# RESPONSE OF ENDOCRINE CELLS OF THE GASTROINTESTINAL TRACT TO 3,6-DICHLOROPICOLINIC ACID

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An urgent problem in contemporary morphology is the study of the structural organization and function of the regulatory and integrative systems of the body. The study of the diffuse endocrine system (DES), formed by a combination of hormone-producing cells, most of which are located in epithelial tissues which occupy a boundary position between the external and internal media of the body [6], is particularly interesting. Many investigations [1, 3, 5, 9] have demonstrated the exceptionally important role of the hormones of DES in regulation of various functions of the digestive system. Meanwhile, the role of the endocrine apparatus of the gastrointestinal tract in the regulation of the barrier function of the gastric and duodenal epithelium during exposure to xenobiotics remains unstudied.

The aim of this investigation was to study the morphological principles and particular features of the response of the endocrine cells in the pyloric and proximal duodenal portions of the gastrointestinal tract in response to administration of a single dose of 3,6-dichloropicolinic acid (DCPA), an herbicide with low toxicity.

## EXPERIMENTAL METHOD

Experiments were carried out on 40 male Wistar rats weighing 250-300 g, of which 20 served as the control. An emulsion of 3,6-DCPA was injected into the stomach in a single dose of 0.75 $LD_{50}$. The control and experimental animals were decapitated in pairs 1, 3, 6, and 24 h after administration of the single dose of the herbicide, using five rats at each time of the experiment. Pieces of mucous membrane from the pyloric part of the stomach and from the proximal part of the duodenum were taken for investigation. The material was fixed in a 10% solution of neutral formalin and embedded in paraffin wax. Electron-microscopic investigations were carried out in the usual way. Argentaffin cells, revealed by the Masson–Hamperl method, were counted in 100 fields of vision under a magnification of 400× of the microscope; other types of enteroendocrine cells were identified electron-microscopically on the basis of the morphological characteristics of their secretory granules, in accordance with the International Nomenclature of Enteroendocrine Cells. The functional state of the argentaffin (Ec) cells was determined as the index of the number of secretory granules in each endocrine cell in five serial sections and in 100 fields of vision, under a magnification of 400× of the microscope. Ultrastructural analysis of functional activity of the individual types of endocrine cells was carried out by determining the density of secretory granules in 1 $\mu^2$ area of the cytoplasm. The numerical data were subjected to statistical analysis by the usual method.

## EXPERIMENTAL RESULTS

The following proximal-distal gradient of distribution of argentaffin cells was found in the intact animals along the course of the gastrointestinal tract: 107 Ec cells in the pyloric part of the stomach and 77 in the proximal part of the duodenum. The index of the

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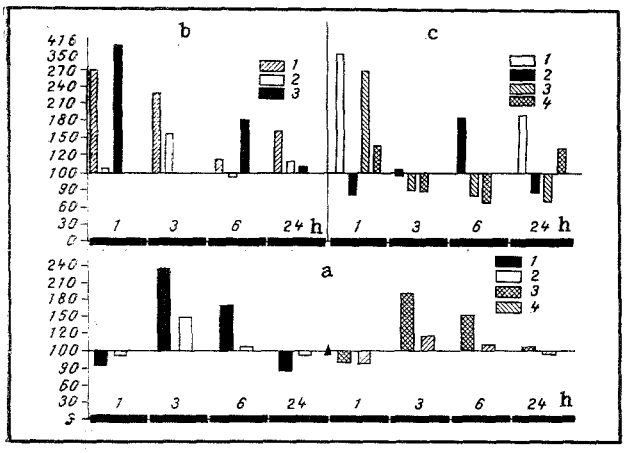


Fig. 1. Secretory activity of endocrine cells of gastrointestinal tract of rats exposed to 3,6-DCPA. a) Change (in %) of absolute number (1) and index of content of secretory granules (2) of argentaffin Ec cells of stomach and same parameters (3, 4, respectively) of duodenum; b) change (in %) in density of secretory granules of G (1), $D_1$ (2), and P (3) gastric cells; c) change (in %) in density of secretory granules of $D_1$ (1), K (2), P (3), and S (4) cells of duodenum.

Fig. 2. Hydration of cytoplasm and secretory granules of an Ec cell in pyloric part of albino rat stomach 1 h after administration of 3,6-DCPA. 6800×.

