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Studies with Bombesin in Man

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The bombesin (BBS) infusion test was performed in 232 subjects with a variety of conditions, including 35 normal individuals, 41 duodenal ulcer patients, 13 gastric ulcer patients, and 14 patients with Zollinger-Ellison syndrome. Side effects occurred in 80% of patients, but in only 6% was the test discontinued due to discomfort. All side effects promptly subsided when BBS infusion was interrupted. The dose of BBS eliciting the maximal gastrin response was 15 ng/kg per minute. In man, BBS showed a powerful stimulatory action on antral and gastrinoma G cells. No effect on duodenal G cells was apparent. Plasma levels of the different molecular forms of gastrin were all augmented by BBS infusion. BBS potentiated the gastrin response to a meal and elicited a prolonged and sustained gastrin response in patients with Menetrier's disease. Cells with BBS-like immunoreactivity were demonstrated in the gastrointestinal tract of man. These data suggest that BBS may play a physiologic role in man.

The clinical value of the BBS test was mainly assessed in the study of patients with postgastrectomy recurrent ulcer. In these patients, the BBS test clearly segregated patients with hypersecretion of gastrin from patients without such hypersecretion, and helped to elucidate the pathophysiologic features causing hypergastrinemia.

In perspective, BBS should be viewed as an endocrine polyreleaser (gastrin, CCK, PP, glucagon) and as a member of the family of immunoreactive brain-gut peptides. The role of BBS in the "brain-gut axis" remains to be determined.

In 1970, Erspamer et al. [1] isolated from fresh skins of frogs of the species *Bombina bombina* and *Bombina variegata* an active tetradecapeptide which they named bombesin (BBS). BBS was shown to have the following amino acid sequence: Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2. In pharmacologic doses, BBS was shown to affect blood pressure, smooth muscle, and blood glucose levels. In particular, BBS displayed a number of effects on the gastrointestinal (GI) tract. BBS was found to be a potent stimulant of gastric acid secretion in gastric fistula dogs. This effect was related to gastrin release from antral mucosa [2] (Fig. 1). In antral pouch dogs, it was demonstrated that the antral gastrin response to BBS was not affected by antral pouch denervation, and was not abolished by antral pouch acidification [2, 3]. From the above experiments, it was concluded that in dogs, BBS is a very potent stimulant of antral gastrin release by direct action on G cells, largely independent of antral pH and vagal innervation. In this paper, some of the studies that we have conducted with BBS in man will be reviewed.

Methods

We have conducted studies in man with natural BBS since 1972. The synthesis of the tetradecapeptide by Farmitalia S.p.a. Laboratories (Milan) made these studies possible. To date, the effects of BBS have been studied in 232 subjects, including 145 males and 87 females, ranging in age between 16 and 72 years. Thirty-five subjects were healthy volunteers, and 197 patients had a variety of GI disorders, as outlined in Table 1.

BBS was usually administered intravenously in a

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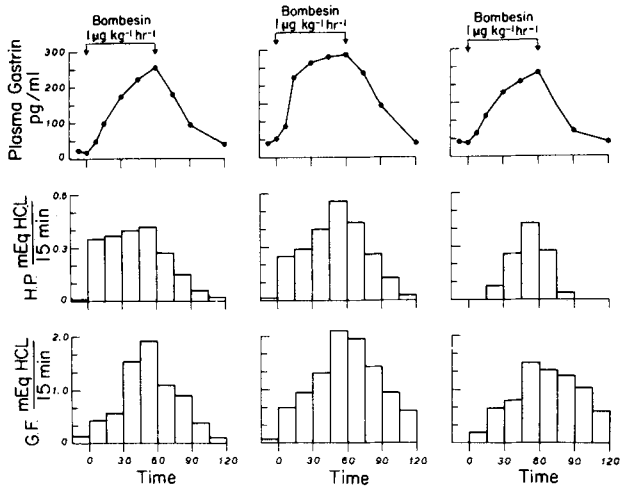

Fig. 1. Plasma gastrin levels and acid output in dogs with Heidenhain pouches (HP) and dogs with gastric fistulas (GF).

