EFFECT OF PRELIMINARY STARVATION ON DEVELOPMENT OF ACTUTE THIOACETAMIDE-INDUCED LIVER NECROSIS IN RATS

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Intraperitoneal injection of thioacetamide (TA) induces the rapid development of centrolobular hepatic necrosis and it is often used in experimental hepatology as a model of pathological processes in the liver. In such cases mitochondrial damage, vacuolation and rupture of the endoplasmic reticulum, and pycnosis and lysis of nuclei are found [10, 14]. Serum aminotransferase activity is raised [3, 13]. The hepatotoxicity of TA is linked with its metabolism in the liver microsomes. Toxic intermediate compounds are probably formed [10]. It has been shown that the cytochrome P-450 concentration falls in acute TA poisoning [2, 7]. Meanwhile cytochrome P-450-dependent enzymes of the mixed-function mono-oxygenase system perform a principal metabolic role [6].

The aim of this investigation was to study the effect of preliminary starvation on the development of morphological disturbances and on changes in the content of cytochromes P-450 and b_5 in acute experimental thioacetamide-induced liver necrosis.

EXPERIMENTAL METHOD

Experiments were carried out on male Wister rats weighing 350-400 g. The animals were divided into four groups: two control groups — intact rats deprived of food for 24 h (group 1) and 72 h (group 2) respectively, immediately before decapitation — and two experimental groups (3 and 4). Animals of the experimental groups received a single intraperitoneal injection of TA in a dose of 100 mg/kg 24 h before decapitation. During this period the animals of both experimental groups were deprived of food, and those of group 4 were additionally starved for 48 h before the injection of TA. Water was given ad lib. The rats were decapitated and their blood serum used for determination of aspartate- and alanine-aminotransferase activity (AsAT and AlAT, respectively) by means of test kits from Boehringer Mannheim (West Germany). The microsomal fraction was obtained from liver homogenate [5] and used for assay of cytochromes P-450 and b_5 [8, 9]. Protein was determined by Lowry's method. The results were subjected to statistical analysis by the Mann—Whitney test. Liver tissue was taken from all the animals before perfusion for histological investigation and for staining by Van Gieson's method. An electron-microscopic investigation of the liver was undertaken on three animals from each group.

EXPERIMENTAL RESULTS

Centrilobular dystrophic and necrotic changes with inflammatory infiltration in the periportal spaces and around the zones of necrosis were found 24 h after injection of TA (group 3) (Fig. 1). Preliminary starvation for 2 days aggravated the dystrophic and necrotic changes induced by TA (Fig. 2). Injection of TA caused destruction of mitochondria. Hyperplasia and hypertropy of the smooth endoplasmic reticulum and reduction of the rough endoplasmic reticulum and disturbance of its arrangement, with rupture and partial degranulation, were observed. The number of seconary lysosomes showed a small increase. As these investigations showed, preliminary starvation causes additional ultrastructural changes: pycnosis of the nuclei, marked polymorphism of the mitochondria, and considerable enlargement of second-

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TABLE 1. Effect of Preliminary Starvation on Serum Aminotransferase Activity and Concentrations of Cytochromes P-450 and b_5 in Liver Microsomes in Rats with Acute Thioacetamide Liver Necrosis

Parameter	Group of animals			
	1 (control)	2 (control + starvation)	3 (TA)	4 (TA + starvation)
AsAT, μcatals/liter	2,8 (2,1—4,0)	3,1 (2,1—4,7)	66,0** (51,8—100,0)	228,0** (113,3—301,6)
			$p<0,01$	
AlAT, μcatals/liter	0,4 (0,1—0,6)	0,5 (0,3—0,8)	22,4** (14,7—21,5)	92,9** (46,7—136,7)
			$p<0,01$	
Microsomal protein, mg/g	12,0 (8,9—15,7)	10,5 (7,8—14,4)	8,6** (4,4—10,4)	8,7 (2,7—12,3)
			$p>0,05$	
Cytochrome, nmoles/mg P-450	0,44 (0,20—0,78)	0,44 (0,22—0,57)	0,36 (0,19—0,58)	0,23** (0,11—0,60)
			$p>0,05$	
b_5	0,39 (0,17—0,76)	0,35 (0,22—0,50)	0,50* (0,23—0,77)	0,48 (0,22—0,81)
			$p>0,05$	

Legend. *p < 0.05, **p < 0.01 compared with control. Values of p given in Table 1 relate to experimental groups. Each group contained eight animals. Limits of variations shown in parentheses.

ary lysosomes. The number of lipid droplets was increased, and some of them were distinctly large in size.

