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LIVER MORPHOLOGY IN ETHANOL - INDUCED ALCOHOL INTOXICATION

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Abstract
We studied the dynamics of hepatocyte proliferation after liver cirrhosis in rats, assessed the ratio of cell proliferation and cell death processes against the background of transforming growth factor β (TGF-β). Morphological changes in the liver in experimental cirrhosis were studied to assess the degree of fibrotic changes, the nature of hepatocyte damage and the state of the microcirculatory bed, the effect of TGF-β on regenerative processes in the liver by analyzing its effect on hepatocyte proliferation, activation of stellate cells and changes in the structure of the liver parenchyma.

Keywords: liver, morphology, rats, cirrhosis, regeneration, experiment

INTRODUCTION

Liver cirrhosis remains one of the leading causes of mortality among chronic liver diseases, despite significant advances in understanding its pathogenesis and treatment methods. The development of cirrhosis is characterized by progressive fibrosis, restructuring of the liver architecture, and loss of its regenerative potential. A key role in these processes is played by transforming growth factor β (TGF-β), which acts as the main mediator of fibrogenesis while simultaneously regulating hepatocyte proliferation. Among mammals, the liver has the most pronounced regenerative capacity [1,4,5,8,9,10].According to WHO data, in 2002, 786,000 people worldwide died from cirrhosis. The mortality rate from cirrhosis averaged 12.6 per 100,000 population (WHO, 2004). In Russia, cirrhosis is responsible for the death of approximately 50,000 people annually, with a mortality rate three times higher than the global average. Cirrhosis is the sixth most common cause of death in Russia, surpassing widespread oncological diseases such as stomach and colon cancers [17]. Mortality from cirrhosis more than doubled between 1999 and 2006, reaching 36 deaths per 100,000 population in 2006. According to WHO criteria, this is classified as a high mortality rate (over 25.0) for cirrhosis.Liver regeneration in cirrhosis is a complex process, hindered by excessive accumulation of the extracellular matrix and activation of hepatic stellate cells. TGF-β, being a multifunctional cytokine, paradoxically combines pro-fibrotic and anti-proliferative effects. Thus, further study of the clinical and morphological features of the liver is required, which will contribute to understanding the mechanisms of cirrhosis development and provide a key to developing effective methods for diagnosing, preventing, and treating the disease.

OBJECTIVE

To study the dynamics of hepatocyte proliferation after liver cirrhosis in rats, to evaluate the ratio of cell proliferation and cell death processes.

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MATERIAL AND METHODS

The work was performed using experimental animals: Wistar rats. The experiment was conducted on laboratory male Wistar rats weighing 200–250 g, which were induced to develop liver cirrhosis in order to model chronic liver damage. All experimental animals were kept in a vivarium equipped in accordance with the requirements of the "Sanitary Rules for the Arrangement, Equipment and Maintenance of Experimental Biological Clinics (Vivariums)" No. 1045-73. Animals were slaughtered using inhalation anesthesia with fluorothane vapor. In the experimental series (n=30), after opening the abdominal cavity, the liver was isolated without damaging it. Excision of biopsy material was performed 3, 7, 30 days after the experiment. Paraffin blocks and sections 5-7 μm thick were prepared, stained with heme-eosin, Van Gieson and Masson. The required areas were photographed. To reproduce the experimental cirrhosis, a classical model of toxic liver damage was used by repeated administration of ethanol in rats. When modeling liver cirrhosis, ethanol was used in experimental studies to study alcoholic liver disease. The effectiveness depended on the dose, duration and route of ethanol administration. Oral administration was performed through a gastric tube, preferably for a more accurate dosage. The accepted dosing scheme: 5-7 g / kg body weight / day (20-30% ethanol solution) in drinking water. A concentration of 20-30% provides a high degree of consumption without giving up liquid. This is equivalent to severe chronic alcohol intoxication in humans. Alternative scheme: 4-5 g/kg body weight/day by gavage. Used for more controlled ethanol consumption. Induction duration ranges from 1 to 3 months. At 8-12 weeks - initial stages of fibrosis and steatosis. At 16-24 weeks - pronounced morphological changes in the liver characteristic of cirrhosis (pseudolobes, necrosis, inflammation) against the background of ethanol intake. The control group received distilled water. Animals' condition was assessed by monitoring body weight, behavior, and blood biochemistry.

