61 Gastric Function

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61.1 Introduction .................................. 1239

61.2 Structure of the Stomach and Glandular Histology .................................. 1239

61.2.1 General Organization of the Stomach .................................. 1239

61.2.2 Gastric Mucosa and Gastric Glands .................................. 1239

61.3 Composition of Gastric Juice .................................. 1241

61.3.1 Mucus and HCO₃⁻ .................................. 1241

61.3.2 Pepsins .................................. 1242

61.3.3 Hydrochloric Acid .................................. 1243

61.3.4 Intrinsic Factor .................................. 1243

61.4 Physiological Regulation of Gastric Secretion .................................. 1244

61.4.1 Methods for Study of Gastric Secretory Control .................................. 1244

61.4.2 Cephalic Phase of Secretion .................................. 1244

61.4.3 Gastric Phase of Secretion .................................. 1245

61.4.4 Intestinal Phase of Secretion .................................. 1246

61.4.5 Integrated Secretory Response to a Meal .................................. 1246

61.5 The Cellular Basis of Secretory Mechanisms .................................. 1247

61.5.1 HCl Secretion by Parietal Cells .................................. 1247

61.5.1.1 Secretagogues and Receptors for Acid Secretion .................................. 1247

61.5.1.2 Cellular Activation of Secretory Function .................................. 1247

61.5.1.3 Cellular and Molecular Basis of HCl Secretion .................................. 1249

61.5.2 Stimulation of Chief Cells .................................. 1251

61.6 Pathophysiology of Gastric Secretion .................................. 1251

61.7 Gastric Motility .................................. 1253

61.7.1 Muscular and Neural Components .................................. 1253

61.7.2 Adjustments to the Meal - Isotonic Relaxation and Contraction .................................. 1253

61.7.3 Peristalsis and Mixing .................................. 1254

61.7.4 Gastric Emptying .................................. 1254

References .................................. 1256

61.1 Introduction

The vertebrate stomach is a sac-like organ, in the upper portion of the gastrointestinal tract between the esophagus and intestine, serving a number of important functions for the initiation of the digestive process. The motor activities of the stomach relate to its functions as a storage organ for food, in the milling and mixing of food with gastric secretions, and in regulating the amount of food reaching the intestine. The secretions of the stomach initiate digestion by acid denaturation of the ingested food and by promoting enzymatic hydrolysis of proteins. In addition to its direct role in digestion, the strongly acidic nature of gastric juice serves to diminish the number of microorganisms that invade the body through the mouth, and one component of the juice, called intrinsic factor, promotes the absorption of vitamin B₁₂, which is essential for normal maturation of red blood cells.

61.2 Structure of the Stomach and Glandular Histology

61.2.1 General Organization of the Stomach

Like most of the gastrointestinal tract, the stomach is organized in several concentric tissue layers (Fig. 61.1) consisting of

- The mucosa lining the lumen of the stomach
- The submucosa
- The muscle coat, composed of several layers of smooth muscle
- The serosa facing the peritoneal cavity.

The stomach is innervated by parasympathetic neurons from the vagus nerve and sympathetic neurons originating from the celiac ganglion. Generally parasympathetic innervation serves to enhance gastric motor and secretory activities, while sympathetic innervation reduces gastric functions. The stomach, like the rest of the gastrointestinal tract, has its own intrinsic system of neuronal organization that sends signals to gastric smooth muscle, secretory cells and endocrine cells. This so-called enteric nervous system is composed of two distinct, but interconnecting, networks of neurons organized between tissue layers: the submucosal plexus within the submucosal layer, and the myenteric plexus between the longitudinal and circular layers of the smooth muscle. The enteric nervous system provides a means of longitudinal communication between different regions of the stomach and along the entire gut wall, as well as of relaying information to and from the stomach via the parasympathetic and sympathetic neural pathways.

61.2.2 Gastric Mucosa and Gastric Glands

Gastric secretory activity occurs within the mucosa, which actually consists of three components.
The epithelium

The lamina propria

The muscularis mucosae.

The epithelium is a single layer of cells, but is quite complex in form and is made up of several different types of exocrine secretory cells. The lamina propria is a connective tissue matrix supporting the gastric epithelium, including the mucosal blood supply and containing local endocrine (paracrine) cells that help regulate secretory activity. The specific function of the thin layer of muscularis mucosae is uncertain.

More extensive discussion of the gastric epithelial histology and detailed description of the cell types can be found in several excellent reviews [26,30,31]; here we will provide a brief overview of the histological organization (Fig. 61.1). The luminal surface of the mucosa is covered by a layer of columnar epithelial cells, called surface mucous cells, that secrete mucus and an alkaline fluid. The surface is studded with numerous invaginations, or pits, that serve as conduits for secretions from the subadjacent tubular gastric glands. Three types of glands are found in gastric mucosa, designated cardiac glands, oxyntic glands, and pyloric glands, according to their general anatomical location. Cardiac glands occur in the delimited region surrounding the gastro-esophageal junction, and are relatively short, mucus-secreting, glands.

The much longer oxyntic glands are present throughout the fundus and main body of the stomach and are responsible for secreting most of the digestive juice. As schematically depicted in Fig. 61.1, oxyntic glands contain three principal epithelial cell types:

- Parietal cells
- Chief cells
- Mucous neck cells.

The large acid-secreting cells are called parietal cells because of their histological orientation with their basal aspects projecting out to the wall of the gland; they have also been called oxyntic cells, based on their functional acid secretory activity, derived from the Greek oxyntos (to form acid). Parietal cells are found throughout the length of the gland, but tend to be more abundant in the neck region of the gland. Parietal cells account for more than one third of the total cells present in the oxyntic mucosa, and because of their large size, they represent about 50%-60% of the mass of the oxyntic tissue (Table 61.1). Chief cells are the principal source of pepsinogen, a precursor form of the gastric proteolytic enzyme pepsin, and are confined to the base of the glands. Mucous neck cells are small cells, located in the region of transition at the base of the pits extending throughout the neck of the glands. Mucous neck cells secrete a mucus glycoprotein that is distinct from that
of surface epithelial cells, and they also secrete some pepsinogen. There are also a number of endocrine and paracrine cells within the epithelium that play important regulatory roles in gastric secretory function. Pyloric glands occur in the terminal portion of the stomach referred to as the pyloric antrum, or gateway to the intestine. The pyloric glands are primarily composed of surface epithelial cells and mucous neck cells, but they also contain a very important cell, the G cell, which is responsible for the endocrine secretion of the gastric regulatory hormone gastrin.

Gastric epithelial cells, like cells in other regions of the gastrointestinal tract, are in a constant state of turnover. A population of small undifferentiated stem cells located in the upper neck region of the glands represent the progenitor cells for all gastric epithelial cell types. Stem cells divide and differentiate into surface epithelial cells, which migrate up the pit and over the luminal surface. These same stem cells are the proliferative source of glandular cells, which migrate down the length of the gland. Parietal cells and mucous neck cells differentiate directly from the stem cells; further differentiation of mucous neck cells gives rise to the chief cells toward the base of the gland. The life time, or turnover, of gastric epithelial cells is different for each cell type. Careful studies monitoring the incorporation of ^3H-thymidine in the mouse stomach provide an indication of the average cell turnover times [32–34]. Surface epithelial cells have a relatively short life of about 3 days. Parietal cells are longer lived, with an average turnover time of 71 days. Mucous neck cells spend about 40 days in the neck region of the gland, and as they migrate to the base they transform into chief cells, which have an average life of about 250 days.

