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Neural, Hormonal, and Paracrine Regulation of Gastrin and Acid Secretion

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Physiological stimuli from inside and outside the stomach converge on gastric effector neurons that are the primary regulators of acid secretion. The effector neurons comprise cholinergic neurons and two types of non-cholinergic neurons: bombesin/GRP and VIP neurons. The neurons act directly on target cells or indirectly by regulating release of the hormone, gastrin, the stimulatory paracrine amine, histamine, and the inhibitory paracrine peptide, somatostatin.

In the antrum, cholinergic and bombesin/GRP neurons activated by intraluminal proteins stimulate gastrin secretion directly and, in the case of cholinergic neurons, indirectly by eliminating the inhibitory influence of somatostatin (disinhibition). In turn, gastrin acts on adjacent somatostatin cells to restore the secretion of somatostatin. The dual paracrine circuit activated by antral neurons determines the magnitude of gastrin secretion.

Low-level distention of the antrum activates, preferentially, VIP neurons that stimulate somatostatin secretion and thus inhibit gastrin secretion. Higher levels of distention activate predominantly cholinergic neurons that suppress antral somatostatin secretion and thus stimulate gastrin secretion.

In the fundus, cholinergic neurons activated by distention or proteins stimulate acid secretion directly and indirectly by eliminating the inhibitory influence of somatostatin. The same stimuli activate bombesin/GRP and VIP neurons that stimulate somatostatin secretion and thus attenuate acid secretion. In addition, gastrin and fundic somatostatin influence acid secretion directly and indirectly by regulating histamine release.

Acid in the lumen stimulates somatostatin secretion, which attenuates acid secretion in the fundus and gastrin secretion in the antrum.

Physiological stimuli from inside and outside the stomach converge on gastric effector neurons that are the primary regulators of gastrin secretion in the antrum and acid secretion in the fundus. The effector neurons comprise cholinergic neurons and two types of non-cholinergic neurons: bombesin/GRP and VIP neurons. In the antrum, the neurons act directly on gastrin cells and indirectly by regulating the release of the inhibitory paracrine peptide, somatostatin. In the fundus, the neurons act directly on parietal cells and indirectly by regulating the release of somatostatin and the stimulatory paracrine amine, histamine; the release of histamine is further regulated by somatostatin and by gastrin.

This review summarizes the experimental evidence on which these postulates are based and provides models illustrating the interplay between neural, hormonal, and paracrine stimuli.

Abbreviation: TTX: tetrodotoxin

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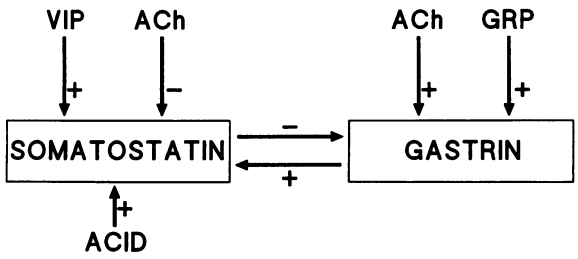

FIG. 1.

REGULATION OF GASTRIN SECRETION

Paracrine Regulation of Gastrin Secretion by Somatostatin

Evidence for the existence of a continuous inhibitory influence of antral somatostatin on gastrin secretion was first obtained in the vascularly perfused rat stomach by Saffouri et al. [1], who showed that addition of excess somatostatin antiserum to the vascular perfusate increased gastrin secretion two- to threefold (about 50 percent of maximal gastrin response) (Fig. 1). This observation has since been repeatedly confirmed in the rat and most recently in the isolated vascularly perfused pig antrum with monoclonal somatostatin antibody [2].

Muscarinic agonists stimulate gastrin secretion in part by eliminating the inhibitory influence of somatostatin [3]. Complete suppression of endogenous somatostatin, whether by immunoneutralization or with cholinergic agonists, accounts, however, for only part of the gastrin response, which implies that muscarinic agonists also stimulate gastrin cells directly to elicit a maximal response.

