DYNAMICS OF DNA SYNTHESIS IN THE GASTRIC MUCOSA DURING ULCERATION

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Changes in DNA synthesis in different phases of ulceration were discovered by a histoautoradiographic method in the gastric mucosa of mice in which an experimental gastric ulcer was produced. At the beginning of ulceration the labeling index (LI) diminished. Formation of an ulcer morphologically similar to the chronic type was accompanied by an increase in the number of DNA-synthesizing cells in its borders. During healing of the ulcer the proliferative activity of the epithelium fell almost to its initial level. Histoautoradiographic investigation of biopsy specimens of the gastric mucosa obtained by direct-vision gastroscopy in patients with gastric ulcer revealed increased proliferative activity of the epithelium at the margins of the ulcer. Similar changes in LI were found in gastritis accompanied by lesions of the glands and in atrophic gastritis.

KEY WORDS: histoautoradiography; DNA synthesis; gastric ulcer; chronic gastritis.

An important role in the morphogenesis and healing of ulcers is played by the state of regeneration taking place in the gastric mucosa. Although there have been many investigations of this problem [1, 2, 4-6, 8] it has been inadequately studied on clinical material.

The aim of the present investigation was accordingly to study the state of regeneration during the formation and healing of ulcers on experimental and clinical material.

EXPERIMENTAL METHOD

The experimental section of the investigation was conducted on 44 CBA × C57BL hybrid mice in which a gastric ulcer was produced by the method of Okabe and Pfeiffer [7] (application of 100% acetic acid to the serous membrane of the stomach in the fundal region for 1 min). With the aid of this model it is possible to carry out investigations both during initial ulcer formation and during chronic transformation of the ulcer. The animals were killed between 1 and 120 days after treatment with acetic acid. Thymidine-^{3}H (1 μCi/g body weight) was injected intraperitoneally into the animals 1 h before sacrifice. The stomach was fixed in 10% formalin, buffered by Lillie's method, and embedded in paraffin wax. Sections were stained with hematoxylin-eosin, by Brachet's method, and by the PAS reaction. For histoautoradiography serial sections were coated with "M" photographic emulsion and exposed at 4°C for 21-28 days; after development, the labeling index (LI; the number of labeled cells per 1000 cells of the given population) was counted. On the basis of changes in the proliferative pool at different stages of ulcer formation the rate of reparative regeneration was judged in the margins of the ulcer in the fundus and pyloric portion of the stomach. Biopsy material taken from the gastric mucosa of patients with gastric (12 cases) and duodenal (seven cases) ulcers also was investigated histoautoradiographically. The process in all patients with peptic ulcer was in a stage of acute exacerbation. Biopsy specimens from patients with gastric ulcers were obtained during gastroscopy from the edge of the ulcer, 1.5-2 cm away from it, and from the pyloric part of the stomach; in patients with duodenal ulcer they were taken from the fundal and pyloric portions. Altogether 76 fragments of gastric mucosa were investigated. The ages of the patients with peptic ulcer ranged from 23 to 66 years. The biopsy material was incubated for 1 h in medium No. 199 to which thymidine-^{3}H was added (10 μCi/ml medium). The samples were incubated at 37°C and aerated with a gas mixture consisting of 95% O_2 and 5% CO_2. After incubation the biopsy material was embedded in paraffin wax and cut into serial sections. Only the first four sections were used for histoautoradiographic study. All numerical data were subjected to statistical analysis.

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TABLE 1. LI in Gastric Mucosa of Mice with Experimental Ulcer (M ± m)

Portion of stomach	Control	Days after beginning of ulcer formation						
		1	3	8	9	10	14	20
Fundal (edge of ulcer)	10,1±1,0	5,6±0,3	14,4±1,1	18,9±1,3	20,0±1,3	18,6±1,2	17,0±1,2	13,2±1,2
Pyloric	20,2±1,6	7,0±0,3	16,0±1,2	15,9±1,3	18,6±1,3	16,9±1,4	17,7±1,1	19,8±1,6

