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Toxic Liver Damage, New Aspects of Pathogenesis

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ABSTRACT

In the analytical article, the author reviews modern scientific studies of foreign and domestic authors devoted to the study of the pathogenesis of toxic liver lesions. The author analyzes the immuno-inflammatory mechanisms, oxidative stress, cytolytic breakdown of hepatocytes and neurointoxication processes, which are the basis of the pathogenesis of toxic liver lesions.

Toxic liver lesions include a wide group of diseases associated with the hepatotoxic effect of substances of various origins that cause morphological changes in liver tissue and associated metabolic disorders to varying degrees of severity. Some household chemicals, pesticides, alcohol, a number of medicines, substances of industrial origin have a hepatotoxic effect. Toxic liver lesions can also occur when poisoning with mushrooms and products containing aflotoxin (overwintered grain, corn, rice). It should be noted that toxic liver lesions can develop independently of the path of penetration of a substance toxic to the liver into the human body – inhalation, parenteral or internal [2].

Industrial toxicants, natural toxins, medicines, alcohol, viruses, etc. cause pathological changes in the liver that are diverse in their mechanisms of action and clinical manifestations [5].

There are more than 2 billion people in the world. a person with various hepatobiliary pathology, which is 100 times higher than the prevalence of HIV infection. The problem of liver diseases of toxic genesis is becoming increasingly relevant due to the high rates of development of the chemical and pharmaceutical industries, the introduction of their products into all spheres of human life. Among the etiological risk factors for the development of toxic liver lesions, irrational pharmacotherapy plays a special role [8].

The danger of environmental influence on the human body consists in its negative impact, both on the health of individuals and on the fitness of the population as a whole. In this regard, the assessment of the influence of external environmental factors on the health of the population is of particular relevance. When production factors act on the body, a nonspecific reaction develops aimed at preserving the biochemical and physiological homeostasis of a person. The severity of the body's responses, manifested in the intensification of the activity of adaptive mechanisms in response to a stressful situation, is determined not only by the strength and duration of exposure,

but also depends on the genetic characteristics of the organism. Among the occupational diseases of workers of petrochemical enterprises, toxic hepatitis is among the most common pathologies. The processes of biotransformation of hydrazine and its derivatives (heptyl), occurring with the participation of cytochrome P450 and flavin-containing monooxygenases in the liver, are associated with the formation of highly reactive intermediates (diazomethane, methyl radical, dimethyl-diazonium ions) and the initiation of free radical processes. Thus, when exposed to chemical toxicants, liver damage and the development of toxic hepatitis are likely [13].

Due to the increase in cases of acute liver diseases as a result of viral, alcoholic and medicinal effects, household and industrial intoxication, timely diagnosis of its lesion remains an urgent clinical task. Taking into account that the liver is the most important organ that ensures the maintenance of optimal blood glucose levels and the metabolism of monosaccharides, the use of stress tests with glucose, galactose in liver damage still remains an important diagnostic technique. It is known that the functional state of the liver can be judged by the results of the glucose tolerance test (GTT), based on the fact that any significant violation of the function and structure of liver cells will lead to a change in the rate of glycogen synthesis. Moreover, the test with the use of galactose (GalTT) is considered even more sensitive, since it is initially converted into glucose, which occurs only in liver cells and requires high energy consumption (ATP molecules), and only then glucose is also converted into glycogen with the consumption of ATP molecules. In pathology, this mechanism is violated first of all, which determines its diagnostic value [10].