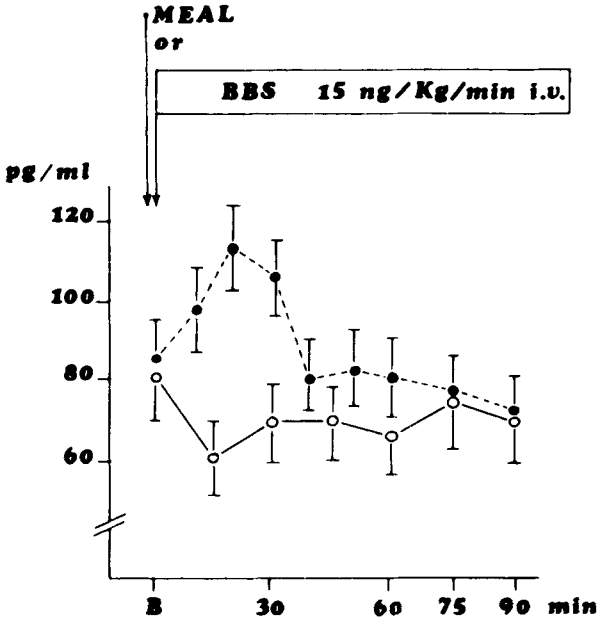

Fig. 2. Mean serum gastrin levels in 4 patients with truncal vagotomy, antrectomy, and gastroduodenostomy following a test meal (*interrupted line*) and during BBS infusion (*solid line*).

dose of 15 ng/kg per minute over a 90-minute period. Undesirable side effects occurred in 80% of subjects (Table 2). The most frequent symptom was nausea, which occurred seconds after the BBS infusion was started, suggesting an effect of BBS on the central nervous system. The side effects were usually minor, and the BBS infusion was discontinued in only 6% of patients due to discomfort. Side effects promptly subsided when the BBS infusion was interrupted. The incidence of side effects following the 8 and 15 ng/kg per minute doses was not significantly different. No long-term side effects were observed. In 1 patient with a stomal ulcer, moderate upper GI bleeding occurred during the BBS infusion; in this patient, upper GI bleeding also occurred during a calcium infusion test and a histamine test. In 25% of the tests, the BBS infusion was performed on outpatients. It is apparent that BBS infusion is safe, and that side effects are moderate and only partly related to the dose of BBS used.

Table 1. Condition of 232 human subjects who underwent BBS studies.

	Number of subjects
Healthy subjects	35
Duodenal ulcer	41
Gastric ulcer	13
Zollinger-Ellison syndrome	14
Menetrier's disease	3
2/3 gastrectomy	22
Stomal ulcer	67
Duodenopancreatectomy	12
Vagotomy plus drainage	16
Total gastrectomy for gastric cancer	6
Gastric cancer	1
Atrophic gastritis	1
Gastrojejunostomy	1
Total	232

Mechanism of Action in Gastrin Release

BBS is a potent stimulant of gastrin release in man [4]; it is more potent as a secretagogue than a protein meal [5]. BBS has no significant effect on duodenal gastrin release [5] (Fig. 2). The clinical relevance of these data will be discussed later.

BBS augmented total radioimmunoassayable gastrin levels, which seems to be related to augmented synthesis and/or release of the different circulating molecular forms of gastrin, as studies in patients with Zollinger-Ellison syndrome (ZES) indicated

Table 2. Side effects of BBS infusion in 232 subjects.

	Percent of subjects
Nausea	64
Hot flush	48
Sweating	18
Epigastric pain	16
Heartburn	15
Weakness	14
Headache	10
Bladder tenesmus	10
Vomiting	5

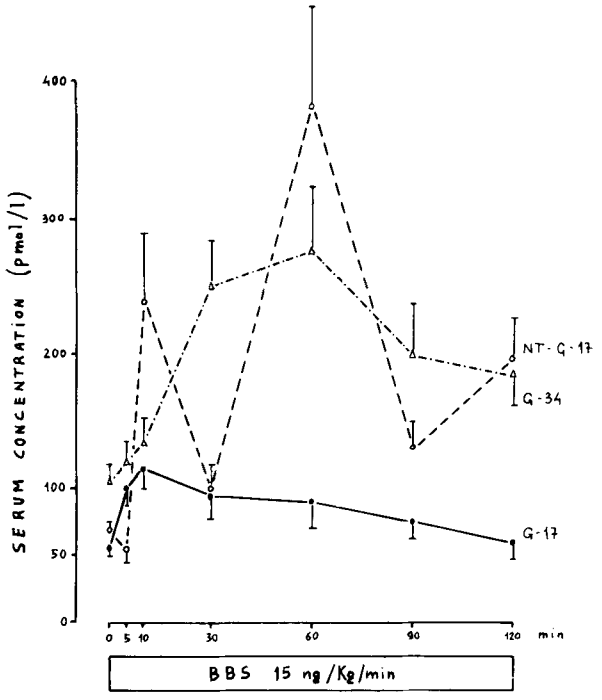

Fig. 3. Serum concentrations of different molecular forms of gastrin after BBS infusion in 4 patients with Zollinger-Ellison symdrome.