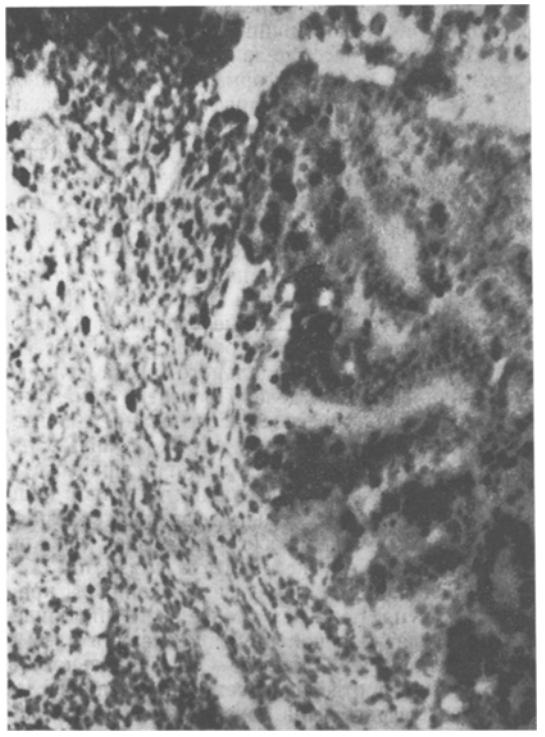

Fig. 1

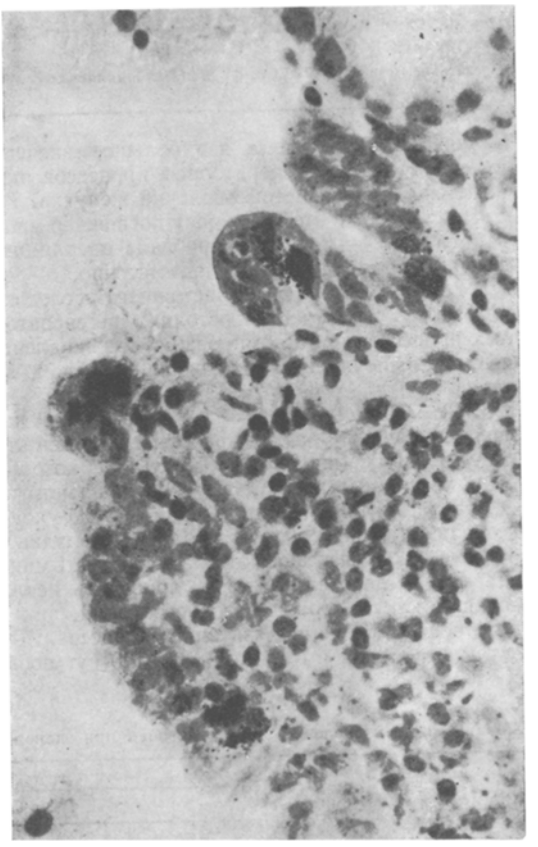

Fig. 2

Fig. 1. Experimental chronic ulcer (10 days). Sharp increase in DNA synthesis in margin of ulcer. Thymidine-^{3}H labels 1 h after injection of isotope. Carazzi's hematoxylin, 70×.

Fig. 2. Atrophic gastritis. DNA-synthesizing cells at apex of rugae. Histoautoradiography with thymidine-^{3}H (incubation 1 h). Carazzi's hematoxylin, 200×.

EXPERIMENTAL RESULTS

A zone of necrosis formed in the fundal portion of the stomach during the first day after treatment with acetic acid. Histoautoradiographic investigation revealed a sharp fall in LI in the mucosa adjacent to the zone of necrosis compared with LI in the control (Table 1). The considerable reduction in DNA synthesis in the mucosa of the fundal and pyloric portions of the stomach at the beginning of ulcer formation can be regarded as an expression of a stress reaction, to correspond with what was observed in an investigation of animals in a state of stress [3].

On the 2nd-3rd day progression of the necrotic changes in the stomach wall was observed and proliferation in the residual part of the stomach was stimulated, as shown by a gradual increase in the number of DNA-synthesizing cells (Table 1). The increase in the proliferative pool in the fundal part of the stomach, where the ulcer was formed, was greater than in the pyloric portion, where there was only a tendency for the original level to be reached.

By the 9th-10th day, when an ulcer morphologically similar to the chronic type was forming (Fig. 1), a sharp increase in the number of DNA-synthesizing cells was observed in its margins (Table 1). Under these

TABLE 2. LI in Gastric Mucosa in Patients with Peptic Ulcer (M ± m)

Location of ulcer	Fundal portion of stomach	Pyloric portion of stomach	Edge of ulcer	Region of ulcer
Gastric	—	21,9 ± 1,3 (n = 9)	34,6 ± 2,6 (n = 12)	16,6 ± 1,7 (n = 12)
Duodenal	11,0 ± 0,6 (n = 6)	18,3 ± 0,7 (n = 7)	—	—

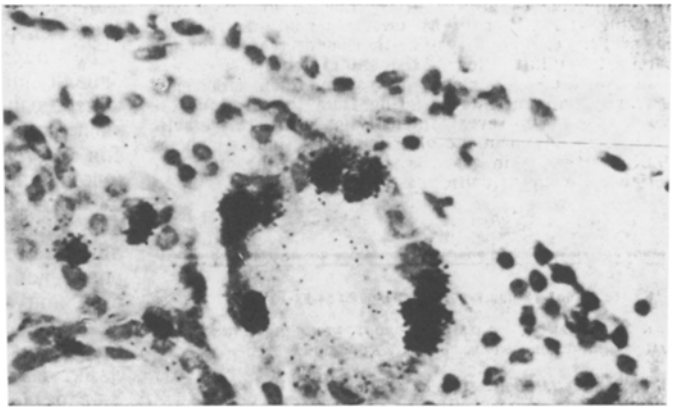

Fig. 3. Atrophic gastritis. Many labeled cells in neck of glands. Autoradiography with thymidine-^{3}H of epithelial cells in neck of glands (incubation for 1 h). Carazzi's hematoxylin, 250×.

