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Vagal Regulation of Acid Secretion and Gastrin Release

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The vagus nerve plays a central role in the regulation of gastric acid secretion and gastrin release. The current understanding of the mechanisms involved in vagal regulation of acid secretion and gastrin release is reviewed. Thyrotropin-releasing hormone from the medullary raphe nuclei appears to be the central excitatory mediator of vagal action in the dorsal motor nucleus. Vagal stimulation of the parietal cell occurs through M3 cholinergic receptors and via the release of histamine and gastrin from enterochromaffin-like cells and G-cells, respectively. Somatostatin exerts a tonic basal inhibition of both the parietal cell and the G-cell. Vagal stimulation suppresses somatostatin release from delta cells, thereby "disinhibiting" these cells.

INTRODUCTION

The vagus nerves play a central role in the regulation of gastric acid secretion and gastrin release. The cornerstone of modern surgery for peptic ulcer disease is vagotomy. Lester Dragstedt, more than any other surgeon, understood both the physiologic and surgical significance of the vagus. Indeed, the introduction of vagotomy in the treatment of peptic ulcer by Dragstedt in 1943 [1] provided the major impetus for the vigorous exploration in the last 50 years of vagal mechanisms that regulate motor and secretory functions of the upper gastrointestinal tract.

Recent advances in immunocytochemistry have defined the nature of the neurons in the vagus and in the enteric nervous system (ENS)[b] as well as the structure of the endocrine cells in the stomach. The advances in cell and molecular biology have improved significantly our understanding of the regulation of acid secretion and gastrin release and the role of the vagus in these processes. The importance of the parietal cell and the antral G-cell has long been understood. In the last 15 years, the crucial role of somatostatin in modulating both parietal cell and G-cell functions has been established. More recently, the enterochromaffin-like (ECL) cell has emerged as an important cell in the oxyntic mucosa in the regulation of acid secretion. The ECL cell releases histamine in response to vagal stimulation and to gastrin, thus mediating, at least in part, the action of the vagus and gastrin on acid secretion.

This paper will review the current understanding of the mechanisms involved in vagal regulation of acid secretion and gastrin release.

VAGAL STIMULATION OF ACID SECRETION

Vagal action in acid secretion is important not only in the cephalic phase of acid secretion but also in the gastric phase in which vago-vagal reflexes mediate acid response

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[b]*Abbreviations:* ENS, enteric nervous system; ECL, enterochromaffin-like; TRH, thyrotropin-releasing hormone; DMN, dorsal motor nucleus; GRP, gastrin-releasing peptide; VIP, vasoactive intestinal polypeptide.

to distention. As much as 50 percent of the maximal acid response to a meal may be due to the cephalic phase [2]. The precise mechanisms for the central activation of the dorsal motor nucleus of the vagus (DMN) are poorly understood. Better definition of the peripheral vagal mechanisms has been recently possible due to the availability of specific inhibitors and better in-vitro preparations.

CENTRAL ACTIVATION OF THE DMN

The cephalic phase of acid secretion is presumed to result from the activation of medullary nuclei. (Figure 1) Convincing evidence is accumulating that activation of the DMN is accomplished by the excitatory action of thyrotropin-releasing hormone (TRH) as well as serotonin containing neurons that project from the raphe pallidus and obscurus to the DMN [3]. Two experiments give evidence to support the role of TRH on the DMN: a) In cats, microinjection of small doses of TRH into the DMN causes significant stimulation of acid secretion and contractions of the antrum and corpus [4] and b) the injection of specific TRH antibody into the cerebrospinal fluid inhibits acid secretion in pylorus-ligated rats [5].

