GASTRIN CATABOLISM IN THE DIGESTIVE TRACT

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It has been concluded from measurements of the arteriovenous difference of the blood gastrin concentration in blood vessels of the limbs, head, kidneys, stomach, intestine, and liver [4, 6, 7] that there are no significant differences in gastrin catabolism in these organs, nor is this peptide destroyed in the bloodstream [6].

The aim of this investigation was to study catabolism of "little" gastrin by determining the half-life of this peptide in vivo in different experimental situations.

EXPERIMENTAL METHOD

The half-life of little gastrin was determined in 22 mongrel dogs, for which purpose a single intravenous injection of synthetic human gastrin (SHG, from "Serva," West Germany) was given in a dose of 0.1 μg/kg. Blood samples were taken from a peripheral or the femoral vein before injection of gastrin and at fixed time intervals thereafter. The blood sera obtained were kept at −30°C. The gastrin concentration was determined with the aid of a kit from CIS International (France). To determine the half-life of the gastrin, the increase in the gastrin concentration in each blood sample was calculated relative to the basal level. The natural logarithm of this parameter was calculated. A graph was plotted to show dependence of this value on the time elapsing after the end of infusion of synthetic gastrin into the bloodstream (Fig. 1). We know that the decline of the concentration of a substance in the bloodstream after cessation of its infusion, especially in the case of gastrin, is exponential in character and can be expressed by the equation:

$$\text{пКГК}_t = \text{пКГК}_0 e^{k} e^{t}.$$

For a reduction of $iBGC_0$ by half we obtain:

$$\frac{1}{2}\,\text{пКГК}_0 = \text{пКГК}_0 e^{k} e^{T}$$

or, taking logarithms:

$$-\ln 2 = k_e T$$

or

$$T = \frac{-0{,}693}{k_e},$$

where $iBGC_0$ is the increase in the blood gastrin concentration relative to basal immediately after the end of gastrin infusion, $iBGC_t$ the increase in the blood gastrin concentration relative to basal at time t after the end of infusion, k_e the elimination constant of gastrin, and T the half-life of gastrin. By taking logarithms of the values of iBGC, the exponential dependence can be presented in the form of a linear function (Fig. 1). From the points obtained a linear graph reflecting the dependence of ln iBGC on time t by means of a linear regression equation can be plotted. The gradient of the straight line thus obtained, equal to the ratio of $(\ln iBGC_t - \ln iBGC_0)/t$, corresponds to the elimination constant of gastrin. Next, the half-life of gastrin is determined by the equation given above. The test of the rate of catabolism of little gastrin was repeated 11 times on animals in the initial state (group 1), 4 times after unilateral nephrectomy combined with division of the soft tissues of the thigh to simulate

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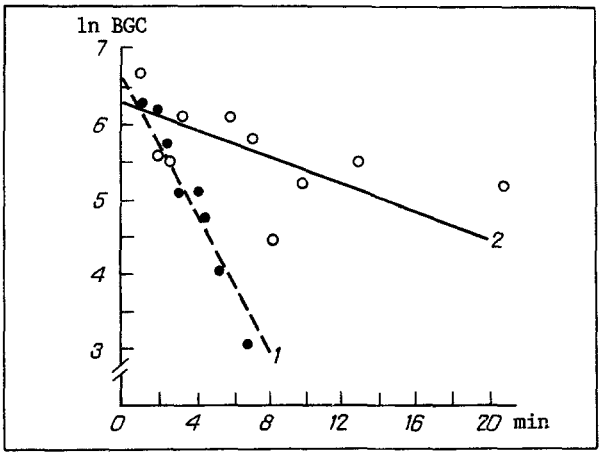

Fig. 1. Test of rate of gastrin catabolism. Straight lines show diminution of blood gastrin concentration in control (1, T = 1.58 min) and after vagotomy (2, T = 7.84 min).

