CHANGES IN PROLIFERATION OF EPITHELIAL CELLS OF THE GASTRIC MUCOSA IN MICE WITH EXPERIMENTAL GASTRIC EROSIONS AND ULCERS

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Experimental erosions and ulcers of the glandular part of the stomach were produced in male CBA × C57BL hybrid mice weighing 20-23 g by immobilizing the animals daily for 30 min over a period of 3-8 days and by injecting hydrocortisone intraperitoneally in a dose of 0.3 mg per mouse daily for 8 days. A significant decrease in the daily number of epithelial cells of the gastric mucosa of the experimental groups of mice synthesizing DNA compared with the control was demonstrated with the aid of thymidine-H^3. It is concluded from these investigations that the slowing of cell renewal in the epithelium of the gastric mucosa is the main cause of its lowered resistance and one of the main causes of formation of steroid gastric ulcers.

Many recent investigations have established the unity of influences of the nervous and endocrine systems in the regulation of gastrointestinal function and in the pathogenesis of peptic ulcer, [2, 3, 7-9]. It has also been shown that, if the resistance of the mucosa is normal and trophic disturbances are absent in the tissues of the gastroduodenal region, exposure to the peptic factor alone is insufficient to cause the development of peptic ulcer [7-9, 12, 15].

The concept of resistance of the mucosa and the amount of protective mucus is linked with the process of renewal of the mucous cells of the epithelium composing it [4, 5, 16].

The cycle of development and the processes of proliferation of the surface-epithelial cells are characterized by their great rapidity [11, 16]. The slowing of these processes leads to weakening of the mucosal protective barrier [5, 15].

The work of Soviet and other investigators has demonstrated a decrease in the number of epithelial cells of the glands of the gastric mucosa synthesizing DNA during exposure to stress or after injection of ACTH and glucocorticoids [5, 14, 16-18, 20]. Many reports of the formation of gastric and duodenal erosions and ulcers in response to stress and to administration of ACTH and glucocorticoids have been published [2, 3, 7, 10, 14, 16-21].

The investigation described below was accordingly carried out in order to produce experimental gastric ulcers in mice and to study changes in the daily number of epithelial cells synthesizing DNA and in the mitotic index (MI) in the mucosa of the secretory part of the stomach of these animals.

EXPERIMENTAL METHOD

Experiments were carried out on 84 male CBA × C57BL hybrid mice weighing 20-23 g (21 mice in the group).

The animals of group 1 received hydrocortisone (Gedeon Richter, Hungary) in a dose of 0.3 mg per mouse daily for 8 days. To mobilize the secretion of endogenous adrenocortical hormones, stress was

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TABLE 1. Formation of Gastric Erosions and Ulcers in Mice after Exposure to Stress and Administration of Hydrocortisone

Conditions	Number of animals with lesions of pylorus		Number of animals with lesions of gastric fundus	
	ulcers	erosions	ulcers	erosions
Stress for 3 days	—	—	—	2
Stress for 8 days	3	3	3	3
Hydrocortisone (0.3 mg per mouse daily for 8 days)	1	2	3	8

TABLE 2. Daily Number of Cells Synthesizing DNA and MI in Epithelial Cells of Mucosa of Secretory Part of Mouse Stomach (M ± m)

Conditions	Surface-epithelial cells of pyloric glands		Mucus-forming surface-epithelial + mucous cells of glands of gastric fundus	
	ILN in %	MI in ‰	ILN in %	MI in ‰
Control	19,3±1,46	9,2±1,00	48±3,90	6,7±1,08
Stress for 8 days	10,8±2,25	3,9±0,80	29±4,20	3,2±0,92
Hydrocortisone (0.3 mg per mouse daily for 8 days)	7,4±1,80	2,64±0,80	23,6±4,30	1,8±0,03
	11,1±2,81	4,9±0,50	33±1,82	2,73±0,47

induced in the animals of groups 2 and 3 by immobilization (tying to a frame for 30 min) daily for 3 and 8 days, respectively. Group 4 acted as the control.

To determine the daily number of cells synthesizing DNA (the index of labeled nuclei; ILN), every 4 h for 24 h all the mice received intraperitoneal injections of thymidine-H^3 in a dose of 0.7 μCi/g. The animals were then killed by decapitation all at the same time. The stomachs were fixed with Carnoy's mixture [11].