[6]. The absolute concentrations of G-17, G-34, and the N-terminal G-17 fragment were all augmented following BBS infusion. In particular, G-34 showed the highest molar concentration, and G-17 the lowest molar concentration (Fig. 3). However, when we consider the biologic activity of the different forms by recalculating the results taking into account the 6-fold difference required to produce half-maximal rates of acid secretion, as shown by Walsh [7], it is clear that G-17 accounted for the greater part of the biologic activity in blood. Studies in normal subjects to confirm these data are underway.

The presence of cells with BBS-like immunoreactivity in the GI tract of man, demonstrated by Pearse, Polak, and Solcia in 1976 [8], supports the hypothesis that BBS plays a physiologic role in man. If such is the case, the question is: does BBS mediate or modulate the stimulatory effect of food on gastrin secretion? As soon as a reliable radioimmunoassay (RIA) for BBS is available, this question can be answered. At present, we have some indirect evidence. In normal individuals, BBS potentiated the gastrin response to a meal, suggesting a modulating effect on the gastrin response to a physiologic stimulus [9] (Fig. 4). In patients with Menetrier's disease, a "continuous" protein meal and BBS infusion for 3 hours elicited a prolonged and sustained gastrin response with comparable values and comparable time courses [10] (Fig. 5). These data suggest that BBS stimulates the release and synthesis

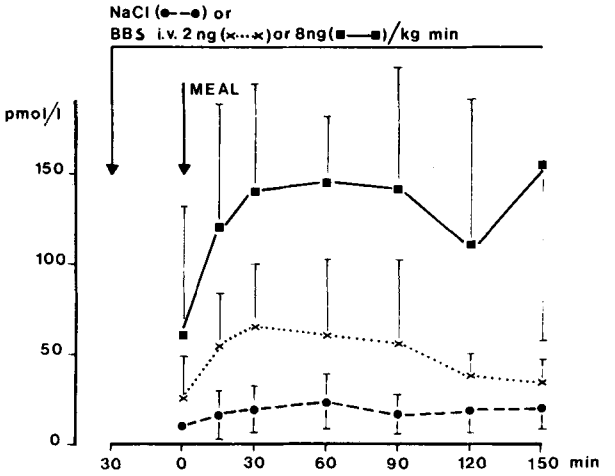

Fig. 4. Plasma gastrin levels in 4 normal subjects following a test meal and a test meal during BBS infusion at different doses.

of antral gastrin, and it may be a physiologic mediator of the release of antral gastrin by a protein meal. Preliminary data on BBS plasma levels in man determined by RIA confirmed the latter hypothesis. In fact, in 6 human subjects, BBS-like immunoreactivity in plasma increased after a standard meat meal. The peak response of BBS preceded that of gastrin by 30 minutes [11].

Studies in healthy volunteers showed that glucagon, secretin, and duodenal acidification did not inhibit the effect of BBS on serum gastrin levels [12] (Fig. 6). These data suggest that BBS may be the

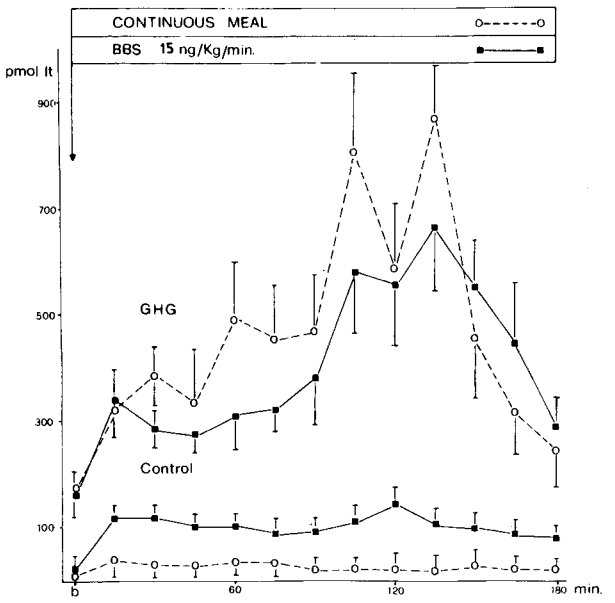

Fig. 5. Serum gastrin levels in 3 patients with Menetrier's disease (GHG) and in 3 normal subjects (control) during BBS infusion for 3 hours and during a "continuous" meal.

