PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **189**, 325–328 (1988)

Inhibition of Gastric Acid Secretion by Peptide YY Is Independent of Gastric Somatostatin Release in the Rat[1] (42814)

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Abstract. The purpose of this study was to determine whether the inhibitory action of peptide YY (PYY) on gastric acid secretion is attributable to the release of gastric somatostatin in rats. Two groups of rats (six rats/group) were anesthetized with urethane and prepared with gastric fistulas and jugular catheters. Pentagastrin (18 μg/kg-h) was given intravenously for 150 min to stimulate gastric acid secretion. Intravenous PYY (130 μg/kg-h) inhibited pentagastrin-stimulated gastric acid secretion significantly ($P < 0.05$). Administration of iv PYY resulted in a 41% reduction ($P < 0.05$) in pentagastrin-stimulated gastric acid secretion. In another group of anesthetized rats, administration of PYY (10^{-7}, 10^{-8} *M*) failed to stimulate a release of somatostatin from the isolated-perfused rat stomach. Our findings indicate that PYY can inhibit gastric acid secretion independently of release of gastric somatostatin in the rat.

Peptide YY (PYY) is a 37 amino acid peptide recently isolated by Tatemoto and co-workers (1, 2) from porcine duodenal extracts. Peptide YY is found primarily in the distal ileum, colon, and rectum of several species (3–5). Intravenous administration of PYY results in an inhibition of pentagastrin-stimulated acid secretion in the dog and man (6–9). Whether PYY inhibits gastric acid secretion through the release of gastric somatostatin is not known. The purpose of this study, therefore, was to determine whether the inhibitory action of PYY on gastric acid secretion is due to release of gastric somatostatin.

Materials and Methods. *Animals.* Adult male Long-Evans rats (375 ± 50 g) were purchased from Harlan-Sprague-Dawley (Indianapolis, IN) and maintained in air-conditioned (23 ± 2°C) and light-regulated (lights on 0500–1900 hr) animal quarters. All rats were fasted in wire-bottom cages for 18–24 hr with free access to water before the gastric acid secretion experiments. All peptides were obtained from Peninsula Laboratories (Belmont, CA).

Rats (six rats/group) were anesthetized with urethane (1.25 g/kg, ip). They were then prepared with gastric fistulas as described below. Rats were then given pentagastrin alone (18 μg [23 nmole]/kg-h, iv) for 150 min to stimulate gastric acid secretion or in combination with PYY (130 μg [31 nmole]/kg-h, iv). PYY was given for 50 min during the middle segment of pentagastrin administration (i.e., 50–100 min). Preliminary studies showed that lower doses of PYY did not inhibit pentagastrin-stimulated gastric acid secretion. Although this dose of pentagastrin is above the ED_{50} for gastric acid stimulation, this dose causes persistent stimulation of gastric acid secretion in the rat preparation.

Measurement of gastric acid secretion. Rats were prepared with fistulas under urethane anesthesia. In brief, a laparotomy was done and the gastric cardia was ligated without damaging the vagus. The pylorus was also ligated. An opening was made into the

[1] Supported by grants from the National Institutes of Health (5R37 DK 15241 and PO1 DK 35608, RO1 DK 37406).

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0037-9727/88 $1.50

anterior wall of the stomach and a gastric cannula was secured with a purse-string suture. The cannula was a double-lumen tube which allowed us to infuse saline intragastrically and to collect gastric secretions. After a stabilization period of 30 min and thorough flushing of the stomach with saline, experiments were started. Ten-milliliter aliquots of saline were flushed through the stomach every 10 min. Gastric secretions were collected and analyzed for acid output.

Gastric acid output was determined by titration with 0.01 *N* NaOH to pH 7.0 by means of an autotitrator.

Isolated-perfused rat stomach. Male rats were anesthetized with pentobarbital sodium (50 mg/kg) following an overnight fast (15–18 hr). Perfusion of the stomach was done as described by Saffouri and colleagues (10). The vasculature of the stomach was perfused via the celiac artery with oxygenated medium 199 containing 0.2% bovine serum albumin at a rate of 2 ml/min at 36°C. Portal vein effluents were collected for radioimmunoassay (RIA) of somatostatin levels as described earlier (11). This somatostatin antiserum does not recognize other gut or pancreatic peptides. The sensitivity of the somatostatin RIA is 2 pg/tube. The intra- and interassay variances are 8 and 12%, respectively. The gastric lumen was perfused with saline via a catheter introduced through the gastroesophageal junction and drained via a catheter introduced through the pylorus. After an equilibration period of 20 min, bombesin (10^{-8} *M*), PYY (10^{-7}, 10^{-8} *M*), or PYY plus bombesin was given for 15 min. Six isolated-perfused rat stomachs were tested in each treatment group.

