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COURSE OF DEVELOPMENT OF ACUTE TOXIC HEPATITIS IN RATS STIMULATED WITH PRODIGIOSAN

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Acute toxic hepatitis was induced in Wistar rats by a single injection of 40% CCl_4 in peach oil in a dose of 0.2 ml/100 g body weight. During stimulation with the bacterial polysaccharide prodigiosan the resistance of the hepatocytes to CCl_4 rose sharply and this was reflected in a decrease in the severity of destruction of the hepatic parenchyma.

KEY WORDS: toxic hepatitis; prodigiosan; resistance of hepatocytes.

Previous investigations showed that the course of reparative regeneration of hepatocytes after partial resection of the liver in rats depends essentially on the initial functional state of the Kupffer macrophages [3]. Blockade of the Kupffer cells with granules of colloidal iron carbonyl, if carried out before or during the first few hours after the operation, appreciably inhibited the rate of DNA synthesis and of mitotic division of the hepatocytes. Conversely, preliminary stimulation of the mononuclear phagocyte system (MPS) with prodigiosan provided the conditions for more rapid regeneration of the hepatocytes in partially hepatectomized rats. The problem thus arose of the course of regeneration of the pathologically charged liver during functional reorganization of its stroma.

The results described in this paper reveal certain special features of the structural recovery of the hepatocytes after CCl_4 poisoning in rats with an activated MPS. The MPS was stimulated by means of the bacterial polysaccharide prodigiosan, a substance which has proved itself to be a reliable inducer of tachyphylaxis in many clinical and experimental investigations [2].

EXPERIMENTAL METHOD

Wistar rats of both sexes weighing 200-250 g were used. Toxic hepatitis was induced by a single injection of a 40% solution of CCl_4 in peach oil in a dose of 0.2 ml/100 g body weight. An intraperitoneal injection of 50 μg prodigiosan (experiment) or of 0.85% NaCl (control) was given to the rats 24 h before poisoning. Changes in the structure of the liver were noted 16, 24, 48, and 72 h after poisoning. Zones of damage were measured under a magnification of 100 times by means of a grid mounted in the ocular, dividing the field of vision into 16 squares, in sections stained with hematoxylin-eosin and by the PAS method. The mean number of points of intersection of the lines of the grid falling on the area of the zone of damage was determined in 30 fields of vision. The numerical results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

In the rats of the control and experimental groups the formation of acute toxic hepatitis on the first day after poisoning was accompanied by the appearance of foci of necrosis in the central zones of the hepatic lobules, and by signs of "balloon" and eosinophilic degeneration spreading from the center of the lobule to its

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TABLE 1. Characteristics of Liver Damage after a Single Injection of CCl_4 in Rats Stimulated by Prodigiosan (from results of morphometry)

Character of changes	16 h after injection of CCl_4		24 h after injection of CCl_4	
	experiment (7)	control (8)	experiment (10)	control (10)
Elimination of glycogen	3,3±0,31	7,0±0,39	2,9±0,30	5,4±0,60
Necrosis, balloon, and eosinophilic degeneration	4,4±0,20*	7,1±0,30	3,3±0,40	8,5±0,39

Legend. 1. Number of animals given in parentheses. 2. In all cases the difference between the experimental and control was statistically significant at $P < 0.05$. 3. (*) Changes limited to eosinophilic degeneration.

