Bombesin-Induced Gastroprotection

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Abstract: Bombesin is an endogenous gut peptide that is prominent in the stomach. In addition to its effects on modulating acid and gut peptide secretion, recent evidence indicates that bombesin is a potent gastroprotective agent. This review article examines the ability of bombesin to prevent gastric injury. Its protective actions appear to be mediated primarily via the release of endogenous gastrin, as gastroprotection is negated by blockade of gastrin receptors. Bombesin-induced gastroprotection and gastrin release are modified by somatostatin. Immunoneutralization of endogenous somatostatin increases the ability of bombesin to prevent gastric injury by increasing gastrin release. In mechanistic studies, ablation of capsaicin-sensitive afferent neurons abolishes bombesin-induced gastroprotection while cyclo-oxygenase inhibition partially reverses this effect. Nitric oxide synthase inhibition also negates bombesin-induced gastroprotection as well as the ability of bombesin to increase gastric mucosal blood flow. Taken together, the available evidence indicates that bombesin causes release of endogenous gastrin that activates sensory neurons located in the gastric mucosa. Activation of sensory neurons causes increased production of nitric oxide through activation of constitutive nitric oxide synthase, which leads to a resultant increase in gastric mucosal blood flow and renders the stomach less susceptible to damage from luminal irritants.

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Bombesin was first discovered in 1970 in extracts taken from the skin of two European amphibians, *Bombina bombina* and *Bombina variegata*.[1] This 14-amino acid peptide was discovered to have a variety of pharmacologic effects in mammals, including the stimulation of both gastrin and cholecystokinin (CCK) release within the gastrointestinal tract.[2] Bombesin was later noted to have a mammalian counterpart that was named gastrin-releasing peptide (GRP).[3] Bombesin or GRP has since been cloned and is present in almost every species. Bombesin staining immunoreactivity has been detected throughout the digestive tract but is particularly prominent in both the acid- and the gastrin-secreting portions of the stomach.[4,5] In the stomach, bombesin-containing neurons modulate acid secretion as well as the secretion of gastrin and somatostatin, which are functionally linked in the antrum.[6–8] Interestingly, bombesin has recently been shown to increase the resistance of the gastric mucosa to injury.[9,10] Consequently, this article reviews the ability of bombesin to act as a gastroprotective agent and examine possible gastroprotective mechanisms through its interaction with other gut peptides.

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GUT PEPTIDES

Gastrin and CCK are endogenous gut peptides that participate in a variety of physiologic functions within the gastrointestinal tract.[11] In addition to their other well-known effects, both gastrin and CCK have been shown to prevent gastric injury from luminal irritants when given exogenously in physiologic doses.[9,11–14] The protective actions of gastrin and CCK are negated by administration of type B and type A CCK receptor antagonists, respectively.[13–16] Because these receptor antagonists are highly selective in their effects, they provide powerful investigational tools to study the effects of exogenous, as well as endogenous, gastrin and CCK in a variety of biologic matrices.[15,16]

As previously mentioned, bombesin prevents gastric injury when given exogenously and is a potent stimulus for gastrin as well as CCK release.[9,10,17] Thus, it was logical to hypothesize that the ability of bombesin to prevent gastric injury was linked to the release of endogenous gastrin or CCK. As a result, studies were undertaken in a conscious rat model of gastric injury to examine the role of endogenous gastrin and CCK in bombesin-induced gastroprotection by using the selective type A and type B CCK receptor antagonists.

Bombesin was found to dose-dependently prevent acidified ethanol-induced gastric injury according to macroscopic and morphologic criteria.[10] Administration of the type B CCK receptor antagonist L-365,260 was able to almost completely abolish bombesin-induced gastroprotection as well as exogenous gastrin-17-induced gastroprotection, as shown in Figure 1. In contrast, the type A CCK receptor antagonist MK-329 failed to reverse or significantly diminish the pro-

