Interaction of calcium and gastrin on gastric acid secretion in duodenal ulcer patients

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SUMMARY A dose response study of the effect on gastric acid secretion of synthetic human gastrin-17 in doses of 50, 200, and 500 ng/kg/h was performed in eight healthy volunteers and in eight patients with duodenal ulcer. The study was repeated on a separate day during intravenous infusion of calcium gluconate (0.1 mmol Ca^{2+} /kg/h). In healthy subjects the acid response to the combined infusion of synthetic human gastrin and calcium did not significantly exceed the response to synthetic human gastrin alone, in contrast with patients with duodenal ulcer in whom the combined infusion did significantly improve acid output compared with infusion of synthetic human gastrin alone. The dose of synthetic human gastrin required for half maximal acid response (D_{50}) was reduced in both groups but significantly more in patients with duodenal ulcer. No difference in serum gastrin concentrations or in serum calcium concentrations were found. It is hypothesised that extracellular calcium plays a role in gastrin stimulated acid secretion in man and that patients with duodenal ulcer are more sensitive to this calcium dependent mechanism than non-duodenal ulcer subjects.

Calcium may participate in the stimulation of gastric acid secretion in man by a dual mechanism – that is, by gastrin release^{1 2} and by an action directly on the parietal cell.^{1 3}

In previous studies it was found that calcium increases the sensitivity of the parietal cells to synthetic human gastrin in healthy subjects.³ Furthermore, that administration of verapamil decreases the sensitivity of the parietal cells to gastrin, suggesting that influx of calcium into the parietal cells is an essential step in the acid secretory process.⁴

The aim of the present study has been to investigate whether calcium dependence of the parietal cells is quantitatively different in normal subjects and patients with duodenal ulcer.

Methods

SUBJECTS

Nine healthy volunteers (five men and four women, aged 21–38 years) and nine patients with duodenal ulcer (six men and three women, aged 26–48 years) were studied. Each subject was studied twice on separate days. All gave informed consent.

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EXPERIMENTAL PROCEDURE

On the first day, synthetic human gastrin-17 (SHG, Imperial Chemical Industries, Cheshire, England) was infused. After an overnight fast, a Levin tube was placed in the stomach under fluoroscopic control. Intermittent mechanical suction producing a subatmospheric pressure of 150 mmHg was used in the collection of the secretion. Through a thin polyvinyl tube welded to the Levin tube, a marker substance was instilled into the stomach (⁵¹Cr-EDTA, flow 30 ml/h) to determine recovery. The opening in the polyvinyl tube was 10 cm proximal to the most proximal opening in the Levin tube. The volume of secretion collected was measured for each 15 minute period, and the concentration of H^+ and ⁵¹Cr-EDTA determined. Synthetic human gastrin was administered by continuous intravenous infusion in doses of 50, 200, and 500 ng/kg/h; each dose was administered for one hour.

On the second day, the experiment was repeated on a background infusion of calcium gluconate (0.1 mmol Ca^{2+} /kg/h). Infusion of calcium started one hour before the infusion of synthetic human gastrin and continued throughout the experiment – that is, for four hours. Calcium gluconate for infusion was prepared by the hospital's pharmaceutical department in a concentration of 0.66 mmol/ml of Ca^{2+} . For further dilution, 0.9% saline was used.

LABORATORY ANALYSIS

The concentration of H^+ was determined by titration with an autotitrator (Radiometer, Copenhagen) to pH 7.0. The concentration of ^{51}Cr -EDTA was determined in a well counter. The volume of the secretion and the output of H^+ were corrected to the actual recovery by the marker substance instilled. Repeated estimations of osmolality by freezing point reduction were taken as an index of the degree of duodenal reflux.⁵ Serum calcium concentration was determined by atomic absorption spectrophotometry and serum gastrin concentration was measured radioimmunochemically.⁶

CALCULATIONS

Correction for non-recovered gastric juice was done for every 15 minute sample according to the formula:

$$V_{cor} = V_{asp} \times C_{inf}/C_{asp}$$

where V_{cor} is the corrected volume, V_{asp} the aspirated volume, C_{inf} the number of 'counts' infused, and C_{asp} the number of counts aspirated.

In the calculations acid output in the last two 15 minute periods of each synthetic human gastrin dose was used.

