Stimulation of Gastric Acid Secretion in the Rhesus Monkey

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Similar maximal rates of gastric acid secretion are achieved with histamine and gastrin stimulation in human, dog, or cat, but gastrin produces higher rates than histamine in the rat. Gastric acid secretion was measured in seven nonsedated, alert, chaired rhesus monkeys (Macaca mulatta). Dose-response studies were performed using intravenous histamine or tetragastrin. These studies showed histamine to be a much more efficacious and more potent stimulant of gastric acid secretion than tetragastrin in the monkey. Both histamine and tetragastrin had similar potency and efficacy in the dog, while tetragastrin, pentagastrin, and hog heptadecapeptide were similarly less active than histamine in the monkey. Background carbachol (4 μg/kg/hr) did not affect the histamine or tetragastrin dose-response curves. Histamine stimulation with background tetragastrin (64 μg/kg/hr) did not produce a dose-response curve statistically different from histamine alone. Tetragastrin stimulation with background histamine (60 μg/kg/hr) increased the tetragastrin dose-response curve, with a probable additive effect. We conclude that the rhesus monkey differs from cat, dog, and man in that gastrin and its analogs are not able to stimulate maximal acid secretion to the level achieved by histamine.

In man, cat, and dog similar maximal rates of gastric acid secretion are seen with histamine, gastrin, and gastrin analog stimulation (1–4). On the other hand, histamine is a poorer stimulant in rat unless H1 antagonists or a pure H2 agonist is given (5). The similarity of the maximal rates of gastric acid secretion in response to histamine and gastrin has been used as evidence that gastrin and histamine stimulate acid secretion via a common pathway. We compared histamine and tetragastrin in the rhesus monkey (Macaca mulatta) with the expectation that this similarity would also be found in the subhuman primate. Instead, we found in our initial studies that histamine stimulated higher maximal rates of gastric acid secretion than the gastrin analog, tetragastrin. We therefore embarked on a series of experiments to verify this observation by studying the effects of pentagastrin and hog gastrin heptadecapeptide as well as tetragastrin over a wide range of dosages. We also tested tetragastrin with low background levels of other secretagogues.

MATERIALS AND METHODS

Surgical Procedures. Seven monkeys (Macaca mulatta, weighing 2.9–7.7 kg) were surgically prepared with a fistula of the entire stomach drained by a plastic cannula (6). Secretory studies started no earlier than 21 days after surgery. Tests were performed on alternate days and no more often than three times a week.

Secretory Stimulants. The stimulants for gastric acid secretion studies were tetragastrin (L-Trp-L-Met-L-Asp-L-Phe amide) (Research Plus Laboratories, Inc., Denville, New Jersey); pentagastrin (Ayerst Laboratories, New York, New York); histamine hydrochloride (Aldrich Chemical Company, Inc., Milwaukee, Wisconsin); hog...
gastrin (kindly supplied by R.A. Gregory, Liverpool, England), and carbamylcholine chloride (carbachol) (Sigma Chemical Company, St. Louis, Missouri). Throughout each test 0.15 M NaCl was given by continuous intravenous infusion at the rate of 20 ml/hr with a peristatic pump.

**Test Procedure.** The monkeys were transiently tranquilized with fentanyl and droperidol and placed in restraint chairs the evening before testing. They fasted for 18 hr prior to testing. During testing they were alert and without sedation. Gastric secretions were collected by gravity drainage every 10 min. Volume was measured to the nearest 0.1 ml and acid concentration was determined by titration with 0.2 m NaOH to pH 7 on an automatic titrator (Radiometer, Copenhagen, Denmark).

Basal secretion was collected for four 10-min periods before giving stimulants. Secretagogue was given in a stepwise manner, that is the lowest dose was given for 40 min and the dose was doubled each 40 min until all doses had been given. The mean rate of gastric secretion (µmol/10 min) during the final two 10-min periods was used as the rate of secretion for analysis.

**Statistical Analysis.** The monkeys were tested twice with each experimental regimen except for the combination studies using tetragastrin and histamine, which were tested once in each animal. The mean acid secretory rate at each dose for individual monkeys was determined by averaging the two studies. The mean secretory rate for all the monkeys tested was plotted on the dose-response graphs. Differences in means were evaluated for significance with Student’s t test. The maximal rate of acid secretion for a given experiment was taken to be the highest rate of secretion on a dose–response graph where doses of secretagogue were given over a sufficient range to observe diminished rates of acid secretion with supramaximal doses.

**RESULTS**

**Comparison of Maximal Rate of Gastric Acid Secretion Achieved with Histamine and Gastrin Analogs.** Seven monkeys were each tested with doses of histamine from 10 to 1280 µg/kg/hr and tetragastrin from 2 to 128 µg/kg/hr. Each monkey was tested twice with both secretagogues for a total of four experiments in each of seven monkeys. The dose–response curves showed that acid secretory rates peaked and then diminished over the range of dose studies (Figure 1). Maximal acid secretion was 289 ± 28 µeq/10 min in response to tetragastrin and 731 ± 140 µeq/10 min for histamine (P < 0.01).

The possibility that tetragastrin might not be as potent a stimulant of gastric acid secretion in the monkey as pentagastrin or hog gastrin heptadecapeptide was evaluated in two monkeys tested with these agents over a range of doses from 0.25 to 16

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