The **histamine** receptor on the parietal cell is an H_2 receptor that is coupled to the Ga_s GTP-binding protein. Histamine activation of the receptor complex stimulates the enzyme adenylyl cyclase, which, in turn, generates cAMP. The resulting activation of protein kinase A leads to the phosphorylation of certain parietal cell–specific proteins, including the H-K pump.

Gastrin is released by both antral and duodenal G cells, and histamine is released by enterochromaffin-like cells in the corpus

The presence of a gastric hormone that stimulates acid secretion was initially proposed in 1905. Direct evidence of such a factor was obtained in 1938, and in 1964 Gregory and Tracey isolated and purified gastrin and determined its amino acid sequence. Gastrin has three major effects on GI cells: (1) stimulation of acid secretion by parietal cells (Fig. 42-5); (2) release of histamine by ECL cells; and (3) regulation of mucosal growth in the corpus of the stomach, as well as in the small and large intestine.

Gastrin exists in several different forms, but the two major forms are G-17, or "little gastrin," a 17–amino acid linear peptide (Fig. 42-7A), and G-34, or "big gastrin," a 34–amino acid peptide (Fig. 42-7B). A single gene encodes a peptide of 101 amino acids. Several cleavage steps and C-terminal amidation (i.e., addition of a $-NH_2$ to the C terminus) occur during gastrin's post-translational modification, a process that occurs in the endoplasmic reticulum, trans-Golgi apparatus, and both immature and mature secretory granules. The final product of this post-translational modification is either G-17 or G-34. The tyrosine residue may be either sulfated (so-called gastrin II) or nonsulfated (gastrin I); the two forms are equally active and are present in equal amounts. Gastrin and **CCK**, a related hormone, have identical C-terminal tetrapeptide sequences (Fig. 42-7C) that possess all the biological activities of both gastrin and CCK. Both G-17 and G-34 are present in blood plasma, and their plasma levels primarily reflect their degradation rates. Thus, although G-17 is more active than G-34, the latter is degraded at a substantially lower rate than G-17. As a consequence, the infusion of equal amounts of G-17 or G-34 produces comparable increases in gastric acid secretion.

Specialized endocrine cells (**G cells**) in both the antrum and duodenum make each of the two gastrins. Antral G cells are the primary source of G-17, whereas duodenal G cells are the primary source of G-34. Antral G cells are unusual in that they respond to both luminal and basolateral stimuli (Fig. 42-8). Antral G cells have microvilli on their apical membrane surface and are referred to as an *open-type* endocrine cell. These G cells release gastrin in response to luminal peptides and amino acids, as well as in response to **gastrin-releasing peptide** (GRP), a 27–amino acid peptide that is released by vagal nerve endings. As discussed later, gastrin release is inhibited by somatostatin, which is released from adjacent D cells.

Somatostatin, released by gastric D cells, is the central mechanism of inhibition of acid secretion

Gastric acid secretion is under close control of not only the stimulatory pathways discussed earlier but also the inhibitory pathways. The major inhibitory pathway involves the release of **somatostatin**, a polypeptide hormone made by D cells in the antrum and corpus of the stomach. Somatostatin is also made by the δ cells of the pancreatic islets (see Chapter 51) and by neurons in the hypothalamus (see Chapter 48). Somatostatin exists in two forms, SS-28 and SS-14, which have identical C termini. SS-28 is the predominant form in the GI tract.

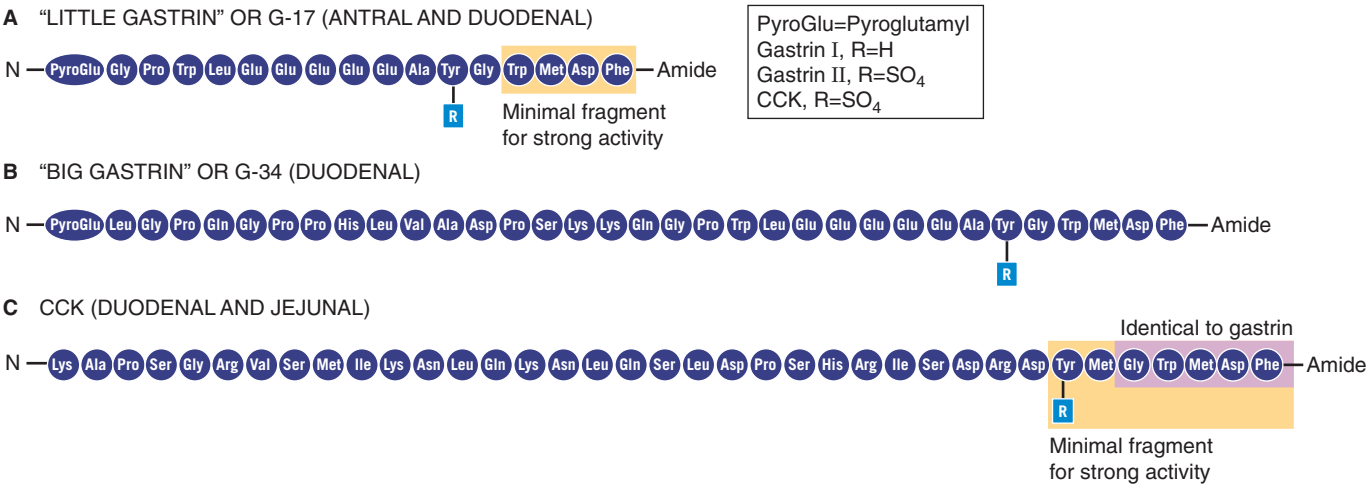

Figure 42-7 Amino acid sequences of the gastrins and CCK. **A,** A single gene encodes a 101–amino acid peptide that is processed to both G-17 and G-34. The N-terminal glutamine is modified to create a pyroglutamyl residue. The C-terminal phenylalanine is amidated. These modifications make the hormone resistant to carboxypeptidases and aminopeptidases. **B,** The final 16 amino acids of G-34 are identical to the final 16 amino acids in G-17. Both G-17 and G-34 may be either *not sulfated* (gastrin I) or *sulfated* (gastrin II). **C,** The five final amino acids of CCK are identical to those of G-17 and G-34.

