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Features of electron microscopic changes in the liver of rats aged 24-26 months under conditions of hyperhomocysteinemia

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Disruption of the metabolism of the essential amino acid methionine causes the syndrome of hyperhomocysteinemia. This pathological condition is associated with the risk of developing a number of diseases, including chronic liver disease. The mechanisms of liver tissue damage in hyperhomocysteinemia remain poorly understood and require more detailed study. The aim of the study is to establish the features of submicroscopic changes in the liver structure of old rats with hyperhomocysteinemia. The experimental study was performed on 22 white nonlinear old (24-26 months) male rats, which were divided into a control group and an experimental group. A model of persistent hyperhomocysteinemia was created by administering to rats of experimental group of thiolactone homocysteine at a dose of 200 mg/kg body weight intragastrically for 60 days. The study of ultrastructural changes in the livers of rats was performed using an electron microscope PEM-125K. At experimental hyperhomocysteinemia in a liver of old rats there are changes in all structural components. Mitochondrial destruction and edema were observed in the vascular endothelium. Organelles have an enlightened matrix, a reduced number of cristae. A significant content of destructively altered mitochondria in endothelial cells indicates a failure of adaptation mechanisms. Erythrocyte sludges are observed in the lumens of the sinusoids. The number of fat-accumulating cells decreases, which indicates their transformation into fibroblasts and leads to the growth of collagen fibers, expansion of the sinusoidal spaces and the development of stromal fibrosis.

Keywords: hyperhomocysteinemia, mitochondria, stellate macrophages, endotheliocytes, fat cells, fibrosis.

Introduction

The problem of chronic liver disease has become extremely relevant recently. Due to its high growth and prevalence, scientists around the world note that chronic liver disease is the second epidemic of our century after the epidemic of cardiovascular disease. Among the known causes of liver disease (metabolic, autoimmune, drug-induced, toxic, genetic) are becoming increasingly important disorders of amino acid metabolism, especially methionine. Methionine is an essential proteinogenic amino acid that enters the human body with food [3, 7, 20]. During its metabolism, S-adenosylmethionine is formed, which participates in a number of transmethylation reactions. This produces S-adenosylhomocysteine, and it, in turn, is broken down into homocysteine and adenosine. It is known that homocysteine is a normal intermediate product of methionine metabolism, but under conditions of its excessive development, the syndrome of hyperhomocysteinemia

(HHC) develops, which is associated with the risk of various pathological conditions. These include non-alcoholic fatty liver disease, coronary heart disease, atherosclerosis, stroke [14, 16, 18]. The causes of HHC are usually genetic defects of enzymes of homocysteine metabolism (methylene tetrahydrofolate reductase, cystathionine- γ -synthase, methionine synthase), deficiency of vitamins B6, B9, B12, renal failure, alcoholism, etc. Under these conditions, it is not utilized by transsulfuration and remethylation reactions and accumulates in cells and blood plasma. It is believed that the most sensitive organ to the effects of HHC is the liver [5, 8, 13, 19]. However, the mechanisms of its damaging action are still being studied. The ability of homocysteine to cause the development of endothelial dysfunction by toxic effects on endothelial cells and the initiation of their apoptosis has been proven. In the cells of various organs, it causes damage to disulfide bonds

in proteins, disrupts transmethylation reactions, enhances the peroxidation of lipids and proteins. There are also data on the occurrence of mitochondrial dysfunction by the action of homocysteine on NO metabolism, and the latter is known to be a regulator of the function of these organelles [1, 2, 7].

Thus, the study of the features of morphological changes in the structure of the liver under HHC conditions at the submicroscopic level will significantly expand the understanding of the mechanisms underlying the pathogenesis of tissue damage of this organ.

The aim of the study is to establish the features of submicroscopic changes in the liver structure of old rats with hyperhomocysteinemia.

