# Modulatory Glucose Effect on Bombesin-Like Immunoreactivity and Gastrin Secretion From Isolated Perfused Rat Stomach

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**SUMMARY**

**Previous studies have demonstrated mostly inhibitory effects of elevated plasma glucose levels on gastric exo- and endocrine as well as motor functions. Because increased plasma glucose levels reduce vagal activity via the central nervous system, it remains unclear if glucose exerts a direct effect on gastric functions. Therefore, our study was designed to determine the effect of acute changes in glucose concentrations on the release of gastrin and bombesin-like immunoreactivity (BLI) from the isolated perfused rat stomach. Acute elevations of perfusate glucose from 100 to 200 mg/dl or from 100 to 300 mg/dl augmented BLI secretion significantly without affecting gastrin release. During an acute decrease from 200 to 30 mg/dl, the secretion of both peptides remained unchanged. When acetylcholine was administered to stimulate BLI and gastrin secretion, the elevation of perfusate glucose to 200 mg/dl and the decrease to 30 mg/dl attenuated BLI secretion, whereas gastrin secretion remained unchanged compared with the control experiments at 100 mg/dl glucose. On the other hand, the perfusion of vasoactive intestinal peptide (VIP) and Leu-enkephalin had no effect on BLI and gastrin secretion during 100 mg/dl glucose perfusion, but both peptides elicited a significant stimulatory effect on BLI secretion during a perfusate glucose concentration of 200 mg/dl without affecting gastrin secretion. In conclusion, our study demonstrates first that an acute increase of glucose augments basal BLI secretion. Second, cholinergically induced BLI secretion is attenuated by hypo- and hyperglycemia. Third, hyperglycemia augments BLI secretion in response to the neuropeptides VIP and Leu-enkephalin. Fourth, basal and stimulated gastrin secretion remains unchanged during acute alterations of perfusate glucose levels. Because bombesin is considered to be a putative peptidergic neurotransmitter, the present data indicate that acute changes in glucose levels can affect neuronal activity, not only in the central nervous system, but also in the autonomic nervous system of the stomach. Our findings may be relevant in the study of disturbances of gastrointestinal functions in diabetes mellitus. DIABETES 1986, 35:791–96.**

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Bombesin was originally isolated from amphibian skin,[1] and subsequent studies have demonstrated the existence of a mammalian bombesin.[2] This larger molecular form, gastrin-releasing peptide (GRP) containing 27 amino acids, shares a decapeptide homology at the COOH-terminal end with bombesin. In response to intravenous administration, both peptides stimulate gastrointestinal exo- and endocrine functions, such as gastric acid, gastrin, and somatostatin secretion, and pancreatic exocrine function, but they inhibit gastric emptying.[3–8] Bombesin-like immunoreactivity (BLI) has been demonstrated to be present in neurons of the myenteric and submucous plexus, indicating that BLI in the gastrointestinal tract acts as a putative neurotransmitter and/or neuromodulator.[9,10]

The release of BLI from the rat stomach is stimulated by the classic neurotransmitter acetylcholine, as well as the putative peptidergic neurotransmitters vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), or growth-hormone–releasing factor (GHRF).[11–13] The intestinal hormone gastric inhibitory peptide (GIP) inhibits BLI secretion.[11] These effects are dependent on the intragastric pH, and they are modified by cholinergic and histamine $H_2$ receptors and by endogenous prostaglandins.[11–14] On the other hand, the stimulatory effect of [$^{14}$C]bombesin on somatostatin but not gastrin secretion is mediated via cholinergic mechanisms, whereas bombesin-induced gastrin release does not depend on cholinergic mechanisms.[5] This indicates that BLI is part of the tightly integrated neuroendocrine regulatory system of the gastrointestinal tract.

Acute changes in blood glucose levels are associated with alterations of central nervous system activities that are most

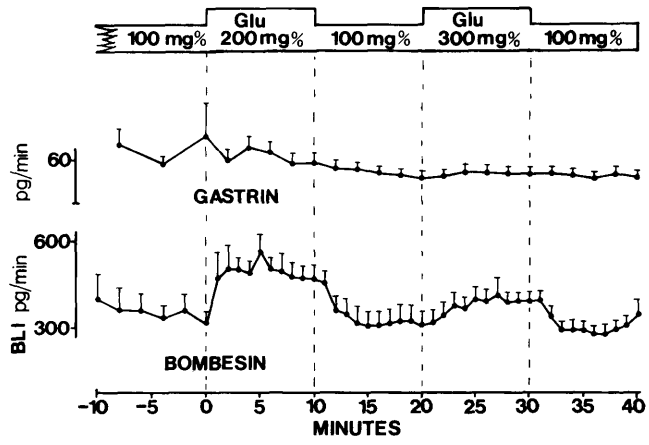


**FIGURE 1. Effect of acute changes in perfusate glucose levels from 100 to 200 mg/dl and from 100 to 300 mg/dl on basal bombesin-like immunoreactivity (BLI) and gastrin secretion from perfused rat stomachs (mean ± SE, *N* = 6).**

evident clinically during attacks of acute hypoglycemia. It is conceivable that acute changes in glucose levels might influence the function of endocrine cells and the intrinsic nervous system of the gastrointestinal tract. Therefore, our study was designed to determine the effect of acute alterations of glucose concentrations on basal and stimulated release of BLI and gastrin from the isolated perfused rat stomach.

