EFFECT OF VAGOTOMY ON HISTAMINE GASTRIC SECRETION AND ITS INHIBITION BY CIMETIDINE

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After the results of investigations into the effect of histamine, gastrin, and cholinomimetics on secretion of isolated glandular cells from the gastric mucosa were published [10, 14] the discussion on the mechanism of the effect of secretogenic agents on gastric secretion could be considered to have been basically settled in favor of Grossman's concept [8] that there are only three types of receptors on glandular cells: acetylcholine, gastrin, and histamine. One of the essential factors of this concept is recognition that these receptors are interdependent. It has been shown, in particular, that pharmacological blocking of acetylcholine or histamine receptors induces marked inhibition of the other two types of receptors. Because of the absence of specific blockers of gastrin receptors, the problem with respect to them has not been solved. Investigations in this direction have been conducted chiefly by methods of pharmacological analysis, i.e., after pharmacological blockade of one or another receptor the action of substances exciting the other secretory receptors was tested. It was considered interesting to approach this problem from another aspect: not by blocking the receptor but by lowering the level of one of the endogenous exciting factors and, against this background, to test the action of the blocker and exciter acting on another receptor. This is done most easily from the technical point of view for acetylcholine and histamine receptors for, on the one hand, a specific blocker of histamine H_2 receptors is available in the form of cimetidine, and on the other hand, the level of secretion of endogenous acetylcholine in the gastric mucosa can be lowered by bilateral vagotomy.

EXPERIMENTAL METHOD

The secretion-stimulating effect of histamine in a dose of 0.055 mg/kg and the ability of cimetidine (0.013, 0.026, and 0.052 mg/kg) to inhibit this secretory effect were studied in experiments on three dogs with fistulas of the fundal portion of the stomach before and after bilateral transthoracic vagotomy. The volume of gastric juice secreted in 30-min samples was measured throughout the period of stimulating action of histamine (1.5 h). Total acidity in the gastric juice thus obtained was measured by titration by Michaelis' method, pepsin was determined by Hunt's method, and their total and half-hourly production was then calculated.

The ability of cimetidine to inhibit gastric secretion when stimulated by histamine (0.01 mg/kg/h) also was investigated in 18 patients with duodenal ulcer, of whom eight were treated by selective proximal vagotomy. The mean effect of inhibition of gastric secretion by cimetidine was compared in the patients of the two groups. The tests were carried out on three patients before and after the operation. The acid-producing function of the stomach was studied in the patients by an aspiration-titration method, with determination of the hourly hydrochloric acid production — basal and histamine-stimulated. Completeness of vagotomy in the secretogenic zone of the stomach was verified by the insulin test.

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TABLE 1. Effect of Vagotomy on Histamine Secretion and on Its Inhibition by Cimetidine in the Human Stomach

Substances administered	Histamine (0.01 mg/kg/h)	
	before vagotomy	after vagotomy
Histamine (0.01 mg/kg/h)	33,8±3,5	8,4±1,5
Histamine (0.01 mg/kg/h) + cimetidine (0.007 mg/kg)	10,6±2,3	1,8±0,5
Percent inhibition of histamine secretion	70,1±4,3	78,4±5,5

TABLE 2. Effect of Vagotomy on Histamine (0.055 mg/kg) Secretion and on Its Inhibition by Cimetidine in the Dog Stomach

Parameter studied	Before vagotomy				After vagotomy			
	histamine	histamine + cimetidine (0.013 mg/kg)	histamine + cimetidine (0.026 mg/kg)	histamine + cimetidine (0.05 mg/kg)	histamine	histamine + cimetidine (0.013 mg/kg)	histamine + cimetidine (0.026 mg/kg)	histamine + cimetidine (0.05 mg/kg)
Volume of juice, ml	49,5±3,7 (100%)	24,5±2,9 (50%)	17,3±2,2 (65%)	0 (100%)	116,2±10,0 (100%)	27,4±3,0 (74,5%)	8,6±1,4 (91,9%)	0 (100%)
Total acid production, mg	6,3±0,8 (100%)	3,0±0,3 (52,4%)	1,5±0,4 (74,4%)	0 (100%)	10,9±0,7 (100%)	3,1±0,5 (78,4%)	0,7±0,3 (94,7%)	0 (100%)
Pepsin production, mg	2,0±0,6 (100%)	1,0±0,4 (50%)	1,1±0,2 (50%)	0 (100%)	3,5±1,0 (100%)	0,8±0,1 (75,5%)	0,5±0,2 (80,4%)	0 (100%)