Materials and methods

The experiments were performed on 22 white nonlinear old (24-26 months) male rats, which were divided into a control group and an experimental group. A stable HHC model was created by administering to rats the experimental group of thiolactone homocysteine at a dose of 200 mg/kg body weight intragastrically for 60 days [9]. Animals were decontaminated by decapitation under thiopental anesthesia. For morphological examination, pieces of liver 0.5-1 mm in size were taken and fixed in a 2.5 % solution of glutaraldehyde with an active reaction medium pH 7.2-7.4, prepared on phosphate buffer. Next, the material was postfixed in a 1 % solution of osmium tetroxide according to Caulfield. Dehydrated in alcohols of increasing concentration (70 %, 80 %, 90 %, 100 %) and acetone [4, 6]. Poured into a mixture of epon-araldite. Semi-thin sections were made from the obtained blocks, which were stained with toluidine blue and according to Hyatt. After aiming at semi-thin sections, ultrathin sections contrast with 2 % uranyl acetate solution and lead citrate were made on LKB III (Sweden) and Reihart (Austria) ultramicrotomes. The preparations were examined and photographed under an electron microscope PEM-125K.

Results

At experimental HHC in the cytoplasm of hepatocytes of old rats, dystrophic changes with destruction of intracellular membrane organelles are revealed. Ultrastructural organization of liver cells is polymorphic. Their nuclei contained depths of condensed chromatin, which are localized both on the inner membrane and diffusely distributed in the karyoplasm. The proportion of euchromatin was lower than in intact old rats. Karyoplasm had a reduced electron density. The nuclear envelope is smooth, moderately fluffy, revealed foci of lysis. Perinuclear spaces are significantly expanded. In some hepatocytes the nuclei are pyknotically altered, while in others karyolysis was detected. The electron density of the cytoplasm of liver cells is not homogeneous, there are dark and light cells. The tubules of the endoplasmic reticulum and the Golgi complex are dilated, the mitochondria are enlarged, and the matrix in them is illuminated, indicating edema. The granular

endoplasmic reticulum had cisterns in the form of electron-transparent vesicles. Significantly fewer number of ribosomes are associated with endoplasmic reticulum membranes, as well as free ribosomes and polysomes, compared to those in intact old rats. Cristae in mitochondria are destructured, in some of them the outer membrane is broken. Inclusion of glycogen in the cytoplasm of hepatocytes was rarely detected. The fat droplets were larger than those in intact old rats. Plasmolemma in some hepatocytes is not continuous. The nuclei are not homogeneous in shape and electron density and, along with spherical ones, showed scallops with chromatin condensed at the edges and single nucleoli. There are hepatocytes with pyknotic nuclei. The lumens of the bile ducts are dilated.

Pathological changes in the structure of mitochondria were more pronounced than in young and mature rats under experimental HHC. The organelles were characterized by signs of edema, were large, and contained isolated disorganized cristae. In part of the mitochondria, the cristae and focal outer membranes are completely destroyed. Internal mitochondrial granules are practically absent (Fig. 1, Fig. 2, Fig. 3, Fig. 4).

Fig. 1. Electronogram of the liver of an old rat with hyperhomocysteinemia: 1 - karyopyknosis; 2 - hepatocyte cytoplasmic edema; 3 - edema of the mitochondrial matrix; 4 - autophagosomes; 5 - collagen fibers in the perisinusoidal space. x3200.

Fig. 2. Electronogram of the liver of an old rat with hyperhomocysteinemia: 1 - karyolysis; 2 - hepatocyte cytoplasmic edema; 3 - numerous lysosomes; 4 - autophagosomes; 5 - mitochondria with destroyed cristae and matrix edema. x6000.

Fig. 3. Electronogram of the liver of an old rat with hyperhomocysteinemia: 1 - edema of the cytoplasm of the hepatocyte; 2 - edema of the mitochondrial matrix; 3 - tubules of the granular endoplasmic reticulum; 4 - autophagosomes; 5 - granules of glycogen. x8000.

Fig. 4. Electronogram of the liver of an old rat with hyperhomocysteinemia: 1 - edema of the cytoplasm of the hepatocyte; 2 - mitochondria; 3 - expanded tanks of the endoplasmic reticulum; 4 - lysosomes. x8000.

