейцина, таурина и аргинина при метаболическом синдроме. Указано нейропротекторное и кардиопротекторное значение L-аргинина, нейротрансмиттерное – глутамата. Акцентировано внимание на роли аминокислот в реализации гепатопротекции.

Выводы. В патогенезе сердечно-сосудистых, гастроэнтерологических, неврологических заболеваний значительное место отведено аминокислотам. Проведенный анализ литературных данных подтверждает рациональность введения препаратов, содержащих аминокислоты с разветвленными цепями для достижения кардиопротекторного, нейропротекторного и гепатопротекторного действия.

Ключевые слова: *аминокислоты; патогенез; кардиология; гастроэнтерология; неврология*

Introduction. Amino acids play an extremely important role in the body, they are substrates for the synthesis of protein molecules, regulate and participate in many biochemical processes. A disorder in the metabolism of these compounds, in particular both their deficiency and excess, is very important in the pathogenesis of various diseases. Therefore, the correction of anabolism and catabolism of amino acids is one of the therapeutic approaches in the treatment of these pathologies.

The **aim of the work** is to determine the role of amino acids in cardiology, gastroenterology and neurology.

Materials and methods. The material of the article was the literature data on the use of amino acids in cardiology, gastroenterology and neurology, which were processed by methods of generalization and systematization.

Results and discussion

Amino acids in cardiology

Heart failure. Branched-chain amino acids (BCAA), which include leucine, isoleucine and valine, play an important role in the physiology of the normal heart and in the pathogenesis of heart failure. Unlike other metabolites, BCAA are inactivated not only in the liver, but also in other tissues: the myocardium, diaphragm, kidneys and brain. It suggests that these amino acids are of particular importance as bioenergy fuels, especially in conditions of chronic hypoxia [1]. In addition, due to the stimulation of mitochondrial biogenesis of BCAA in the myocardium and skeletal muscles the adaptive properties of eukaryotic organisms are improved, and the average life expectancy increases [2].

The key enzyme for BCAA catabolism is mitochondrial protein phosphatase (PP2Cm), which provides phosphorylation and activation of branched-chain dehydrogenase complex (BCAA conversion product under the effect of aminotransferase). In the normal heart, the active expression of PP2Cm in cardiomyocytes indicates a high level of catabolism of these compounds.

However, under severe heart failure, there is a significant reduction in the expression of this enzyme, which leads to an increase in the number of free BCAAs. At first glance, it has a beneficial effect since under hypoxia they serve as supplementary nutrients for cardiomyocytes: stimulate their hypertrophy and participate in further heart remodeling processes.

Moreover, it has been found that PP2Cm deficiency and BCAA degradation are not compensatory, but, on the contrary, are pathogenetic factors in the development of the disease. Continuous activation of mTOR pathway, suppression of cardioprotective autophagy of damaged cells, a change of the bioenergetic activity of cardiomyocytes and disturbance of regulation of mitochondrial biochemical processes due to the formation of free radicals are all "side effects" of increasing the amount of BCAA in the heart [1].

Atherosclerosis. It is well-known that exogenous alimentary factors play an important role in the pathogenesis of atherosclerosis, and consequently, in coronary heart disease (CHD) [3]. But if cholesterol and other lipid metabolism products as the etiological factors of these diseases have been studied in detail, the role of amino acids, their mechanisms of action and the content of the diet of patients have not been studied so widely. Nowadays, data is available on the involvement of some specific amino acids in the process of foamy cell formation – modified macrophages that absorb lipid deposits in the intima of blood vessels and are components of an atherosclerotic plaque.

Analyzing the properties of 20 basic amino acids they can be classified as pro- and anti-atherogenic ones by the nature of the action on the metabolism. Thus, glycine, cysteine, alanine, leucine, glutamate and glutamin have the anti-atherogenic effect. They directly participate in the foam cells formation, mainly due to modulation of the cellular metabolism of triglycerides. In the study on cultured macrophages of J774A.1, these amino acids significantly (by 24-38 %) decreased the content of triglycerides in these cells and weakened the capture of very low density lipoprotein (VLDL), carriers of triglycerides by macrophages. In contrast, glutamate and glutamine had the pro-atherogenic effect as they contributed to the accumulation of lipids in macrophages (by 107 % and 129 %).

Addition of glycine to apolipoprotein E-deficient (apoE-/-) mice for 40 days significantly decreased the triglyceride levels in the serum and in peritoneal macrophages (MPMs) isolated from the mice (by 19 %). In contrast, glutamine addition significantly increased MPM free radical generation and the accumulation of cholesterol and triglycerides (by 48 %), via enhanced uptake of LDL and VLDL [4].

A possible mechanism of the anti-atherogenic effect of glycine consists in its activating chlorine channels, providing glycine-dependent entry of these ions into a cell. By regulating the intracellular concentration of chlorine the amino acid reduces the accumulation of triglycerides by foamy cells [5].

The studies in human populations, in mice and cultured macrophages have found that leucine modifies the lipid metabolism by enhancing mitochondrial respiration. This amino acid is also able to suppress the accumulation of fat by tissues [6].

