RESISTANCE OF THE REGENERATING LIVER TO HEPATOTOXINS

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Administration of CCl_4 and paracetamol to mice causes massive necrosis of the central regions of the hepatic lobule. Preliminary stimulation of hepatocyte proliferation by partial hepatectomy greatly reduces the intensity of the toxic effect or abolishes it completely, depending on the time elapsing after the operation. The liver was virtually insensitive to hepatotoxins 48 h after the operation. Damage to the liver by CCl_4, paracetamol, and other hepatotropic poisons is associated with conversion of these compounds by the liver cells into toxic metabolites. In the regenerating liver metabolism is reorganized in favor of proliferative processes. Some tissue-specific functions of the hepatocyte are temporarily lost under these circumstances, notably the ability to metabolize foreign substances; this explains the resistance of the liver to hepatotoxins.
KEY WORDS: *resistance to hepatotoxins; centrilobular necrosis; proliferation of hepatocytes.*

In the modern view the toxicity of many substances depends on their metabolism in the body, as a result of which initially chemically inert compounds are converted into active metabolites which can damage the tissue [3, 6, 8]. Since the principal site for metabolism of foreign substances is the liver, the toxicity of chemical compounds may be determined by the state of the function of its parenchyma. The mechanism of selective damage by hepatotropic poisons (CCl_4, paracetamol, bromobenzene, etc.) of the center of the hepatic lobule, which remained unknown for a long time, is associated with the functional heterogeneity of the lobule and, in particular, with the existence of enzymes metabolizing foreign substances in the cells of its central part [4, 5].

It might be supposed that in the period of recovery after partial hepatectomy the parenchymatous cells temporarily lose some of their special functions, notably their ability to metabolize foreign substances, and that this could explain the resistance of the liver to the toxic action of these compounds. The investigation described below was carried out to test the validity of this hypothesis.

EXPERIMENTAL METHOD

Two-thirds of the liver was removed from male CBA/C57BL/6 mice weighing 21-26 g by the standard method. Some of these animals were exposed 18, 24, 48, 72, 96, and 120 h later to the action of CCl_4 vapor [1]. To do this, nine animals at a time were placed for 15 min in a 3-liter exsiccator into which 0.05 ml CCl_4 had been introduced. In each batch of nine animals four were intact and were used as the control of the toxic action of CCl_4. The mice were killed by decapitation under ether anesthesia after 2 days. Paraffin sections were cut from pieces of liver. Altogether 18 mice were used in the experiments with CCl_4.

Another seven intact mice and six mice hepatectomized 28, 52, and 76 h after the operation were given paracetamol in a dose of 400 mg/kg, which induces necrosis of the liver [7]. Pharmaceutical paracetamol tablets were dissolved in distilled water and the solution

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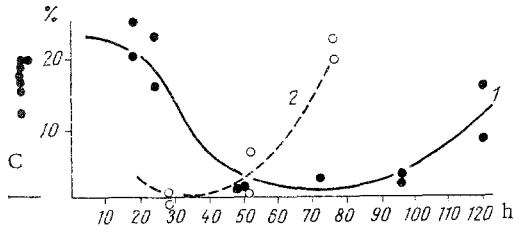

Fig. 1. Area of damage to liver parenchyma in control mice produced by action of CCl_4 (C) and in mice treated with CCl_4 and paracetamol after partial hepatectomy: 1) CCl_4, 2) paracetamol. Abscissa, time (in h) elapsing after operation and before administration of CCl_4 or paracetamol; ordinate, total area of damage to parenchyma, including necrosis, vacuolated cells, and zones of inflammatory infiltration (in % of total area of parenchyma in section).

injected intraperitoneally into the mice in a dose of 1 ml/25 g body weight. The surviving animals were killed 24 h later and paraffin sections were cut from the liver.

An area measuring 4 mm^2 of a section stained with hematoxylin-eosin was drawn with a drawing apparatus under a magnification of 6x. The degree of liver damage was determined as the ratio between the area of the toxic lesions and the total area of parenchyma in the section, by weighing their projection on paper.

EXPERIMENTAL RESULTS

Massive zones of necrosis, centrilobular in position and amounting to 12-20% of the area of the parenchyma in the section, were found 48 h after exposure to CCl_4 in all the control animals (Fig. 1). The initial zone of injury must have been much larger, for after 2 days it was reduced as a result of absorption of the cells and proliferation of intact hepatocytes in the periportal region of the lobule [4, 5]. Administration of CCl_4 during regeneration of the liver after partial hepatectomy gave different results. The liver of animals receiving CCl_4 48-50 h after the operation was virtually resistant to the hepatotoxin. It contained only solitary necrotic and vacuolated cells next to the lumen of the central veins, amounting altogether to 1.5% of the parenchyma in the section. The radii of the centrilobular foci of necrosis were increased 3, 4, and 5 days after the operation because of spread to an increasing number of cells. The larger zone of necrosis in animals receiving CCl_4 18-20 h after hepatectomy than in the control must be noted. This most probably reflects slowing of repair processes in these animals.

The protective effect of hepatectomy against the action of paracetamol was more marked still. Paracetamol also damages the centrilobular zone of the hepatic lobule. Unlike CCl^4, during the action of which the centrilobular foci of necrosis were scattered diffusely throughout the parenchyma, the action of paracetamol also was characterized by hemorrhagic changes, which varied in severity in different lobes of the liver. This feature added to the difficulty of quantitative estimation of the toxic effect of this drug. Of the seven control mice, two died 1 day after administration of paracetamol, and in the rest massive hemorrhagic foci, originating from the region of the large vessels and frequently spreading to the whole lobe, were found macroscopically. Microscopically, these foci consisted of masses of cell debris, intermingled with red blood cells. Outside the focus of hemorrhage, only the centrilobular zones of the lobules were damaged, but the predominant cells in them were not necrotic, as with the action of CCl_4, but vacuolated cells.

Paracetamol, if administered after hepatectomy, did not exhibit its usual toxic action. Macroscopically, the liver of none of the animals showed any sign of hemorrhage. In two animals taken 28 h and in one animal 52 h after the operation, no necrosis and no vacuolated cells likewise could be found microscopically. Administration of paracetamol 52-76 h after hepatectomy again caused typical zones of vacuolated and necrotic cells to appear.

The differences between the two hepatotoxins as regards the time of development of the protective effect can be partly explained by differences in the mode of their administration and also by possible differences in the rate and pathways of their metabolism.

The results showed that the condition for the toxic action of these chemical compounds is that the cells metabolizing these substances must be in a certain state, although the mechanisms responsible for that state are unknown. All that is clear is that the temporary loss of function is connected with a reorganization of cell metabolism, favoring the course of proliferative processes. This conclusion is based on comparison of the kinetics of the indices of hepatocyte proliferation in the regenerating liver [2] with the development of

resistance of the liver to hepatotoxins. The phenomenon described here is an example of the well-known antagonism between differentiation and proliferation. Its manifestation in different cases may be based on common mechanisms. In that case it might be supposed that CCl_4 and paracetamol are not exceptional among the hepatotropic poisons and that hepatectomy will also have a protective action against the numerous substances of different chemical nature whose toxic metabolites are formed primarily by the liver cells.

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