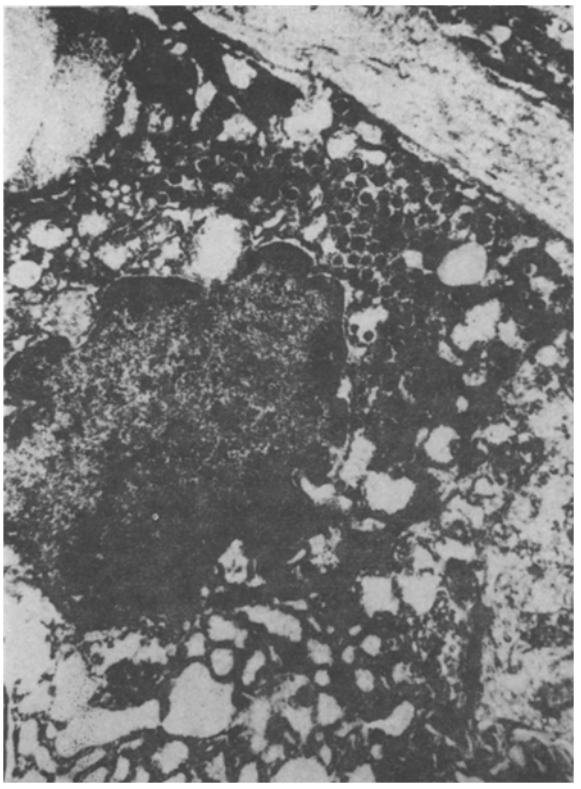

Fig. 3. Accumulation of secretory granules (extrusion block) in a $D_1$ cell in the albino rat stomach 3 h after administration of 3,6-DCPA. 9500×.

content of secretory granules in the Ec cells was 2.15 in the stomach and 2.17 in the duodenum. Electron-microscopy revealed Ec, $D_1$, G, and P cells in the mucous membrane of the pyloric part of the stomach and Ec, $D_1$, K, P, and S cells in the proximal part of the duodenum.

The results of the investigation (Fig. 1a) showed a sharp decrease in the absolute number of argentaffin Ec cells discovered in the pyloric part of the stomach as early as 1 h after a single dose of 3,6-DCPA, accompanied by some reduction of the index of the content of secretory granules in them ($p > 0.1$). This suggests that the primary response of Ec cells to administration of a xenobiotic is the intensive release of the secretory product. The ultrastructural manifestation of this process was marked dehydration and degranulation of the cytoplasm of the Ec cells (Fig. 2). Both these parameters were significantly higher than the control level ($p < 0.001$) 3 h after administration of the herbicide. This indicates that from 1 to 3 h after administration of the irritant, argentaffin Ec cells, having released their secretory product, entered synchronously into the phases of synthesis, accumulation, and storage of secretory granules. Later, 6 and 24 h after exposure to 3,6-DCPA, the absolute number of argentaffin Ec cells discovered and the index of their content of secretory granules both decreased, i.e., the Ec cells switched to the phase of release of secretion.

A similar tendency was observed in the changes in both parameters in the argentaffin Ec cells of the proximal part of the duodenum (Fig. 1a). According to the electron-microscopic observations, the primary response of the G and P cells in the pyloric part of the stomach (Fig. 1b) appeared 1 h, and that of the $D_1$ cells 3 h, after administration of the single dose of 3,6-DCPA, but on the other hand there was a sharp increase in the density of secretory granules ($p < 0.001$) contained in them, evidence of excessive accumulation of secretory material due to the development of an extrusion block (Fig. 3). Later the $D_1$, G, and P cells escaped from the block and entered into a phase of release of secretion.

An extrusion block also involved the $D_1$, K, and S cells 1 h after, and the P cells 6 h after administration of a single dose of the herbicide in the proximal part of the duodenum. Later the number of secretory granules in these cells fell below the control level

($p < 0.001$), evidence of the onset of a phase of hormone secretion and escape from the extrusion block (Fig. 1c).

The particular features of the response of individual types of endocrine cells in the pyloroduodenal region revealed by these experiments were essentially that an extrusion block developed 1 h after administration of the herbicide in the P and G cells of the stomach and in the $D_1$, K, and S cells of the duodenum, whereas the corresponding state was discovered later in the $D_1$ cells of the stomach and the P cells of the duodenum, namely 3 and 6 h respectively after administration of the xenobiotic. Escape from the extrusion block through release of the secretory product took place most rapidly in the $D_1$ cells of the stomach, between 3 and 6 h, followed by the G cells of the stomach and the S cells of the duodenum, namely from 1 to 6 h, in the P cells of the stomach and K and S cells of the duodenum from 1 to 24 h after administration of the single dose of 3,6-DCPA.

The opposite direction of response of individual types of cells of the DES thus revealed is of essential importance for endocrine regulation of the function of the epithelial barrier of the pyloroduodenal part of the gastrointestinal tract and development of the primary defensive response of the body. Intensive release of serotonin, motilin, and substance P, produced by the Ec cells is the reason for stimulation of mucus secretion, reduction of absorption of water and electrolytes, inhibition of hydrochloric acid secretion, stimulation of motor activity, and the appearance of nociceptive stimulation in the region of the gastrointestinal tract [2, 4, 10]. Conversely, blocking of the release of the vasoactive intestinal polypeptide, which is a product of the $D_1$ cells, and of bombesin, gastrin, and secretin, products of the P, G, and S cells, induces vasoconstriction, reduces the metabolic activity of the tissues, and inhibits the digestive function and contact digestion [7, 8], thus restricting resorption of 3,6-DCPA. The diverse response of the endocrine apparatus of the pyloroduodenal part of the gastrointestinal tract thus revealed in rats is evidence of activation of a protective mechanism regulating the barrier function of the epithelium during exposure to a xenobiotic.

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