The dose of synthetic human gastrin required for one-half maximal acid secretion (D_{50}) and the calculated maximal response were calculated by linear transformation of the Michaelis-Menten equation according to Dowd-Riggs:

$$V = CMR - D_{50} (v/d)$$

where v is acid response and d , the dose of synthetic human gastrin administered. These calculations were performed on the individual data by computerised estimation of the regression line according to the method of least squares. For the statistical analysis, paired t test and the coefficient of correlation (r) were used. Values of $p < 0.05$ were considered significant.

Results

Acid secretion in the control subjects is shown in Fig. 1 and in patients with duodenal ulcer in Fig. 2. In healthy subjects calcium increased the acid response to the lowest dose of synthetic human gastrin (50 ng/kg/h) significantly, whereas the integrated acid output over the total dose range of synthetic human gastrin was not significantly increased. This is in contrast with findings in duodenal ulcer patients where calcium significantly increased the integrated acid output to synthetic human gastrin.

Calculated maximal response and D_{50} are shown in Table 1. No significant difference was found

Fig. 1 Gastric acid secretion in eight healthy subjects during infusion of increasing doses of synthetic human gastrin and during infusion of synthetic human gastrin + calcium.

between control subjects and patients with duodenal ulcer. Calcium infusion did not alter calculated maximal response in healthy subjects, whereas calculated maximal response was non-significantly increased in patients with duodenal ulcer. D_{50} was reduced significantly in both groups, 55% in patients with duodenal ulcer and 29% in the control group. Reduction of D_{50} was significantly greater in the patients than in the control subjects.

Serum gastrin concentrations are shown in Table 2. No difference was found between patients and control subjects. This is true also for serum calcium concentration (Table 3).

Fig. 2 Gastric acid secretion in eight duodenal ulcer patients during infusion of increasing doses of synthetic human gastrin and during infusion of synthetic human gastrin + calcium.

Table 1 Calculated maximal response (mmol H⁺/h) and D₅₀ for synthetic human gastrin (pmol/kg/h) during infusion of synthetic human gastrin alone and during infusion of synthetic human gastrin + calcium

	D ₅₀		Calculated maximal response	
	C	DU	C	DU
Synthetic human gastrin	138	129	34.2	33.8
Synthetic human gastrin + calcium	98	58	36.5	40.3

C = control subjects, DU = duodenal ulcer patients.

Table 2 Serum gastrin concentrations (pmol/l) in duodenal ulcer patients (DU) and control subjects (C) during infusion of synthetic human gastrin and during infusion of synthetic human gastrin + calcium

		Dose of synthetic human gastrin (pmol/kg/h)			
		0	25	100	250
- Calcium infusion	DU	18±2	44±3	248±75	580±100
	C	16±2	46±4	215±65	520±90
+ Calcium infusion	DU	20±2	52±4	235±55	525±80
	C	19±2	49±3	200±50	535±90

Table 3 Serum calcium concentration (mmol/l) in duodenal ulcer patients (DU) and control subjects (C) during infusion of synthetic human gastrin and during infusion of synthetic human gastrin + calcium

		Dose of synthetic human gastrin (pmol/kg/h)			
		0	25	100	250
- Calcium infusion	DU	2.35±0.06	2.39±0.08	2.32±0.06	2.33±0.09
	C	2.34±0.04	2.40±0.04	2.40±0.05	2.38±0.06
+ Calcium infusion	DU	2.34±0.04	2.58±0.02	2.65±0.06	2.81±0.11
	C	2.47±0.03	2.63±0.07	2.71±0.05	2.82±0.08

Discussion

It is well documented that calcium is able to induce gastric acid secretion in man.⁷ One mechanism is by release of antral gastrin,^{1,2,8} where transport of calcium over the cellular membrane seems to play a role in the stimulus-secretion coupling in the gastrin cell.² Another mechanism by which calcium may stimulate acid secretion is by a direct effect on the parietal cell where transmembrane influx seems to be an essential step as suggested by previous studies on the effect of calcium antagonists.^{3,4}

In gastrin stimulated acid secretion calcium flux across the cell membrane or alteration of membrane calcium may be part of a second effector system,⁹ a concept which is indirectly supported by our previous studies.^{3,4} If this is true the increased sensitivity could be due to an increased sensitivity to calcium or to facilitated influx of calcium into the parietal cell. The present study shows that the same amount of calcium administered to healthy subjects and to patients with duodenal ulcer, significantly increased the acid response to synthetic human gastrin and reduced D₅₀ in the patients.

This finding, as well as previous studies^{3,4} support, although indirectly, the view that influx of calcium across or into the cell membrane plays a role

for gastrin stimulated acid secretion, and furthermore that patients with duodenal ulcer are more sensitive to this mechanism than healthy subjects.

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