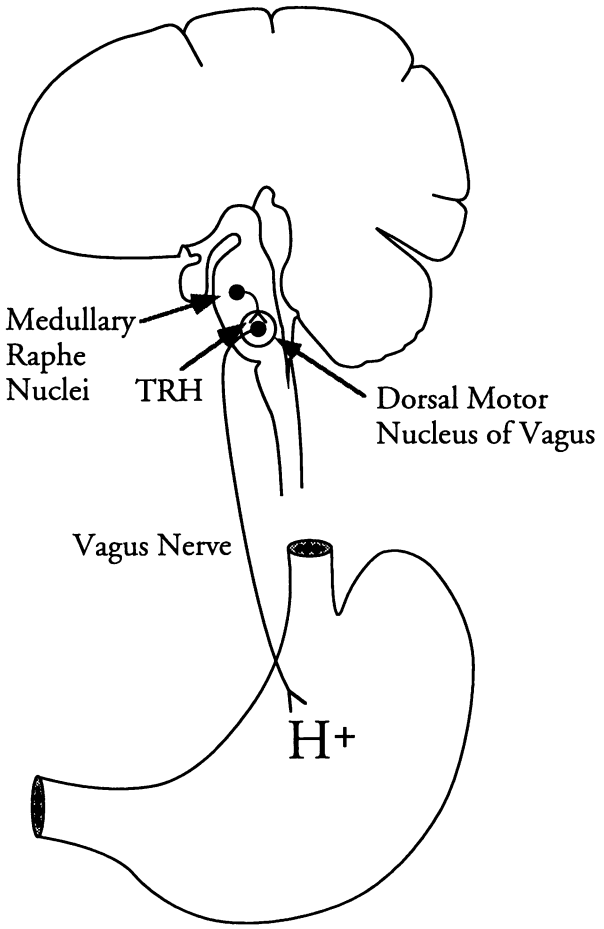

Figure 1. Thyrotropin-releasing hormone (TRH) appears to be the central excitatory mediator of vagal action. Neurons with their cell bodies in the raphe pallidus and obscurus (medullary raphe nuclei) release TRH in the dorsal motor nucleus leading to vagal action.

PERIPHERAL MECHANISMS OF VAGAL ACTION

Vagal stimulation of acid secretion within the stomach has at least four components: a) direct receptor-mediated action of acetylcholine on the parietal cell; b) indirect action through cholinergic release of histamine from ECL cells; c) removal of tonic inhibition by somatostatin due to cholinergic suppression of somatostatin release from fundic delta cells; and d) indirect action through the release of gastrin from antral G-cells via gastrin-releasing peptide (GRP) neurons.

Direct Vagal Stimulation of the Parietal cell [6]

The parietal cell contains M3 receptors for acetylcholine. Vagal stimulation releases acetylcholine from post-ganglionic cholinergic neurons adjacent to the parietal cell. When acetylcholine binds to its receptor, phospholipase C activated rise in cytosolic calcium results in the elaboration of H^+/K^+-ATPase in the parietal cell, and secretion of H^+.

Indirect Action through the Release of Histamine

Recent studies have shown that vagal stimulation and the administration of cholinergic agents release histamine from ECL cells [7]. Histamine, of course, is a crucial stimulant of acid secretion through receptor-mediated increase in adenylate cyclase. The extent to which this histamine pathway is important in vagal stimulation of acid secretion is unknown. Some have cited the inhibition of vagally-stimulated acid secretion by H_2-receptor antagonists as additional evidence of the important role histamine plays in vagally-mediated acid secretion [8]. However, the inhibitory effect of H_2-receptor blockers on the acid response to vagal stimulation could represent inhibition of post-receptor interactions.

It is now thought that the physiologically relevant pool of histamine that lies within diffusion distance of the parietal cell is that contained within ECL cells [9]. The ECL cells make up approximately 65 percent and 35 percent of the entire population of the endocrine cells of the oxyntic mucosa of the rat and man, respectively. Unlike mast cells, which are predominantly located in the lamina propria, ECL cells are rich in histidine decarboxylase, the enzyme responsible for histamine synthesis. Recently, the vagus nerve has been shown to exert a regulatory influence on the metabolism of histamine in the human oxyntic mucosa [10].

Vagal Action on Somatostatin Release

The prime paracrine inhibitor of acid secretion is somatostatin. Somatostatin exerts tonic inhibition of acid secretion from the parietal cell through G-protein coupled receptors that suppress adenylate cyclase activity [11]. Acetylcholine released from postganglionic, cholinergic vagal nerve endings in the oxyntic mucosa inhibits the release of somatostatin from delta cells. The decrease in somatostatin in the interstitial fluid surrounding the parietal cells, results in the "disinhibition" of this cell, which then becomes more sensitive to stimulation by histamine, acetylcholine and gastrin [11]. The inhibitory regulation of somatostatin on the basal function of the parietal cell has been assessed by the administration of highly specific monoclonal antibodies to somatostatin. The result is 70 percent augmentation of acid secretion [12]. The delta cell also regulates parietal cell function indirectly through its influence on the ECL cell. Somatostatin inhibits histamine release and acid secretion in isolated rabbit gastric glands [12].

