ROLE OF DYSLIPOPROTEINEMIA IN THE GENESIS OF CHRONIC HEPATITIS

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According to the concept in [11], hereditary dyslipoproteinemia (DLP) and the "atherogenic" potential of the blood are closely connected with the state of the liver function and, in particular, with a receptor defect of the hepatocytes. It was shown previously that DLP is accompanied by generalized disturbances of the microcirculation (MC) and structural and functional shifts in a number of target organs [2, 3, 8]. Meanwhile the problem of the character of the structural changes in different organs in DLP and during its correction has not been adequately discussed in the literature. We know that disorders of MC are not abolished during temporary regression of atherosclerosis [4] and remission of ischemic heart disease [9].

The aim of this investigation was to study the time course of structural changes in the liver at different stages of atherogenesis and during prolonged spontaneous regression.

EXPERIMENTAL METHOD

Experiments were carried out on 48 male Chinchilla rabbits weighing 2.5-3 kg. The animals were given cholesterol (CHS) with their food in a dose of 0.3 g/kg body weight together with vegetables (atherogenic diet – ATD). Rabbits of group 1 were kept on the ATD for between 4 and 12 weeks, animals of group 2, after 8 weeks on ATD, were transferred to the ordinary diet (36 weeks). The experimental animals were killed simultaneously with the controls by air embolism. Serum levels of the different lipoprotein fractions were studied [4] and the index of atherosclerotic involvement of the aorta (IAIA) was determined by G. G. Avtandilov's method. Traditional staining methods (hematoxylin and eosin, Goldman's and Van Gieson's) were used for light microscopy. Pieces of liver for electron microscopy were fixed in 1% buffered osmic acid solution at 0°C and embedded in Araldite; sections were stained with uranyl acetate and lead citrate by Reynolds' method and examined in the JEM-7A electron microscope.

EXPERIMENTAL RESULTS

In animals kept on the ATD for 4 weeks (group 1) IAIA was 2%, whereas after 8 and 12 weeks on ATD it was 22 and 41% respectively. After 8 weeks on ATD the blood level of atherogenic lipoproteins (LDL) was increased by 27 times, and that of the antiatherogenic (HDL) fourfold compared with the initial value.

The portal tracts in the liver after 4 weeks on ATD were dilated, with perivascular infiltration of lymphocytes and histiocytes; the number and size of the stellate reticulocytes (SR) in the sinusoids were increased. Hepatocytes (HC) were polymorphic, with signs of vacuolar and fatty degeneration; many binuclear cells and mitoses were observed. Signs of interlobular sclerosis were present.

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With an increase in the duration of the experiment (8-12 weeks on ATD) the structural changes in the liver were more marked. The portal tracts and central venules were drawn together, and massive foci of mononuclear infiltration and evidence of interlobular sclerosis were observed along the course of the portal tracts. Lipemic plasma and erythrocytic aggregates were seen in the lumen of the terminal parts of the portal vein and hepatic artery, accompanied by plasmarrhagia. Lipid inclusions and residual bodies were found in the endotheliocytes of the sinusoids, the number of endocytotic vesicles was reduced, the endothelium in some places was desquamated, erythrocytic aggregates and cell debris were present in the lumen of the microvessels and the Disse's spaces, and SR were reduced in number and size. The dystrophic changes in HC were progressive: the organelles contained vacuoles but no glycogen, the nuclei showed focal chromatolysis, the cytoplasmic reticulum was fragmented and its membranes degranulated, and the number of ribosomes and polysomes was reduced.

Reduction of the number of microvilli and pinocytotic vesicles at the sinusoidal pole, the subcytolemmal edema, and depletion of organelles at the biliary pole can evidently be interpreted as evidence of a disturbance of the absorptive and excretory functions of HC. A picture of micronodular cirrhosis was observed after 12 weeks.

Disturbances of MC, intensification of phagocytic activity of the RES, activation of metabolism in HC of the periportal zone with predominance of dystrophic changes in cells of the third zone of a simple acinus, and infiltration of the portal tracts with lymphocytes and histiocytes, discovered in the early stages of atherogenesis, are evidently connected with the entry of increased amounts of catecholamines and other stress-inducing agents into the blood stream.

Progression of the disorders of MC and blockade of RES by lipid degradation products and also, evidently, by immune complexes [7], discovered in the late stages of atherogenesis, are accompanied by "overstrain" of the function of the RES, structural rearrangement of the interstices, separating the microvessels and HC, and by the development of sclerotic and fibrotic changes.

To correct DLP, after 8 weeks on ATD some of the animals were returned to a normal diet (group 2). After 36 weeks of spontaneous regression a new rise of the blood level of the LDL fraction was observed in the animals, accompanied by a small and not significant rise of the HDL level; IAIA was 2.7.

In the liver the portal tracts were infiltrated by macrophages, the changes in the microvessels still remained, and perilobular bands of connective tissue were found. The endothelium of the sinusoids was reduced in thickness, and many clasmosomes were found in the lumen, in contact with SR and erythrocytes. Mainly small lipid inclusions were found in HC, various organelles (mitochondria, glycogen) were restored, accumulation of mitochondria around the lipid droplets and concentration of the latter near the nuclei took place, the number of secondary lysosomes was increased, and SR were activated. In some cases the structure of the sinusoids and Disse's spaces was disturbed, with capillarization of the sinusoids and increased synthesis of collagen fibrils.

Consequently, during long-term correction of DLP the vascular and tissue changes in the liver were not completely abolished despite regression of the atherosclerotic changes in the aorta, and they correlated with the intensity of DLP. Elevation of the blood LDL level during prolonged spontaneous regression was evidently due not only to resorption of lipids from the plaques and an increase in endogenous CHS synthesis, but also to its membrane pool.

These changes observed in the liver as a whole in the presence of short-term and stable DLP can be interpreted as different stages of nonspecific reactive hepatitis. It will be evident that prolonged exposure to a pathogenic factor such as DLP may be accompanied by the transition to a chronic pathological process in the target organs [5].

Since disturbances of MC in the liver arise before the appearance of atheromatous changes in the main vessels, the existence of a certain "independence" of the hepatic from the systemic circulation can be postulated.

The results of this investigation indicate an important role of DLP as a risk factor not only of cardiovascular diseases, but also of chronic noninfeotiolls pathology of the target organs.

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