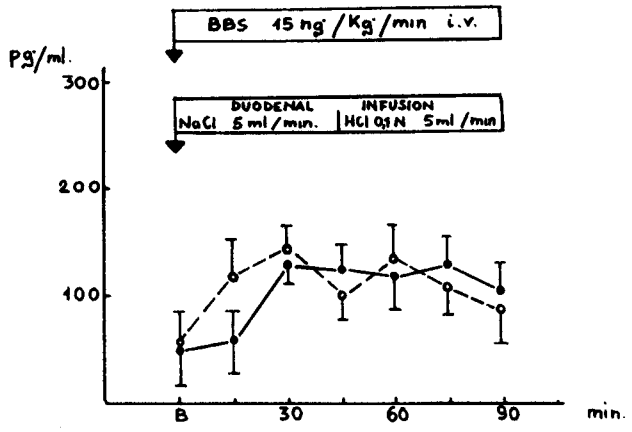

Fig. 6. Serum gastrin levels in basal conditions and after administration of BBS (*broken line*), BBS in conjunction with NaCl duodenal perfusion, and BBS in conjunction with HCl 0.1 N (5 ml/min) duodenal perfusion (*solid line*) in 7 normal subjects.

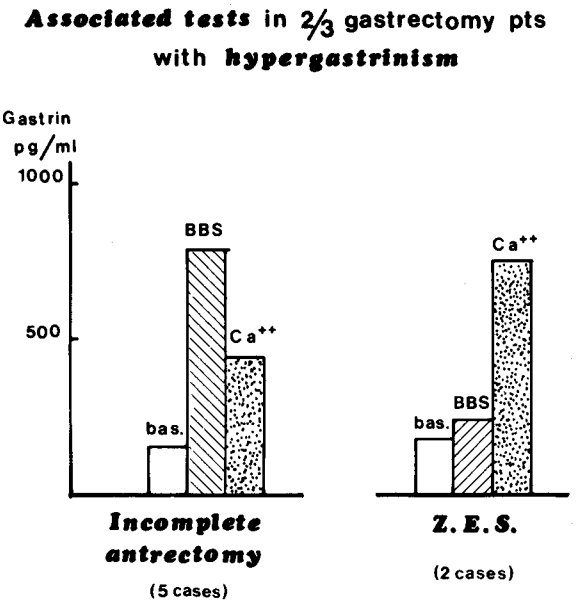

Fig. 7. Associated gastrin stimulation tests in stomal ulcer patients with hypergastrinemia.

physiologic link in the chain: stimulus/G cell/release of gastrin.

On the basis of these data, the following hypotheses may have validity: (a) BBS plays a physiologic role in man; (b) BBS is a potent stimulant of antral and gastrinoma G cells, but has no effect on duodenal G cells; (c) BBS stimulates the release and synthesis of gastrin; (d) BBS increases serum concentrations of different forms of circulating gastrin; (e) BBS is the physiologic mediator of the release of food-stimulated antral gastrin; (f) BBS modulates the gastrin response to a meal; and (g) in the chain: stimulus/G cell/release of gastrin, BBS is intimately connected to the G cells.

Clinical Investigations

The potential use of BBS infusion in the diagnosis of GI diseases has been tested in a variety of conditions. BBS was infused at doses of 2, 4, 8, 10, and 15 ng/kg per minute. Preliminary studies on the dose-response curve led us to conclude that a dose of 15 ng/kg per minute elicited a maximal gastrin response. Therefore, the standard BBS test consisted of intravenous infusion of 15 ng/kg per minute for 90 minutes.

During the BBS test, gastric acid secretion and plasma gastrin levels were measured at 15-minute intervals. When repeated in the same patient, the test elicited comparable results, confirming the reliability of the test. The reproducibility of the test, and the fact that BBS is the most potent gastrin-releasing agent in normal individuals and in peptic ulcer patients, may allow a "functional biopsy of the antrum." Such a "functional antral biopsy" could make it possible to segregate peptic ulcer patients into a category with low-grade antral gastrin and a category with high-grade antral gastrin, in whom antrectomy should be performed. Such a "functional antral biopsy" has been obtained in patients with antral G cell hyperplasia [13].

The clinical relevance of the BBS test has been assessed in patients with postoperative recurrent ulcer [14]. Identification of hypergastrinemia and its pathophysiology in patients with peptic ulcer recurring after gastrectomy is an essential step for adequate therapy. All stomal ulcer patients should have serum gastrin studies. A series of serum gastrin determinations using all of the various stimuli available (BBS, calcium, secretin, protein meal) would permit a more accurate diagnosis [15]. However, it is not practical to perform all of the gastrin stimulation tests in all stomal ulcer patients. For this reason, we have devised a protocol of study [16] designed to differentiate patients with hypergastrinemia from patients without this condition, and to elucidate the pathophysiologic features causing hypergastrinemia when it is found. BBS has been particularly useful in accomplishing these goals, since it selectively stimulates gastrin-producing cells in the antrum and in gastrinomas, but has no significant effect on duodenal and jejunal G cells.

