EFFECT OF β-ADRENORECEPTOR EXCITATION ON GASTRIC SECRETION STIMULATED BY HISTAMINE, ACETYLCHOLINE, AND PENTAGASTRIN

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Although the problem of sympathetic regulation of gastric secretion has been a frequent subject for research in the last 50 years it is still by no means solved. This is largely due to technical problems associated with the difficulty of ensuring complete desympathization of the stomach and with vasoconstrictor effects of the sympathetic nervous system, which themselves may affect gastric secretion. These difficulties can be avoided by the use of pharmacological methods of analysis. However, investigations using these methods have yielded conflicting results. For example, some workers [1-4, 7] obtained a stimulating effect on gastric secretion or on individual components of the gastric juice under the influence of adrenomimetics, whereas others found marked inhibition of the basic indices of gastric secretion [5, 6, 10].

EXPERIMENTAL METHOD

Experiments were carried out on dogs with Basov—Pavlov gastric fistulas and with polyvinyl chloride catheters introduced into the jugular vein. The dogs took part in the experiments after starvation for 16-18 h. Gastric secretion was stimulated by intravenous infusion of carbachol (0.003 mg/kg in the course of 1 h), pentagastrin (0.0002 mg/kg in the course of 1 h), or histamine (0.1 mg/kg in the course of 1 h). Parallel with stimulation of gastric secretion, a solution of isoproterenol sulfate in physiological saline was infused intravenously in doses of 0.0125, 0.0250, 0.05, and 0.1 mg/kg in the course of 1 h. In one series of experiments propranolol (Inderal) (0.5 mg/kg in 1 h) and isoproterenol (0.05 and 0.1 mg/kg in 1 h) were infused simultaneously against the background of gastric secretion stimulated by carbachol. Gastric juice was collected in 30-min samples, the volume of which was measured (in ml), and its total acidity and free hydrochloric acid were determined by Michaelis' method, pepsin by Hunt's method, and the total increase in acid and pepsin was then calculated. The numerical results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

In control experiments during infusion of carbachol for 60 min 174.8 ± 12.2 ml of gastric juice with marked acidity (increase in acid production 15.56 ± 1.2 meq/liter, in free hydrochloric acid 13.44 ± 1.0 meq/liter) and with peptic activity (increase in pepsin 13.82 ± 4.0 mg) was secreted. Simultaneous injection of carbachol and isoproterenol inhibited gastric secretion (Fig. 1). During infusion of isoproterenol in a dose of 0.0125 mg/kg in 1 h a threshold inhibitory effect was observed, and subsequent injection of double doses of isoproterenol (0.025 and 0.05 mg/kg in 1 h) was accompanied by proportional potentiation of the inhibitory effect. However, although doubling the dose of isoproterenol again (0.1 mg/kg in 1 h) led to a further deepening of inhibition of gastric secretion, the degree of inhibition was no longer proportional to the dose of isoproterenol and the inhibitory effect was weakened. In the largest of the doses tested isoproterenol inhibited the intensity of gastric secretion by 70.1%, acid production by 82.3%, free hydrochloric acid by 83.2%, and pepsin by 82.3%. Complete inhibition of carbachol-stimulated secretion of gastric juice was not achieved. Analysis of these results shows that isoproterenol not only inhibited the intensity of secretion of gastric juice, but also reduced somewhat the concentrations of hydrochloric acid and pepsin in it. Infusion of isoproterenol inhibited not only the stimulated

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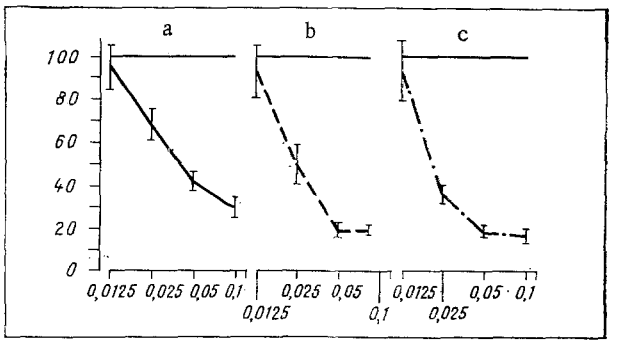

Fig. 1

Fig. 1. Effect of various doses of isoproterenol on gastric secretion stimulated by carbachol in dogs: a) volume of gastric secretion (in ml), b) increase in free hydrochloric acid (in meq/liter), c) increase in pepsin (in mg). Abscissa, dose of isoproterenol (in mg/kg in 1 h); ordinate, effect (in %, normal values taken as 100%).

