EFFECT OF REGULATORY PEPTIDES ON PANCREATIC ENDOCRINE FUNCTION IN EXPERIMENTAL ACUTE PANCREATITIS

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Among the spectrum of conservative treatment of acute pancreatitis in recent years clinicians are increasingly turning to highly active biological regulators of pancreatic external secretory function such as somatostatin, glucagon, calcitonin, enkephalins, etc. The effect of these peptides on external secretory activity of the normal and pathological pancreas has been sufficiently well studied experimentally and clinically [4]. The high biological activity and broad spectrum of action of the regulatory peptides are nowadays well known, including indirect indications of their influence on the pancreatic islet apparatus. The aim of the investigation described below was accordingly to compare the action of somatostatin, calcitonin, and dalargin on pancreatic endocrine function in the early stage of development of experimental acute pancreatitis.

EXPERIMENTAL METHOD

The following synthetic analogs were used: somatostatin (Stilamine, from "Serono," Switzerland), calcitonin (Sandox, West Germany), and dalargin, synthesized at the All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR.

Experiments were carried out on noninbred male rats weighng 150-180 g. Acute pancreatitis was induced in anmals deprived of food for 18 h, by ligating the common bile duct where it enters the duodenum, and subsequently stimulating pancreatic exocrine function with 1% pilocarpine solution [5]. Immediately after the operation the animals were given a single intraperitoneal injection of a solution of somatostatin (4 μg/kg body weight), calcitonin (2 U/kg body weight), or dalargin (50 μg/kg body weight). The animals were killed 30 min and 1, 2, 3, 6, and 18 h after the operation. Five rats were killed at each time. Blood was collected in cold tubes containing contrykal, for determination of glucose, insulin, c-peptide, and glucagon concentrations. The peripheral blood glucose level was determined by the glucose oxidase method [8]. Hormones were determined by radioimmunoassay using the following commercial kits: insulin (RIO-INS-PG-^{125}I, USSR), c-peptide ("Mallinckrodt," West Germany); glucagon ("Biodate," Austria). The numerical results were subjected to statistical analysis by Student's test [3].

EXPERIMENTAL RESULTS

The development of acute pancreatitis is accompanied by the rapid release of glucose into the peripehral blood flow, its concentration rising almost threefold during 30 min of observation (14.3 ± 1.7 mM), and this is accompanied by a parallel increase in the insulin concentration to 70 ± 12.7 μU/ml. The peak glucagon concentration (420 ± 20 mg/ml) was recorded 1 h after the operation, coinciding with a sharp fall of the insulin level to 22.3 ± 6.8 μU/ml. The monotonic character of the fall of the blood glucose level will be noted, although it exceeded normal values at all times of observation (Fig. 1d).