Indirect Action through the Release of Gastrin

Vagal stimulation releases gastrin by activating GRP neurons and by suppressing somatostatin release from antral delta cells, thus eliminating the inhibitory action of this

peptide [13]. The contribution of gastrin to the cephalic phase of acid secretion is uncertain. In a study of antral vagotomy in dogs, Hirschowitz and Fong suggest that the contribution of gastrin is small and that vagal stimulation of acid secretion occurs almost exclusively through its fundic pathways [14].

VAGAL STIMULATION OF GASTRIN RELEASE

Vagal stimulation of gastrin release has two components: a) GRP-mediated release of the peptide and b) inhibition of somatostatin release from antral delta cells, thereby removing the inhibitory control of somatostatin on the G-cells. GRP, the mammalian analog of the amphibian peptide bombesin, is released from peptidergic, post-ganglionic, parasympathetic, intramural vagal fibers and neurons of the ENS [15]. Gastrin release in response to electrical vagal stimulation is inhibited by bombesin antagonists, indicating the importance of GRP as the mediator of vagal release of gastrin [16]. Somatostatin exerts tonic inhibitory regulation of gastrin secretion. Both muscarinic agonists and immunoneutralization of gastric somatostatin with monoclonal antibodies to somatostatin cause a two- to three-fold increase in gastrin release [17, 18]. Electrical vagal stimulation results in decreased secretion of somatostatin from the vascularly perfused stomach [19].

The physiologic contribution of gastrin during the cephalic phase of acid secretion is unclear. In man, dog and rat, gastrin mediates a portion of acid secretion during the cephalic phase. In dogs, approximately 70 percent of acid secretion induced by insulin hypoglycemia was blocked by the administration of a gastrin monoclonal antibody [20]. In humans, a small but significant rise in plasma levels of gastrin is seen during sham-feeding [21]. Small doses of atropine enhance gastrin response to sham-feeding, presumably by blocking the vagal effect on somatostatin release [22].

VAGAL INHIBITORY MECHANISMS

Activation of the vagus invariably results in stimulation of acid secretion. As discussed earlier, this response is mediated in part through the inhibitory effect of the vagus on somatostatin release. Several inhibitory peptidergic pathways are activated by vagal stimulation. These include vasoactive intestinal polypeptide (VIP), neuropeptide Y, calcitonin gene-related peptide, substance P and galanin. To what extent these neural pathways exert inhibitory control of acid secretion is unknown. For example, vagal action releases VIP from the ENS of the fundus to mediate muscular relaxation. VIP also releases somatostatin in the fundus. Whether this action is physiologically significant in acid secretion is unknown [23].

If the inhibitory vagal regulation of the oxyntic cell is not clear, the evidence for inhibitory regulation of the G-cell is strong. Indeed, with respect to gastrin release, the inhibitory role of the vagus appears more significant than its stimulatory action. Following all types of vagotomy, basal and post-prandial hypergastrinemia develops [24]. There appears to be a tonic vagal inhibitory mechanism that is removed by vagotomy [25]. Furthermore, the vagal fibers that stimulate gastrin release appear to be those distributed to the antrum through the nerves of Latarjet. Division of these antral nerves abolishes vagally-stimulated gastrin release [14]. On the other hand, interruption of the vagal supply to the proximal stomach, as in highly selective or parietal cell vagotomy, leads to hypergastrinemia. Undoubtedly, one cause of the hypergastrinemia is reduction in luminal acid. However, post-vagotomy hypergastrinemia is not totally explainable on this basis. The mediation of this acid-independent mechanism of inhibition of gastrin release by fundic vagal pathways is not yet elucidated.

EFFECT OF VAGOTOMY ON ACID SECRETION AND GASTRIN RELEASE

Vagotomy results in 85 percent and 50-60 percent inhibition of basal and post-prandial acid secretion, respectively. Vagotomy also results in significant inhibition of pepsin secretion. The rationale for vagotomy in the treatment of peptic ulcer disease is based on these observations. These effects are largely mediated by the fall of acetylcholine release within the gastric wall. Vagotomy also has known effects on the two other primary stimulants of acid secretion, histamine and gastrin. (Figure 2).

