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ROLE OF INTESTINAL HORMONES IN THE PATHOGENESIS OF EXPERIMENTAL PANCREATITIS

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UDC 616.37-002-092.9-07: 616.37-008.6-092: 616.342-008.6: 577.175.73

The course of disturbances of secretory reactions of the pancreas in response to adequate stimulation by intestinal hormones was studied in acute experiments on dogs with preinduced pancreatitis. Activity of combined preparations of intestinal hormones obtained from the duodenal mucosa was found in the acute period of the disease in these dogs. In chronic experiments an increased rate of acid formation in the stomach and a change in the pH of the duodenal contents toward the acid side in pancreatitis were found in chronic experiments. It is concluded that intestinal hormones play an important pathogenetic role in the mechanism of disturbances of the external secretory activity of the pancreas in pancreatitis.

KEY WORDS: pancreas; experimental pancreatitis.

The secretin test, used in the differential diagnosis of diseases of the pancreas, is based on changes in the reactivity of the pancreas under pathological conditions to "exogenous" secretin [1, 5-7, 9-11]. To discover whether these changes reflect general changes in the reactivity of the body during pancreatitis or whether they are directly related to the pathogenesis of the disturbances of external secretory activity of the pancreas, the investigation whose results are given in this paper was undertaken.

EXPERIMENTAL METHOD

Experiments were carried out on 19 dogs. Acute pancreatitis was induced by injecting the dogs' own bile into the pancreatic duct in a volume of 0.5 ml/kg body weight. To study the responses of the pancreas to "exogenous" intestinal hormones and also for biological standardization, a combined preparation of intestinal hormones (CPIH) obtained in the laboratory by means of a standard technology [2], but without the final stages of purification, was used.

In consequence of the technology of preparation and according to the results of biological standardization tests on rabbits, the CPIH contained several intestinal hormones (secretin, pancreozymin-cholecystokinin) and a certain quantity of biologically inactive denatured protein. The preparation was obtained in sufficient quantity for all the series of experiments from the duodenal mucosa of healthy dogs. To determine changes in the activity of the intestinal hormones in pancreatitis, samples of CPIH were obtained by the same technology from the duodenal mucosa of dogs killed at different times after the beginning of the disease.

To study changes in the reactivity of the pancreas to "endogenous" secretin, responses to intraduodenal injection of 20 ml of 0.3% HCl, the physiological stimulus causing an increase in the secretin concentration in the portal blood and in the general circulation [8], were studied.

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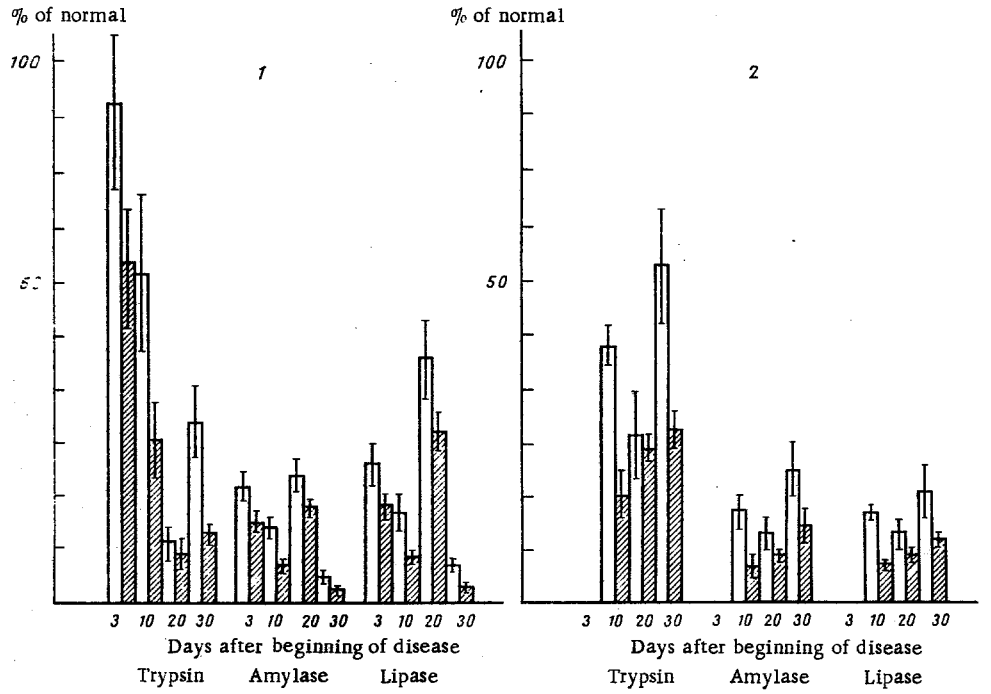