DISCUSSION AND RESULTS

Under experimental conditions, chronic alcohol intoxication with ethanol led to pronounced morphometric changes in the liver. A characteristic macroscopic change was an increase in liver size (hepatomegaly). The liver color changed to a yellowish-brown hue, and by the 7th day after ethanol exposure, the liver exhibited slight firmness. Microscopically, fine-droplet dystrophy was observed, with some hepatocytes showing signs of pyknosis and karyorrhexis. By the 30th day of the experiment, both macroscopic and microscopic signs had progressed. The liver color shifted from yellowish-brown to a grayish hue (Fig1**)**. Due to increased tissue density, fibrotic changes became evident, accompanied by pronounced granularity on the cut surface. Simultaneously, a decrease in the nuclear-cytoplasmic ratio is observed, which is attributed to cytoplasmic edema. Changes also affect the structure of hepatic trabeculae: their thickness increases, and instead of the normal 1–2 rows of cells, 3–4 rows are formed, which is characteristic of intoxication conditions. The density of sinusoids decreases due to their compression by hypertrophied hepatocytes (Fig 2). Pathological processes in the vascular system include a reduction in capillary density as well as disruption of the hepatic lobule architecture, which significantly impacts microcirculation and metabolic processes in liver tissue.

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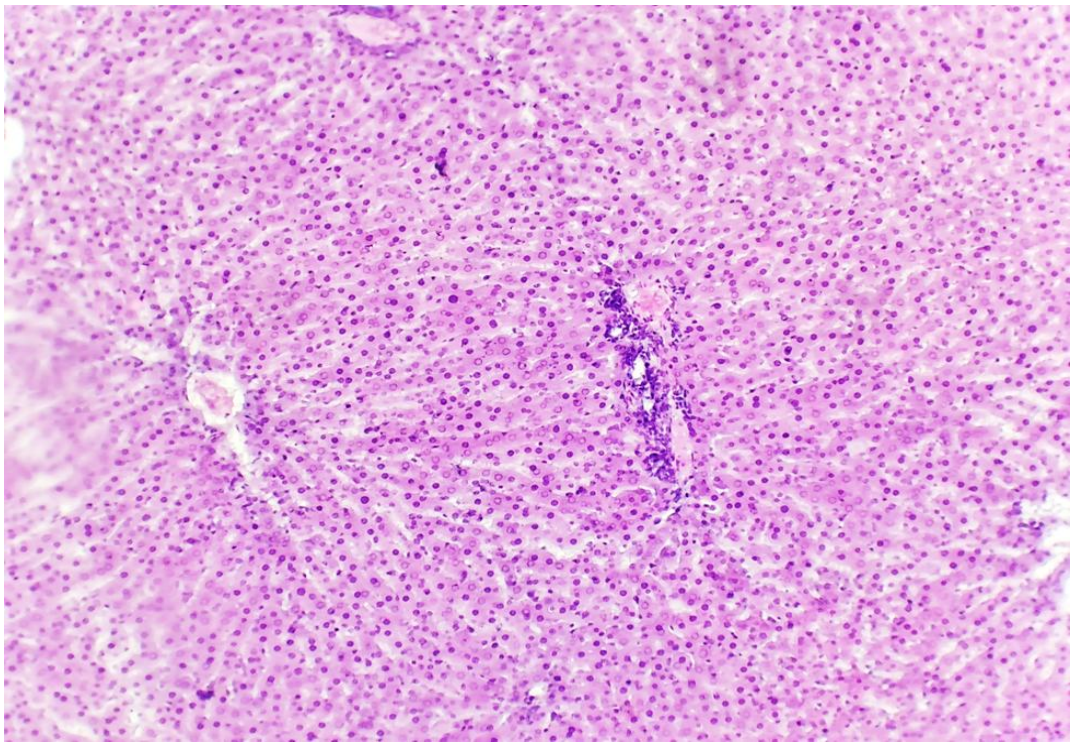

Fig 1 Microscopic view of the liver in the control group of rats. No changes were observed in the liver hepatocytes. The central lobule has a normal structure. Staining GE. Size 10x10.

