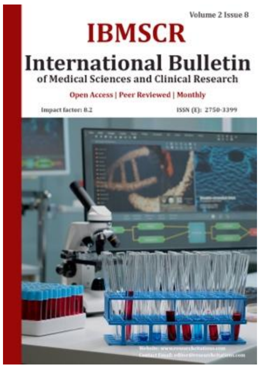

MORPHOLOGICAL FEATURES OF THE LIVER IN EXPERIMENTAL GELATRIN TOXIC HEPATITIS

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Relevance. In recent decades, there has been a steady increase in liver diseases. The forecasts for the growth rate of these pathologies are disappointing: it is assumed that against the backdrop of continuing chemicalization and environmental pollution, an increase in the incidence of hepatitis and cirrhosis of the liver by another 30-50% should be expected in the coming decades. According to the WHO, the incidence of toxic liver damage has increased 6-8 times worldwide since 1960.

Active study of protein and nucleic acid biosynthesis in pathological conditions and diseases is of great interest, since it is these processes that primarily characterize the degree and depth of functional disorders and determine the level of reparative processes in organs and tissues. Until now, it has been generally accepted that organ regeneration, including that of the liver, is ensured by cell division, compensatory hypertrophy, multinucleation, and polyploidy of cells.

As is well known, all these factors are most pronounced in the liver. However, there are still some aspects that have not yet been fully studied. To address this issue, we reproduced a model of hepatitis—chronic poisoning of the liver with a hepatotropic poison, heliotrine. The test animals were also white mongrel rats with a body weight of 160-180.0 g.

The bait was produced according to the scheme of H.Y. Karimov (1979). [3]. Toxic liver damage is the most common pathology. Toxic liver damage, accompanied by subsequent diffuse damage to hepatocytes due to liver ischemia, causes serious metabolic disorders, in particular protein metabolism [4].

Active study of protein and nucleic acid biosynthesis in pathological conditions and diseases is of great interest, since it is these processes that primarily characterize the degree and depth of functional disorders and determine the level of reparative processes in organs and tissues [5].

Objective. To study the morphology of extrusion of the granular apparatus of hepatocyte nucleoli in the dynamics of experimental chronic toxic hepatitis in rats.

Research objectives:

- to establish the relationship between the regenerative process and its connection with the nuclear apparatus, in particular with the state of nucleoli during the development of the pathological process (heliotrin hepatitis) in an experiment with white rats;

- to study the possibility of hepatocyte nucleoli migration in patients without liver pathology and with liver pathology (to prove the universality of this process in mammals).

Materials and methods. The study material consisted of 48 livers from white, sexually mature rats of both sexes, weighing 180-200 g. The animals were subjected to modeling of

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heliobacter toxic hepatitis, for which a 1% solution of heliobacter was administered intraperitoneally once a week for 2 months at a dose of 0.05 mg/g (5 mg of heliobacter per 100 g of rat weight), according to the scheme of H.Ya. Karimov (1979).

The livers of white rats were examined, both normal and affected by toxic hepatitis. The experimental study was conducted in accordance with ethical standards for the treatment of animals, and the criteria of the international community and the European Convention for the Protection of Vertebrates Used for Experimental and Other Purposes were also observed. The animals were euthanized under light anesthesia (10 mg/kg body weight of sodium etaminal) [9]. Pieces of liver tissue for histological examination were fixed in a 12% solution of neutral formalin and, after standard processing, were embedded in paraffin wax.

Sections for histological examination were stained with hematoxylin and eosin. Photographs of the preparations were taken using a DN-300m microscope with a digital camera attached to a computer.

Morphometric methods: For morphometric data analysis, we used a manual method, an eyepiece micrometer, which is based on visual calculations directly under a microscope or on microphotographs using special devices.

Micrometer eyepiece — a micrometer scale on glass or photographic film inserted into the eyepiece of a microscope, with a division value of 0.01 mm. The dimensions of the structures under study are determined by the number of whole divisions on the micrometer scale, which has a millimeter pitch, and are supplemented by hundredths of a millimeter, counted on a rotating drum.

Results and discussion. Without going into detail about the morphological picture of toxic hepatitis caused by the administration of heliothrin (which has been described in numerous studies), we note that on day 60 we obtained a picture of toxic hepatitis. At the same time, it was established that in the liver parenchyma, along with foci of cell necrosis, there were also less altered hepatocytes, mainly consisting of mononuclear hepatocytes.

The structure of most hepatocytes is significantly altered, their cytoplasm is vacuolated or subjected to fatty degeneration, the contours of the nuclei are convoluted, chromatin forms small clusters in places, and most importantly, the structure of the nucleolus is not clearly differentiated or is revealed as coarse lumps in the nucleus. Due to the significant disruption of the nucleolus structure, their release in hepatocytes is less noticeable.

Nevertheless, mitotic division figures are observed in pathologically altered hepatocytes, although the completeness of these divisions is questionable. The disappearance of two- and multinucleated cells is apparently associated with a sharp decrease in the number of polyploid cells, which are the source of their formation during nucleolar regeneration.

The biological significance of binuclear hepatocytes remained unclear for a long time. Currently, many researchers believe that the formation of binuclear hepatocytes from mononuclear hepatocytes during reparative regeneration represents a reserve for polyploidization [7,8].

Thus, the activation of hepatocyte polyploidization in rat fetuses coincides with a decrease in mitotic activity and an increase in the formation of binuclear cells. Therefore, according to a number of authors, polyploidization is, from a biological point of view, equivalent to cell reproduction [1].