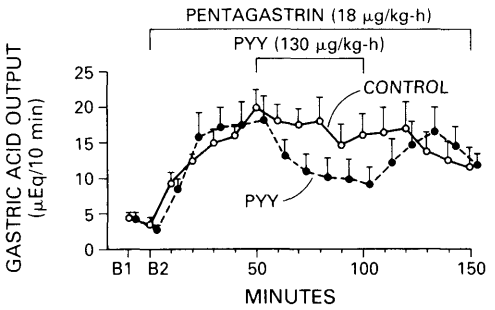

FIG. 1. Gastric acid output in response to iv pentagastrin alone or in combination with iv PYY.

TABLE I. PYY INHIBITION OF PENTAGASTRIN-STIMULATED GASTRIC ACID SECRETION

Gastric acid output (μeq/10 min)[a]	
Without PYY (20–50 min)	With PYY (70–100 min)
17.6 ± 3.1	9.8 ± 2.7*

[a] Values (mean ± SEM) are expressed as mean gastric acid output per 10 min during the 30-min period.
* $P < 0.05$ versus gastric acid output without PYY.

Statistics. Data are given as the mean ± SEM. Data were evaluated by analysis of variance followed by a Newman–Keuls test (12).

Results. Gastric acid secretion increased and remained elevated in response to intravenous administration of pentagastrin (Fig. 1). Administration of iv PYY during the middle segment of pentagastrin administration (50–100 min) resulted in a 41% reduction in pentagastrin-stimulated gastric acid secretion during the last 30-min (70–100 min) segment. Table I shows the mean gastric acid output per 10-min period during the last 30-min period of PYY administration. Pentagastrin-stimulated gastric acid output was significantly decreased during iv administration of PYY.

Administration of PYY (10^{-7}, 10^{-8} *M*) (10^{-7} *M* data not shown) to the isolated-perfused rat stomach failed to stimulate release of gastric somatostatin (Fig. 2). In contrast, administration of bombesin resulted in a release of gastric somatostatin. In addition, PYY did not inhibit bombesin-stimulated release of somatostatin.

Discussion. The present study demonstrates that intravenous administration of PYY can inhibit pentagastrin-stimulated gastric acid secretion in rats. These data agree with earlier reports which showed that PYY inhibited gastric acid secretion in the dog and man (6–9). In addition, the present study shows that the inhibition of gastric acid secretion by PYY is not attributable to

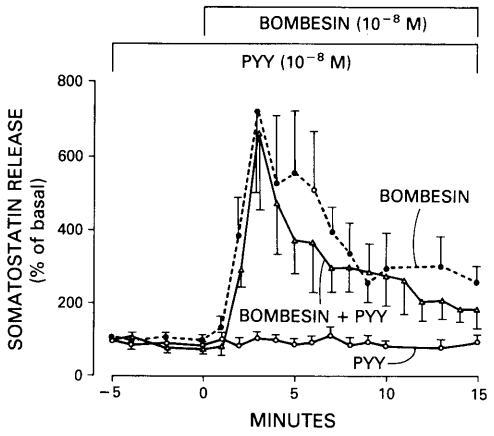

FIG. 2. Somatostatin release from the isolated-perfused rat stomach in response to bombesin, PYY, or bombesin plus PYY.

the release of gastric somatostatin by PYY in the rat.

In this study, approximately an equimolar dose of PYY (31 nmole/kg-h) inhibited pentagastrin-stimulated (23 nmole/kg-h) gastric acid secretion. The observation that the inhibitory action of PYY on gastric acid secretion is not due to somatostatin release stands in contrast to the action of other gut peptides (i.e., cholecystokinin [CCK], gastric inhibitory polypeptide [GIP]) which inhibit secretion of gastric acid (13, 14). CCK and GIP have been shown to inhibit gastric acid secretion, at least in part, by stimulation of release of gastric somatostatin (13, 14). Somatostatin has been shown to be a potent inhibitor of gastric acid secretion (15).

The dose of PYY chosen for the *in vivo* experiments was 130 μg/kg-h which is approximately equivalent to 30×10^{-9} nmole/kg-h. We chose this dose of PYY since lower doses of PYY were ineffective *in vivo* in the rat. As mentioned in the description of the experimental design, this dose of PYY approximates the dose of pentagastrin used in these experiments. In the isolated perfused rat stomach experiments, we used both 10^{-8} and 10^{-7} *M* PYY and both doses of PYY failed to modify release of somatostatin.