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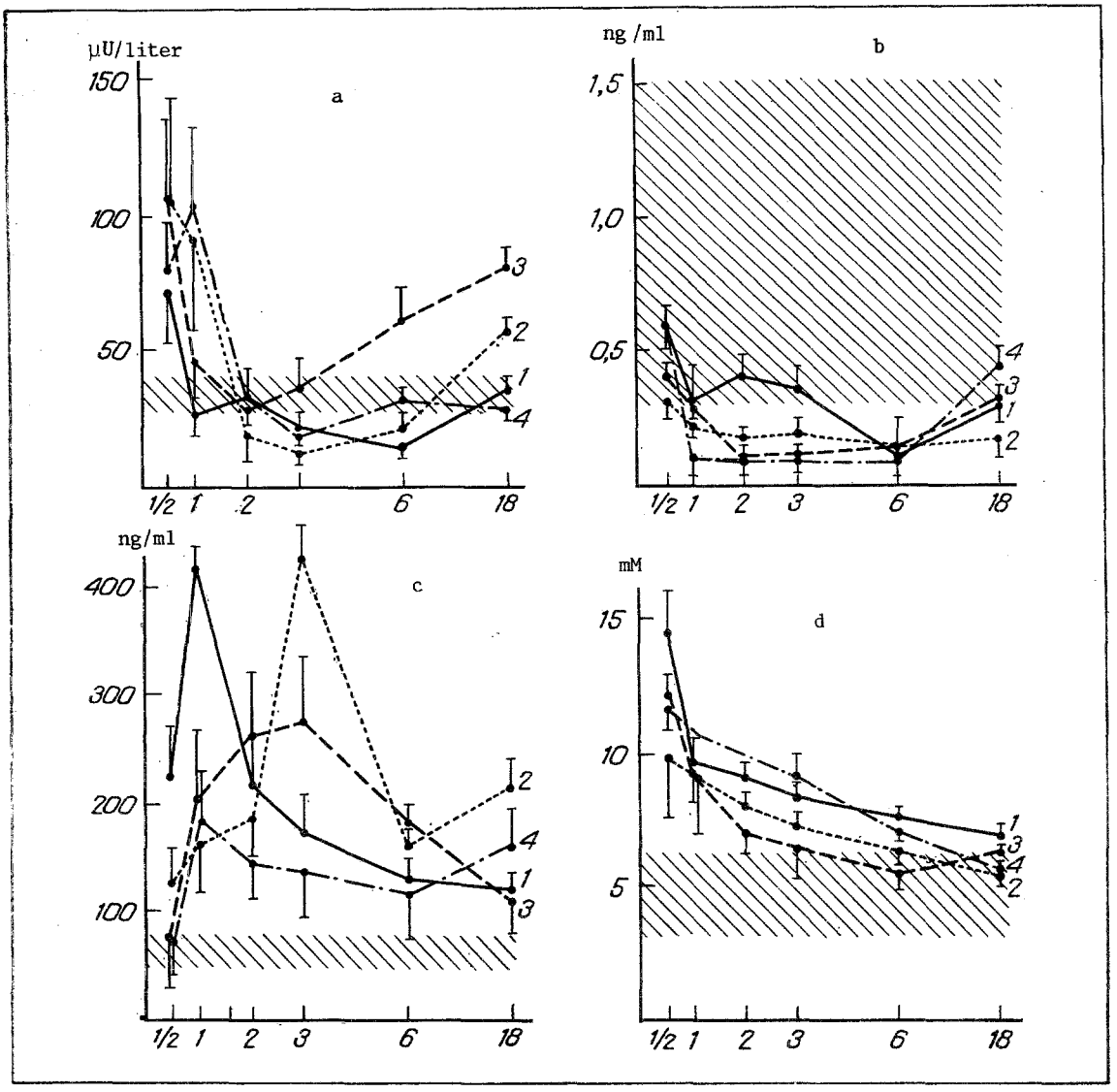

Fig. 1. Peripheral blood levels of insulin (a), c-peptide (b), glucagon (c), and glucose (d) in rats at various times after initiation of experimental acute pancreatitis and administration of regulatory peptides. 1) Acute pancreatitis; 2) somatostatin; 3) calcitonin; 4) dalargin; range of normal values is added.

A single injection of somatostatin had no effect on the blood sugar level, changes in which in this group of animals were similar to those observed in rats with acute pancreatitis only. The insulin level (Fig. 1a) at the 30th minute of observation was 107.7 ± 21.5 μU/ml, it fell to a minimum after 2 h of observation, after which its level rose and remained above normal throughout the rest of the experiment. Changes in the peripheral blood glucagon concentration were inversely proportional to the insulin level (Fig. 1c).

After injection of calcitonin the profile of changes in the blood glucose level differed only a little from those in the group with acute pancreatitis. Synchronized release of insulin and glucagon into the peripheral blood stream took place 1 h after the operation and intraperitoneal injection of calcitonin (Fig. 1a, c). Synthesis of c-peptide also was sharply inhibited at all times of observation (Fig. 1b).

Intraperitoneal injection of dalargin after initiation of pancreatitis had a stronger effect on the glucose concentration: after 30 min it was not more than twice the normal level (9.99 ± 0.14 mM), and after 6 h it was virtually the same as normal. The reactions of insulin and glucagon were opposite in direction but coincided in time (Fig. 1a, c). One of the most interesting aspects of the action of dalargin was a sharp rise in the peripheral blood glucagon concentration, which was observed 3 h after initiation of pancreatitis (423 ± 8.8 ng/ml), and this was accompanied by lowering of the insulin level to 12.3 ± 3.4

μU/ml and a low c-peptide level (Fig. 1b). Nevertheless, this release of glucagon did not lead to an increase in the serum glucose concentration of the experimental animals.

The operation to ligate the common bile duct and stimulation of the external secretory function of the pancreas by pilocarpine, as well as the response to ether anesthesia and to the operation itself, i.e., the total operative aggression, were manifested as a sharp rise of the peripheral blood glucose concentration, to almost 3 times the normal values. Simultaneously with the release of glucose into the blood stream, insulin and glucagon were secreted, and under these circumstances changes in levels of these hormones during the first hour of observation were opposite in direction and coincided with lowering of the blood sugar. By the second hour of observation the glucagon concentration had fallen by half, but still remained higher than normal at all times of observation. The high glucose concentration was maintained, on the one hand, by the development of pancreatitis and, on the other hand, the inhibition of secretion and synthesis of insulin associated with a high glucagon level.

