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HISTOENZYMOLOGIC FEATURES OF THE ADRENOCORTICAL RESPONSE IN SOME VERSIONS OF EXPERIMENTAL PANCREATITIS

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KEY WORDS: adrenal cortex; pancreatitis; pancreas.

The role of the adrenal cortex in the pathogenesis of acute and chronic pancreatitis has not been adequately studied. Clinical, laboratory, biochemical, and experimental investigations have demonstrated changes in adrenal function in acute pancreatitis [1, 2, 5]. The morphofunctional state of the adrenals in acute pancreatitis and the stage of transition to the chronic type of pathological process are virtually unstudied.

It was accordingly decided to study the character of morphofunctional changes in the adrenal cortex during the development of experimental pancreonecrosis, including a study of correlation between structural changes in the pancreas and in the adrenal cortex. To determine the more precise role of structural-metabolic changes in the adrenals in the pathogenesis of pancreatitis, the substance methapyrone, a specific stablizer of steroid production, was used.

EXPERIMENTAL METHOD

Experiments were carried out on 80 noninbred male albino rats weighing 150-180 g, divided into groups: intact (six rats), undergoing a mock operation (20 rats), with experimental pancreonecrosis (30), with pancreonecrosis and receiving methapyrone (24). Experimental pancreonecrosis was produced by the method in [3]. Methapyrone was injected subcutaneously in a dose of 11 mg/100 g body weight 24 h after production of the disease, and thereafter daily for 14 days. The adrenals were studied on the 1st, 3rd, 7th, 14th, and 30th days of the experiment. Activity of NAD- and NADP-diaphorases, glucose-6-phosphate dehydrogenase (G6PDH), and of 3 β-OH-steroid dehydrogenase (3β-OH-SDH) was determined histochemically in frozen sections 10 μ thick. The intensity of the histochemical reactions was assessed by indirect cytophotometry, photographs being taken on the MUF-6 instrument, and the negatives subjected to photometry on the MF-4 instrument. The results of photometry were subjected to statistical analysis on the EC-10-22 computer using a program prepared for functional morphologic analysis of the endocrine system [4].

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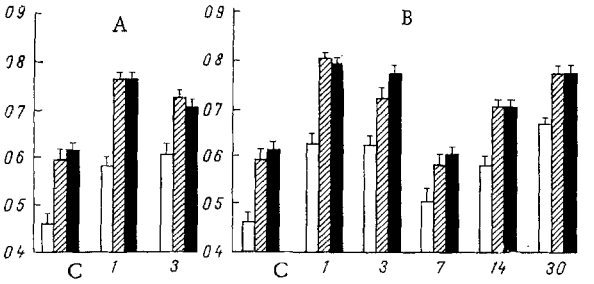

Fig. 1. Changes in 3β-OH-SDH activity in experimental pancreatitis. A) Mock operation; B) acute pancreatitis. Abscissa, stage of experiment (in days); ordinate, enzyme activity (in density units). Unshaded columns zona glomerulosa; obliquely shaded columns) zona fasciculata; black columns) zona reticularis. C) Control.

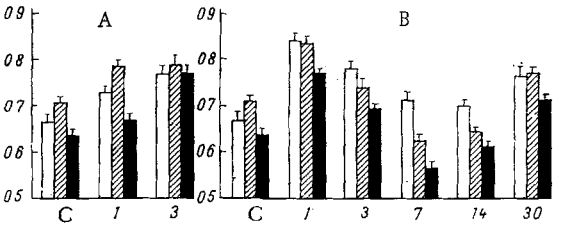

Fig. 2. Changes in NADP diaphorase activity in experimental pancreatitis. A) Mock operation; B) acute pancreatitis. Abscissa, time of experiment (in days); ordinate, enzyme activity (in density units). Unshaded colums) zona glomerulosa; obliquely shaded columns) zona fasciculata; black columns) zona reticularis. C) Control.