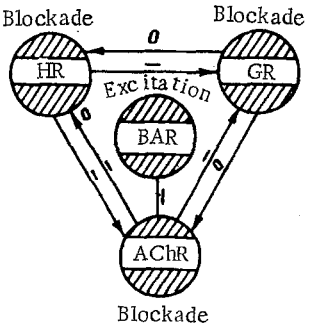

Fig. 2

Fig. 2. Diagram showing relations between receptors on parietal cells of gastric mucosa. HR) Histamine receptor, GR) gastrin receptor, β-AR) β-adrenoreceptor, AChR) acetylcholine receptor. —) Inhibition of secretion, 0) no effect.

gastric secretion, but also intensified salivation in response to injection of carbachol. Infusion of isoproterenol also had a marked inhibitory action on gastric secretion stimulated by pentagastrin (Table 1). This effect was more marked than during stimulation of gastric secretion by carbachol. The smallest dose of isoproterenol used (0.0125 mg/kg in 1 h), which was at the threshold level for its action on carbachol-induced secretion, inhibited pentagastrin-induced secretion by 77.9%, and reduced the increase in free hydrochloric acid by 85.3% and the increase in pepsin by 87.2%. In the last case, just as during carbachol-induced secretion, not only the intensity of secretion of gastric juice, but also its acidity, and pepsin secretion were reduced. If given against the background of carbachol-induced and pentagastrin-induced gastric secretion of equal intensity, isoproterenol in a dose of 0.0125 mg/kg in 1 h inhibited pentagastrin-stimulated secretion more strongly (by 75-80%). Starting with a dose of 0.025 mg/kg in 1 h, isoproterenol inhibited it completely. In the largest of its doses used (0.1 mg/kg in 1 h) isoproterenol did not give a significant inhibitory effect on histamine-stimulated gastric secretion. Against the background of simultaneous infusion of isoproterenol (0.1 mg/kg in 1 h) and pentagastrin (0.0002 mg/kg in 1 h), subcutaneous injection of histamine (0.1 mg/kg) induced gastric secretion which corresponded in all its indices to the secretory effect of histamine alone in the dose mentioned above.

During simultaneous infusion of carbachol (0.003 mg/kg in 1 h), isoproterenol (0.1 mg/kg in 1 h), and propranolol (0.5 mg/kg in 1 h) the inhibitory effect of isoproterenol on the intensity of secretion was reduced by 84%, but isoproterenol had no inhibitory effect on the other indices of gastric secretion.

These results are evidence that excitation of β-adrenoreceptors has a marked inhibitory effect on carbachol- and pentagastrin-induced gastric secretion. These findings agree with those obtained by Curwain et al. [11]. Since β-adrenomimetics increase the blood flow in the gastric mucosa, unlike α-adrenomimetics which reduce it, their inhibitory effect on gastric secretion is evidence that the secretory cells of the gastric glands contain β-adrenoreceptors. The specificity of the effects of isoproterenol on gastric secretion, stimulated by various agents, sheds some light on the mechanism of action of β-adrenomimetics. Excitation of β-adrenoreceptors evidently does not produce metabolic changes in the secretory cells of the gastric mucosa, but reduces their sensitivity to various mediators.