circumstances LI rose to twice its initial level. This increased DNA synthesis in the edges of the ulcer can be regarded as a manifestation of compensatory processes. Changes were observed in the localization of the DNA-synthesizing cells. Whereas under normal conditions they were located only in the neck of the glands and in the epithelium of the pit, during the period of increased regeneration DNA-synthesizing cells appeared in the middle and lower thirds of the glands.

After 120 days, the fundal glands at the site of the ulcer were replaced by simpler glands of the pyloric type. LI in this region became 13.2 ± 0.2. In the pyloric portion of the stomach, where the structure was completely preserved, LI was the same as its initial value (Table 1).

In biopsy material from the gastric mucosa obtained by biopsy on patients with gastric ulcer a sharp increase in proliferative activity was observed at the edge of the ulcer (Table 2). At a distance of 1.5-2 cm from the edge of the ulcer, where a picture of gastritis with involvement of the glands or of atrophic gastritis was present in the mucosa (Table 2), LI was lower than at the edges of the ulcer but was higher than normally ($P < 0.05$). Not only the rate of renewal of the epithelium was changed, but also the zone of proliferation. DNA-synthesizing cells were observed to have appeared at the rim of the glands, where normally cells which have completed their life cycle should be found (Fig. 2). Changes in proliferative activity also were observed in the pyloric part of the stomach, where the picture was one of atrophic gastritis (Fig. 3, Table 2). During epithelization of the ulcer, the greatly flattened epithelium lining it did not contain DNA-synthesizing cells.

Biopsy material also was studied from the mucosa of the fundal and pyloric portions of the stomach of patients with duodenal ulcers (Table 2). In the mucosa of the fundal portion of the stomach of five of the seven patients there was a picture of superficial gastritis, and in the pyloric portion of all patients a picture of atrophic gastritis. Changes in the structure of the mucosa were accompanied by changes in the rate of renewal of the epithelium: the more marked the atrophic changes in the mucosa, the higher the rate of proliferation.

No correlation was found between the rate of DNA synthesis and the period of healing of the ulcer, i.e., despite the high proliferative activity of the epithelium, cicatrization of the ulcer took more than 45 days. The rate of renewal of the epithelium likewise did not depend significantly on the patients' ages.

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EFFECT OF COLD STRESS ON POSTNATAL FORMATION OF MECHANISMS OF CARBOHYDRATE HYDROLYSIS AND TRANSPORT IN THE RAT SMALL INTESTINE

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Acute experiments using the accumulating mucosal preparation (AMP) method showed that cold adaptation (exposure for 2 h daily to a temperature of 6-7°C) of young rats during the first week after birth has a lasting inhibitory action on postnatal formation of the maltase transport and γ-amylase-transport digestion-assimilating systems but does not change the dynamics of development of the intrinsic transport systems. The same adaptation at the age of 10 to 17 days after birth, on the other hand, appreciably quickened the rates of formation of the hydrolytic-transport conveyor on the outer surface of the cell membranes.

KEY WORDS: cold; small intestine; accumulation of glucose; maltose, starch.

Previous investigations showed that in rats exposed to cold from the 1st to the 7th days after birth there is very persistent inhibition of the rates of development of the enzyme systems concerned in the initial and final stages of intestinal carbohydrate hydrolysis. Meanwhile, similar exposure between the 10th and 17th days after birth stimulated the formation of mechanisms of membrane hydrolysis of starch and sucrose in rats [2-4].

The investigation described below was aimed at a further study of the effect of stressors on the formation of the intestinal function in the growing organism, and in particular, to characterize possible modifications at the stage of interaction between systems of carbohydrate hydrolysis and transport after cold stress to which the animals were exposed at different times of early postnatal development.

EXPERIMENTAL METHOD

Rats born in the laboratory animal house and kept in groups of eight to each lactating mother were divided into two groups. The rats of one group were exposed for 2 h daily to cold (6-7°C) from the 1st until the 7th day after birth, the animals of the other group were similarly exposed from the 10th until the 17th day. The rats of the control groups, like those of the experimental groups also, were taken from their mothers for 2 h daily and kept in an incubator at a thermoneutral temperature (33-35°C).

To obtain quantitative data, the animals were killed six at a time both from the experimental and from the control groups on the day of ending of exposure to cold and 1, 2, 3, and 7 weeks later. After sacrifice,

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