ELECTRON-MICROSCOPIC ANALYSIS OF COMPENSATORY-ADAPTIVE PROCESSES IN THE SMALL INTESTINE AFTER PANCREATIC ALLOGRAFTING AND IN CHRONIC PANCREATITIS

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An important problem in modern pathology is the study of injuries based on immune mechanisms. The localization of immune trauma may differ, but at any level of integration it is indissolubly connected with processes of protection and compensation, which take place in three stages: activation of the specialized functions of the injured cells, and reversible and irreversible injuries [1]. Fluctuation in activity and normalization of disturbed functions at all levels of organization are effected by single stereotyped structural changes, the most general reactions of homeostasis [5]. Cells, their membranes, and subcellular structures are the material substrate for these processes, but it is this aspect of compensatory-adaptive proceses which has been inadequately studied [2, 7].

EXPERIMENTAL METHOD

Experiments were carried out on 29 mongrel dogs. Allografting of the pancreas was performed in a heterotopic position, by anastomosing the main vessels of the graft with the recipient's femoral artery and vein. To reproduce chronic pancreatitis, the animals were sensitized three times at intervals of seven days by subcutaneous injection of saline antigen of the pancreas (up to 1 mg protein/kg body weight) and of blood vessels (up to 0.3 mg protein/kg body weight). After seven days the dogs were anesthetized, laparotomy was performed, and the pancreatic vein ligated. The animals were killed 3, 7, and 10 days and 1.5-2 months after the operation. Two dogs were reimmunized, 3.5 months after sensitization by tissue antigens, by a single injection of the same antigens, and they were killed seven days later.

For electron-microscopic investigations fragments of small intestine were fixed in 2.5% glutaraldehyde at pH 7.4, transferred to 1% osmium tetroxide solution, dehydrated in alcohols of increasing strength and embedded in Araldite. An open test system [4, 8] was used for morphometric analysis of the relative volume of the mitochondria.

EXPERIMENTAL RESULTS

A previous study of the preparations in a light-optical microscope showed that at the different stages of formation of chronic pancreatitis dystrophic changes developed in the small intestine and the intramural circulation and reaction of the lymphoid follicles were disturbed, the picture resembling the changes observed in the peripheral organs of immunity [3].

The present investigation shows that this reaction was particularly marked after allografting of the pancreas and reimmunization with tissue antigens. Under these cirumstances besides dystrophic changes in the epithelium of the mucous membrane, hyperplasia, and corresponding cellular transformations in the follicles, microerosions were formed at the base of the villi and in the crypts (Fig. 1a, b).

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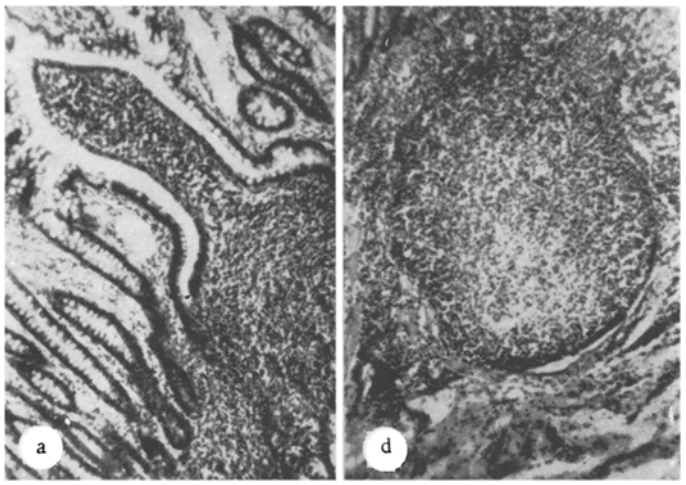

Fig. 1. Reaction of lymphoid follicles and mucous membrane of dog's small intestine to revaccination with tissue antigens: a) hyperplasia of follicle and dystrophic changes in epithelium of villi; b) formation of microerosions against the background of hyperplasia of a lymphoid follicle. Hematoxylin–eosin, 96 ×.

