Pool of free blood plasma amino acids in cardiovascular insufficiency and substantiation of methods for its metabolic correction (mini-review)

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Abstract
A mini-review of data on the mechanisms of formation of the pool of free amino acids in cardiovascular insufficiency and methods for correcting of metabolic imbalance.

Key words: amino acids, derivatives, cardiovascular insufficiency.

Introduction
The relevance of studies on the role of amino acids in the pathogenesis, prevention and treatment of cardiovascular pathology and cardiovascular insufficiency (CVI) is primarily due to the significant practical results of the use of highly purified substances of this class of compounds and their compositions in the treatment of cardiovascular pathology [1-5].

Numerous results on the determination of amino acids and their derivatives in human fluids and tissues made it possible to systematize the accumulated data and determine the areas of exploitation of their biological action and first of all in laboratory diagnostics and use in clinical practice as preventive medications [3].

At the same time, the most significant number of applied research is devoted to the search for marker amino acids or their derivatives for the diagnosis of heart and vascular diseases. It turned out that the overwhelming majority of diagnostic significance are group shifts in the concentrations of individual compounds of this class [6]. At the same time, the character of the amino acid profiles of fluids and tissues was also quite informative when compared with the use of methods of multivariate mathematical analysis and modeling [7].

It has been convincingly demonstrated that elimination or correction of changes in intermediate metabolism can be achieved by using individual amino acids and their derivatives, or by combining them as universal natural bioregulators - compounds that directly affect the mechanisms of myocardial cell metabolism in physiological (endogenous) concentrations [1-8].

To date, there is evidence of the importance of amino acids not only as building blocks for protein synthesis, but also regulators of gene expression at the level of mRNA translation by the mTOR-dependent mechanism, signaling molecules and modifiers of biological responses, as well as precursors of a wide range of bioregulators that play a key role in integration of the main metabolic flows in vascular pathology [9-10].

The human heart uses a large amount of free amino acids as regulators of both myocardial protein metabolism and as substrates for energy metabolism. The dependence of the myocardium on the amino acid fund of the heart increases in heart failure due to the high activity of anabolism in the myocardium and a lack of energy for cardiomyocytes. Anabolic reactions in the heart are dependent on the oxidation of fatty acids, amino acids and glucose. So, normally, the functional activity of the Krebs cycle (TCAC) largely depends on the concentration of amino acids. Free amino acids stimulate the energy of mitochondria under anaerobic conditions, and also contribute to the substrate supply of TCAC [11-12].

Essential to the availability of amino acids is that their uptake by the myocardium depends solely on their arterial levels. The content of BCAA (branched chain amino acids) in the myocardium is the most important activator of anabolism in the heart, the level of which does not depend on insulin. A slight increase in the concentration of “arterial” amino acids leads to a significant increase in their absorption by the myocardium. Amino acids play a crucial role in the metabolism of proteins and energy in the heart. In heart failure, the arterial pool of free aromatice amino acids (AAA), which is the determining factor in the absorption of amino acids by the myocardium, has not been practically studied. Thus, in comparison with the control, in patients with CVI, arterial levels of amino acids were reduced. This decrease was associated with the severity of chronic heart failure and left ventricular dysfunction, in particular the level of aspartic acid [9]. Therefore, amino acids are now becoming more and more widely used in practice as cardioprotective substances, promoting metabolism in
the heart under anaerobic conditions and hypoxia [13-14].

Comparative assessment and interpretation of changes in the pool of free amino acids at different stages of cardiovascular failure and in the dynamics of its treatment are devoted to only a few works [15]. At the same time, the question of the informativeness of the established changes in the levels of individual amino acids and their significance in comparison with other clinical and biochemical criteria remains practically unclear. The problem of the choice of individual amino acids in the used aminosols for the targeted correction of metabolic imbalance in cardiac and vascular pathology remains unsolved. The importance of amino acids in the regulation of the functions of pathological conditions (vasoconstriction, arterial thrombosis) of the cardiovascular system has been convincingly established in a number of studies [16]. The decrease in plasma lipid levels under the action of glycine and its derivatives, the positive effect of cystine and aspartate in patients with hyperlipidemia, the hypolipidemic effect of arginine, characterized by a decrease in VLDL levels and an increase in HDL in plasma, has been repeatedly described [17].

High concentrations of amino acids and their derivatives in platelets have been demonstrated [18], upon activation of which the agonist binds to a specific receptor to form a complex, thereby transmitting an energy signal to the cell that activates phosphatase and mobilizes ionized calcium from the dense tubular system. A study of the amino acid sequences of glycoprotein receptor polypeptides that specifically bind hemocoagulation substrates has shown the ability to inhibit platelet aggregation, adhesion, and thrombus formation with synthetic and natural (snake venom) polypeptides containing arginine, glycine, valine, asparagine.