TABLE 1. Half-Life (T) of Little Gastrin

Group of animals	n	T, min	t				
			1	2	3	4	5
1	11	2,3±0,27	—	—	—	—	—
2	4	1,97±0,35	0,66	—	—	—	—
3	14	6,63±1,13	3,46**	3,48**	—	—	—
4	6	4,39±0,98	2,9*	2,09	1,0	4	—
5	9	8,56±1,27	5,3**	3,36**	1,12	2,25*	—
6	6	9,09±2,60	3,57**	2,18	1,03	1,62	0,2

Legend. $*p < 0.05$, $**p < 0.01$.

operative trauma (group 2), 14 times after gastrectomy in acute and chronic experiments (group 3), 6 times after resection of the small and large intestine, excluding the duodenum and rectum (group 4), 9 times — after gastrectomy combined with resection of the intestine (group 5), and 6 times — after truncal vagotomy (group 6). All the experiments were done under pentobarbital anesthesia. The animals were given an overdose of pentobarbital at the end of the experiment.

EXPERIMENTAL RESULTS

The results are given in Table 1 and are evidence of a significant increase in the half-life of little gastrin after removal of the stomach and intestine (either separately or together). Gastrin catabolism also was retarded after vagotomy. It can be concluded from these results that catabolism of little gastrin takes place in the stomach and intestine, conjecturally on gastrin receptors of secretory cells. The parasympathetic division of the autonomic nervous system is involved in the regulation of gastrin catabolism. Vagotomy reduces the intensity of gastrin catabolism.

The arteriovenous difference of the blood gastrin concentration in vessels of the stomach has been investigated previously: some workers [4] studied gastrin clearance in the body of the stomach after compression of the boundary between antrum and body, and found a 30% arteriovenous difference in the blood gastrin concentration (just as in the other organs mentioned above), whereas others [8] did not compress the antrum — body boundary but stimulated the vagus nerve by electric pulses. In that study [8] the arteriovenous difference of the gastrin concentration in the vessels of the body of the stomach was 80%. We found that gastrin clearance in the body of the stomach is 52.1 ± 4.23% in the basal period, falling to 46.9 ± 6.76% during stimulation of endogenous gastrin secretion by perfusion of the antral portion of the stomach with acetylcholine [2]. They likewise did not compress the antrofundal boundary, for this procedure greatly distorts the results of measurement of the arteriovenous difference of the gastrin concentration in vessels of the body of the stomach. This may explain the absence of significant differences in the gastrin clearance in the body of the stomach and in other organs reported in [4]. According to our data, gastrin clearance for the organ as a whole in the kidney, spleen, and intestine amounts to 15.4-22.7% [2].

The results of the present investigation suggest the following mechanism of regulation of the gastric secretory function. In the first, cerebral phase of the secretory cycle, the parasympathetic division of the autonomic nervous system stimulates internal secretion of gastrin by antral G cells and activates the gastrin receptors of the secretory cells of the stomach. This last action can be realized through an increase in the number of receptors or a change in their configuration and an increase in their affinity for the gastrin molecule. Gastrin molecules take part in interaction with receptors and activate secretory cells. The gastrin molecule thereafter undergoes catabolism, conjecturally by one of three routes: fragmentation into small peptides followed by their utilization in the liver, internalization and degradation of lysosomes [1], and secretion of gastrin into the lumen of the gastrointestinal tract [5]. This mechanism ensures negative feedback for gastrin regulation of the secretory function of the stomach. An increase in gastrin internal secretion is accompanied by the formation of a larger number of gastrin-receptor complexes and, correspondingly, by acceleration of gastrin catabolism.

Considering the high rate of gastrin catabolism, it must be noted that the blood gastrin concentration reflects the difference between the intensity of internal secretion and of catabolism of gastrin. The suggested mechanism of gastrin regulation explains the hypergastrinemia observed in atrophic gastritis through marked slowing of gastrin catabolism on account of the absence of receptors on the secretory cells. The hypogastrinemia associated with duodenal ulcer may perhaps be due to acceleration of gastrin catabolism on a larger number of gastric secretory cells and, correspondingly, of receptors, than in healthy subjects. The hypergastrinemia after vagotomy is due to slowing of gastrin catabolism, and not to disinhibition of its internal secretion, as has been suggested [2]. Extensive resection of the small intestine leads to hypergastrinemia [3], which, according to the results of our own investigation, is due to a decrease in the intensity of gastrin catabolism.

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