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LIVER MONO-OXYGENASE SYSTEM FUNCTION IN EXPERIMENTAL MYOCARDIAL INFARCTION

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KEY WORDS: myocardial infarction; liver mono-oxygenase; lipid peroxidation.

Changes in the structure and functions of the liver in myocardial infarction have been the subject of much research [3, 6]. However, changes in the mono-oxygenase system of the liver, responsible for metabolic conversions of cholesterol [7], saturated and unsaturated fatty acids [14], steroid hormones [9], and most drugs [5], in myocardial infarction have not yet been studied.

The aim of this investigation was to study the functional activity and content of enzymes of the liver mono-oxygenase system in experimental myocardial infarction, in its early and late stages.

EXPERIMENTAL METHOD

Experiments were carried out on 100 male albino rats weighing 200-240 g. There were two series of experiments. In series I the animals were anesthetized with ether, thoracotomy performed, the pericardium incised, and the left descending coronary artery ligated. In series II thoracotomy was performed and the pericardium incised but the coronary artery was not ligated (mock operation). Intact rats kept under standard animal house conditions served as the control. The animals were decapitated on the 1st, 3rd, 7th, 14th, and 21st days after the operation, the liver washed out with physiological saline, and the microsomal fraction was isolated by differential centrifugation [1]. The velocity of N-demethylation of aminopyrine and of p-hydroxylation of aniline, and concentrations of cytochromes P-450 and b_5 in the microsomes were determined as described previously [11]. The concentration of the microsomal cytochromes was recorded on a Hitachi-356 double-beam spectrophotometer (Japan). Activity of spontaneous lipid peroxidation (LPO) of the microsomal membranes was estimated from the malonic dialdehyde (MDA) concentration in the microsomal fraction [2] on the 1st, 7th, and 21st days after the operation. The protein concentration in the microsomes was determined by the method in [13]. Differences between the mean values compared were considered significant at the $p<0.05$ level (Student's t test).

EXPERIMENTAL RESULTS

The acute period (1st-3rd days) after the operation was characterized by inhibition of function and by a fall in the concentrations of the principal microsomal mono-oxygenases. In animals undergoing the mock operation, the fall in the velocity of N-demethylation of aminopyrine and of p-hydroxylation of aniline was maximal (by 49.6 and 32.4% respectively) on the 1st day, after which levels of activity of the parameters of microsomal metabolism were gradually restored on the 7th day after the operation (Table 1). A quantitative study of microsomal cytochromes P-450 and b_5 also revealed a significant decrease in the acute period after the operation, followed by recovery to the initial level on the 7th day.

The time course of changes in microsomal mono-oxygenase activity in the group of animals with occlusion of the coronary artery differed in character. The velocity of N-demethylation

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TABLE 1. Changes in Velocity of Microsomal N-Demethylation of Aminopyrine and of p-Hydroxylation of Aniline at Different Periods of Acute Occlusive Myocardial Infarction (M±m)

Parameter	Experimental conditions	Time after ligation of coronary artery, days					Control (intact animals)
		1-	3-	7-	14-	21-	
N-demethylation of aminopyrine, nmoles HCHO/min/mg protein	Myocardial infarction	1,334±0,021* (74,7)	0,969±0,022* (54,3)	0,844±0,028* (47,3)	1,226±0,040* (68,7)	1,583±0,020* (88,7)	1,785±0,040
	Mock operation	0,904±0,030* (50,6)	1,089±0,031* (61,0)	1,735±0,049 (97,2)	1,773±0,022 (99,3)	1,737±0,149 (97,3)	
p-Hydroxylation of aniline, nmoles microsomal p-aminophenol/min/mg protein	Myocardial infarction	0,240±0,009* (64,3)	0,174±0,006* (46,6)	0,138±0,004* (37,0)	0,246±0,008* (66,0)	0,303±0,004* (81,2)	0,373±0,07
	Mock operation	0,256±0,013* (68,8)	0,204±0,003* (54,7)	0,368±0,009 (98,7)	0,386±0,005 (103,5)	0,366±0,035 (98,1)	

Legend. Here and in Table 2: asterisk indicates significance of differences from control ($p<0.05$); numbers in parentheses show percentages of control, taken as 100; number of animals in groups was 6-10.

TABLE 2. Changes in Concentrations of Cytochromes P-450 and b_5 in Microsomal Fraction of Liver during Acute Occlusive Myocardial Infarction (M±m)

Parameter	Experimental conditions	Time after ligation of coronary artery, days					Control (intact animals)
		1-	3-	7-	14-	21-	
Cytochrome P-450, nmoles/mg protein	Myocardial infarction	0,640±0,023* (59,6)	0,631±0,030* (58,8)	0,476±0,025* (44,4)	0,629±0,014* (58,6)	1,172±0,014 (109,2)	1,073±0,084
	Mock operation	0,578±0,018* (53,9)	0,653±0,022* (60,8)	1,078±0,030 (100,5)	1,021±0,028 (95,2)	1,177±0,117 (109,7)	
Cytochrome b_5, nmoles/mg protein	Myocardial infarction	0,629±0,022* (75,9)	0,525±0,008* (63,3)	0,596±0,017* (71,9)	0,653±0,012* (78,8)	0,714±0,012 (86,1)	0,829±0,052
	Mock operation	0,632±0,024* (76,2)	0,753±0,025* (90,8)	0,812±0,013 (97,9)	0,823±0,011 (99,3)	0,840±0,061 (101,3)	