The role of free amino acids in the processes of tissue ischemia tolerance and post-ischemic recovery deserves special attention [18]. The protective effect of BCAA amino acids in the myocardium is manifested in maintaining contractility, levels of macroergs (ATP, creatinine phosphate), normalization of aortic and coronary blood flow, cardiac output and cardiac output. BCAA activate the production of catabolites of the adenine system during postischemic reperfusion [18] and the utilization of administered amino acids to high-energy substrates of TCAC and promotes the restoration of the functional capabilities of smooth muscle structures [19].

It is well known that the heart is "metabolically omnivorous" because it is able to actively oxidize fatty acids, glucose, ketone bodies, pyruvate, lactate, amino acids, and even its structural proteins (in decreasing order of preference). The energy of these substrates provides not only mechanical contraction, but also the operation of various transmembrane pumps and transporters required to maintain ion homeostasis, electrical activity, metabolism, and myocardial catabolism. Cardiac ischemia and the resulting coronary and heart failure alter both the electrical and metabolic activity of the myocardium [1-21].

The effects of ischemia on metabolic preference for substrates are poorly understood, although hypoxia during ischemia significantly alters the relative selectivity of the heart in the use of different substrates. Metabolic changes in case of heart rhythm disturbances are the main component of cardiac myopathies. At the same time, the potential contribution of amino acids to the maintenance of cardiac electrical conduction and stability during ischemia is underestimated. Despite clear evidence that amino acids have a cardioprotective effect in ischemia and other cardiac disorders, their role in the metabolism of the ischemic heart has not yet been fully elucidated [22].

Studies on the determination of taurine and a number of amino acids prevailing in the myocardium (glutamate, aspartate, glutamine and asparagine) in coronary insufficiency showed their differences in content in the left and right ventricles in coronary insufficiency. Comparison of the levels of these amino acids in aortic stenosis and coronary heart disease in myocardial biopsies showed higher concentrations of taurine in the left ventricle in both situations [3-23]. With pronounced, progressive atherosclerosis in the myocardium of rabbits, the content of phenylalanine and tyrosine increased, which was also found in patients with coronary heart disease, and the degree of increase in the level of amino acids varied depending on the clinical forms of coronary atherosclerosis (angina pectoris of various functional classes, myocardial infarction).

The antiatherogenic properties of the derivative of sulfur-containing amino acids taurine (Tau) are due to the fact that the synthesis of taurocholates promotes the absorption of lipids, lipolysis, and the absorption of fatty acids in the intestine. On the other hand, the conjugation of Tau with bile acids affects the elimination of cholesterol from the body and thereby controls cholesterogenesis in atherosclerosis [5-8]. It is possible that the high level of taurocholates in some mammalian species (rats) makes it difficult to model experimental atherosclerosis, because the exchange rate of bile acids is increased due to the formation of chololithaurine.

Sulfur containing amino acids (SAAs) are recognized as one of the most potent lipid metabolism modulators among the amino acids. SAA has been shown to act on HDL (high density lipoprotein) cholesterol levels and reduce LDL (low density lipoprotein) lipoprotein. So SAAs have some beneficial effects in atherosclerosis and related diseases (metabolic syndrome) [4-25].

The relative availability of SAA, as well as their amount in dietary proteins, determine lipid metabolism. Although it is not completely clear how SAAs affect gene expression and lipid metabolism at the molecular level, it has been shown that SAAs affect metabolism through the activation of transcription and post-translational modification of a number of regulatory proteins [26-27].

Amino acids arginine and glycine induce a decrease, lysine and branched chain amino acids - an increase in serum cholesterol levels. It has been hypothesized that the control of cholesterol by insulin and glucagon is regulated by dietary and endogenous amino acids. So the insulin / glucagon ratio has been proposed as an early metabolic index of the effect of dietary proteins on serum cholesterol levels, a risk factor and a general mechanism by which nutritional factors influence the development of atherosclerosis and cardiovascular disease [28-40]. Recently, new evidence has been obtained for the participation of amino acids in the pathogenesis of CVF. For example, glutamate and aspartate are components of the malate / aspartate shunt and their concentrations control the rate of mitochondrial oxidation of glycolytic NADH. Glutamate also controls the rate of urea synthesis, not only as a precursor of ammonia and aspartate, but as a substrate for the synthesis of N-acetylglutamate, an essential activator of carbamoyl phosphate synthase. This mechanism makes it possible to regulate the synthesis of urea at a relatively constant concentration [41].