Fig. 5. Electronogram of the liver of an old rat with hyperhomocysteinemia: 1 - lumen of the sinusoid; 2 - cytoplasm of endothelial cells; 3 - the nucleus of the stellate macrophage; 4 - cytoplasm of stellate macrophage; 5 - pyknotic nucleus of the hepatocyte; 6 - lysis of the cytoplasm of the hepatocyte; 7 - collagen fibers. x3200.

In some hepatocytes, the tubules of the granular endoplasmic reticulum are fragmented. In their cytoplasm only single granules of glycogen are found. The Golgi complex is hypertrophied, consisting of disorganized smooth membranes and large electron-transparent bubbles of irregular shape. Significant destructive changes of mitochondria and membranes of the endoplasmic reticulum

are characteristic, as well as low electron density of hyaloplasm, which indicates edema and disruption of compensation processes.

Plasma membranes are significantly fluffy, foci lysed. The lumens of the bile ducts are dilated, contain virtually no microvilli. Perisinusoid spaces are expanded, filled with shortened, swollen microvilli and remnants of destroyed organelles.

The cytoplasm of endothelial cells in the walls of the sinusoids is electron-light and contains a small number of organelles, which manifests its edema. Reduced number of ribosomes and polysomes freely located in the cytoplasm, autophagosomes are available. The nuclei of endothelial cells contained mainly condensed chromatin, the granules of which are located not only under the nucleoplasm, but also in the central regions of the nuclei. The nuclear membrane is significantly fluffy, perinuclear spaces are unevenly expanded. In the cytoplasm of endothelial cells of old rats at HHC, mitochondria with signs of edema were detected, which contained single cristae, in some mitochondria the outer membranes and cristae were destroyed. The granular endoplasmic reticulum is poorly developed and is represented by vacuoles located separately in the cytoplasm. The number of ribosomes associated with its membranes is smaller compared to those in older intact rats. The Golgi complex is reduced. In endotheliocytes of sinusoidal walls the adluminal cytoplasmic membrane is focally lysed, fluffy, weakly contoured. Detritus, osmophilic, degeneratively altered fragments of membranes and organelles were detected in the lumens of sinusoids.

In old rats with hyperhomocysteinemia, the ultrastructure of stellate macrophages is polymorphic. Some of them contained well-developed organelles, but adjacent cells in which the organelles are dystrophically and destructively altered located along. In their cytoplasm, mitochondria are swollen, have a coarse fibrous matrix, cristae and outer membranes are lysed. The membranes of the granular endoplasmic reticulum are loosened and destroyed in some places. In the cytoplasm of stellate macrophages, the number of autophagosomes and heterophagosomes is higher than in intact old rats. Perisinusoid spaces are expanded, filled with collagen fibers, among which are fibroblasts. In the cytoplasm of the latter there is a well-developed granular endoplasmic reticulum, Golgi complex and numerous mitochondria with densely arranged cristae, which indicated increased functional activity of these cells. Destructively altered organelles, numerous vacuoles, and residual osmophilic bodies were often found in the cytoplasm of stellate macrophages. Along with endotheliocytes with hyperchromic nuclei and electron-light cytoplasm, which contained swollen mitochondria and a small number of pinocytic vesicles, those characterized by electron-dense cytoplasm were found, and their peripheral zone was thickened in comparison with that in the old intact. The lumens of the sinusoids are dilated, they contain sludge of

Fig. 6. Electronogram of the liver of an old rat with hyperhomocysteinemia: 1 - lumen of the sinusoid; 2 - cytoplasm of endothelial cells; 3 - collagen fibers. x8000.

erythrocytes, numerous platelets and leukocytes (Fig. 5).

In the lumens of the sinusoids, numerous stellate macrophagocytes and platelets, which were in contact with the plasmalemma of endothelial cells, were often found. In the cytoplasm, their vacuoles, endoplasmic reticulum tubules, and Golgi complexes were dilated. Mitochondria are polymorphic. Enlightened mitochondria with destructured cristae were often identified. The nuclei in endothelial cells are swollen, osmophilic (Fig. 6).

Discussion

Research suggests a close link between HHC syndrome and the onset and progression of liver disease. Below are some of them, which are consistent with the results of our experiment.