If the anti-atherogenic effect of leucine is undoubted, then with two other BCAAs, valine and isoleucine, this is not all that clear. The studies of the peripheral blood of patients with atherosclerosis show a connection between this disease and a disorder of the BCAA metabolism. An increase in the level of these two amino acids in the blood gives grounds for using laboratory analysis results as affirmation of the patients' diagnosis [7]. This is due to the fact that in conditions of constant hypoxia, catabolism of BCAA is disturbed; therefore, they accumulate both in the blood and in the cells [8]. Although some scientists suggest that elevation of BCAA in the peripheral blood is explained by the activity of the intestinal microflora rather than food factors [9].

These data confirm the rationality of introducing drugs or adding an appropriate amount of leucine, glycine and other anti-atherogenic amino acids to the diet of patients in order to achieve the cardioprotective effect. At the same time, patients should reduce the use of products or medicines containing pro-atherogenic amino acids glutamate and glutamine. In turn, BCAA can be included in the diagnostic markers of atherosclerosis.

Metabolic syndrome. The role of BCAA metabolism products in the development of the metabolic syndrome, in particular insulin resistance, obesity and arterial hypertension, has been experimentally confirmed. The metabolic syndrome in mice was induced by feeding them with a diet rich in fats and BCAA. As a consequence, constant phosphorylation processes were observed in animals in mTOR, JNK and IRS1 (ser307) pathways, and the accumulation of acylarnitin in muscles [10].

Recently, it has been suggested that the effects of BCAA depend on the metabolic status of the body [11]. In addition, the correlation between BCAA and cardio-

metabolic diseases has been shown to be age-related and more common in younger individuals than in the elderly [12].

It is believed that taurine, a cysteine derivative, and arginine may be components of the standard therapy for diabetic patients with cardiovascular complications. Experimental results in streptozotocin-induced diabetes mice indicate that taurine directly affects the functional activity of the myocardium, while in combination with arginine, it eliminates the disturbance of the ultrastructure of cardiomyocytes due to hyperglycemia. This is confirmed by echocardiography and electron microscopy, and *in vivo* catheterization [13].

It should be noted that taurine and arginine have pronounced antioxidant properties, regulate the content of Ca^{2+} in the cells of the heart, thus protecting cardiomyocytes against oxidative stress, calcium mechanisms of damage and necrosis. [14-16] In addition, taurine induces an anti-apoptotic protein Bcl-2 and thus protect the heart cells [13].

Therefore, in patients with the metabolic syndrome it is expedient to control the level of BCAA and their metabolic products, and diabetic patients with cardiovascular complications should be included in the treatment plan for arginine and taurine.

Amino acids in neurology

It is well-known that amino acids play an extremely important role in the functioning of the central and peripheral nervous system: tryptophan, tyrosine, histidine and arginine are precursors of many neurotransmitters. Therefore, both the deficit and the excess of these substances lead to a variety of neurological disorders [17]. We propose to pay attention to the amino acids arginine and glutamate, which metabolic disorders play an important role in the pathogenesis of many pathologies of the nervous system.

L-Arginine is an extremely important amino acid for the normal brain function. It is not only included in the synthesized polypeptide chains in the nerve cells, but is a substrate for the formation of urea, creatine, nitric oxide, glutamic acid, ornithine, proline and polyamines. In turn, these metabolites are involved in many physiological processes in the central nervous system [18].

Depressive disorders. It is known that L-arginine has a neuroprotective property. Nitric oxide (NO), the final product of the metabolism of this amino acid, provides expression of the hypoxia-inducible factor-1 α, thereby preventing neuronal necrosis. [19] In the pathogenesis of depressive disorders an important role is played by inflammatory changes and expressed oxidative processes in the patient's body. That is why the disorder of arginine catabolism, and consequently, the reduction of NO production, leads to increased oxidative stress and necrotic changes in the brain of patients, thus exacerbating depression [20].

The **MELAS-syndrome** (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes). After a 9-year clinical study of sick children and adults with this syndrome scientists concluded that oral and intravenous administration of L-arginine yields good results in relieving the symptoms of this pathology. Oral administration of the amino acid prevents the development of stroke and reduces the degree of their severity. Intravenous administration of L-arginine helped to eliminate the main four symptoms of the disease: headaches, nausea/vomiting, loss of consciousness and visual impairment [21].

Alzheimer's disease (AD). Some scientists believe that L-arginine may be a potential marker for AD in older adults since in clinical trials in patients with this diagnosis the plasma level of this amino acid is significantly elevated. This indicates a significant imbalance of the metabolism of arginine in the central nervous system. [22] In contrast to patients with AD, individuals with good memory have lower levels of L-arginine [23].

In patients with AD the disturbance of expression of arginase [24] and NO-synthase [25], enzymes that provide catabolism of arginine and contribute to its transformation into nitric oxide (NO), is also observed in the brain. In the experimental modeling of AD in mice the introduction of arginase significantly reduced the symptoms of the disease [26].

