Inhibitory Effect of Somatostatin on Gastric Acid Secretion in Rats

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Abstract—Effects of somatostatin on parasympathetically induced increases in gastric acid secretion and mucosal blood flow (MBF) were studied in anesthetized rats with a gastric fistula. Intravenous infusion of small doses of somatostatin (0.1–0.5 μg/kg/min) dose-dependently inhibited the increases in the vagally stimulated gastric acid secretion. Larger doses of somatostatin (0.5–2.5 μg/kg/min) also dose-dependently inhibited the bethanechol-induced gastric acid secretion. The dose of somatostatin required to inhibit the gastric acid secretion by about 50% of the preinfused control values was 0.25 μg/kg/min for vagally stimulated acid secretion and 2.5 μg/kg/min for bethanechol-induced acid secretion. Thus, the inhibitory potency of somatostatin on the vagally stimulated gastric acid secretion was about 10-fold higher than that on bethanechol-induced acid secretion. Somatostatin had no effect on the increase in gastric MBF during vagus nerve stimulation or bethanechol infusion. Pretreatment with indomethacin or phentolamine had no effect on the inhibitory effect of somatostatin on the increase in gastric acid secretion during vagus nerve stimulation or bethanechol infusion. These results suggest that somatostatin exerts an inhibitory effect on gastric acid secretion by acting on the parasympathetic neurons in the gastric wall more than on the structures peripheral to the parasympathetic nerve terminals, and it reduces parasympathetically stimulated gastric acid secretion in rats. This inhibitory effect of somatostatin on the gastric acid secretion is independent of the changes in the gastric MBF and probably not related to prostaglandin-involved or alpha adrenoceptor-mediated mechanisms.

Immunohistochemical investigations have demonstrated that somatostatin-like immunoreactivity (SLI) is present throughout the gastrointestinal tract (1, 2), and SLI is localized in both D-cells and neurons (3, 4). In the antrum, D-cells are located close to gastrin cells (G-cells), while in the oxyntic mucosa, they lie in the vicinity of parietal cells (5). Somatostatin-containing nerve cell bodies locate in both the myenteric and submucosal plexuses (3, 6).

Somatostatin exerts a wide range of effects on gastro-intestinal functions: e.g., regulation of motility, inhibition of the release of gut peptides and inhibition of gastric acid secretion (7, 8). The inhibitory effect of somatostatin on acid secretion have been shown to result from a direct effect on the parietal cells or a secondary effect on G-cells. The mechanisms involved in the inhibitory effect of somatostatin on the acid secretion, however, are complex and much less clearly understood. Chew (9) proposed that inhibition of gastrin-stimulated gastric acid secretion by somatostatin is partly mediated via inhibition of histamine release. Prostaglandin-mediated inhibition of acid secretion by somatostatin was also claimed by Ligumsky et al. (10). Furthermore, in vitro studies have demonstrated that somatostatin inhibits parietal cell function via an inhibition of cyclic AMP production (11).

In the present study, we examined the effect of somatostatin on parasympathetically...
stimulated gastric acid secretion and mucosal blood flow in rats. Our findings led to the conclusion that somatostatin acts on the parasympathetic neurons in the gastric wall more potently than the structures peripheral to the postganglionic parasympathetic nerve terminals to reduce the parasympathetically stimulated gastric acid secretion.

