MECHANISMS OF GASTRIC SECRETION IN DOGS INDUCED BY INFUSION OF HISTAMINE, CARBACHOL, AND PENTAGASTRIN

A. L. Korshak, A. F. Kosenko, and L. G. Shulyak

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H_2-Receptor blockade confirmed the view that histamine is a direct physiological stimulator of the parietal cells of the gastric mucosa [1, 6]. However, the hypothesis that histamine participates in the mechanism of gastric secretion as the final stage of extracellular regulation of the secretory process has been disputed. For instance, investigations on isolated parietal cells have demonstrated the existence of separate histamine, gastrin, and acetylcholine receptors [9]. Blockade of H_2-receptors by cimetidine revealed interconnection between individual receptors, in which gastrin receptors play the role of final stage in the secretory effects of different secretogens [10]. By blocking H_2-receptors cimetidine increases adenylate cyclase activity [3] during stimulation of secretion *in vitro* by tetragastrin, evidence of different pathways of acid secretion stimulated by histadine and gastrin.

The aim of this investigation was to study the mechanism of stimulation of gastric secretion during infusion of histamine, carbachol, and pentagastrin into the blood stream in chronic experiments on dogs with histamine receptors blocked by cimetidine.

EXPERIMENTAL METHOD

Chronic experiments were carried out on dogs with Basov's gastric fistulas and catheters permanently implanted into the jugular vein, after starvation for 16-18 h and in the absence of gastric secretion and with a neutral reaction of the gastric mucus. In background tests the level of gastric secretion was determined during intravenous infusion of histamine hydrochloride (0.1 mg/kg/h), carbachol (0.003 mg/kg/h) and pentagastrin (0.0002 ng/kg/h). After complete blockade of histamine secretion in the dogs by one-stage intravenous injection of cimetidine in a dose of 1.5-2.0 μg/kg, carbachol or pentagastrin was infused from the other

TABLE 1. Effect of Cimetidine on Gastric Secretion Stimulated by Histamine, Carbachol, and Pentagastrin in Dogs

Parameters of secretion	Secretion induced by		
	histamine	carbachol	pentagastrin
Volume of gastric juice, ml	336,00±32,05 / 0	327,40±11,30 / 234,75±16,67	410,00±39,24 / 295,75±27,71
Absolute secretion of free hydrochloric acid, meq/liter	44,71±6,47 / 0	25,37±1,33 / 19,98±0,94	58,52±5,69 / 41,28±4,52
Absolute secretion of pepsin, μg	18,92±2,89 / 0	23,00±3,10 / 35,21±6,19	53,10±4,24 / 43,89±6,07

Legend. Background tests shown in numerator; effect of cimetidine on stimulated gastric secretion in denominator.

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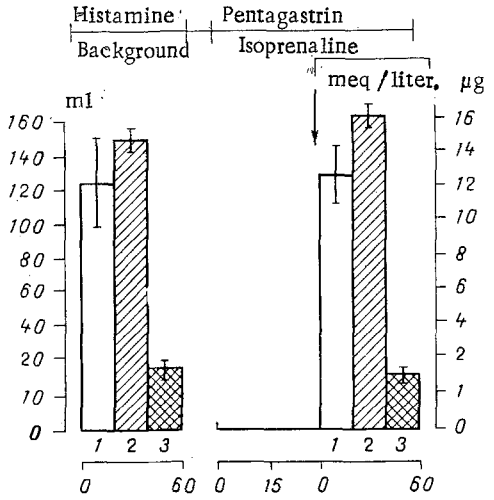

Fig. 1. Gastric secretion in dogs during infusion of pentagastrin, isoprenaline, and parenteral injection of histamine. 1) Volume of gastric juice, 2) free hydrochloric acid, 3) pepsin.

syringe of the infusion apparatus. In another series of experiments, after complete blockade of adrenergic receptors by isoprenaline, pentagastrin was infused from the same apparatus, and histamine was injected parenterally in the dose mentioned above. During investigation of gastric secretion the volume (in ml) was measured, free hydrochloric acid was titrated by Michaelis' method and pepsin by Hunt's method, after which the rate of production of free hydrochloric acid and pepsin was calculated. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