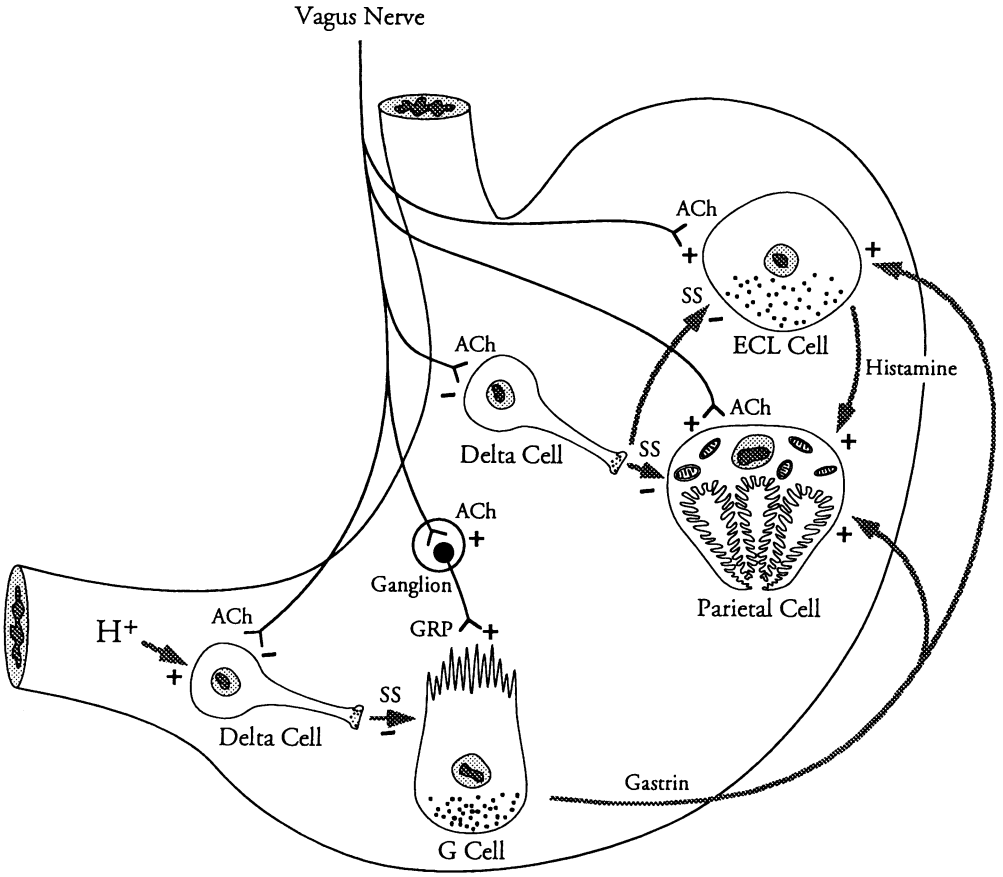

Figure 2. The known interactions of the vagus affecting acid secretion and gastrin release is illustrated (GRP, gastrin-releasing peptide; ACh, acetylcholine). Vagal stimulation of the parietal cell occurs through M3 cholinergic receptors and via the release of histamine and gastrin from enterochromaffin-like (ECL) cells and G-cells, respectively. Somatostatin (SS) exerts a tonic basal inhibition of both the parietal cell and the G-cell. Vagal stimulation suppresses somatostatin release from delta cells, thereby "disinhibiting" these cells.

Following proximal gastric vagotomy in patients with duodenal ulcer, histamine content in the oxyntic mucosa rises without a concomitant increase in histidine decarboxylase activity [10]. However, the ability of pentagastrin to induce new histamine formation is impaired. It has been suggested that the clinical effect of vagotomy may be partly due to the reduction in the amounts of endogenous histamine synthesized and released in response to various stimuli [10].

Both basal and post-prandial hypergastrinemia follow vagotomy. This hypergastrinemia is rarely higher than two to three times the pre-vagotomy level. The cause of post-vagotomy hypergastrinemia is three-fold: a) Withdrawal of the vagus-dependent fundic inhibitory mechanism; b) decrease in luminal acid, resulting in the decrease of somatostatin-dependent negative feed-back regulation; and c) G-cell hyperplasia.

CONCLUSION

The vagus plays an important physiologic role on the regulation of acid secretion, gastrin release, and histamine production. Despite many recent advances in the understanding of these interactions, further research is needed to understand the following questions: what are the mediators of the dorsal motor nucleus? What is the contribution of vagally-mediated histamine release on acid secretion? By what mechanism does H_2-receptor antagonists inhibit acid response to vagal stimulation? In conjunction with somatostatin, what other neuropeptides inhibit acid secretion? What is the mechanism of vagal inhibition on gastrin release? These questions will certainly be answered in the near future further advancing our understanding of vagally-mediated acid secretion.

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