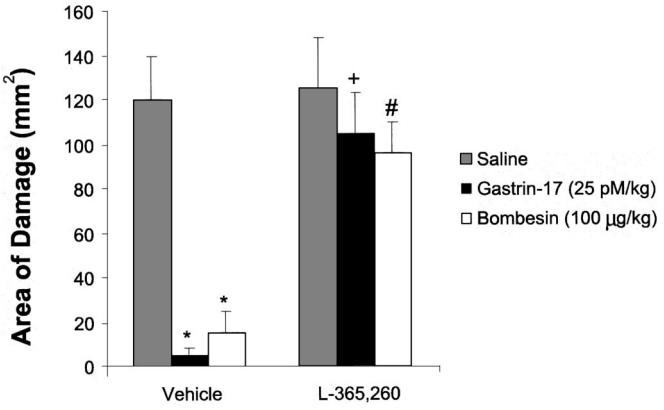

FIGURE 1. Effect of intraperitoneal type B CCK/gastrin receptor blockade (L-365,260) given 30 minutes before a 30-minute subcutaneous pretreatment with saline or bombesin (100 μg/kg) or a 10-minute intravenous treatment with gastrin-17 (25 pmol/kg) on macroscopic gastric injury from acidified ethanol; expressed as mean ± standard error of mean, n ≥ 5 for all groups. *$P < 0.05$ versus saline counterpart. +$P < 0.05$ versus vehicle/gastrin. #$P < 0.05$ versus vehicle/bombesin.

tective actions of bombesin but did negate CCK-induced gastroprotection (Table 1). Taken together, the receptor antagonist studies suggested that bombesin-induced gastroprotection is mediated primarily via the release of endogenous gastrin.[10]

More recent studies have demonstrated both endogenous and exogenous bombesin have a protective effect on intestinal microcirculation during ischemia-reperfusion injury in rats.[18] In addition, bombesin has been shown to improve maintenance of gut mucosal integrity after severe burn by decreasing burn-induced gut mucosal atrophy and epithelial cell apoptosis.[19,20] These studies demonstrate that bombesin may play a role in the intrinsic gastric mucosal defense system against a variety of luminal irritants.

Because endogenous somatostatin exerts a tonic inhibitory effect on gastrin release,[21] and because bombesin-induced gastrin released is enhanced in the presence of somatostatin monoclonal antibody,[22] additional studies were undertaken to examine what effect immunoneutralization of endogenous somatostatin had on both bombesin-induced gastroprotection and gastrin release. It was hypothesized that if the protective actions of bombesin are dependent upon release of gastrin, then bombesin-induced gastroprotection and gastrin release should be augmented in the presence of somatostatin monoclonal antibody. This study clearly demonstrated that low-dose bombesin (10 μg/kg) had minimal, if any, gastroprotective actions and resulted in an insignificant increase in gastrin release.[10] However, after somatostatin antibody, this same dose of bombesin resulted in significant gastroprotection and a more than 2-fold increase in serum gastrin levels (Table 2). These data indicate that bombesin-induced gastroprotection involves release of endogenous gastrin and that both the gastroprotective effects, as well as the release of endogenous gastrin, are modified by somatostatin. Under control conditions, endogenous somatostatin exerts a restraint on gastrin release such that low-dose bombesin is unable to prevent gastric injury from luminal irritants. However, when the tonic inhibitory restraint of somatostatin is removed, bombesin is able to maximally stimulate gastrin release and, as a result, even low doses of bombesin are able to prevent gastric injury.[10]

PROSTAGLANDINS AND SENSORY NEURONS

Sensory neurons and endogenous prostaglandins play an important role in gastric mucosal defense.[23,24] The activation of sensory neurons in the gastric mucosa has been

TABLE 1. Effect of Type A CCK Receptor Blockade on Bombesin- and CCK-Induced Gastroprotection From Acidified Ethanol in the Rat

Pretreatment	Area of Damage (mm^2)
Vehicle/saline	120 ± 18
Vehicle/CCK	7 ± 4*
Vehicle/bombesin	14 ± 8*
MK-329/saline	134 ± 22
MK-329/CCK	98 ± 14†
MK-329/bombesin	38 ± 15*

CCK (5 nmol/kg) was given intravenously 10 minutes prior to exposure to orogastric acidified ethanol (150 mmol/L hydrochloric acid, 50% ethanol) for 5 minutes. Bombesin (100 μg/kg) was given subcutaneously 30 minutes prior to acidified ethanol. MK-329 (1 mg/kg) was given intraperitoneally 30 minutes before saline, CCK, or bombesin.

*$P < 0.05$ vs. saline counterpart.

†$P < 0.05$ vs. vehicle/CCK.