## MATERIALS AND METHODS

The experiments were performed in an isolated rat stomach preparation by use of a modification[11] of the previously described model of McIntosh et al.[15] The stomachs of overnight-fasted rats were isolated and perfused through the celiac artery at the rate of 1.5 ml/min with Krebs-Ringer buffer solution containing 100, 200, 300, or 30 mg/dl of glucose. For equilibration after the end of surgery, the stomach was perfused with the respective glucose-containing buffer for 30 min before the start of the experiment. The gastric venous effluent was collected via a catheter in the portal vein. The lumen of the stomach was perfused with isotonic saline at pH 7.

Acetylcholine (Sigma, Munich, FRG), Leu-enkephalin (Serva, Heidelberg, FRG), VIP (generously provided by Dr. Jean Rivier, Salk Institute, La Jolla, CA), or naloxone (generously provided by Endo Laboratories, Garden City, NY) was added to the perfusate at the concentrations indicated below.

Bombesin-like immunoreactivity was determined by radioimmunoassay as described recently[11] with an antibody raised against Lys$^4$-bombesin.[16] The antibody was generously provided by Dr. Marvin Brown (Salk Institute). Tyr$^4$-bombesin for the preparation of labeled bombesin and synthetic [$^{14}$C]bombesin as standard were generously supplied by Dr. Jean Rivier. Gastrin was determined as described elsewhere[17] with the Becton and Dickinson (Heidelberg, FRG) gastrin kit.

For statistical evaluation of the data we used analysis of variance, and *P* values of ≤.05 were considered significant.

## RESULTS

**Effect of hyper- and hypoglycemia on basal BLI and gastrin secretion.** As shown in Figure 1, the increase of perfusate glucose levels from 100 to 200 mg/dl elicited a significant increase in BLI secretion. The integrated BLI response was 999 ± 116 pg/10 min, which was significantly increased ($P < .01$) compared with control experiments in which the perfusate glucose concentration was maintained at 100 mg/dl during the entire experimental period ($N = 8$, see Table 1). The increase from 100 to 300 mg/dl was only 372 ± 75 pg/10 min ($P < .05$). No effect was observed on gastrin secretion.

The decrease of perfusate glucose from 200 to 30 mg/dl had no significant effect on BLI and gastrin secretion (Figure 2).

**Effect of hyper- and hypoglycemia on acetylcholine-induced BLI and gastrin secretion.** Acetylcholine elicited a stimulation of BLI secretion at a dose of $2 \times 10^{-6}$ M, whereas the higher dose of $4 \times 10^{-6}$ M had no significant effect (Figure 3). Gastrin secretion was stimulated by both doses of acetylcholine. The reduction of perfusate glucose levels to 30 mg/dl abolished the cholinergic stimulation of BLI secretion, whereas the gastrin response remained unaffected (Figure 4). Elevation of perfusate glucose to 200 mg/dl reduced the BLI response to the lower dose of acetylcholine significantly, whereas the small response to the higher dose was

TABLE 1
Integrated BLI and gastrin secretion from the isolated perfused rat stomach during perfusion with acetylcholine, VIP, and Leu-enkephalin at various glucose levels.

