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# MECHANISM OF ACTION OF AMINO ACIDS ON GASTRIC SECRETION

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It was I. P. Raznikov who first showed that proteins contained in food, when absorbed in the intestine and entering the blood stream, may act as stimulators of gastric secretion. These investigations pointed to the primary role of amino acids in that process. The study of the effect of amino acids on function of the digestive system has been continued in Shlygin's laboratory [5, 6].

However, the question of the mechanism of action of amino acids circulating in the blood stream on gastric secretory function has not yet been finally settled. Gastric secretion in its 3rd phase not only enables the final stage of digestion in the stomach to be completed, but it also helps to maintain intestinal digestion, by inducing the release of intestinal hormones. Elucidation of the mechanism of action of amino acids on the functions of the digestive tract is also directly linked with the solution to the clinical problems of parenteral feeding.

For a long time research workers are unable to distinguish between the action of amino acids entering the blood stream and the gastrin mechanism.

It was only by means of radioimmunoassay that it was shown that protein food from the intestine does not cause the serum immunoreactive gastrin level to rise [10]. However, the role of gastrin in the mechanism of action of parenterally administered amino acids on gastric secretion has not yet been solved.

To study this problem several series of investigations were conducted on dogs: experiments were set up using gastrin inhibitors and with direct determination of the blood gastrin level after intravenous injection of various amino acids (lysine, glutamine).

## EXPERIMENTAL METHOD

Milid-proglumide and secretin (Boots, England) were used as gastrin blockers. Milid was synthesized in Italy (Milid 200 $^{50}$, Rottalab, Monza, Milan). It contains a benzene ring and two isopropyl groups. As a result of substitution of the terminal amino acid of gastrin by these groups, milid acts as a competitive inhibitor of gastrin at the cell receptor level.

In experiments on three dogs with an isolated Pavlov gastric pouch the action of milid was studied on gastric secretion induced by intravenous injection of glycine and of casein hydrolysate. Milid was injected intravenously in a dose of 400 mg in 5 ml of solution before parenteral injection of nitrogenous substances; secretin was infused at the rate of 50 units/h intravenously after injection of the amino acid.

To study the blood gastrin level, experiments also were carried out on four dogs with an intact innervation of the stomach, but which had undergone operations by the techniques of Basov and Pavlov. The blood gastrin level was determined by radioimmunoassay using standard kits from CIS International (France). Blood samples were taken before and 1 h after the beginning of injection of the amino acid, and again h later, to coincide with the end of in-

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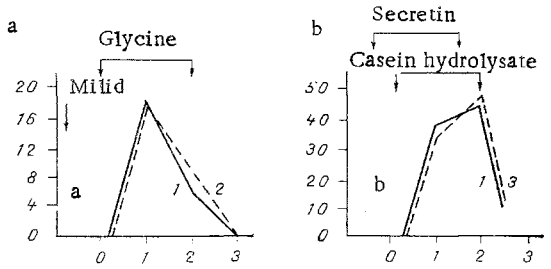


Fig. 1

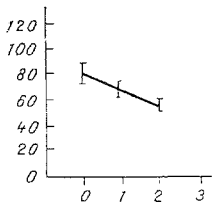

Fig. 2

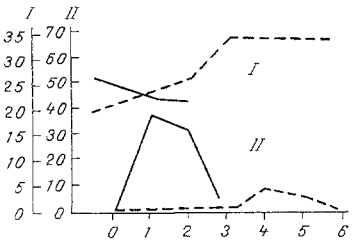


Fig. 3

Fig. 1. Absence of action of gastrin inhibitors (milid, secretin) on gastric secretion induced by glycine (a) and by casein hydrolysate (b). Abscissa, time (in h); ordinate, secretion (in ml). 1) Control; 2) milid; 3) secretin.

Fig. 2. Changes in serum gastrin concentration (in pg/ml) during intravenous injection of amino acids (lysine, glutamine). Abscissa, time (in h).

Fig. 3. Secretion of gastric juice (I) and change in gastrin concentration (II) in dogs fed with butter (broken lines) or receiving glutamine by intravenous injection (continuous lines). Abscissa (time, in h); ordinate: I) secretion (in ml); II) gastrin concentration (in pg/ml).

jection of the amino acid. Secretion of gastric juice was recorded every 15 min throughout the experiment. The blood gastrin level was investigated for comparison in dogs fed with fat (50 g of butter). Altogether 10 experiments were carried out to determine gastrin levels, in which 33 blood samples were tested.

## EXPERIMENTAL RESULTS

Secretion of gastric juice induced by injection both of glycine (0.3M solution) and of casein hydrolysate into the blood stream was not inhibited by milid (Fig. 1a). Statistical analysis of the results (of eight experiments) confirmed that there was no difference between the control and experimental data.

Another gastrin inhibitor, namely secretin, also was used. Many workers [12, 15] have demonstrated its inhibitory action on gastric secretion induced by gastrin. In the present experiments on dogs with intravenous infusion of pentagastrin (80 g/h) and secretin (50 units/h) this effect also was confirmed. Secretion induced by glycine or by casein hydrolysate (six experiments), however, was not inhibited by secretin (Fig. 1b).

Thus, neither milid or secretin affects gastric secretion induced by parenteral injection of the nitrogenous preparations in dogs with intact gastric innervation. These data are in agreement with the results of our previous investigations in which the same blockers were used [1, 3].

The blood gastrin level also was studied during intravenous infusion of amino acids (lysine, glutamine). These experiments showed that neither lysine nor glutamine increases the serum immunoreactive gastrin concentration throughout the secretory period of the stomach (Fig. 2). By contrast, in amimals fed with fat (butter) a marked rise of the serum gastrin level was observed 3-5 h after feeding (Fig. 3).

The results of the experiments with gastrin inhibitors, and also of determination of the blood gastrin concentration thus indicate that the gastrin mechanism, under ordinary conditions, does not participate in excitation of the gastric glands during parenteral injection of the amino acids studied.

These findings do not confirm the opinion expressed by many workers [9, 11, 13, 14] that gastrin participates in the mechanism of action of the amino acids, entering the blood stream, on gastric secretion. As our own investigations showed [6-8], this mechanism is linked with the action of amino acids (injected directly into the blood stream or absorbed from the intestine) on the nervous centers responsible for regulation of gastric secretion, and onward transmission of the signal along the vagus nerves to the gastric glands. This view is supported by the following facts: pharmacological blockage of the vagus nerves by atropine, platyphylline, or Arfonad (trimetaphan) strongly inhibits gastric secretion in response to

the entry of amino acids into the blood stream. Subdiaphragmatic vagotomy and denervation of the isolated gastric pouch also abolish the effect of amino acids on gastric secretion.

Experiments in which amino acids were injected into the carotid artery or a peripheral vein demonstrate that the action of the amino acids is located centrally [4]. Electroencephalographic investigations of hypothalamic structures, of the mesencephalic reticular formation, and of the cerebral cortex during intravenous injection of amino acids and also during their injection directly into the brain revealed the appearance of characteristic bursts of high-amplitude (50-150 μV), high-frequency (10-20 Hz) waves, not observed after intravenous injection of 5% glucose, of physiological NaCl solution, or of lipid emulsion [2].

These observations indicate that, besides nervous and hormonal mechanisms, there exists also a special form of regulation of gastric secretion, triggered by amino acids entering the blood stream. The amino acids act on brain structures, and the stimuli arising under these circumstances are transmitted along the vagus nerves to the gastric glands.

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