MORPHOLOGICAL CHANGES IN THE LIVER ASSOCIATED WITH SMALL INTESTINAL FISTULAS

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UDC 616.341-007.253-07:616.36-091

KEY WORDS: small intestinal fistulas; pathomorphosis of the liver; hepatic failure.

Small intestinal fistulas are known to cause changes in the state of liver function [3-5]. Despite much research into the state of the liver in association with small intestinal fistulas [6, 7] many aspects of this pathology remain unclear. The character of the morphologic changes in the liver tissue and the times of their onset have received little study. Some investigators have found marked vascular disturbances in the liver parenchyma in patients with small intestinal fistulas during the first week of their function. Considerable disruption of the hepatic trabecular complexes, fatty degeneration, and dystrophy of the hepatocytes are most marked in patients with high small intentinal fistulas [6]. Profound disturbances in the structure and function of the liver, leading to changes in homeostasis throughout the body [2, 9], explain why, despite modern methods of operative treatment and progress in intensive care, mortality from small intentinal fistulas remains high (20-60%) [1, 8, 10]. Determination of the character of the morphological changes in liver tissue and the times of their development, and also the study of the reversibility of this process, are of great importance for elucidation of the pathogenesis of hepatic failure associated with small intestinal fistulas.

In the investigation described below morphological changes in the liver associated with high, intermediate, and low small intestinal fistulas were studied in relation to the time of their functioning.

EXPERIMENTAL METHOD

Experiments were carried out on 360 non-inbred albino rats weighing 200-300 g, in which complete small intestinal fistulas were formed at different levels. All rats undergoing the operations were kept on an ordinary diet. Depending on the experimental conditions the animals were divided into five groups: 1) intact rats (control); 2) rats undergoing laparotomy only; 3) rats with low small intestinal fistulas; 4) rats with intermediate small intestinal fistulas; 5) rats with high small intestinal fistulas. The height of the fistula, assuming the total length of the small intestine in rats to be 80 cm, measured from the ileocecal angle, was as follows: low fistulas 5 cm, intermediate 35 cm, and high 75 cm. Loss of the intestinal contents through the fistulas caused severe wasting of the animals. In rats with high fistulas, by the end of the first week these losses amounted to 65%, and with intermediate fistulas 45% of the original body weight. Against the background of this progressive emaciation animals with high fistulas died toward the end of the 3rd week, and rats with intermediate fistulas toward the end of the 5th week. In rats with low fistulas, after loss of 30% of their body weight at the 3rd week, this parameter recovered by the 6th week. All the surviving rats were removed from the experiments at the end of the 6th week.

Animals from each group were killed synchronously by decapitation in intervals of 1 week. Pieces of liver tissue measuring 1 × 0.3 × 0.3 cm were taken from the right lobe of the liver for histological investigation. Part of the material was fixed in 10% neutral formalin solution, the rest in Carnoy's fluid. Paraffin sections were stained with hematoxylin and eosin and by Van Geison's method. Glycogen was studied by the PAS reaction, RNA was determined by Brachet's method, and fat was stained with Sudan III.

Chair of General Surgery, N. I. Pirogov Second Moscow Medical Institute. Department of Pathological Morphology, A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 11, pp. 606-609, November, 1986. Original article submitted January 13, 1986.

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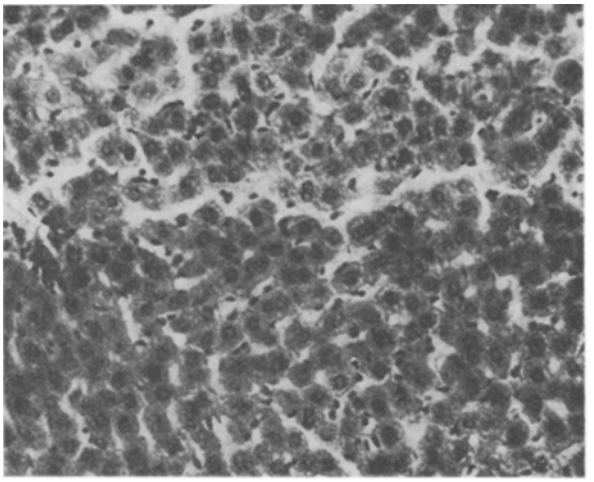

Fig. 1

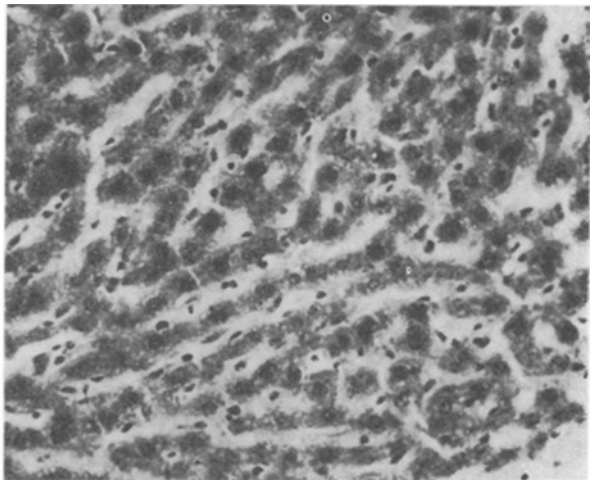

Fig. 2

Fig. 1. Morphologic pattern of the liver 3 weeks after formation of a low fistula in a rat. Moderate widening of Disse's spaces. Structure of hepatic lobules preserved. Many binuclear cells. Here and in Figs. 2 and 3: hematoxylin-eosin, 200×.