| Group | *N* | BLI (pg/10 min) | Gastrin (pg/10 min) |
|---|---|---|---|
| 100 mg/dl glucose | 6 | | |
| + Ach $2 \times 10^{-6}$ M | | 2893 ± 174* | 228 ± 38* |
| + Ach $4 \times 10^{-6}$ M | | 424 ± 62* | 126 ± 20* |
| 200 mg/dl glucose | 6 | | |
| + Ach $2 \times 10^{-6}$ M | | 413 ± 76* | 225 ± 25* |
| + Ach $4 \times 10^{-6}$ M | | 713 ± 90* | 274 ± 24* |
| 30 mg/dl glucose | 11 | | |
| + Ach $2 \times 10^{-6}$ M | | −311 ± 105 | 303 ± 28* |
| + Ach $4 \times 10^{-6}$ M | | 68 ± 85 | 229 ± 17* |
| 100 mg/dl glucose | 6 | | |
| + enk $10^{-9}$ M | | 86 ± 110 | 5 ± 18 |
| + enk $10^{-6}$ M | | −189 ± 122 | −46 ± 15 |
| 200 mg/dl glucose | 6 | | |
| + enk $10^{-9}$ M | | 3226 ± 256* | 39 ± 17 |
| + enk $10^{-6}$ M | | 1260 ± 96* | −44 ± 14 |
| 200 mg/dl glucose + naloxone | 6 | | |
| + enk $10^{-9}$ M | | 348 ± 112 | −6 ± 12 |
| + enk $10^{-6}$ M | | 48 ± 76 | −23 ± 14 |
| 100 mg/dl glucose | 8 | | |
| + VIP $10^{-11}$ M | | 53 ± 64 | 18 ± 13 |
| + VIP $10^{-8}$ M | | −212 ± 85 | −5 ± 10 |
| 200 mg/dl glucose | 8 | | |
| + VIP $10^{-11}$ M | | 1001 ± 195* | 20 ± 11 |
| + VIP $10^{-8}$ M | | 2111 ± 276* | −4 ± 12 |
| controls | 8 | | |
| 100 mg/dl | | −156 ± 74 | −25 ± 15 |
| 200 mg/dl | | −136 ± 68 | −16 ± 20 |
| 30 mg/dl | | 86 ± 52 | 17 ± 12 |

Data are calculated as sums of differences of each time point during treatment to mean value of immediately preceding 5-min baseline period where buffer only was perfused through stomach. During control experiments, buffer with 100, 200, or 30 mg/dl glucose was perfused through stomach for entire experimental period (mean ± SE). Ach, acetylcholine; VIP, vasoactive intestinal peptide; enk, Leu-enkephalin.
*Significant difference ($P \leq .05$) compared with control experiment.

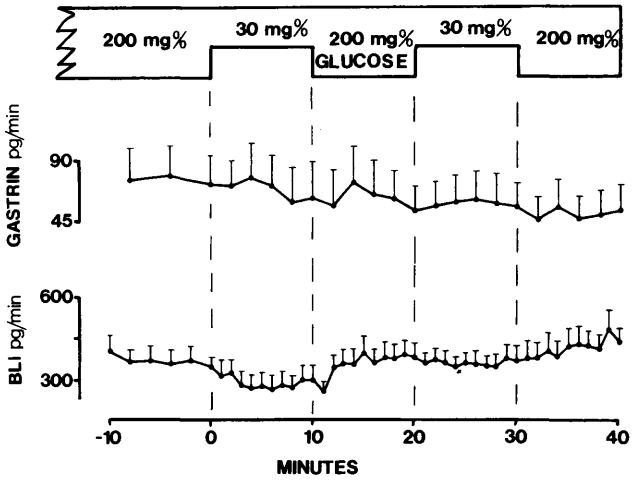


**FIGURE 2. Effect of acute changes in perfusate glucose levels from 200 to 30 mg/dl and vice versa on basal bombesin-like immunoreactivity (BLI) and gastrin secretion from perfused rat stomachs (mean ± SE, *N* = 8).**

not changed (Figure 5). Gastrin secretion was similar to the control experiments with 100 mg/dl glucose. The incremental BLI and gastrin secretion are summarized in Table 1.

**Effect of hyperglycemia during administration of Leu-enkephalin and VIP.** As shown in Figures 6 and 7, neither Leu-enkephalin nor VIP elicited a significant effect on BLI and gastrin secretion at the doses employed. When perfusate glucose levels were raised to 200 mg/dl, Leu-enkephalin ($10^{-9}$ M) elicited a significant stimulation of BLI secretion, and the higher dose of $10^{-6}$ M augmented BLI secretion

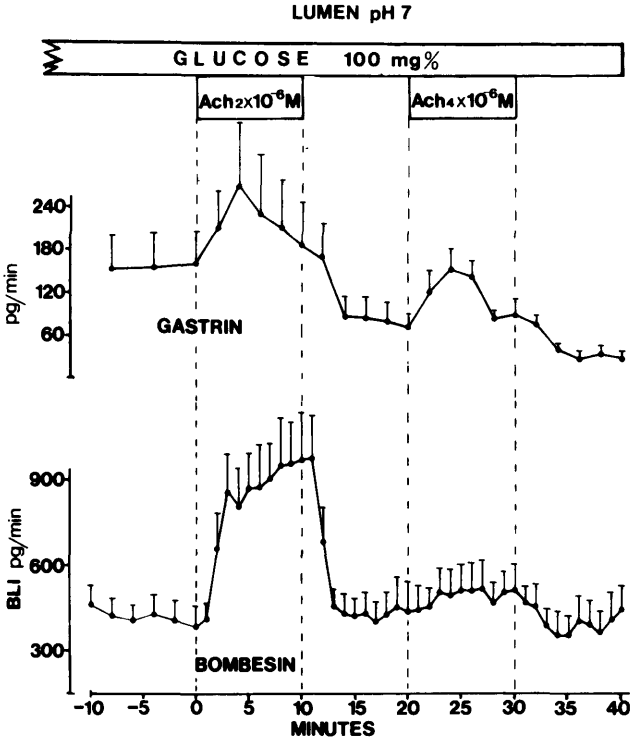


**FIGURE 3. Effect of acetylcholine infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 100 mg/dl from perfused rat stomachs (mean ± SE, *N* = 6).**