Other agents, for example, bombesin/GRP and the β-adrenergic agonist, isoproterenol, elicit an increase in both gastrin and somatostatin secretion [4]. The gastrin response is attenuated by the concomitant increase in somatostatin but can be augmented to maximal levels by the addition of somatostatin antiserum.

Thus, cholinergic stimulation of gastrin secretion is partly mediated by inhibition of somatostatin secretion, and optimal stimulation of gastrin secretion by an agonist requires suppression of ambient somatostatin.

Paracrine Regulation of Somatostatin Secretion by Gastrin

Recent studies have established the existence of a reciprocal paracrine pathway, whereby gastrin secretion acts to restore somatostatin secretion [5]. When bombesin/GRP is added to antral mucosal segments that retain neural and paracrine pathways, there is an increase in gastrin and somatostatin secretion. The increase in somatostatin secretion is abolished by the gastrin receptor antagonist, L365,260, and is thus mediated by gastrin. The elimination of somatostatin secretion by the gastrin antagonist leads to a twofold increase in gastrin secretion. As noted above, neutralization of somatostatin with antiserum augments twofold the gastrin response to bombesin/GRP. Thus, gastrin and somatostatin secretion in the antrum are linked by a dual paracrine feedback system (Fig. 1). One paracrine pathway stimulates gastrin secretion by suppressing somatostatin secretion; this pathway is activated pharmacologically by muscarinic agonists and physiologically by cholinergic neurons. The other paracrine pathway is activated by gastrin itself, which restores somatostatin secretion and thereby attenuates the gastrin response.

It is worth noting that there is no direct effect of bombesin/GRP on antral somatostatin cells consistent with the absence of bombesin/GRP receptors on these cells.

Neural Regulation of Gastrin Secretion

Gastrin secretion is regulated by cholinergic neurons and two types of non-cholinergic neurons: bombesin/GRP and VIP neurons (Fig. 1) [6]. Cholinergic neurons stimulate gastrin secretion directly as well as indirectly by eliminating the inhibitory influence of somatostatin. Bombesin/GRP neurons stimulate gastrin secretion directly; their effect on somatostatin is indirectly mediated by the increase in gastrin (see above). VIP neurons stimulate somatostatin secretion and thus attenuate gastrin secretion [7,8].

In the antrum, these neurons can be activated experimentally by nicotinic agonists (e.g., DMPP), or by electrical field stimulation of the antral region, and physiologically by chemical (digested protein or peptone) and mechanical (distention) stimuli.

Electrical field stimulation of the antral region of the perfused stomach elicits an increase in gastrin and decrease in somatostatin secretion [6]. Both responses are abolished by the axonal conductance blocker, tetrodotoxin (TTX). Atropine inhibits gastrin secretion by 20–30 percent, and a bombesin antiserum inhibits gastrin secretion by 60 percent. Together, atropine and bombesin antiserum inhibit gastrin secretion by 80–90 percent. The pattern of inhibition implies that activation of cholinergic and bombesin/GRP neurons accounts for virtually the entire gastrin response.

Activation of Cholinergic and Non-Cholinergic Neurons in the Antrum by Physiological Stimuli

Response to Luminal Protein When added to the lumen of the vascularly perfused stomach or to the medium bathing antral mucosal segments, peptone (0.5 percent) stimulates gastrin and inhibits somatostatin secretion [9]. The pattern of response is identical to that elicited by electrical field stimulation (Fig. 1). Both gastrin and somatostatin responses are abolished by TTX and are thus neurally mediated. Atropine partly inhibits (40–50 percent) the gastrin response and converts the decrease in somatostatin to an increase above basal levels; the pattern reflects a residual effect of bombesin/GRP neurons and implies that both cholinergic and non-cholinergic neurons mediate the response to peptone. A selective bombesin/GRP antagonist inhibits the gastrin response by 65 percent and decreases the somatostatin response further below basal levels; the pattern reflects the residual effect of cholinergic neurons. Like TTX, a combination of atropine and bombesin/GRP antagonist abolishes gastrin and somatostatin responses. Activation of cholinergic and bombesin/GRP neurons accounts for the entire gastrin response to luminal peptone. The inhibitory influence of cholinergic neurons on somatostatin secretion predominates, which permits cholinergic and bombesin/GRP neurons to elicit an optimal response from gastrin cells.