Infusion of histamine intravenously through a permanently implanted catheter evoked a marked secretory response of the gastric glands. For instance, during infusion of histamine for 90 min the volume of gastric juice was 336.0 ± 32.13 ml, and the absolute secretion of free hydrochloric acid was 44.71 meq/liter and of pepsin 18,92 μg. Intravenous injection of cimetidine in a dose of 1.5-2.0 mg/kg before the beginning of histamine infusion caused complete blockade of gastric secretion in response to histamine, but in some experiments, with the same dose of cimetidine, a very small but just perceptible secretory response of the gastric glands was observed.

The next investigations (Table 1) showed that H_2-receptor blockade by cimetidine, accompanied by intravenous infusion of histamine and carbachol or histamine and pentagastrin, gave a marked secretory response of the gastric glands to either stimulator of secretion. For instance, after intravenous injection of cimetidine followed by infusion of carbachol or of histamine and carbachol the volume of gastric juice was 74.7% of the background level, when secretion was determined in response to infusion of carbachol alone. During H_2-receptor blockade by cimetidine and infusion of carbachol the absolute secretion of free hydrochloric acid of the gastric juice was 78,7% and that of pepsin was 53.5% greater than in the control.

The free hydrochloric acid content determined in milliliters of gastric juice, incidentally, was unchanged compared with the background data, whereas the pepsin content in milliliters of gastric juice was greater.

Cimetidine also appreciably increased the secretion of visible gastric mucus. Infusion of carbachol in this case was accompanied by salivation, a characteristic feature of the action of carbachol on glands of the oral cavity in dogs.

During H_2-receptor blockade by cimetidine and infusion of pentagastrin or of histamine and pentagastrin, the volume of gastric juice in these experiments was 70.2% of the background level and the absolute secretion of free hydrochloric acid and pepsin was 70.3 and 80.2% respectively. Cimetidine reduced the absolute secretion of free hydrochloric acid and pepsin but did not change the content of these parameters of secretion in milliliters of gastric juice.

The other series of experiments showed that total inhibition of pentagastrin-induced gastric secretion by infusion of the β-adrenomimetic drug isoprenaline did not prevent gastric secretion in response to histamine. For instance, the volume of gastric juice in response to histamine was 142.0 ± 12.48 ml and the absolute secretion of free hydrochloric acid was 20.6 ± 2.87 meq/liter and of pepsin 3.4 ± 1.78 μg (Fig. 1). In background investigations, when histamine was injected by the same method, the parameters of gastric secretion were 130.46 ± 13.58 ml, 15.19 ± 2.71 meq/liter, and 4.57 ± 0.79 μg respectively. Differences in the parameters of gastric secretion were not statistically significant ($P > 0.05$).

The results are thus evidence that H_2-receptor blockade by cimetidine in a dose of 1.5-2.0 mg/kg completely inhibits gastric secretion to histamine and weakens the secretory response to carbachol and pentagastrin. Blockade of pentagastrin-induced gastric secretion by isoprenaline does not change the secretion of the gastric glands stimulated by histamine.

These experiments show that histamine, like pentagastrin, is not the final stage in the secretory process, by means of which these amines interact with the secretory cell of the gastric mucosa.

Histamine, carbachol, and pentagastrin evidently modify the inflow of calcium ions in the process of secretion, and stimulate inhibition of the adenylate cyclase system of the cell through the intermediary of adenylate cyclase and phosphodiesterase [4, 11]. Calcium ions are known to activate adenylate cyclase, and this precedes the increase in gastric secretion stimulated by the above amines [2]. H_2-receptor blockade by cimetidine, however, inhibits adenylate cyclase activity [8]. The decrease in gastric secretion following H_2-receptor blockade in response to infusion of carbachol and pentagastrin is in conformity with the view expressed above on the presence of interreceptor connection during gastric secretion [5, 12].

Inhibition of gastric secretion stimulated by pentagastrin on infusion of the β-adrenomimetic isoprenaline is evidently connected with the inhibitory effect of cyclic AMP [7].

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