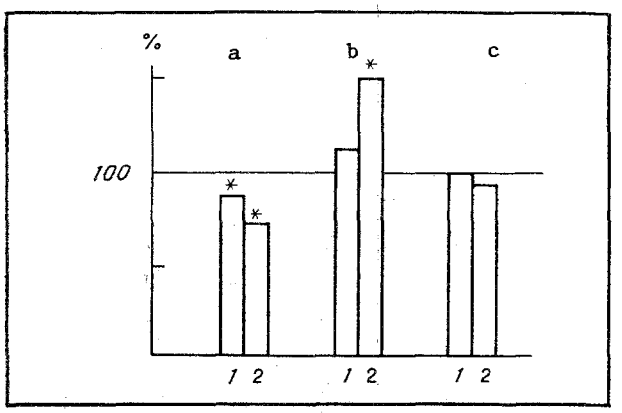

Fig. 1. Changes in MDA concentration (in % of control) in microsomal fraction of liver of animals undergoing mock operation (1) and in course of myocardial infarction (2). a) 1st, b) 7th, c) 21st days after operation. Asterisk indicates significant difference from control ($p<0.05$).

of aminopyrine and of p-hydroxylation of aniline was reduced on the 1st day by 26.3 and 36.7% respectively. Disturbances of microsomal hydroxylation of substrates were aggravated until the 7th day, when the rate of metabolism of aminopyrine and aniline was reduced by 53.7 and 63% respectively. On the 21st day of myocardial infarction the velocity of N-demethylation of aminopyrine and of p-hydroxylation of aniline remained 12.3 and 19.8% respectively below the control level. These changes in activity of microsomal hydroxylation of substrates were connected with a change in the concentrations of cytochromes P-450 and b_5 in the liver microsomes in myocardial infarction. The cytochrome P-450 concentration fell from the 1st day (by 41.4% of the control) until the 7th day (by 56.6% of the control) and returned to the control level on the 21st day after coronary arterial occlusion. The cytochrome b_5 concentration fell in the course of myocardial infarction by a lesser degree, but it also was completely restored to its initial level on the 21st day after the operation (Table 2). This difference in the time of recovery of cytochrome P-450 and the velocity of hydroxylation of aminopyrine and aniline is evidently attributable to changes in the catalytic activity of the hemoprotein relative to the above-mentioned substrates.

In consideration of the direct dependence of inhibition of mono-oxygenase activity on intensification of LPO [10, 12], it was decided to study the MDA concentration in the liver microsomes in the course of myocardial infarction. As will be clear from Fig. 1, activity of spontaneous LPO in the microsomes of animals undergoing the mock operation fell during the 1st day, returned to the initial value on the 7th day, and thereafter remained unchanged until the 21st day. Changes in LPO activity in the liver microsomes in myocardial infarction were phasic in character. Inhibition of LPO activity on the 1st day (the MDA concentration fell by 27% below the control) was followed by its intensification on the 7th day, as shown by an increase in MDA by 1.5 times in this period. Restoration of the initial LPO activity was observed on the 21st day of myocardial infarction. Inhibition of LPO activity in the acute period both after myocardial infarction and in animals undergoing the mock operation may evidently be regarded as an adaptive reaction, triggering activation of the antioxidative system [8]. In the animals undergoing the mock operation this reaction led to restoration of metabolic activity on the 7th day, whereas in myocardial infarction, the reserves of antioxidants were exhausted by this time, and this was followed by activation of LPO and by damage to the lipid components of membranes of the endoplastic reticulum and to the lipid-dependent enzymes of the mono-oxygenase system connected with them. Reduction of mono-oxygenase activity in acute myocardial infarction, which is a cause of modification of the pharmacokinetics of drugs [4], has a significant influence on the efficacy and safety of pharmacotherapy, and it accordingly implies the need for pharmacologic correction of the disturbances mentioned.

Thus in acute myocardial infarction hydroxylating activity is depressed for a period of 3 weeks and concentration of enzymes of the liver mono-oxygenase system are reduced as a result of damage to membranes of the endoplastic reticulum of the hepatocytes due to peroxidative processes.

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TIME COURSE OF LIVER ACID PHOSPHATASE ACTIVITY DURING INVOLUTION OF CIRRHOSIS

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KEY WORDS: involution of cirrhosis of the liver; partial hepatectomy; acid phosphatase; hepatocytes; connective-tissue cells.

Collagenolytic activity of lysosomal enzymes has been found in the normal and cirrhotic liver in a number of biochemical investigations [2, 6-10, 12, 13, 15]. Changes in enzyme activity in the liver during cirrhosis also have been observed in the few histochemical studies which have been undertaken of this problem [3, 4, 11, 14].

To determine the link between lysosomal activity of various intracellular enzymes of the liver and the process of collagen resorption, changes in acid phosphatase (AP) activity were investigated by quantitative histochemical methods in the cirrhotically changed liver after cessation of exposure to the pathogenic factor causing cirrhosis.

EXPERIMENTAL METHOD

Cirrhosis of the liver was induced by injection of 0.2 ml of a 40% solution of CCl_4 in olive oil subcutaneously into noninbred male albino mice once a week for 5 months. The injections of CCl_4 were then stopped and animals developing cirrhosis were divided into two groups. The animals of group 1 underwent resection of the left lobe of the liver 5 days after the last injection of CCl_4. Animals of group 2 were not subjected to operation. Material for investigation was taken during resection and 5, 10, 20, 30, and 60 days after resection, concurrently in animals of both groups. Experiments were carried out on 30 animals (15 in each group).

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