Response to Distention Distention activates cholinergic and non-cholinergic neurons [7]. Low-grade distention stimulates somatostatin and inhibits gastrin secretion. In contrast, high-grade distention inhibits somatostatin and stimulates gastrin secretion. Responses to high- and low-grade distention are abolished by TTX, implying that they are neurally mediated. Atropine has no effect on the

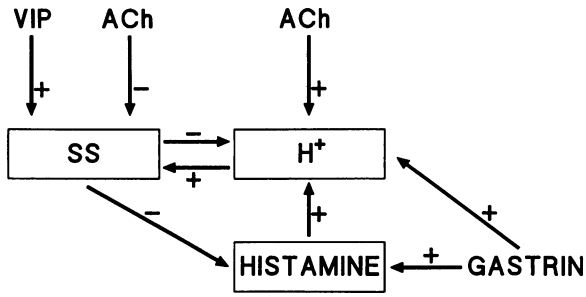

FIG. 2.

response to low-grade distention but converts the response to high-grade distention to that observed with low-grade distention (i.e., inhibition of gastrin and stimulation of somatostatin secretion). Both high- and low-grade distention are accompanied by an increase in VIP release, which is known to stimulate somatostatin secretion. A VIP antagonist (VIP10-28) abolishes the gastrin and somatostatin responses to low-grade distention. The pattern of response to distention implies that *(i)* low-grade distention activates preferentially VIP neurons that stimulate somatostatin and thus inhibit gastrin secretion; *(ii)* increasing distention leads to progressive recruitment of cholinergic neurons that cause a reversal of response to stimulation of gastrin and inhibition of somatostatin; and *(iii)* elimination of the cholinergic influence with atropine returns the response to that observed with low-grade distention.

Physiologically, the full effect of distention by a meal is exerted initially, causing activation of cholinergic neurons and stimulation of gastrin secretion. As the meal is emptied, distention decreases, leading to preferential activation of VIP neurons that stimulate somatostatin and suppress gastrin secretion. Furthermore, as the meal is emptied, its buffering effect declines, exposing somatostatin cells in the antrum and fundus to the stimulatory effect of luminal acid (see below).

REGULATION OF ACID SECRETION

Measurement of Acid Secretion in the Intact Stomach in Vitro

The isolated luminally perfused mouse stomach retains intact paracrine and intramural neural pathways and secretes acid in response to exogenous secretagogues and to activation of intramural neurons by field stimulation and by physiological stimuli (luminal protein and distention). In the absence of vascular perfusion, paracrine agents and neural transmitters are secreted into the lumen, the path of least diffusional resistance. The influence of gastrin in this luminally perfused preparation is absent.

Reciprocal Paracrine Regulation of Somatostatin and Acid Secretion

Acid secretion in response to histamine or gastrin is accompanied by somatostatin secretion. The latter is triggered by the presence of acid in the lumen and can be suppressed by neutralization of acid in the lumen or by inhibition of acid secretion with H_2-receptor antagonists (Fig. 2).

The concomitant secretion of somatostatin attenuates the acid response. Neutralization of somatostatin with somatostatin antiserum augments submaximal responses to histamine and gastrin by 90–160 percent. The inhibitory influence of somatostatin

can also be eliminated by pre-incubating the stomach with pertussis toxin, which inactivates a G protein coupled to inhibition of adenylate cyclase activity. The toxin augments the response to histamine, which acts by stimulating cAMP, but not the response to gastrin.