61.3 Composition of Gastric Juice

The fluid that is secreted into the stomach is called gastric juice. Secretion of gastric juice is regulated, through specific neural and hormonal pathways, by the act of eating and by the presence of food in the stomach and intestine. Gastric juice is the admixture of secretions from the various specialized epithelial cells, both on the surface and within the glands. Three major constituents of gastric juice are the mucus component, the enzyme component and the aqueous component. For the most part, these components are secreted by separate cells, and differential rates of secretion account for the composite variation.

61.3.1 Mucus and HCO$_3^-$

Mucus is a viscous, slippery, gel that covers most of the mucosal surfaces throughout the gastrointestinal tract [1,41]. The consistency and specialized properties of mucus are primarily due to its constituent gel-forming glycoprotein molecules, which are referred to as mucins. In the stomach, mucins are the major organic secretory product of the surface epithelial cells, forming a gelatinous coating over the mucosal surface (Fig. 61.2). Mucous neck cells within the gastric glands also secrete a mucin, but one that is chemically distinct from that of the surface cells. The output, or secretion, of gastric mucins is under both local and neural control [41]. Irritation of the mucosal surface, either by direct mechanical means, such as rubbing the surface, or by exposure to chemical agents that damage the mucosa, effectively activate mucin secretion. Stimulation of the vagus nerve, or splanchnic nerves, or administration of parasympathomimetic drugs induces the release of copious amounts of viscous mucus into the stomach. Gastrin and histamine, which are effective secretagogues for other gastric epithelial cells, do not stimulate secretion of mucins.

Mucin monomers are glycoproteins with a molecular mass of approximately 50 kDa; they are very heavily glycosylated, with only about 15%–20% of mass represented by the protein core [1]. Some 100–200 oligosaccharides are linked along the length of the protein core via hydroxyl groups (O-linked glycosylation) of serine and threonine residues. Each of the monomers has the molecular appearance of a bottle brush, with the protein as the central core and the oligosaccharides as the projecting bristles. Intact gastric mucin molecules consist of four mucin monomers linked as a tetrad by disulfide bridges, and as secreted by surface cells this tetrmeric mucin forms a highly viscous gel layer through which protein molecules, such as pepsin, cannot penetrate. The heavy glycosylation provides protection from peptic hydrolysis along the length of the core protein, but the oligosaccharide-free tetrad center is sensitive to pepsinolysis at the luminal surface of the gel. Thus, steady-state maintenance of the protective gel layer requires continued synthesis and secretion of mucus commensurate with luminal surface degradation by pepsin.

<table>
<thead>
<tr>
<th>Cellular composition as % of mucosal cells (range)</th>
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<tbody>
<tr>
<td>Parietal cells</td>
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<td>32 (24–38)*</td>
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</table>

Total weight of stomach: 143 ± 18 g; wt. of body of stomach as % of stomach wt.: 8 ± 2%; wt. of body mucosa as % of somach wt.: 38 ± 2%

*Parietal cells constitute about one third of the mucosa cell population, but because of their relatively larger size they represent about 50–60% of the mucosa mass

(Data from [29])
In addition to the visible cloudy mucus, the surface mucous cells secrete a fluid that is rich in NaHCO₃. The NaHCO₃ secretory activity of surface mucous cells appears to be similar to HCO₃⁻ secretion by cells of the duodenal epithelium, being dependent upon carbonic anhydrase activity and stimulated by low mucosal pH, cholinergic agonists, and elevated Ca²⁺ levels. It has been proposed that this gastric NaHCO₃ secretion, acting in concert with the layer of surface adherent mucus, provides a protective environment against the low pH and peptic conditions of the gastric lumen. The interstices of the loosely meshed mucus gel layer are impermeable to proteins, but not to acid; although the measured H⁺ diffusion rate is somewhat slower through mucus than diffusion in free solution (2- to 3-fold), H⁺ (and HCO₃⁻) can diffuse through the gel. As a defense against high acidity, the function of the adherent mucus is to provide a stable unstirred layer that prevents convective mixing and rapid dissipation of the small amounts of HCO₃⁻ secretion at the mucosal surface [19,44]. Studies with microelectrodes to probe the pH within the gel matrix have demonstrated that the relatively low steady secretion of HCO₃⁻ serves as a neutralizing force and thus sets up a pH gradient within the unstirred layer of mucus. Even with a bulk luminal pH of 1–3, a pH of 5–7 is maintained directly at the surface mucous cells [44].

The viscoelastic properties of mucin molecules make them an ideal substratum for lubricating biological surfaces [1,41]. Moreover, non-digested food, inert particles, bacteria and sloughed mucosal cells become coated with mucin, which facilitates the slippage of these materials through the gastrointestinal tract. It has been shown experimentally that a thick continuous layer of mucus is also important to protect the gastric mucosa from the damaging effects of acid, pepsin, alcohol, and other noxious luminal agents. However, the loosely meshed mucus gel layer is not an absolute permeability barrier to acid within the stomach, as H⁺ can readily diffuse through the gel. Rather, it has been proposed that the primary function of the adherent layer of mucus in protecting against acid is to provide a stable unstirred layer at the mucosal surface, supporting the neutralization of H⁺ by a low level of HCO₃⁻-rich secretion from the surface epithelial cells [19,44]. The layer of mucus thus acts as a barrier against convective mixing, preventing the rapid dissipation of the small amounts of HCO₃⁻ secretion with the large amounts of acid in the luminal juice.

61.3.2 Pepsins

The principal enzyme of gastric juice is pepsin, although several other enzymes are present in smaller amounts. The less abundant enzymes include a gastric lipase, which is maximally effective against triglycerides with short-chain fatty acids, and the proteolytic enzymes cathepsin and gelatinase, both of which, like pepsin, are derived from chief cells. Gastric pepsin is actually a heterogeneous group of proteins responsible for the proteolytic activity of gastric juice [51]. These peptic proteins are secreted in the form of inactive precursor zymogens called pepsinogens. The pepsinogens can be broadly divided into two immunochemically distinct types, pepsinogen I (PG I) and
pepsinogen II (PG II). In the human PG I is synthesized, stored and secreted by chief cells and mucous neck cells only in the oxyntic region of the mucosa, whereas PG II is also secreted by mucous neck cells in the antral and pyloric mucosa. Both PG I and PG II consist of molecular variants (isozymes) that differ in net charge and/or molecular weight, as can be readily demonstrated by a number of molecular separating techniques. The heterogeneity of the pepsinogens (and pepsins) appears to arise from several factors, including variable numbers of pepsinogen genes, allelic variation within the genes, and post-translational modifications that may occur during processing [55]. Independently of the heterogeneity, all the pepsinogens share the feature of conversion to an enzymatically active form catalyzed by the acidity of gastric juice: the lower the pH the more rapid the conversion, which is almost instantaneous below pH 2. As the pH falls, pepsinogen with a molecular weight of about 42 000 D begins to unfold, and the N-terminal portion splits off, yielding the active enzyme pepsin of about 35 000 D (precise sizes differ with the isozyme). Pepsin is stable at low pH, and has optimal proteolytic activity in the same pH range (i.e., pH 1–3). When gastric juice is neutralized as it passes into the duodenum, pepsin is denatured and thus eliminated from further digestive function. The catalytic activity of pepsin is that of an endoprotease, preferentially cleaving peptide linkages involving aromatic amino acids (e.g., phenylalanine, tryptophan or tyrosine) and an adjacent amino acid, thus producing polypeptide digestion products of very diverse size.