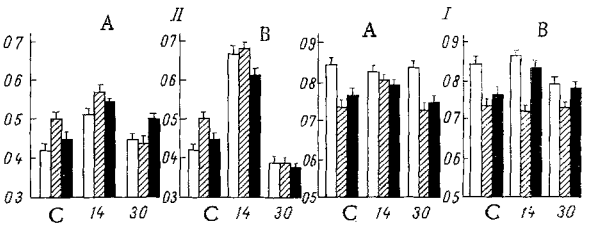

Fig. 3. Changes in NAD-diaphorase and G6PHD activity in experimental pancreatitis and treatment with methapyrone. I) NAD-diaphorase activity; II) G6PDH activity. In I and II: A) acute pancreatitis; B) acute pancreatitis + methapyrone. Abscissa, duration of experiment (in days): ordinate, enzyme activity (in density units). Unshaded columns) zona glomerulosa; obliquely shaded columns) zona fasciculata; black columns) zona reticularis.

EXPERIMENTAL RESULTS

Comparison of the results of quantitative histochemical analysis showed (Fig. 1) that changes in 3β-OH-SDH activity on the 1st day of the experiment connected with synthesis of steroid hormones were nonspecific in character, i.e., both in rats undergoing the mock operation and in animals with pancreonecrosis activation of the enzyme was observed 24 h later in all three zones of the adrenal cortex, with a similar time course of their dispersions.

On the 3rd day the activity of the enzyme remained relatively high in all three zones. Differences in the character of these changes in the group of animals undergoing the mock operation and animals with pancreonecrosis were not detectable, and only by analysis of dispersion among the animals with pancreonecrosis could certain differences be found. Damage to the pancreas in the early stages of the experiment (1st-3rd days) was thus accompanied by mainly nonspecific changes in 3β-OH-SDH activity, evidently reflecting severe stress changes in the animals. By the 7th day the original 3β-OH-SDH level was restored.

Analysis of another metabolic parameter (G6PDG) at the same time revealed a similar time course, i.e., in all three zones increased activity of the enzyme was observed after 1 day, similar to that in animals undergoing the mock operation. By the 3rd day, however, some difference was found from the mock operation group; in all three zones activity of the enzyme was reduced, i.e., disparity was observed between the 3β-OH-SDH and G6PDH levels. By the 7th day both G6PDH and 3β-OH-SDH activity was back to the control level.

Comparison of the two parameters of steroid hormone synthesis revealed that in the early stages of injury to the pancreas some definite differences were observed in the adrenal cortex. These differences were manifested more clearly by a study of enzymes of energy production. For instance, during the first day of the experiment differences were observed in the time course of NAD- and NADP-diaphorases in animals with a damaged pancreas (Fig. 2). NAD-diaphorase activity remained virtually unchanged from its level in animals undergoing the mock operation but NADP-diaphorase exhibited much greater activation than in the animals of the mock operation group (Fig. 3). On the 3rd day activity of these two enzymes was close to that observed in animals after the mock operation, but the topographic distribution of the enzymes among the tissues was changed. By the 7th day activity of both enzymes was below the control level, and sharp changes in their distribution among the tissues also were present.

After the 1st day of damage to the pancreas, structural and metabolic changes were thus observed in the adrenal cortex, namely changes in the interzonal relations and disparity in the time course of activity of enzymes responsible for energy provision and steroid hormone synthesis. On the 7th day of experiental pancreonecrosis, when regeneration in the pancreas predominated over inflammation, restoration of structure and function were observed in the adrenal cortex. By the 14th day of the experiment, when a capsule was forming around the necrotic masses, i.e., a pseudocyst was being formed, appreciable circulatory disturbances and dystrophic changes developed again in the adrenal cortex. The boundary between the zona fasciculata and zona reticularis became indistinct. On the 30th day a "second attack" took place in the pancreas: Foci of necrosis of individual lobules and fibrinoid necrosis of the blood vessel walls were found, accompanied by focal infiltration of the stroma and parenchyma of the pancreas with lymphocytes. Analysis of the enzymes of steroid hormone synthesis (3β-OH-SDH and G6PDH) on the 14th day of the disease showed that they were reactivated in all three zones, but by the 30th day, despite continued activation of 3β-OH-SDH, G6PDH activity lagged behind again, just as it did in the early periods of the experiment. This fact is evidence that during exacerbation of the pathological process in the pancreas, divergence was observed between the principal metabolic parameters in the adrenal cortex. This was confirmed more clearly by analysis of the enzymes of energy production. On the 14th day, for instance, despite activation of 3β-OH-SDH and G6PDH, a low level of NAD- and NADP-diaphorase activity still persisted; changes also were observed in the topographic distribution of these enzymes. On the 30th day some degree of activation of these enzymes was observed, but only a very little above the control level.