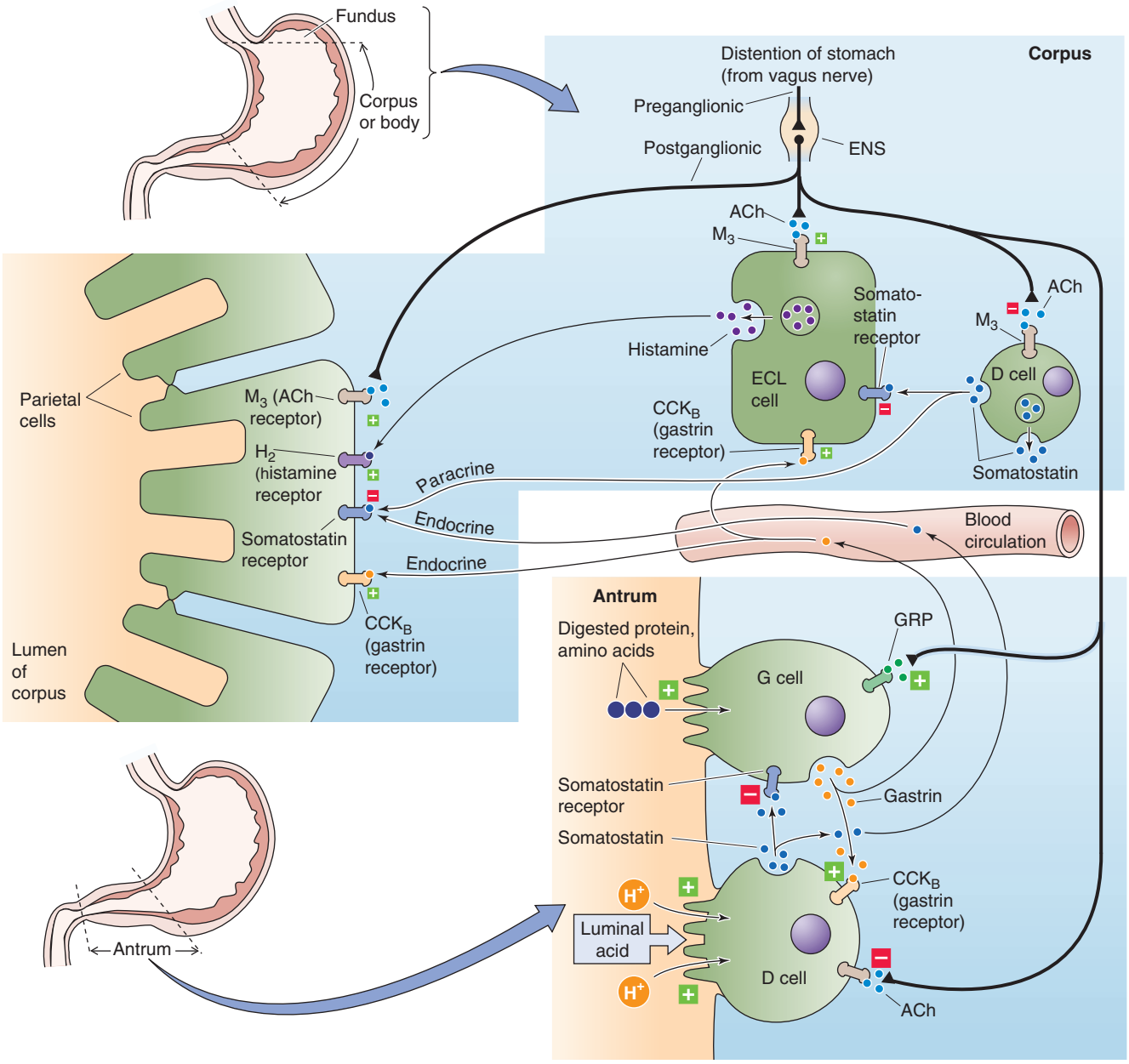

Figure 42-8 Regulation of gastric acid secretion. In the corpus of the stomach, the vagus nerve not only stimulates the parietal cell directly by releasing ACh but also stimulates both ECL and D cells. Vagal stimulation of the ECL cells enhances gastric acid secretion through increased histamine release. Vagal stimulation of the D cells also promotes gastric acid secretion by inhibiting the release of somatostatin, which would otherwise inhibit—by paracrine mechanisms—the release of histamine from ECL cells and the secretion of acid by parietal cells. In the antrum of the stomach, the vagus stimulates both G cells and D cells. The vagus stimulates the G cells through GRP, thus promoting gastrin release. This gastrin promotes gastric acid secretion by two endocrine mechanisms: directly through the parietal cell and indirectly through the ECL cell, which releases histamine. The vagal stimulation of D cells by ACh inhibits the release of somatostatin, which would otherwise inhibit—by paracrine mechanisms—the release of gastrin from G cells and—by an endocrine mechanism—acid secretion by parietal cells. Luminal H^+ directly stimulates the D cells to release somatostatin, which inhibits gastrin release from the G cells, thereby reducing gastric acid secretion (negative feedback). In addition, products of protein digestion (i.e., peptides and amino acids) directly stimulate the G cells to release gastrin, which stimulates gastric acid secretion (positive feedback).