TABLE 2. Effect of Somatostatin Antibody on Bombesin-Induced Gastrin Release and Gastroprotection From Acidified Ethanol in the Rat

Pretreatment	Serum Gastrin (pmol/L)	Area of Damage (mm^2)
Control antibody/saline	5.1 ± 0.28	125 ± 25
Control antibody/bombesin	8.0 ± 0.36	100 ± 20
Somatostatin antibody/saline	10.1 ± 0.40*	75 ± 15*
Somatostatin antibody/bombesin	17.1 ± 0.48†	30 ± 10†

Control and somatostatin monoclonal antibodies (2 mg) were given intraperitoneally 36 hours before subcutaneous saline or bombesin (10 μg/kg) pretreatment, followed by orogastric acidified ethanol after 30 minutes.

*$P = 0.05$ vs. control antibody/saline.

†$P = 0.05$ vs. control antibody/bombesin.

proposed to play a pivotal role in gastric mucosal defense through release of vasoactive neuropeptides with a resultant increase in gastric mucosal blood flow.[25] Similarly, prostaglandins have been shown to prevent gastric injury and increase gastric mucosal blood flow.[26] Because bombesin causes release of endogenous gastrin, which in turn increases gastric mucosal blood flow,[27] the role of sensory neurons and prostaglandins as potential mediators of bombesin-induced gastroprotection was assessed. The role of capsaicin-sensitive afferent neurons was studied by functionally ablating these neurons with the selective neurotoxin capsaicin given in a desensitizing dose 2 weeks prior to experimentation. The role of prostaglandins was assessed by utilizing the cyclo-oxygenase inhibitor indomethacin. In these studies, functional ablation of capsaicin-sensitive afferent neurons negated bombesin-induced gastroprotection. In contrast, cyclo-oxygenase inhibition with indomethacin only partially reversed the protective effects of bombesin (Table 3). These findings indicated that bombesin requires intact capsaicin-sensitive afferent neurons as well as the presence of endogenous prostaglandins to fully exert its gastroprotective actions.[28,29]

Because the gastroprotective actions of gastrin are also inhibited by capsaicin desensitization[13] and because the gastroprotective actions of bombesin are primarily mediated via release of endogenous gastrin, it seems reasonable to conclude that bombesin elicits the release of endogenous gastrin, activating sensory neurons located locally within the gastric mucosa. In comparison, the incomplete reversal of bombesin-induced gastroprotection with indomethacin suggests that, in addition to prostaglandins, other mediators are also involved in this process. One logical candidate is nitric oxide. Both nitric oxide and prostaglandins share similar effects that may be related to their ability to maintain mucosal integrity. Moreover, evidence suggests that there is an interaction between endogenous prostaglandins and nitric oxide in gastric mucosal defense.[30] Consequently, additional studies were undertaken to study the role of nitric oxide in bombesin-induced gastroprotection.

TABLE 3. Effects of Capsaicin and Indomethacin on Bombesin-Induced Gastroprotection From Acidified Ethanol in the Rat

Pretreatment	Area of Damage (mm^2)
Vehicle/saline	115 ± 15
Vehicle/bombesin	25 ± 10*
Capsaicin/saline	138 ± 20
Capsaicin/bombesin	110 ± 7†
Indomethacin/saline	135 ± 15
Indomethacin/bombesin	70 ± 5*†

Capsaicin (125 mg/kg) was given subcutaneously 14 days prior to pretreatment with saline or bombesin, followed 30 minutes later by orogastric acidified ethanol. Indomethacin (5 mg/kg) was given intraperitoneally 30 minutes before pretreatment with saline or bombesin, followed by acidified ethanol.

*$P < 0.05$ vs. saline counterpart.

†$P < 0.05$ vs. vehicle/bombesin.

NITRIC OXIDE AND BLOOD FLOW

The importance of nitric oxide in mucosal defense has been illustrated by numerous investigators. It is a potent vasodilator and not surprisingly is involved with regulation of the gastric mucosal microcirculation.[31] Nitric oxide, whether it be given exogenously or produced endogenously, has been shown to protect the gastric mucosa against injury from luminal irritants.[32,33] It is produced by both constitutive and inducible isoforms of nitric oxide synthase (NOS). Most evidence suggests that the constitutive isoforms of NOS (endothelial and neural) primarily function to maintain homeostasis and have protective roles in the gastric mucosa.[30,34–36] However, recent evidence suggests that the inducible isoforms of NOS may play a protective role in the stomach under certain conditions.[37] Interestingly, there are considerable data indicating that the protective actions of sensory neurons in the gastric mucosa are mediated via increased production of nitric oxide.[38,39] Because bombesin-induced gastroprotection is mediated primarily via release of endogenous gastrin and subsequent activation of capsaicin-sensitive sensory neurons, it was hypothesized that nitric oxide likely plays a role in mediating bombesin-induced gastroprotection. It was further hypothesized that bombesin-induced gastroprotection requires functioning constitutive neural or endothelial isoforms of NOS.

