Chapter 3
Gastric Physiology

Eugene B. Chang and Po Sing Leung

1 Introduction to the Gastric Functions

Our **stomach** produces about 2L/day of gastric acid secretion/juice. Its high H^+ ions (pH=1–2) kill most of the ingested germs; it catalyzes the conversion of inactive pepsinogen to pepsin. The presence of ***acid/pepsin*** begins the digestion of dietary protein. However, pancreatic proteases can hydrolyze all ingested protein in the absence of pepsin. An important component of gastric juice is ***intrinsic factor*** (IF), which binds vitamin B_{12} in the duodenum, allowing it to be eventually absorbed in the distal ileum (see B_{12} absorption of Chap. 9); it is the only indispensable substance of gastric juice. Its deficiency, following gastric surgery or in pernicious anemia, must take injections of B_{12} or oral B_{12} with IF. The surface epithelia cells of stomach secrete mucus and bicarbonate that protect the mucosa from acid/pepsin erosion.

Understanding gastric physiology is important for all physicians in light of the numerous patients who present with stomach diseases. The pharmaceutical industry has taken advantage of the knowledge gained through basic research to develop therapeutic compounds that have revolutionized the treatment of acid peptic-related diseases. In fact, medications for the treatment of dyspepsia and peptic ulcer diseases are currently the most frequently prescribed on the market (see Sect. 5.2).

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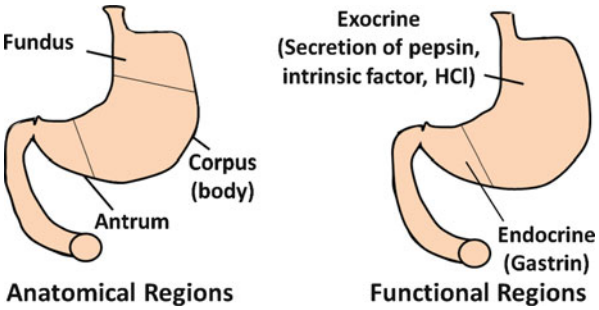

Fig. 3.1 Anatomical and functional regions of the stomach. The anatomical division of the stomach consists of the fundus, antrum, and corpus (body) that reflects differences in motor function. Functionally speaking, the stomach has two major regions: an exocrine or glandular portion that consists of the fundus and body or acid-secreting area, and an endocrine portion that is located in the antrum or gastrin-secreting area

1.1 Functional and Anatomical Organization of the Stomach

As shown in Fig. 3.1, the **anatomical subdivision** of the stomach into the ***fundus, antrum*** and ***body (corpus)*** mirrors differences in motor function (Chap. 2). The fundus functions as a reservoir for ingested meals, the body as the initial site of peristalsis, and the antral-pyloric region as the site of the greatest mechanical agitation and mixing of food with gastric secretions. In terms of **gastric mucosal function,** however, the stomach can be divided into **two major regions:** the ***"exocrine" or glandular portion (acid-secreting area)*** found in the mucosa of the fundus and body and the ***"endocrine" part (hormone-secreting area)*** located in the antral mucosa. Discussion in this chapter will focus on the gastric mucosal functions.

Acid-Secreting (Exocrine) Area

The mucosa of the exocrine portion of the stomach consists of **simple columnar epithelial cells** that line the luminal surface. These cells secrete mucus and an alkaline fluid, both necessary for protecting the stomach against its own potentially harmful juices. Opening into the mucosal surface are numerous gastric pits that serve as conduits for the secretions of 3–7 oxyntic gastric glands (Fig. 3.2a) into the gastric lumen. The area occupied by the gastric pits is at least 50 % of the total luminal surface area. As shown in Fig. 3.2b, the remainder of the gastric or oxyntic gland can be further divided into **two regions.** The ***neck*** of the oxyntic gland contains ***parietal*** and ***mucous neck cells***, the latter resembling intestinal goblet cells and secreting mucus. The neck region is also the site of germinal cell proliferation and differentiation, giving rise to surface cells that migrate up to the surface or glandular cells that move downward toward the base. Cells progressively mature as

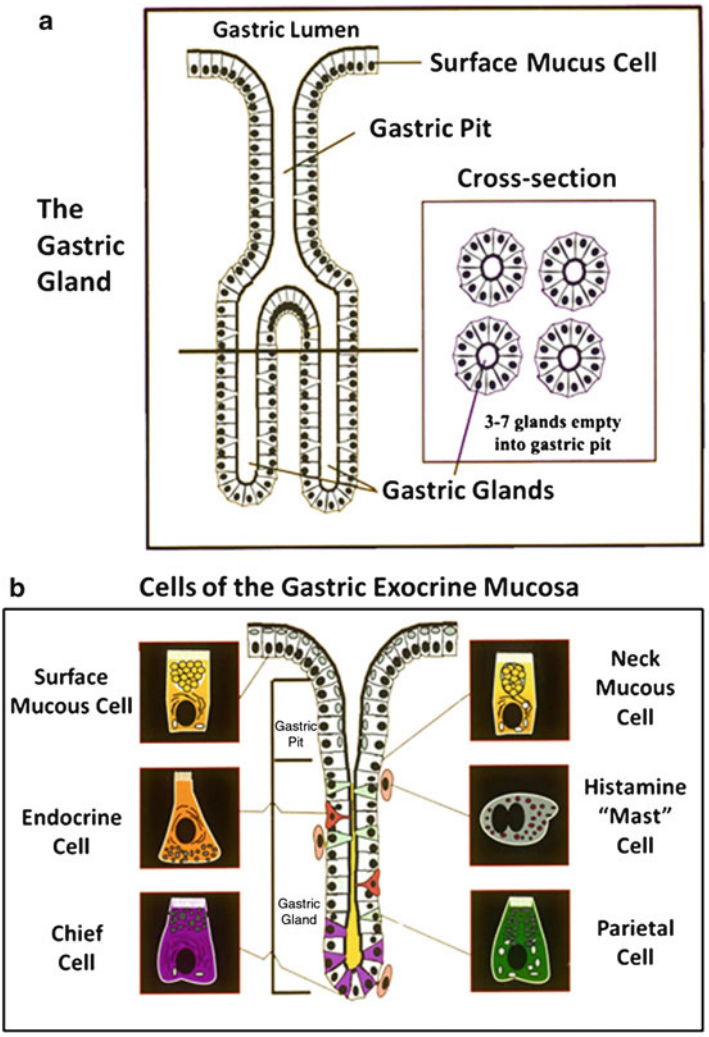

Fig. 3.2 The structure of gastric gland. (**a**) Side and cross-sectional views of gastric pits. (**b**) Various types of cells that are found in the gastric exocrine mucosa

they reach their final destinations and then are continuously replaced by new cells, the turnover of various cell types ranging from days to weeks. The ***base*** of the gland contains ***chief cells*** in addition to some parietal and mucous neck cells. The oxyntic gland also contains a number of endocrine-type cells dispersed among chief and parietal cells that play a role regulating their secretory functions.