Injection of TA increased the serum aminotransferase activity, and the effect was potentiated by preliminary starvation, confirmed previous data [3, 13]. The microsomal protein level was reduced. A very small decrease in the cytochrome P-450 concentration was found in TA-induced liver damage, and after preliminary starvation the difference compared with the control groups was statistically significant. Conversely, however, the cytochrome b_5 concentration was increased (Table 1).

Analysis of the results shows that more marked changes in serum aminotransferase activity under the influence of starvation in rats with TA-induced necrosis (group 4) were associated with more severe morphological changes in the liver. The potentiating effect of starvation is probably the result of more rapid conversion of TA by mixed-function microsomal oxygenase. Starvation increases the metabolic rate of several toxic substances [11, 12]. Since prelimi-

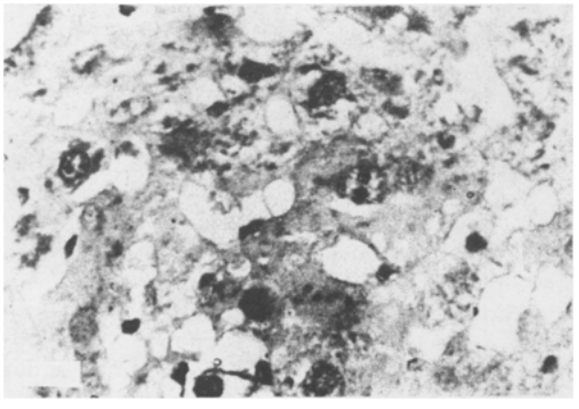

Fig. 1

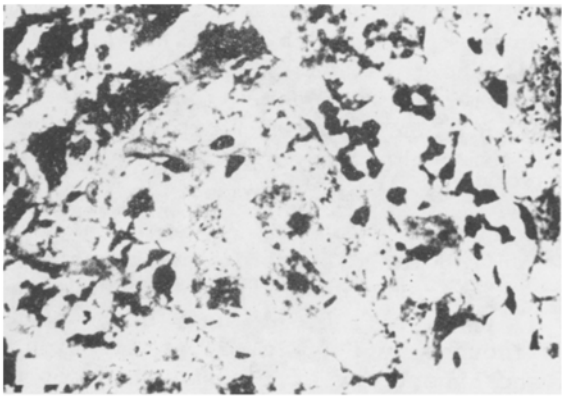

Fig. 2

Fig. 1. Liver tissue in acute thioacetamide necrosis with development of parenchymatous, balloon, fatty, and acidophilic degeneration. Here and in Fig. 2: Van Geison's stain, 630 ×.

Fig. 2. Liver tissue in acute thioacetamide necrosis after preliminary starvation for 2 days, with development of more severe fatty and acidophilic degeneration of hepatocytes.

nary starvation alone (control group 2) did not increase the total content of cytochrome P-450, it is possible that only certain forms of cytochrome P-450, converting TA, and induced under its influence, and the concentration of the remaining forms was reduced. Meanwhile, participation of cytochrome P-450-independent microsomal oxygenase in TA metabolism is now accepted [4].

The preliminary rise of the cytochrome b_5 level under the influence of TA is very interesting. These data correlate with hyperplasia of the smooth endoplasmic reticulum. An increased cytochrome b_5 concentration also has been found in galactosamine-induced hepatitis [1]. The cause of the opposite changes in concentrations of cytochrome P-450 and b_5 in acute parenchymatous lesions of the liver, still awaits explanation.

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EFFECT OF HYDROCORTISONE ON THE LIPID COMPOSITION OF THE RAT LIVER NUCLEAR MATRIX

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It is now generally agreed that the nuclear matrix can play an important structural and functional role in cellular activity. Proteins of the nuclear matrix can take part in regulation and transcription processes and in establishment of the complex superstructure of chromatin [8, 11]. Although lipids are present in the matrix in small quantities, they may also possibly play a role in these processes, especially because lipid components of other nuclear structures, according to some workers [6], carry a definite functional load. Despite the ever-increasing interest of research workers in problems of the nuclear matrix, its lipid composition has been inadequately studied.

The aim of this investigation was to study the phospholipid and neutral lipid composition of the nuclear matrix of rat liver under the influence of hydrocortisone, in an attempt to shed some light on the role of the lipids of nuclear structures in hormonal regulation of the genome.

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