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Amino Acid Imbalance and its Role in Atherosclerosis

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Abstract

This concise review delves into existing literature to investigate the mechanisms contributing to the buildup of free amino acids and their derivatives in atherosclerosis. Furthermore, the document examines strategies for rectifying metabolic imbalances linked to these amino acids.

Keywords: Amino Acids, Derivatives, Atherosclerosis.

Review

Our keen interest in exploring the role of amino acids in the pathogenesis, prevention, and treatment of atherosclerosis, along with its associated cardiovascular pathology in circulatory failure, stems from multiple reasons. Atherosclerosis is not only characterized by disruptions in carbohydrate metabolism (inhibition of gluconeogenesis and activation of glycolysis), lipid metabolism (activation of lipolysis, ketosis), but also protein metabolism (resulting in protein- and hypoalbuminemia), hyperglobulinemia, and negative nitrogen balance [1-18].

Despite the extensive literature available on changes in carbohydrate and lipid metabolism in atherosclerosis, there is relatively limited data on alterations in the spectrum (pool or fund) of free plasma amino acids. Only a handful of works delve into a comparative assessment and interpretation of changes in the pool of free amino acids at various stages of atherosclerosis and during its treatment [19,20]. The question regarding the informative nature of the established changes in the levels of individual amino acids in atherosclerosis, and their significance when compared to other clinical and biochemical criteria, remains largely unclear.

The selection of specific amino acids for targeted correction of metabolic imbalances in atherosclerosis is an unresolved problem. The significance of amino acids in regulating the functions of pathological conditions such as vasoaterogenesis and arterial thrombosis in the cardiovascular system has been convincingly established through various studies. Numerous reports highlight the decrease in blood lipid levels through the influence of glycine and its derivatives, the positive effects of cysteine and aspartate in patients with hyperlipidemia, and the lipid-lowering impact of arginine in plasma [21].

Elevated concentrations of amino acids and their derivatives within platelets have been observed, particularly upon activation. When an agonist binds to a specific receptor during activation, a complex is formed. This complex transmits an energy signal that activates phosphatase and mobilizes ionized calcium from the dense tubular system to the cytoplasm [22,23].

A study investigating the amino acid sequences of glycoprotein

receptor polypeptides, specifically binding hem coagulation substrates, revealed the potential to inhibit platelet aggregation, adhesion, and blood clot formation. Synthetic and natural (snake venom) polypeptides containing arginine, glycine, asparagine, valine, proline, phenylalanine, and cysteine were found to play a role in this inhibition [24].

The involvement of free amino acids in tissue ischemia tolerance and post-ischemic recovery is noteworthy. Branched-chain amino acids (BCAA) such as valine, leucine, and isoleucine demonstrate a protective effect on myocardial function. This is evident in the maintenance of contractility, levels of macroerg (ATP, creatinine phosphate), normalization of aortic and coronary blood flow, cardiac output, and cardiac output. BCAA activation during post-ischemic reperfusion stimulates the production of catabolites of the adenine system, facilitates the utilization of introduced amino acids for high-energy substrates in the Krebs cycle, and contributes to the restoration of functional capabilities in smooth muscle structures [25,26].

Recent research underscores the role of amino acid derivatives, specifically biogenic amines, in cardiovascular pathology, thrombosis progression, and damage to the vascular wall, concomitant with the activation of platelet function [27]. Evidence-based findings indicate an increase in adrenaline and norepinephrine content in the blood of atherosclerosis patients, accompanied by heightened levels of other vasoconstrictor biogenic amines. The prevalence of α-adrenergic receptors in arterial blood establishes conditions for vasoconstriction in atherosclerosis patients. Notably, amino oxidase activity in the blood, utilizing biogenic amines like serotonin, tyramine, and tryptamine, is significantly reduced in individuals with atherosclerosis, creating conditions for the vascular effects of vasoconstrictor amines [29].

Platelet-dense granules are reservoirs for Ca2+, serotonin, other biogenic amines, ADP, and ATP, released during the release reaction. Ca2+ ions play a crucial role in triggering the formation of platelet clots, blood vessel spasms, and the acceleration of blood coagulation. Biogenic amines induce only primary aggregation [28]. Promisingly, the use of serotonin antagonists and the activation of catabolism enzymes for vasoconstrictor biogenic amines appear to be a potential direction for the pathogenetic treatment of atherosclerosis to eliminate the spastic component of ischemia.