Each cell type has different functions. **Parietal cells** are the acid-secreting cells, and their cellular physiology will be covered in greater detail later in the chapter. **Chief cells** make and secrete pepsinogen, which is converted by gastric acid to

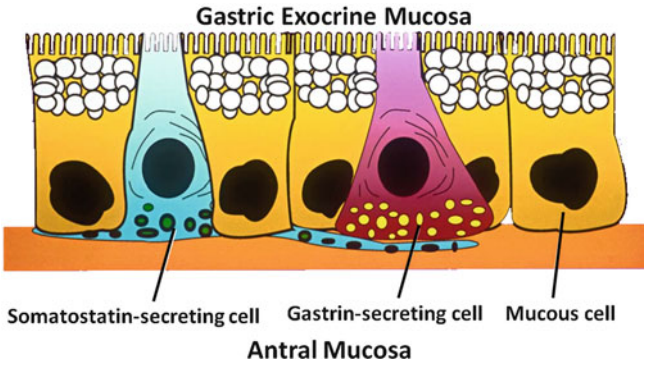

Fig. 3.3 Cells of the gastric endocrine antral mucosa. The two major endocrine cells of the antral mucosa are somatostatin-secreting D cells and gastrin-secreting G cells. The D cells are believed to have dendritic-like extensions of their cell membranes that span to adjacent G cells, which are consistent with the paracrine regulation of mucosal function

the active form pepsin. **Mucous cells** make mucus, an essential component that lubricates and protects the gastric mucosa, and those at surface and in gastric pits also secrete bicarbonate. Interspersed among these cells of the oxyntic gland are ***enterochromaffin-like (ECL)* cells** that regulate their functions by secretion of bioactive amines and peptides. Finally, a number of **mast-like cells** found in close apposition to epithelial cells of the gastric gland secrete histamine. In humans, they are believed to be important physiological regulators of gastric acid and pepsin secretion, an effect mediated through a paracrine action.

Hormone-Secreting (Endocrine) Area

The **antral-pyloric or hormone-secreting area** contains **mucus-secreting cells** similar to those seen in oxyntic glands, as well as a limited number of **parietal and pepsinogen-secreting cells.** However, this region of the stomach is the major source of *gastrin* secreted by the ***endocrine G cells*** of the mucosa. These cells are pyramidal in shape and have a narrow apical surface with long microvilli (Fig. 3.3). Secretory granules are located at the base of the cell, and the release of gastrin occurs by fusion and exocytosis with the basolateral membrane. ***Endocrine D cells***, also found in the antral-pyloric region, elaborate *somatostatin*, an important physiological regulator of gastrin release and gastric acid secretion. D cells appear to have dendritic-like extensions of their cell membranes that span to adjacent G cells, consistent with a paracrine regulation of mucosal function. These processes make the delivery of somatostatin to G cells rapid and highly selective. At least seven additional types of ***enteroendocrine cells*** can be found in the gastric mucosa; however, their physiological role in the regulation of gastric function is not as well-defined.

2 Gastric Acid Secretion

2.1 Neural and Hormonal Regulation of Gastric Acid Secretion

Acid secretion is regulated by nerves and GI hormones. Although the understanding of their mechanisms of actions is still incomplete, accumulated evidence has been learned about the regulation and cell biology of acid secretion to have had a major impact on the treatment of patients with peptic ulcer disease.

There are **three major stimulators of acid secretion: (1)** ***gastrin*** (predominantly secreted by antral G cells), **(2)** ***histamine*** (in humans probably arising from mast-like cells in the lamina propria subjacent to the gastric epithelium), and **(3)** ***acetylcholine*** (secreted from postsynaptic vagal fibers innervating the gastric mucosa). On the other hand ***Somatostatin***, secreted from *antral* and *oxyntic gland D cells* as well as *pancreatic islet cells*, and ***prostaglandins*** from *mucosal cells*, are the **major paracrine inhibitors of gastric acid secretion.**

The interaction of these regulators is extremely complex, and several issues remain controversial. For instance, it is still not clear at what level certain agents regulate acid secretion. Specific receptors on parietal cells for histamine, gastrin, and acetylcholine have been demonstrated, and their stimulation results in acid secretion (Fig. 3.4). **Histamine** stimulates *H_2-type receptors* and activates adenylate cyclase to increase cellular content of cyclic adenosine monophosphate (cAMP). The increase in cAMP, in turn, activates cAMP-dependent protein kinase, which appears to be an important mediator in initiating acid secretion. However, there is evidence that histamine may also increase cytosolic Ca^{2+} concentrations, through coupling with another signal transduction pathway such as phospholipase C (mediating phosphatidylinositol metabolism). Gastrin and acetylcholine appear to activate the *phosphatidylinositol (PI) pathway*, **gastrin** through the stimulation of a specific *gastrin receptor (CCK_B)* and **acetylcholine** through activation of a *M_3-type muscarinic receptor*. These agonists both increase intracellular free calcium concentrations. However, there are some differences in the activation pathways. Acid secretion stimulated by acetylcholine is dependent on the presence of extracellular calcium, whereas the effects of gastrin are only partially affected by this manipulation. Thus, the cellular mechanisms mediating these responses are clearly more diverse and complex than previously thought. The physiological role of ***protein kinase C***, which is activated by the generation of diacylglycerol from phosphatidylinositol metabolism, is unclear. Some evidence suggests that it has a minor role in stimulation of acid secretion and may be more important in feedback inhibition of parietal cell function. Finally, cAMP and calcium may interact in a variety of ways to modulate cell activation. For example, potentiation can be seen between agents that increase cytosolic calcium (gastrin and acetylcholine) and cAMP (histamine), an observation that may have considerable clinical and therapeutic relevance. The nature of this interaction remains undetermined.

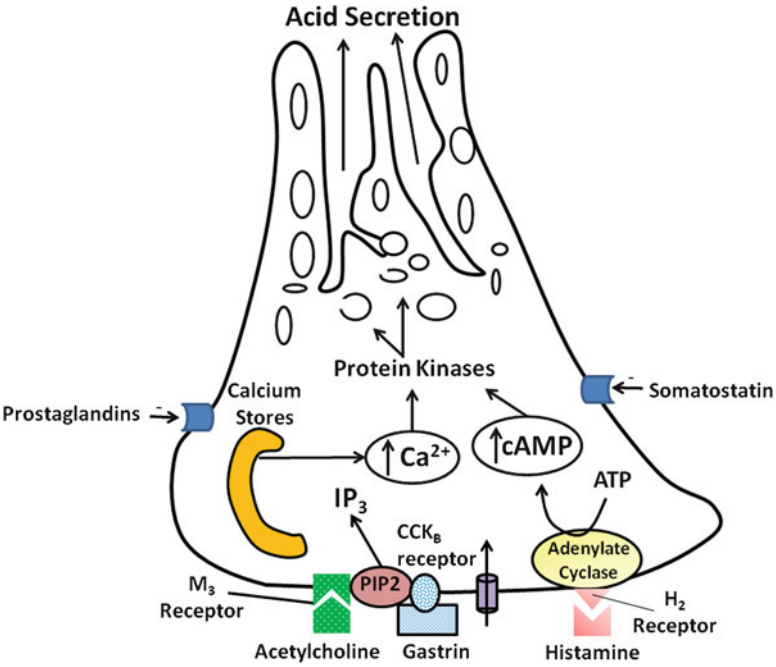

Fig. 3.4 Cellular mechanism of acid secretion by the parietal cell. There are three basic acid stimulants involved in the regulation of acid secretion, i.e. the neurocrine, acetylcholine; the endocrine, gastrin; the paracrine, histamine. *PIP_2* phosphatidyl-4,5-bisphosphate, *IP_3* inositol 1,4,5-triphosphate

In addition to their direct effects on parietal cell function, these agents appear to affect other target cells involved in the regulation of acid secretion (Fig. 3.5). For example, *gastrin* from antral G cells and acetylcholine from cholinergic neurons stimulate specific receptors on mast or ECL cells, promoting the secretion of histamine. *Histamine* potentiates the effects of each of these agents on parietal cell secretion. Noradrenergic nerves inhibit histamine release from mast cells through activation of β receptors, the net effect being the inhibition of acid secretion.