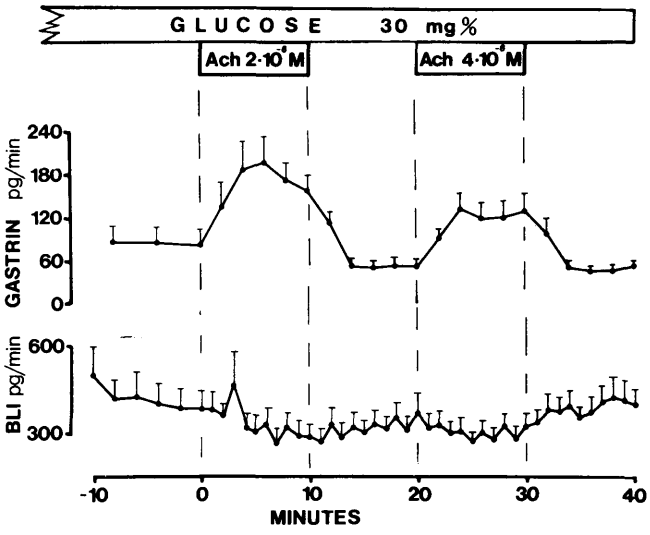


**FIGURE 4. Effect of acetylcholine infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 30 mg/dl from perfused rat stomachs (mean ± SE, *N* = 11).**

significantly (Figure 8). Gastrin levels remained unchanged. The stimulatory effect of Leu-enkephalin was completely blocked by the specific opiate-receptor antagonist naloxone (Figure 9). Similarly, VIP stimulated BLI secretion significantly at both doses with a perfusate glucose concentration of 100 mg/dl (Figure 10).

**Effect of synthetic [$^{14}$C]bombesin on BLI and gastrin levels.** Because the foregoing experiments showed alterations of BLI secretion that were not paralleled by changes in gastrin release, we examined the effect of a bombesin infusion on portal vein BLI and gastrin levels. In five stomachs the infusion of synthetic [$^{14}$C]bombesin at a concentration of $10^{-9}$ M, which has previously been shown to be a stimulus of gastrin secretion from the isolated perfused rat stomach,[5] elicited a significant stimulation of gastrin release from a

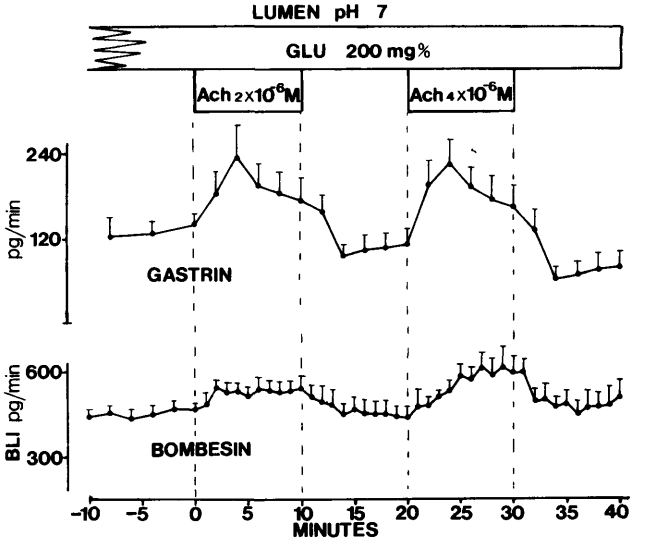


**FIGURE 5. Effect of acetylcholine infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 200 mg/dl from perfused rat stomachs (mean ± SE, *N* = 6).**