Fig. 1. Content of enzymes in pancreatic juice of dogs with pancreatitis at different times after beginning of disease (in % of control). 1) In secretion in response to CPIH, 2) in response to intraduodenal injection of HCl solution; unshaded columns denote enzyme concentrations; shaded columns hourly rate of secretion of enzymes.

There were three series of experiments. In series I the pancreatic duct of dogs in which pancreatitis had previously been induced was cannulated 3, 10, 20, and 30 days after the beginning of the disease, under urethane anesthesia, and the pure secretion in response to the above stimuli (CPIH, 2 mg/kg intravenously, or 20 ml of 0.3% HCl solution intraduodenally) was subject to quantitative and qualitative investigation. In the experiments of series II activity of CPIH samples obtained from the duodenal mucosa of dogs with pancreatitis was compared by biological standardization tests with the activity of samples obtained from healthy dogs. In series III observations were made in chronic experiments on seven dogs on the secretory activity of the stomach and the pH of the duodenal contents in the course of development of pancreatitis.

EXPERIMENTAL RESULTS

The volume of pancreatic secretion in response to intravenous injection of CPIH was much less than the control at all times of the disease. The concentration and hourly secretion of bicarbonates and pancreatic enzymes (trypsin, amylase, lipase) also were significantly below the control values ($P < 0.05$). After intraduodenal injection of HCl solutions secretory reactions of the pancreas were completely absent on the third day from the beginning of the disease. Later they reappeared but remained low in all their parameters.

Some special features of the disturbances of enzyme-secreting activity of the pancreas were noted depending on the type of the stimulus and the stage of the disease.

A characteristic feature of the responses to CPIH was a gradual decrease in the concentration and hourly rate of secretion of the corresponding enzymes. For trypsin the value of these indices was minimal on the 20th day of the disease, but for amylase on the 10th day. In the third week of the disease the changes in activity and hourly secretion of the various enzymes showed a form of reciprocity: the lowest indices of concentration and quantity of trypsin secreted on the 20th day corresponded to the highest values of these indices for amylase and lipase. Later, on the 30th day, indices characterizing trypsin secretion increased, and this coincided with their lowest values for the other two enzymes (Fig. 1, graph 1).

The dynamics of responses to intraduodenal injection of HCl solutions was characteristically different: the concentrations and, in particular, the gross rates of secretion of enzymes during the experiment increased for all enzymes relatively steadily until the 30th day (Fig. 1, graph 2). Figure 1 clearly shows that on the

TABLE 1. Indices of Gastric Secretion and pH of Duodenal Contents of Dogs with Acute Experimental Pancreatitis (mean results of experiments on 6 dogs, M ± m)