The role of **somatostatin-secreting D cells** in both the antral and acid-secreting regions of the stomach also appears to be a major component of the regulatory systems. In the ***antrum***, somatostatin inhibits G-cell secretion of gastrin and is released by the presence of luminal acid and gastrin (serving as negative feedback mechanisms) and by stimulation from enteric neurons containing acetylcholine, vasoactive intestinal peptide (VIP), and gastrin-releasing peptide (GRP). In the ***exocrine portion of the stomach,*** D-cell release of somatostatin directly inhibits parietal cell acid secretion. Alternatively, somatostatin also inhibits acid secretion by decreasing histamine release by **mast-like and ECL cells**. *Gastrin and cholecystokinin (CCK)* stimulate somatostatin secretion, whereas cholinergic neurons inhibit it.

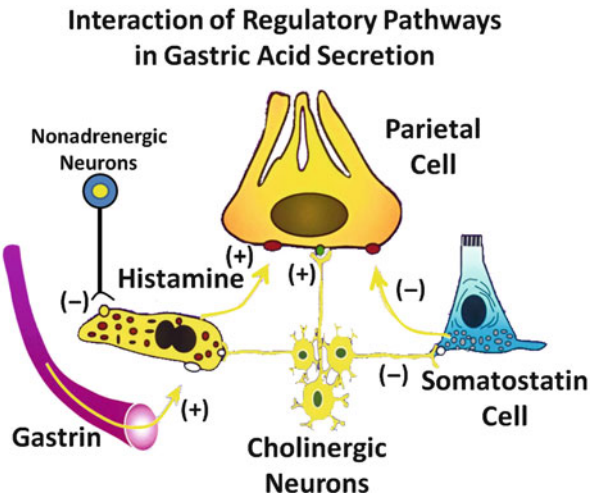

Fig. 3.5 Interaction of regulatory pathways in gastric acid secretion. Apart from the direct effects of the three basic acid stimulants of histamine, gastrin and acetylcholine on parietal cell functions, various regulatory agents also affect other target cells for modulating acid secretion such as the inhibitory action of somatostatin

The relative contribution of each of the aforementioned pathways in regulating gastric acid secretion is highly variable among mammalian species and not entirely elucidated in humans. However, it does appear that histamine plays a major role in stimulating gastric acid secretion. Specific inhibitors of the histamine H_2 receptor, such as *cimetidine* and *ranitidine,* are clinically and experimentally very effective in reducing acid secretion, in spite of the fact that the stimulatory effects of gastrin and acetylcholine are still present. How can this be accounted for? A possible explanation is that in the absence of histamine stimulation of parietal cells, there is no potentiation of the gastrin or acetylcholine effects, thus diminishing acid secretion. In addition, gastrin stimulation of somatostatin release would continue unabated, further rendering a decrease in acid secretion.

2.2 Cellular Mechanisms Mediating Gastric Acid Secretion

Cellular Events

When the **parietal cell** is stimulated, it undergoes rapid, dramatic morphologic changes that are now known to be important in setting up the acid-secretory apparatus. The resting, or non-secreting, parietal cell has a specialized network of narrow channels that extend from the luminal surface through much of the cell body (Fig. 3.6a). These are **secretory canaliculi**, lined by short, stubby microvilli. There is also an elaborate system of tubular and vesicular membranes **(tubulovesicles)** in the luminal aspect of the cell. Large mitochondria, characteristically seen in these cells, are essential for providing a high oxidative capacity during acid secretion.

Within a few minutes of stimulation, microvilli lining the canaliculi become longer and more elaborate. It is estimated that the luminal surface area increases

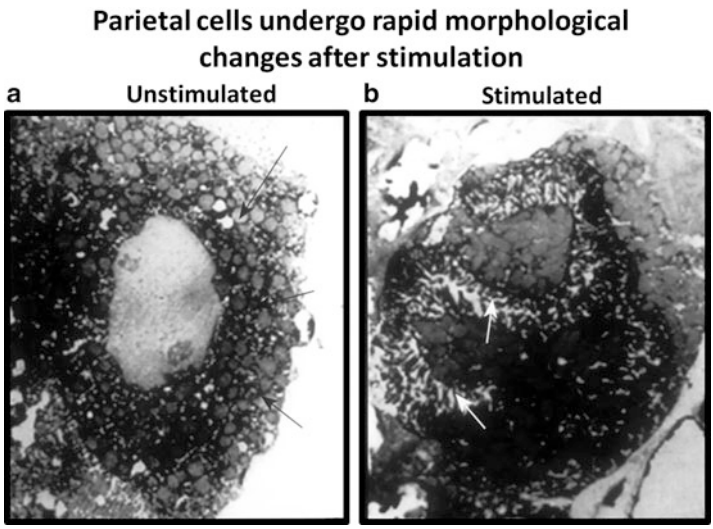

Fig. 3.6 Morphological changes associated with parietal cell activation and secretion. (**a**) The resting, or nonsecreting, parietal cell has many mitochondria and an elaborate system of tubular and vesicular membranes near the luminal aspect of the cell. (**b**) With stimulation, the luminal surface area increases six to tenfold, with a concomitant disappearance of tubulovesicle membranes. These changes are caused by the fusion of the tubulovesicle membranes with the plasma membrane, increasing the number and density of proton pumps in the apical surface (Courtesy of Dr. George Sachs)

to 6–10 times that of the resting state (Fig. 3.6b). Concomitant with these changes is the disappearance of tubulovesicle membranes. Withdrawal of the stimulating agents leads to a collapse of the canaliculi spaces and a return of the tubulovesicle forms in the cytoplasm. These observations are consistent with the membrane recycling that occurs during the stimulated and resting states of the parietal cell. Tubulovesicles contain large amounts of the gastric proton-pump enzyme ***H^+/K^+-ATPase***. Following stimulation of the parietal cell, tubulovesicle membranes fuse with the plasma membrane, increasing the number and density of proton pumps in the apical surface. Conversely, withdrawal of the stimulus leads to endocytosis of these membranes, a decrease in the density of proton pumps in the apical membrane, and decreased acid secretion. The proton pump is only active when inserted in the luminal membrane; it is inactive when re-sequestered into tubulovesicle membranes.

Electrolyte Transport

The mechanism for proton secretion into the lumen is fairly well understood and summarized in Fig. 3.7. The essential element here is a membrane-bound enzyme

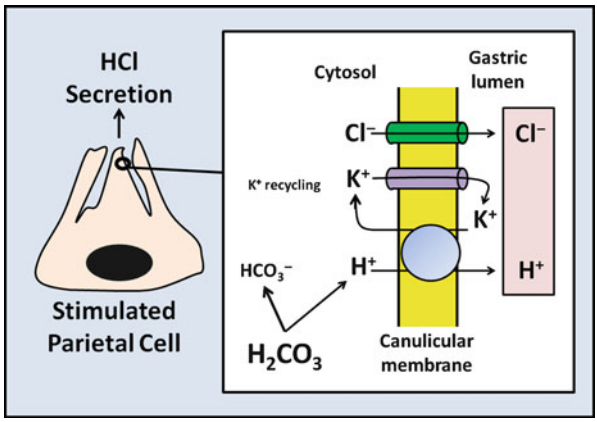

Fig. 3.7 Electrolyte transport and acid secretion at the luminal membrane of a stimulated parietal cell. The major component of acid secretion is the H^+/K^+-ATPase, or proton pump, which actively exchanges H^+ for K^+. For vectorial H^+ secretion to occur, conductance pathways for K^+ and Cl^- must exit for recycling of K^+ ions and extrusion of Cl^-, respectively