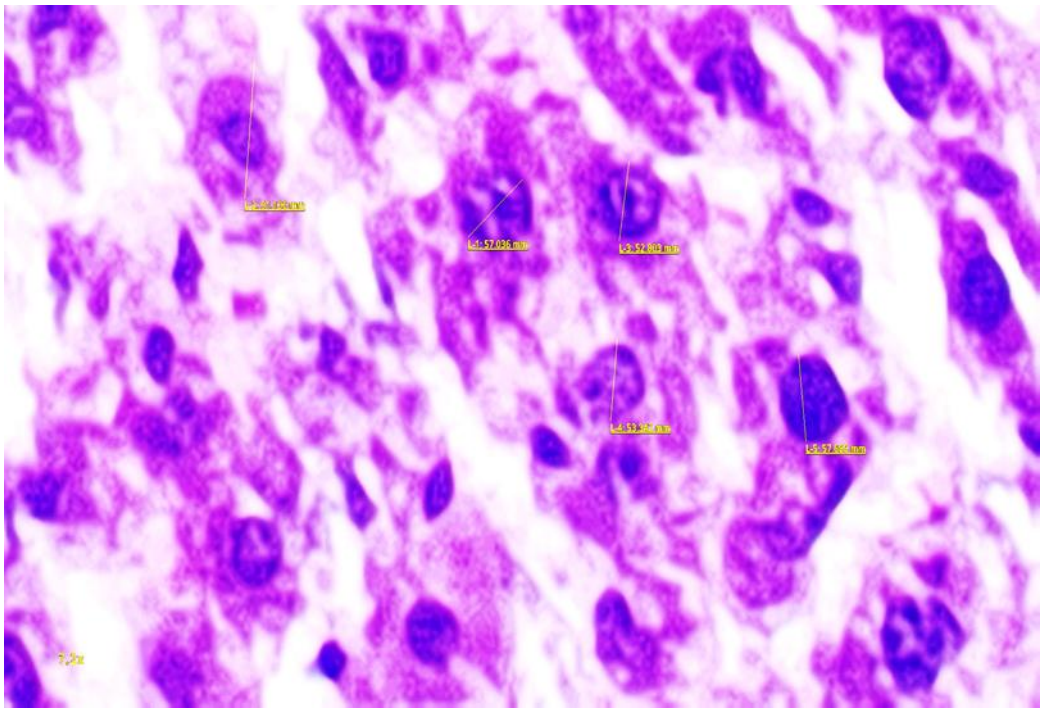

Fig 2. Morphometric changes in the liver under alcohol intoxication on the 7th day of the experiment in rats. Signs of parabiosis and dystrophic changes in hepatocytes are observed.. Staining GE. Size 10x40.

Table 1.

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Morphometric Parameters of Liver Vessels in Rats with Alcohol Intoxication in the Experiment

№	Diameter of the Hepatic Microcirculatory Bed	Control Group	Experimental Group with Ethanol-Induced Cirrhosis (μm))	Group with TGF-β Modulation on the Background of Ethanol-Induced Cirrhosis (μm)	**P <0,01**
1	**Central vein**	57,03 ±0,76	59,03 ±0,86*	58,05 ±0,26	0,01*
2	Interlobular vein	89,73±1,74	91,33±1,34*	90,55±1,27	0,01*
3	**Interlobular artery**	27,63±1,98	29,23±1,79*	28,53±1,41	0,01*
4	**Bile duct**	15,73±0,72	17,23±0,22*	16,53±0,25	0,01*
5	**Sinusoidal capillaries**	29,13±0,81	31,01±0,55*	30,15±0,51	0,01*

Morphometric parameters of liver vessels in rats with alcohol intoxication demonstrate statistically significant changes against the background of ethanol-induced cirrhosis and subsequent TGF-β modulation.In the experimental group, where alcohol intoxication with cirrhosis development was modeled, an increase in the diameter of all examined vascular structures was observed compared to the control group. Specifically, the diameter of the central vein increased from 57.03 ± 0.76 μm in the control group to 59.03 ± 0.86 μm in the experimental group (*P < 0.01). A similar trend was noted for the interlobular vein, whose diameter increased from 89.73 ± 1.74 μm to 91.33 ± 1.34 μm (*P < 0.01).The diameter of the interlobular artery also increased from 27.63 ± 1.98 μm in the control group to 29.23 ± 1.79 μm in the alcohol intoxication group. The diameter of the bile duct increased from 15.73 ± 0.72 μm to 17.23 ± 0.22 μm, while sinusoidal capillaries expanded from 29.13 ± 0.81 μm to 31.01 ± 0.55 μm (*P < 0.01 for all parameters).In the group of animals that received TGF-β modulation alongside alcohol intoxication, the vessel sizes were somewhat smaller than in the cirrhosis group but remained higher than the control values.

CONCLUSION

Morphometric changes in alcohol intoxication on the 7th day of the experiment are characterized by a significant increase in the size of hepatocytes, nuclei, and vacuoles, as well as progressive dystrophic changes and disruption of the structure of sinusoidal capillaries. These indicators allow for a quantitative assessment of the degree of liver damage under experimental conditions. Таким образом, алкогольная интоксикация приводит к увеличению диаметра всех исследованных сосудов печени, что отражает деструктивные процессы в тканях и сосудистом русле.

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Модуляция TGF-β несколько нивелирует данные изменения, что свидетельствует о его потенциальном защитном эффекте.

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