Oxyntomodulin (glucagon-37 or bioactive enteroglucagon): A potent inhibitor of pentagastrin-stimulated acid secretion in rats

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The action of oxyntomodulin and glucagon on pentagastrin-stimulated gastric secretion from the perfused rat stomach have been compared: both hormones inhibit secretion in a dose-dependent manner.

In the last decade, it has been suggested that glucagon and/or 'gut glucagon-like immunoreactive peptides' may play a physiological role in the regulation of gastric acid secretion (1,2). We have recently isolated from the distal small bowel a 37-amino-acid glucagon-related peptide referred to as 'bioactive enteroglucagon' or glucagon-37 (3,4) that displayed a tissue specificity at the gastric level. Indeed, in contrast to its lower potency versus glucagon in liver, this peptide was about 20 times more potent than glucagon in stimulating cyclic AMP in isolated rat fundic glands (5). Accordingly, we proposed to call this peptide 'oxyntomodulin' (5).

The purpose of the present work was to compare the action of oxyntomodulin and glucagon on the stimulated gastric acid secretion in the rat. We used the perfused stomach in the anesthetized rat, which seems suitable to study the inhibition caused by drugs of stimulated acid secretion (6).

Materials and Methods

Operative technique

Male Wistar rats weighing 300 ± 25 g were fasted for 18 h before experiments but were allowed access to water. The technical aspects of the operation have been described by Ghosh and Schild and modified by Lai (7). The rats were anesthetized with urethane (0.6 to 0.7 ml of a 25% solution per 100 g) given by intramuscular injection.

A polyethylene catheter, introduced into the oesophagus and passed to the level of the cardia, was connected to a peristaltic pump (Desaga) set to deliver a solution of 0.9% NaCl at a constant rate of 0.8 to 1.0 ml/min. The perfusate was collected through another catheter placed through the pylorus and secured with a ligature. Whenever necessary, the temperature of the rats was maintained at 34°C with the aid of electric lamps.

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A 0.5-mm butterfly catheter was introduced into the dorsal vein of the penis in order to infuse the stimulants. A 0.45-mm needle joined to a 602-105 silastic tube was introduced into a fundic branch of the coeliac artery, thus permitting direct injection of the substances to be tested into the fundic area.

**Pharmacological agents and doses used**

Pentagastrin (Peptavlon ICI) 0.125 µg·kg⁻¹·h⁻¹; histamine (Sigma) 1.5 mg·kg⁻¹·h⁻¹; glucagon (Novo, Copenhagen) 0.3 to 4 nmol·kg⁻¹; oxyntomodulin (Bataille et al., submitted) 0.01 to 0.2 nmol·kg⁻¹; somatostatin (Clin Midy, France) 1.2 nmol·kg⁻¹. The last three agents were dissolved in 0.1 ml of saline.

**Experimental protocol**

The tests were begun after stabilization of the gastric perfusion, usually within 30 to 60 min after completion of the surgical preparation. The gastric secretion, diluted with the perfusate of 0.9% NaCl, was collected every 20 min and the acidity was measured by titrating the entire sample with 0.01 N NaOH to the phenolphthalein end-point. Pentagastrin and histamine were infused at a rate of 2.4 ml·h⁻¹. The plateau stimulation was obtained 1.5 h after the beginning of infusion. Glucagon and oxyntomodulin were carefully administered as a 0.1-ml bolus and the catheter rinsed with 0.1 ml of saline. The injections, performed in random order, were separated by an interval of 2 h. Each experimental group consisted of 5 or 6 rats, and 98 rats were used for the present study.

**Expression of results**

Changes in gastric secretion were evaluated during the 40-min period following injection and expressed as % of inhibition, the plateau value being taken as the reference.