### 61.3.3 Hydrochloric Acid

In the adult human, the stomach will typically secrete about 2–3 l of gastric juice per day, and in some individuals up to 3–4 l/day is secreted. The acidity and ionic composition of the gastric secretory product is not constant, but varies with the rate of volume flow, or secretory rate, as demonstrated in Fig. 61.3. The concentrations of H⁺ and Na⁺ show the closest dependence on secretory rate: H⁺ concentration asymptotically approaches a maximum of about 150–160 mmol/l (pH ∼ 0.8) at high secretory rates, with a concomitant decline in Na⁺ concentration of the juice. In addition, there are smaller increases in the concentrations of Cl⁻ and K⁺ as the flow of juice increases [42]. These interrelations between ionic composition and secretory rate are conveniently explained in terms of a two-component theory of gastric juice formation: a small, relatively constant, flow of a Na⁺-rich alkaline juice from surface epithelial cells and other nonoxyntic cells; and a variable flow of isotonic HCl from parietal cells [35]. The volume of the oxyntic HCl secretion is dependent upon the nature and intensity of gastric secretory stimuli. At high rates of glandular stimulation, and thus high secretory flow, the gastric juice approaches the composition of isotonic HCl.

### 61.3.4 Intrinsic Factor

Based on experimental observation and tests, Castle proposed that absorption of vitamin B₁₂ from the diet required some factor that is secreted into gastric juice, which he called intrinsic factor [7]. In the absence of intrinsic factor a severe, and potentially fatal, anemia develops because of failure of red blood cells to mature (pernicious anemia). We now know that intrinsic factor is a glycoprotein of 55 000 D, which in the human is secreted by parietal cells along with HCl. The same secretagogues and intracellular messengers that stimulate HCl secretion also promote the secretion of intrinsic factor [17]. Intrinsic factor binds to vitamin B₁₂, forming a complex that is resistant to digestion and binds to surface receptors in the ileum to promote the absorption of B₁₂. Patients with pernicious anemia are characterized by achlorhydria, the inability to secrete HCl, and by chronic atrophic gastritis with progressive degeneration of gastric glandular cells and extreme thinning of the gastric epithelium. The condition is one of a group of autoimmune diseases in which antibodies to parietal cell proteins, including intrinsic factor, are found in the serum. For such individuals, parenteral injection of vitamin B₁₂ is required to circumvent the anemia.
61.4 Physiological Regulation of Gastric Secretion

61.4.1 Methods for Study of Gastric Secretory Control

Gastric secretory function is under neural and humoral control that is regulated by the alimentary intake of food and the location and nature of the ingested materials within the gastrointestinal tract. Our current understanding of the mechanisms of gastric secretory control comes from a whole spectrum of experimental preparations, extending from the intact stomach to isolated cells and membranes. A great deal of information can be gleaned from the least invasive preparation, in which a subject simply swallows a tube that is used to aspirate the gastric contents. A variation frequently used in whole animal studies involves the surgical creation of a fistula, or hole, through the gastric wall and exteriorization to the abdominal surface by a cannula that can be closed, or open to collect gastric juice. In fact, several cases of accidental gastric fistulae in humans have been used for study. An abdominal gunshot wound resulted in a permanent gastric fistula in Alexis St.-Martin, a French-Canadian trapper whose gastric secretory and digestive functions were studied by William Beaumont in the early nineteenth century, providing an historic base of information [2].

Surgically prepared pouches from the oxyntic gland area with an exteriorized cannula have been used to study gastric secretion without contamination by salivary juice, food, or intestinal regurgitation. The pouches are prepared with and without parasympathetic or sympathetic innervation to allow experimental discrimination among neural and hormonal pathways regulating secretion (e.g., see Fig. 61.4). The innervated pouch (also called the Pavlov pouch) retains all autonomic connections, whereas parasympathetic innervation is interrupted in the vagally denervated pouch (called the Heidenhain pouch), and all neural connections are severed in the totally denervated pouch. In addition to the relatively intact gastric preparations mentioned above, the use of isolated gastric tissue, cells and organelle preparations has provided the basis for identifying and localizing receptors and secretory processes to specific cellular and subcellular loci.

61.4.2 Cephalic Phase of Secretion

Functional activity within the stomach is carefully coordinated with alimentation and digestive function throughout the entire gastrointestinal tract. For convenience of discussion, gastric secretory output can be divided into three phases of control [14,15]:

- The cephalic phase
- The gastric phase
- The intestinal phase.

The cephalic phase initiates and accounts for about 30% of the response to a meal. As its name implies, the cephalic phase is directly controlled by the brain and it is mediated through efferent fibers of the vagus nerve. Afferent stimuli from taste and smell receptors converge on the vagal nucleus in the medulla, which regulates parasympathetic output to the stomach, as depicted in Fig. 61.5A. Vagal nerve impulses excite postganglionic fibers in the myenteric and submucous plexi, which in turn liberate acetylcholine in the region of the secretory cells in the main body of the stomach. Acetylcholine has both direct and indirect effects in promoting secretion by gastric eoxinic cells. One of the indirect effects of acetylcholine is to promote the local release of histamine from a group of enterochromaffin-like cells (ECL cells) in the oxyntic mucosa. Histamine acts as a powerful paracrine stimulant of HCl output by parietal cells.

Vagal efferent impulses also travel to the gastric antrum, where postganglionic neurons release a transmitter peptide called gastrin-releasing peptide (GRP). GRP acts on a population of G cells in the antral mucosa to effect the endocrine release of the peptide hormone gastrin (Fig. 61.6), which enters the circulation and stimulates receptors on parietal cells and chief cells [18,56]. All elements of the cephalic phase are eliminated by vagotomy, since the efferent nerve traffic to the stomach is carried via the vagus. Atropine is an antagonist of acetylcholine, and thus will abolish the vagal response in the main body of the stomach; however, atropine does not alter the vagal response in the antrum, which uses GRP as the transmitter. The
in the stomach. The physical presence of food provides a distending force for activating receptors in the mucosa. Distension receptors in the fundus and corpus (3) and in the antrum (4) activate afferent neural traffic to the vagal nucleus, which in turn relays afferent impulses back to the stomach (1,2). Since both the afferent and efferent limbs use the vagus nerve, this is called a vago-vagal reflex. Distension also has small direct effect on postganglionic intramural neurons (5,6). 7 Peptides and amino acids, from partial digestion of protein in the food, have a profound effect in directly stimulating the release of gastrin from antral G cells, and activating the endocrine pathway.

cephalic phase is responsible for initiating the response to a meal and will usually begin within a few minutes after the appropriate afferent stimuli. It will also occur in response to stimuli that have been conditioned to be associated with feeding, e.g., the sight of a well-prepared meal or the sound of bacon sizzling in the pan.