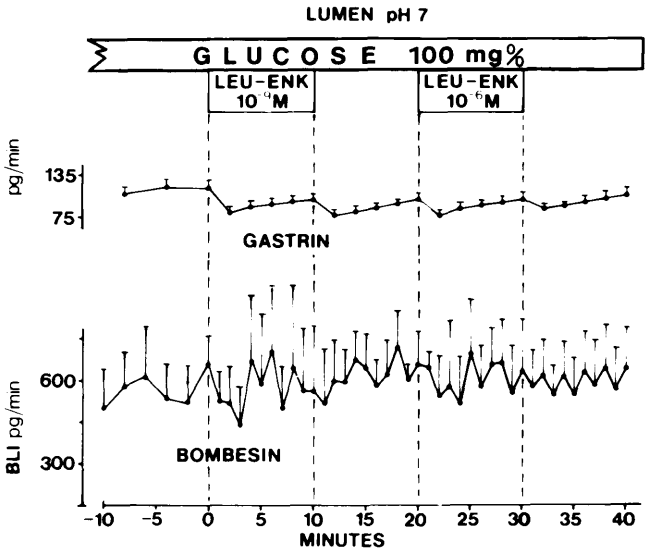


**FIGURE 6. Effect of Leu-enkephalin (LEU-ENK) infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 100 mg/dl from perfused rat stomachs (mean ± SE, *N* = 6).**

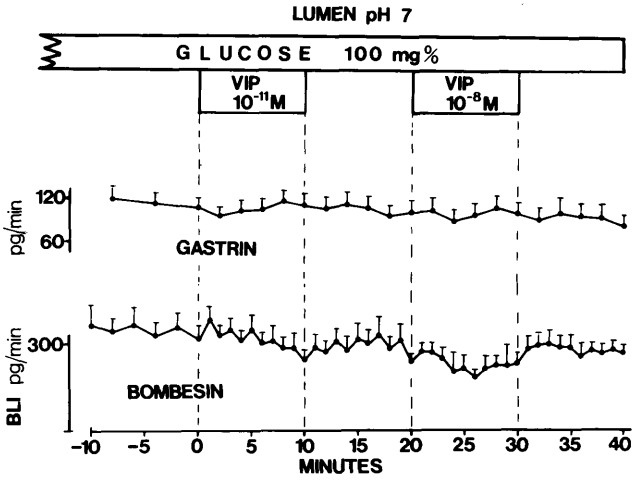


**FIGURE 7. Effect of vasoactive intestinal peptide (VIP) infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 100 mg/dl from perfused rat stomachs (mean ± SE, *N* = 8).**

mean baseline of 90 ± 12 pg/min to a maximum of 186 ± 18 pg/min ($P < .01$). Bombesin-like immunoreactivity secretion in the portal venous effluent rose from a baseline of 510 ± 65 pg/min to 720 ± 105 pg/min ($P < .05$). The radioimmunologically determined bombesin level in the arterial perfusate was 1720 pg/ml. These data demonstrate that stimulation of gastrin secretion by bombesin is compatible with rather small changes in BLI secretion when assessed by measurements in the portal venous effluent. Because of the changes in BLI secretion in some of the foregoing experiments, the concentrations of bombesin at the level of the G cell should have been high enough to elicit a stimulatory effect.

## DISCUSSION

Our study demonstrates, first, that an acute increase of glucose levels from normo- to hyperglycemia augments basal BLI secretion from the isolated pefused rat stomach, whereas a decrease from hyper- to hypoglycemic values has no effect. Second, an increase as well as a decrease of glucose levels attenuates cholinergic stimulation of BLI secretion. Third, hyperglycemia augments the BLI response to the two neuropeptides VIP and Leu-enkephalin. Fourth, basal and stimulated gastrin secretion remain unchanged during alterations of perfusate glucose levels.

Bombesin-like immunoreactivity has been demonstrated to be present in neurons of the gastrointestinal intrinsic nervous system, and thus it has to be considered as a putative neurotransmitter and/or neuromodulator.[9,10] Bombesin-like immunoreactivity and gastrin secretion are stimulated by acetylcholine,[11] and because of the potent stimulatory effect of bombesin on gastrin secretion, a tight functional linkage in the way that bombesin release is mandatory for gastrin secretion has been postulated.[18]

Previous studies have described an effect of hyper- or hypoglycemia on several gastric functions. Thus elevation of plasma glucose levels reduces gastric acid secretion, gastric emptying,[19-21] and gastrin release.[22] In all these studies, however, the increase of plasma glucose was always accompanied by augmented insulin secretion. Furthermore, effects of high glucose levels on central nervous system mechanisms and thus indirect effects on gastrointestinal functions have to be considered.[23] All these facts make it very difficult to determine the role of glucose on gastric functions.

