EFFECT OF NEUROTROPIC DRUGS ON THE EARLY SIGNS OF NEUROGENIC TROPHIC DISTURBANCES IN THE STOMACH WALL

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The nervous regulation of trophic processes has been the subject of many physiological and pathophysiological investigations which have established the close relationship between the tissue disorders and changes in the function of the nervous system [2, 6-8].

The action of pharmacological substances on trophic processes has received little study. The mechanisms of trophic processes in the early stages of development of neurogenic trophic disorders have never been studied by means of the latest cytological methods.

The object of the present investigation was to examine from various aspects the early stages of trophic disturbances by means of pharmacological and cytological analysis, using the electron microscope.

EXPERIMENTAL METHOD

Experimental trophic disorders in the mucous membrane of the stomach wall were produced by O. N. Zabrodin's [3] method by electrical stimulation of immobilized rats and traumatization of the duodenum [4].

The intensity of the injury to the gastric mucous membrane was determined microscopically. For the cytological analysis, the number of mitoses was counted in 4000 cells from 100 glands cut longitudinally, and the results were subjected to statistical analysis; the glandular epithelium of the stomach was also studied in the electron microscope. Experiments were carried out on adult sexually mature rats. The cytological examinations of the experimental material were carried out 1 and 3 h after electrical stimulation of the immobilized rats. The material for electron microscopy was fixed, treated, and embedded in methacrylates by Palade's method. Ultrathin sections were cut on an LKB ultratome and studied in the UEMV-100 electron microscope with an overall optical magnification of 25 000 times.

EXPERIMENTAL RESULTS

The development of trophic disturbances in the gastric mucous membrane at the submicroscopic level was observed 1 h after stimulation for 15 min, before any changes were visible in the optical microscope. They took the form of disturbances of the ultrastructures of the chief and parietal cells, with changes in the endoplasmic reticulum, a decrease in the number of ribosomes, and destructive changes in the mitochondria. The latter had lost their usual shape and their internal structure, and the electron density of their matrix was reduced. Some mitrochondria were fragmented. These changes were more marked in the parietal cells (Fig. 1).

The nuclei of the chief cells showed an increase in osmiophilia and a more marked condensation than normal of the nucleoprotein granules. The osmiophilic granules of the nucleus correspond to the macromolecules of desoxyribonucleoproteins and ribonucleoproteins (DNP and RNP) [9, 10, 11]. Consequently, in the early stages after stimulation, changes visible submicroscopically and reflecting disturbance of RNP resynthesis developed in the chief and parietal cells of the glands in the mucous membrane of the fundus of the stomach.

At these stages the disturbance of protein metabolism in the gland cells is also revealed by changes in the rate of incorporation of S^{35}-labeled amino acids [5]. The changes in resynthesis of the tissue proteins

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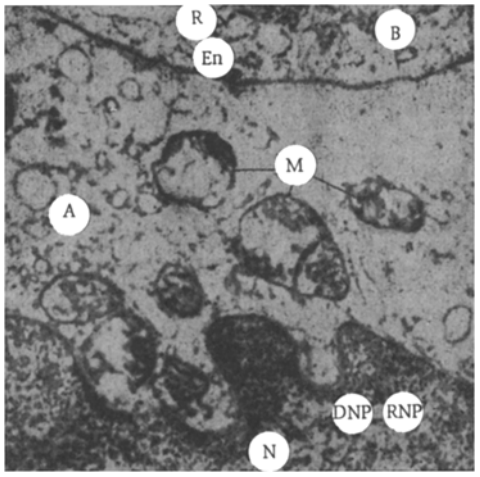

Fig. 1. Submicroscopic changes in the chief and parietal cells of the gastric mucous membrane. A—Part of a parietal cell: nucleus (N) granules of DNP and RNP; modified mitochondria (M) (vacuolation, swelling, destruction of internal membranes); B—part of the cytoplasm of the chief cells: En) endoplasmic reticulum with dilated tubules; R) ribosomes. Magnification 25 000 times.