As in the antrum, muscarinic agonists inhibit somatostatin secretion, whereas bombesin/GRP stimulates somatostatin secretion (Fig. 2). The mechanism of action of bombesin/GRP in the fundus, however, is different: the somatostatin response to bombesin/GRP is abolished by TTX, implying that it is mediated by activation of non-cholinergic neurons, possibly VIP neurons (Fig. 2). In the antrum, as in the fundus, bombesin/GRP does not act directly on somatostatin cells. Bombesin/GRP, in effect, inhibits secretagogue-stimulated acid secretion by stimulating, albeit indirectly, somatostatin secretion.

Neural Regulation of Acid Secretion

Activation of fundic neurons by electrical field stimulation causes an increase in acid and somatostatin secretion [12] (Fig. 2). Atropine abolishes the acid response and augments the somatostatin response. A selective bombesin/GRP antagonist augments acid secretion nearly twofold and inhibits somatostatin secretion significantly below basal levels. A combination of the two antagonists, like TTX, abolishes acid and somatostatin secretion. The pattern of response implies that electrical field stimulation activates cholinergic neurons that stimulate acid secretion and inhibit somatostatin secretion, as well as bombesin/GRP neurons that stimulate somatostatin secretion. The concomitant increase in somatostatin attenuates the acid response. Elimination of the effect of somatostatin by pre-incubation with somatostatin antiserum augments acid secretion twofold, to the same extent as exposure to the bombesin/GRP antagonist. Thus, in the fundus, cholinergic neurons stimulate acid secretion directly as well as indirectly by eliminating the inhibitory influence of somatostatin, whereas non-cholinergic neurons (bombesin/GRP and VIP neurons) inhibit acid secretion, stimulating somatostatin secretion.

Activation of Cholinergic and Non-Cholinergic Neurons in the Fundus by Physiological Stimuli

Response to Luminal Proteins Perfusion of the lumen of the mouse stomach with 0.5 percent peptone stimulates acid and somatostatin secretion [13]. TTX abolishes both acid and somatostatin responses. Atropine abolishes acid secretion and augments somatostatin secretion, whereas a bombesin/GRP antagonist augments acid and inhibits somatostatin secretion. A combination of atropine and bombesin/GRP antagonist abolishes acid and somatostatin secretion. The pattern of response to luminal peptone is identical to that elicited by electrical field stimulation (Fig. 2).

Response to Distention Graded distention of the mouse stomach causes a progressive increase in acid and somatostatin secretion [14]. TTX abolishes the acid and somatostatin responses to all grades of distention. Atropine abolishes the acid response, and a bombesin/GRP antagonist abolishes the somatostatin response. Thus, distention, like intra-luminal proteins, activates cholinergic neurons that stimulate acid secretion and bombesin/GRP neurons that stimulate somatostatin secretion.

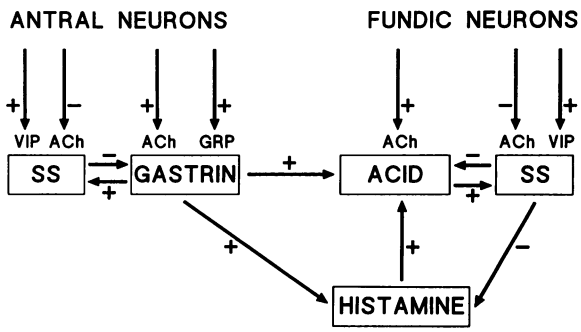

FIG. 3.

Neural and Hormonal Regulation of the Paracrine Stimulant, Histamine

Increasing evidence suggests that histamine secretion is mediated by low concentrations of gastrin within the range observed after meals [15] (Fig. 2). While most of the evidence is based on studies in ruminants, recent studies suggest that a subpopulation of histamine cells in canine mucosa is sensitive to both gastrin and somatostatin [16]. The sensitivity to somatostatin raises the possibility that secretion of histamine could be modulated by intramural neurons, such that cholinergic neurons augment histamine secretion by eliminating the paracrine influence of somatostatin, whereas non-cholinergic neurons inhibit histamine secretion by stimulating somatostatin secretion (Fig. 2). Thus, there may exist a serial paracrine mechanism, involving somatostatin and histamine, that can regulate the secretion of histamine and thus of acid secretion. The mechanism acts in concert with the paracrine mechanism involving a reciprocal influence of acid and somatostatin secretion. Both mechanisms are regulated by intramural neurons.

