Upsala J Med Sci 86: 259–267, 1981

Effect of Parathyroid Hormone on Gastrin and Somatostatin Release from the Gastric Antrum

Örjan Selking,[1] Sven Gustavsson,[1] Henry Johansson[1] and Gudmar Lundqvist[2]

From the Departments of Surgery[1] and Clinical Chemistry[2], University Hospital, Uppsala, Sweden

ABSTRACT

The release of immunoreactive gastrin and somatostatin from the gastric antrum was studied in anesthetized pigs after parathyroid hormone (PTH) infusion into the antral circulation. PTH (40 units/20 min) was infused into the right gastro-epiploic artery. Blood was sampled from the right gastro-epiploic vein (antral venous blood) and from the superior vena cava (mixed venous blood). The basal gastrin concentration in antral venous blood was 17 times higher than that in mixed venous blood (1220 ± 367 versus 71 ± 25 pmol/l, mean ± SE). The somatostatin concentrations in antral and mixed venous blood were 127 ± 20 and 82 ± 23 pg/ml (mean ± SE), respectively. After PTH infusion the gastrin level both in antral and mixed venous blood increased significantly without inducing systemic hypercalcemia. PTH infusion did not significantly influence the somatostatin level either in antral venous blood or in mixed venous blood. The findings demonstrate that PTH can induce gastrin release from the gastric antrum without concomitant systemic hypercalcemia and that this release of gastrin is not accompanied by a change in the somatostatin level in antral venous blood.

INTRODUCTION

The connection between the parathyroid glands and gastrointestinal hormones is illustrated by the hypergastrinemia which often occurs in hyperparathyroid patients (10) and which possibly contributes to an increase in the incidence of peptic ulcer in hyperparathyroidism (HPT) (3, 10, 11). Concerning the etiology of peptic ulcer disease in HPT, calcium certainly plays some role and in man hypercalcemia may stimulate gastric secretion by liberating gastrin. It has also been suggested that parathyroid hormone (PTH) may exert direct effects on gastrin release, and experimental studies in pigs have revealed that infusion of PTH results in a release of immunoreactive gastrin into antral venous blood (5)

The mechanism governing the release of gastrin is not, however, completely known. In view of the inhibitory effect of somatostatin on gastrin and gastric

acid secretion, somatostatin has been proposed to be a physiological moderator of gastrin release (6, 12, 15, 21), a hypothesis favored by the presence of somatostatin-producing cells in the neighbourhood of the gastrin cells in the antral mucosa (16). In experimental studies in pigs physiological stimulation of gastrin release by intraluminal alkalinization as well as by instillation of a meat extract has been found to be accompanied by a decrease in the level of immunoreactive somatostatin in antral venous blood (12) indicating an inverse relationship between gastrin and somatostatin.

The aim of the present investigation was to determine whether or not the release of gastrin in response to PTH is associated with changes in the somatostatin level in the blood similar to those seen during physiological stimulation of gastrin release.

MATERIAL AND METHODS

Animals

Five pigs of Swedish country breed (body weight 21-28 kg) were purchased from the same breeder. The pigs were starved for 18 hours before the experiments but were allowed free access to water.

Anesthesia

Anesthesia was induced by an intramuscular injection of ketamine (Ketalar^R 250-500 mg) and maintained by repeated intravenous injections of phenoperidine (Lealgin^R, 4 mg every 30-45 min) and pancuronium bromide (Pavulon^R, 4 mg every 30-45 min). After endotracheal intubation positive pressure ventilation was given with a mixture of N_2O and O_2 (4:1) by means of a respirator. Arterial blood pressure was monitored through a catheter (infant feeding tube No 5) introduced into the left common carotid artery. Another catheter was inserted into the superior vena cava via the internal jugular vein of the left side for measurement of the central venous pressure and for blood sampling (mixed venous blood). During each experiment the fluctuations in arterial blood pressure and heart rate did not exceed 35 mm Hg and 20 beats/min, respectively. The central venous pressure was below 10 cm H_2O throughout the experiment.