61.4.3 Gastric Phase of Secretion

The gastric phase of secretion is regulated by events within the stomach and usually provides the largest part, about 60%, of the response to a meal [14]. The stimulus can be due to the simple physical presence of the food and/or to the chemical nature of the food, and involves both neural and hormonal components (Fig. 61.5B). Distension of the stomach activates intrinsic neurons of the plexuses, leading to both an intramural local reflex and an extramural vagal reflex response. The local reflex involves direct stimulation of postganglionic neurons and supports very little secretory response unless potentiated by other secretagogues; it is insensitive to vagotomy, but can be abolished by atropine. The extramural response to distension is called a vago-vagal reflex because it uses the vagus nerve to transmit afferent impulses to the medulla and return via vagal efferent neurons to stimulate secretion. All aspects of the vagal efferent response for the gastric phase are similar to those described for the cephalic phase. The nature of the food within the antrum has a profound effect on secretion through the hormone gastrin, and this
aspect of the gastric secretory phase is not abolished by vagotomy or atropine. Gastrin is a peptide hormone, 17 amino acids in length, that is synthesized and stored in a group of cells within the antral and pyloric mucosa called G cells [16,25]. Studies with synthetic peptides have shown that only the last four C-terminal acids, sometimes called tetra gastrin, are required for the gastric secretory activity of the hormone. Peptides from partially digested protein directly stimulate G cells within the antral and pyloric mucosa to release gastrin, which enters the circulation and stimulates acid and pepsinogen secretion. Carbohydrate and fat, like undigested protein, do not stimulate gastrin release except by distension. Lowering of pH (pH 2 or less) at the surface of the antral mucosa greatly inhibits the gastric phase of secretion, and this can be attributed to the prevention of gastrin release by another peptide called somatostatin. Somatostatin is contained within and secreted by endocrine-like cells, called D cells, located throughout most of the gastric mucosa [58]. D Cells in the antral and pyloric mucosa respond to low luminal pH by releasing somatostatin, which acts in a local paracrine manner to turn off gastrin secretion by G cells. This mechanism of inhibiting the release of gastrin by low antral mucosal pH, as schematically outlined in Fig. 61.6, is an important aspect of negative feedback regulation of gastric HCl output.

61.4.4 Intestinal Phase of Secretion

There is very little stimulation associated with the intestinal phase of gastric secretion, less than 10% of the secretory response to a meal. Immunocytochemical data show that a few G cells spread through the pyloric area into the duodenum, and these may be responsible for some weak stimulatory effects in a manner similar to that described for the gastric phase. There are also reports that another hormone, tentatively called enteroglucagon, may respond to duodenal distension and stimulate the oxyntic mucosa. However, the most important regulatory aspects of the intestinal phase are those associated with inhibition of both gastric secretion and gastric emptying. The duodenum provides a means of feedback inhibition and termination of gastric secretion after a meal. The nature of the partially digested food materials that enter the duodenum, particularly solutions of high acidity, high fat content, or high osmotic pressure, represent the major stimuli for feedback inhibition of gastric secretion. On the other hand, if the duodenum is surgically bypassed and gastric contents are emptied further down in the intestine, the secretory output of the oxyntic mucosa is greatly enhanced. The principal means of feedback regulation is through the action of several hormones that are released from the duodenal mucosa. For example, acid in the duodenum causes the release of the peptide hormone secretin, which, in addition to its major role to stimulate the output of HCO₃⁻ by the pancreas and liver (see Chap. 20), has an inhibitory effect on both gastric acid secretion and motility. Secretin inhibits acid secretion by causing the release of somatostatin, which in turn attenuates the output of gastrin by G cells [11,50,58]. Additionally, acid in the duodenum feeds back to inhibit gastric acid secretion via an intramural nervous reflex that might also operate via somatostatin release. Fats in the duodenum, especially triglyceride digestion products such as fatty acids and monoglycerides, cause the release of two additional hormones, known as cholecystokinin (CCK) and gastric inhibitory polypeptide (GIP). CCK is the major hormone regulating pancreatic enzyme secretion and biliary output (see Chap. 20), but it also has both stimulatory and inhibitory actions on gastric secretion. CCK is a 33-amino-acid polypeptide containing the same five C-terminal amino acids as does gastrin, and CCK can be shown to act on parietal cells both as a poor agonist for gastrin and, in higher doses, as an antagonist to gastrin [47]. Because of the dose range there may be little physiological significance for these actions of CCK on gastric acid secretion. However, CCK does stimulate chief cells to secrete pepsinogen, and CCK has a possible role in inhibition of gastric emptying by enhancing pyloric constriction. GIP, which has some sequence homology with secretin, came to be accepted as a distinct peptide hormone only after adequate procedures had been developed for separating it from other hormones present in extracts of duodenal mucosa, such as secretin and CCK [6]. GIP inhibits both parietal cell secretion and the output of gastrin by its action in promoting the paracrine release of somatostatin in the antrum and body of the stomach. In the antrum, somatostatin prevents the release of gastrin; in the fundic and body mucosa, somatostatin has a direct inhibitory effect on parietal cells, as discussed below.

61.4.5 Integrated Secretory Response to a Meal

In the interdigestive period the stomach has a basal secretory activity in the absence of extrinsic digestive stimulatory input [15]. The amount of basal secretion varies among species, and even shows a circadian rhythm, but in a healthy human basal secretion does not represent more than 10% of the maximal secretory response to a meal. Basal secretion can be reduced by atropine and histamine-H2-receptor antagonists, showing that there is some background level of stimulation. In the absence of food, and the buffering capacity that the food represents, the pH of the gastric contents can be quite low, often less than 2.0. The acidic luminal pH operates to minimize any additional secretion. High activity of H⁺ on the mucosal surface stimulates D-cells to release somatostatin locally in both the antrum and the main body of the stomach. Somatostatin inhibits release of gastrin by G-cells, and also has some direct inhibitory effect on parietal cells, so that the normal stomach is maintained in a minimal basal secretory state. The ingestion of a meal has a series of primary, secondary and tertiary effects in turning on secretory activity and eventually restoring the resting state. The immediate effects are those afferent stimuli that activate vagally medi-
ated cephalic phase, including direct cholinergic stimulation, and the action of vagal efferents to inhibit somatostatin cells and thus release G-cells and parietal cells from somatostatin inhibition. The food that enters the stomach provides a buffering action, raising gastric luminal pH and releasing the inhibitory effects of somatostatin. Physical distension and the consequent local responses initiate the gastric phase of secretion. Peptide digestion products directly stimulate gastrin release from G-cells, providing the large hormonal stimulation of gastric secretory output.

As gastric digestion proceeds, several gastric and intestinal processes act to reduce HCl secretory output [15]. Alimentary satiety, operating through a hypothalamic center, abolishes the cephalic phase of stimulation. The buffer capacity of the meal is exceeded and gastric pH falls, stimulating the local release of somatostatin, which inhibits gastrin output. The partially digested food moves into the duodenum where the acidity, fats and osmolarity produce the neural and hormonal responses of the intestinal phase that reduce H+ secretion and return the stomach to the resting state.

61.5 The Cellular Basis of Secretory Mechanisms

61.5.1 HCl Secretion by Parietal Cells

61.5.1.1 Secretagogues and Receptors for Acid Secretion

There are three primary physiological stimulants, or secretagogues, of acid secretion:

- Acetylcholine, a neurotransmitter released by postganglionic neurons of the vagus nerve
- Gastrin, a classic endocrine stimulant released by G-cells in the antrum of the stomach
- Histamine, a paracrine stimulant released by enterochromaffin-like cells that are in close proximity to the basal aspect of parietal cells.

All three secretagogues most certainly operate to stimulate acid secretion, but there is considerable variation among different animal species as to the relative abundance of the receptor types specifically on parietal cells, and this has been the source of a long-standing controversy on the physiological role of histamine. Views on the specific role of histamine have ranged from one extreme with uncertainty as to whether it has any physiological function at all, to the extreme hypothesis that histamine is the sole final common mediator for parietal cell activation, with acetylcholine and gastrin operating by the local release of histamine from the histamine-containing cells in the lamina propria [12].

