SOME MECHANISMS CONTROLLING CELL RENEWAL IN THE GASTRIC MUCOSA IN PEPTIC ULCER

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The gastric epithelium belongs to the group of labile tissues which have the property of continuous cell renewal. Every minute about 500 thousand cells become detached from the surface of the human gastric mucosa [10] and the same number of newly formed epitheliocytes replace them. Under pathological conditions, in chronic gastritis and in the margins of ulcers, the intensity of renewal is increased [6].

To ensure the steady state of a tissue, or homeomorphosis [7], strict coordination of extrusion and new formation of cells is necessary. These processes are regulated by a number of factors (nervous, endocrine, immunologic), among which an important place must be allotted to local regulators of regeneration, or chalones. In recent years more than 20 tissue-specific chalones have been discovered [1-3, 8, 12]. However, in the already extensive bibliography on chalones there is only one paper devoted to gastric chalones. Phillpott [13] showed that an aqueous extract of gastric mucosa of newly hatched chicks partially inhibits mitotic activity of the gastric epithelium of chick embryos but does not affect mitotic activity of epithelial cells in the embryonic intestine, skin, or mesenchyme. The tissue specificity of this inhibitor also was confirmed by the fact that extracts of other tissues did not act on mitotic activity of the gastric epithelium.

The object of this investigation was to look for chalones in the human gastric mucosa and to evaluate correlation between the "chalone effect" and changes in the mucosa.

EXPERIMENTAL METHOD

To obtain extracts of gastric mucosa, material taken from patients at operations (gastrectomy) for gastric ulcer (4 cases), duodenal ulcer (5 cases), or carcinoma of the stomach (3 cases) was used. Because of the species-nonspecificity of chalones [1, 8, 12], the test object used to reveal them was the stomach of male albino mice weighing 16-20 g, previously deprived of food for 24 h. The mucosa of the fundal and pyloric regions of the human stomach was separated from the submucosa, cut into pieces with scissors, and homogenized in the cold in a hand-operated homogenizer; this was followed by alcoholic fractionation of the protein components [5, 8]. The fraction precipitated by alcohol in 70% concentration was discarded. The supernatant was reprecipitated by alcohol in 81% concentration. The residue was separated by centrifugation (3,000 rpm at 4°C for 10 min) and lyophilized. The freeze-dried residue was dissolved in 0.2 M phosphate buffer (pH 7.2) in a concentration of 20 mg/ml, colchicine 0.5 mg/ml was added, and the product was injected intraperitoneally in a dose of 0.2 ml per animal. The animals were decapitated under ether anesthesia 3 h after the injection. Altogether 380 mice were used. A group of mice receiving an intraperitoneal injection of colchicine solution (0.5 mg/ml) in the same volume of phosphate buffer as in the experimental series served as the control to each series of experiments. Pieces of mucosa from the stomach and small intestine were fixed in neutral formalin and embedded in paraffin wax; sections were stained with hematoxylin–eosin. To determine mitotic activity the number of mitoses per thousand epithelial cell nuclei from the pits and necks of the glands was counted. The results were subjected to statistical analysis.

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TABLE 1. Effect of Gastric Mucosal Extract from Patients with Various Forms of Peptic Ulcer on Mitotic Activity of Gastric Epithelial Cells of Mice (in percent of control)

Location of ulcer	Extract of human gastric mucosa	Mouse gastric mucosa
Gastric ulcer	Fundal region	52.8 ± 5.6
Duodenal ulcer	" "	38.1 ± 4.9

EXPERIMENTAL RESULTS

Aqueous extract of human gastric mucosa had a statistically significant inhibitory action on mitotic activity of mouse gastric epithelial cells ($P < 0.001$). The number of mitoses per thousand nuclei in this case was reduced by more than half (48.5 ± 6.1%) compared with the control. Marked tissue specificity of the human gastric mucosal extract was found when its effect on mitotic activity of epithelial cells of the small intestine was studied. No significant change in the number of mitoses was found under these circumstances (98.7 ± 2.8%). Meanwhile extract of mucosa from the pyloric region of the stomach depressed mitotic activity of the epithelial cells of the mouse mucosa more intensively than mucosal extract from the fundal region. These results suggest that the human gastric mucosa contains a species-nonspecific inhibitor of mitosis — a chalone which acts on the L_2-phase of the cell cycle.

Comparison of the effect of gastric mucosal extracts from patients with peptic ulcer (Table 1) showed that if the ulcer was located in the duodenum more marked inhibition of mitotic activity was observed than in the case of a gastric ulcer. The "chalone" effect ought to be more marked in tissues containing a larger number of mature differentiated cells [2, 3]. Differences in the action of gastric mucosal extracts from patients with ulcers in different situations can be explained from this standpoint. It has been shown [9] that the mucosa of the fundal region of the stomach in duodenal ulcer contains almost twice as many parietal cells as in gastric ulcer. Furthermore, differentiation of parietal cells is accelerated in duodenal ulcer and mature cells occupy all parts of the fundal glands [4], whereas cell renewal is retarded [11]. The effect of all this is that more mature, differentiated cells are present in the same volumes of gastric mucosa in duodenal ulcer and, for that reason, their inhibitory effect is greater than in gastric ulcer.

Aqueous extract of gastric mucosa is thus characterized by a well-marked "chalone effect" and a tendency for chalone from the pyloric region to act more strongly than that from the fundal region can be detected. The inhibitory effect of the chalone is stronger in duodenal ulcer than in gastric ulcer.

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