Surgical procedure

An upper laparotomy was performed, with a midline incision. Two catheters were introduced, one (PE50) into the right gastro-epiploic artery for perfusion of the gastric antrum with PTH or saline, the other (infant feedingtube No. 5) into the right gastro-epiploic vein immediately before its entrance into the gastro-duodenal vein for blood sampling from the antral venous effluent. Both catheters were exteriorized through a stab wound in the abdominal wall and the laparotomy wound was closed. By injection of ink into both catheters at the end

of each experiment a check was made that the position of the catheters had been correct for antral perfusion and collection of antral venous effluent blood, respectively.

Experimental protocol

After initial blood sampling on two occasions with a 15 min interval (base-line period) a control infusion of saline (0.9 %) was administered at a rate of 0.5 ml/min through the catheter in the right gastro-epiploic artery for 20 min (saline infusion). Thirty min after the completion of the saline infusion 40-USP units of PTH (Para-Thor-Mone, Eli-Lilly) in 10 ml of saline was infused through the arterial catheter in 20 min (First PTH infusion). In each animal a second infusion of PTH (Second PTH infusion) was given in the same dose and at the same rate, starting 60 min after the beginning of the first hormone infusion. Blood was sampled from the catheter in the right gastro-epiploic vein and from the central venous catheter every 10th min during the whole experiment after the base-line period until 60 min after the second PTH infusion. Diagram illustratiang the experimental protocol is given in Fig. 1. Gastrin and somatostatin were analyzed in antral venous blood and in mixed venous blood and calcium in mixed venous blood. In different experiments the drip rate of blood from the catheter in the right gastro-epiploic vein varied between 20 and 60/min. Within each experiment the constancy of the drip rate (±10%) was taken as evidence that the venous blood flow did not change.

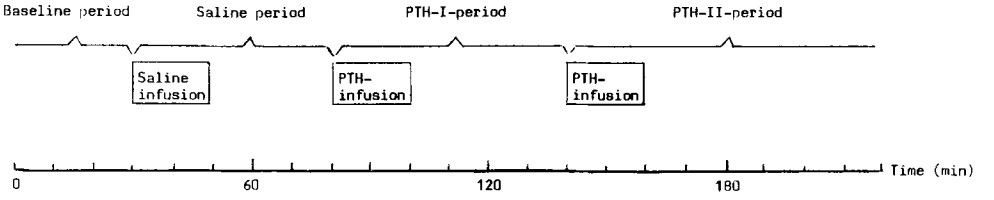

Fig. 1.

Blood samples (5 ml each) were collected in chilled tubes containing heparin (143 USP-units) and Trasylol (400 KIE/ml). After centrifugation at -4°C plasma was decanted and frozen at -20°C pending radioimmunoassay. The blood loss created by the blood sampling was compensated with 500-1000 cc glucose-salt solution (Normodex^{R}).

Radioimmunoassay

Plasma gastrin was determined by a radioimmunoassay technique described earlier (17) and plasma somatostatin by a solid phase radioimmunoassay method (18) with somatostatin antibodies coupled to microcrystalline cellulose. Before radioimmunoassay of somatostatin, plasma samples were extracted with acetone-

-petroleum-ether as suggested by Arimura et al. (1). The antiserum used, R 141, is well characterized with respect to its reactivity to different parts of the somatostatin molecule as well as to its lack of reactivity to other gastro-intestinal peptides (1). Tyr-1-somatostatin (Beckman, Geneva) was used for iodination with the lactoperoxidase method and synthetic somatostatin (Beckman, Geneva) was used for preparation of standards.

Calcium determination

The calcium concentration in mixed venous blood was measured by conventional-atomic adsorption spectrophotometry. The reference value was 2.25 - 3.0 mmol/l.

Statistical methods

The degree of significance of differences in hormone levels between different periods was determined by analysis of variance. For all experimental periods (baseline, saline, PTH I and PTH II) the mean (± SE) hormone level in each animal was calculated. All the comparisons between periods were made within animals. In the tables the results are presented as the mean of the five animals within each period ± SE (Tables 1-4).