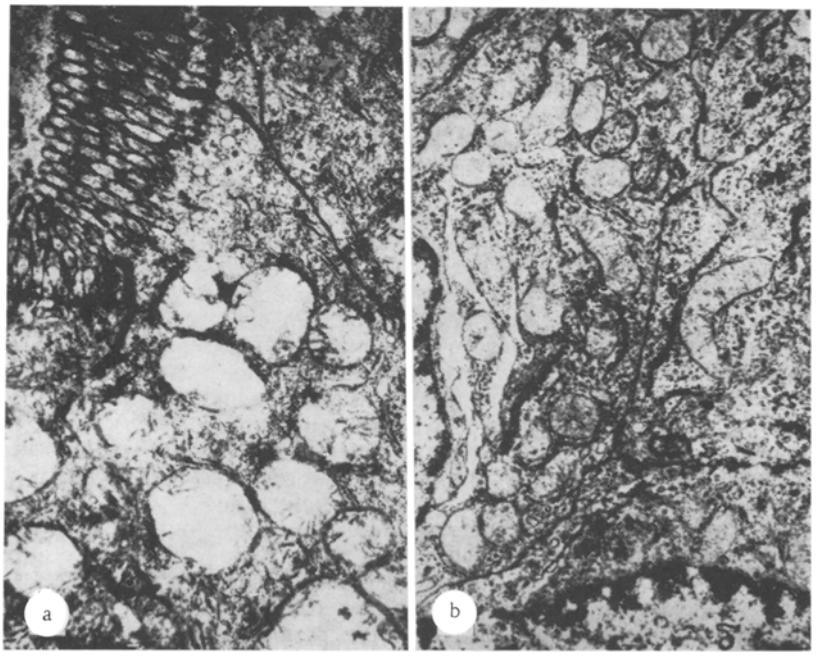

Fig. 2. Ultrastructural changes in enterocytes of dog small intestine after pancreatic allografting. a) Destruction of mitochondria of enterocytes three days after operation. Electron micrograph, 77,000 ×; b) regeneration of mitochondria, free and bound polysomes, marginal condensation of chromatin in enterocytes ten days after operation. Electron micrograph, 13,000 ×.

Examination of the electron micrographs showed that three days after allografting of the pancreas, the plasma membranes and junction structures of the enterocytes and microvilli were unchanged (Fig. 2a). Pinocytotic vesicles 60-80 nm in diameter, the membrane of which had a border of average density facing the central part of cell, were found in the cytoplasm. Ribosomes were distributed on the membranes of the rough endoplasmic reticulum, and polysomes were occasionally seen. The smooth endoplasmic reticulum was concentrated in the region of the Golgi apparatus. The mitochondria were enlarged and swollen, with a reduced number of cristae and a translucent matrix, containing electron-dense granules 20-80 nm in diameter, concentrated in the perinuclear and apical zones, and they accounted for 14.2 ± 0.7% of the total volume of the cytoplasm. Phago- and cytolysosomes were present in the cytoplasm.

