ACTION OF HYDROCORTISONE ON THE MITOTIC CYCLE OF MUCUS-FORMING CELLS OF THE GASTRIC FUNDAL EPITHELIUM

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It was shown by the use of thymidine-H^3 that a single injection of hydrocortisone in doses of 0.1 and 3 mg into male C57BL × CBA mice increases the length of the mitotic cycle but reduces the index of labeled nuclei and the mean diurnal mitotic index, thereby considerably inhibiting physiological regeneration of the mucus-forming cells of the gastric fundal epithelium. This may be the chief cause of weakening of the epithelial defensive barrier of the mucous membrane and of the formation of steroid gastric ulcers.

The mechanism of action of steroid hormones on the state of the mucosal epithelial defensive barrier of the stomach wall requires further investigation [6, 8, 9].

It has been shown [1, 3-5] that a characteristic property of the adrenocortical hormone hydrocortisone, when given in physiological doses, is to delay cell renewal in tissues with a short mitotic cycle. Under those conditions physiological doses of hydrocortisone had no action either on the mitotic cycle or on cell renewal of tissues with a longer mitotic cycle (the esophageal and corneal epithelium) [1,4].

On the basis of these experiments it was postulated that hormonal disturbances play a decisive role in the pathogenesis of duodenal ulcer on account of their influence on renewal of the mucosal epithelium [5, 6, 8, 9]. In view of the frequent occurrence of gastric ulcers it was decided to study how glucocorticoids act on the mitotic cycle and proliferative pool of the epithelial cells in different parts of the stomach.

The gastric epithelium is one of the tissues with a rapid rate of renewal [11-13]. The mucus-forming cells of the gastric fundal epithelium proliferate by mitotic division in the isthmus and neck of its glands [7, 13].

There are no data in the literature on the duration of the mitotic cycle or its phases in the cells of the epithelium lining the surface of the gastric fundus [14].

This paper describes the results of a determination of the duration of the mitotic cycle and its phases in mucus-forming cells of the gastric fundal epithelium under normal conditions and after administration of two different doses of hydrocortisone.

EXPERIMENTAL METHOD

Experiments were carried out on male C57BL × CBA hybrid mice weighing 20-23 g. The animals were divided into one control and two experimental groups.

The mice of the experimental groups received hydrocortisone (Gedeon Richter, Hungary) in a dose of 0.1 mg (small dose – group SD) and 3 mg (group LD) by intraperitoneal injection at 5 a.m. To determine the index of labeled mitoses (ILD) the animals received thymidine-H^3 (USSR, specific activity 1.4 Ci/mmole) in a dose of 0.7 μCi/g by injection at 6 a.m.

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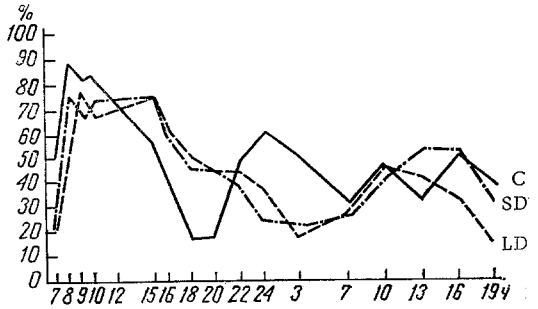

Fig. 1. Changes in percentage of labeled mitoses in mucus-forming cells of gastric fundus in control (C) and after injection of hydrocortisone in doses of 0.1 mg (SD) and 3 mg (LD). Abscissa, time of sacrifice; ordinate, ILM (in %). Abscissa on 24 h time.

The animals were sacrificed in groups of three at a time from each group at the following times after injection of thymidine: at 7, 8, 9, and 10 a.m., 12 noon, 3, 4, 6, 8, and 10 p.m. and midnight on the first day, and at 3, 7, and 10 a.m. and 1, 4, and 7 p.m. on the subsequent days.

To fix the material, Carnoy's mixture was injected into the stomach through the duodenum until both were filled [12]. Dewaxed sections through the fundus of the stomach (1-1.5 mm from the pyloric part), 5 μ in thickness, were coated with photosensitive type R emulsion (exposure 9 days), developed, stained with hematoxylin-eosin, and mounted in balsam. The percentage of labeled mitoses was calculated in 100 longitudinally sectioned gastric fundal glands in the surface-epithelial and mucous cells of the neck, at the various times after injection of thymidine-H^3 in the control and experimental groups of mice. The index of labeled nuclei (ILN) was also determined for the first four times of sacrifice taken together. The mean diurnal mitotic index was determined in sections not coated with emulsion. Graphs of these indices were then plotted against time for the experimental and control groups.

EXPERIMENTAL RESULTS

Changes in the percentage of labeled mitoses with time in the control and experimental groups are shown in Fig. 1. The curve representing the percentage of labeled mitoses shows that during the period of the experiment the mucus-forming cells of the gastric fundus in the mice of the control group passed through two mitotic cycles.

The method of Quastler and Sherman [15] was used to determine the following values of parameters of the mitotic cycle: T = 16 h, G_2 = 1 h, S = 8.5 h, M = 0.5 h (II), G_1 = 6 h. One mitotic cycle with a total duration T = 29 h was observed in the same cells in mice of one of the experimental groups (SD), with the following durations of its phases: G_2 = 1.5 h, S = 10 h, G_1 = 17 h.

Injection of hydrocortisone in a dose of 0.1 mg thus lengthened the post-synthetic period by 0.5 h, the period of DNA synthesis by 1.5 h, the presynthetic period by 11 h, and the mitotic cycle as a whole by 13 h. Injection of the large dose of the hormone lengthened the postsynthetic period by 1 h (G_2 = 2 h), and the period of DNA synthesis by 2 h (S = 9.5 h). However, the total duration of the mitotic cycle was the same after administration of large and small doses of hydrocortisone.

In these experiments, ILM in the control group was 9.2% and in the SD group 8%. Having regard to the small number of animals sacrificed at each time all that can be stated about the mitotic activity is that in these experiments the mean diurnal mitotic activity in the control group was 7.8 $^0/_{00}$ while in the SD group it fell to 5.1 $^0/_{00}$. According to Timashkevich [13] the mean diurnal mitotic activity for mucus-forming cells of the gastric fundal epithelium of intact C57BL mice is 10.4 $^0/_{00}$.

It can be concluded from the above description that the epithelium of the gastric fundal mucous membrane is a tissue with a short mitotic cycle (T = 16 h).

A single injection of hydrocortisone in small and large doses increased the duration of all phases of the mitotic cycle. The considerable slowing of physiological regeneration of the epithelium during the prolonged action of the hormone may increase the sensitivity of the mucous membrane of the gastric fundus to ulcerogenic factors and could be the chief cause of development of gastric ulcer. This mechanism can be taken to lie at the basis of the formation of steroid gastric ulcers.

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