RESULTS

Baseline gastrin, somatostatin and calcium levels

The mean plasma level of gastrin in the five pigs was 17 times higher in antral venous blood as compared with that in mixed venous blood (Table 1). The somatostatin concentration was also higher in antral than in mixed venous blood but the difference was less pronounced than for gastrin, though it was evident in all animals, and was statistically significant ($p < 0.01$). The mean calcium concentration in mixed venous blood was 2.05 ± 0.09 mmol/l (mean ± SE) (Table 1).

Table 1. Baseline hormone levels in antral and mixed venous blood. Mean ± SE

	Mixed venous blood		Antral venous blood
Gastrin pmol/l	71 ± 25	($p < 0.05$)	1220 ± 367
Somatostatin pg/ml	83 ± 23	($p < 0.01$)	127 ± 20

Saline infusion

Infusion of saline into the right gastro-epiploic artery did not

significantly affect the levels of gastrin and somatostatin in antral venous blood (Table 2).

Table 2. Effect of control infusion (saline) on gastrin and somatostatin in antral venous blood. Mean ± SE

	Before saline infusion		After saline infusion
Gastrin pmol/l	1220 ± 367	(N.S.)	1073 ± 204
Somatostatin pg/ml	127 ± 20	(N.S.)	123 ± 15

PTH infusion

Both infusions of PTH resulted in a statistically significant ($p < 0.01$) increment in the gastrin level in antral venous blood (Table 3). The second infusion gave a relatively larger increase than the first one (increase by factors of 1.07 and 1.86, respectively). The PTH infusions did not, however, significantly affect the somatostatin level in antral venous blood in either direction.

The first PTH infusion increased the gastrin level in mixed venous blood but the somatostatin level remained unchanged (Table 4). The increase in gastrin, however, was not statistically significant. The second PTH infusion increased the gastrin level significantly ($p < 0.001$), but did not affect the somatostatin level.

The first PTH infusion did not increase the serum calcium level in mixed venous blood, but after the second infusion the mean serum calcium value increased by 0.21 mmol/l as compared with the baseline level (from 2.09 ± 0.09 to 2.30 ± 0.13, mean ± SE).

DISCUSSION

In studies of gastrointestinal endocrinology the pig has been found to be very suitable as an experimental animal. The main reason for this is the similarities between humans and pigs in their intestinal peptides and also in their gastrointestinal physiology (7, 14). The experimental model used in the present study permitted selective blood sampling during a period of several hours without apparent changes in regional or central circulation. A further advantage of this model was the possibility of confirming that the collected venous blood did in fact drain the gastric area into which the test hormone was infused. By infusion of PTH into a limited region like the gastric antrum, the

Table 3. Effect of PTH-infusions on hormone levels in antral venous blood of the five animals within each period. Statistical significance was evaluated by analysis of variance. Mean ± SE

	Before first PTH-infusion		PTH-I-period		PTH-II-period
Gastrin pmol/l	1122 ± 256	($p < 0.01$)	1199 ± 159	($p < 0.01$)	2097 ± 170
Somatostatin pg/ml	125 ± 13	(N.S.)	112 ± 15	(N.S.)	152 ± 31

Table 4. Effect of PTH-infusions on hormone and calcium levels in mixed venous blood of the five animals within each period. Statistical significance was evaluated by analysis of variance. Mean ± SE

	Before first PTH-infusion		PTH-I-period		PTH-II-period
Gastrin pmol/l	109 ± 14	(N.S.)	186 ± 101	($p < 0.001$)	310 ± 216
Somatostatin pg/ml	101 ± 20	(N.S.)	100 ± 17	(N.S.)	122 ± 25
Calcium mmol/l	2.05 ± 0.03	(N.S.)	2.23 ± 0.08	($p < 0.001$)	2.30 ± 0.13

effects of this hormone upon gastrin release could be investigated without induction of hypercalcemia, although a significant increase in serum calcium - but not beyond the normal range - was noted.