Materials and Methods

Male Wistar rats weighing about 350 g, deprived of food overnight, were used in the present experiments. While they were under urethane anesthesia (1.0 g/kg, i.p.), the bilateral femoral veins were cannulated for infusion of drugs. The right femoral artery was cannulated to collect blood samples. The esophagus was ligated, and bilateral vagus nerves were carefully separated and cut in the cervical region. The peritoneal cavity was opened by a small midline incision; a round-tip polyethylene cannula (3.5 cm in length and 0.4 cm in diameter) was inserted into the stomach via an incision in the duodenum. The cannula was held in place by two ligatures around the duodenum, one at the oral site and the other at the anal site of the duodenal incision, and the abdominal incision was then sutured. After washing out the stomach with saline, 2.0 ml of gastric solution, prewarmed at 38°C, was instilled and replaced with fresh solution at 15 min intervals. The gastric solution was composed of a 1/5 (v/v) mixture of glycine/mannitol adjusted to 300 mOsmole and to pH 3.5 by addition of 0.1 N of HCl, according to Blair et al. (12). Two successive collections of basal acid secretion were made to confirm that there were steady levels of secretion. After these collections, gastric acid secretion was stimulated either by an intravenous infusion of bethanechol (10 μg/kg/min) or by continuous stimulation of the peripheral end of the left cervical vagus nerve, using bipolar platinum electrodes, as described in our previous papers (13-15). The stimulus parameters used were square-wave pulses of 0.5 msec duration, at 3 Hz, of supramaximal intensity (0.5 mA). The bethanechol-induced gastric acid secretion was abolished by atropine (0.1 mg/kg, i.v.), but was not influenced by hexamethonium (2 mg/kg, i.v.). The vagally stimulated gastric acid secretion was abolished by atropine (0.1 mg/kg, i.v.) or hexamethonium (2 mg/kg, i.v.), as shown in the previous papers (13, 14). Levels of gastric acid secretion were determined as follows: the gastric samples recovered from the stomach every 15 min and 2.0 ml of fresh solution (pH 3.5) were titrated to pH 7.0 with 0.01 N of NaOH, using a pH meter. By subtracting the latter from the former titration, acid contents secreted for 15 min were calculated and expressed as μEq/15 min.

Gastric mucosal blood flow (MBF) was measured by the aminopyrine clearance technique developed by Jacobson et al. (16). Thirty min after a primary dose of aminopyrine (30 mg/kg, i.v.), the same agent (6.6 mg/kg, hr) was infused in a volume of 2.3 ml per hour through the femoral vein, throughout the experiment, to maintain a constant blood level of aminopyrine. For the stabilization of aminopyrine concentration in the circulating blood, 1 hr was allowed to elapse before the start of each experiment. Arterial blood samples (0.5 ml) were obtained before and after each experiment through the cannula inserted into the femoral artery. The level of aminopyrine in the plasma and gastric samples was assayed by the method of Brodie and Axelrod (17). The plasma level of aminopyrine at each 15 min interval during the experimental period was estimated by interpolating between two measured points, just before and after each experiment, and then paired with each aminopyrine level in the gastric juice (18, 19). After these measurements, the gastric MBF was calculated to be gastric output of aminopyrine (μg/15 min)/arterial plasma aminopyrine (μg/ml). Thus, gastric MBF was expressed as ml/15 min.

Somatostatin (0.1–2.5 μg/kg min) was infused through the femoral vein for 30 min to observe its effects on basal and parasympathetically stimulated gastric acid secretion and MBF. In some experiments, indomethacin (10 and 50 mg/kg, i.p.) or phentolamine (5.0 mg/kg, i.m.) was administered 45 min before the start of vagal stimulation or bethanechol infusion. The doses of indomethacin or phentolamine were determined on the basis of the findings in previous reports.
Since the absolute values of acid secretion and MBF varied with individual animals, the effects of somatostatin infusion on the gastric parameters were expressed as percentage of the values observed before somatostatin infusion. Results were expressed as the mean±S.E. Statistical significance was compared with the values of the corresponding control rats, using Student’s t-test for unpaired comparisons.

The following drugs were used: betahanechol chloride and indomethacin (Sigma, Chemical Co., St. Louis, MO); phentolamine mesylate (Ciba-Geigy, Basel, Switzerland); and somatostatin-14 (Protein Research Foundation, Osaka, Japan).

