HYPOTRYPSINEMIA AS A POSSIBLE FACTOR IN ACTIVATION OF DUODENAL MOTOR FUNCTION IN RATS WITH ATROPHY OF THE PANCREAS

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The numerous clinical observations and abundant experimental data do not give a completely clear idea of the state of motor activity of the small intestine in hypofunctional states of the pancreas. Besides communications describing changes of hyperkinetic type in motor activity [5, 7], other data indicate hypokinesia of the intestine [8-10].

The aim of this investigation was to study the character of disturbances of periodic motor activity of the duodenum in rats with experimental pancreatic atrophy and to assess possible connections with changes in pancreatic hydrolase activity in the blood.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 84 male Wistar rats weighing 250-300 g. Periodic motor activity of the duodenum was studied by electromyography [12]. For this purpose, loop electrodes made from tungsten wire 64 μm in diameter were implanted under hexobarbital anesthesia (40 mg/kg) into the proximal and distal parts of the duodenum. At the same time the common bile duct was ligated after preliminary introduction of a catheter into it, so that the outflow of pancreatic juice could be stopped while the outflow of bile continued. Myoelectrical activity (MEA) of the duodenum was recorded on an electroencephalograph (Medicor, Hungary) with time constant of 0.03 sec. The animals were deprived of food for 18-20 h before the experiment, but allowed water ad lib. The state of periodic motor activity was assessed by the duration of the phases of the myoelectrical complex (MEC) on the 3rd, 7th, 14th, 21st, and 28th days after ligation of the ducts. Changes in MEC were studied in 12 rats of this group receiving daily injections of trypsin solution (Spofa, Czechoslovakia) through a gastric tube in a dose of 10 mg/kg. Trypsin began to be given on the 3rd day after ligation of the common bile duct. Changes in pancreatic hydrolase activity in the blood were monitored in a group of 62 rats. Activity of trypsin [2], of alpha-1-antitrypsin and alpha-2-macroglobulin [4], lipolytic activity [6], and alpha-amylase activity in the blood serum were determined with the aid of a standard kit of reagents (Czechoslovakia). The experimental results were subjected to analysis of variance by traditional methods.

EXPERIMENTAL RESULTS

Fasting MEA of the duodenum was characterized by the presence of NEC in which four main phases could be distinguished: I) rest or absence of spike activity (2.90 ± 0.20 min), II) irregular spike activity (2.44 ± 0.16 min), III) regular spike activity (2.05 ± 0.12 min), IV) irregular spike activity preceding the resting phase (2.02 ± 0.16 min) (Fig. 1). The total duration of MEC was 9.0 ± 0.43 min.

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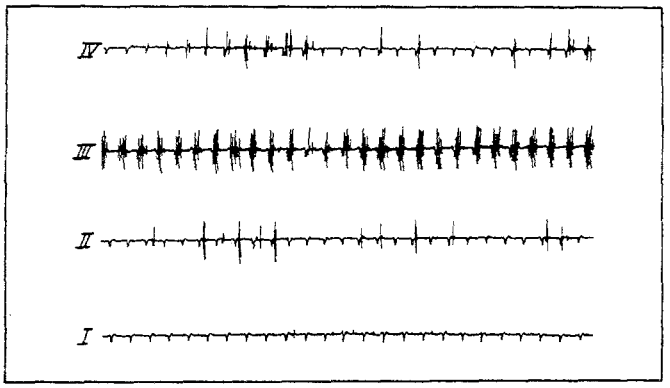

Fig. 1. Electromyogram of rat duodenum: I) phase of rest, II) phase of irregular spike activity, III) phase of regular spike activity, IV) phase of irregular spike activity preceding phase of rest.

