CHANGE IN ACTIVITY OF OXIDATIVE ENZYMES OF THE MYOCARDIUM DURING DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS

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During the development of experimental cholesterol atherosclerosis in rabbits a decrease in activity of pyruvate, α-ketoglutarate, succinate, and malate dehydrogenases is observed.

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It is becoming increasingly clear from the results of experimental researches and clinical observations in recent years that the pathogenesis of atherosclerosis is based on profound disturbances of the general metabolism of the body [1, 3-7].

My previous investigations [8-11] showed that in the course of development of experimental atherosclerosis the intensity of cell respiration and other indices of oxidative metabolism are depressed in a number of tissues of the internal organs. It is therefore necessary to study the activity of enzymes taking part in the oxidation of substrates of the citrate cycle in the heart muscle during the development of this pathological condition.

The object of the present investigation was to study the activity of pyruvate, α-ketoglutarate, succinate, and malate dehydrogenases in the tissues of the heart muscle during the production of experimental atherosclerosis.

EXPERIMENTAL METHOD

Experiments were conducted on 32 male chinchilla rabbits weighing 3.0-3.5 kg, 12 of which acted as controls. Experimental atherosclerosis was reproduced by N. N. Anichkov's method. The experimental rabbits were fed on cholesterol for 120-130 days in a daily dose of 0.2 g/body weight.

To determine the degree of development of experimental atherosclerosis, the total cholesterol and phosphatide content in the blood serum was estimated periodically, once every 2 weeks, by the usual method [2]. After the animals had been sacrificed the degree of atherosclerotic changes in the aorta were assessed macroscopically on a four-point system. The heart was freed from connective and fatty tissue. A 10% homogenate of the muscle tissue of the left ventricle was then prepared in physiological saline. The enzyme activity was assayed quantitatively by means of tetrazolium salts [12], followed by measurement of the optical density of the formazan formed as a result of the catalytic effect of the corresponding enzyme systems with a photoelectric colorimeter. The comparative activity of the enzymes studied was expressed in units of optical density of formazan.

EXPERIMENTAL RESULTS

The degree of development of experimental atherosclerosis in animals fed with cholesterol for the same period of time (120-130 days) varied. The total blood cholesterol content of some animals was increased 3-5 times, for instance, whereas in others it rose by 15-20 times above the control level. Similar individual variations were also observed in the morphological changes in the aortic wall of the experimental animals. Three degrees of aortic involvement were distinguished: severe, moderate, and mild. The criterion used to assess the severity of the changes in the aorta was as follows. In severe lesions large, densely confluent connective tissue thickening, forming whitish atherosclerotic plaques, were found in all

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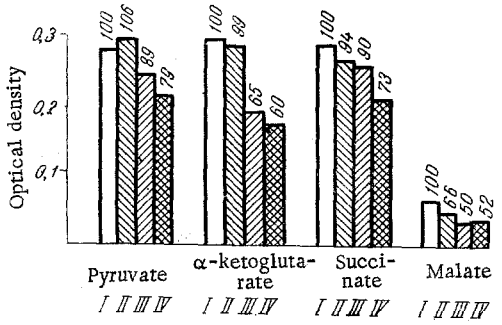

Fig. 1. Comparative activity of dehydrogenases of myocardial tissues or rabbits with various degrees of development of experimental atherosclerosis (mean data): I) control; II) mild atherosclerosis; III) moderately severe atherosclerosis; IV) severe atherosclerosis. The numbers above the columns denote enzymic activity of myocardial tissues of animals expressed as a percentage of control value.

parts of the aorta and projected to a marked degree into its lumen. In moderately severe lesions changes were present in certain parts of the aorta, mainly the arch, and the plaques were comparatively small in size. If isolated and very small atherosclerotic plaques, sometimes yellowish in color, were present the lesion in the aorta was described as mild. In our experimental conditions a severe lesion (3.7+) was observed in 50%, a moderately severe (2.2+) also in 25% of the experimental animals.

Comparison of the indices of lipid metabolism and the macroscopic picture of the atherosclerotic changes in the aorta suggests that experimental atherosclerosis of a varied degree of severity was produced in the experimental rabbits. This pathological model was used to investigate the enzymic activity of the heart muscle tissue.

The results (see Fig. 1) show that the catalytic activity of the investigated dehydrogenases in the heart muscle tissue of the animals with experimental atherosclerosis was reduced. Quantitatively, this decrease was dependent on the degree of development of the experimental atherosclerosis in different ways.

The greatest decrease in activity of the enzyme systems was observed in animals with severe atherosclerosis (4+).

Whereas the mean activity of the pyruvate, α-ketoglytarate, succinate, and malate dehydrogenases in the myocardium of healthy rabbits, expressed as optical density units, was 0.276 ± 0.016, 0.290 ± 0.023, 0.285 ± 0.012, and 0.056 ± 0.013 unit respectively in severe atherosclerosis of the aorta the pyruvate dehydrogenase activity was lowered by 21%, the α-ketoglutarate by 40%, the succinate by 27%, and the malate dehydrogenase activity by 48% compared with the control level ($P < 0.001$).

These results demonstrate that the degree by which the activity of the various enzyme systems was reduced in experimental atherosclerosis was different. It was greatest for malate dehydrogenase. This enzyme system is probably the weakest link of the tricarboxylic acid cycle.

A less-marked decrease in the enzyme activity of the myocardium was observed in the presence of moderately severe changes in the aorta (2.2+). In animals with mild changes in the aorta (0.2+), in most cases no change or only very slight changes were observed in the activity of the oxidative enzymes.

Comparison between the magnitude of the decrease in activity of the investigated dehydrogenases in the muscle tissue of the animals' heart and the severity of the atherosclerotic changes in their aorta reveals that their course is parallel to some extent. The greater the decrease in enzyme activity of the heart muscle, the more severe the atherosclerotic changes in the aorta.

The results obtained thus show that in experimental atherosclerosis profound disturbances of the activity of a series of dehydrogenases connected with important stages of oxidative metabolism take place in the heart muscle.

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