that actively extrudes protons into the lumen in exchange for potassium ions. This enzyme requires adenosine triphosphate (ATP) and hence is referred to as the **H^+/K^+-ATPase, or proton pump**. Gastric H^+/K^+-ATPase is a member of the phosphorylating, ion-motive ATPase gene family, which includes Na^+/K^+-ATPase and Ca^{2+}-ATPase. It is a heterodimer consisting of a ***larger catalytic subunit (α)*** and a ***smaller (β) glycosylated subunit***. The role of the β subunit is unknown, but it appears to be required for the proton to work as a functional unit. The proton pump is electrically neural; that is, there is a one-for-one exchange of H^+ and K^+, with no net transfer of charge. Essential to the proton pump and acid secretion is the presence of an exit pathway for K^+, which is then recycled in exchange for H^+. This occurs through the coupled transport of K^+ and Cl^- out of the cell via respective conductive channels. The Cl^- channel is distinct from the cystic fibrosis transmembrane regulator (CFTR) channel. These exit pathways operate in tandem with the proton pump, the net effect being the rapid secretion of hydrochloride into the canalicular lumen. The **K^+ and Cl^- exit pathways** may be the major rate-determining factors in acid secretion, as both are regulated by cAMP-dependent protein kinase. In addition, being voltage-gated channels, they are active only when inserted into the luminal membrane where a favorable membrane potential exists. To date, there is no evidence that supports direct kinase regulation of the proton pump.

The **proton pump** is somewhat unique in its actions. It has an enormous active secretory capacity, capable of secreting protons against large electrochemical gradients. As a consequence, luminal pH can approach the 1–2 range, representing a 5–6 log unit difference from intracellular pH values of approximately 7. No other part of the body can approach this level of acidification. Recently, several highly specific and clinically useful inhibitors of the proton pimp have been developed, ***specifically substituted-benzimidazole compounds*** such as *omeprazole* and *lansoprazole*. Being weak acids with pK_a values of approximately 4, these agents are selectively (if not exclusively) taken up and concentrated in the acidified

secretory canaliculi of gastric parietal cells. In this acid environment, they are converted to sulfonamides that are reactive with cysteine SH-thiol, but not cysteine disulfides. Thus, these agents bind to specific sites in the extracellular (luminal) domain of the α subunit of the H^+/K^+-ATPase. As a result, ATPase activity and proton transport cease. Because proton pump inhibitors block the final pathway, acid secretion can be virtually shut down, and patients may become a state, called ***achlorhydria***. *Omerprazole* has therefore become a major part of the medical armamentarium for treating peptic ulcer diseases.

Because of the voluminous secretion of protons at the apical surface, equivalent amounts of base must be delivered by the cell into blood plasma to maintain normal intracellular pH. This is accomplished through a **Cl^-/HCO_3^- exchange mechanism** located in the basolateral membrane of parietal cells. This pathway serves a dual purpose because it provides an entry pathway for chloride ions that are then vectorially secreted with protons. Coupled with Cl^-/HCO_3^- exchange is **Na^+/H^+ exchanger**, which is important for providing intracellular sodium for recycling out of the cells via the sodium pump. This allows the sodium pump to operate efficiently at high capacity to maintain the electrochemical gradients required for proton secretion and to provide an entry pathway for potassium ions (since gastric juices typically contain potassium concentrations that exceed plasma potassium concentrations by twofold or more).

2.3 Organismal Regulation of Gastric Functions

Meal-Stimulated Gastric Acid Secretion

At the organismal level, **meal-associated stimulation of gastric secretion** can be divided into **three phases** (Fig. 3.8a). The ***cephalic phase*** includes responses evoked by stimuli from the central nervous system, which can be initiated by the sight, smell, or taste of food, as well as conditioned reflexes such as the sound of a bell, and hypoglycemia induced by insulin injections or experimental administration of a GABA-like agonist. This can best be demonstrated experimentally by "sham feeding," in which food is chewed but not allowed to enter the stomach. As the duration of sham feeding lengthens, the magnitude of the gastric acid and motor response increases. **Three areas of the brainstem** appear to be important in **relaying information to the stomach:** the area ***postrema, nucleus tractus solitarii (NTS),*** and the ***dorsal motor nucleus (DMN).*** A variety of *neural peptides, such as pancreatic polypeptide, neuropeptide Y,* and *peptide YY*, may mediate the cephalic-phase response, since administration of these peptides into the brain can initiate the response. When these areas receive input from other parts of the brain (sensory processing areas), and from peripheral hormonal and metabolic signals, they activate gastric secretions through vagal nerve stimulation. Preganglionic vagal fibers synapse with enteric neurons containing gastrin-releasing peptide (GRP) and

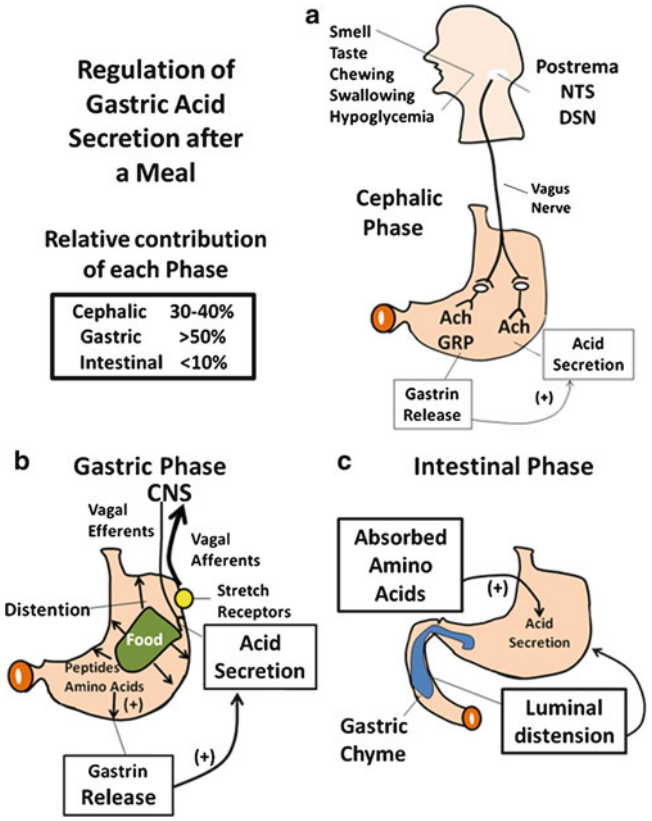

Fig. 3.8 Meal-stimulated gastric acid secretion. There are three phases that are important for regulation of meal-stimulated gastric acid secretion; they are cephalic phase (**a**), gastric phase (**b**), and intestinal phase (**c**). Of these, the gastric phase is believed to be the most important. *NTS* nucleus tractus solitarii, *DMN* dorsal motor nucleus, *Ach* acetylcholine, *GRP* gastrin releasing polypeptide

acetylcholine, which stimulate gastrin release in the antrum and acid secretion in the body and fundus. Surgical secretion of the vagal nerve will completely abolish the cephalic phase of gastric acid stimulation.

The ***gastric phase*** (Fig. 3.8b) occurs when fluid or food is present in the gastric lumen. This phase accounts for approximately *60 % of the total acid secretion* stimulated by a meal. A major component of this response is **gastric distention** produced by luminal contents, particularly in the antrum. The greater the distention is, the greater the gastric acid output. This response is mediated by both vagal nerve fibers and local intrinsic factors, the latter being gastrin in particular. When the stomach is minimally distended, vagal innervation appears to predominate, since gastrin release is minimal. However, when the antrum is further distended, large amounts of gastrin are promptly released, and acid secretion increases accordingly.

Another major component of the gastric phase is the stimulation of gastrin release by luminal nutrients, especially peptides and aromatic amino acids (phenylalanine and tryptophan). Their presence is somehow sensed by antral G cells, which are then stimulated to release gastrin. In addition, these **luminal agents** appear to activate afferent enteric neurons that initiate reflex neural networks stimulating G-cell secretion. In contrast to protein hydrolysates, carbohydrates and fats are not potent stimuli of gastric acid secretion.