Most hepatotoxic substances are artificially synthesized chemical compounds that do not have specific detoxification pathways. The complex chemical structure does not always allow them to be immediately included in the conjugation processes, which are mostly represented by enzymatic transformation reactions during natural detoxification. At the same time, there is a danger of a possible increase in the toxic effect, since a number of toxic metabolites (ammonia, mercaptan, phenols, pyrrole derivatives) have a pronounced hepatotropic effect and inhibit many liver enzyme systems. But, regardless of origin, all hepatotropic 12 poisons are characterized by the development of a wide range of dystrophic changes in hepatocytes, mainly with centrolobular localization of necrosis up to acute massive necrosis of the liver parenchyma. At the same time, protein and lipid metabolism usually suffers, which is expressed in a decrease in the content of prothrombin, albulin, β-lipoproteins, cholesterol and phospholipids in the blood, as well as in an increase in the concentration of bilirubin and the release into the blood of many enzymes, both specific and nonspecific for the liver. Despite the fact that the proportion of chemical liver lesions in the overall structure of organ diseases is relatively small (2-3%), the etiological role of chemicals, the number and variety of which is constantly growing, is very significant. The solution of a number of issues of the pathogenesis of severe forms of liver damage with the formation, in particular, of acute liver failure, protein and fatty liver dystrophy, is impossible in a clinic due to the limited suitability of clinical material for a detailed study of the mechanism and dynamics of the development of the pathological process in the liver with toxic organ damage [1,3,4,9]

Consequently, in the conditions of modeling toxic liver damage in experimental animals, the antitumor effect of cyclophosphane is not realized according to the assessment of the growth of the primary tumor node LLC. When combined with probucol, the growth rate of the primary tumor was 21.5%. The IIM index of the spontaneous metastasis of LLC into the lungs of mice with THP during treatment with cyclophosphane was insignificant and equal to 15.4%, compared with group III (without THP). With the combined use of cyclophosphane and probucol, this indicator increased by more than 4 times. In the most damaged organ, cyclophosphane inhibited the metastasis process by 24.3% [7].

Most of the medications that enter the body orally are lipophilic, non-polar substances, and therefore the transfer of their molecules through the bilipid layer of the cell membrane of the intestinal epithelium occurs by passive transport along a concentration gradient or, if they are hydrophilic polar substances, then their absorption occurs with the help of transport proteins such as albumins. In the liver, further elimination of medicinal substances is carried out by their transformation from nonpolar hydrophobic compounds into polar hydrophilic, as well as other stages of biotransformation of foreign compounds. This process takes place with the participation of hepatocyte enzymes (monooxygenases), which are located in microsomes and the Golgi complex, while the main active component of the oxidation processes is the multi-enzyme complex hemoprotein cytochrome P450 and the coenzyme nicotinamide adenine dinucleotide phosphate (NADP) [11].

Carbon tetrachloride (CCl4) and the products of its metabolic activation, being membranotropic poisons, are capable of causing the destruction of arachidonic acid, and this biochemical indicator is regarded by the authors as one of the main markers of toxic liver damage [7].

The main sources of cells for the treatment of liver diseases are: differentiated hepatocytes, stem cells obtained from fetal organs and organs of the adult body, including bone marrow – mesenchymal cells. The most promising source of human hepatocytes are embryonic stem cells and cells with induced pluripotency [8].

One of the integral elements of modern agrarian policy is the introduction of intensive forms of animal husbandry. However, the desire to maximize productivity through the introduction of intensive industrial technologies without sufficient consideration of the physiological needs of animals leads to metabolic reorientation, functional overload of organs and body systems against which pathology develops. At the same time, metabolic and liver diseases are the most widespread. Currently, there is no doubt about the pathogenetic role of free radical oxidation (SRO) processes in many diseases, including liver damage. This may be due to the direct modification of hepatocyte proteins by lipid peroxidation products (POL) and the indirect effect of the latter on the barrier function of membranes and the metabolism of structural proteins. The accumulation of bile acids in violation of bile secretion also initiates the formation of free radicals, the inactivation of which is suppressed in liver damage [6].

Hepatorenal syndrome (according to clinical data) and macroscopic changes in the kidneys were caused by the development of toxic nephropathy. The widespread lesion of tubules with mixed, fatty and protein epithelial dystrophy was accompanied by the accumulation of pigment masses of various shades of yellow, green and brown in their lumen by liver dystrophy along with toxic damage to internal organs. Massive necrosis usually occurs against the background of previous liver pathology (chronic hepatitis, cirrhosis). Necrotic changes and fatty infiltration of liver cells predominate in the picture of toxic hepatopathy, which distinguishes it from infectious hepatitis. Persistent liver alterations with mixed dystrophy and intrahepatic cholestasis are a feature of the action of this hepatotropic poison. The fatal outcome usually occurs in the stage of yellow dystrophy from organ failure [12].

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