Our study demonstrates clearly that alterations of glucose levels have no influence on basal or cholinergically stimulated gastrin release. Similar observations have been made for basal and cholinergically inhibited somatostatin secretion from the rat stomach.[24] These findings suggest that pertur-

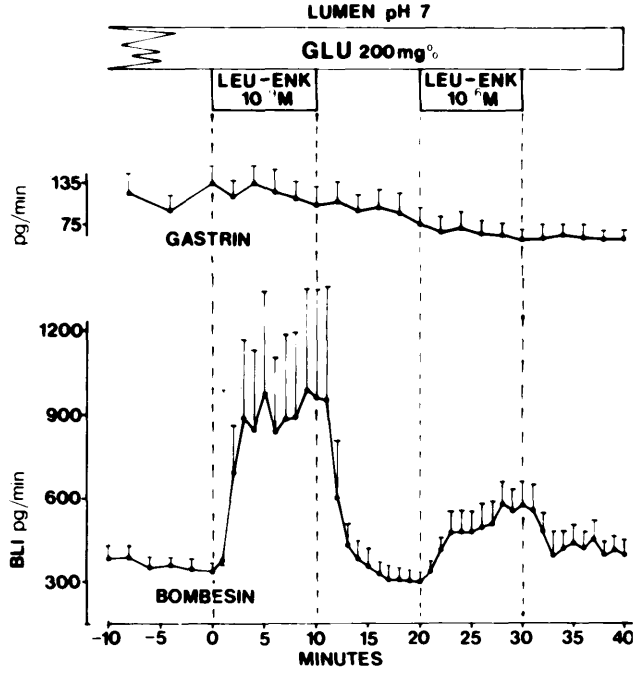


**FIGURE 8. Effect of Leu-enkephalin (LEU-ENK) infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 200 mg/dl from perfused rat stomachs (mean ± SE, *N* = 6).**

bations of glucose concentrations per se have no direct effect on gastric G-cell functions. The reduction in gastrin levels after intravenous glucose[22] is more likely to be the result of glucose-induced reduction of vagal nerve activity at the central nervous system level.[23]

In contrast to gastrin, the release of the putative peptidergic neurotransmitter bombesin is influenced substantially by alterations of glucose levels.

The effect of glucose depends on the stimulus employed. Bombesin secretion in response to cholinergic stimulation is attenuated by hypo- or hyperglycemia, whereas the response to Leu-enkephalin and VIP, two other putative peptidergic neurotransmitters of the intrinsic nervous system, is augmented during hyperglycemia. This demonstrates that acute changes in glucose levels can affect not only the function of the central nervous system, but also that of the peripheral autonomic nervous system of the stomach. Because peptidergic neurotransmitters such as bombesin, VIP, and enkephalins are of potential importance for the regulation of gastric motility and emptying,[7,25,26] it could be speculated that these findings have some implication for alterations of gastric emptying in patients with diabetes mellitus without diabetic autonomic neuropathy.[27]

The hypothesized functional linkage between bombesin and gastrin[18] is not supported by our experiments. This is not necessarily an effect of variations in glucose levels because previous studies have already demonstrated that these two peptides seem to be released rather independently. Thus, at low intragastric pH, VIP, PHI, and GRF stimulate bombesin but not gastrin secretion.[13] In the presence of histamine $H_2$-receptor antagonists, acetylcholine stimulates gastrin but not bombesin release,[12] and during endogenous prostaglandin deficiency, bombesin secretion is augmented substantially and gastrin remains unaffected.[14]

Changes of BLI in the portal venous effluent during bombesin-induced stimulation of gastrin secretion are rather low compared with the changes observed during stimulation of endogenous BLI secretion. This suggests that the amount of endogenously released bombesin should result in concentrations that are high enough to stimulate gastrin secretion.

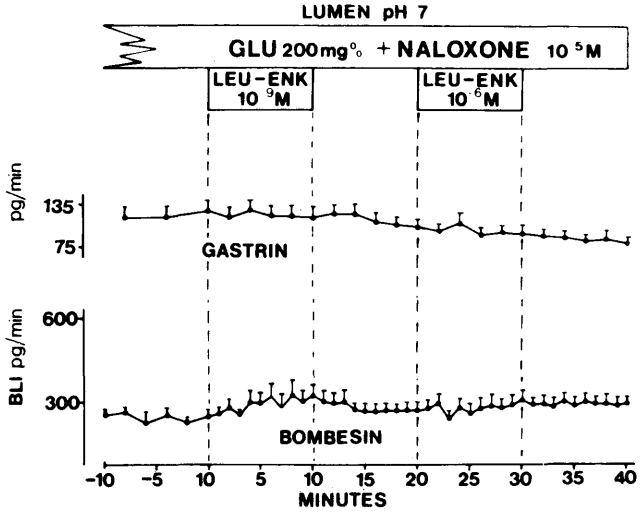


**FIGURE 9. Effect of Leu-enkephalin (LEU-ENK) infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during concomitant infusion of opiate-receptor antagonist naloxone and perfusate glucose concentration of 200 mg/dl from perfused rat stomachs (mean ± SE, *N* = 6).**

