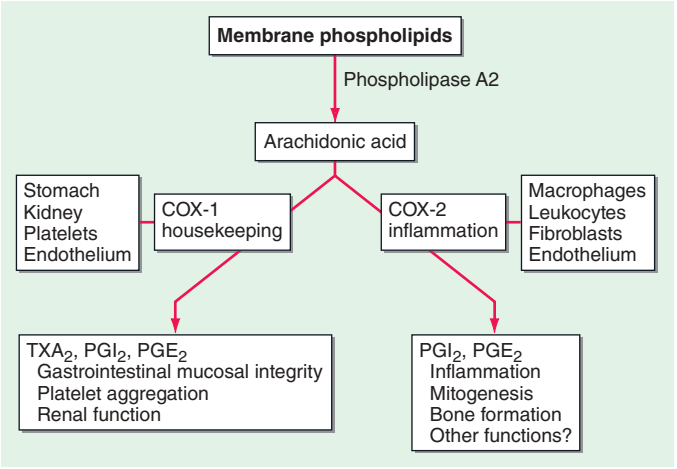

FIGURE 348-4 Schematic representation of the steps involved in synthesis of prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2). Characteristics and distribution of the cyclooxygenase (COX) enzymes 1 and 2 are also shown. TXA_2, thromboxane A_2.

chemical energy of adenosine triphosphate (ATP) to transfer H^+ ions from parietal cell cytoplasm to the secretory canaliculi in exchange for K^+. The H^+,K^+-ATPase is located within the secretory canaliculus and in nonsecretory cytoplasmic tubulovesicles. The tubulovesicles are impermeable to K^+, which leads to an inactive pump in this location. The distribution of pumps between the nonsecretory vesicles and the secretory canaliculus varies according to parietal cell activity (Fig. 348-2). Proton pumps are recycled back to the inactive state in cytoplasmic vesicles once parietal cell activation ceases. Small G proteins of the Rab family and secretory carrier membrane proteins (SCAMPS) are postulated to participate in parietal cell membrane translocation. In addition, acid secretion requires a number of apical and basolateral parietal cell membrane chloride and potassium channels.

The chief cell, found primarily in the gastric fundus, synthesizes and secretes pepsinogen, the inactive precursor of the proteolytic enzyme pepsin. The acid environment within the stomach leads to cleavage of the inactive precursor to pepsin and provides the low pH (<2) required for pepsin activity. Pepsin activity is significantly diminished at a pH of 4 and irreversibly inactivated and denatured at a pH of ≥7. Many of the secretagogues that stimulate acid secretion also stimulate pepsinogen release. The precise role of pepsin in the pathogenesis of PUD remains to be established.

PATHOPHYSIOLOGIC BASIS OF PEPTIC ULCER DISEASE

PUD encompasses both gastric and duodenal ulcers. *Ulcers* are defined as breaks in the mucosal surface >5 mm in size, with depth to the submucosa. Duodenal ulcers (DUs) and gastric ulcers (GUs) share many common features in terms of pathogenesis, diagnosis, and treatment, but several factors distinguish them from one another. *Helicobacter pylori* and NSAIDs are the most common risk factors for PUD, with estimated odds ratios in the United States of 3.7 and 3.3, respectively. Additional risk factors (odds ratio) include chronic obstructive lung disease (2.34), chronic renal insufficiency (2.29), current tobacco use (1.99), former tobacco use (1.55), older age (1.67), three or more doctor visits in a year (1.49), coronary heart disease (1.46), former alcohol use (1.29), African-American race (1.20), obesity (1.18), and diabetes (1.13). The mechanisms by which some of these risk factors lead to ulcer disease are highlighted below.

Epidemiology • ***DUODENAL ULCERS*** DUs are estimated to occur in 6–15% of the Western population. The incidence of DUs declined steadily from 1960 to 1980 and has remained stable since then. The death rates, need for surgery, and physician visits have decreased by >50% over the past 30 years. The reason for the reduction in the frequency of DUs is likely related to the decreasing frequency of *H. pylori*. Before the discovery of *H. pylori*, the natural history of DUs was typified by frequent recurrences after initial therapy. Eradication of *H. pylori* has greatly reduced these recurrence rates.

GASTRIC ULCERS GUs tend to occur later in life than duodenal lesions, with a peak incidence reported in the sixth decade. More than one-half of GUs occur in males and are less common than DUs, perhaps due to the higher likelihood of GUs being silent and presenting only after a complication develops. Autopsy studies suggest a similar incidence of DUs and GUs.

Pathology • ***DUODENAL ULCERS*** DUs occur most often in the first portion of the duodenum (>95%), with ~90% located within 3 cm of the pylorus. They are usually ≤1 cm in diameter but can occasionally reach 3–6 cm (giant ulcer). Ulcers are sharply demarcated, with depth at times reaching the muscularis propria. The base of the ulcer often consists of a zone of eosinophilic necrosis with surrounding fibrosis. Malignant DUs are extremely rare.

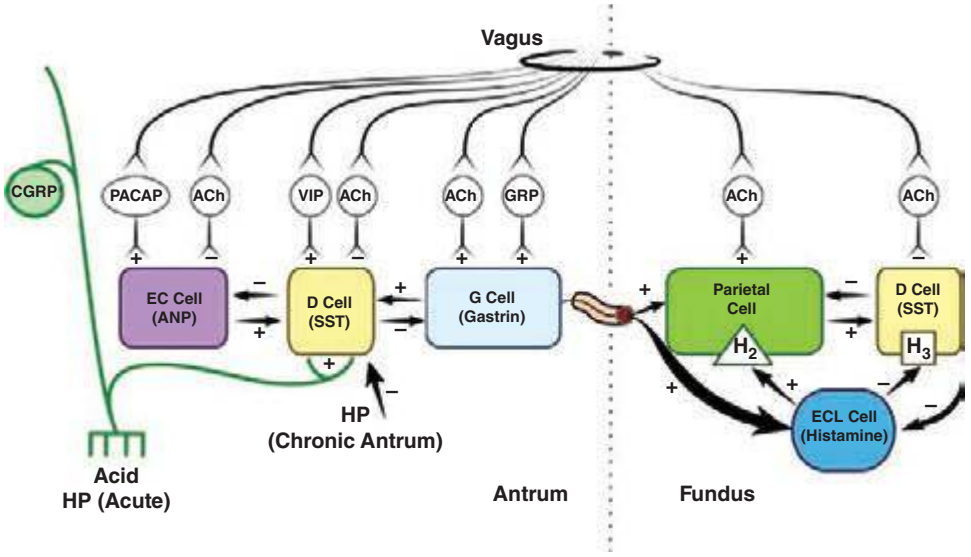

FIGURE 348-5 Regulation of gastric acid secretion at the cellular level. ACh, acetylcholine; ANP, atrial natriuretic peptide; CGRP, calcitonin gene-related peptide; EC, enterochromaffin; ECL, enterochromaffin-like; GRP, gastrin-releasing peptide; PACAP, pituitary adenylate-cyclase activating peptide; SST, somatostatin; VIP, vasoactive intestinal peptide.