It is established that chronic HHC is the cause of non-alcoholic fatty liver disease. In patients with this condition, a significant increase in blood homocysteine levels is registered. There is also an increase in transaminases (AST, ALT), gamma-glutamyltranspeptidase, alkaline phosphatase, hyperbilirubinemia. The reason for these changes is a violation of the structural and functional integrity of hepatocytes with the development of cholestasis syndrome and disorders of detoxification function of the liver. In addition, patients showed hypoproteinemia, dysproteinemia and hyperlipidemia, which significantly worsened the course of the disease and was a risk of complications [15].

In acute methionine HHC in the liver of rats, disturbances of methylation and transsulfation processes are registered, due to increased activity of methionine adenosyltransferase, cystathionine- β -synthase, cystathionine- γ -lyase and decreased activity of betaine-homocysteine methyltransferase and S-adenosylhomocysteine hydrolase. In addition, the level of NADPH oxidase, the major producer of superoxide anion, and the decrease in thioredoxin reductase, a key enzyme in the thioredoxin system, increase. The latter is involved in the regulation of the activity of redox-sensitive proteins and the formation of deoxyribonucleotides. It is likely that the HHC-induced decrease in thioredoxin reductase activity will have a negative effect on the functional state of redox-sensitive proteins and the replication process [17].

Prolonged administration of thiolactone initiates hepatic fibrogenesis in rats, which is manifested by hepatomegaly, increased serum hyaluronic acid, increased liver hydroxyproline. One of the mechanisms of fibrogenic action of homocysteine, according to researchers, is the activation of oxidative stress, manifested by symptoms of oxidative modification of proteins, decreased activity of aconitase and thioredoxin reductase, activation of prooxidant enzymes NADPH oxidase and xanthine oxidase in the liver [10, 11].

Chronic HHC causes liver fibrosis. Histological examination revealed dilation of the intercellular spaces of hepatocytes and perisinusoidal spaces, which were filled with collagen fibers, stellate macrophages, lymphocytes and numerous fibroblasts. The most intense accumulation of connective tissue was found around the portal tracts. Observed the presence of fatty degeneration, and sometimes necrosis of hepatocytes. Most of them were polymorphic, there are elongated hepatocytes around the foci of necrosis. Macrophages had a spherical shape, enlightened cytoplasm, hyperchromic nuclei with marginal chromatin. The lumens of the sinusoidal capillaries were dilated, hyperemic, revealed the marginal position of erythrocytes and diapedesis of leukocytes through the capillary wall. The cytoplasm of endothelial cells was heterogeneous, with both hypochromic cells with signs of edema and hyperchromic cells with pyknotic nuclei. The endothelial layer contained areas of endothelial cell desquamation and foci of proliferation. The walls of the arterioles were thickened due to hyperplasia and hypertrophy of smooth myocytes in the middle membrane, as well as due to sclerosis and fibrosis of the outer shell. The walls of the bile ducts were also thickened, sclerosed [12].

Conclusions

Ultrastructural analysis showed that at experimental HHC in the liver of old rats there are changes in all structural components. Destruction and edema of mitochondria are observed in the vascular endothelium. Organelles have an enlightened matrix, a reduced number of cristae. A significant number of destructively altered mitochondria in endothelial cells indicates a failure of adaptation mechanisms. Changing the structure of endothelial cells leads to increased adhesion of platelets, erythrocytes and leukocytes. Erythrocyte sludge appear in the lumens of the sinusoids. In the latter, the number of stellate macrophagocytes is greater than in intact rats and their migration to the sinusoidal spaces is enhanced. Fewer number of fat cells indicate their transformation into fibroblasts, which leads to the growth of collagen fibers, expansion of the sinusoidal spaces, the development of stroma fibrosis, as well as the compaction of the basement membrane around sinusoidal endothelial cells and thickening of the barrier between blood and hepatocytes, and hence, disruption of transport of substances, oxygen. The latter caused the development of hypoxia and oxidative stress.