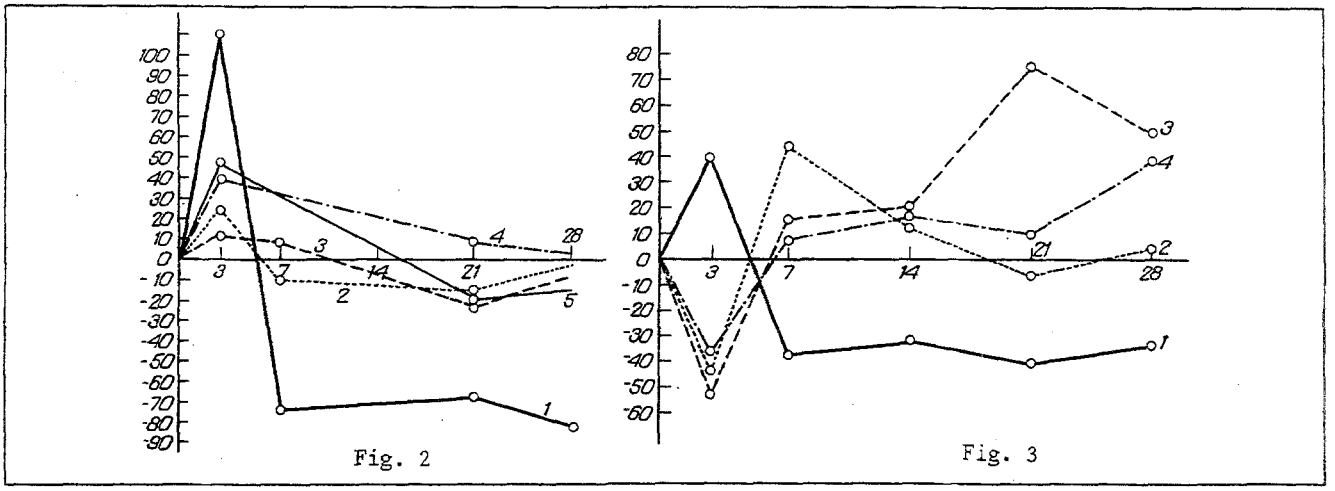

Fig. 2. Changes in blood levels of activity of pancreatic hydrolases and their inhibitors after ligation of common bile duct. 1) Activity of trypsin, 2) of alpha-1-antitrypsin, 3) of alpha-2-macroglobulin, 4) of alpha-amylase; blood lipolytic activity. Abscissa, time after operation (in days). Ordinate, deviations from control (in %). Points with significant differences are indicated by circles.

Fig. 3. Changes in duration of phases of duodenal MEC in rats after ligation of common bile duct: 1) phase IV, 2) phase III, 3) phase II, 4) phase I. Abscissa, time after operation (in days); ordinate, deviations from control (in %). Points of significant differences are circled.

Ligation of the common bile duct led to a considerable change in the phases of MEC and of activity of pancreatic hydrolases and their inhibitors in the blood. On the 3rd day of the investigation, because of an increase of pressure in the pancreatic ducts, internal secretion of enzymes was increased, leading to an increase in activity of pancreatic enzymes and their inhibitors in the blood (Fig. 2). Against this background the periodic motor activity of the duodenum was inhibited, as shown by an increase in the duration of phase I of MEC and a decrease in the duration of phases II, III, and IV (Fig. 3). The total duration of MEC was reduced by 25% ($p = 0.04$).

Starting with the 7th day of the investigation pancreatic atrophy developed. Under these circumstances the acinar tissue was replaced by connective tissue, the mass of the pancreas was reduced, and by the 28th day it was 201.7 ± 27.0 mg compared with 401.4 ± 24.2 mg in the control ($p = 0.01$). Blood trypsin activity was considerably reduced, and on the 21st day of the investigation activity of alpha-1-antitrypsin and alpha-2-macroglobulin dropped

TABLE 1. Duration of Phases of MEC in Pancreatic Atrophy and after Intragastric Injection of Trypsin in a Dose of 10 mg/kg

Time after operation, days	Duration of phases of MEC, min			
	I	II	III	IV
Control	1,57±0,12	3,51±0,31	1,14±0,18	3,04±0,31
7	2,11±0,19	2,63±0,45	0,61±0,06	2,24±0,51
	p=0,02	p=0,13	p=0,01	p=0,2
14	1,98±0,27	3,37±0,28	0,91±0,10	3,09±0,47
	p=0,2	p=0,7	p=0,3	p=0,9
21	1,77±0,27	2,90±0,75	1,30±0,19	3,53±0,57
	p=0,4	p=0,4	p=0,6	p=0,4
28	1,74±1,80	3,80±0,40	1,03±0,20	3,40±0,50
	p=0,5	p=0,5	p=0,5	p=0,5

below the control level. Alpha-amylase and lipase activity was within the control limits. Atrophy of the secretory part of the pancreas led to changes in motor activity of the duodenum of hyperkinetic type. This is shown by a lasting decrease in the duration of the resting phase and an increase in the duration of the phases of spike activity. The duration of MEC was the same as in the control.

Investigation of correlation between the parameters revealed high positive correlation between phase I of MEC and alpha-1-antitrypsin activity ($r = 0.98$, $p = 0.01$). Since changes in alpha-1-antitrypsin activity reflect changes in the internal secretion of trypsin by the pancreas [3, 11], this suggested that changes affecting MEC of the duodenum after ligation of the common bile duct are determined by the blood trypsin level. This hypothesis was confirmed by experiments in which trypsin was administered to rats during developing atrophy of the secretory part of the pancreas, which showed not only compensation of the changes in MEC, but also some inhibition of periodic activity during the first day of intragastric trypsin administration (Table 1).

Ligation of the common bile duct thus leads to marked changes in activity of pancreatic hydrolases and trypsin inhibitors in the blood and in the periodic motor activity of the duodenum. The increase in internal secretion of enzymes immediately after ligation of the duct leads to inhibition of motor activity, and the subsequent atrophy of the secretory part of the pancreas lowers blood levels of activity of trypsin and its inhibitors, leading to intestinal hyperkinesia.

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