The cardiovascular system operates under a neuro-humoral regulatory mechanism, and the development of pathological conditions involves various types of metabolism and cellular structures. The adhesion-aggregation activity of platelets significantly influences thrombosis occurrence. Platelet adhesion and aggregation lead to hemostasis in small vessels, with adhesion promoted by changes in the vascular wall, platelet contact with collagen fibers, and the release of ADP, biogenic amines, and traces of thrombin from damaged cells. Platelet activation is a crucial step in the hemostatic process, playing a vital role in thermogenesis and vascular lesions [26,27].

The anti-atherogenic properties of the derivative of sulfur-containing amino acids Tau may be attributed to its promotion of lipid absorption, lipolysis, and fatty acid absorption in the intestine through taurocholate synthesis. Additionally, the conjugation of taurine (Tau) with bile acids influences cholesterol elimination from the body, thereby controlling cholesterogenesis [28]. In rats on a high-fat diet supplemented with Tau, it inhibits the increase in cholesterol in the liver and its intestinal absorption. Tau, at certain doses, also activates the transport of cholesterol from the blood and its metabolism to bile acids. Adding Tau to the diet reduces the concentration of bile acids and cholesterol in monkey bile and enhances taurocholate synthesis in piglets [19,20]. The high level of taurocholates in some mammalian species, such as rats, may complicate the modeling of experimental atherosclerosis due to increased bile acid exchange resulting from chlotaurin formation.

The anti-atherogenic impact of S-adenosylmethionine, assessed by elevating glutathione levels and enhancing macro- and microcirculation, was explored in contrast to the atherogenic effect of cholesterol. S-adenosylmethionine is recommended as an additive in amino acid mixtures for parenteral nutrition, with notable commercial preparations such as Samyr, Samet, and Gambrel available in Europe. In conclusion, the rational use of amino acid preparations for atherosclerosis should be guided by the elimination of amino acid imbalances inherent in the disease and the correction of the stock of free sulfur-containing amino acids, including the promising consideration of taurine's anti-atherogenic properties [1-18].

Recent evidence highlights the involvement of amino acids in the pathogenesis of atherosclerosis. Changes in extracellular levels of neurotransmitter amino acids during atherosclerotic brain damage reveal an increase in the concentration of both excitatory (glutamate, aspartate) and inhibitory amino acids (GABA and taurine) compared to the control [29].

It's essential to recognize that amino acids are not only crucial precursors for protein synthesis and other nitrogen-containing compounds but also play a role in regulating major metabolic pathways. For instance, glutamate and aspartate are components of the malate/aspartate shunt, where their concentrations control the rate of mitochondrial oxidation of glycolytic NADH. Glutamate also influences the rate of urea synthesis not just as a precursor to ammonia and aspartate but also as a substrate for the synthesis of N-acetyl glutamate, a significant activator of carbonyl phosphate synthase, enabling the regulation of urea synthesis at a relatively constant concentration.

Certain amino acids, like leucine, stimulate protein synthesis and inhibit autophagy degradation of proteins, regardless of changes

in cell volume, as they activate motor and protein kinase. This kinase is a component of insulin signal transduction. In cases of low cellular energy supply, motor stimulation with amino acids is inhibited by the activation of camp-dependent protein kinase. Amino acid-dependent signaling also promotes insulin production by β-cells, fostering the anabolic effect of amino acids [30].

The heart, known for its "metabolically omnivorous" nature, exhibits active oxidation of various substrates such as fatty acids, glucose, ketone bodies, pyruvate, lactate, amino acids, and even its structural proteins (in decreasing order of preference). These substrates not only fuel mechanical contraction but also sustain essential processes like maintaining ionic homeostasis, electrical activity, metabolism, and myocardial catabolism. However, during cardiac ischemia and subsequent coronary and heart failure, both the electrical and metabolic activities of the myocardium are altered. While the preference for substrates has been minimally studied, hypoxia during ischemia significantly impacts the heart's relative selectivity in using different substrates. Despite the cardio-protective evidence of amino acids in ischemia and cardiac disorders, their role in the metabolism of the ischemic heart remains incompletely understood [31-33].

