ROLE OF HISTAMINE H2 RECEPTORS IN THE MECHANISM OF FORMATION OF EXPERIMENTAL GASTRIC ULCERS INDUCED IN RATS BY VARIOUS STRESSORS

L. K. Gavroskaya and I. Yu. Agranovskaya

UDC 616.33-002.44-092.9-02: 616.45-001.1/.3

Dystrophic lesions of the gastric mucosa were observed to be formed and the pepsinogen content was reduced by 57% in the gastric mucosa of rats exposed to various experimental stressors (immobilization with electrical stimulation, immobilization at 6°C, trauma to or ligation of the pylorus). and the changes correlated with the degree of injury to the stomach. Pharmacological blockade of H2 receptors by cimetidine (100 μmoles/kg) and methiamide (410 μmoles/kg) largely prevented the formation of experimental ulcers and the decrease in the pepsinogen level. The results indicate that endogenous histamine participates in the mechanism of formation of dystrophic gastric lesions.

KEY WORDS: histamine H2 receptors; experimental gastric ulcers; pepsinogen; stress.

The role of endogenous histamine in the mechanism of formation of experimental gastric ulcers has recently attracted attention because of the introduction of substances blocking histamine H2 receptors and possessing a marked therapeutic effect.

The object of this investigation was to study the role of these receptors in the formation of experimental ulcers induced in rats by the action of various stressors, and also their role in changes in the tissue pepsinogen concentration.

EXPERIMENTAL METHODS

Experiments were carried out on male albino rats weighing 250-300 g deprived of food for 2 days but allowed water ad lib. Experimental ulcers were induced in the animals by exposure to various stressors: 1) ligation of the pyloric part of the stomach (by Shay's method), 2) trauma to the duodenal region (by Zavodskaya's method [4]), 3) fixation of the animals to metal grids in the outstretched prone position at 4-6°C (immobilization stress), and electrical stimulation of the immobilized animals (by Zabrodin's method [5]).

The animals of the experimental groups were decapitated 3 h after stimulation. A small group of animals (five rats) was kept for 24 h after stimulation. The stomachs were investigated, the number of lesions (ulcers, erosions) counted, and the index of damage calculated in millimeters by adding together the diameters of the lesions in each animal; the pepsinogen content in the fundus of the stomach was determined by the method of Anson and Myrsky [7], using bovine hemoglobin as the standard substrate. Proteolytic activity was determined against a scale of dilutions of a solution of standard crystalline pepsin (from Merck, West Germany), 1 mg of which was taken as 1 proteolytic unit.

In the experimental group which underwent ligation of the pylorus the volume of juice (in ml) and the titratable acidity as phenolphthalein (in meq/ml) were determined.

Cimetidine and methiamide, which block histamine H2 receptors, were injected intraperitoneally 20 min before and 1.5 h after the beginning of exposure to stress in doses of 100 and 410 μmoles/kg respectively. Each group of experimental animals consisted of 10 rats.

The results were subjected to statistical analysis and the degree of significance determined [6].

Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 8, pp. 151-153, August, 1979. Original article submitted August 9, 1978.

0007-4888/79/8808-0841$07.50

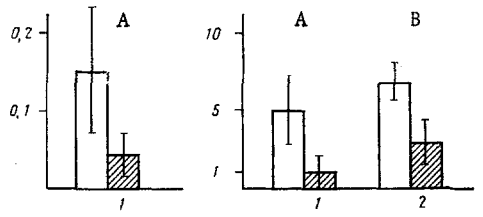

Fig. 1. Effect of H2 receptor blockers on formation of experimental ulcers induced by ligation of the pylorus (A) and by trauma to the duodenal region (B) of the rat stomach. Unshaded columns, exposure to stressors; shaded columns: 1) after preliminary administration of methiamide (410 μmoles/kg), 2) after preliminary administration of cimetidine (100 μmoles/kg). Ordinate: on left, HCl production (in meq), on right, index of damage (in mm).

TABLE 1. Degree of Damage to Mucosa and Pepsinogen Content in Animals with Experimental Gastric Ulcers

Indices of state of gastric mucosa	Intact animals	Immobilization and electrical stimulation		Immobilization at 6°C	
		without administration of drugs	after preliminary administration of cimetidine, 100 μmoles/kg	without administration of drugs	after preliminary administration of cimetidine, 100 μmoles/kg
Number of lesions per animal	0	8,0±2,0 (2,5—13,5)	0	8,0±1,1 (4,1—11,9)	0
	$n=10$	$n=10$	$n=10$	$n=10$	$n=10$
Index of damage, mm	0	8,0±2,0 (2,5—13,5)	0	15±2,8 (7,2—22,8)	0
Pepsinogen content in gastric mucosa, proteolytic units/mg tissue	12,1±1,6 (8,5—15,7)	5,3±0,4 (4,2—6,4)	7,7±0,9 (5,4—10,0)	5,0±0,9 (2,6—7,4)	10,1±1,2 (7,0—13,2)
	100%	$P<0,01$ 43,8%	$P<0,05$ $P_1<0,05$ 63,6%	$P<0,01$ 41,3%	$P<0,05$ $P_1<0,01$ 83,5%
Coefficient of correlation (r) between pepsinogen content and degree of damage	—	—0,70	—	—0,98	—

Legend. P) For comparison of data for intact and experimental animals; P_1) comparison of data within experimental group.

EXPERIMENTAL RESULTS

In all the experimental groups of animals exposed to stress lesions of the gastric mucosa were observed in the form of hemorrhagic erosions and ulcers. The index of damage of the animals in the group varied from 8 to 15 mm.