After preliminary investigation of the gastric mucosa under a binocular loupe for erosions and ulcers (objective 1, ocular 7) autoradiographs of the pylorus and fundus of the stomach were prepared in the usual way.

The value of ILN for the surface-epithelial cells of 50 longitudinally divided glands of the pylorus and in the mucus-forming cells of the fundus of the stomach (the number of glands was the same) was calculated in percent. The mitotic index (MI) in promille was calculated in the cells of the pyloric glands (or the gland as a whole) and in the mucus-forming cells of the glands in the fundus of the stomach.

The numerical results were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

The results of examination of the stomachs of the experimental groups of mice are given in Table 1. The least marked changes were observed after stress for 3 days and the most marked changes after stress for 8 days and after administration of hydrocortisone.

Calculation of ILN for the surface-epithelial cells of the pyloric glands showed that this parameter was considerably higher in the intact mice than in mice exposed to stress for 3 and 8 days and in mice receiving hydrocortisone (Table 2). The differences were statistically significant ($P \leq 0.002$, $P \leq 0.005$, $P \leq 0.001$).

Statistically significant differences were observed between MI for cells of the pyloric glands of mice of the control and experimental groups ($P \leq 0.01$, $P \leq 0.003$, $P \leq 0.001$; Table 2).

The percentage of mucus-forming cells synthesizing DNA in the fundus of the stomach in 24 h showed a marked decrease in their number in all the experimental groups compared with the control ($P \leq 0.024$, $P \leq 0.008$, $P \leq 0.003$). MI of the mucus-forming cells of the gastric fundus of the experimental groups was significantly lower than in the control ($P \leq 0.003$, $P \leq 0.019$, $P \leq 0.009$; Table 2).

ILN of the surface-epithelial cells both of the pylorus and of the mucus-forming cells of the gastric fundus was lowest in the mice exposed to stress for 8 days.

Differences between the indices of proliferation of this and the other experimental groups were close to significant ($P \leq 0.043$, $P \leq 0.027$, $P \leq 0.021$).

The difference between ILN of the epithelial cells of the gastric fundus in the mice of groups 2 and 3 was not statistically significant ($P = 0.079$).

Hence, both stress and administration of hydrocortisone considerably lowered the activity of the processes of cell renewal in the surface-epithelial cells of the pyloric glands and the mucus-forming cells of the glands of the gastric fundus. These results agree with those obtained by other workers who found a decrease in the number of DNA-synthesizing cells in the epithelium of the gastric mucosa during stress and administration of ACTH and glucocorticoids [16-20].

In the present experiments ulcers and erosions of the gastric mucosa were found in mice exposed to stress for 8 days or receiving hydrocortisone by daily injections in a dose of 0.3 mg for 8 days. Small erosions in the gastric fundus were observed in only two animals exposed to stress daily. Meanwhile, ILN for the mice of this group was reduced by a lesser degree than by the mice in group 3, indicating that ulcer formation is directly dependent on the degree of lowering of epithelial proliferation during exposure to stress.

The fact must also be noted that administration of hydrocortisone for 8 days gave rise to erosions and ulcers of the mucosa of equal intensity as exposure to stress for 8 days. Yet after repeated injections of massive doses of hydrocortisone the decrease in ILN was smaller than during prolonged stress.

Under normal conditions the adrenals of mice do not produce hydrocortisone [13], and its action thus differs from that of endogenous hormones. Besides its inhibitory action on proliferation hydrocortisone may possibly also have a destructive action on the gastric epithelial cells like that observed in lymphoid organs [10]. However, this is a problem for special study. The investigations carried out justify the conclusion that slowing of cell renewal in the epithelium of the gastric mucosa is the main cause of the lowering of its resistance and one of the chief causes of the formation of stereoid gastric ulcers.

The formation of gastric ulcers, including steroid, can be regarded as a special case of a dystrophic disturbance of tissue integrity. From that point of view the conclusion drawn from this investigation confirms the general principal first enunciated by Lebedinskii [6] that all dystrophic ulcers are based on a disturbance of physiological regeneration of the tissues, i.e., a disturbance of the ratio between the number of tissue cells lost and the number formed by mitotic division.

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