Certain amino acids (leucine) stimulate protein synthesis and inhibit autophagic protein degradation regardless of changes in cell volume, since they stimulate mTOR and protein kinase, which is one of the components of insulin signal transduction. In the case of low energy supply to cells, stimulation of mTOR with amino acids is inhibited by activation of cAMP-dependent protein kinase. Amino acid-dependent signaling also promotes β-cell insulin production. This stimulates the anabolic action of amino acids [29-37].

In relation to coronary heart disease, a special role is played by disturbances in the formation of methionine, leading to the accumulation of its precursor, homocysteine, in the blood and urine. Examination and treatment of patients with homocysteinuria revealed early and active development of atherosclerosis in young patients: hyperhomocyst(e) mia is a significant risk factor for the development of atherosclerosis...
and coronary heart disease. Clinical studies have revealed a significant effect of methionine on the proliferation of smooth muscle cells, followed by vascular endothelial dysfunction and the development of arterial hypertension with a high risk of thrombosis.

Lysine is involved in the formation of collagen, strengthening the vascular wall, in the formation of carnitine, promotes the utilization of fatty acids for the energy potential of cells and the preservation of the body’s immune reactivity. When the walls of the arteries rupture, collagen filaments, connected to each other by lysine, separate and protrude into the lumen of the vessels, like the remains of lysine, and are washed by circulating blood. Lipoprotein A, a specific form of cholesterol present in the bloodstream, has receptors for lysine, binds to it and penetrates into the intima of the vessels, thus triggering the generation of hydrogen peroxide and superoxide radicals [5].

Arginine, a semi-essential amino acid, serves as a precursor of nitric oxide, which affects platelet aggregation and adhesion, decreasing the ability to thrombus formation and decreasing vascular reactivity of atherosclerotic arteries and promotes collagen formation in the vessel walls [24]. In the blood plasma of patients with endothelial disruption in atherosclerosis, the levels of citrate, GABA, glutamate and cysteine were significantly different in comparison with myocardial ischemia in the content of glutamate and phenylalanine. On this basis, a differential diagnosis of aortic injury with ischemic heart disease is considered possible [25].

The development and progression of atherosclerosis, which ultimately leads to cardiovascular disease, is causally related to hypercholesterolemia. Mechanistically, the interaction between lipids and the immune system during the progression of atherosclerotic plaques contributes to the chronic inflammation seen in the artery wall during atherosclerosis. Localized inflammation and increased cell-cell communication can affect the polarization and proliferation of immune cells through changes in amino acid metabolism. In particular, the amino acids L-arginine (Arg), L-homoarginine (hArg), and L-tryptophan (Trp) have been extensively studied in the context of cardiovascular disease and have been shown to act as key regulators of vascular homeostasis, similar to the functions of immune cells. Cyclic effects between endothelial cells, innate and adaptive immune cells occur when the metabolism of Arg, hArg and Trp changes, which has a significant effect on the development of atherosclerosis. Thus, the metabolism and biological functions of Arg, L-homoarginine, and Trp make it possible to reasonably use them for the therapy of atherosclerosis [25–29].

It has been proven that free amino acids, especially branched-chain amino acids (BCAAs), have significant regulatory functions in the processes of protein synthesis. Thus, recent studies have shown that BCAAs protect the cardiovascular system from the metabolic consequences of ischemia / reperfusion (I / R). The authors investigated the signaling pathways and functions of mitochondria, as well as the levels of BCAAs that influence the listed processes [30]. Thus, the in vivo I / R damage model was tested in controls, mTOR + / + and mTOR +/-.. The mice received BCAA, rapamycin, or BCAA + rapamycin. In addition, isolated cardiomyocytes were subjected to modeling ischemia with a quantitative assessment of their death. The degree of mitochondrial swelling was also assessed. In mice treated with BCAAs, there was a significant reduction in the size of the infarction. In addition, BCAAs prevent mitochondrial swelling, which was controlled by the addition of rapamycin. BCAAs significantly retained cell viability. Thus, BCAAs are protective against I / R myocardial injury, in which mTOR plays an important role [30–41].

Summarizing the above, it should be noted that the use of amino acid preparations for pathology of the heart and blood vessels is rational, and the strategy for their use should be based on the elimination of the existing amonic acid imbalance in this disease, correction of the pool of free sulfur-containing amino acids, including the use of taurine, arginine and lysine, angio- and cardioprotective properties of which should be considered sufficiently reasonable and promising. Our methodological approach for the development of formulas of new multicomponent infusion solutions based on amino acids and related compounds, intended for the correction of metabolic imbalance arising in cardiovascular diseases, is based on the application of the results of studying the patterns of formation of the amino acid pool in biological fluids and human tissues with pathology of the cardiovascular system.

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