To study the role of NOS in bombesin-induced gastroprotection, studies were undertaken with the nonselective NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) as well as the selective inducible NOS inhibitor aminoguanidine. In these studies, L-NAME, but not aminoguanidine, reversed the gastroprotective actions of bombesin (Table 4) and bombesin-induced increases in gastric mucosal blood flow (Fig. 2). The effects of L-NAME on bombesin-induced gastroprotection as well as gastric mucosal blood flow were reversed by L- but not D-arginine. These studies suggested that bombesin-induced gastroprotection and gastric hyperemia are mediated via increased release of nitric oxide produced from the constitutive isoforms of NOS as opposed to the inducible isoform because aminoguanidine failed to reverse or attenuate the effects of bombesin. When the role of NOS isoforms was further examined, with Western immunoblot analysis of gastric NOS isoforms, bombesin increased endothelial NOS immunoreactivity but not neural or inducible NOS immunoreactivity. These latter findings suggested that it is nitric oxide produced from the endothelial isoform of NOS that participates in the ability of bombesin to increase

TABLE 4. Effects of Nitric Oxide Synthase Inhibition on Bombesin-Induced Gastroprotection From Acidified Ethanol in the Rat

Pretreatment	Area of Damage (mm^2)
Saline/saline	118 ± 22
Saline/bombesin	21 ± 5*
Aminoguanidine/saline	115 ± 25
Aminoguanidine/bombesin	17 ± 4*
L-NAME/saline	147 ± 21†
L-NAME/bombesin	126 ± 23‡

Bombesin (100 μg/kg) was given subcutaneously 30 minutes prior to treatment with orogastric acidified ethanol. Aminoguanidine (45 mg/kg) was given intraperitoneally 30 minutes before acidified ethanol. L-NAME (10 mg/kg) was given subcutaneously 30 minutes before acidified ethanol.

*$P < 0.05$ vs. saline counterpart.

†$P < 0.05$ vs. saline/saline.

‡$P < 0.05$ vs. saline/bombesin.

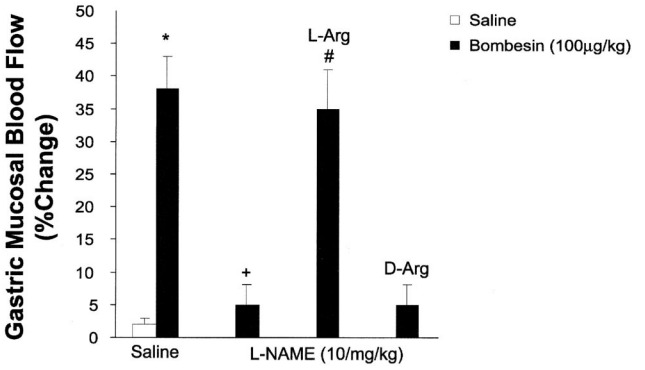

FIGURE 2. Effect of nitric oxide synthase inhibition with subcutaneous L-NAME (10 mg/kg) and the effect of L-NAME combined with intraperitoneal L-arginine (L-Arg; 300 mg/kg) or D-arginine (D-Arg; 300 mg/kg) on bombesin (100 μg/kg)-induced gastric hyperemia. Data are presented as percent change from baseline blood flow determinations and represent the mean ± SEM; n ≥ 5/group. *$P < 0.05$ versus saline counterpart. +$P < 0.05$ versus saline/bombesin. #$P < 0.05$ versus L-NAME/bombesin.

gastric mucosal blood flow and maintain the integrity of the gastric epithelium in the face of a damaging luminal insult.[40]

CONCLUSION

Bombesin, gastrin, somatostatin, sensory neurons, prostaglandins, and nitric oxide, among many substances, interact and have been implicated in mucosal defense. Interestingly, most of these peptides or mediators cause an increase in gastric mucosal blood flow. In addition to supplying nutrients and oxygen to the epithelium, the microcirculation functions to dilute or remove toxic substances that diffuse into the mucosa from the gastric lumen.[41,42] Increases in blood flow also assure that those intracellular processes that underlie mucosal resistance to injury can proceed unabated.