Patients can be divided into 2 groups on the basis of their serum gastrin response to BBS, namely, patients in whom there is no significant effect on serum gastrin levels, and patients in whom BBS infusion results in augmented serum gastrin levels. In our studies, BBS infusion in about 80% of stomal

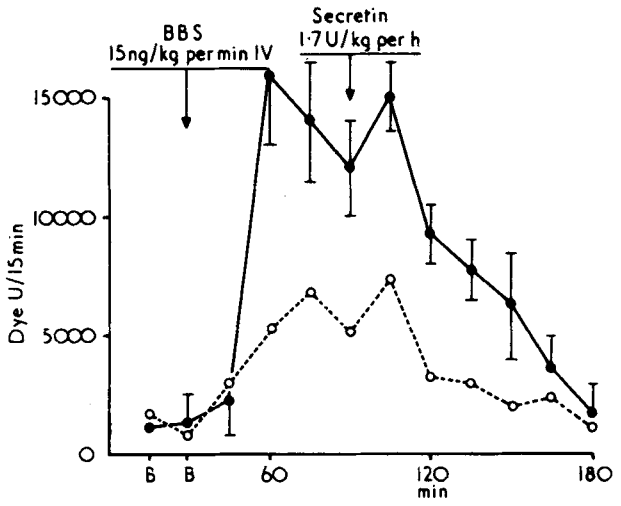

Fig. 8. Amylase output in the duodenal aspirate in basal conditions and after administration of BBS, BBS in conjunction with secretin, and secretin. • = mean ± SEM results obtained in 7 experiments in 7 healthy volunteers. ○ = mean results obtained in 2 experiments in 2 patients with $^2/_3$ gastrectomy and external pancreatic fistula.

ulcer patients showed no effect on serum gastrin [16]. In these patients, the presence of gastrin-producing antral G cells or gastrinoma cells was ruled out. The remaining 20% of stomal ulcer patients showed significantly augmented gastrin levels following BBS infusion. The presence of either an incomplete antrectomy or a gastrinoma had to be considered. Only in these patients were studies of gastrin levels following another stimulus performed to determine the correct diagnosis.

Although a positive secretin test accurately indicates the presence of a gastrinoma (ZES), a review of the literature shows the occurrence of a significant number of ZES patients with a false-negative response [17, 18]. In our experience, the evaluation of the gastrin response to both calcium infusion and BBS infusion has been a more accurate diagnostic approach. In patients with an incomplete antrectomy, BBS was more effective in raising serum gastrin levels than was calcium. On the other hand, calcium produced higher levels than BBS when a gastrinoma was present [19] (Fig. 7). The comparative evaluation of the gastrin responses to BBS and calcium has allowed a correct diagnosis in all our patients [16]. These data have been confirmed by postoperative results.

The BBS test allowed a quantitative evaluation of the hypergastrinemia related to retained antral mucosa or excluded antral mucosa in patients following gastrectomy, confirming that remnants of antral mucosa, whether retained or excluded, lead to hypergastrinemia, although excluded antrum has a higher ulcerogenic potential [20]. The ulcerogenic potential of retained antrum was demonstrated in a study conducted in patients following pancreaticoduodenectomy, in whom GI bleeding from stomal ulcer or stomatitis was shown to be due to retained antral tissue in the gastric remnant by the BBS test [21].

Bombesin as an Endocrine Polyreleaser

The effect of BBS as a gastrin releaser is well established. In addition, evidence is accumulating to indicate that BBS causes release of other hormones. In the dog, it has been shown that BBS stimulates gallbladder contraction [22] and pancreatic enzyme secretion, and these effects have been demonstrated in human studies [23, 24] (Fig. 8). Pancreatic enzyme secretion was stimulated in 2 antrectomized patients, ruling out involvement of endogenous gastrin as the mediator of the BBS effect on the pancreas. No effect of BBS on bicarbonate secretion was observed [24]. These data may be due to a direct CCK-like effect of BBS, or to stimulation of the release of CCK from the duodenum by BBS. Experimental data in dogs strongly support the latter hypothesis. BBS had no effect on isolated strips of dog gallbladder, while caerulein had a normal spasmogenic effect [22]. In the isolated duodenum-pancreas preparation, the stimulatory effect of BBS on pancreatic secretion was inhibited by duodenectomy, and it was restored by cross-perfusing with an intact BBS-infused animal [25]. Preliminary data in the dog showed increased plasma levels of CCK following BBS infusion [26, 27].