The discovery that HCl secretion was inhibited by specific histamine receptor antagonists of the H2 type (H2 antagonists) was a milestone in gastric secretory physiology, providing an effective treatment for conditions of hyperacidity and peptic ulcers without surgical intervention [4]. The use of H2 antagonists to inhibit acid secretion in vivo stimulated by acetylcholine and gastrin, as well as by histamine, definitively demonstrated that histamine was a physiological stimulant and offered some support for the final common mediator hypothesis. The histamine hypothesis was further supported by data from several in vitro gastric preparations, in which histamine was shown to be the most effective stimulant (i.e., maximal rates); the in vitro data also show that acetylcholine and/or gastrin can cause the local release of histamine [3]. However, potentiating effects of multiple secretagogues are well known. Moreover, it has been clearly shown in some species that parietal cells have receptors for all three secretagogues, acetylcholine, gastrin and histamine, and that an acid secretory response can occur without the involvement of histamine [52]. In fact, these varied observations are consistent with a more moderate hypothesis proposing a convergence of biochemical information from different secretagogue receptors at the basal surface to a common intracellular step for parietal cell activation [8, 23, 53]. Different animal species or types of experimental preparations may have widely differing densities of the three receptor types, but if the means for parietal cell activation converged to the same final events of cellular transformation, a scheme such as that shown in Fig. 61.7 would explain preparation-dependent variation in response to secretagogues, as well as providing the basis for the observed potentiating responses when more than one secretagogue is given.

61.5.1.2 Cellular Activation of Secretory Function

Stimulation of gastric HCl secretion by the primary secretagogues is mediated by at least two distinct sets of biochemical pathways, or cascades, each operating through its own intracellular, or second, messenger (see also Chap. 6). Although there are differences in receptors and second-messenger signalling systems, evidence strongly suggests that there is convergence within the terminal steps to effect the final secretory processes. The primary parietal cell secretagogues and their second messenger pathways are shown schematically in Fig. 61.7.

H2 receptors on the basal surface of parietal cells are linked to the activation of adenylate cyclase through stimulatory G-proteins, Gs [8]. Thus, stimulation of gastric secretion by histamine, but not by acetylcholine or gastrin, leads to enhanced formation of cyclic AMP (cAMP) as a principal second messenger in parietal cells. Additional and unequivocal support for the cAMP hypothesis comes from observations that gastric acid production can be stimulated by:

- Membrane-permeable derivatives of cAMP
- Blockers of cAMP catabolism, such as caffeine
- Agents that directly activate adenylate cyclase, such as forskolin
The stimulatory action of cAMP is mediated by activation of cAMP-dependent protein kinases (PKA) whose function in parietal cells is to promote a cascade of protein phosphorylations and cell activation. The so-called histamine/cAMP/PKA pathway has been shown to increase phosphorylation of several parietal cell proteins, including cytoskeletal proteins and possible K⁺ conductance proteins [9,21]; however, details as to how these and other phosphoproteins initiate the HCl secretory process is a subject of intense current investigation.

Both direct and indirect studies to monitor intracellular Ca²⁺ concentration have demonstrated that acetylcholine and its agonists cause an increase in cytosolic Ca²⁺ activity [10,40]. Thus, the parietal cell conforms to the model established in other tissues in which cholinergic receptor stimulation works via a Ca²⁺-dependent pathway. The action of gastrin on parietal cells appears to be similar to cholineric stimulation, involving an increase in cytosolic Ca²⁺, and no change in cAMP concentration. This is distinct from the effect of histamine, which, in addition to stimulating the cAMP/PKA pathway described above, has been shown to cause a spike in intracellular Ca²⁺ concentration, although a much more modest one than appears with cholineric agonists [10].

When Ca²⁺ ionophores are used to elevate cytosolic Ca²⁺ no parietal cell secretion occurs if other secretagogues are not present, whereas the secretory response to histamine is slightly potentiated [59]. The mechanism by which elevated cytosolic Ca²⁺ levels facilitate HCl secretion is uncertain, but it is likely to require concomitant changes in the phosphorylation of specific proteins. Increased levels of cytosolic Ca²⁺ are themselves the result of another major intracellular signalling system involving receptor activation of phospholipid hydrolysis, producing inositol (1,4,5)-trisphosphate and diacylglycerol from phosphatidylinositol (cf. Chap 5; Fig. 61.7). Inositol trisphosphate is responsible for liberating Ca²⁺ from intracellular bound stores and for increasing entry of Ca²⁺ from the external milieu. Diacylglycerol acts as a second messenger to activate protein kinase C (PKC), which like PKA promotes protein phosphorylation. Whether, and to what extent, specific gastric phosphoproteins produced by PKC and PKA are similar, and how they converge on a final common pathway, remains to be determined.

Figure 61.7 also indicates that there are several inhibitory receptor pathways on parietal cells. Somatostatin acts as a paracrine agent to inhibit parietal cell secretion, being liberated by local D cells. Somatostatin receptors activate an

![Diagram](image_url)

**Fig. 61.7.** Secretagogue-receptor relationships and signal transduction pathways for activation of HCl secretion by parietal cells. The most prominent stimulation is via histamine and the so-called cyclic AMP/protein kinase A (cAMP/PKA) pathway. Histamine acts on H₂ receptors to activate stimulatory G proteins (G₁) and adenylyl cyclase (AC). The resulting production of cAMP activates PKA, which catalyzes the phosphorylation of several phosphoproteins. The specific role of these phosphoproteins in parietal cell activation is uncertain, but one of them, ezrin, is a membrane cytoskeletal linker possibly involved in membrane recycling of the H₂K-ATPase. Breakdown of cAMP occurs via phosphodiesterase (PDE); inhibition of PDE, e.g., by caffeine, has the same effect as activation of AC. Somatostatin, and also prostaglandins and epidermal growth factor (not shown), interact with parietal cell receptors to effect an inhibition of cell function, by activating an inhibitory G protein (G₂) which turns off AC. Acetylcholine (ACh) and gastrin have a major stimulatory effect by causing the local liberation of histamine from enterochromaffin-like cells (paracrine stimulation), and thus promote the cAMP/PKA pathway. The parietal cell also has receptors for ACh (M₁ receptors) and gastrin (CCK-B receptors), which activate phospholipase C (PLC) through a different class of G proteins. PLC hydrolyzes phosphatidylinositol to its products, inositol (1,4,5)-trisphosphate (IP₃) and diacylglycerol (DAG). IP₃ mobilizes intracellular Ca²⁺, and together with DAG, activates protein kinase C to catalyze phosphorylation of other proteins. Ca²⁺/calmodulin-mediated protein kinases may also be involved via Ca²⁺ mobilization. Ultimately, the protein phosphorylation pathways converge on the critical, but currently uncertain, cell-activation processes.
inhibitory G protein, Go, that lowers adenylate cyclase activity and cAMP concentration. Output of somatostatin ordinarily occurs at a sustained level, and is inhibited by cholinergic stimulation. This suggest that parietal cells are under a tonic state of inhibition that is relaxed by suppressing D-cell secretion. Epidermal growth factor (EGF) has an negative effect on histamine-mediated HCl secretion. This most probably occurs via an inhibitory phosphorylation pathway, possibly through a tyrosine kinase. Prostaglandins can be shown to inhibit HCl output, but the required concentrations are high and it is difficult to sort out specific parietal cell effects from other mucosal protective actions of prostaglandins (see Sect. 61.6).