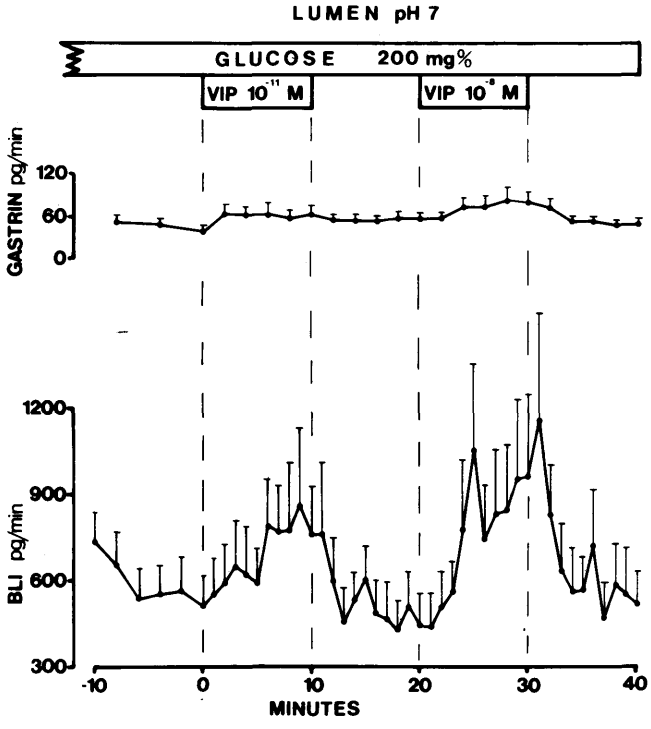


**FIGURE 10. Effect of vasoactive intestinal peptide (VIP) infusion on secretion of bombesin-like immunoreactivity (BLI) and gastrin during perfusate glucose concentration of 200 mg/dl from perfused rat stomachs (mean ± SE, *N* = 8).**

Somatostatin is a potent inhibitor of gastrin secretion. This raises the possibility that the lack of a gastrin response during a substantial augmentation of BLI secretion may be due to an increase of somatostatin secretion. Because the gastric D cell is more sensitive to infused bombesin than is the G cell,[5] it may be that endogenously released bombesin stimulates primarily somatostatin release that in turn may restrain gastrin secretion. However, measurements of somatostatin secretion in these experiments have shown that alterations in glucose levels do not change basal as well as cholinergically inhibited somatostatin release.[24] Similarly, VIP-induced stimulation of somatostatin release is abolished by elevated glucose levels.[28] Thus, somatostatin can be excluded as a factor responsible for the dissociation of BLI and gastrin secretion, and other as yet unidentified mechanisms have to be considered.

All these findings suggest that bombesin may contribute to gastrin release under certain conditions. However, there is considerable independent regulation of the secretion of these two peptides that might provide the basis for an effect of bombesin, for example, on gastric motility without having a gastrin-mediated augmentation of gastric acid secretion.

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## REFERENCES

[1] Anastasi, A., Erspamer, V., and Bucci, M.: Isolation and structure of bombesin and alytesin, two analogous active peptides from the skin of the European amphibians, *Bombina* and *Alytes*. Experientia 1971; 27:166–67.

[2] McDonald, T. J., Jornvall, H., Nilsson, G., Vague, M., Ghatei, M., Bloom, S. R., and Mutt, V.: Characterization of a gastrin releasing peptide from porcine nonantral gastric tissue. Biochem. Biophys. Res. Commun. 1979; 90:227–33.

[3] Bertaccini, G., Erspamer, V., Melchiorri, P., and Sopranzi, N.: Gastrin release by bombesin in the dog. Br. J. Pharmacol. 1974; 52:219–25.

[4] Chiba, T., Taminato, T., Kadowaki, S., Inoue, Y., Mori, K., Seino, Y., Abe, H., Chirhara, K., Matsukura, S., Fujita, T., and Goto, Y.: Effects of various gastrointestinal peptides on gastric somatostatin release. Endocrinology 1980; 106:145–49.

[5] Martindale, R., Kauffman, G. C., Levin, S., Walsh, J. H., and Yamada, T.: Differential regulation of gastrin and somatostatin secretion from isolated perfused rat stomachs. Gastroenterology 1982; 83:240–44.

[6] Bertaccini, G., Erspamer, V., and Impicciatore, M.: The actions of bombesin on gastric secretion of the dog and rat. Br. J. Pharmacol. 1973; 49:437–44.

[7] Scarpignato, C., Micali, B., Vitulo, F., Zimbavo, G., and Bertaccini, G.: Inhibition of gastric emptying by bombesin in man. Digestion 1982; 23:128–31.