Group of animals	Secretory responses										pH after beginning of disease
	to histamine					to carbachol					
	volume of juice, ml	free HCl		proteolytic activity		volume of juice, ml	free HCl		proteolytic activity		
		conc., g %	hourly prodn., meq	conc. μg/ml	hourly prodn., mg.		conc., g %	hourly prodn., meq	conc. μg/ml	hourly prodn., mg.	
1. Normal	69 ± 9	0,17 ± 0,01	3,1 ± 0,1	40 ± 9	4,3 ± 2	49 ± 6	0,10 ± 0,04	1,6 ± 0,2	340 ± 18	10,7 ± 4	7,5—8,0
2. Pancreatitis, days after beginning of disease											
3—5	55 ± 6	0,25 ± 0,01	4,3 ± 0,3	140 ± 22	9,6 ± 4	42 ± 7	0,16 ± 0,04	1,9 ± 0,4	540 ± 28	25,6 ± 6	3,5—4,0
7—10	78 ± 8	0,21 ± 0,01	5,2 ± 0,4	163 ± 34	22,7 ± 6	38 ± 5	—	—	—	—	4,5—5,5
15	52 ± 3	0,19 ± 0,02	2,8 ± 0,2	140 ± 32	11,9 ± 2	45 ± 6	0,14 ± 0,06	1,5 ± 0,3	290 ± 72	12,0 ± 3	5,5—6,0
20	53 ± 8	0,20 ± 0,02	2,8 ± 0,2	121 ± 32	7,1 ± 3	60 ± 7	—	—	—	—	6,5—7,0
30	73 ± 5	0,17 ± 0,02	3,3 ± 0,3	86 ± 50	6,2 ± 4	50 ± 7	0,12 ± 0,02	1,6 ± 0,3	260 ± 30	13,0 ± 2	6,5—7,0
45	46 ± 4	0,20 ± 0,02	2,6 ± 0,2	70 ± 25	4,1 ± 2	43 ± 6	—	—	—	—	—
60	78 ± 19	0,17 ± 0,02	4,7 ± 0,4	49 ± 10	4,1 ± 2	60 ± 8	—	—	—	—	7,5—8,0

whole, for responses both to CPIH and to HCl, the secretion of amylase and lipase was inhibited more than the secretion of trypsin. These observations indicated a possible disturbance of the formation of intestinal hormones in the duodenal mucosa in pancreatitis.

The experiments of series II showed that the lowest secretory effect was caused by administration of CPIH samples obtained from the duodenal mucosa of dogs on the 3rd day of the disease. Samples obtained on the 10th, 20th, and 30th days showed higher activity, although below the level of the controls. For instance, injection of CPIH from healthy dogs in a dose of 2 mg/kg induced pancreatic secretion in a volume of 1.55 ± 0.11 ml, whereas in dogs with pancreatitis the same dose induced secretion of 0.73 ± 0.02 ml on the 3rd day, 0.88 ± 0.03 ml on the 10th day, 1.1 ± 0.01 ml on the 20th day, and 1.24 ± 0.02 ml on the 30th day of the disease. The lowest level of activity thus amounted to 47% of the control value, with a subsequent increase to 58, 70, and 80% respectively.

Determination of the bicarbonate alkalinity and the concentration and hourly production of pancreatic enzymes in this series showed that the ability of the CPIH samples to stimulate the secretion of trypsin was least affected, and their action on amylase and lipase secretion was much more marked. Recovery of the levels of secretion of trypsin took place relatively rapidly and steadily. For instance, a sample of CPIH obtained from dogs with pancreatitis on the third day of the disease induced a total secretion of trypsin in the course of the experiment amounting to 35% of the initial value, whereas for amylase and lipase the figures were only 10 and 11%, respectively. The CPIH sample obtained on the 30th day of the disease stimulated secretion of trypsin in an amount equal to 75% of the initial volume, compared with only 23 and 41%, respectively for amylase and lipase.

The experiments of series III showed that in acute pancreatitis during the first 7-10 days after the beginning of the disease there was an increase in the acidity and an increase in the proteolytic activity of the gastric juice obtained in response to injection of histamine and carbachol. This was accompanied by corresponding acidification of the duodenal contents. By the 15th-30th day the indices of secretion gradually approached their original level (Table 1).

These results were similar to those obtained previously in experiments on rabbits [3, 4]. They indicate that in acute pancreatitis the apparatus producing the combination of intestinal hormones becomes exhausted. Under the influence of acidification of the duodenal contents and the accompanying duodenitis, the sensitivity of the pancreas to the action of exogenous or endogenous intestinal hormones is probably changed. The possibility of disturbances of interoceptive responses of the duodenal mucosa to adequate stimulation by HCl solutions and by other stimuli likewise cannot be ruled out.

It can accordingly be concluded that the disturbances thus revealed are an important pathogenetic mechanism of the changes in the external secretory activity of the pancreas in acute pancreatitis.

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