The effect of BBS on pancreatic polypeptide (PP) levels in plasma in dogs was studied by means of a specific RIA [28]. The results showed that BBS is at least equally as potent in releasing PP as it is in releasing gastrin.

Recent data on the effect of BBS on plasma glucagon levels in man showed a stimulatory action [29]. In the experimental animal, BBS stimulated the release of prolactin and growth hormone [30]. Finally, BBS has been shown to have effects on the myoelectric and motor activities of the gut, especially of the antrum, duodenum, jejunum, and ileum [31-35]. These effects cannot be explained completely on the basis of the release of gastrin or CCK by BBS. Other agents must be involved in these phenomena, and it is possible that BBS causes release of such agents.

At present, studies in healthy volunteers on the effects of BBS on circulating levels of VIP, GIP, PP, and CCK are underway. It appears likely that BBS acts as an endocrine polyreleaser.

Perspectives

The presence of BBS cells has been demonstrated in different portions of the GI tract [8]. Furthermore, BBS immunoreactive structures have been found in the hypothalamus of the rabbit [36], and in the rat brain [37]. When directly injected into rat brain ventricula, BBS showed a thermoregulatory action, 10,000-fold more potent than neurotensin [38]. Therefore, BBS seems to be another member of the family of so-called "brain-gut hormones." However, BBS may be a peculiar member of this family, in that it seems to be an endocrine polyreleaser, and the released hormones are candidates or established members of the brain-gut axis. Is it possible that BBS is indeed a "modulator" of the brain-gut axis?

Résumé

Un test de perfusion à la Bombésine (BBS) a été réalisé chez 232 sujets comprenant, entre autres, 35 normaux, 41 ulcères duodénaux, 13 ulcères gastriques, 14 syndromes de Zollinger-Ellison. Des effets secondaires ont été observés dans 80% des cas; mais le test n'a dû être interrompu que dans 6% des cas où le patient était franchement incommodé. Tous les effets secondaires ont rapidement disparu dès l'arrêt de l'administration de BBS. La dose de BBS produisant la réponse gastrinique maximale est de 15 ng/kg/min. Chez l'homme, BBS exerce un puissant effet stimulant sur les cellules G de l'antre et de gastrinomes. Aucune action sur les cellules G du duodénum n'a été observée. La perfusion de BBS augmente les taux plasmatiques de toutes les formes moléculaires de la gastrine. BBS potentialise la riposte gastrinique à un repas et provoque une réponse gastrinique prolongée chez le malade atteint de maladie de Ménétrier. La présence de cellules avec une immunoréactivité type BBS a été démontrée dans le tube digestif de l'homme. Cet ensemble de données suggère que BBS peut jouer un rôle physiologique chez l'homme.

La valeur clinique du test à la BBS a été principalement étudiée chez les malades atteints de récidive ulcéreuse après gastrectomie: le test sépare nettement les malades avec et sans hypersécrétion de gastrine et précise les causes physiopathologiques de l'hypergastrinémie.

BBS doit être considérée comme un libérateur d'hormones multiples (gastrine, CCK, PP, glucagon) et comme un membre de la famille des peptides immunoréactifs des apudomes. Le rôle de la BBS dans l' "axe cerveau-tube digestif" n'est pas encore défini.