The ***intestinal phase*** (Fig. 3.8c) is that component of gastric acid secretion stimulated by the presence of food in the small intestine. It is the least important of the various phases, accounting for less than *10 % of total gastric acid secretion*. The recognized initiators of this intestinal phase are distention and the digestion products of protein. Part of the humoral mechanism of the intestinal phase is probably due to absorbed amino acids, since intravenous administration of amino acids does stimulate gastric acid secretion. The intestinal phase by itself is a weak stimulus of gastric acid secretion but does appear to strongly potentiate the effects of histamine and gastrin.

Inhibitory Mechanisms of Gastric Acid Secretion

In each phase of the gastric response to meals, factors inhibit the acid secretion that accompanies stimulatory events. They play an important role in providing negative feedback to control the magnitude of the secretory response and in eventually bringing the stomach back to its resting state during interdigestive periods.

Inhibition in the cephalic phase can be demonstrated by injection of *bombesin, calcitonin, neurotensin, interleukin-1 (IL-1), prostaglandins,* or *corticotropin-releasing factor (CRF)* into the brain. Their inhibitory effects appear to be mediated by vagal and sympathetic fibers to the stomach. During the gastric phase, acidification in the antral mucosa inhibits gastrin release stimulated by sham feeding or by distention of the antrum. This effect is probably mediated by enteric neurons, as administration of atropine inhibits it. Increased luminal acid concentration also appears to stimulate the release of somatostatin from antral D cells, which inhibits gastrin release via a paracrine action. In the intestinal phase, three agents are known to inhibit acid secretion when instilled in the small intestine; they are acid, hyperosmolar solutions, and fat (the latter being most potent). The inhibition appears to be mediated by humoral substances collectively called **"*enterogastrones*."** Although no agent has been definitively identified, the candidate hormones for enterogastrones include *gastric inhibitory peptide (GIP), neurotensin, somatostatin, secretin, vasoactive intestinal peptide (VIP), enteroglucagon*, and *peptide YY*. Of these, peptide YY is the most likely agent. It is released by fat from the distal small intestine and inhibits pentagastrin-stimulated acid secretion. In addition to these mechanisms, gastric secretion is also inhibited by *secretin, gastrin releasing polypeptide (GRP), and cholecystokinin (CCK)* (see Chap. 1).

3 Pepsinogen Secretion

Pepsin is an important digestive enzyme secreted predominantly from gastric chief cells in the form of **pepsinogen**, its precursor **zymogen**. These peptic cells are located on the walls of the ***oxyntic glands*** and appear to be regulated by many of the same agents involved in the regulation of gastric acid secretion. Not surprisingly, therefore, pepsinogen secretion parallels that of acid secretion. Agents such as *gastrin, acetylcholine, CCK,* and *GIP* **stimulate pepsinogen release** by increasing cytosolic Ca^{2+} through receptor-mediated phosphatidylinositol metabolism (Fig. 3.9). Agents such as *secretin, VIP, E-series of prostaglandins,* and *β-adrenergic receptor agonists* **stimulate peptic cells** by activating adenylate cyclase, resulting in the generation of cAMP and activation of a cAMP-dependent protein kinase. Both signal transduction pathways appear to stimulate the release of pepsinogen via exocytosis of secretory granules, but cAMP-mediated stimuli may also directly stimulate *de novo* synthesis of pepsinogen.

On release into the lumen, pepsinogen is immediately activated by acid, with optimum pH being about 2. The formation of pepsin has a **positive feedback effect**, leading to a more rapid and complete conversion of pepsinogen into pepsin (Fig. 3.10).

Pepsin belongs to the general class of **aspartic protease**, so named because of the presence of two aspartic acid residues that are part of the catalytic site. It is a very good proteolytic enzyme and, because of its high activity on collagen, is more important for the digestion of meat than for vegetable protein. However, pepsin digestion of proteins is usually incomplete, since large peptides called peptones are

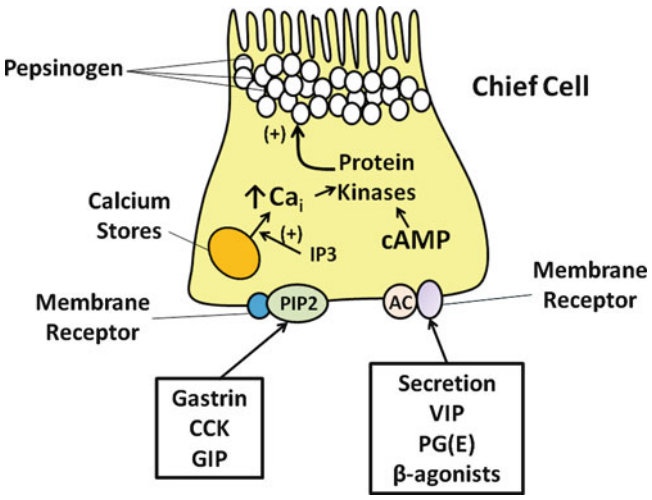

Fig. 3.9 Regulation of pepsinogen secretion by gastric chief cells. Cellular mechanisms and mediators involved in the action of regulatory agents of pepsinogen secretion illustrated above

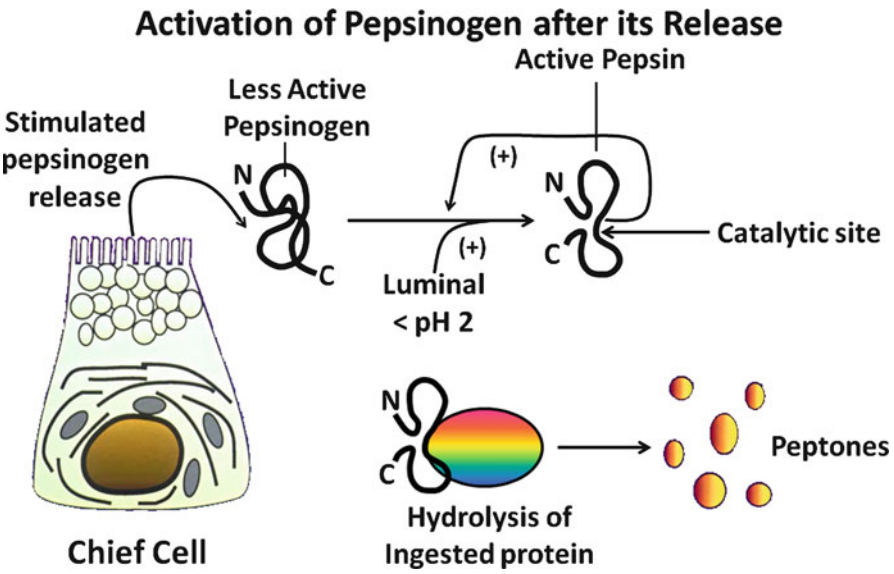

Fig. 3.10 Activation of pepsinogen. After its release into the lumen, pepsinogen is immediately activated by acid, at an optimum pH of 2. Activated pepsin has a positive feedback effect, leading to more rapid and complete conversion of pepsinogen into pepsin

frequently found in gastric chyme entering the small intestine. Peptones serve as potent signals for the release of various hormones, including gastrin and CCK.

