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COMPARATIVE MORPHOFUNCTIONAL CHARACTERISTICS OF THE LIVER OF WHITES RATS WITH TOXIC CIRRHOSIS

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Annotation. The work is devoted to the analysis of the morphological features of the processes of folliculogenesis in the comparative aspect of studying the liver of humans and rats to identify morphofunctional correlations in experimental studies.

Keywords: rat, liver, toxic cirrhosis.

Relevance. The adverse effects of toxicants (and their metabolites) on the male and female organs of the reproductive system can be due to both direct cytotoxic effects and indirect effects due to disruption of the mechanisms of physiological regulation of their functions.

The direct effect of chemicals lies in their structural similarity to endogenous hormones (endocrine disruptors). Estrogen-like effects are inherent in a large number of different chemical compounds, which include herbicides, fungicides, insecticides, nematicides, organophosphates, pyrethroids, heavy metals, polychlorinated biphenyls (PCBs), phthalates [6, 8, 11, 12, 16, 19, 20, 22] . Interaction with endogenous hormones is possible through various mechanisms. First, xenobiotics affect the synthesis, secretion, transport, effects, metabolism and release of hormones. The second group of foreign compounds interferes with hormones at the receptor level. This group includes the phytoestrogens coumestrol, daidzein, genistein, drugs diethylstilbestrol, ethinyl estradiol, tamoxifen, as well as industrial products dichlorodiphenyl trichloromethylmethane (DDT), p-nonylphenol and bisphenol A. These substances interact with estrogen receptors and interfere with the process binding of endogenous hormones. The third group of substances - DDT metabolite p, p'-EEE and vinclozolin metabolites - block androgen receptors.

Chemical substances that act through metabolic activation and transformation into toxic metabolites include polycyclic aromatic hydrocarbons, cyclophosphamide, and ethanol. This also includes substances that cause induction or inhibition of various enzymes. Thus, ovarian dysfunction was observed with changes in the activity of microsomal monooxygenases, epoxide hydrases and transferases, which are actively involved in the metabolism of certain chemicals in the ovaries.

In addition, chemicals have an effect (stimulating or inhibiting steroid secretion) and changing the rate of hormonal synthesis. Changes in hormonal balance were observed in rodents under the influence of polycyclic halogenated hydrocarbons, including DDT, polychlorinated and polybrominated biphenyls, and tricresol [1,21,22,23,24,25,26,27,28].

High chemical reactivity underlies the action of heavy metals lead, cadmium, mercury, boron, which cause disturbances in the reproductive function of animals.

A large number of works are devoted to the study of the structure of the white rat and human liver under normal conditions and with toxic damage [1,15,16,17,18,19,20]. Among the current problems of morphology, comparative data on morphofunctional characteristics deserve special attention

experimental animals and humans and their species differences [1,29,30,31,32]. The scientific literature contains scattered data on the morphometric parameters of rat and human liver hepatocytes in normal conditions and in the dynamics of the development of toxic cirrhosis. There is practically no information revealing morphofunctional changes in the liver of rats in

the dynamics of the development of toxic cirrhosis, taking into account sex differences [1,2,3,4,5,6,7]. There is practically no information on the significance of lipofuscin in normal conditions and in cases of toxic liver damage [11,12,13,14]. There are few works that consider the quantitative histochemical assessment of glycogen content in the liver [1,8,9,10]. There are no precise morphometric indicators and histochemical studies of the activity of succinate dehydrogenase (SDH) and cytochrome oxidase (COX) in rat and human liver hepatocytes under normal conditions and with toxic damage.

Thus, modern ideas about morphofunctional

The normal state of the white rat and human liver and the dynamics of the development of toxic cirrhosis are fragmentary and contradictory; the need for further research.

The purpose of the study is to establish the morphofunctional characteristics of the liver in normal white rats and women and with its toxic damage.

Research methods. The studies were carried out in the experimental biological clinic of the Bukhara State University named after Abu Ali Ibn Sina on 30 white male Wistar rats weighing 150-180 g, kept under standard vivarium conditions and a diet for laboratory animals, in accordance with the rules of laboratory practice when conducting preclinical studies in UzR (GOST 3 51000.3-96 and GOST 51000.4-96).