During the development of acute pancreatitis a single injection of the standard therapeutic dose of somatostatin actively inhibited the 30-min release of glucagon into the blood stream, while preserving the insulin response. Lowering of the blood sugar level virtually to normal values can be explained by the continuing response of the β-cells of the islets of Langerhans, reflected in the time course of the insulin and c-peptide levels in the peripheral blood.

Injection of calcitonin during the development of acute pancreatitis was not reflected in the blood sugar level. However, changes in the insulin and glucagon concentrations showed a similar and parallel course, i.e., the counter-regulatory function of the islet-cell apparatus was disturbed. Elevation of the glucagon level took place from normal values to reach a maximum after 1 h, after which its reaction was the weakest of all the groups. The maximal insulin concentration also was recorded after 1 h; this shift of the maximum and the rather slower rate of fall of the blood glucose level can be explained by reduced reactivity of the β-cells. In the modern view, calcitonin modifies Ca^{++} transport through cell membranes and affects its intracellular distribution [1]. Restoration of the intracellular Ca^{++} level plays an important role in coordinating stimulation of secretion of the α-cells [2].

The effect of endorphins and enkephalins on the endocrine and exocrine function of the pancreas has been extensively studied and their specific receptors have been found in the islets of Langerhans [5]. Administration of dalargin during the development of acute pancreatitis enabled a lower level of blood sugar to be maintained than by the use of other preparations, reflecting its antistress properties. The responses of insulin and glucagon were distinct and opposite in direction, reflecting the physiological response of the pancreatic islet-cell apparatus to stimulation. These results are in agreement with observations on regulation of insular secretion by neuropeptides during stress [6], when a decrease in insulin secretion and elevation of the glucagon level also were observed. Active release of glucagon into the blood stream, which we observed at the 3rd hour of observation is most probably connected with activation of glucagon-like compounds in the gastrointestinal tract, for dalargin has an activating influence on its movements.

The results are thus evidence of a disturbance of the counter-regulating relations of insulin and glucagon during calcitonin administration. Somatostatin and dalargin do not modify the responses of the hormones, but dalargin, when exhibiting its antistress properties, makes a more active contribution to maintenance of normoglycemia during the development of experimental acute pancreatitis.

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PATHOMORPHOLOGY OF THE SUPERIOR CERVICAL SYMPATHETIC GANGLIA IN BURNS

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The cervical sympathetic nerve is the superior part of the lateral vertebral ganglionic chain. Arranged vertically on the transverse processes of the cervical vertebrae, this chain consists of 2-3 ganglia, joined by connecting nerve fibers [5, 10]. The superior cervical sympathetic ganglion, as a peripheral center for nervous regulation, plays a very important role in the pathogenesis of various diseases of the cardiopulmonary system [4, 11, 13]. The efferent innervation of the lungs is provided by the parasympathetic and sympathetic nervous system, for it has been shown that some bodies of postganglionic neurons, located in the cervical and stellate sympathetic ganglia, are connected with effectors of various tissue formations in the lungs [7, 8]. The study of the structural changes in the superior cervical sympathetic ganglia in burns is accordingly of great theoretical and practical importance, more especially because burn trauma is known to be complicated frequently by pneumonia and with manifestations of cardiopulmonary failure [3, 6, 9]. Similar investigations have been undertaken in diseases of the cardiovascular system, essential hypertension, and so on [1, 11]. In spite of the very important role of the nervous system in the pathogenesis of burns, no systematic studies have yet been undertaken of the dynamics of the morphological changes in the peripheral nervous system during thermal burning, or of the reversibility of these changes. Analysis of structural changes in the superior cervical sympathetic ganglia in burn trauma by the use of classical neurohistological and modern neurohistochemical methods is still awaited, and the investigation described below was undertaken for this purpose.

EXPERIMENTAL METHOD

The investigation was conducted on autopsy material from 75 cadavers of patients dying at different periods of burns (shock, toxemia, septicotoxemia, burn cachexia.) The ages of the patients was between 19 and 85 years. Autopsy was performed at various times from 3 to 6 h after death. The test objects were the superior cervical sympathetic ganglia. After fixation in 12-20% solutions of neutral formalin the material was embedded in paraffin wax. Sections were stained with hematoxylin and eosin and picrofuchsine by Van Gieson's method and were impregnated with silver nitrate by the methods of Bielschowsky–Gros and Campos. Nissl's method and neurohistochemical methods of staining adrenergic structures by incubation of sections in a 2% solution of glyoxylic acid in the modification in [12] also were used. Cholinergic nerve structures were detected by the method of Karnovsky and Roots.

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