Comparative analysis of the effects of isoproterenol on secretory reponses of the stomach induced by pentagastrin, carbachol, and histamine showed that the ratio between them was 9:1:0. It can accordingly be concluded that isoproterenol specifically blocks gastrin receptors. On that basis it is possible to add to Grossman's concept [8] of the mechanisms of stimulation of parietal cells. Grossman considers that there are three types of receptors on parietal cells: gastrin, acetylcholine, and histamine receptors. Excitation of

TABLE 1. Effect of Isoproterenol and Propanolol on Gastric Secretion Stimulated by Histamine, Pentagastrin, and Carbachol (M ± m)

Index of gastric secretion	Histamine (0.1 mg/kg in 1 h)		Carbachol (0.003 mg/kg in 1 h)		pentagastrin (0.0002 mg/kg in 1 h)
	histamine + isoproterenol (0.1 mg/kg in 1 h)	histamine + Pentagastrin + isoproterenol (0.1 mg/kg in 1 h)	carbachol + isoproterenol (0.0125 mg/kg in 1 h)	carbachol + isoproterenol (0.1 mg/kg in 1 h) + propranolol (0.5 mg/kg in 1 h)	pentagastrin + isoproterenol (0.0125 mg/kg in 1 h)
Volume of gastric juice, ml	144,0±31,0 / 123,3±33,0	144,0±31,0 / 147,0±7,0	174,8±12,2 / 166,8±7,8	166,2±12,8 / 146,2±2,9	114,7±15,1 / 25,4±7,2
Increase in acid production, meq/liter	18,3±4,4 / 17,0±5,5	18,3±4,4 / 19,7±1,4	15,5±1,2 / 14,6±2,1	16,2±0,8 / 16,9±1,2	15,0±3,7 / 2,12±0,6
Increase in free hydrochloric acid, meq/liter	17,0±3,9 / 16,1±4,3	17,0±3,9 / 18,1±1,5	13,4±1,0 / 12,5±1,7	13,9±0,8 / 10,2±1,7	12,5±3,5 / 1,8±0,5
Increase in pepsin, mg	3,8±1,6 / 2,8±0,3	3,8±1,6 / 3,0±0,4	13,8±4,0 / 12,9±2,0	10,4±2,7 / 10,0±2,0	5,3±2,1 / 0,7±0,1

Legend. Numerator — control, denominator — experiment.

any one of these can lead to a secretory effect, for its action is based on preservation of functional excitability of the remaining two types of receptors. Blocking histamine receptors by cimetidine in fact weakened the secretory responses to gastrin and acetylcholine [9] and correspondingly, blockade of acetylcholine receptors by atropine weakened secretory responses to histamine and acetylcholine. However, this rule does not apply to the gastrin receptors, and Grossman's statement [8] that ". . . when a specific blocker of gastrin receptors is found it will inhibit the action of histamine and acetylcholine as well as of gastrin itself" can be confirmed.

Changes in excitability of each of the two principal types of receptors on the secretory cells of the stomach during inhibition of the third type of receptor, and also the effect of excitation of β-adrenoreceptors of all three types of receptors are reflected in the general scheme in Fig. 2. This scheme is based on the results of the present investigation and of data in the literature.

LITERATURE CITED

1. Yu. V. Anshelevich and K. V. Okun', Ter. Arkh., No. 2, 20 (1969).
2. Yu. V. Anshelevich, T. O. Zikmane, and K. V. Okun', Sov. Med., No. 4, 86 (1974).
3. L. L. Grechishkin, "Pharmacological analysis of the role of biogenic amines in gastric secretion processes," Author's Abstract of Doctoral Dissertation, Leningrad (1970).
4. I. M. Iof, Ter. Arkh., No. 1, 49 (1977).
5. A. L. Korshak and S. D. Groisman, in: Current Problems in the Diagnosis and Treatment of Diseases of the Digestive Organs [in Russian], Perm' (1978), pp. 29-34.
6. Yu. D. Popov, in: Fundamental Problems in Gastroenterology [in Russian], L'vov (1977), pp. 110-111.
7. A. Geumei, L. Issa, and J. Abd-el-Samil, Pharmacology, 7, 29 (1972).
8. M. I. Grossman, Mayo Clin. Proc., 50, 515 (1975).
9. M. I. Grossman and S. Konturek, Gastroenterology, 66, 517 (1974).
10. C. F. Code and A. P. Forrest, Pharmacol. J., 10, 447 (1954).
11. B. Curwain, P. Holton, and J. Spencer, Proc. Br. Pharmacol. Soc., 45, 1312 (1959).