In a separate study (16), we have reported that PYY can inhibit gastric acid secretion in rats given intragastric cysteamine. Cysteamine is a thiol that can selectively deplete gastric stores of somatostatin when given intragastrically (17–19). Together, the findings of the present report along with the cysteamine study suggest that PYY can inhibit gastric acid secretion independently of gastric somatostatin.

1. Tatemoto K, Mutt K. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. Nature (London) **285**:417–418, 1980.
2. Lundberg JM, Tatemoto K, Terenius L, Hellstrom PM, Mutt V, Hokfelt T, Hamberger B. Localization of peptide YY (PYY) in gastrointestinal endocrine cells and effects on intestinal blood flow and motility. Proc Natl Acad Sci USA **79**:4471–4475, 1982.
3. Taylor IL. Distribution and release of peptide YY in dog measured by specific radioimmunoassay. Gastroenterology **88**:731–737, 1985.
4. Adrian TE, Ferri G-L, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology **89**:1070–1077, 1985.
5. Greeley GH Jr, Hill FLC, Spannagel A, Thompson JC. Distribution of peptide YY in the gastrointestinal tract of the rat, dog, and monkey. Regul Pept **19**:365–372, 1987.
6. Pappas TN, Debas HT, Goto Y, Taylor IL. Peptide YY inhibits meal-stimulated pancreatic and gastric secretion. Amer J Physiol **248**:G118–G123, 1985.
7. Adrian TE, Savage AP, Sagor GR, Allen JM, Bacarese-Hamilton AJ, Tatemoto K, Polak JM, Bloom SR. Effect of peptide YY on gastric, pancreatic, and biliary function in humans. Gastroenterology **89**:494–499, 1985.
8. Guo Y-S, Singh P, Greeley GH Jr, Thompson JC. Peptide YY: Effect of peptide YY on cephalic, gastric and intestinal phases of gastric acid secretion and on gastrointestinal hormones. Gastroenterology **92**:1202–1208, 1987.
9. Guo Y-S, Fujimura M, Lluis F, Tsong Y, Greeley GH Jr, Thompson JC. Inhibitory action of peptide YY on gastric acid secretion. Amer J Physiol **253**:543–548, 1987.
10. Saffouri B, Weir GC, Bitar KN, Makhlouf GM. Gastrin and somatostatin secretion by perfused rat stomach: Functional linkage of antral peptides. Amer J Physiol **238**:G495–G501, 1980.
11. Guo Y-S, Mok L, Cooper CW, Greeley GH Jr, Thompson JC, Singh P. Effect of gastrin-releasing peptide analogs on gastrin and somatostatin release from isolated rat stomach. Amer J Physiol **253**:G206–G210, 1987.

12. Snedecor GW, Cochran WG. Statistical Methods. Ames, IA, Iowa State Univ Press, 7th ed, 1980.
13. Soll AH, Amirian DA, Park J, Elashoff JD, Yamada T. Cholecystokinin potently releases somatostatin from canine fundic mucosal cells in short-term culture. Amer J Physiol **248:**G569–G573, 1985.
14. Wolfe MM, Reel GM. Inhibition of gastrin release by gastric inhibitory peptide mediated by somatostatin. Amer J Physiol **250:**G331–G335, 1986.
15. McIntosh CHS. Gastrointestinal somatostatin: Distribution, secretion and physiological significance. Life Sci **37:**2043–2058, 1985.
16. Greeley GH Jr, Gomez G, Lluis F, Thompson JC. Peptide YY inhibition of gastric acid secretion in the rat is independent of exogenous somatostatin. Gastroenterology **90:**1436, 1986. [Abstract]
17. Szabo S, Reichlin S. Somatostatin in rat tissues is depleted by cysteamine administration. Endocrinology **109:**2255–2257, 1981.
18. Patel YC, Peirzchala I. Cysteamine induces a loss of tissue somatostatin-$28_{(15-28)}$-like immunoreactivity but not when assessed as somatostatin-$28_{(1-4)}$-like immunoreactivity: Evidence for the importance of the disulfide bond for cysteamine action. Endocrinology **116:**1699–1702, 1985.
19. Brown MR, Fisher LA, Sawchenko PE, Swanson LW, Vale WW. Biological effects of cysteamine: Relationship to somatostatin depletion. Regul Pept **5:**163–179, 1983.

Received March 28, 1988. P.S.E.B.M. 1988, Vol. 189.
Accepted July 29, 1988.