References

1. Anastasi, A., Erspamer, V., Bucci, M.: Isolation and structure of bombesin and alytesin, two analogous active peptides from the skin of the European amphibians "Bombina" and "Alytes." Experientia *27*:166, 1970
2. Erspamer, V., Melchiorri, P., Bertraccini, G., Sopranzi, N., Impicciatore, M.: Gastrin release by bombesin in the dog. Br. J. Pharmacol. *52*:219, 1974
3. Basso, N., Improta, G., Melchiorri, P., Sopranzi, N.: Gastrin release by bombesin in the antral pouch of dog. Rend. Gastroenterol. *6*:95, 1974
4. Erspamer, V., Melchiorri, P., Sopranzi, N., Torsoli, A., Corazziari, E., Improta, G.: Preliminary data on the action of bombesin on secretion and motility of the gastrointestinal tract in man. Rend. Gastroenterol. *5*:68, 1973
5. Basso, N., Lezoche, E., Materia, A., Giri, S., Speranza, V.: Effect of bombesin on extragastric gastrin in man. Am J. Dig. Dis. *20*:923, 1975
6. Basso, N.: Different forms of gastrin during bombesin infusion in the Zollinger-Ellison syndrome. In Abstract of International Symposium on Gastrointestinal Hormones and Pathology of the Digestive System: New Trends in Pathophysiology, Diagnosis and Therapy. Rome, 1977 p. 42
7. Walsh, J.H., Maxwell, V., Isenberg, J.I.: Biological activity and clearance of human big gastrin in man. Clin. Res. *23*:259A, 1975
8. Polak, J.M., Bloom, S.R., Hobbs, S., Solcia, E., Pearse, A.G.E.: Distribution of a bombesin-like peptide in human gastrointestinal tract. Lancet *1*:1109, 1976
9. Lezoche, E., Matarazzo, P.F., Vagni, V., Basso, N., Speranza, V.: Potentiation of food-stimulated gastrin by bombesin. Gastroenterology *74*:1132, 1978
10. Materia, A., Vagni, V., Minervini, S., Matarazzo, P., Bagarani, M., Giri, S.: Basal and stimulated serum gastrin levels in Menetrier's disease. In Abstracts of International Symposium on Gastrointestinal Hormones and Pathology of the Digestive System: New Trends in Pathophysiology, Diagnosis and Therapy. Rome, 1977 p. 167
11. Erspamer, V., Melchiorri, P.: Amphibian skin peptides active on the gut. J. Endocrinol. *70*:12P, 1976
12. Basso, N., Giri, S., Lezoche, E., Materia, A., Melchiorri, P., Speranza, V.: Effect of secretin, glucagon and duodenal acidification on bombesin-induced hypergastrinemia in man. Am. J. Gastroenterol. *66*:448, 1976
13. Vezzadini, P., Bonora, G., Cipollini, F., Sternini, C., Ferri, G.L.: La gastrinemia nella diagnosi di gastrinoma. In La Sindrome di Zollinger-Ellison. Abstract of the III Meeting of the G.I.S.O.G.I., Bologna, December 1976
14. Basso, N., Lezoche, E., Giri, S., Percoco, M., Speranza, V.: Acid and gastrin levels after bombesin and calcium infusion in patients with incomplete antrectomy. Am. J. Dig. Dis. *22*:125, 1977
15. Basso, N., Lezoche, E., Materia, A., Bagarani, M., Minervini, S., Fiocca, F.: Surg. Gt. *9*:46, 1979
16. Basso, N.: La sindrome di Zollinger-Ellison. Arch. Atti Soc. Ital. Chir. *1*:119, 1977
17. Walsh, J.H.: Use of radioimmunoassay in endocrine G.I. tumors. In Endocrine-secreting Tumors of the G.I. Tract. Clinics in Gastroenterology, Philadelphia, W.B. Saunders, 1974
18. Zollinger, R.M., Martin, E.W., Carey, L.C., Sparks, J., Vinton, J.P.: Observations of the postoperative tumor growth behavior of certain islet cell tumors. Ann. Surg. *184*:525, 1976
19. Basso, N., Materia, A., Giri, S., Lezoche, E., Speranza, V.: Effect of bombesin on serum gastrin levels in formae frustae of the Z.E.S. and in patients with retained antrum. Gastroenterology *72*:811, 1977
20. Speranza, V., Basso, N., Lezoche, E.: Hypergastrinism in retained and excluded antra. In Gastrointestinal Hormones and Pathology of the Digestive System, Grossman, M.I.,