Lesions of the stomach were accompanied by a marked decrease, on average by 57%, in the pepsinogen content in the tissue. The pepsinogen content of the intact animals averaged 12.1 ± 1.6 proteolytic units/g tissue in animals deprived of food for the previous 2 days. The duration of starvation was not significantly reflected in the content of proteolytic enzymes.

Preliminary administration of histamine H2 receptor blockers methiamide and cimetidine largely prevented the development of lesions in the stomach (Table 1, Fig. 1). The index of damage in the animals with ligation of the pylorus was reduced from 5.0 ± 1.0 to 0.8 ± 0.6 mm, and in animals with trauma to the pylorus from 6.9 ± 0.5 to 2.9 ± 0.7 mm, and in those with electrical stimulation and immobilization, from 8.0 ± 2.0 to 0 mm. Simultaneously the drugs had a normalizing action on the pepsinogen contents in the stomach wall, although the proteolytic enzyme level did not reach that observed in the intact animals (Table 1).

In the animals with ligation of the pylorus methiamide inhibited gastric secretion. For instance, HCl production in animals receiving this drug averaged 0.04 meq per animal, whereas in the absence of the drug it was considerably more, namely 0.15 meq (Fig. 1).

Numerous investigations by S. V. Anichkov's school have demonstrated the role of central brain structure in the closure of pathological reflexes and also the role of the sympathetic nervous system in exhaustion of the catecholamine reserves leading to depression of energy metabolism in the cell, the main cause of development of dystrophic changes [1, 2]. Other humoral factors, especially an increase in the level of the hormone gastrin [10, 13], corticosteroid hormones, and also an increase in histamine biosynthesis, followed by a decrease [3], also play a role in the development of experimental gastric ulcers under the influence of stress. The study of the properties of new blockers of histamine H2 receptors in experiments on animals has shown that these drugs possess a marked ability to prevent gastric lesions induced by various factors (stress, drugs) [9, 13, 14]. The high therapeutic activity of these substances in clinical gastroenterology, for the treatment of peptic ulcers, has attracted particular attention [12, 15].

The results of the present investigation confirm those obtained by other workers who observed the antiulcerative effect of histamine H2 receptor blockers and indicate the important role of this amine in the mechanism of development of dystrophic lesions. Histamine [8], like catecholamines, through its action on the specific receptor cells, is known to activate the adenylate cyclase system, increasing the output of cyclic AMP in it, and, in the case of excessive stimulation, can disturb energy metabolism. This must evidently explain the pathological role of endogenous histamine in trophic disturbances. The increased secretory activity arising under the influence of free histamine may play the role of a secondary "aggressive" factor, acting on the mucous membrane in a state of dystrophy. The production of gastric juice during exposure to stressors is known to be considerably reduced [1]. In the present experiments with ligation of the pylorus, histamine H2 receptor blockers considerably reduced the output of HCl in the stomach, and this additional action also evidently has a preventive role.

The question of whether the chief peptic cells are involved in the dystrophic changes has so far received little study. The pepsinogen content in the tissues of the stomach is known to fall during the formation of experimental ulcers in rats [11]. The results of the present investigation confirm these findings and also demonstrate statistically significant correlation between the degree of damage in the stomach and the pepsinogen content. The ability of histamine H2 receptor blockers to prevent to some extent the fall in the pepsinogen level points to a possible role of endogenous histamine in this process. The correlation noted above means that the pepsinogen content in the stomach tissues can be used as a reliable indicator of the degree of the dystrophic changes.

LITERATURE CITED

1. S. V. Anichkov, I. S. Zavodskaya, E. V. Moreva, et al., in: Neurogenic Dystrophies and Pharmacotherapy [in Russian], Leningrad (1969), p. 56.
2. S. V. Anichkov, The Selective Action of Mediators [in Russian], Leningrad (1974), p. 212.
3. L. L. Grechishkin and T. K. Mustafina, Byull. Éksp. Biol. Med., No. 3, 31 (1970).
4. I. S. Zavodskaya, Byull. Éksp. Biol. Med., No. 1, 26 (1954).
5. O. N. Zabrodin, Annual Report of the Institute of Experimental Medicine for 1961-1962 [in Russian], Vol. 7-8, Leningrad (1963), p. 212.
6. R. B. Strelkov, A Method of Calculating Standard Error and Confidence Intervals of Arithmetic Means by Means of a Table [in Russian], Sukhumi (1966).
7. M. L. Anson and A. E. Myrsky, J. Gen. Physiol., 16, 69 (1932-1933).
8. R. I. Bersimbaev, S. V. Argutinskaya, and R. I. Salganik, Experientia, 27, 1389 (1971).
9. J. Bugajski, J. Hano, and L. Danek, Eur. J. Pharmacol., 36, 237 (1976).
10. L. R. Dragstedt, in: Surgery of the Stomach and Duodenum, Boston (1962), p. 461.
11. L. L. Grechishkin, Pharmacology, 13, 260 (1975).
12. D. J. Hetzel, G. J. Taggart, J. Hansky, et al., Med. J. Aust., 1, 317 (1977).
13. S. J. Konturek, T. Demitrescu, T. Radecki, et al., in: International Symposium on Histamine H2 Receptor Antagonists, London (1973), p. 247.
14. S. J. Konturek, T. Radecki, T. Demitrescu, et al., Digestion, 10, 267 (1974).
15. C. Richardson, B. A. Bailey, J. Walsh, et al., J. Clin. Invest., 55, 536 (1975).