**Results**

**Effects of somatostatin on gastric acid secretion and MBF increased by vagus nerve stimulation:** The basal gastric acid secretion and MBF immediately before electrical stimulation were 4.4±0.8 μEq/15 min and 2.6±0.4 ml/15 min (n=10), respectively. In preliminary experiments, graded doses of somatostatin (0.1, 0.25, 0.5, 1.0 and 2.5 μg/kg/min) were infused intravenously for 30 min after the basal acid secretion had reached a steady level. Somatostatin had no significant influences on the basal acid secretion and MBF (data not shown). When the vagus nerve was continuously stimulated (0.5 mA, 3 Hz, 0.5 msec duration), gastric acid secretion and MBF gradually increased, reaching a steady level within 60 min, this steady level was maintained for at least 2 hr, as described in previous reports (13, 15). Thus, infusion of somatostatin was carried out for two consecutive 15-min collection periods from 90 min after the beginning of vagal stimulation. Intravenous infusion of somatostatin (0.1, 0.25 and 0.5 μg/kg/min), superimposed on vagal stimulation, caused a dose-dependent reduction in gastric acid secretion. Maximal inhibitory effects on the acid secretion were obtained at the second 15 min collection period. In this period, the mean inhibitions in the somatostatin-infused rats, expressed as a percent of the preinfusion control values, were: 27.3% (0.1 μg/kg/min, n=4), 38.5% (0.25 μg/kg/min, n=4) and 63.1% (0.5 μg/kg/min, n=4) (Fig. 1). In subsequent studies, a dose of 0.25 μg/kg/min was used. Infusion of somatostatin (0.25 μg/kg/min) significantly decreased the vagally increased acid secretion, but had no effect on the MBF (Fig. 2). The acid secretion and MBF immediately before the administration of somatostatin were 74.1±2.5 μEq/15 min and 15.1±2.5 ml/15 min (n=10), respectively.

**Effects of somatostatin on gastric acid secretion and MBF increased by betahanechol infusion:** The basal gastric acid secretion and MBF immediately before betahanechol infusion were 4.3±0.4 μEq/15 min and 3.3±0.3 ml/15 min (n=10), respectively. After the onset of betahanechol infusion (10 μg/kg/min), acid secretion and MBF both gradually increased to reach higher steady levels within 60 min; this level was nearly equal to that of the vagally stimulated gastric acid secretion.
secretion and was also maintained for at least 2 hr, as described in a previous paper (14). Then, infusion of somatostatin was carried out for two consecutive 15-min collection periods, 90 min after the beginning of bethanechol infusion. Infusion of a small dose of somatostatin (0.25 μg/kg/min) had no significant effect on acid secretion and MBF (Fig. 3). The acid secretion and MBF in the second 15-min collection period were, respectively, 91.0±6.7% and 112.9±7.0% of the preinfusion values at 0.25 μg (n=5). The acid secretion and MBF immediately before the administration of somatostatin were 82.8±6.5 μEq/15 min and 8.3±0.4 ml/15 min (n=10), respectively. Large doses of somatostatin (0.5–2.5 μg/kg/min) demonstrated dose-dependent inhibition of bethanechol-stimulated acid secretion (Fig. 1). Maximal inhibitory effects on acid secretion were obtained in the second 15-min collection period when the mean inhibitions in somatostatin-infused rats, expressed as a percent of the preinfusion values, were: 13.8% (0.5 μg/kg/min, n=4), 30.7% (1.0 μg/kg/min, n=4) and 41.0% (2.5 μg/kg/min, n=4). The inhibitory effect of somatostatin (2.5 μg/kg/min) on bethanechol-stimulated acid secretion was similar to those of somatostatin (0.25 μg/kg/min) on vagally stimulated acid secretion. Therefore, this higher dose was employed in subsequent studies. As shown in Fig. 3, somatostatin (2.5 μg/kg/min) significantly reduced the acid secretion, but the effects on the MBF were negligible. Acid secretion and MBF at the second 15-min collection period were.
respectively, 59.0±5.5% and 86.0±6.7% of the preinfusion values. The acid secretion and MBF before somatostatin infusion were 73.0±8.2 μEq/15 min and 8.6±0.7 ml/15 min (n=15), respectively.

### Influences of indomethacin and phentolamine on the inhibitory effects of somatostatin on vagally stimulated gastric acid secretion:

Pretreatment with indomethacin (10 and 50 mg/kg) or phentolamine (5.0 mg/kg) had no remarkable effect on the basal or vagally stimulated gastric acid secretion, at least during the next 4 hr. In the indomethacin (10 and 50 mg/kg)-treated rats, somatostatin (0.25 μg/kg/min) infusion produced a significant reduction in the vagally stimulated acid secretion in the second 15-min collection period. In the phentolamine-treated rats, the vagally stimulated acid secretion was significantly reduced by somatostatin (0.25 μg/kg/min) infusion (Table 1).

The acid secretion and MBF immediately before the administration of somatostatin were 53.7±3.1 μEq/15 min for indomethacin (10 mg/kg)-treated rats (n=10). 67.3±3.3 μEq/15 min for phentolamine (5.0 mg/kg)-treated rats (n=5).