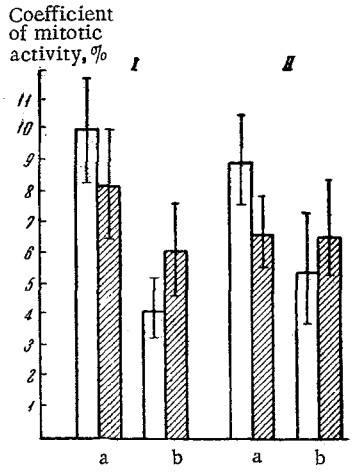

Fig. 2. Changes in mitotic activity of the gastric mucous membrane 1 (I) and 3 (II) h after electrical stimulation of the immobilized rats. a—Control; b—electrical stimulation of animals for 15 min. Unshaded columns—prophase and metaphase (P+M). Shaded columns—anaphase and telophase (A+T).

were accompanied by disturbances of physiological regeneration. Quantitative analysis showed that the coefficient of mitotic activity was modified, with an abnormal ratio between the phases of mitosis (Fig. 2). The delay in the passage of the cell from the interkinetic state into mitosis during synthesis of RNA demonstrated a disturbance of this process. The trophic disturbances developing in the early stages in the cells of the gastric mucous membrane could thus be detected electron-microscopically (at the ultrastructural level), biochemically (by the rate of incorporation of labeled amino acids) and functionally (by changes in the mitotic cycle).

However, the trophic changes in the gland cells described above were not massive in character in the early stages of development of the process. The intensity of the trophic changes in the gastric mucous membrane increased 3 h after stimulation, but as before, they were selective and local in character. At this time the development of necrobiotic changes could be observed in the optical microscope. A vascular reaction was clearly visible, characterized by foci of infiltration and diapedesis.

Analysis of the mechanism of the experimental gastric ulcers thus produced showed that they developed by a reflex mechanism, because they could be prevented by division of the vagus nerves and also by administration of pharmacological substances interrupting different links of the reflex arc [1].

The results of pharmacological investigations using neurotropic drugs provide additional information regarding the pathways of transmission of impulses disturbing the nutrition of the stomach wall and the participation of neural elements in the reflexes giving rise to the trophic changes. Furthermore, they can provide a rational basis for the medical treatment of neurogenic trophic disturbances of the gastric mucous membrane.

The results of the authors' earlier investigations [1] showed that the most effective drugs for preventing the development of neurogenic trophic disturbances are the bulbar sedatives (barbiturates), the central muscarine-like cholinolytic, and the peripheral sympathicolytics.

Comparison of the results obtained showed that the most effective of the centrally activing compounds were those blocking the transmission of nervous impulses through the reticular formation (barbiturates and central muscarine-like cholinolytic).

The efferent part of the arc of the reflexes causing trophic disturbances can be assumed to sympathetic fibers. This assumption is supported by experiments with hexamethonium, preventing reflex trophic disturbances only when given in doses of 10 mg/kg, blocking sympathetic ganglia. Peripheral sympathicolytics such as sympatholytin (dibenamine) and guanethidine, which prevent the development of neurogenic trophic disorders caused both by traumatization of the duodenum and by electrical stimulation of immobilized animals, were also effective.

The results of experiments carried out by E. V. Moreva, working in the laboratory of experimental pharmacology, showed that electrical stimulation of the hypothalamus in rabbits causes the appearance of destructive changes in the gastric mucous membrane similar to those produced by a reflex maechanism. These destructive changes could be prevented by division of the vagus nerves below the diaphragm and by preliminary administration of phenobarbital.

After application of an excessively strong stimulus to the reflexogenic zone, the impulses arriving via the activating reticular formation evidently produce intensive excitation of the sympathetic centers situated in the hypothalamus. A stream of impulses running from the hypothalamus along sympathetic pathways causes trophic disturbances in the mucous membrane of the stomach, which can be detected in the early stages by cytological methods.

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