EFFECT OF PROLONGED HISTAMINE STIMULATION ON CELL POPULATION OF THE FUNDAL GLANDS

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UDC 612.353.014.2.014.46:615.218.1

Chronic histamine stimulation produces regular structural changes in the gastric mucous membrane in dogs: the number of parietal, chief, and mucous cells increases considerably. As a rule this hyperplasia develops rapidly and starts from the neck of the gland. After the number of secretory cells has reached a maximum (which differs individually for each animal), further administration of histamine is ineffective.

Clinical and experimental studies have demonstrated that prolonged hypersecretion of acid gastric juice, from whatever cause, leads to the development of gastric and duodenal ulcers [2-4, 12]. However, the morphological basis of the hypersecretion has not yet been adequately studied.

Persistent hypersecretion with gastric and duodenal ulcers can be obtained experimentally by means of prolonged histamine stimulation [7, 12]. According to some reports, parenteral administration of histamine causes an increase in the number of parietal cells in guinea pigs [9], rats [6, 11], and dogs [16, 17]; the number of chief cells is also increased in dogs. However, according to other investigators [10, 14], prolonged histamine stimulation has no hyperplastic effect.

The character, times, and degree of changes in the different types of secretory cells in the gastric mucous membrane following administration of histamine have not yet been adequately studied, and a special investigation was therefore carried out for this purpose. It is important to determine the dynamics of structural changes in the gastric mucous membrane under these conditions not only because histamine is one of the most powerful stimulants of the gastric glands, but also because it is most probably the final physiological stimulus for the parietal cells [1, 8, 13].

EXPERIMENTAL METHOD

Experiments were carried out on four adult male dogs weighing from 14 to 18.9 kg, with a Bassov gastric fistula. A mixture of histamine with wax was injected daily for 11-60 days, in the evening, in a dose equivalent to 30 mg histamine base [7].

Every 3-6 days, gastric juice was obtained through the fistula and a specimen of the whole thickness of the mucous membrane of the body of the stomach obtained by biopsy. The pieces of tissue were fixed in Hamperl's fluid and embedded in paraffin wax. Sections were stained with hematoxylin-eosin; to count the parietal, chief, and mucous cells a combined staining method suggested by M. G. Shubich was used (Feulgen reaction, PAS reaction, active yellow 2K, alcian blue), staining the DNA of the nuclei, and cytoplasmic structures containing proteins and neutral and acid polysaccharides, with a good degree of contrast.

Cells were counted by means of an ocular micrometer in a square with length of side 0.1 mm on the microscope image (ocular 15, objective 40). Cells were counted in a specified volume of mucous membrane, shaped like a parallelepiped with base equal to 0.1 mm $\times 7\mu = 7 \times 10^{-4}$ mm^2 (thickness of section 7μ)

Department of Operative Surgery, Stavropol' Medical Institute. Department of Histology, Kuban Medical Institute. (Presented by Academician V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 70, No. 11, pp. 53-55, November, 1970. Original article submitted January 14, 1970.

TABLE 1. Changes in Number of Cells of Gastric Fundal Glands during Prolonged Histamine Stimulation (per 7×10^{-4} mm^2 surface of mucous membrane)

Dog number	Parietal cells						Chief cells						Mucous cells	
	neck of gland		body of gland		total		neck of gland		body of gland		total			
	1	2	1	2	1	2	1	2	1	2	1	2	1	2
1	3,3	38,0	31,2	144,5	34,6	182,5	1,0	18,8	70,2	166,4	71,2	185,2	3,5	9,8
2	7,4	29,2	23,9	147,8	31,3	177,0	1,2	14,0	71,3	180,1	72,5	185,2	14,8	15,6
3	10,4	49,9	80,7	214,4	91,1	264,3	0	5,4	163,7	118,6	163,7	120,4	13,0	13,3
4	4,4	25,2	43,2	163,1	47,7	178,9	1,4	2,3	91,7	156,8	93,1	157,7	4,9	11,0
$\bar{X}$	6,4	35,6	44,8	167,5	51,2	200,7	0,9	10,1	99,2	155,5	100,2	162,1	9,1	12,4
$\pm m$	1,72	6,0	13,79	16,97	15,52	21,19	0,34	4,0	22,69	14,93	22,43	15,73	2,75	1,41

Legend: 1) background; 2) maximum during administration of histamine–wax mixture.

[15]. To determine the true number of cells a correction was used [5]. The number of cells was counted separately into two zones: 1) in the neck, and 2) in the body and fundus of functional glands; the ratio between the length of the body and fundus and the length of the neck was taken as 3 : 1.

The results were expressed as the number of cells per unit surface (7×10^{-4} mm^2) of mucous membrane, which evidently corresponds to the number of cells in a specified volume of mucous membrane. For statistical analysis of the data, the original values and maxima observed in the course of the experiment were taken into account.

EXPERIMENTAL RESULTS

During prolonged histamine stimulation, despite individual differences, an increase in volume of gastric juice, and in the output of acid and pepsin was observed. The study of the character and degree of structural changes in the mucous membrane revealed a clear increase in the number of secretory cells in the fundal glands.

Hyperplasia of the parietal cells was found in all four dogs taking part in the experiment, hyperplasia of the chief cells was found in three dogs, and hyperplasia of the mucous cells in two animals. At the height of the secretory response to injected histamine the number of parietal cells was increased on the average by 339.5% (amplitude of individual variations from 189.8 to 465.5%), the number of chief cells was increased by 89.5% (69.4-159.7%), and the number of mucous cells by 78.1% (2.3-180%) (Table 1). Further administration of the histamine–wax mixture after secretion reached its maximum had no effect on the number of cells or actually reduced it slightly. The duration of stimulation leading to a maximum increase in the cell population of the fundal glands differed for the three types of cells. The dynamics of changes in some parts of the fundal glands showed partial changes in the number of parietal and chief cells. In animals with developing hyperplasia the increase in number of these cells began at the neck, where it was clearly visible by the third day and reached a maximum by the 6th-28th day. The number of parietal and chief cells reached a maximum in the body of the gland by the 6th-38th day. In three dogs (nos. 1, 2, 3) the degree of increase in the number of parietal cells in the neck of the gland was ahead of its increase in the body of the gland.

If the number of cells before the beginning of stimulation was taken as 100%, at the height of stimulation its maximum for the parietal cells in the neck of the gland was 644.7 ± 183.7% (394.6-1151.5%), and in the body of the gland 431.2 ± 85.6% (265.7-618.4%), and for the chief cells the corresponding figures were 1070.3 ± 586.1% (163.3-1880%) and 183.3 ± 43.7% (72.4-252.6%).

It is clear from Table 1 that under normal conditions the ratio between the number of parietal and chief cells in all animals was 1 : 2. Histamine stimulation disturbed this very stable ratio, changing it to 1 : 1 at its maximum in three dogs, and actually to 2 : 1 in one dog (No. 3). The results show that chronic histamine stimulation produces regular structural changes in the mucous membrane of the stomach: a marked increase in the number of parietal cells, chief cells, and mucous cells. As a rule this hyperplasia develops fairly rapidly and starts from the neck of the gland. After the number of secretory cells had reached a maximum, further administration of histamine is ineffective. This is probably due to the action of autoregulatory mechanisms controlling the level of cell populations of the fundal glands.

Hyperplasia of cells of the fundal glands observed in patients with peptic ulcer and with the Sollinger-Ellison syndrome may also be due to excessive stimulation of the secretory apparatus of the stomach (in the manner of working hyperplasia of the organ).

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