### Table 1. Influences of indomethacin and phentolamine on the inhibitory effect of somatostatin on the gastric acid secretion increased by vagus nerve stimulation

| Treatments                        | N  | % Acid secretion* |
|-----------------------------------|----|-------------------|
| Control                           | 5  | 107.6±3.5         |
| Somatostatin                      | 5  | 60.3±3.3*         |
| Indomethacin (10) alone           | 5  | 99.1±5.9          |
| Indomethacin (10)+Somatostatin    | 5  | 46.5±5.1*         |
| Indomethacin (50) alone           | 5  | 101.8±4.4         |
| Indomethacin (50)+Somatostatin    | 5  | 41.6±5.3*         |
| Phentolamine (5) alone            | 5  | 94.4±1.5          |
| Phentolamine (5)+Somatostatin     | 5  | 46.6±3.3*         |

Ninety min after the beginning of the vagus nerve stimulation, somatostatin (0.25 μg/kg/min) was intravenously infused for 30 min. Indomethacin (10 and 50 mg/kg, i.p.) or phentolamine (5.0 mg/kg, i.m.) was administered at 45-min before the beginning of vagus nerve stimulation. Acid secretions obtained in the second 15-min collection period during somatostatin infusion are expressed as percentage of the preinfusion control values. *: Significantly different (P<0.05) from the corresponding values of vagally stimulated control rats in each group.

### Table 2. Influences of indomethacin and phentolamine on the inhibitory effect of somatostatin on the gastric acid secretion increased by bethanechol infusion

| Treatments                        | N  | % Acid secretion* |
|-----------------------------------|----|-------------------|
| Control                           | 5  | 99.4±6.5          |
| Somatostatin                      | 5  | 59.4±5.5*         |
| Indomethacin (10) alone           | 5  | 95.4±4.9          |
| Indomethacin (10)+Somatostatin    | 5  | 68.8±6.7*         |
| Indomethacin (50) alone           | 5  | 97.7±1.6          |
| Indomethacin (50)+Somatostatin    | 5  | 67.3±3.0*         |
| Phentolamine (5) alone            | 5  | 110.1±6.0         |
| Phentolamine (5)+Somatostatin     | 5  | 44.7±4.4*         |

Ninety min after the beginning of bethanechol infusion, somatostatin (2.5 μg/kg/min) was intravenously infused for 30 min. Indomethacin (10 and 50 mg/kg, i.p.) or phentolamine (5.0 mg/kg, i.m.) was administered at 45-min before the beginning of bethanechol infusion. Acid secretions obtained in the second 15-min collection period during somatostatin infusion are expressed as percentage of the preinfusion control values. *: Significantly different (P<0.05) from the corresponding values of vagally stimulated control rats in each group.
μEq/15 min for indomethacin (50 mg/kg)-treated rats (n=10) and 52.4±0.8 μEq/15 min for phenotolamine (5.0 mg/kg)-treated rats (n=10).

Influences of indomethacin and phentolamine on the inhibitory effect of somatostatin on gastric acid secretion stimulated by bethanechol infusion: Pretreatment with indomethacin (10 and 50 mg/kg) or phenotolamine (5.0 mg/kg) had no effect on the bethanechol-stimulated gastric acid secretion. In the indomethacin-treated rats, somatostatin (2.5 μg/kg/min) infusion significantly inhibited bethanechol-stimulated acid secretion in the second 15-min collection period; and in the phentolamine-treated rats, somatostatin infusion also produced a significant reduction in acid secretion (Table 2).

The acid secretion and MBF immediately before the administration of somatostatin were 69.0±6.4 μEq/15 min for indomethacin (10 mg/kg)-treated rats (n=10), 87.2±7.6 μEq/15 min for indomethacin (50 mg/kg)-treated rats (n=10) and 82.2±9.1 μEq/15 min for phenotolamine (5.0 mg/kg)-treated rats (n=10).