Fig. 2. Morphological pattern of the liver 1 week after formation of a high fistula in rat. Vacuolar degeneration of hepatocytes, thinning of hepatic trabeculae.

EXPERIMENTAL RESULTS

The liver preserved its ordinary trabecular-looped structure in the control rats and in animals undergoing only laparotomy. In animals with low fistulas 1 week after the operation marked dystrophic changes were observed: considerable edema, which separated the bands of liver cells, small vacuoles in the cytoplasm of the hepatocytes, and single foci of fatty infiltration in the substance of the hepatic parenchyma. The distribution of glycogen in the liver tissue was mosaic: areas rich in glycogen alternating with areas containing none. RNA deposits were preserved only in cells located in the center of the hepatic lobules. Infiltration of lymphocytes and plasma cells was not present in the hepatic lobules, and thin connective-tissue fibers were arranged around the periphery of the lobules. Edema of the parenchyma 2 weeks after the operation was less marked than at the previous time, but the dystrophic changes in the hepatocytes were more severe. Signs of vacuolar degeneration of the hepatocytes were particularly conspicuous. Evidence of fatty degeneration, accompanied by a reduction in the glycogen concentration in the liver parenchyma, was much more apparent. RNA granules in the cytoplasm of the liver cells were present in small numbers. Severe dystrophic changes in the hepatocytes 3 weeks after the operation were preserved only in a few animals, and they were most marked in the center of the lepatic lobules. In the majority of animals moderate dystrophic changes were observed in the liver parenchyma: widening of Disse's spaces and vacuolar degeneration of single hepatocytes. Many binuclear cells appeared in the hepatic perenchyma, evidence of regenerative processes in it (Fig. 1). Only solitary foci of fatty infiltration were present in the substance of the parenchyma. Glycogen granules in the liver cells were numerous. A positive reaction for RNA was present in the cytoplasm of the binuclear cells. In the 4th and 5th weeks after the operation, moderate degenerative changes were still present in the hepatic tissue. Edema of the liver tissue was found in the 6th week after the operation. No sclerotic changes were present in the stroma of the organ. Near the central veins solitary foci of infiltration of lymphocytes were observed.

Considerable degenerative changes were present in the liver of animals with high fistulas. Edema appeared in the liver tissue 1 week after the operation and congestive capillaries with thrombi in some of them were found. Against the background of marked circulatory disturbances vacuolar degeneration of the hepatocytes took place, with necrosis of some of them (Fig. 2). Fatty infiltration was local in character: Glycogen was absent from areas of the liver rich in fat, and conversely, areas of tissue not containing lipids were packed with glycogen granules. Meanwhile compensatory processes were taking place in the liver parenchyma: many binuclear cells and also cell darkening. Degenerative changes in the liver tissue 2 weeks after the operation were more severe, marked edema of the liver tissue was

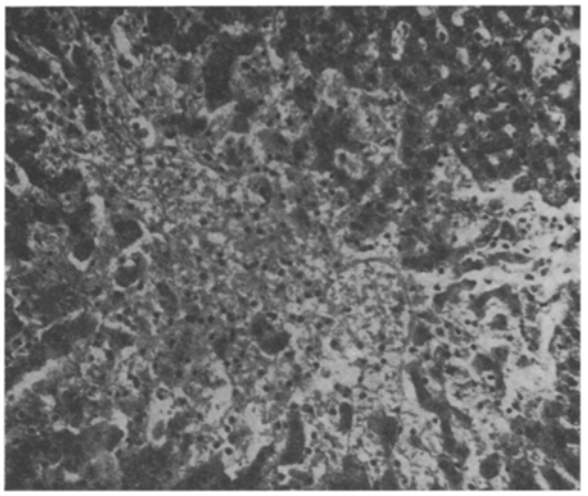

Fig. 3. Morphological pattern of the liver 3 weeks after formation of a high fistula in a rat. Massive areas of necrosis of the hepatic parenchyma.

observed, with thinning of the hepatic trabeculae, and considerable foci of necrosis in the center of the hepatic lobules. Large vacuoles were observed in the cytoplasm of those hepatocytes that were preserved around the periphery of the lobule. These cells were filled with small lipid droplets, but no glycogen was present in the cells rich in lipids, nor did they contain RNA granules. Necrobiotic processes in the liver became particularly intensive 3 weeks after the formation of high fistulas. By this time multiple massive areas of necrosis appeared in the liver tissue, accompanied by total fatty degeneration of the liver (Fig. 3). Meanwhile, evidence of compensation appeared, in the form of binuclear cells.