Experimental studies on animals were carried out in accordance with the instructions recommended by the Uzbek Regulations, 1987 and "The Guide for the Care and Use of Laboratory Animals (National Academy Press Washington, D.C. 1996)." Efforts were made during the research to minimize animal suffering and reduce the number of samples used.

Experimental design. All experimental animals were divided into three groups (n=10). Animals of experimental groups I and II were administered a single dose of TiO2 NPs at a dose of 13.3 mg/kg and 133.3 mg/kg. The control group of animals was administered an isotonic solution of sodium chloride 0.9% in an equivalent volume. The selected concentrations of nanoparticles did not exceed the maximum tolerated dose (MTD) for a given metal. On the first, seventh and fourteenth days, blood was taken from the tail vein for morphological and biochemical studies.

Toxic cirrhosis of the liver was caused by intragastric priming with a 40% oil solution of carbon tetrachloride at a dose of 0.2 ml/100 g of animal weight twice a week (week) in the morning, 4 hours before feeding for 19 weeks. In parallel with this, instead of drinking water, the rats received a 5% ethanol solution from drinking bowls in the

free access throughout the entire experience. Animals were removed from the experiment after 3, 6, 9, 12, 16 and 19 weeks in the morning by decapitation using a guillotine under local anesthesia of the cervical region.

The rats in the control group were removed from the experiment at the end of the experiment.

Results. During the development of toxic liver cirrhosis in white rats, the individual characteristics and gender of the animals mattered. Pathological signs of cirrhosis were observed after 9 weeks in 55.00% of males, and after 12 weeks - in 100.00% of males and 30.00% of females. After 16 weeks, all animals were diagnosed with cirrhosis. In the liver of females, compared to males, pathological changes were less pronounced and were delayed by 3 weeks. In the liver of males and females at all stages of the experiment, diffuse necrosis of hepatocytes, focal hemorrhages and serous edema were detected. Focal areas of hydropic degeneration of hepatocytes were observed only at the first stage (3 weeks). After 3 weeks, there were no dark

hepatocytes in the liver of males and females. From the 6th to the 19th week, their group accumulations were detected. In females, in certain sections of the sections, swelling of the nuclei in the cells of the bile ducts was observed, and after 16 weeks, a pronounced proliferation of the bile ducts was detected in 35.00% of cases.

A similar, but mildly expressed pathology was observed only in the liver of one male after 19 weeks of the experiment. In the liver of animals, two ways of developing cirrhosis have been clearly identified: alterative and proliferative.

Against the background of established mono-multibular cirrhosis, mild focal interstitial hepatitis developed. In people at all stages of ALD, diffuse foci of hepatocyte necrosis, discomplexation of the lamellar structure and small foci of hemorrhage were detected. In some preparations at the OAH stage, a sharp blood filling of the sinusoidal capillaries was observed. Dark hepatocytes were rarely observed. Liver cirrhosis was preceded by focal interstitial hepatitis.

At all stages of the experiment, male and female white rats were found to have

polymorphism of hepatocytes, cloudy swelling of the cytoplasm and unclear boundaries of most cells. An increase in the average area of hepatocytes in males compared to the control was observed up to the 9th week by 1.62 ($p = 0.000$), and in females - up to the 12th week of the experiment by 1.86 times ($p = 0.000$). At the stage of cirrhosis, this indicator increased in males by 1.50 ($p = 0.000$), in females by 1.75 times ($p = 0.000$) compared to the control. Sex differences were revealed in the 3rd week of the experiment ($p=0.002$).

In people at the stage of steatosis and ADC, the intercellular boundaries of most

hepatocytes were well expressed, and the average cell area did not differ from the control group. At the same time, at the stage of OAS in men and

In women, this indicator decreased by 1.11 times ($p = 0.000$) compared to the control. The degree of influence of cirrhogenic factors on this indicator was 44.75% ($p = 0.000$) in rats, and 5.36% ($p = 0.000$) in humans.

The development of cirrhosis in male and female white rats was accompanied by polymorphism of hepatocyte nuclei and a significant increase in their average area with a predominance of euchromatin and an increase in the number of nucleoli (2-4).

At the stage of cirrhosis, the indicator increased in males by 1.26 ($p = 0.000$), in females by 1.44 times ($p = 0.000$) compared to the control. Sex differences were detected at week 6 ($p=0.002$).