Research on taurine and certain amino acids prevalent in the myocardium (glutamate, aspartate, glutamine, and asparagine) in cases of coronary insufficiency revealed differences in their content between the left and right ventricles. The examination of myocardial biopsy specimens in aortic stenosis and coronary heart disease demonstrated higher concentrations of taurine in the left ventricle in both situations. Progressive cardiosclerosis in the rabbit myocardium, as well as in patients with coronary heart disease, exhibited an increase in the content of phenylalanine and tyrosine, varying with clinical forms of coronary atherosclerosis. Methionine, a key essential amino acid, plays a pivotal role in carbohydrate, fat, and amino acid metabolism, antioxidant activation, and detoxification. Alterations in methionine formation leading to the accumulation of its precursor, homocysteine, were linked to atherosclerosis and coronary heart disease risk factors. The examination of patients with homocysteinuria revealed early and active development of atherosclerosis, emphasizing the role of methionine in vascular health. Lysine, involved in collagen formation and vascular wall strengthening, had implications for lipoprotein A binding to blood vessels, triggering oxidative stress. Arginine, a semi-essential amino acid, served as a precursor to nitric oxide, affecting platelet function and vascular reactivity in atherosclerotic arteries. Essential amino acids, including arginine, when added to the diet of the elderly, demonstrated lipid-lowering effects, presenting an anti-atherosclerotic impact [33].

Sulfur-containing amino acids (SAAs), recognized as powerful modulators of lipid metabolism, acted on HDL cholesterol and lowered LDL lipoprotein, exhibiting beneficial effects in atherosclerosis and related diseases. Taurine inhibited atherosclerosis development and had an anxiolytic effect through systemic effects on neurotransmitter synthesis. Soy protein, in contrast to casein, had a hypocholesterolemic effect due to its greater content of arginine and glycine. Amino acids, particularly sulfur-containing amino acids, played a significant role in modulating lipid metabolism, with their relative availability determining lipid metabolism. The amino acid and peptide composition of dietary protein, particularly sulfur-containing amino acids, affected serum cholesterol levels, influencing atherosclerosis and cardiovascular disease development. Additionally, the amino acids citrate, GABA, glutamate, and cysteine showed significant differences in the blood plasma of patients with endothelial disorders in atherosclerosis.

The human heart utilizes numerous free amino acids as regulators of both myocardial protein and energy metabolism. During heart failure, the myocardium's dependence on the amino acid pool increases due to high anabolic activity and insufficient energy for cardiomyocytes. Amino acids play a crucial role in protein and energy metabolism in the heart. In heart failure patients, arterial amino acid levels were reduced compared to the control, with this decrease associated with the severity of chronic heart failure and left ventricular dysfunction.

A plant-based protein diet with a low Lys:Arg ratio demonstrates a beneficial normalizing effect on total serum cholesterol, LDL, and adiponectin. The assessment of atherosclerosis also involves considering the Met:Gly ratio. Amino acids, functioning as transceptors and regulators of nutrient fluxes, impact metabolic fluxes, both intracellular and extracellular, through their influence on motor proteins [33].

Increasingly recognized as cardio-protective substrates, amino acids play a role in promoting heart metabolism under anaerobic conditions and hypoxia. The specificity, ionic dependence, and kinetic properties of amino acid transport systems in endothelial cells have been studied, and the regulation of the transport of vascular tone modulator by nitric oxide (NO) during hypoxia has been investigated. The joint localization of cationic transporter CAT-1 and nitric oxide synthase (eNOS) in endothelial cells introduces a new mechanism for regulating NO formation when L-arginine enters the bloodstream.

Conclusion

The "homocysteine" theory of arteriosclerosis gained recognition with evidence that after exogenous methionine loading, patients with cardiovascular disease showed higher concentrations of homocysteine and cysteine compared to healthy controls. Increased homocysteine levels have been linked to coronary artery disease and atherosclerosis, with mice on a methionine-enriched diet exhibiting significant athermanous aortic pathology even at normal plasma homocysteine levels.

The development and progression of atherosclerosis, leading to cardiovascular disease, are causally associated with hypercholesterolemia. The interaction between lipids and the immune system during the progression of atherosclerotic plaques contributes to chronic inflammation in the artery wall. Localized inflammation and increased intercellular interaction can affect the polarization and proliferation of immune cells through changes in amino acid metabolism. Notably, amino acids like L-arginine, L-homoarginine, and L-tryptophane have been extensively studied in the context of cardiovascular diseases, establishing their roles as key regulators of vascular homeostasis, similar to their functions in immune cells. The cyclic effects between endothelial cells and immune cells, coupled with alterations in the metabolism of Arg, hArg, and Trp, significantly influence the development of atherosclerosis. Consequently, the metabolism and biological functions of these amino acids present reasonable prospects for the treatment of atherosclerosis.

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