In intermediate small intestinal fistulas the pathological changes in the liver developed in two phases. In the 1st week after the operation vacuolar degeneration of the hepatocytes and necrosis in some of them were observed, together with the formation of small foci of necrosis of hepatocytes. The Disse's spaces were considerably widened. The hepatic parenchyma showed marked fatty degeneration. In the 2nd and 3rd weeks reparative processes were observed in the liver tissue: Edema was less marked than at the previous time, the liver tissue was compact in structure, and numerous dark cells and binuclear cells appeared. These cells were rich in RNA granules. Areas of fatty infiltration were very small. A brisk reaction of the Kupffer cells was observed. Sclerotic changes were not present in the parenchyma. In the 4th and 5th weeks edema of the liver tissue increased and this was accompanied by marked disturbance of the complex organization of the liver cells. Hepatic trabeculae were considerably thinner than before and fatty infiltration of the liver tissue was mosaic in character: regions rich in lipids alternating with regions without them.

Vacuolar degeneration of the hepatocytes is thus the basic form of liver pathology associated with small intestinal fistulas. It is reversible in the case of low fistulas, it is partially compensated in the case of intermediate fistulas, and it leads to profound necrobiotic changes in the liver tissue in association with high fistulas. According to the results of biochemical analysis, levels of lipolysis and proteolysis are raised in the presence of small intestinal fistulas, hypo- and dysproteinemia develop, and the serum fatty acid level rises [3, 4]. Considering the familiar morphological changes accompanying hepatic failure [4], it can be postulated that failure develops by the 4th week of functioning of intermediate fistulas and by the 2nd week of functioning of high fistulas. However, the fact is worthy of attention that even in the presence of advanced necrobiotic lesions in the hepatic parenchyma regenerative processes, characterized by the appearance of dark cells and binuclear cells, also are observed in the liver tissue. This suggests that reversibility of the severe structural changes in the liver associated with small intestinal fistulas can be expected as a result of the use of methods stimulating regeneration, and this is a matter of great importance for clinical practice.

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MORPHOLOGY OF THE ADRENERGIC AND CHOLINERGIC INNERVATION OF THE KIDNEY IN RATS WITH SPONTANEOUS AND GOLDBLATT HYPERTENSION

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UDC 616.12-008.331.1-02:616.136.7-007.271]-07:616-018.86

KEY WORDS: innervation of the kidney; morphology; arterial hypertension.

A special pattern of functioning, or "resetting" of the kidney is nowadays regarded as one of the most important steps in the pathogenesis of arterial hypertension [1, 2, 7]. Although the importance and pathogenetic role of "resetting" as a whole are not disputed, the intrarenal and extrarenal mechanisms of its realization have not been adequately studied. For instance, very little is known about the role of the intramural nerves in the development of "resetting" or in the pathogenesis of hypertension in general, even though their regulatory effect on various renal structures has been proved. In some investigations the development of spontaneous hypertension in rats was delayed after division of the renal nerves [4, 11, 12, 17], but neurophysiological investigations disagree in their conclusions regarding the importance of the renal nerves in the formation and prolongation of this hypertension. For instance, it was shown by recording activity of efferent sympathetic nerves [8, 14] that its level is much higher in spontaneously hypertensive rats (SHR) than in control animals. However, no differences in activity of the sympathetic renal innervation have been found between SHR and the normotensive control [6, 16]. Denervation of the kidneys in ischemic renal (Goldblatt) hypertension was shown that their nerves participate in the development of this form of hypertension also [5], although only the ischemic kidney has been studied by morphological methods, and no publications dealing with the state of the nerves in the contralateral "intact" kidney could be found (except [3]).

In accordance with the facts described above, it was decided to undertake a morphological study of the adrenergic and cholinergic nerves of the kidney at different stages of spontaneous and ischemic renal hypertension in rats.

EXPERIMENTAL METHOD

Experiments were carried out on male SHR rats aged 4, 8, 20, and 27 weeks, weighing on average 49 × 2, 222 × 6, 291 × 15, and 427 × 26 g. Normotensive rats (NTR) of the WKY line (Wistar-Kyoto), of the same sex and age, served as the control. Ischemic renal hypertension (bilateral, according to Goldblatt) was produced in inbred Wistar rats (from the Stolbovaya nursery, Academy of Medical Sciences of the USSR) by constriction of the left renal artery. The nonischemic, "intact," kidney was investigated. In these experiments intact rats of the same line, chosen by sex and age, served as the control. The investigation was conducted 4, 8-9, 20-22, and 27-28 weeks after the beginning of the experiment. The systolic arterial

(Presented by Academician of the Academy of Medical Sciences of the USSR A. I. Strukov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 11, pp. 609-612, November, 1986. Original article submitted February 21, 1986.