61.5.1.3 Cellular and Molecular Basis of HCl Secretion

The H⁺/K⁺-ATPase, the Primary Gastric Proton Pump. The transport of gastric H⁺ is powered by a membrane-bound pump that uses ATP to drive an electroneutral one-for-one H⁺/K⁺ exchange, with a stoichiometry for H⁺:K⁺:ATP of 1:1:1 [24,49], (see also Chap. 8). This gastric proton pump enzyme is called the H⁺/K⁺-ATPase; a schematic representation of the operation of the gastric H⁺/K⁺-ATPase is shown in Fig. 61.8. Although the H⁺/K⁺-ATPase is highly enriched in, and unique to, parietal cells, it is closely related to the Na⁺/K⁺-ATPase and the Ca²⁺-ATPase, sharing a number of structural and functional features. All three of these cation-transporting systems belong to a larger family of ATPases, called P-type ATPases since the enzymes undergo phosphorylation/dephosphorylation and ligand-dependent conformational rearrangements during their transport/catalytic cycles. These is an especially high degree of homology between the H⁺/K⁺-ATPase and the (Na⁺+K⁺)-ATPase: the primary amino acid sequence shows about 60% identity; both pumps work as exchangers, transporting H⁺ or Na⁺ in exchange for K⁺; and they operate in the membrane as heterodimers, being composed of α- and β-subunits.

The Membrane Recycling Hypothesis for HCl Secretion. While the H⁺/K⁺-ATPase provides the molecular mechanism for the transduction of metabolic energy into secreted gastric H⁺, the physiological activity of the pump is intimately related to the changes in parietal cell morphology that are associated with the turning on and off of HCl secretion at the time of the meal. A schematic representation of the ultrastructure of parietal cells in the resting and secreting states is shown in Fig. 61.9. Parietal cells are among the most metabolically active cells in the body, with numerous, large mitochondria to support the enormous energy demand required to secrete H⁺ against a gradient of more than a million-fold, i.e., from a cytosolic pH ~7.0 to luminal pH of less than 1.0. However, the most distinctive structural features are the highly specialized membranes, at the apical cell surface and within the cytoplasm, whose stimulation-dependent structural changes form the basis for the membrane recycling hypothesis of HCl secretion [22]. The apical surface of the parietal cell has a unique arrangement of invaginations, or secretory canaliculi, that extend to and radiate through the cell. The secretary canaliculi of the resting, or nonsecreting, cell are relatively narrow, and the entire apical surface is covered with short, stubby microvilli containing an organized array of actin microfilaments. Parietal cells also have an extensive system of cytoplasmic membranes, called tubulovesicles. In resting cells, during the interdigestive period, the H⁺/K⁺-ATPase is localized to the tubulovesicles. When parietal cells are stimulated there is a profound morphological change whereby the tubulovesicles fuse with the apical membrane, leading to a 5- to 10-fold expansion of the apical surface area within the secretory canaliculi. According to the membrane recycling hypothesis these dynamic membrane transformations provide access for the intrinsic proton pumps to the gland lumen. Parietal cell stimulation, primarily under the direction of the cAMP/PKA system, not only incorporates the H⁺/K⁺-ATPase to the apical plasma membrane, but also results in the activation of two ionic pathways at the apical membrane, K⁺ channels and and Cl⁻ channels [20,46,57]. Membrane fractionation studies strongly support the membrane recycling hypothesis. In resting parietal cells H⁺/K⁺-ATPase-rich membranes are isolated in the form of tubulovesicles with low intrinsic ionic (K⁺ and Cl⁻) permeability, and thus poor proton transport (H⁺/K⁺+ exchange) capability. For stimulated parietal cells H⁺/K⁺-ATPase is associated with large vesicles that (1) are derived from the apical canalicular plasma membrane, (2) have high intrinsic conductive pathways for K⁺ and Cl⁻, and (3) effectively
accumulate large proton gradients in the presence of K⁺, Cl⁻ and ATP.

A functional representation of the resting/stimulated transition for parietal cells is given in Fig. 61.10. In the resting cell, low ATP turnover in maintained by relative impermeability of tubulovesicle membranes. In the stimulated cell, where tubulovesicles have fused with the apical membrane, passive flux of K⁺ and Cl⁻ from cell to lumen occurs in parallel to K⁺-for-H⁺ exchange by the pump, resulting in the recycling of K⁺ and a net flow of HCl into the lumen accompanied by an osmotic equivalent of water. For each mole of H⁺ secreted by the pump, an equivalent amount of base must also be produced, and it must be eliminated from the cell. The parietal cell uses CO₂ and carbonic anhydrase to convert the base into HCO₃⁻, which is then transported out of the cell by an efficient basolateral membrane Cl⁻/HCO₃⁻ exchanger [39,43]. This mechanism provides the source of Cl⁻ that will accompany H⁺ in gastric juice, as well as the source of HCO₃⁻ that is released into the plasma as part of the alkaline tide of the meal. Withdrawal of the stimulus from the parietal cell reverses the activation process; the apical surface area is diminished by mass endocytosis and tubulovesicles reform within the apical pole of the cytoplasm [20].
61.5.2 Stimulation of Chief Cells

Receptors and Activation Pathways. Chief cells synthesize pepsinogen through a very active synthetic machinery. Newly formed pepsinogen granules are stored in the apical pole of the cell until the appropriate stimuli come to bear, when the granules fuse with the apical membrane and release their contents into the lumen of the gastric gland, much like zymogen release from pancreatic acini.

A scheme of receptor/activation pathways in chief cells is shown in Fig. 61.11. Release of pepsinogen is strongly regulated by cholinergic receptors, which operate as they do in parietal cells by stimulating phospholipid turnover and generating the second messengers, inositol trisphosphate and diacylglycerol, elevating cytosolic \( \text{Ca}^{2+} \) and activating PKC [45]. The specific proteins (e.g., phosphoproteins) regulating the pepsinogen release process are not known. Gastrin is not a potent stimulant of pepsinogen release, but chief cells are stimulated by two other peptide hormones secreted by the duodenum, cholecystokinin and secretin. Interestingly, each of the duodenal hormones operates through a different intracellular activation pathway (Fig. 61.11). Cholecystokinin uses the PKC and \( \text{Ca}^{2+} \) pathway, while secretin receptors activate the cAMP/PKA pathway. Thus, as in parietal cells there appear to be separate, and possibly convergent, pathways for activating chief cells. Studies with isolated chief cells have also demonstrated the presence of adrenergic receptors that elevate cAMP, but their physiological relevance in vivo is uncertain. Chief cells do not have histamine receptors, and the small increase in output of pepsinogen that is seen in response to injection of histamine has been attributed to a washout of pepsinogen with the volume flow of acid.

61.6 Pathophysiology of Gastric Secretion

One of the most interesting questions regarding the overall functional activity of the stomach concerns its resistance to autodigestion; that is, why does the stomach not digest itself? Gastric digestive secretions can destroy almost any cell and hydrolyze almost any biological protein. In fact, the gastric mucosa itself is rapidly destroyed and hydrolyzed if the acid and pepsin normally present in gastric juice are placed on the serosal side, but the tissue is endowed with special mechanisms, collectively referred to as the gastric mucosal barrier, that protect the luminal surface from autodigestion. However, there are conditions in which the gastric mucosal barrier is challenged or functionally defective, and this leads to painful conditions of gastritis and erosion and the potentially fatal degenerative conditions of ulceration.