[8] Erspamer, V., and Melchiorri, P.: Actions of bombesin on secretions and motility of the gastrointestinal tract. *In* Gastrointestinal Hormones. Thompson, J. C., Ed. Austin, Univ. of Texas Press, 1975:575–89.

[9] Polak, J. M., Hobbs, R., Bloom, S. R., Solcia, E., and Pearse, A. G. E.: Distribution of a bombesin-like peptide in human gastrointestinal tract. Lancet 1976; 2:1109–10.

[10] Dockray, G. J., Vaillant, C., and Walsh, J. H.: The neuronal origin of bombesin-like immunoreactivity in the rat gastrointestinal tract. Neuroscience 1979; 4:1561–68.

[11] Schusdziarra, V., Bender, H., and Pfeiffer, E. F.: Release of bombesin-like immunoreactivity from the isolated perfused rat stomach. Regul. Pept. 1983; 7:21–29.

[12] Schusdziarra, V., Bender, H., Pfeffer, A., and Pfeiffer, E. F.: Modulation of acetylcholine-induced secretion of gastric bombesin-like immunoreactivity by cholinergic and histamine $H_2$-receptors, somatostatin and intragastric pH. Regul. Pept. 1984; 8:189–98.

[13] Schusdziarra, V., Schmid, R., Bender, H., Rivier, J., Vale, W., and Pfeiffer, E. F.: Effect of VIP, PHI and GRF on the release of gastric bombesin-like immunoreactivity. Dig. Dis. Sci. 1984; 29 (Suppl.):765.

[14] Schusdziarra, V., Bender, H., Pfeffer, A., Schmid, R., and Pfeiffer, E. F.: Modulation of acetylcholine-induced release of gastric bombesin-like immunoreactivity. Dig. Dis. Sci. 1984; 29 (Suppl.):775.

[15] McIntosh, C. H. S., Pederson, R. A., Koop, H., and Brown, J. C.: Gastric inhibitory polypeptide stimulated secretion of somatostatin-like immunoreactivity from the stomach: inhibition of acetylcholine or vagal stimulation. Can. J. Physiol. Pharmacol. 1981; 59:468–72.

[16] Brown, M., Allen, R., Villarreal, J., Rivier, J., and Vale, W.: Bombesin-like activity: radioimmunologic assessment in biological tissues. Life Sci. 1978; 23:2721–28.

[17] Yalow, R. S., and Berson, S. A.: Radioimmunoassay of gastrin. Gastroenterology 1970; 58:1–14.

[18] Saffouri, B., Weir, G. V., Bitar, K. N., and Kakhlouf, G. M.: Gastrin and somatostatin secretion by perfused rat stomach. Functional linkage of antral peptides. Am. J. Physiol. 1980; 238:495–501.

[19] Aylett, P.: Gastric emptying and change of blood glucose level as affected by glucagon and insulin. Clin. Sci. (Lond.) 1962; 22:171–79.

[20] Moore, J. G.: Gastric acid suppression by intravenous solutions. Gastroenterology 1973; 64:1106–12.

[21] Solomon, S. P., and Spiro, H. M.: The effects of glucagon and glucose on the human stomach. Am. J. Dig. Dis. 1959; 4:775–81.

[22] Byrnes, D. J., Coleman, M. J., and Lazarus, L.: Radioimmunoassay of serum gastrin in patients with peptic ulceration using antiserum against pentagastrin. *In* Gastrointestinal Hormones. Demling, L., Ed. Stuttgart, FRG, Thieme, 1972:7–18.

[23] Hirano, T., and Niijima, A.: Effects of 2-deoxy-D-glucose, glucose and insulin on efferent activity in gastric vagus nerve. Experientia 1980; 36:1197–98.

[24] Schusdziarra, V., and Schmid, R.: Physiological and pathophysiological aspects of somatostatin. In press. Scand. J. Gastroenterol.

[25] Edin, R., Lundberg, J., Terenius, L., Dahlström, A., Hökfelt, T., Kewenter, J., and Ahlman, H.: Evidence for vagal enkephalinergic neural control of the feline pylorus and stomach. Gastroenterology 1980; 78:492–97.

[26] Said, S. I.: Vasoactive intestinal peptide. *In* Gastrointestinal Hormones. Thompson, J. C., Ed. Austin, Univ. of Texas Press, 1975:591–97.

[27] Campbell, I. W., Heading, R. C., Tothill, P., Buist, T. A. S., Ewing, D. J., and Clarke, B. F.: Gastric emptying in diabetic autonomic neuropathy. Gut 1978; 18:462–67.

[28] Schusdziarra, V., Schmid, R., and Eberl, T.: Peptidergic stimulation of gastric somatostatin release is modulated by insulin and glucose. Acta Endocrinol. Suppl. 1986; 274:30.