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ОСОБЛИВОСТІ ЕЛЕКТРОННО-МІКРОСКОПІЧНИХ ЗМІН В ПЕЧІНЦІ ЩУРІВ ВІКОМ 24-26 МІСЯЦІВ ЗА УМОВ ГІПЕРГОМОЦИСТЕІНЕМІЇ

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Порушення обміну есенціальної амінокислоти метіоніну стає причиною виникнення синдрому гіпергомоцистеїнемії. Даний патологічний стан асоціюється з ризиком розвитку цілого ряду захворювань, в тому числі і з хронічними хворобами печінки. Механізми ураження тканини печінки за умов гіпергомоцистеїнемії залишаються недостатньо розкритими та потребують більш детального вивчення. Метою дослідження є встановлення особливостей субмікроскопічних змін структури печінки старих щурів при гіпергомоцистеїнемії. Експериментальне дослідження проведено на 22 білих неплітних старих (24-26 місяців) щурах-самцях, яких було поділено на групу контролю та дослідну групу. Модель стійкої гіпергомоцистеїнемії створювали шляхом введення щурам дослідної групи тіолактону гомоцистеїну в дозі 200 мг/кг маси тіла інтрагастрально протягом 60 днів. Вивчення ультраструктурних змін в легенях щурів проводили за допомогою електронного мікроскопу ПЕМ-125К. При експериментальній гіпергомоцистеїнемії в печінці старих щурів відбуваються зміни в усіх структурних компонентах. В ендотелії судин спостерігали деструкцію та набряк мітохондрій. Органели мають просвітлений матрикс, зменшену кількість крист. Значний вміст деструктивно змінених мітохондрій в ендотеліоцитах вказує на зрів адаптаційних механізмів. Спостерігаються складні еритроцитів в просвітах синусоїдів. Зменшується кількість жиронакопичувальних клітин, що свідчить про трансформації їх в фібробласти та призводить до розростання колагенових волокон, розширення перисинусоїдальних просторів і розвитку фіброзу стромі.

Ключові слова: гіпергомоцистеїнемія, мітохондрії, зірчасті макрофаги, ендотеліоцити, жиронакопичувальні клітини, фіброз.

ОСОБЕННОСТИ ЭЛЕКТРОННО-МИКРОСКОПИЧЕСКИХ ИЗМЕНЕНИЙ В ПЕЧЕНИ КРЫС В ВОЗРАСТЕ 24-26 МЕСЯЦЕВ В УСЛОВИЯХ ГИПЕРГОМОЦИСТЕИНЕМИИ

Галаган Ю. В., Маевский А. Е., Гуминский Ю. И., Король А. П., Прокопенко С. В.

Нарушение обмена эссенциальной аминокислоты метионина становится причиной возникновения синдрома гипергомоцистеинемии. Данное патологическое состояние ассоциируется с риском развития целого ряда заболеваний, в том числе и с хроническими болезнями печени. Механизмы поражения ткани печени в условиях гипергомоцистеинемии остаются недостаточно раскрытыми и требуют более детального изучения. Целью исследования является установление особенностей субмикроскопических изменений структуры печени старых крыс при гипергомоцистеинемии. Экспериментальное исследование проведено на 22 белых нелинейных старых (24-26 месяцев) крысах-самцах, которые были разделены на группу контроля и исследовательскую группу. Модель устойчивой гипергомоцистеинемии создавали путем введения крысам исследовательской группы тиолактона гомоцистеина в дозе 200 мг/кг массы тела интрагастрально в течении 60 дней. Изучение ультраструктурных изменений в легких крыс проводили с помощью электронного микроскопа ПЭМ-125К. При экспериментальной гипергомоцистеинемии в печени старых крыс происходят изменения во всех структурных компонентах. В эндотелии сосудов наблюдали деструкцию и отек митохондрий. Органеллы имеют просветленный матрикс, уменьшенное количество крист. Значительное содержание деструктивно измененных митохондрий в эндотелиоцитах указывает на срыв адаптационных механизмов. Наблюдаются сладжи эритроцитов в просветах синусоидов. Уменьшается количество жиронакопительных клеток, что свидетельствует о трансформации их в фибробласты и приводит к разрастанию коллагеновых волокон, расширению пересинусоидальных пространств и развитию фиброза стромы.

Ключевые слова: гипергомоцистеинемия, митохондрии, звездчатые макрофаги, эндотелиоциты, жиронакопительные клетки, фиброз.