Gastric and duodenal ulcers form when endogenous mucosal protective devices are overwhelmed by the damaging properties of acid and pepsin. Both gastric and duodenal ulcers are generically called peptic ulcer disease, because acid and pepsin is required for the ulcer forma-

Fig. 61.11. Secretagogue—receptor activation of the chief cell. Activation, fusion and release of pepsinogen granules is a function of phosphorylation of certain critical proteins, which in turn are regulated by independent pathways via specific protein kinases. The major stimulatory pathway involves cholinergic \( \text{M}_1 \) type receptors and CCK-B type receptors, which activate phospholipase C (PLC) to hydrolyze phosphatidylinositol (PIP\(_2\)), yielding the intracellular messengers inositol (1,4,5)-trisphosphate (IP\(_3\)) and diacylglycerol (DAG). IP\(_3\) mobilizes intracellular \( \text{Ca}^{2+} \) and, together with DAG, activates protein kinase C. \( \text{Ca}^{2+} \) mobilization may also be involved in activating \( \text{Ca}^{2+}/\text{calmodulin}-\text{mediated protein kinase}. A separate pathway occurs via secretin receptors (or \( \beta \)-adrenergic receptors, not shown) to activate stimulatory G protein (\( \text{G}_s \)) and adenylyl cyclase (AC). The resulting production of cAMP activates cAMP-dependent protein kinase (PKA). Stimulation by multiple pathways leads to convergence and potentiation of the activation process. Somatostatin has an inhibitory influence on pepsinogen output by activating an inhibitory G protein (\( \text{G}_i \)) which turns off AC.
Excess gastric acid can be countered to some extent by ingestion of antacids or buffering mixtures, but advances in receptor biology and some fundamental understanding of the gastric proton pump have led to the development of drugs that are extraordinarily effective in controlling the output of HCl by parietal cells. H2-receptor antagonists, such as cimetidine and ranitidine, block the action of histamine on parietal cells with very little effect on non-gastric histaminergic sites, and they have therefore been extensively used to treat peptic ulcer disease. More recently, drugs have been developed that directly inhibit the H⁺/K⁺-ATPase [49]. One of these, omeprazole, obtains its specificity by being concentrated and activated in the acidic environment of the parietal cell canalliculus, where it covalently modifies the pump enzyme. Additional H⁺/K⁺-ATPase inhibitors that compete reversibly with pump ligands, such as K⁺, are currently being developed with a view to increasing their specificity of action.

Physiological defense within the stomach is the result of a complicated and cooperative group of factors, collectively known as the gastric mucosal barrier, and better understood on the basis of causal experimentation than from fundamental mechanisms. Experimental tests have shown that competency of barrier resistance depends upon physiological integrity of the tight junctions between epithelial cells, mucus and bicarbonate secretion by surface mucous cells, adequacy of mucosal blood flow, and processes of cell renewal, as well as being negatively affected by damaging drugs and bacterial infection [28]. It is also reasonable to conclude that the exterior surface of apical plasma membranes of gastric epithelial cells must have highly specialized structural and biochemical adaptations that resist the caustic acidic and peptic conditions, yet the nature of these specializations remains elusive.

As noted above, mucus forms a viscoelastic meshwork covering the surface of the mucosa, serving to protect the surface epithelium from abrasion by food particles, and acting in concert with HCO₃⁻ secretion to minimize the concentration of H⁺ at the surface epithelial cells. Conditions that destroy the layer of mucus or inhibit HCO₃⁻ secretion lead to greater H⁺-induced surface damage. A number of drugs, or even endogenous components like bile salts moving retrogradely from duodenum to stomach, cause concentration-dependent surface erosion by damage to surface cells and tight junctions. Aspirin, and the related group of non-steroidal anti-inflammatory drugs (NSAIDs), are a frequent cause of gastric ulceration because of their wide use. The precise mechanism of injury is unknown, but it almost certainly occurs by virtue of the reduced prostanoïd synthesis caused by the NSAIDs. Gastric mucosal injury induced by NSAIDs and a variety of noxious agents, including alcohol and boiling water, can be attenuated by the luminal application of prostaglandins [48]. Such observations have led to the suggestion of treatment with prostanoïd drugs for certain degenerative conditions.

In the past several years gastroenterologists have become increasingly aware of the possibility that peptic ulcers may

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Fig. 61.12. Human gastric acid secretion after a steak meal in normal subjects and those with a diagnosed duodenal ulcer. (Reproduced from [5])

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bition, but the two conditions differ in etiology and locus within the mucosal lining. In general, gastric ulcers in the body or antrum of the stomach are more typically the result of a weakening of the defense mechanisms, while duodenal ulcers in the prepyloric and duodenal mucosa are more often related to abnormally high secretory levels.

Although duodenal and prepyloric ulcers are generally associated with high endogenous rates of acid secretion (Fig. 61.12) there is a lot of variance in the population. High secretory rates are due to any one or any combination of the following factors: increased circulating levels of gastrin (hypergastrinemia), an especially high sensitivity to gastrin, and increased parietal cell mass. Individuals with duodenal ulcers usually do not have hypergastrinemia in the non-feeding state, but their responses to a meal, in both gastrin output and sensitivity of parietal cell secretion, are greater than normal. There is also an interesting correlation between the measured levels of pepsinogen I circulating in the serum and the occurrence of duodenal ulcers in patients. Although there is no explanation for the elevated serum pepsinogen, and at the pH of blood the enzyme is totally inactive, it has been proposed that the serum pepsinogen level might be used as a predictor of susceptibility [51].

Acid hypersecretion and the presence of duodenal ulcers occur in individuals with Zollinger-Ellison syndrome. This syndrome is the result of tumors that secrete gastrin (gastrinomas), usually occurring in the pancreas, but also found in duodenum and stomach. The sustained hypergastrinemia produces high acid output and severe ulcers. High levels of gastrin also have a trophic effect on parietal cell growth, which can further exacerbate the problem.
have an infectious origin. In 1984 Marshall and Warren [37] proposed that an unusual bacterium was the cause of peptic ulcer disease. This microorganism, now known as *Helicobacter pylori*, thrives only in the unusual environment of the surface of the human gastric epithelium, beneath the mucous coat, and has an active urease that hydrolyzes urea to produce abundant levels of ammonia. Known infections with *H. pylori* are associated with chronic gastritis and thus the organism may be another “barrier breaker” leading to erosion and ulceration. Recent studies have shown that, although antisecretory drugs are effective in healing peptic ulcers over the short term, long-term prevention of recurrence was more closely correlated with eradicating the infection as well [27].

6.1.7 Gastric Motility

6.1.7.1 Muscular and Neural Components

The stomach has three major motile functions associated with digestion:

- To serve as a reservoir as the meal is ingested (the stomach can accommodate up to 1.51)
- To mix the ingested food with gastric secretions
- To empty gastric contents into the duodenum.

These motile functions are accomplished by coordinated activity of three layers of smooth muscle: an outermost longitudinal layer, a middle circular layer, and an inner oblique layer [38]. The longitudinal and oblique layers are incomplete, and not represented along the full length of the stomach. The longitudinal layer is present only in the distal two-thirds of the stomach, while the oblique layer of muscle can be distinguished only in the proximal half of the stomach. The circular layer is prominent throughout, although its thickness is obviously increased in the antrum of the stomach, where the force of contraction is greatest. The fundamental characteristics of excitability and contractility for gastric smooth muscle are similar to those described in Chap. 63 for intestinal smooth muscle. Although innervation is intrinsic to the smooth muscle cells themselves, coordination is highly dependent upon the enteric neural plexuses, especially the myenteric plexus, and the intensity of contractile activity is under the influence of parasympathetic and sympathetic efferent neural activity.

