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ENDOCRINE DISTURBANCES IN THE EARLY STAGES OF DEVELOPMENT OF EXPERIMENTAL CHRONIC PANCREATITIS

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Information on hormonal activity of the pancreas and the character of changes in carbohydrate tolerance in chronic pancreatitis is inadequate and contradictory. The urgency of this problem is due to the difficulty of diagnosis and treatment of this disease and the possibility of development of profound endocrine disturbances, culminating in diabetes mellitus [1].

In diabetes insulin secretion is reduced, as shown by a decrease in insulin release in response to glucose intake, which may be associated with damage to the receptor for this carbohydrate or a defect in the nervous or metabolic chain of insulin release [6, 8].

A comparative study of the secretion of insulin and glucagon [13] alters the traditional idea of diabetes mellitus. It was suggested that changes in glucagon secretion also play an important role in the development of severe diabetic hyperglycemia, for it is the principal regulator of glucose release by the liver, through activation of glycogenolysis and gluconeogenesis, inhibition of glycogen synthesis, and changes in glucokinase activity [9], i.e., it has an action opposite to that of insulin. The normal response of the A cells is characterized by reduced glucagon production in response to hyperglycemia; insulin plays a role in the penetration of glucose into these cells [13]. The molar ratio of the two hormones may provide an indicator of the direction of metabolism [14] and it is the principal factor affecting the glucose level. Under normal conditions this index varies from 0.4 to 70 [5]. According to data in the literature [10] no increase in the molar ratio of the hormones was found in diabetics after taking food, and the degree of these disturbances, moreover, corresponds to the severity of the clinical state. There is little information regarding changes in this parameter under normal conditions or in diabetes. Even less has been written about the

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TABLE 1. Concentration (in nmoles/liter) of Hormones in Blood Draining from Pancreas after Intra-Arterial Glucose Loading

Experimental conditions	Insulin		Glucagon		Insulin/glucagon	
	normal	pancreatitis	normal	pancreatitis	normal	pancreatitis
Fasting state	2,114±112	1830±81*	8,4±5,12	26,4±0,96*	26,1±3,73	69,3±14,7*
After injection of glucose, sec						
0	2 911±280	2758±352	84,2±9,28*	21,4±2,45*	37,1±5,64	129,0±16,7**
10	4 552±353	3608±201*	90,0±8,08	21,70±3,98**	52,0±9,15	183,0±37,6**
20	5 775±512	4223±347*	64,3±8,2	28,9±3,96**	90,3±15,8	150,0±28,7
30	10 721±2101	3823±426**	55,0±12,6	26,0±2,05*	168,0±36,5	141,0±26,8
40	14 596±3223	4203±458**	57,8±10,5	19,2±2,8**	233,0±64,5	212,0±31,5
50	14 155±4176	4592±875*	53,5±10,4	21,5±3,16*	275,0±56,8	213,0±35,1
60	13 929±3377	5535±435*	57,6±9,67	21,5±3,16**	235,0±49,9	263,0±54,9
70	11 831±3203	5422±422	57,69±10,3	21,0±2,56**	231,0±52,7	272,0±79,8
80	8 874±1502	4920±440*	54,2±10,2	30,1±5,54*	196,0±27,7	133,0±9,9
90	7 435±1528	5125±1112	71,3±3,99**	26,4±3,99**	112,0±27,5	201,0±50,4

Legend. $^{*}p < 0.05$, $^{**}p < 0.01$; otherwise $p < 0.1$

disturbances of its dynamics in other diseases with loss of carbohydrate tolerance. In this connection it is interesting to study glucagon secretion in the early stages of chronic pancreatitis.

The aim of this investigation was to study the dynamics of insulin and glucagon secretion in this disease.

EXPERIMENTAL METHOD

Considering that chronic pancreatitis is the result of an acute process in the pancreas, it was induced in seven dogs by injection of autologous bile (0.25 ml/kg body weight) into the duct; seven dogs formed the control group. After 2 weeks, when the acute phenomena had subsided, laparotomy was repeated and the superior pancreaticoduodenal vein and artery (through the right gastroepiploic artery) were catheterized for pancreatic perfusion in situ [3]. Immunoreactive insulin was assayed with the aid of standard kits (CEA-IRE-Sorin, France) and glucagon with the aid of kits from RSL (USA). In parallel tests glucose was determined by the orthotoluidine method using standard Bio Test kits (Lachema, Czechoslovakia).

Glucose was injected intra-arterially in a dose of 2 mg/kg in 0.2 ml of physiological saline. Samples were taken from the pancreaticoduodenal vein every 10 sec for 90 sec, and then after 2, 3, 5, 10, and 20 min. The experiment was repeated 3 or 4 times with an interval of 30 min. Pieces of the pancreas were stained with hematoxylin and eosin or with aldehyde fuchsin by Falin's method for morphological investigation.