**Results**

Gastric-acid secretion induced by pentagastrin was readily inhibited by both glucagon and oxyntomodulin. A linear log-dose effect was obtained for both (see Fig. 1). The apparent ID₃₀ were 1.26 and 0.086 nmol·kg⁻¹ body wt. for glucagon and oxyntomodulin, respectively. As little as 10 pmol·kg⁻¹ oxyntomodulin was able to produce a significant effect (see Fig. 1).

Table 1 displays the comparative effect of oxyntomodulin, glucagon, and somatostatin on pentagastrin- and histamine-stimulated acid secretion. At doses where the three peptides were able to produce a 50% inhibition when pentagastrin was the stimulant, the decrease in histamine-induced secretion was less than 10% for the peptides of the glucagon family and not significant for somatostatin.
Fig. 1. Dose-effect of oxyntomodulin (G-37) and pancreatic glucagon (G-29) on pentagastrin-stimulated gastric acid secretion in anesthetized rat. Data (means ± S.E.M.) are expressed as % of inhibition as a function of the amount (in nmol/kg body wt.) of peptide injected (see 'Materials and Methods'); the plateau value obtained with the perfusion of pentagastrin was taken as the reference (0%). The dotted line represents the observed 50% inhibition used for estimating the ID50 for both peptides (see results). The number of experiments performed with each dose of peptide is indicated near each experimental point.

Table 1. Comparative effects of oxyntomodulin, glucagon, and somatostatin, at dosage levels inhibiting by 50% the pentagastrin-stimulated secretion, on histamine-stimulated secretion

<table>
<thead>
<tr>
<th>Drug and dose (nmol/kg)</th>
<th>Inhibition (%) of pentagastrin-stimulated secretion</th>
<th>Inhibition (%) of histamine-stimulated secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxyntomodulin 0.086</td>
<td>50</td>
<td>9.6 ± 0.6</td>
</tr>
<tr>
<td>Glucagon 1.26</td>
<td>50</td>
<td>6.2 ± 2.2</td>
</tr>
<tr>
<td>Somatostatin 1.2</td>
<td>50</td>
<td>5</td>
</tr>
</tbody>
</table>

Means ± S.E.M., n = 7.
Discussion

The present data clearly show that, in anesthetized rat, both pancreatic glucagon and a newly isolated glucagon-like intestinal peptide, oxyntomodulin, are able to inhibit pentagastrin-stimulated acid secretion in a dose-dependent manner. On a molar basis, oxyntomodulin is, in our experimental conditions, 10-20 times more potent than glucagon. It is noteworthy that a similar ratio between the potencies of the two peptides has been previously observed in gastric glands isolated from the rat oxyntic area (5), which suggested the presence in those glands of a specific oxyntomodulin-sensitive system (5,8). The present data strongly support the idea (3) that the glucagon-related peptides are operative through this system on pentagastrin-stimulated acid secretion. The existence of a direct effect of these peptides on the oxyntic glands is further supported by the fact that 5-10 times lower doses of either glucagon or oxyntomodulin are necessary when injected in situ (fundic branch of the coeliac artery) than when injected in systemic blood (data not shown). The quantitative ultrastructural changes and the increase in gastric potential difference induced by glucagon (9) could be facilitated by this local administration.

Our data on histamine-stimulated gastric acid secretion are in agreement with the results obtained by Wilson (10); they should, however, be examined in light of the poor effect of peptides on this secretion, which is well documented in the case of somatostatin (6).

It has been suggested that 'enteroglucagon' released during the intestinal phase of digestion plays a role in the regulation of gastric secretion (11). The glucagon-like intestinal peptide involved could well be oxyntomodulin. Indeed, the effect of low doses of oxyntomodulin on gastric-acid secretion evidenced by the present data together with with the predominance of this peptide among the glucagon-like bioactive peptides in porcine (4) and human (12) gut argue in favor of this regulatory function.

Although the precise mechanisms involved in the inhibition of gastric secretion by oxyntomodulin have to be explored more deeply both from a physiological and a biochemical point of view, our data suggest that this intestinal peptide plays a key role in the regulation of the intestinal phase of gastric secretion.

References