Speranza, V., Basso, N., Lezoche, E., editors. New York, Plenum Press 319, 1978
21. Basso, N., Simi, M., Lezoche, E., Giri, S., Materia, A., Leardi, S., Speranza, V.: Retained antral mucosa in pancreaticoduodenectomy patients. Am. J. Surg. *134*:259, 1977
22. Erspamer, V., Improta, G., Melchiorri, P., Sopranzi, N.: Evidence of colecystokinin release by bombesin in the dog. Br. J. Pharmacol. *52*:227, 1974
23. Corazziari, E., Torsoli, A., Melchiorri, P., Delle Fave, G.F.: Effect of bombesin on human gallbladder emptying. Rend. Gastroenterol. *6*:52, 1974
24. Basso, N., Giri, S., Improta, G., Lezoche, E., Melchiorri, P., Percoco, M., Speranza, V.: External pancreatic secretion after bombesin infusion in man. Gut *16*:994, 1975
25. Mennini, G., Basso, N., Minervini, S., Longo, R., Paduos, A., Speranza, V.: Mechanism of action of bombesin on pancreatic secretion. Abstract of the VI World Congress of Gastroenterology: 6, 1978
26. Miyata, M., Guzman, S., Rayford, P.L., Thompson, J.C.: Response of cholecystokinin, secretin and pancreatic secretion to graded doses of bombesin. Surg. Forum (*in press*)
27. Miyata M., Guzman, S., Rayford, P.L., Thompson, J.C.: Effect of bombesin on release of gastrin, CCK, secretin and pancreatic exocrine secretion. Gastroenterology *74*:1137, 1978
28. Taylor, I.L., Walsh, J.H., Carter, D.C., Wood, J., Grossman, M.I.: Effect of atropine and bethanechol on release of pancreatic polypeptide (PP) and gastrin by bombesin in dog. Abstract of the 2nd International Symposium on Gastrointestinal Hormones, Boitostøeen, Norway, 1978
29. Fallucca, F., Delle Fave, G.F., Gambardella, S., Mirabella, C., De Magistris, L., Carratu, R.: Glucagon secretion induced by bombesin in man. Lancet *2*:609, 1977
30. Rivier, C., Rivier, J., Vale, W.: Effect of bombesin and related peptides on prolactin and growth hormone secretion in the rat. Endocrinology *102*:519, 1978
31. Corazziari, E., Torsoli, A., Delle Fave, G.F., Melchiorri, P., Habib, F.I.: Effect of bombesin on the mechanical activity of the human duodenum and jejunum. Rend. Gastroenterol. *6*:55, 1974
32. Caprilli, R., Melchiorri, P., Improta, G., Vernia, P., Frieri, G.: Effect of bombesin and bombesin-like peptides on gastrointestinal myoelectric activity. Gastroenterology *62*:1228, 1975
33. Bertaccini, G., Impicciatore, M., Molina, E., Zappia, L.: Action of bombesin on human gastrointestinal motility. Rend. Gastroenterol. *6*:45, 1974
34. Impicciatore, M.: Evidence that substances capable of increasing the duodenal content exert a spasmogenic action on the pylorus. Br. J. Pharmacol. *52*:467P, 1974
35. Kowalewski, K., Kolodej, A.: Effect of bombesin, a natural tetradecapeptide, on myoelectrical and mechanical activity of isolated ex-vivo perfused, canine stomach. Pharmacology *14*:8, 1976
36. Polak, J.M., Wharton, J., Bloom, S.R., Ghatei, M.A., Solcia, G., Brown, M.R.: Bombesin, possible role of a new gut and brain peptide. Gastroenterology *74*:1078, 1978
37. Walsh, J.H., Dockray, G.J.: Localization of bombesin-like immunoreactivity (BLI) in gut and brain of rat. Gastroenterology *74*:1108, 1978
38. Brown, M., Rivier, J., Vale, W.: Bombesin: potent effects on thermoregulation in the rat. Science *196*:998, 1977

Invited Commentary

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Basso and his colleagues, in a series of extended experiments, have provided us with glimpses of the wide range of bombesin (BBS) activities. What strikes the reader is the important role BBS has in a number of varied physiologic activities. Its action in the release of gastrin is at once the best understood and perhaps its most important role. BBS is a potent releasor of antral gastrin and augments the gastrin response to a standard meal. It is unaffected by antral vagotomy or acidification.

Most, if not all, of these studies have been done with the administration of exogenous BBS. To carefully delineate the physiologic role of endogenous BBS, studies are needed to quantitate the amount of BBS released during a meal.

Interestingly, although BBS appears to be ineffective in releasing duodenal gastrin, it is capable of releasing gastrin for gastrinomas. In doing this, it is more consistently effective than secretin, but only 1/3 as potent as a calcium infusion test. This discrepancy in BBS's ability to release antral, but not duodenal, gastrin makes it an important tool in understanding the mechanism by which gastrin is released from these two sites. This has been put to good clinical use by the Rome group in determining which patients have clinically significant antral tissue remaining after partial gastrectomy.

In this rapidly expanding field, no sooner has a gastrointestinal hormone been identified than a search is made for conditions in which it may play a pathologic role. Although a surprising amount of information about BBS has been accumulated, the lack of a precise, reliable radioimmunoassay (RIA), heretofore, has been a major obstacle to further investigations. Using a newly devised, preliminary RIA test, the authors have explored the role of BBS in the development of the hydrochlorhydric hypergastrinemic state not associated with gastrinomas. If our experience with other hormones is a guide, disease states in which there is an excessive release of BBS (hyperplasia) or excessive production (bombesinemia) will probably be uncovered. Is it possible that the development of gastrinomas is preceded by defects in the BBS modulation of gastrin release?