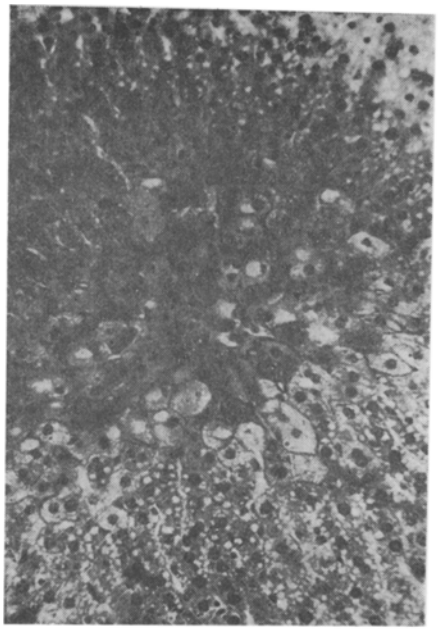

Fig. 1

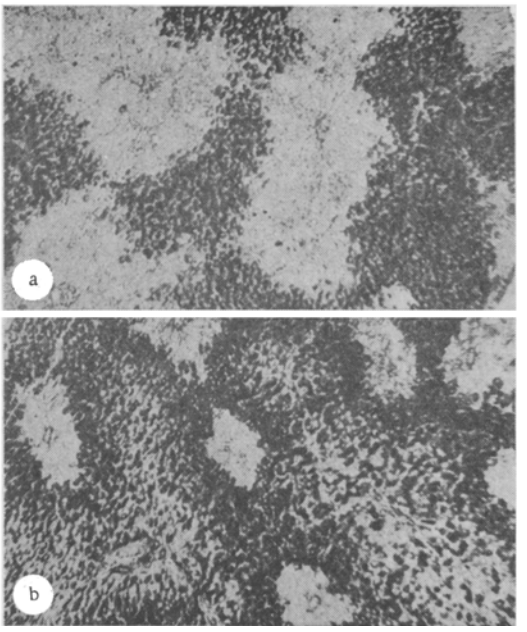

Fig. 2

Fig. 1. Section through liver 24 h after injection of CCl_4. Foci of necrosis and balloon degeneration of hepatocytes in center of hepatic lobule. Hematoxylin-eosin, 200×.

Fig. 2. Section through liver stained by PAS method, 24 h after CCl_4 poisoning. 70×. a) Control, extensive areas of glycogen elimination in centrolobular areas of liver; b) experiment, inhibition of glycogen elimination.

periphery (Fig. 1). In rats stimulated with prodigiosan, the zones of damage 16 and 24 h after CCl_4 poisoning occupied a smaller area, namely 60 and 40% respectively, of the size of this area in the control. In the experimental rats, moreover, severe forms of damage, such as necrosis and signs of balloon degeneration of the hepatocytes, were found much less frequently and changes of the eosinophilic degeneration type were predominant (Table 1).

Besides differences in the intensity of injury to the hepatocytes, differences also were observed in the degree of glycogen elimination. There were almost twice as many zones free from glycogen in the control as in the experimental series ($P < 0.05$; Table 1, Fig. 2).

Mononuclear cells accumulated in the zones of necrosis 48 h after injection of CCl_4. The degree of fatty infiltration of the liver cells was about the same in the experiment and the control. Mononuclear infiltration was much more marked in the rats stimulated with prodigiosan.

The inflammatory reaction was weaker 72 h after injection of CCl_4. Extensive areas of cells filled with fat were detected in the liver of the experimental rats, whereas in the control there were only traces of fatty infiltration.

In rats stimulated with prodigiosan the resistance of the hepatocytes to CCl_4 thus increased regularly. In the experimental animals the destructive and infiltrative components of the process were manifested less strongly. To what can the marked protective effect of bacterial polysaccharide observed in these experiments be due? The increase in the resistance of the liver cells to CCl_4 observed in the animals stimulated with prodigiosan was probably due primarily to activation of the Kupffer cells, which belong to the chief section of the MPS, and include different classes of organ- and tissue-specific macrophages [9]. Injection of prodigiosan causes activation of lysosomal enzymes and of the catabolic functions of the peritoneal and Kupffer macrophages. Activation of the macrophages coincides in time with increased resistance to infection [1]. Activation of the lysosomal system of organ-specific macrophages can evidently not only determine the high level of natural resistance to infection, but also increased resistance to harmful factors of noninfectious nature. In particular, stimulation of the MPS by bacterial polysaccharides is accompanied by increased resistance to trauma [4] through an increase in the absorptive capacity and catabolic functions of the reticuloendothelial system under the influence of the stimulators. In the present experiments the protective action of prodigiosan could have been due to increased ability of the stimulated Kupffer cells to catabolize the breakdown products of the liver cells [5]. This reduced autointoxication and, at the same time, promoted the production of metabolites for the regenerating hepatocytes. Later, the increased resistance of the hepatocytes to CCl_4 could be connected with stimulation of the barrier-fixing [7], secretory [8], and corticosteroid-metabolizing function [6] of the Kupffer cells during their stimulation by prodigiosan. Finally, the ability of the stimulated cells of the hepatic reticuloendothelial system to metabolize the hepatotropic poison could have been increased. The possibility cannot be ruled out that this action of prodigiosan extended also to the hepatocytes.

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