In people at all stages of ALD, heterochromatin and 1-2 nucleoli were predominantly detected in the nuclei of hepatocytes. The average nuclear area was 1.06 times lower than the control value in men and women ($p=0.000$) only at the OAS stage. The degree of influence of cirrhosogenic factors on this indicator was 43.22% ($p = 0.000$) in rats, and 3.88% ($p = 0.006$) in humans.

Against the background of hypertrophy of hepatocytes and their nuclei, the NCO was reduced compared to the control by 1.20 times ($p = 0.000$): in male white rats at all stages of the experiment, and in females - from the 6th to the 19th week of the experiment. Sex differences were detected at weeks 3 and 9 ($p=0.000$).

In both men and women, the NCR index was 1.07 times higher than the control level ($p = 0.026$) only at the ADC stage. The degree of influence of cirrhogenic factors for this indicator was 16.38% ($p = 0.000$) in rats, and 3.76% ($p = 0.007$) in humans.Calculation of the average number of binucleate hepatocytes showed that this indicator in the white rat was significantly

lower than the control level throughout the entire experiment. After 19 weeks, the number of binucleate hepatocytes in the liver of males and females was 2.40 times lower than the control level (p=0.000).

In men and women at the stage of fatty steatosis and ADC, the amount binucleate hepatocytes were 1.14 (p=0.000) and 1.60 times (p=0.000) higher than the control value, respectively. At the OAH stage, this indicator decreased by 1.20 times (p=0.000) in both men and women. The degree of influence of cirrhosogenic factors on this indicator was 58.08% (p = 0.000) in rats, and 56.73% (p = 0.000) in humans.

In the rat liver, fatty degeneration to the stage of development of cirrhosis in some In cases (in 45.00% of males and 70.00% of females) it was localized diffusely, and in other cases (in 55.00% of males and 30.00% of females) - along the periphery of the lobules. After 3 weeks of the experiment, the average lipid area in the liver of males was 14.22%, in females 13.70%, and after 19 weeks – 11.90% and 16.07%, respectively. Sex differences were revealed at the 6th (p=0.000), 9th (p=0.000), 12th (p=0.000), 16th (p=0.000), 19th (p=0.000) weeks.

In both men and women, a pronounced accumulation of lipids in hepatocytes was observed at the stage of steatosis (16.00%) and ADC (17.50%), and was detected mainly focally. The degree of influence of cirrhosogenic factors on this indicator was 13.97% (p = 0.000) in rats, and 49.90% (p = 0.000) in humans.

At the stage of cirrhosis, the average area of connective tissue compared to the control in male white rats increased by 18.00 times (p=0.000), in females – by 24.00 times (p=0.000), in men – by 14.00 times (p= 0.000), and in women – 13.00 times (p=0.000). In rats, sex differences were established at the 9th (p = 0.023), 12th and 19th weeks (p = 0.000). In animals, predominantly bridging fibrosis was detected, and in humans, perihepatocellular fibrosis was detected, which predominated over centrilobular and portal fibrosis. The degree of influence of cirrhosogenic factors on this indicator was 82.12% (p = 0.000) in rats, and 78.66% (p = 0.000) in humans.

In white rat hepatocytes throughout the experiment, compared with the control, a significant decrease in the activity of SDH and COX was detected.

At the stage of cirrhosis, the average area of SDH activity decreased in males and females by 3.39 times (p=0.000), and CCO - by 1.39 times (p=0.000) compared to the control.

Conclusion. The development of experimental cirrhosis in white rats occurs slowly and is determined in all animals only 16 weeks after the start of the experiment. In male white rats, cirrhosis is detected 3 weeks earlier than in females. Pathological and histological signs of cirrhosis are observed after 9 weeks in 55.00% of males, and after 12 weeks - in 100.00% of males and 30.00% of females. The morphology of toxic liver damage in white rats is generally similar to that in humans; it has general patterns of development, characterized by typical structural and functional changes: necrosis of hepatocytes, severe fatty degeneration, proliferation of connective tissue and formation of false lobules. After 3 weeks of the experiment, the average area of lipids in the liver of males was 14.22%, in females 13.70% (p = 0.338). At the stage of cirrhosis, the average area of connective tissue compared to the control in male white rats increases by 18.00 times (p = 0.000), in females – by 24.00 times (p = 0.000).

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