EXPERIMENTAL RESULTS

Endocrine disturbances were found in experimental chronic pancreatitis and mechanisms affecting correction of primary changes of function were discovered. Elevation of the insulin level after intra-arterial injection of glucose during the period of maximal rise of its concentration relative to the initial level was reduced by almost 50% ($p < 0.05$) in chronic pancreatitis compared with the control. The overall increase in the concentration of this hormone in efferent vessels of the pancreas 20 and 90 sec after glucose loading was sharply reduced (Table 1). This is not always observed as a general rule after peroral or intravenous carbohydrate loading [2].

Data showing the time course of changes in the glucagon concentration are given in Table 1. A decline of its secretion was observed 10 min after injection of glucose into the control animals, to reach a minimum after 50 sec, which corresponded to maximal insulin release. The glucagon concentration began to rise after 1.5 min, and after 20 min it reached 159.0 ± 15.6 nmoles/liter. By this time the blood insulin level had returned to its initial value (4837 ± 545 nmoles/liter).

The glucose concentration in animals with pancreatitis, in the fasting state and after glucose loading, was lower than in the control group. The fall of the hormone concentration was smaller, the curve was flattened, and its greatest increase did not exceed the level of

TABLE 2. Glucagon Concentration in Efferent Vessels of Pancreas during Perfusion of the Organ in Situ (n = 7)

Parameter	Control	Chronic pancreatitis
Initial glucagon concentration:		
Maximal	1,97±0,48	2,03±0,74
Minimal	0,71±0,05	0,70±0,03
Overall decline of glucagon level in 20 sec, nmoles/liter	239,0±58,8	215,0±46,7

Fig. 1. Insulocyte 1 month after induction of pancreatitis: reduced number of bound ribosomes (20,000 ×).

53 ± 2.9 nmoles/liter ($p < 0.01$) after 20 min. Meanwhile the glucagon concentration showed no significant change compared with its initial level (Table 2). The overall fall of the glucagon level during the 20 sec after carbohydrate loading did not differ significantly from the control. This evidently indicates that at this stage of the course of the pathological process, sensitivity of the A cells to glucose was undisturbed.

In chronic pancreatitis the molar ratio of insulin and glucagon in the fasting state was significantly increased and was almost 3 times higher than in the control group ($p < 0.05$). After injection of glucose the highest value of this parameter was close to that in intact animals, but it was observed after 70 sec, i.e., somewhat later.

In the morphological study of the B cells the intensity of staining with aldehyde fuchsin was reduced, reflecting a fall of their insulin content [7]. As a result of hydropic degeneration and fibrosis, the architectonics of the islets of Langerhans was disturbed in chronic pancreatitis and the number of B cells was considerably reduced relative to the number of A cells [12, 15]. Reduction of hormone secretion in acute or chronic pancreatitis may be due also to inhibition of insulin synthesis, as is shown by a decrease in the number of bound and an increase in the number of free polysomes. This was observed on electron micrographs of B insulocytes (Fig. 1).

The results are evidence of inhibition of the early insulin response, although the A cells remain capable of inhibiting glucagon secretion in response to exogenous glucose. The reduction of glucagon secretion combined with reduction of insulin release in chronic pancreatitis leads to correction of their molar ratio to a level similar to that observed in intact dogs, so that the normal glucose concentration in the body is maintained in the first stages of the disease.

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INHIBITION OF GASTROINTESTINAL MOTILITY BY LOW-MOLECULAR-WEIGHT PEPTIDES FROM KAPPA CASEIN

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KEY WORDS: motility; inhibition; peptides of K (kappa) casein.

Since gastroduodenal pathology associated with hypersecretion is one of the most widespread diseases of the digestive system, the search for new and effective remedies of a peptide nature for the treatment of this disease is a very important problem. The search for such preparations is mainly proceeding on the lines of isolation of endogenous regulatory peptides and the synthesis of their longer-acting analogs. A new and very promising trend may be the search for analogous regulatory peptides among proteolysis products of food proteins. For instance, α_S- and β-caseins from cows' milk contain in their structure amino acid sequences which, in the course of proteolysis, are liberated in the form of physiologically active peptides [1, 7, 14], capable of influencing CNS activity [1, 10] and the hormonal status of the body [8, 9].

The writers found previously that a glycomacropeptide (GMP) released from Kappa (K) casein during curdling of milk is an inhibitor of gastric secretion [6] and motility [3]. Since the inhibitory effect of GMP on gastric and duodenal motility was accompanied by side effects,

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