Many researchers have noted an increase in the number of binuclear hepatocytes after exposure to various damaging factors [12, 6]. Apparently, this gives reason to believe that this phenomenon is directly related to the restoration of the organ's structure. The biological significance of binuclear hepatocytes remained unclear for a long time.

Currently, many researchers believe that the formation ofbinucleated hepatocytes from mononucleated ones during reparative regeneration represents a reserve for polyploidization [7, 8]. During our research, we became convinced that the regeneration of liver hepatocytes in experimental animals occurs mainly due to hepatocyte hypertrophy. Morphometric research methods helped us in this.

When examining liver sections from the intact group of rats, well-defined hepatic lobules, beams converging toward the central vessel, and individual cells are observed. The sinusoids are smooth and elongated, and their boundaries are clearly visible. The central vein is large, with blood cells visible in it. Numerous blood cells are also visible in the sinusoids.

In addition to hepatocytes, endothelial cells lining the vessels from the inside are also visible, with their flattened nuclei being particularly noticeable. Hepatocytes are irregularly rounded in shape, ranging in size from 173 to 316 micrometers. The total number of hepatocytes per 0.1 mm^2 averages 218 cells. Binucleated hepatocytes are found, some of which have nuclei of different sizes. The nuclei are large and rounded, ranging in size from 77 to 119 µm, with clearly visible nucleoli; nuclei with two or more nucleoli are often observed.

Microscopically, most hepatocytes affected by fatty degeneration are round in shape, with oxyphilic cytoplasm and a single large nucleus in the center. However, there are numerous areas in the parenchyma where hepatocytes are in a state of necrosis.

The foci of necrosis vary from small focal areas to large extensive areas. Obviously, necrosis begins with cell damage by a pathogenic factor, and the pathologically altered cell becomes a target for interaction with lymphocytes. Next to the damaged hepatocyte is a small cell with a very dense nucleus but with a long cytoplasmic outgrowth that contacts its surface. This cell may be a Kupffer cell or a T-lymphocyte, which usually destroy foreign elements.

Along with necrosis, numerous nucleoli are found in well-preserved hepatocytes, which are in the process of leaving the nucleus. Several nucleoli are at different stages of passing through the nuclear envelope or entering the cytoplasm.

Sometimes nucleoli were found freely floating in the cytoplasm of hepatocytes (Fig. 4a). Cytological analysis of the condition of hepatocyte nucleoli showed that in pathological conditions, nucleoli also migrate from the nucleus to the cytoplasm of the cell. At high microscope magnifications, hepatocyte necrosis and the release of nucleoli into the cytoplasm are clearly visible.

Among the necrotic cells, there are hepatocytes in contact with a small cell with a dark nucleus, probably a lymphocyte. Evidently, in chronic hepatitis, when the liver is under the influence of a strong pathogenic or stress factor, the release of nucleoli increases sharply, but the karyoplasm of the hepatocyte nucleus becomes significantly lighter.

The results of morphological and morphometric studies showed a sharp increase in the number of binuclear hepatocytes on days 3-7 ($P1<0.0000$), with a sharp increase in the yield of nucleoli on the same days. The diameter of hepatocyte nuclei throughout the experiment was statistically significantly larger ($P1<0.0000$) than in the control ($P1=0.0008$) rats. The diameter of binuclear hepatocytes increased significantly on day 5 (P1<0.0000), while on the other days they did not differ significantly from the control group.

In addition, the diameter of single-nucleated hepatocytes also increased on the fifth day. Thus, it can be concluded that when toxic hepatitis is treated with anti-inflammatory drugs, along with the mitotic division of liver cells, the migration of hepatocyte nuclei also occurs. Moreover, this process is stimulated, especially on the 3rd, 5th, and 7th days, which may indicate the participation of nucleolus migration in the regenerative processes of the liver.

Thus, as our experimental studies show, prolonged administration of heliotrine causes toxic hepatitis, the main manifestations of which are fatty degeneration and necrosis of hepatocytes. In a pathologically altered liver, the nucleolus also migrates from the nucleus to the cytoplasm, but nuclei that have lost their nucleoli undergo structural changes and destruction.

Therefore, unlike control animals, in helotrin-induced liver damage, nucleolus migration is accompanied by disorganization of the nucleus structure, leading to cell death. In general, even in the presence of pathological processes, the intracellular mechanisms of nucleolus migration from the nucleus to the cytoplasm are preserved; however, after this process, the cells are likely to undergo death.

In cases of toxic liver damage, the number of polyploid cells decreases sharply. The structure of the nucleolus is also disrupted, and reparative regeneration of the liver is carried out through mitotic division of hepatocytes. According to many authors, the development of morphofunctional disorders in the body is associated with a violation of protein and nucleic acid metabolism in the liver, the main organ of detoxification. [10.]

Most researchers believe that the restoration of both normal and pathologically altered tissue occurs through the mitotic division of differentiated hepatocytes themselves. Thus, the regeneration of hepatocytes in the livers of experimental animals occurs mainly through hepatocyte hypertrophy [11.]

Conclusions: The results of our studies showed that the granular component of the nucleolus is present in all experimental groups, with the highest yield occurring on the 3rd and 5th days after treatment with Tuglizid. Moreover, in the experimental rats, it is possible to more clearly trace all stages of the nucleolus movement, especially the moment of penetration through the nuclear membrane.

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