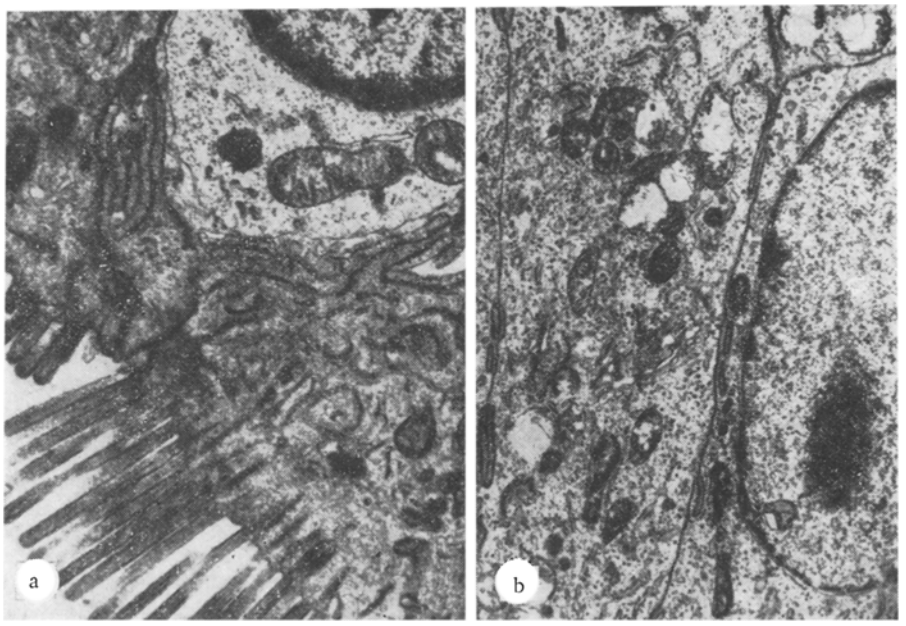

Fig. 3. Ultrastructural changes in enterocytes in small intestine of dog with chronic pancreatitis. a) Destruction of microvilli, reduction in number of mitochondria, dystrophic changes in mitochondria of enterocytes one month after operation. Migrating medium-sized lymphocytes can be seen. Electron micrograph, 36,000 ×; b) destruction and repair of mitochondria, reduction in number of membranes of endoplasmic reticulum, free ribosomes in enterocytes two months after operation. Electron micrograph, 9,200 ×.

The perinuclear space was somewhat widened, and marginal condensation of chromatin could be seen in the nuclei of individual cells. The changes described are evidence of some increase in functional activity of the cells.

After seven days the relative volume of the mitochondria was reduced to 7.6 ± 0.2% of the volume of the cytoplasm, but among them there were many juvenile forms. The number of free ribosomes was appreciably increased. The electron density of the hyaloplasm of the microvilli was reduced, and the spaces between them were enlarged, evidence of loss of glycoproteins and disturbance of the permeability of the brush border of the enterocytes.

The cells contained numerous secondary lysosomes and lipofuscin granules, degradation products of lysosomes, mitochondria, and endoplasmic reticulum, indicating depression of respiration and death of some of the cells. Marginal condensation of chromatin was observed in the nuclei of most cells, and in some of them the nuclear membrane formed bulbous evaginations.

After ten days the relative volume of the mitochondria, evenly distributed in the cytoplasm, increased to 11 ± 0.7%. The smooth membranes of the Golgi complex showed hyperplasia and the number of vacuolated tubules containing finely granular material was increased. Membranes of the rough endoplasmic reticulum and the terminal reticulum had increased electron density. In most enterocytes there were numerous polysomes, evidence of intensified synthesis of structural proteins and enzymes. The number of pinocytotic vesicles was increased. The perinuclear space in places was dilated, resembling cisterns, and the nucleoli had increased electron density. The number of "pale" and "dark" enterocytes in the intestinal epithelium was increased (Fig. 2b).

Ultrastructural changes in the enterocytes in chronic pancreatitis and the course of these injuries were identical with those described above, but were formed at later periods and reached the maximum of their development after 1.5-2 months (Fig. 3a, b).

The results of this investigation thus showed that after pancreatic allografting and in chronic pancreatitis, ultrastructural changes of a compensatory-adaptive character, similar in their morphological features, arise in the enterocytes of the small intestine. They are due to the reaction to antigenic stimulation and are aimed at maintaining the necessary level of functional activity under the conditions of the immune response.

This type of reparative regeneration, namely regeneration "at a distance" [6], evidently not only includes potential powers of compensation of the disturbed function in immunologic trauma, but is at the same time one of the nonspecific components of reactions of immune homeostasis. The results must be taken into account when the clinical manifestations of chronic pancreatitis are assessed and during management of the post-transplantation period after transplantation of the pancreas.

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ROLE OF NEUROMUSCULAR SYNAPSES IN MORPHOGENETIC PROCESSES TAKING PLACE IN TRANSPLANTED AMPHIBIAN MUSCLE

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Dependence of plastic (structural) processes in a skeletal muscle on its contacts with nerve tissue has been examined in amphibians in experiments on regeneration of muscles damaged *in situ* [1, 5, 7 13].

The ability of skeletal muscle tissue of amphibians to undergo morphogenetic changes after autografting of minced muscle [6] was demonstrated previously and subsequently confirmed by investigations on frogs [9, 14] and axolotls [10, 11].

Umnova [8] first performed autografting on a whole muscle in frogs and described the process of transplantation regeneration taking place in a muscle completely separated from the body and reimplanted, with which a nerve was put in contact during the operation.

The object of the present investigation was to compare the dynamics of the morphogenetic process taking place in an autograft of a whole amphibian muscle, deprived of its connections with the nervous system, and on reinnervation of the graft. The results of this investigation have been published previously only in short abstracts [3].

EXPERIMENTAL METHOD

Experiments were carried out in the fall and winter on 52 pond frogs *(Rana ridibunda)* weighing 50-80 g. The animals were kept at room temperature in an animal house and were fed

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