There are **two immunologically distinct classes of pepsinogens**. ***Group I pepsinogens*** are secreted by the peptic and mucous neck cells of the *oxyntic gland*, whereas ***group II pepsinogens*** are made in *pyloric and Brunner's glands*. There has been considerable interest in pepsinogen as a possible etiologic agent in the formation of gastric and duodenal ulcers. For example, several studies have shown that instillation into the stomach of hydrochloride alone does not cause ulceration, but the inclusion of gastric juice or pepsin with the acid results in ulcer formation. In many duodenal ulcer patients, both basal and stimulated pepsin secretion are greater than in normal controls. These observations suggest a possible contributory, albeit minor, role for pepsin in ulcer formation.

4 Mucus Bicarbonate Secretion

4.1 Mucus Secretion

Mucus is made up of glycoproteins that have very interesting physiochemical properties. They are extremely hydrophilic and can form gels that contain up to 95 % water. They consist of a **polypeptide core** and are **highly glycosylated at serine and threonine residues** (Fig. 3.11). The ***glycosidic portion*** of the molecule makes

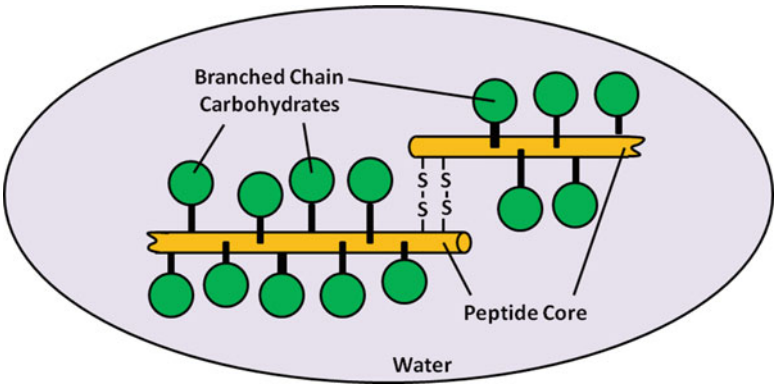

Fig. 3.11 Mucin structure and polymerization. Gastric mucin glycopeptides are extremely hydrophilic and can form gels that contain 95 % water. They consist of a polypeptide core that is highly glycosylated at serine and threonine residues

up 80 % the total molecular weight, which usually exceeds 500 kD. It also confers resistance to proteolytic digestion, an important property since mucus appears to protect the stomach against acid-pepsin damage. The ***non-glycosylated regions*** of mucin proteins serve as sites for polymerization, which occurs via disulfide linkages. Proteolysis or reduction of these linkages by N-acetyl-L-cysteine (Mucomyst) or dihydrothiothreitol (DTT) depolymerizes mucus molecules, destroying their gel-like properties and making the glycoproteins soluble.

Two forms of mucus are found in the stomach, namely a ***soluble*** and an ***insoluble*** form. Insoluble or adherent mucus is a viscous, slippery gel that covers most of the mucosal surface of the stomach and is continuously secreted by surface and gastric pit cells. It has an important role in providing protection against acid-peptic injury (discussed below). Soluble mucin results from the degradation of insoluble mucus by peptic action. The **soluble fraction** mixes with and lubricates gastric chyme during gastric motility. The **insoluble fraction** forms a semi-impermeant layer that protects underlying cells from damage by gastric acid (Fig. 3.12). Thus, the gel slows the permeation of acid from the lumen and bicarbonate secreted from underlying epithelial cells, establishing a buffer zone where the pH near the surface of the epithelial cells is in fact alkaline.

Factors That Affect Mucus Secretion

Mucus secretion and hence the thickness of the mucus layer can be affected by a number of neuro-hormonal agents. **Cholinergic stimulation**, for example, results in copious release of mucus in the stomach, whereas noradrenergic and adrenergic neurotransmitters do not appear to influence the function of these cells. Other agents that stimulate mucus secretion include ***serotonin and prostaglandins E and F.*** A possible contributory factor in **aspirin-induced gastric ulceration** is the inhibition

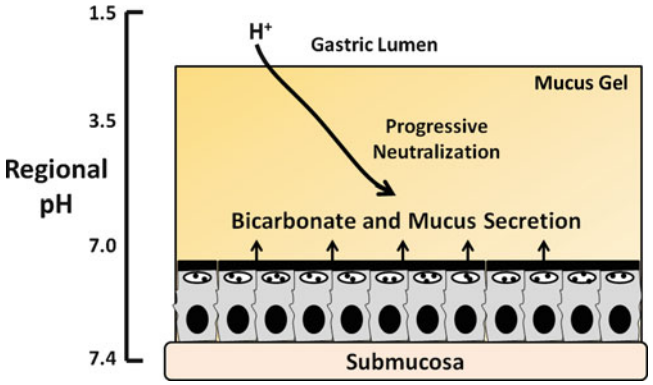

Fig. 3.12 Essential role of mucus in gastric mucosa protection. The gastric mucus gel slows the permeation of acid from the lumen and of bicarbonate secreted from underlying epithelial cells. This establishes a buffer zone, where the pH near the surface of the epithelial cells is in fact alkaline

of prostaglandin formation resulting in a decrease in the mucus protective barrier. In addition, **peptic ulcers** and **gastritis** associated with *Helicobacter pylori* infection (see below) may also be caused by compromise of the gastric mucus layer.

4.2 Bicarbonate Secretion

A major function of cells at the surface and in gastric pits is the secretion of bicarbonate, which in conjunction with the mucus layer serves to protect the gastric epithelium against acid-pepsin damage or called ***gastric mucosal barrier.*** Bicarbonate secretion alone is insufficient to counteract the magnitude of proton secretion. The mechanism of bicarbonate secretion remains unknown, although some studies have implicated the presence of a bicarbonate channel or Cl^-/HCO_3^- exchange. Bicarbonate production is dependent on **carbonic anhydrase** activity. Its transport appears to be active and stimulated by *vagal nerves* and *E-series prostaglandins*.

5 Pathogenesis of Peptic Ulcer Diseases

5.1 Pathophysiology

Over the past several decades, the understanding and treatment of acid-peptic diseases of the stomach have significantly advanced. The original concept of no acid/no ulcer still appears correct, but is also recognized that the balance between

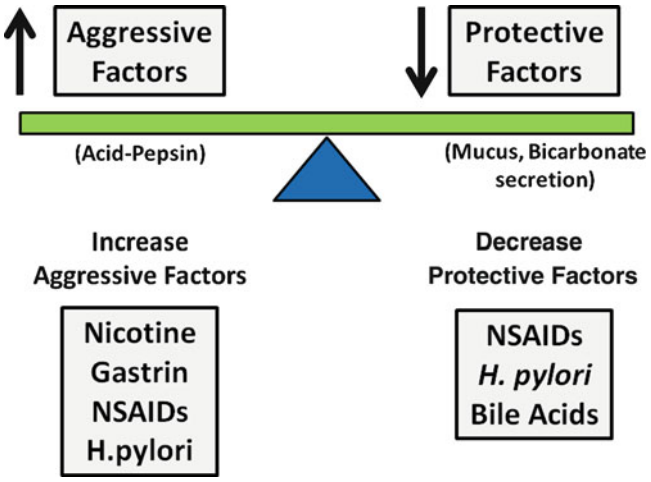

Fig. 3.13 Some factors that are believed to be important for the development of peptic ulcer disease. The well-being of the gastric mucosa is dependent on protective factors that counteract the effects of aggressive factors such as acid in pepsin. Agents that are involved in increasing aggressive factors are shown in the lower *left* and those that decrease protective factors are shown on the *right*

aggressive and protective factors is critical for maintaining the well-being of the stomach. **Peptic ulcers** and **gastritis (inflammation of the stomach lining)** result if there is an increase in aggressive factors or a decrease in protective factors (Fig. 3.13). ***Aggressive factors*** include increased acid-pepsin activity stimulated by *smoking (nicotine), excessive gastrin secretion (gastrinoma),* and *non-steroidal anti-inflammatory drugs (NSAIDs).* **NSAIDs** have a variety of effects that can promote ulcer formation, including the inhibition of prostaglandin especially PGE_2, which suppresses acid secretion. Thus, NSAIDs usage may augment the acid-secretory response to histamine and gastrin. Another important aggressive factor recently recognized is ***H. pylori*****,** a small, gram-negative bacterial organism that is the likely cause of most *non-NASID-associated* peptic ulcer diseases and gastritis. In fact, *H. pylori* now appear to be the most common infection worldwide, found in both ulcer and non-ulcer subjects. Unlike most bacterial organisms, *H. pylori* can survive the harsh acid milieu of the stomach, colonizing the mucus layer of the gastric antrum. Its ability to survive this environment is due, in part, to the production of *urease*, an enzyme that converts urea to NH_3, which is used to buffer H^+ by forming NH_4. Though being not invasive, the organism can elicit an inflammatory response of the underlying mucosa. How *H. pylori* elicits this response is not entirely clear, but elaboration of lipopolysaccharide (endotoxin), toxins, adhesions, and chemotactic substances by the organism has been implicated.

