VASCULAR ENDOTHELIAL DYSFUNCTIONS WITH HYPERLIPOPROTEINEMIA

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ABSTRACT

Relevance.

Cardiovascular diseases and, primarily coronary heart disease, remain among the leading causes of disability and mortality worldwide.

Aim. *To study the relationship between vascular endothelial dysfunction and hyperlipoproteinemia in experimental atherosclerosis.*

Materials and methods. *The experiments were carried out on 28 Chinchilla rabbits with an average weight of 2.5-3.0 kg. The action of drugs was studied in dynamics: the initial 3-month condition and after one month of drug administration. The results obtained were compared with those of the control and intact groups.*

Results. *Long-term administration of cholesterol is accompanied by the development of hypertriglyceridemia, the severity of which depends on the duration of the experiment.*

Conclusion. *An important role in the development of endothelial dysfunction in hypercholesterolemia is played by a decrease in the synthesis of endothelial nitric oxide and an increase in its active radicals, causing modification of low-density lipoproteins and their deposition in the vascular endothelium.*

Keywords: *endothelial dysfunction, atherosclerosis, autoimmune processes, hypercholesterolemia, hyperlipoproteinemia*

Introduction. Cardiovascular diseases and, primarily coronary heart disease, remain among the leading causes of disability and mortality worldwide [1, 2]. In recent years, a lot of new data have appeared that have made it possible to significantly expand our understanding of the pathogenesis of atherosclerosis. Currently, much attention is paid to the study of the cellular and molecular basis of endothelial dysfunction. This is due to the important role of the endothelium in maintaining homeostasis in the body, regulating vascular tone and providing local hormonal functions [3, 4].

Endothelial dysfunctions are observed in many diseases: inflammation, atherosclerosis, autoimmune processes, mechanical damage, and others. But its important role is subject to the development of atherosclerosis. Endothelial dysfunction is one of the most important steps in atherogenesis. This is confirmed by the results of numerous studies conducted in patients with coronary heart disease with angiographically unchanged and slightly altered coronary arteries. Under physiological conditions, the vascular endothelium provides not only adequate vasodilation, but also inhibits the activation and adhesion of platelets, inhibits blood clotting, and prevents the inflammatory process, which is based on the activation of leukocyte adhesion [5].

The formation of atherosclerotic vascular changes also involves the interaction of peroxide-modified Apo-B containing mLDL with cells of internal organs and tissues, mainly the vascular wall [6, 7]. These macromolecules and the increased permeability of the arterial walls for them are necessary and sufficient for the occurrence of a pathological process in the intima of the artery. This process can only develop in the presence of inflammatory cells [8].

Aim. Investigate the relationship between vascular endothelial dysfunction and hyperlipoproteinemia in experimental atherosclerosis.

Materials and methods. The experiments were carried out on 28 Chinchilla rabbits with an average weight of 2.5-3.0kg, kept on a standard diet. The model of experimental hypercholesterolemia in experimental animals was reproduced using the Anichkov method. Experimental hypercholesterolemia was caused by oral administration of dissolved cholesterol in sunflower oil in a ratio of 0.2g per 1kg of body weight daily for 3 months [9].

After 2 months from the start of the experiment, the rabbits were divided into the following groups:

group 1 - intact (3 rabbits), which were injected with vegetable oil daily at a rate of 1.0 ml/kg through the oral cavity;

group 2 model of experimental hypercholesterolemia with water intake - control (5 rabbits);

group 3 model of experimental hypercholesterolemia with gemfibrazil 100 mg/kg (5 rabbits);

group 4 model of experimental hypercholesterolemia with the intake of chitosan derivative No. 1 at 25 μg/kg (5 rabbits);

group 5 model of experimental hypercholesterolemia with the intake of chitosan derivative No. 2 at 50 μg/kg (5 rabbits);

Group 6 model of experimental hypercholesterolemia with heparin at 15 units/kg (5 rabbits).

The action of drugs was studied in dynamics: the initial 3-month condition and after one month of drug administration. The results obtained were compared with those of the control and intact groups.

In the study of the characteristics of lipid metabolism disorders in various diseases, an important role belongs to the determination of lipid metabolism metabolites. For these purposes, laboratories determine the concentration of metabolites of lipid metabolism in blood serum. We used methods for determining total

blood lipids, triglycerides, phospholipids, fatty acids, cholesterol and its esters, and some other indicators of lipid metabolism.

For the study, blood was taken from the ear vein of rabbits after a 12-hour fast. Serum was isolated by centrifugation after 30 minutes of incubation. In the blood serum, the content of total cholesterol, cholesterol in its transport forms was determined : cholesterol in very low, low and high density lipoproteins, triglyceride content on an automated human biochemical combine manufactured by Human (Germany) using special sets of reagents and programs. On the basis of the data obtained, the atherogenic coefficient was calculated.

The content of total cholesterol in the blood serum of a healthy person ranges from 150-250 mg / dl (average value 200 mg / dl). Cholesterol esters with fatty acids account for 60–70% of total cholesterol and 30–40% for free cholesterol. In blood serum, the ratio of free cholesterol to ester-bound cholesterol is a constant value. An increase in plasma cholesterol (hypercholesterolemia) is observed with myxedema, meningitis, diabetes, atherosclerosis, and some liver diseases. Hereditary hypercholesterolemia has also been described. A decrease in plasma cholesterol (hypocholesterolemia) is observed in chronic heart failure, acute infectious diseases, acute pancreatitis, hyperthyroidism.