Comparison of activity of the enzymes responsible for energy production and for steroid hormone synthesis again showed divergence between the course of the principal metabolic parameters in the adrenal cortex and a disturbance of interzonal relations, but in the early stages this process was a response to injury of the pancreas, whereas in the second period of the experiment it preceded the development of secondary lesions in the pancreas. A comparative study of the pancreas on the 14th-30th days of observation in animals receiving and not receiving methapyrone showed that in one-third of the animals which did receive methapyrone no pseudocysts were found. Leukocytic infiltration of the necrotic tissues was present to only a very weak degree in the animals of this group. In the adrenal cortex of animals with acute pancreatitis, treated with methapyrone, a number of distinguishing features were found. The most conspicuous of these features was a distinctive readjustment of the energy providing enzymes. In particular, on the 14th day clear activation of NAD-diaphorase was observed in the animals of this group, by contrast with those with acute pancreatitis, mainly in the zona glomerulosa and zona reticularis (Fig. 3), whereas NADP-diaphorase activity re-

mained below the control level. Parallel with activation of NAD-diaphorase a sharp increase was observed in G6PDH activity in all three zones, which was not found in animals with acute pancreatitis. This comparison showed that restriction of the active participation of the adrenal cortex in the response to acute stress reduces the degree of divergence between the principal metabolic processes in the adrenal cortex during the period of formation of secondary changes in the pancreas.

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MORPHOLOGICAL CHANGES IN HEMATOPOIETIC ORGANS AND PANCREAS PRODUCED EXPERIMENTALLY BY 5-FLUOROURACIL

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KEY WORDS: 5-fluorouracil; pancreas; hematopoietic organs.

The treatment of acute pancreatitis still remains a difficult problem in emergency surgery. The mortality from destructive forms is extremely high [3, 4, 6]. Several workers [2, 8, 9] have suggested using antimetabolities (5-fluorouracil — 5FU, Ftorafur) which inhibit RNA synthesis, prevent protein synthesis in pancreatic exocrine cells, depress enzyme secretion, and block autolysis of the treatment of acute pancreatitis.

In the present investigation the effect of 5FU was studied experimentally on the parenchyma of the pancreas, liver, bone marrow, and spleen during absorption of the compound introduced into the peritoneal cavity. The need for such an investigation is evident because of the extensive use of 5FU in clinical practice for producing a block of Kappis-Roman type in patients with acute pancreatitis. Confirmation that the compound has no adverse effect on pancreatic tissue and on the hematopoietic organs would be objective evidence of the safety of the method under clinical conditions.

EXPERIMENTAL METHOD

Experiments were carried out on 30 mongrel dogs weighing 6-19 kg. The control group consisted of five dogs. Laparotomy was performed under thiopental anesthesia. A polyvinyl chloride tube was led to the pancreas and fixed with a suture to the parietal peritoneum, whereas its proximal end was brought out through an incision in the neck. Through this catheter the peritoneal cavity was irrigated with 5FU in a dose of 5 mg/kg body weight at times chosen beforehand. The animals were killed by artifical pneumothorax under anesthesia 3, 5, 10, and 60 days later, after irrigation with the compound for 2, 3, and 5 days. Biopsy of the internal organs was carried out at relaparotomy before sacrifice of the animals. The material was fixed in 12% neutral formalin and embedded in a paraffin wax. Sections were stained with hematoxylin and eosin and with picrofuchsin by van Gieson's method.

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