H. pylori do appear to cause **increased basal acid output** and **meal-related hypergastrinemia** in some subjects, especially patients with duodenal ulcer disease. The mechanism for increased gastrin release from antral G cells is not clear,

but it may involve inhibition of somatostatin release from antral D cells, which is important for tonically inhibiting gastrin release. After eradication of the organism, the basal acid output and meal-stimulated hypergastrinemia response appear to normalize, suggestive of a causative relationship.

It is intriguing that *H. pylori* do not cause acid-peptic diseases in everyone. In fact, a large proportion of carriers appear who have no symptoms or gastric mucosal abnormalities. This observation underscores the importance of other contributing factors in the pathogenesis of peptic ulcer disease. Among these, **decreases in mucosal barrier function** are thought to be the most important. Several agents and factors can alter or compromise mucosal-barrier function. ***H. pylori***, for instance, either by direct effect or through its stimulation of mucosal inflammation, decreases mucosal-barrier function by altering mucus and bicarbonate secretion and breaks the gastric epithelial lining. Breaches in mucosal barrier allow acid-pepsin to enter, further compromising mucosal function and causing tissue injury. Aside from *H. pylori,* other factors can also decrease gastric-protective functions. ***NSAIDs*** inhibit arachidonate metabolism by blocking cyclooxygenase activity, thus resulting in decreased prostanoid formation, which is believed to be important for maintaining mucus and bicarbonate secretion (see above). ***Smoking*** and ***increased nicotine exposure*** may also inhibit mucus and bicarbonate secretion, accounting for the increased incidence of gastric acid-peptic disorders in smokers.

5.2 Pharmacological Approaches to the Treatment of Peptic Ulcer Diseases

The management of most peptic ulcer diseases has now moved into the arena of medical therapy because of the enormous advances made in the development of effective and safe pharmacological agents (Fig. 3.14). Detailed discussion of these agents is beyond the scope of this text. The following therefore represents a brief overview of the classes of compounds that have been used to decrease acid secretion and/or increase mucosal cyto-protective functions. It should be noted that the medical treatment of *H. pylori*-associated peptic ulcer disease now includes the concomitant use of antibiotics. In this regard, the most frequent and effective regimen called **"triple therapy"** is the use of either a ***proton pump inhibitor (omeprazole)*** plus ***two to three antibodies*** (e.g. amoxicillin and clarithromycin). Below are some treatments and the proposed mechanisms of action for peptic ulcer diseases.

Antacids. Antacids, compounds that **neutralize acid**, have been the mainstay of medical therapy. These agents include preparations containing *aluminum hydroxide, calcium carbonate*, and *magnesium hydroxide*. Although these agents are effective in treating patients with peptic ulcers, they must be taken frequently and in large quantities, making for poor patient compliance.

Treatment	Mechanism of action
Antacids e.g. $Al(OH)_3$, $Mg(OH)_2$ Mg-induced diarrhea & Al-induced constipation	Neutralization of gastric acid - Nonspecific with many disadvantages
H_2 receptor antagonists e.g. Cimetidine & ranitidine	Inhibition of histamine-dependent acid secretion
H^+/K^+-ATPase inhibitors e.g. Omeprazole & Lansoprazole (Losec)	Inhibition of proton pump - More potent & longer lasting, e.g. DU caused by gastrinoma
Muscarinic receptor antagonist (Anticholinergic) e.g. Pirenzipine & atropine	Inhibition of Ach-stimulated acid secretion
Prostaglandin agonist e.g. Misoprostol	Inhibition of acid secretion; "Direct cytoprotection", such as mucus and HCO_3^- stimulation
Sucralfate	Stimulation of prostaglandin synthesis
Bismuth salts	Eradication of H. pylori
Carbenoxolone	Stimulation of prostaglandin synthesis
Vagotomy/Antrectomy	Removal of Ach- or gastrin-mediated acid secretion
Antimicrobials e.g. Amoxycillin, clarithromycin	Eradication of H. pylori *Triple therapy =H^+/K^+-ATPase blocker + Two antibiotics for 2 weeks ↑ Healing rate ↓ Recurrence (relapse) rate

Fig. 3.14 Some treatments for peptic ulcer disease and the mechanisms of action

Anticholinergics. In theory, anticholinergics should be included in the medical treatment of peptic ulcer diseases because they can **reduce acid secretion**. However, these agents are companied by a number of ***side effects*** that patients find intolerable. In addition, these agents *slow gastric motility,* promoting *increased contact time between gastric acid and the gastric mucosa*, potentially a confounding factor to their efficacy.

H_2-receptor antagonists. Histamine appears to be a major regulator of gastric acid secretion. In fact, in some mammalian species, but to a lesser extent in humans, histamine mediates the actions of gastrin. Thus, **inhibition of actions of histamine by blocking H_2 receptors** is an extremely effective way to suppress gastric acid secretion. Thus, agents such as *cimetidine, ranitidine, and famotidine* work as competitive antagonists and have been clinically effective. Although they do not completely inhibit gastric acid secretion, their effects on total acid output is sufficient in most cases to allow the stomach to heal.

Proton pump inhibitors. **Substituted benzimidazoles**, such as *omeprazole*, are extremely potent **inhibitors of gastric acid secretion**. They are weak bases that are selectively taken up and concentrated by gastric parietal cells. In an acid milieu, these agents are converted to **sulfonamides**, which *irreversibly* bind to α subunit of the H^+/K^+-ATPase (proton pump). Omeprazole can completely inhibit all acid secretion. In view of this, the use omeprazole as an acid suppressant is potent (it binds to the final pathway of acid secretion) and long-lasting (it binds irreversibly to the H^+/K^+-ATPase).

Prostaglandin agonists. Prostaglandins, especially of the E and I series, have a number of actions that make them useful in the treatment of peptic ulcer diseases. First, these agents **inhibit parietal cell secretion,** possibly through the activation of receptors linked to inhibitory G proteins of adenylate cyclase; these results in the inhibition of effects of histamine on acid secretion. In addition to anti-acid secretory actions, these agents also appear to have **cytoprotective actions**. Though the factors mediating this effect are not well understood, they may involve the stimulation of mucus and bicarbonate secretion by gastric surface cells.

Cytoprotective agents. These agents include compounds such as *sucralfate* and *colloidal bismuth subcitrate* that avidly bind to the base of ulcers, physically providing a **protective layer against acid injury.** ***Sucralfate*** is an octasulfate of sucrose that is highly, negatively charged, allowing it to interact with positively charged protein molecules. ***Colloidal bismuth subcitrate*** is a complex bismuth salt of citric acid that has a similar mode of action, especially in an acid milieu. Both agents have been effective in treating peptic ulcer disease.