The results obtained were compared with those of the control and intact groups. The digital material was processed by the method of variation statistics.

Results and discussion. To assess the development of hypercholemtherinemia and its role in vascular endothelial disorders, we studied the parameters of the lipid spectrum of the blood serum of experimental animals. Studies have shown that 30-, 60- and 90-day exogenous administration of cholesterol to experimental animals (0.2 g per 1 kg of body weight) was accompanied by serious changes in the studied parameters of lipid metabolism. Thus, the level of triacylglycerides in the blood serum after a 30-day administration increased statistically significantly to 0.870±0.016 mmol/l, while the value of this indicator in intact rabbits was 0.686±0.018 mmol/l, exceeding them by 1.27 times.

As the duration of cholesterol administration increases, the level of triglycerides in the blood serum progressively increases to 1.38±0.06 and 1.50±0.06 mmol/l, which exceeds the indices of intact rabbits by 2 and 2.19 times, respectively. As can be seen from the above data, prolonged administration of cholesterol is accompanied by the development of hypertriglyceridemia, the severity of which depends on the duration of the experiment.

The content of total cholesterol in the blood serum of rabbits with hypercholesterolemia also progressively increases. So, if on the 30th day of the experiment we noted an increase in the level of total cholesterol only by 1.38 times, then on the 60th and 90th days this indicator exceeded the values of intact animals by 1.92 and 2.3 times, according to deadlines.

The level of cholesterol in very low density lipoprotein after a monthly injection of cholesterol increased statistically significantly by 1.27 times, and after 2 and 3 months of administration - by 2 and 2.18 times, respectively, compared with the parameters of the intact group of rabbits. The content of cholesterol in low-density liporothy in the same terms of the experiment increased by 1.89; 2.81 and 3.65 times, respectively, relative to the values of intact rabbits, respectively, relative to the values of intact rabbits. At the same time, the level of cholesterol in high density lipoprotein decreased statistically significantly in 1.31; 1.27 and 1.61 times, respectively, on the 30th, 60th and 90th day of experiments compared with the indices of the intact group of animals.

As can be seen from the above data, in rabbits with exogenous administration of cholesterol, the development of dyslipoproteinemia is noted. Animals develop type III dyslipoproteinemia - dysbetalipoproteinemia [10] . According to the literature, this type of hyperlipoproteinemia is characterized by the presence of very low density lipoprotein and low density lipoprotein, which have a high cholesterol content and high electrophoretic mobility, i.e. the presence of pathological lipoproteins of very low density. The content of triglycerides and cholesterol is increased. It is this type that is often observed in atherosclerosis, combined with the development of coronary

insufficiency, a high degree of damage to the entire vascular bed, in some cases impaired glucose tolerance.

To determine the atherogenic risk in experimental animals, we calculated the coefficient of atherogenicity. The most dangerous situation for the body is when a high level of very low density lipoproteins or low density lipoproteins is combined with a low content of high density lipoproteins. The calculation of the coefficient of atherogenicity showed a high risk of atherosclerosis in experimental animals.

The coefficient of atherogenicity increases progressively with the duration of the administration of cholesterol to rabbits. This indicator, if after 1-month administration increased from 1.46±0.10 in intact rabbits to 3.47±0.18, statistically significantly exceeding the normative values by 2.38 times. In subsequent terms, this indicator progressively increases to 5.53±0.66 and 8.75±0.91, exceeding the values of intact animals by 3.79 and 6 times, respectively, in terms of 2 and 3 months.

The results obtained show that experimental atherosclerosis is characterized by an increase in the content of triglycerides and total cholesterol in the blood serum, and type III dyslipoproteinemia develops - dysbetalipoproteinemia. The severity of changes in the lipid spectrum of blood serum progressively increases as the duration of exogenous cholesterol administration increases with a sharp increase in the atherogenic coefficient. These data indicate the need to take into account their influence on the vascular wall and the formation of its dysfunction.

Conclusions . Experimental hypercholesterolemia is manifested by endothelial dysfunction. This is due to interrelated changes in the level of C-reactive protein, endothelin-1 and homocysteine, the severity of which depended on the duration of the experiment and the concentration of cholesterol in LDL, which leads to atherogenesis, disruption of the integrity of the vascular endothelium and its dysfunction. In the dynamics of hypercholesterolemia and atherosclerosis in the blood serum, there are noticeable disturbances in the NO -ergic system. These disorders are characterized by NO_x deficiency due to low NOS activity , as well as accumulation of peroxynitrite, a nitric oxide bioconversion product, due to an increase in nitrate reductase activity and,

apparently, failure of the antioxidant defense system. Undoubtedly, the definitions of nitric oxide in the blood serum are accompanied by defective functioning of mechanisms aimed at regulating the functional activity of not only the vascular endothelium, but also blood cells, contribute to the launch of the corresponding endothelial mechanisms on the feedback principle, which negatively affects the course and outcome of the studied pathology. This circumstance requires taking into account the violations we have identified in the choice of strategy and tactics for the treatment of hypercholesterolemia and atherosclerosis.

An important role in the development of endothelial dysfunction in hypercholesterolemia is played by a decrease in the synthesis of endothelial nitric oxide and an increase in its active radicals, causing modification of low-density lipoproteins and their deposition in the vascular endothelium.

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