The present findings demonstrated that PTH infused into the right gastro--epiploic artery induced gastrin release as measured as an increase in serum gastrin concentration, confirming the report by Bolman et al. (5). The experimental protocol in our study was similar to that of Bolman et al. (5) with respect both to the surgical procedure and to the dosage of PTH. These authors noted an approximately tenfold rise in gastrin after infusion of PTH - in contrast to our doubled value. However, in both studies the gastrin increase after the second PTH infusion was enhanced.

Exogenous somatostatin has been shown in many investigations to be a potent inhibitor of gastrin release (4, 6, 15, 19, 20). This long-held view has recently been challenged by Hayes et al. (13) and Schrumpf (21), who claim that only stimulated gastrin release (arginine-stimulated or meal-stimulated) is inhibited by exogenous somatostatin, whereas the basal gastrin secretion is unaffected by somatostatin. Concerning the relation between gastrin and somatostatin, it is suggested that the gastric release of gastrin may be regulated at least partially by a local release of somatostatin (paracrine effect) (22). Larsson et al. (16) have recently reported that somatostatin-producing D-cells in the antrum have long cytoplasmic processes which terminate on gastrin--producing G-cells in the rat and in man. It is supposed that the presence of somatostatin containing processes that end on putative effector cells indicates that somatostatin may directly affect the secretion of gut hormones and enzymes. These processes may mediate local (paracrine) release of secretory products from these cells (15).

It has been demonstrated that there is an inverse relationship between gastrin and somatostatin immunoreactivity in the antral lumen of cats during vagal stimulation (22). Another example of the inverse gastrin-somatostatin relationship is given by Chiba et al. (8), who found that perfusion of the left gastric artery in the isolated rat stomach with VIP, secretin, or glucagon evoked an increase in somatostatin secretion, which was simultaneous with the expected inhibition of gastrin release. In a similar experimental model the same authors (9) showed that infusion of calcitonin caused a dose-dependent increase in gastric somatostatin release concomitant with a decrease in gastrin secretion. These findings indicate the possibility of somatostatin-mediated suppression of gastrin by calcitonin. Using a technique similar that in the present experiments, Gustavsson & Lundqvist (12) also found an inverse relationship between somatostatin and gastrin in antral venous blood when gastrin release was stimulated by instillation of bicarbonate or meat extract into the antrum.

The most striking finding in the present study was that the release of gastrin in response to PTH was not accompanied by a change in somatostatin release into the antral venous circulation, indicating that the inverse relationship between gastrin and somatostatin is not obligatory. A reason for the different outcomes between the study by Gustavsson & Lundqvist (12) and the present investigation may be that the stimulation of gastrin release in the former study was of a physiological nature, with the stimulus administered intraluminally, while in our experiments the stimulus was administered intra-arterially, probably in a non-physiological dose. The most plausible explanation for the different somatostatin responses is that this hormone does not participate in the gastrin release after PTH stimulation. On the other hand, the unchanged somatostatin levels in antral venous blood do not exclude the possibility of paracrine somatostatin regulation of PTH-induced gastrin release.

ACKNOWLEDGEMENT

This study was supported by the Swedish Medical Research Council (project Nos 04787 and 04534)