Sensory Pathways Mediating the Effects of Luminal Proteins and Distention

In the antrum and fundus, peptone and distention activate sensory pathways coupled to intramural effector cholinergic and non-cholinergic neurons [17,18]. Both acid and gastrin responses are abolished by pre-treatment of the isolated stomach with the sensory neurotoxin, capsaicin. This fact implies that in the acutely isolated stomach, an intramural sensory pathway is retained that can be inactivated by capsaicin. This pathway could consist of *(i)* bipolar sensory neurons coupled to effector neurons or *(ii)* neurons with extrinsic cell bodies that project axons to effector neurons (i.e., axon reflex). These two possibilities can be distinguished by extrinsically denervating the stomach (i.e., vagotomy and celiac ganglionectomy) two weeks before isolation, so as to allow axonal projections of extrinsic sensory neurons to degenerate. When this procedure is done, gastrin and acid responses to peptone and distention are abolished [17,18]. The effector cholinergic and non-cholinergic neurons remain intact and can be activated by DMPP or electrical field stimulation. Thus, responses to intraluminal stimuli appear to be mediated by axon reflexes.

CONCLUSION

Figure 3 incorporates Figs. 1 and 2 and illustrates the interplay of neural, hormonal, and paracrine pathways in the antrum and fundus of the stomach. Physiological stimuli originating in the central nervous system or within the lumen of

the stomach (proteins and distention) are relayed to intramural cholinergic and non-cholinergic (mainly VIP and bombesin/GRP) neurons that regulate the secretion of hormonal (gastrin) and paracrine (somatostatin and histamine) agents. The following aspects should be noted:

1. Cholinergic neurons act directly on target cells (gastrin cells in the antrum and parietal cells in the fundus); they also act indirectly by suppressing the inhibitory influence of somatostatin.

2. The inhibitory influence of somatostatin in the fundus is restored by the secretion of acid into the lumen. This mechanism also operates to restore somatostatin secretion in the antrum (not shown in Fig. 3); in the antrum, moreover, gastrin acts in a reciprocal fashion to restore somatostatin secretion. Both these mechanisms are typical feedback mechanisms.

3. VIP neurons act preferentially on somatostatin cells and are activated by low-grade distention in the antrum; high-grade distention activates both VIP and cholinergic neurons (see text for details). Thus, gastrin secretion is inhibited with low- and stimulated with high-grade distention.

4. At physiological concentrations, gastrin stimulates parietal cells directly, as well as indirectly, by enhancing the secretion of histamine. At these concentrations, gastrin probably has no influence on somatostatin cells. Its effect on these cells in the antrum is paracrine and thus exerted at higher ambient concentrations.

5. In the fundus, cholinergic neurons stimulate acid secretion directly, as well as indirectly, by suppressing somatostatin secretion. The latter enhances acid secretion via two mechanisms: by eliminating a direct inhibitory influence on the parietal cell as well as an inhibitory influence on the paracrine stimulatory histamine cell.

6. Bombesin/GRP neurons stimulate gastrin in the antrum but inhibit acid in the fundus. In the fundus, bombesin/GRP neurons activate other neurons (probably VIP neurons) that stimulate somatostatin secretion. Thus, in both regions of the stomach, bombesin/GRP neurons lead to somatostatin secretion. The mechanisms in the antrum and the fundus differ (see text for details).

7. Axonal projections of sensory neurons that relay intraluminal stimuli (peptone, distention) to effector cholinergic and non-cholinergic neurons are not shown in Figs. 1–3.

A note on reading Figs. 1–3: (+) = stimulation; (−) = inhibition. Thus, two (−) arrows in series in a pathway reflect suppression of an inhibitory influence. Two (+) arrows in series reflect augmentation of a stimulatory influence.

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