Glutathione S-Transferase Activity in the Liver in Acute Pancreatitis at Various Terms of Disease and during Treatment with Inducers

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Glutathione S-transferase activity increased in rats with acute pancreatitis: 2.2 times on day 2, 2-fold on day 4, and 1.5 times on day 10. Inducers of microsomal enzymes aroclor 1254 and phenobarbital notably inhibited glutathione S-transferase activity in animals with experimental pancreatitis on days 2-4 of the disease (3.1-2.5 times in comparison with sham-operated induced animals). Hence, the activity of enzymes of phase II of liver xenobiotic metabolism is altered in acute pancreatitis.

Key Words: *pancreatitis; induction; glutathione S-transferase*

Acute pancreatitis (AP) causes inflammatory and degenerative changes in the liver and modulates activity of cytosol enzymes alanine and aspartate aminotransferases, arginase, histidase, *etc.* [1]. Many drugs are used for the treatment of AP, therefore it is important to evaluate activities of enzymes involved in phase II of xenobiotic metabolism, specifically glutathione S-transferase (GST). The GST family is an important enzyme system involved in detoxication of many xenobiotics, electrophilic alkylating agents, and lipid peroxidation products [8]. However, GST activity has never been measured in humans or animals with AP. Inducers of the monooxygenase system, *e. g.* phenobarbital, increase activity of cytochrome P-450 isoforms and GST isoenzymes through activation of translation mechanisms [6].

We investigated the time course of GST activity in rat liver and the effects of inducers aroclor 1254 and phenobarbital on this parameter.

MATERIALS AND METHODS

Wistar rats weighing 200 g were used. AP was induced intraoperatively by injuring the pancreas without damaging its serous membrane [2]. Microsomal enzymes were induced by a single intraperitoneal injection of aroclor 1254 in a dose of 200 mg/kg or injections of phenobarbital in a dose of 80 mg/kg for 2 or 4 days. The animals were divided into 7 experimental groups.

The duration of AP was 48 h in group 1, 4 days in group 2, and 10 days in group 3. The animals of groups 4 and 5 were injected with aroclor 1254 or oil 48 and 96 h after induction of AP, respectively, and sacrificed after 48 h. The animals of groups 6 and 7, were injected with phenobarbital (2 or 4 doses) 48 h after AP induction and sacrificed 48 h or 10 days postinjection, respectively. Sham-operated rats treated similarly and sacrificed at the same terms were controls.

Microsomal fraction of the liver was isolated by differential centrifugation [7], GST was measured in the supernatant. Protein was measured by Lowry's method [5], GST activity by spectrophotometry [4]. 1-Chloro-2,4 dinitrobenzene was used as glutathione acceptor. The data were processed by Student's t test using Statgraphics software.

RESULTS

On days 2 and 4 of the disease GST activity increased 2.2- ($p<0.01$) and 2-fold ($p<0.05$), respectively, in comparison with the control (Table 1). By day 10 GST

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activity decreased in comparison with day 4, but remained 1.5 times above the initial level ($p<0.01$). This indicates activation of phase II enzymes, specifically GST, in rats with AP.

On day 2 of AP, GST activity in rats injected with aroclor 1254 and oil was 1.8- ($p<0.01$) and 1.4-fold below the respective control values (Table 2). On day 4, GST activity decreased 1.8 times in group 4 and 2-fold in group 5 in comparison with the respective controls ($p<0.01$). In sham-operated rats aroclor 1254 increased GST activity 1.3 and 1.5 times on days 2 and 4, respectively ($p<0.05$). Phenobarbital produced similar effects (Table 2). On day 4 of AP, GST activity in group 6 was 2.1 times below the respective control ($p<0.05$). In sham-operated rats phenobarbital injected 2 days postoperation increased GST activity 1.4 times on day 4 ($p<0.05$).

TABLE 1. Time Course of GST Activity (in μmol/mg/min) in AP ($M\pm m$)

Day after induction of AP	Control	AP
2	253.08±5.34	567.33±80.06*
4	206.96±78.34	409.20±54.06**
10	137.59±0.39	201.65±6.04*

Note. Here and in Table 2: *$p<0.01$, **$p<0.05$ *vs.* the control.

TABLE 2. Time Course of GST Activity (in μmol/mg/min) in Rats with AP Treated with Inducers ($M\pm m$)

Day after induction of AP	Inducer					
	aroclor 1254		oil		phenobarbital	
	control	AP	control	AP	control	AP
2	342.85±3.52	193.64±13.66*	403.08±47.95	289.86±41.12**	—	—
4	302.56±16.28	165.48±20.77*	336.46±12.08	170.47±38.36*	281.15±82.53	130.39±26.12**

Therefore, aroclor 1254 reduced GST activity in rats with AP: 2.9 times on day 2 ($p<0.01$), 2.5 times on day 4 ($p<0.01$), and 1.2 times on day 10 ($p<0.01$). Injections of phenobarbital starting from day 2 of AP decreased GST activity 3.1 times on day 4 ($p<0.05$).

Hence, GST activity in rats increased during the early (days 2-4) period of AP, which may be due to activation of lipid peroxidation. This is confirmed by the data on GST involvement in detoxication of various aldehydes forming due to oxidation of lipids [6]. Aroclor 1254 and phenobarbital increased GST activity in control (sham-operated) animals due to activation of translation mechanisms [3]. Injection of the inducers during the early period of AP essentially decreased GST activity. The mechanism of this effect remains unclear. Presumably the inducers activated the synthesis of physiological inhibitors of GST.

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