REFERENCES

1. Arimura, A., Lundqvist, G., Rothman, J. & Chang, R.: Radioimmunoassay of somatostatin. Metabolism 27:1139-1143, 1978.
2. Arnold, R., Neuhof, Ch., v Hülst, M. & Creutzfeldt, W.: Gastrin-producing G-cells and somatostatin-producing D-cells in different states of gastric acid secretion, Regulatory Peptides, Suppl. 1:5, 1980.
3. Barreras, R.F.: Calcium and gastric secretion. Gastroenterology 64: 1168-1184, 1973.
4. Bloom, S.R., Mortimer, C.H., Thorner, M.O., Besser, G.M., Hall, R., Gomez-Pan, A., Roy, V.M., Russell, R.C.G., Coy, D.H., Kastin, A.J. & Schally, A.V.: Inhibition of gastrin and gastric-acid secretion by growth-hormone release-inhibiting hormone. Lancet 1106-1109, 1974.
5. Bolman, R.M., Cooper, C.W., Garner, S.C., Munson, P.L. & Wells, S.A.: Stimulation of gastrin secretion in the pig by parathyroid hormone and its inhibition by thyrocalcitonin. Endocrinology 100:1014-1021, 1977.
6. Bolman, R.M., Cooper, C.W. & Wells, S.A.: Somatostatin inhibition and reversal of parathyroid hormone-, calcium-, and acetylcholine-induced gastrin release in the pig. Endocrinology 103:259-266, 1978.
7. Bustad, L.K., McClellan, R.O., Burns, M.P.: Swine in biomedical research. Proceedings of a symposium at the Pacific Northwest Laboratory, Richland, Washington. Batelle Memorial Institute, 1966.
8. Chiba, T., Taminato, T., Kadowaki, S., Abe, H., Chihara, K., Seino, Y., Matsuhura, S. & Frijita, T.: Effects of glucagon, secretin, and vasoactive intestinal polypeptide on gastric somatostatin and gastrin release from isolated perfused rat stomach. Gastroenterology 79:67-71, 1980.
9. Chiba, T., Taminato, T., Kadowaki, S., Goto, Y., Mori, K., Seino, Y., Abe, H., Chihara, K., Matsukura, S., Fujita, T. & Kondo, T.: Effects of /Asu^{1,7}/-eel calcitonin on gastric somatostatin and gastrin release. Gut 21:94-97, 1980.
10. Christiansen, J.: Primary hyperparathyroidism and peptic ulcer disease. Scand J Gastroenterol 9:111-114, 1974.
11. Dent, R.J., James, J.H., Wang, C., Defton, L.J., Talamo. R. & Fischer,

J.F.: Hyperparathyroidism: gastric acid secretion and gastrin. Ann Surg 6:360-369, 1972.
12. Gustavsson, S. & Lundqvist, G.: Participation of antral somatostatin in the local regulation of gastrin release. Acta Endocrinol 88:339-346, 1978.
13. Hayes, J.R.. Johnson, D.G., Koerker, D. & Williams, R.H.: Inhibition of gastrin release by somatostatin in vitro. Endocrinology 96:1374-1376, 1975.
14. Holst, J.J.: Extraction, gel filtration pattern, and receptor binding of porcine gastrointestinal glucagon-like immunoreactivity. Diabetologica 13: 159-169, 1977.
15. Konturek, S.J., Tasler, J., Cieszkowski, M., Coy, D.H. & Schally, A.V.: Effect of growth hormone release-inhibiting hormone on gastric secretion, mucosal blood flow and serum gastrin. Gastroenterology 70:737-741, 1976.
16. Larsson, L-I., Goltermann, N., Mazistrin, L., Rehfeld, J. & Schwartz, T.: Somatostatin cell processes as pathways for paracrine secretion. Science 205:1393-1395, 1979.
17. Lundqvist, G. & Wide, L.: Serum gastrin determination with a radioimmunosorbent technique. Clin Chim Acta 79:357-362, 1977.
18. Lundqvist, G., Gustavsson, S., Elde, R. & Arimura, A.: Radioimmunosorbent assay for plasma somatostatin. Clin Chim Acta 101:183-191, 1980.
19. Phillip, J., Domschke, S., Domschke, W., Urbach, H-J., Reiss, M. & Demling, L.: Inhibition by somatostatin of gastrin release and gastric acid responses to meals and to pentagastrin in man. Scand J Gastroneterol 12: 261-265, 1977.
20. Raptis, S., Dollinger, H.C., von Berger, L., Schlegel, W., Schröder, K.E. & Pfeiffer, E.F.: Effects of somatostatin on gastric secretion and gastrin release in man. Digestion 13:15-26, 1975.
21. Schrumpf, E.: The inhibitory action of somatostatin on the stomach. Adv Exp Med Biol 106:235-240, 1978.
22. Uvnäs-Wallensten, K., Efendic, S. & Luft, R.: Vagal release of somatostatin into the antral lumen of cats. Acta Physiol Scand 99:126-128, 1977.

Received August 20, 1981

Adress for reprints:

Örjan Selking, M.D.
Department of Surgery
University Hospital
S-750 14 Uppsala
Sweden