# EFFECT OF SOME REGULATORY PEPTIDES ON PANCREATIC FUNCTION IN EXPERIMENTAL ACUTE PANCREATITIS

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The wide distribution and sustained rise in the incidence of acute pancreatitis urgently demand a search for new ways of preventing and treating this disease [6]. In the treatment of patients with acute pancreatitis and to prevent postoperative pancreatitis, preparations belonging to the group known as regulatory peptides are coming into use because of their ability to inhibit activity of the exocrine part of the pancreas: somatostain, calcitonin, and the Soviet synthetic Leu-enkephalin analog dalargin (synthesized in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR by Professor M. I. Titov) [1, 5, 7, 11]. Information on the mechanism of the cytoprotective action of these peptides in the literature is extremely limited.

The aim of this investigation was to study the effect of somatostatin, calcitonin, and dalargin on pancreatic function in experimental acute pancreatitis.

## EXPERIMENTAL METHOD

Experiments were carried out on 205 noninbred male albino rats (average weight 200 g) with experimental acute pancreatitis, induced by ligation of the main efferent duct of the pancreas. The rats were killed by decapitation and used in the experiments 1, 2, and 3 h after initiation of pancreatitis. The following series of experiments were carried out: I) intraperitoneal injection of somatostatin (Serono, West Germany) in a dose of 4 μg/kg; II) intraperitoneal injection of calcitonin (Sandoz, Switzerland) in a dose of 2 U/kg; III) intraperitoneal injection of dalargin in a dose of 10 μg/kg. All the peptides mentioned were injected soon after ligation of the pancreatic duct, and in order to stimulate secretory activity of the pancreocytes, a subcutaneous injection of pilocarpine hydrochloride in a dose of 100 μg/kg was given at the same.

Animals undergoing the same operation and receiving a subcutaneous injection of pilocarpine and an intraperitoneal injection of 0.9% NaCl in the corresponding volumes and at the same times, served as the control.

An important role in the development of a pathological process is known to be played by disturbance of integrity of the cell, due in particular to intensification of lipid peroxidation (LPO) in cell membranes [2, 13]. Xanthine oxidase (EC 1.2.3.2) is an enzyme which catalyzes the formation of hydrogen peroxide and the superoxide anion-radical. Accordingly, determination of xanthine oxidase activity accompanied by investigation of lipid peroxidation in the pancreatic tissue at different stages of the inflammatory process, and against the background of administration of somatostatic, calcitonin, or dalargin, can serve as an important metabolic criterion for assessing the efficacy of action of the preparations mentioned above.

Xanthine oxidase activity in pancreatic tissue was determined by the method in [10] and expressed in nanomoles reduced ferricytochrome per milligram protein; the level of lipid peroxidation was determined by the method in [12] and expressed in nanomoles malonic dialdehyde (MDA) per milligram protein.

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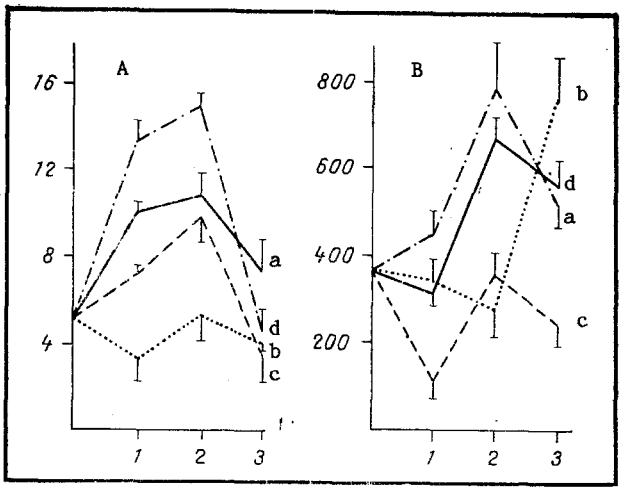


Fig. 1. Effect of regulatory peptides on XO activity (A) and MDA level (B) in pancreatic tissue in experimental acute pancreatitis (EAP). Abscissa, time after injection of peptides (in h); ordinate: A) XO activity in nanomoles reduced ferricytochrome per milligram protein (in nmoles FC/mg protein). B) Level of LPO (in mnoles MDA/mg protein). a) EAP + pilocarpine + dalargin; b) EAP + pilocarpine + dalargin; c) EAP + pilocarpine + somatostatin, d) EAP + pilocarpine + calcitonin.

