



FIGURE 348-2 Gastric parietal cell undergoing transformation after secretagogue-mediated stimulation. cAMP, cyclic adenosine monophosphate. (Adapted from SJ Hersey, G Sachs: *Physiol Rev* 75:155, 1995.)

process requiring high energy, occurs at the apical canalicular surface. Numerous mitochondria (30–40% of total cell volume) generate the energy required for secretion.

Gastroduodenal Mucosal Defense The gastric epithelium is under constant assault by a series of endogenous noxious factors, including hydrochloric acid (HCl), pepsinogen/pepsin, and bile salts. In addition, a steady flow of exogenous substances such as medications, alcohol, and bacteria encounter the gastric mucosa. A highly intricate biologic system is in place to provide defense from mucosal injury and to repair any injury that may occur.

The mucosal defense system can be envisioned as a three-level barrier, composed of preepithelial, epithelial, and subepithelial elements (Fig. 348-3). The first line of defense is a mucus-bicarbonate-phospholipid layer, which serves as a physicochemical barrier to multiple molecules, including hydrogen ions. Mucus is secreted in a regulated fashion by gastroduodenal surface epithelial cells. It consists primarily of water (95%) and a mixture of phospholipids and glycoproteins (mucin). The mucous gel functions as a nonstirred water layer impeding diffusion of ions and molecules such as pepsin. Bicarbonate, secreted in a regulated manner by surface epithelial cells of the gastroduodenal mucosa into the mucous gel, forms a pH gradient ranging from 1 to 2 at the gastric luminal surface and reaching 6 to 7 along the epithelial cell surface.

Surface epithelial cells provide the next line of defense through several factors, including mucus production, epithelial cell ionic transporters that maintain intracellular pH and bicarbonate production, and intracellular tight junctions. Surface epithelial cells generate heat shock proteins that prevent protein denaturation and protect cells from certain factors such as increased temperature, cytotoxic agents, or oxidative stress. Epithelial cells also generate trefoil factor family peptides and cathelicidins, which also play a role in surface cell protection and regeneration. If the preepithelial barrier were breached, gastric epithelial cells bordering a site of injury can migrate to restore a damaged region (*restitution*). This process occurs independent of cell division and requires uninterrupted blood flow and an alkaline pH in the surrounding environment. Several growth factors, including epidermal growth factor (EGF), transforming growth factor (TGF) α , and basic fibroblast growth factor (FGF), modulate the process of restitution. Larger defects that are not effectively repaired by restitution require cell proliferation. Epithelial cell regeneration is regulated by prostaglandins and growth factors such as EGF and TGF- α . In tandem with epithelial cell renewal, formation of new vessels (*angiogenesis*) within the injured microvascular bed occurs. Both FGF and vascular endothelial growth factor (VEGF) are important in regulating angiogenesis in the gastric mucosa.

An elaborate microvascular system within the gastric submucosal layer is the key component of the subepithelial defense/repair system, providing HCO_3^- , which neutralizes the acid generated by the parietal cell. Moreover, this microcirculatory bed provides an adequate

supply of micronutrients and oxygen while removing toxic metabolic by-products.

Prostaglandins play a central role in gastric epithelial defense/repair (Fig. 348-4). The gastric mucosa contains abundant levels of prostaglandins that regulate the release of mucosal bicarbonate and mucus, inhibit parietal cell secretion, and are important in maintaining mucosal blood flow and epithelial cell restitution. Prostaglandins are derived from esterified arachidonic acid, which is formed from phospholipids (cell membrane) by the action of phospholipase A_2 . A key enzyme that controls the rate-limiting step in prostaglandin synthesis is cyclooxygenase (COX), which is present in two isoforms (COX-1, COX-2), each having distinct characteristics regarding structure, tissue distribution, and expression. COX-1 is expressed in a host of tissues, including the stomach, platelets, kidneys, and endothelial cells. This isoform is expressed in a constitutive manner and plays an important role in maintaining the integrity of renal function, platelet aggregation, and gastrointestinal (GI) mucosal integrity. In contrast, the expression of COX-2 is inducible by inflammatory stimuli, and it is expressed in macrophages, leukocytes, fibroblasts, and synovial cells. The beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on tissue inflammation are due to inhibition of COX-2; the toxicity of these drugs (e.g., GI mucosal ulceration and renal dysfunction) is related to inhibition of the COX-1 isoform. The highly COX-2-selective NSAIDs have the potential to provide the beneficial effect of decreasing tissue inflammation while minimizing toxicity in the GI tract. Selective COX-2 inhibitors have had adverse effects on the cardiovascular system, leading to increased risk of myocardial infarction. Therefore, the U.S. Food and Drug Administration (FDA) has removed two of these agents (valdecoxib and rofecoxib) from the market (see below).

Nitric oxide (NO) is important in the maintenance of gastric mucosal integrity. The key enzyme NO synthase is constitutively expressed in the mucosa and contributes to cytoprotection by stimulating gastric mucus, increasing mucosal blood flow, and maintaining epithelial cell barrier function. The central nervous system (CNS) and hormonal factors also play a role in regulating mucosal defense through multiple pathways (Fig. 348-3).

Physiology of Gastric Secretion Hydrochloric acid and pepsinogen are the two principal gastric secretory products capable of inducing mucosal injury. Gastric acid and pepsinogen play a physiologic role in protein digestion; absorption of iron, calcium, magnesium, and vitamin B_{12} ; and killing ingested bacteria. Acid secretion should be viewed as occurring under basal and stimulated conditions. Basal acid production occurs in a circadian pattern, with highest levels occurring during the night and lowest levels during the morning hours. Cholinergic input via the vagus nerve and histaminergic input from local gastric sources are the principal contributors to basal acid secretion. Stimulated gastric acid secretion occurs primarily in three phases based on the site where the signal originates (cephalic, gastric, and intestinal). Sight, smell, and taste of food are the components of the cephalic phase, which stimulates gastric secretion via the vagus nerve. The gastric phase is activated once food enters the stomach. This component of secretion is driven by nutrients (amino acids and amines) that directly stimulate the G cell to release gastrin, which in turn activates the parietal cell via direct and indirect mechanisms. Distention of the stomach wall also leads to gastrin release and acid production. The last phase of gastric acid secretion is initiated as food enters the intestine and is mediated by luminal distention and nutrient assimilation. A series of pathways that inhibit gastric acid production are also set into motion during these phases. The GI hormone somatostatin is released from endocrine cells found in the gastric mucosa (D cells) in response to HCl. Somatostatin can inhibit acid production by both direct (parietal cell) and indirect mechanisms (decreased histamine release from ECL cells and gastrin release from G cells). Additional neural (central and peripheral) and humoral (amylin, atrial natriuretic peptide [ANP], cholecystokinin, ghrelin, interleukin 11 [IL-11], obestatin, secretin, and serotonin) factors play a role in counterbalancing acid secretion. Under physiologic circumstances, these phases occur simultaneously. Ghrelin, the appetite-regulating hormone expressed in Gr cells in the