***Triple therapy*.** It is the most frequent and effective regimen that contains either a **proton pump inhibitor** (e.g. omeprazole) or **H_2 receptor antagonist** plus **two to three antibiotics** (e.g. amoxycillin and clarithromycin) for 2 weeks. This sort of treatment not only heals the ulcers but also prevents the recurrence of ulcers.

Summary

- Acid is secreted by the parietal cells which contain the enzyme **H^+/K^+-ATPase** on their apical secretory membranes.
- The three major stimulants of acid secretion are the **hormone gastrin**, the **neurocrine Ach,** and the **paracrine histamine**, the latter being released from ECL cells in response to gastrin and Ach.
- The gastric mucosal barrier of a normal individual can protect the stomach even in the elevation of HCl and pepsin levels.
- When HCO_3^- and/or mucus are suppressed, the barrier is compromised and ulceration may occur.

Clinical Correlations

Case Study 1

A 40-year-old man presents to the emergency room with history of episodic, sharp, epigastric abdominal pain frequently accompanied by nausea and vomiting. He noted that his vomitus often looked like coffee grounds and that he had been passing dark-colored, tarry-like stools. He had endured his pain by drinking milk and taking two aspirins four times a day, but frequently wakes up in the middle of the night with abdominal pain. His past history is essentially negative, except that he is a heavy smoker. Because he is anemic and orthostatic (blood pressure falls when he stands up, indicating vascular volume depletion), he is admitted to the hospital for treatment and further evaluation. After receiving several units of blood, he undergoes an endoscopic examination, which reveals large duodenal and gastric ulcers. A mucosal biopsy is performed and subjected to a *Campylobacter-*

like organisms (CLO) test, a colorimetric assay for the presence of bacterial urease, a marker of *H. pylori* (formerly known as *Campylobacter pylori*). The CLO test is markedly positive.

Questions

1. **What caused the gastric lesions in this patient?**
   Answer: This patient has **peptic ulcer disease** that could have been caused by several factors. Since the patient's symptoms preceded his use of aspirin, it is likely that his duodenal ulcer was caused by *H. pylori* infection and perhaps increased acid secretion stimulated by smoking. Although the pathogenic mechanisms mediating *H. pylori*-associated peptic ulcer disease are not entirely clear, increased acid secretion and decreased mucosal-barrier function are likely to be involved. Duodenal and gastric ulcers are, however, also caused by aspirin. **Aspirin and other NSAIDs** inhibit the synthesis of prostaglandins, which are important for maintaining mucus and bicarbonate secretion and barrier function by surface epithelium. As a consequence, mucosal-barrier function is compromised, and the gastric mucosa becomes vulnerable to acid-peptic injury. Decreased endogenous production of prostaglandins also results in increased acid secretion, as prostaglandins may stimulate somatostatin release. It is also possible that NSAIDs decrease mucosal blood flow by inhibition of prostaglandin production, further compromising mucosal integrity.
2. **What would you recommend as treatment for this patient?**
   Answer: The treatment would involve the use of **antibiotics**, possibly **bismuth-containing compounds** (e.g., Pepto-Bismol), and **acid-suppressing medications**. Antibiotics are necessary to eradicate *H. pylori* infection; otherwise, the rate of ulcer recurrence can be substantial. Bismuth compounds are effective, possibly by counteracting some of the deleterious actions of *H. pylori*; acid-suppression by H_2-receptor blockers or proton-pump inhibitors (e.g. Omeprazole) can accelerate ulcer healing. Currently, triple therapy with the use of one proton pump inhibitor (e.g. omeprazole) and antibiotics (e.g. amoxicillin and clarithromycin) is the most effective treatment option. The patient should also be strongly advised to quit smoking, a known risk factor in the development of peptic ulcer disease, and to stop taking aspirin or other NSAIDs.

Case Study 2

A medical student presents to the emergency room with a 2-day history of probable viral gastroenteritis, characterized by severe nausea and vomiting. He has been unable to keep down any fluids and says that he is weak and dizzy (especially when he stands up). Serum electrolytes are drawn for further assessments.

Questions

1. **What kind of metabolic abnormalities would you expect?**
   Answer: Serum electrolytes showed **hypokalemia (low K^+), hypochloremia**, and the presence of **metabolic alkalosis.** These abnormalities arise from **two sources**. First, the ***loss of gastric juices***, rich in H^+, K^+, and Cl^-, accounts

for a major part of the metabolic disturbance, especially since the student is unable to replace them orally. These are ions secreted by parietal cells via the transport processes present in the luminal or canalicular membrane. The metabolic abnormalities are further exacerbated by the ***dehydration*** of the student. The contraction of vascular volume activates renal mechanisms, i.e. activation of the renin-angiotensin-aldosterone system, important for preserving volume. As a consequence, water and Na^+-bicarbonate are reabsorbed at the cost of urinary excretion of K^+ and H^+.

Case Study 3

A 32-year-old woman presents with severe abdominal pain, weight loss, and occasional nausea and vomiting. She was diagnosed as having duodenal ulcer disease on two previous occasions when she presented with identical symptoms. Since her last episode 2 months ago, she has been religiously taking her medications, which include a histamine H_2 blocker and antacids. She denies any history of smoking or use of NSAIDs. On upper endoscopic examination, several severe duodenal ulcers are found, some post-bulbar (past the first portion of the duodenum) and in the jejunum. Stool examination reveals some fat malabsorption and occult blood.

Questions

1. **Because of the severity of the symptoms, what important blood test should be drawn?**
   Answer: This patient has a rare cause of duodenal ulcer disease. **Serum gastrin levels** should be obtained, and in this patient they are found to be profoundly elevated. With her history of ulcer disease refractory to conventional medical management, together with increased serum gastrin, a **diagnosis of gastrinoma** or **Zollinger-Ellison syndrome** must be entertained. After an extensive work-up, this diagnosis is confirmed. Gastrinomas are characteristically slow growing, and the major immediate morbidity to this patient is related to complications of severe peptic ulcers, including *bleeding*, *perforation,* and *obstruction from duodenal scarring*.

   The **pathophysiology of this disease** involves excessive gastrin secretion **(hypergastrinemia)** by a tumor, causing gastric acid hypersecretion. The increased acid load to the duodenum and jejunum can often exceed the capacity of the pancreas to secrete bicarbonate. Thus, luminal pH of the proximal small intestine can be very low and injurious to the mucosa. In addition, the abnormal luminal pH prevents activation of pancreatic-proenzyme activation and proper micellar formation. This causes maldigestion of luminal nutrients and malabsorption, explaining this patient's loss of weight.
2. **How would you medically treat this patient if she refuses surgical intervention?**
   Answer: The mainstay of medical management of this condition is acid secretion suppression. Use of H_2-receptor blockers is often inadequate because they are overwhelmed by the potency of gastrin-stimulated acid secretion. By

blocking at the final pathway of acid secretion, i.e. using ***omeprazole*** to block the proton pump, acid secretion can often be significantly diminished or blocked. Alternatively, patients have been effectively treated with ***Octreotide***®, a somatostatin analog that suppresses the synthesis and release of gastrin by tumor cells. In addition, Octreotide may inhibit acid secretion by inhibiting histamine release and parietal cell acid secretion. Finally, it should be noted that omeprazole is so effective in inhibiting acid secretion in many patients that it actually causes **achlorhydria** (complete absence of gastric acid). Because luminal acid is a negative feedback mechanism for gastrin secretion by antral endocrine cells, the use of omeprazole can cause increases in serum gastrin levels **(hypergastrinemia)** by itself.

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