Thus, in the case of depressive disorders and the MELAS- syndrome, there is a deficiency of L-arginine, which elimination is the aim of the pathogenetic therapy. On the contrary, in the case of Alzheimer's disease the disorder of the catabolism of this amino acid and the accumulation of it over the normal level cause the characteristic symptoms. Therefore, the substitution enzyme therapy is indicated for this disease.

Glutamate is a powerful excitatory neurotransmitter secreted by nerve cells in the brain. It transmits signals between neurons and under normal conditions plays an important role in the learning and memory processes, the storage of information in the brain.

Multiple sclerosis. A neurotransmitter glutamate is involved in autoimmune demyelination in multiple sclerosis (MS). This is confirmed by statistical studies of the level of this amino acid in the cerebrospinal fluid [27], plasma [28], lacrimal gland secretion [29]: the level of this amino acid was much higher in patients with MS compared to control groups of healthy adult patients. The pathogenesis of lesions in MS is due to neurotoxic effects of glutamate on oligodendrocytes and neurons in the central nervous system. The experimental studies have shown that the excitatory glutaminergic effects mediated by N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (AMPA) receptors also cause damage to axons, which causes characteristic symptoms of the disease [27].

Frontotemporal dementia. Currently, the clinical studies prove that glutamate is a key neurotransmitter in the pathogenesis of front-temporal dementia (FTD). Experimental animals with FTD showed selective hypofunction of NMDA and AMPA receptors in glutaminergic pyramidal neurons normally accumulated in the frontal and temporal cortex. Other *in vivo* experiments using noninvasive transcranial magnetic stimulation indicate the involvement of the glutaminergic system in the development of both sporadic and hereditary forms of FTD [30].

Thus, if MS is characterized by a significant increase in the amount of glutamate in the brain, in FTD, on the contrary, there is a deficiency of it. Regulation of the metabolism of glutamate and the use of receptor blockers to it should be one of the directions of MS therapy, whereas in FTD, the treatment approach should be aimed at eliminating the deficit of the neurotransmitter, like dopaminergic therapy in Parkinson's disease and cholinergic one in Alzheimer's disease.

Amino acids in gastroenterology

Disturbances of metabolism of branched-chain amino acids occur also in the pathogenesis of diseases of the gastrointestinal tract, in particular liver pathologies.

BCAA is not only a substrate for the synthesis of proteins – they are also involved in the regulation of the metabolism of different nutrients. Patients with chronic liver diseases (chronic and alcoholic hepatitis, primary biliary and cryptogenic cirrhosis) are characterized by a deficiency of BCAA and, therefore, have a variety of metabolic disorders. A significant decrease in the concentration of BCAA is considered a diagnostic marker of cirrhosis and a criterion for the severity of liver damage.

Liver encephalopathy (LE) is a severe consequence of cirrhosis and is due to the toxic effects of bile acids on neurons and, consequently, the development of the hepatic coma. It is important that a mild form of LE is typical for almost 80 % of patients with chronic liver disease, and it significantly affects their level of life. A major factor in the development of BCAA deficiency is hyperammonemia. In addition to the urea cycle in the liver, ammonium is also detoxified in the skeletal muscle with the participation of BCAA. Thus, the prescription of these amino acids is a potential therapeutic strategy to eliminate the symptoms of LE [31]. These data have been confirmed by 11 randomized clinical trials [32].

Taking into account that cirrhosis is a precancerous condition it should be noted that the amino acid imbalance is a significant risk factor for the development of hepatocellular carcinoma (HCC) in patients with cirrhotic changes in the liver. The studies have shown that BCAA administration reduces HCC risk and prolongs life expectancy in these patients [33]. This is due to the fact that BCAA not only promotes detoxification and elimination of hyperammonemia, but also prevents proliferation of tumor cells by inducing apoptosis [34]. They also stimulate the selection of growth factors, enhance regeneration of hepatocytes, and increase the number of parenchymal cells.

In addition, BCAA increases immunity in patients with cirrhosis: improves the phagocytic function of neutrophils and affects the proliferation of lymphocytes, preventing irreversible damage to dendritic cells that release interleukin-12, a powerful natural killer activator. The immuno-stimulating effect of these amino acids is particularly important since bacterial (often opportunistic) infections are considered one of the most common causes of death in patients with cirrhosis.

Thus, the presciption of BCAA (as granules or as food products) is pathogenetically feasible as it prevents the development of liver failure and infectious diseases in patients with cirrhosis [33].

Conversely, in patients with nonalcoholic fatty liver disease (NAFLD) and obesity an increase in the concentration of BCAA (including isoleucine and valine) in the plasma is observed. Scientists consider the excess of BCAA as a result of high insulin resistance in these patients and an enhanced disintegration of proteins [35].

Consequently, in the pathogenesis of liver disease, both deficiency and excess BCAA are possible. Taking this into account the amino acid exchange in these patients can be corrected.

Conclusions and prospects of further research

In the pathogenesis of cardiovascular, gastroenterological, neurological diseases a significant role is given to amino acids. The analysis of the literature data confirms the rationality of the introduction of drugs containing branched-chain amino acids in order to achieve cardioprotective, neuroprotective and hepatoprotective effects.

Conflict of interests: authors have no conflict of interests to declare.

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