EXPERIMENTAL RESULTS

Vagotomy differed in its effect on histamine secretion in man and the dog. Whereas in the human subjects vagotomy depressed histamine secretion of hydrochloric acid by 70-75% (Table 1), in dogs it increased the volume of juice produced by 122% and the total acid production by 73% (Table 2). The pepsin production showed no significant change. It is unlikely that this difference could be due to the fact that in dogs a trunk vagotomy was performed, whereas in the human subjects it was a selective proximal vagotomy. In the first place, selective proximal vagotomy in the present investigation caused inhibition of histamine-secretion by a no lesser degree than trunk vagotomy; second, as Matrosova points out on the basis of a survey of the literature and our own data: "Differences in the results of different types of vagotomy are found only under special experimental conditions — when food secretion is studied in gastric pouches of Heidenhain type, after initial vagus denervation, and considered to be indicators of the action of antral hormone" [2]. In the present experiments tests were carried out not on a Heidenhain gastric pouch, but on the whole stomach.

Vagotomy in the human patients and dogs differed in its effect not only on the histamine gastric secretion but also on the ability of cimetidine to inhibit this secretion. In patients undergoing selective proximal vagotomy the relative degree of inhibition of histamine secretion was unchanged: 70.1 + 4.3% before the operation and 78.4 + 5.5% after the operation. However, in connection with the overall considerable weakening of histamine secretion after vagotomy the absolute decrease caused by cimetidine in the volume of acids produced was smaller. In dogs after vagotomy the ability of cimetidine to inhibit secretion was reduced and the secretion of hydrochloric acid was increased on average by 25% (Table 2). Considering that the general background level of histamine secretion was increased after vagotomy, in absolute values the inhibition of histamine acid secretion by cimetidine in vagotomized dogs was 255% greater than in dogs with intact vagus nerves. The rate of pepsin production showed no significant change under these circumstances.

The results of these experiments, showing that vagotomy in man weakens histamine secretion, are in agreement with those obtained by other workers [7, 12, 13]. Although most investigators consider that vagotomy does not change histamine secretion in dogs, there are no

indications in the literature of potentiation of the histamine secretory effect in vagotomized dogs [4, 5]. Changes in the effect of cimetidine after blocking of parasympathetic receptors and, in particular after vagotomy, have been studied much less thoroughly. According to Feldman et al. [6], pharmacological blockade of parasympathetic receptors enhances and deepens the inhibitory effect of cimetidine on secretion. In the only publication of which we are aware on the effect of vagotomy on the effectiveness of cimetidine, Kenyon [11] states that the ability of cimetidine to inhibit gastric secretion is sharply reduced after vagotomy.

The difference in the effect of vagotomy on the ability of cimetidine, which blocks histamine H_2 receptors, to inhibit histamine secretion in man and the dog must be considered to be due to the different action of vagotomy on histamine secretion itself in man and the dog. The first problem to arise is: Why does vagotomy in dogs not inhibit, but even potentiate histamine secretion? Inhibition of histamine secretion by vagotomy in man is in agreement with Grossman's concept of interconnection between the different receptors on glandular cells. The simplest solution would be to suggest that this interconnection between receptors is absent in dogs as a species trait. However, this is contradicted by the fact that atropinization of dogs causes marked inhibition of histamine secretion [1]. Consequently, the cause of the absence of an inhibitory effect of vagotomy on histamine secretion in dogs is more likely to be some form of compensatory mechanism. One such compensatory mechanism may be an increase in formation of the endogenous exciter of gastric secretion. The most likely candidates for this role are gastrin and histamine. An increase in gastrin formation in vagotomized humans and dogs is a firmly established fact [3, 9]. However, the fact that vagotomy in man inhibits histamine secretion but potentiates it in dogs suggests that besides gastrin, vagotomy increases the liberation of histamine in dogs. This suggestion is supported by the potentiation of the inhibitory action of cimetidine found in the present experiments in vagotomized dogs. The relative potentiation of the inhibitory effect of cimetidine in vagotomized dogs may perhaps be determined by the raised endogenous histamine level in these animals. This suggestion is supported by the fact that, with initially different levels of hydrochloric acid production in response to the same dose of histamine in dogs with intact and divided vagus nerves (6.3 + 0.8 and 10.9 + 0.7 meq hydrochloric acid), after injection of equal doses of cimetidine (0.013 mg/kg) in dogs with intact and divided vagus nerves approximately equal quantities of hydrochloric acid were secreted (3.0 + 0.3 and 3.1 + 0.5 meq). Because of the absence of any such mechanism in man, after vagotomy the level of histamine secretion falls and there was a corresponding decrease in the absolute inhibition of this secretory response by cimetidine.

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