The motile functions of the stomach can be divided into two general classes of activity:

- Adjustments to the volume of the meal
- Peristaltic mixing and propulsion.

Furthermore, these activities can be categorized with respect to the anatomical region [36,38]. The proximal stomach behaves as a reservoir and accommodates to its volume by modulating tonic contractile activity. In contrast, the distal stomach generates phasic peristaltic waves of contraction for mixing, grinding and propelling the contents (Fig. 6.13).

6.1.7.2 Adjustments to the Meal—Isotonic Relaxation and Contraction

It is important for normal digestion that the stomach be able to store food, initiating the digestive process and allowing the passage of food only when the intestine is prepared to receive it. Fundamental to serving as a reservoir is the ability of the muscle to undergo isotonic relaxation and contraction as the contents of the stomach radically change. During feeding, the stomach can greatly expand in

![Fig. 6.13. Regional motor functions within the stomach. The proximal stomach shows no basal electrical activity, but it serves as a highly "distensible" gastric reservoir via tonic contraction and relaxation that accommodates the filling and emptying associated with a meal. The distal stomach has basal electrical slow waves that originate from a pacemaker region and lead to phasic peristaltic contractions, as well as the more vigorous grinding patterns that occur in the distal antrum](image-url)
volume with virtually no change in the steady-state intragastric pressure. The accommodation of large volume changes comes about by active relaxation of smooth muscle in the more proximal half of the stomach, and has been called receptive relaxation, or isotonic relaxation. Receptive relaxation is mediated by a vago-vagal reflex, involving vagal afferent signals that travel from gastric stretch receptors to the central nervous system, and return via efferent signals to the muscle also through the vagus. The complementary half of this total reflex activity involves the gradual decrease in volume via isotonic contraction of the gastric smooth muscle and restoration of tone as the stomach empties. Because of the role of the vagus, isotonic relaxation and contraction are predictably abolished by vagotomy; however, since it is not very much altered by atropine, the reflex response is probably not cholinergic, but the specific neurotransmitter is unknown [38].

61.7.3 Peristalsis and Mixing

As food is ingested it tends to remain in relatively unmixed layers within the proximal half of the stomach because of the absence of mixing waves. Integrated and regular waves of contractile activity are a fundamental property of the smooth muscle in the distal half of the stomach. These contractions are peristaltic in nature and serve as mixing waves, but they also tend to move the contents toward the pylorus. The contractile waves originate in mid-stomach with very little force, and gradually build up in strength and velocity as they migrate through the antrum to the pylorus. High pressures are developed in the region of the pylorus, forcing a small amount of the contents through the sphincter into the duodenum and propelling the remainder back into the stomach, thus serving to pulverize as well as thoroughly mix the contents (Fig. 61.14). The mixing waves of peristaltic contraction are initiated by the intrinsic electrical activity of the smooth muscle cells and occur with regular frequency, e.g., about three per minute in humans. The frequency of the peristaltic pressure wave is based on the pacemaker activity in smooth muscle cells of the corpus [54]. Comparisons of the electrical activity of progressive regions from proximal to distal stomach are shown in Fig. 61.15. For contraction to occur, the depolarizing slow wave must reach the threshold to produce a spike potential [54]. The amplitude or strength of contraction is a function of the magnitude of the plateau of the slow wave of depolarization and the frequency of spike potentials during the plateau. In the fasted stomach, contractile activity is almost imperceptible, and although slow waves of depolarization occur with about the same frequency as in the fed state, they are not sufficient to trigger spikes and the contractile event. Thus, rhythmicity of the slow waves is an intrinsic property of the smooth muscle cells, but the intensity of activity and translation into peristaltic waves of contraction depend on the digestive conditions, such as food within the stomach. The neural and hormonal activities associated with the early stages of digestion markedly alter the amplitude of the slow waves, the generation of spike potentials, and the consequent force of peristaltic contraction.

Stimulation of the vagus nerve increases the force and frequency of gastric contraction. The neurotransmitter for this vagal effect is acetylcholine, and it is totally blocked by atropine. The local effect of acetylcholine on gastric smooth muscle cells is to increase the amplitude and duration of the slow waves of depolarization, promoting spikes and enhancing the peristaltic force of contraction, as exemplified in Fig. 61.16a [54]. Stimulation of the sympathetic nerves inhibits gastric motility, most probably with norepinephrine as transmitter (e.g., Fig. 61.16c). Norepinephrine decreases the amplitude and duration of the rhythmic slow waves in the smooth muscle cells. Gastric smooth muscle is also influenced by certain digestive hormones. For example, gastrin and CCK have been shown experimentally to stimulate contractile activity (e.g., Fig. 61.16b), while secretin and GIP decrease it. However, it is uncertain whether, and to what extent, these modulating effects operate at the normal circulating levels of the hormones [38].

61.7.4 Gastric Emptying

The emptying of the stomach following a meal is regulated by a number factors, generally related to
optimizing the ultimate digestion and absorption of the material. The volume of the stomach after a meal may be as much as 1–1.5, including the ingested solids and liquids and the gastric juice. For a typical balanced meal this volume might be expected to empty into the duodenum in about 3h. The emptying is a function of the force of the peristaltic wave moving through the antrum and squeezing particles of food through the resistance of the pyloric constriction. Code et al. [13] have provided a classic description of this process in what has been called the antropyloric propulsion/retropulsion mechanism, as depicted in Fig. 61.14. In fact, the rate of emptying depends on the volume of material in the stomach, the physical state of the contents, and the chemical nature of the food itself. Other factors being equal, the greater the volume within the stomach, the more rapid the emptying. This response is an intrinsic property of gastric smooth muscle and the coordination provided by the myenteric plexus. As would be expected, the physical consistency is an important.

Fig. 61.15. Intracellular recordings of electrical activity of smooth muscle strips from various regions of a dog stomach. Note that rhythmic slow waves are absent in fundus, weak in the orad corpus, and uncease in strength toward the antrum. Spikes of action potentials are seen in mid-corpus, and their frequency, on the plateau of slow waves, increases in the terminal portions of the antrum, where contractile force in greatest. In these records from isolated muscle strips there are slight regional differences in the intrinsic slow wave frequency. In the intact stomach, slow waves have the same frequency in all parts of the stomach, because they are all driven by the same pacemaker. (From [54])
determinant. Liquids empty faster than solids, and efficient exit occurs when the particle diameter is 1 mm or less. The rate of gastric emptying is also greatly influenced by the chemical nature of the material reaching the duodenum, especially the lipid content, pH and osmolarity of the duodenal contents [36]. Food rich in carbohydrate clears the stomach relatively quickly, a protein-rich diet more slowly, and emptying is slowest for a meal rich in fat (Fig. 61.17).

The precise neural and hormonally mediated pathways controlling the rate of gastric emptying are poorly defined, but the process clearly involves duodenal and jejunal receptors sensing the chemical nature of the material reaching the duodenum. As fats reach the duodenum CCK is released, and apart from its hepatopancreatic effects CCK induces contraction of the pyloric musculature, reducing the exit probability for gastric particles. Other duodenal influences, such as low pH and altered osmolarity of the contents, are known to slow gastric emptying possibly via inhibitory effects of secretin and GIP on motility.

References