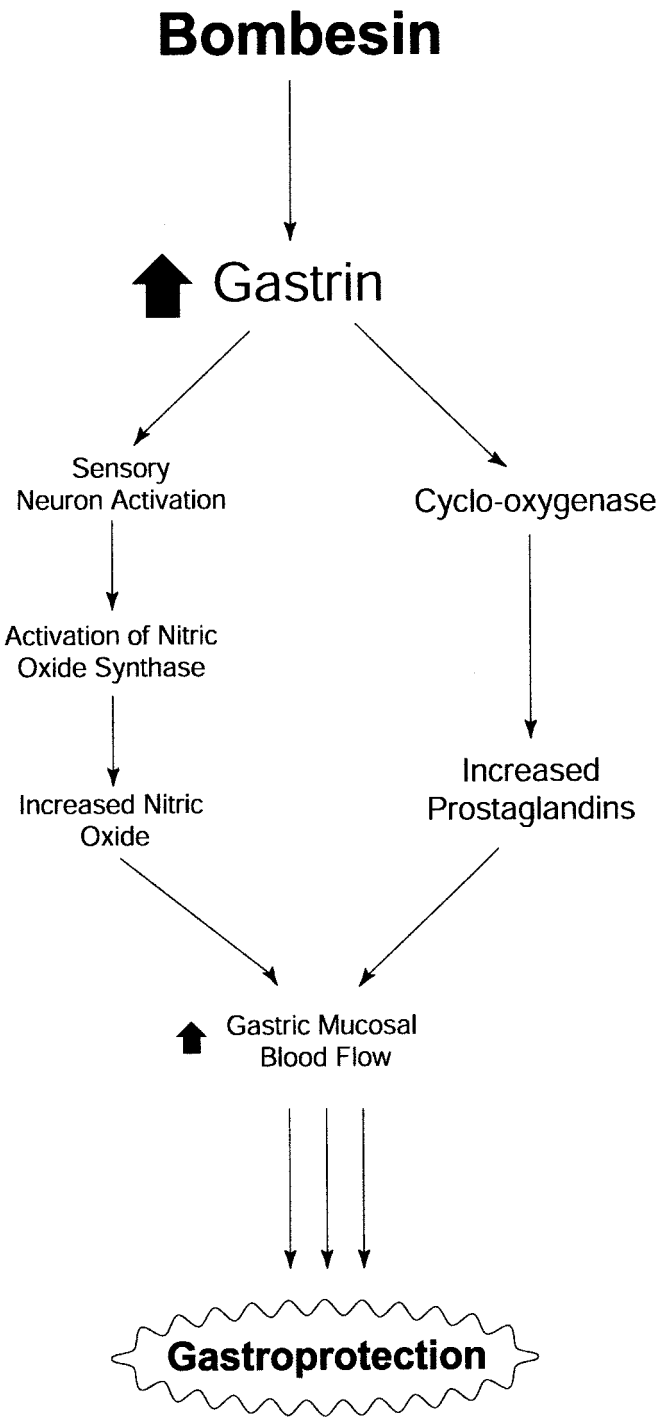

FIGURE 3. Schematic representation of mechanism(s) responsible for bombesin-induced gastroprotection.

The proposed mechanism responsible for bombesin-induced hyperemia and gastroprotection is shown schemati-

cally in Figure 3. Bombesin causes the release of endogenous gastrin, the subsequent activation of sensory neurons, and perhaps increases cyclo-oxygenase activity as well. Activation of sensory neurons in turn increases production of nitric oxide through activation of constitutive NOS isoforms, and increased cyclo-oxygenase activity leads to increased production of prostaglandins. Both nitric oxide and prostaglandins then act upon the gastric microcirculation to cause an increase in gastric mucosal blood flow. Thus, it appears that bombesin-induced gastroprotection involves the release of gut peptides that interact with sensory neurons, nitric oxide, and prostaglandins to augment gastric mucosal blood flow that enables the gastric mucosa to withstand damaging luminal insults.

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