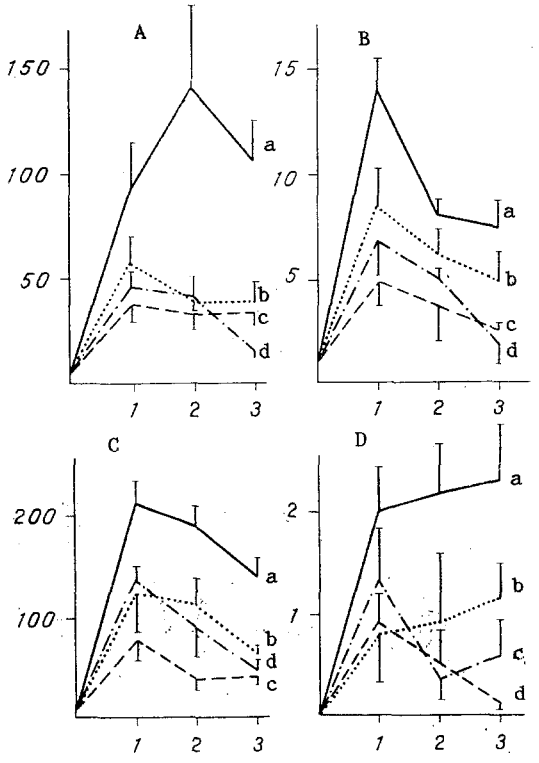


Fig. 2. Serum α-amylase (A), trypsin (B), lipase (C), and transaminase (D) activity in rats with experimental acute pancreatitis, after injection of regulatory peptides. A) In U/liter·$10^3$, B, C) in U/liter; D) in U/ml/h. Remainder of legend as in Fig. 1.

To monitor the state of pancreocyte membranes, activity of the following pancreatic enzymes was determined simultaneously in the blood serum: α-amylase by the method in [8], trypsin as in [9], lipase as in [4], and transaminase, as in [3].

## EXPERIMENTAL RESULTS

The data given in Fig. 1a show that dalargin has a marked inhibitory action on pancreatic xanthine oxidase (XO) activity, manifested most clearly 1 h (by 65.8%; $p < 0.001$) and 2 h (by 48.9%; $p < 0.01$) after injection of the peptide. Somatostatin also has an inhibitory action on XO, but it is weaker than the action of dalargin. Calcitonin not only does not inhibit XO activity to any marked degree, but actually stimulates it (by 30-34%).

Much the same data were obtained by a study of lipid peroxidation: dalargin inhibits MDA formation 2 h after injection (by 55.8%; $p < 0.05$). At all times of investigation somatostatin inhibits MDA formation (by 62.9%; $p < 0.001$; by 45.5%, $p < 0.05$; by 47.9%, $p < 0.01$ after 1, 2, and 3 h, respectively). Calcitonin, just as during the study of XO activity, does not induce reaction of MDA formation and shows a certain tendency for it to increase. Thus, of the three regulatory peptides tested, only dalargin and somatostatin exhibit a well marked antioxidant effect.

The results of determination of α-amylase (Fig. 2A), trypsin (Fig. 2B), lipase (Fig. 2C), and transaminase (Fig. 2D) activity in the blood serum after injection of the regulatory peptides showed that all acted in the same direction: all the peptides tested reduced activity of the pancreatic enzymes. However, whereas in the case of dalargin and somatostatin, a quite clear parallel was observed with the results of determination of XO activity and lipid peroxidation, calcitonin had a dissimilar action on the parameters examined above. Whereas in the case of dalargin and somatostatin, the reduction in the release of pancreatic enzymes into the blood stream was due both to inhibition of the exocrine function of the pancreas and to the simultaneous protective action of these peptides on the pancreas, leading to inhibition of LPO, stabilization of the pancreocyte membrane and, ultimately, to reduction of the release of the enzymes studied into the blood stream, the fall in activity of the pancreatic enzymes observed in blood serum following injection of calcitonin, which does not exhibit any antioxidant activity, was evidently due entirely to the inhibitory action of the peptide on pancreatic secretory activity.

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