Discussion

Previous studies showed that gastric acid secretion induced by pentagastrin or histamine was directly inhibited by somatostatin in cats and dogs (21, 22). However, it cannot be concluded from those studies that somatostatin had a direct inhibitory effect on acid secretion without ruling out its effects on gastric mucosal blood flow (MBF). The present experiments demonstrated that somatostatin inhibited the gastric acid secretion induced by vagus nerve stimulation or bethanechol infusion without affecting the gastric MBF. These observations appear to be consistent with the recent findings of Leung and Guth (23) who reported that intravenous infusion of somatostatin inhibited pentagastrin-stimulated gastric acid secretion without any inhibitory effect on the gastric MBF measured by hydrogen gas clearance. Thus, it is apparent that somatostatin-induced reduction in the acid secretion is independent of changes in the gastric MBF.

Somatostatin has been shown to produce marked inhibition of basal, food- and neurally stimulated gastrin release and acid secretion induced by agents such as bethanechol, pentagastrin, food and insulin (7, 8). In the antrum, somatostatin containing D-cells are located close to G-cells at the bases of glands, while in the oxyntic mucosa, they are in the vicinity of parietal cells (5). From these observations, it has been suggested that somatostatin acts on parietal cells and G-cells and directly or secondarily causes an inhibitory effect on the gastric acid secretion, in a paracrine-like manner.

In the present experiments, the inhibitory effect of somatostatin on the vagally stimulated acid secretion was about ten-fold more potent than that on the bethanechol-induced acid secretion. While vagus nerve stimulation involves the entire pathway of the parasympathetic nervous system from preganglionic neurons to parietal cells, bethanechol stimulates only the postsynaptic parasympathetic effector organs (e.g., parietal cells and G-cells) in the gastric wall (24). Therefore, it is possible that somatostatin acts on the parasympathetic neurons in the gastric wall and reduces parasympathetic neural activity, in addition to the action on the parietal cells and G-cells. Guillemin (25) showed that somatostatin inhibits the electrically induced release of acetylcholine from the myenteric plexus-longitudinal muscle of the guinea-pig ileum in vitro. These inhibitory effects of somatostatin on cholinergic neurotransmission may be operative in the inhibitory effect of somatostatin on the vagally stimulated gastric acid secretion described here. As regards to the endogenous somatostatin, it has been shown that vagal stimulation produces a decrease in the release of somatostatin (26), and methacholine also inhibits the secretion of somatostatin (27) in the isolated vascularly perfused rat stomach. Therefore, such endogenous somatostatin seems to be not responsible for the difference in inhibitory potencies of somatostatin on vagally stimulated and bethanechol-induced acid secretion.

There are many neuropeptides in the enteric nervous system, including somatostatin (6), as well as the classical neurotransmitters norepinephrine and acetylcholine. They act on the gastrointestinal tract...
as neurotransmitters or neuromodulators (28, 29). However, the details of such mechanisms remain obscure. In our previous studies, we demonstrated that alpha-2 adrenoceptor-mediated (24) and substance P-mediated (30) inhibition of vagally stimulated acid secretion were operated on the parasympathetic neurons in the gastric wall. Thus, it is reasonable to assume that somatostatin also acts on the parasympathetic neurons in the gastric wall and modulates the vagally stimulated gastric acid secretion.

Ligumsky et al. (10) suggested that somatostatin-induced inhibition of the acid secretion is mediated through prostaglandin-involved mechanisms. In the present experiments, pretreatment with indomethacin, at doses that were reported to be sufficient to reduce the prostaglandin synthesis in the rat stomach (20), did not influence the inhibitory effect of somatostatin on the acid secretion induced by vagal stimulation or bethanechol infusion. These results may provide evidence against prostaglandin-mediated inhibition of somatostatin on the gastric acid secretion; this was confirmed recently in bethanechol-, pentagastrin- or methacholine-stimulated acid secretion (20, 31, 32). Furthermore, we obtained no evidence for the involvement of alpha-adrenoceptors in the inhibitory effects of somatostatin on the parasympathetically stimulated acid secretion, as reported in insulin secretion (33).

In conclusion, somatostatin inhibits both vagally stimulated and bethanechol-induced gastric acid secretion without changes in the MBF, and such inhibitions are not related to prostaglandin- and alpha-adrenoceptor-mediated mechanisms. Somatostatin probably acts on the parasympathetic neurons in the gastric wall as well as on the parietal cells and G cells in the mucosa, and it reduces the parasympathetically stimulated gastric acid secretion.

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