Chapter 4
Gastric Acid and Pepsin Roles in Reflux Disease

Claude Nganzeu, Jonathan M. Bock, and Nikki Johnston

Gastric Acid

Secretion of Gastric Acid

Gastric acid is produced by highly differentiated epithelial cells in the fundic glands of the gastric mucosa called parietal cells. Parietal cells contain an extensive secretory network, called canaliculi, from which gastric acid is secreted into the lumen of the stomach. Gastric acid is approximately pH 2 in the lumen of the stomach, the acidity being maintained by H^+/K^+ ATPase proton pumps. The resulting highly acidic environment in the stomach lumen causes proteins from food to denature, thus exposing the protein's peptide bonds. Additionally, the acidic environment of the stomach inhibits growth of many microorganisms; the gut's bacterial load is controlled, and this helps prevent infection.

C. Nganzeu
Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: cnganzeu@mcw.edu

J. M. Bock
Department of Otolaryngology & Communication Sciences, Division of Laryngology & Professional Voice, Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: jbock@mcw.edu

N. Johnston (✉)
Department of Otolaryngology and Communication Sciences, Division of Laryngology and Professional Voice and Pediatric Otolaryngology, Department of Microbiology and Immunology, Milwaukee, WI, USA
e-mail: njohnston@mcw.edu

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Gastric acid secretion happens in several steps. Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi ultimately forming hydrochloric acid (HCl). This acid is then secreted into the lumen of the oxyntic gland and gradually reaches the stomach lumen. Chloride and sodium ions are secreted actively from the cytoplasm of the parietal cell into the lumen of the canaliculus. This creates a negative potential of −40 mV to −70 mV across the parietal cell membrane that causes potassium and sodium ions to diffuse from the cytoplasm into the parietal cell canaliculi. The enzyme carbonic anhydrase catalyzes the reaction between carbon dioxide and water to form carbonic acid. This acid immediately dissociates into hydrogen and bicarbonate ions. The hydrogen ions leave the cell through H^+/K^+ ATPase antiporter pumps. At the same time, sodium ions are actively reabsorbed. The majority of secreted potassium and sodium ions therefore return to the cytoplasm. The highest concentration of gastric acid that reaches the stomach is 160 mM in the canaliculi. This is about three million times that of arterial blood but is isotonic with other bodily fluids. The lowest pH of the secreted acid is 0.8, but as the acid is diluted in the stomach lumen with other secretions, the intragastric pH will range between 1 and 3.

Nerves and hormones are responsible for gastric acid secretion. Stomach glands receive stimuli from the brain, stomach, and small intestine to modulate gastric acid secretion. These stimulations are done in three phases called the cephalic, gastric, and intestinal phases [1, 2]. The cephalic phase, also called the reflex phase, occurs prior to food entering the stomach. This phase is relatively brief and occurs when the brain receives sensory input after the sight, smell, taste, or even the thought of food. The brain then relays the signal to the gastric mucosa to increase gastric juice production for digestion. The gastric phase is the longest of all three phases, lasting around 3–4 hours [3]. This occurs when food enters the lumen of the stomach and causes it to distend. Distention then activates stretch receptors, and the stretch receptors stimulate the vagus nerve, mediated by gastrin-releasing peptide (GRP) and neurocrine bombesin, through the parasympathetic pathway, and cause the secretion of acetylcholine. Acetylcholine increases production of gastric juice. As proteins are digested in the stomach, this increases pH in the stomach lumen. The rise in the pH induces the secretion of gastrin from G cells located in the pyloric antrum of the stomach. Gastrin binds to cholecystokinin B receptors and causes the release of histamine from enterochromaffin-like (ECL) cells. Histamine binds to H_2 receptors of the parietal cells causing H^+/K^+ ATPase pumps to insert in the parietal cells' canaliculi and transport H^+ into the stomach lumen to create gastric acid [1–3]. The intestinal phase is a relatively brief phase that occurs in the duodenum. When chyme enters the duodenum, the small intestine's mucosa cells secrete intestinal gastrin, which increases gastric juice secretion. Gastric juice secretion is inhibited by enterogastric reflex that is activated when chyme, filling the duodenum, causes distention. The enterogastric reflex is important for the closure pyloric sphincter to prevent further entry of chyme in the small intestine [1–3].

Regulation of Secretion

Gastric acid production is regulated by both the autonomic nervous system and several hormones. The parasympathetic nervous system, via the vagus nerve, and the hormone gastrin stimulate the parietal cell to produce gastric acid, both directly acting on parietal cells and indirectly by stimulating secretion of the hormone histamine from ECL cells. Vasoactive intestinal peptide, cholecystokinin, and secretin all inhibit production. The production of gastric acid in the stomach is tightly regulated by positive regulators and negative feedback mechanisms. Four types of cells are involved in this process: parietal cells, G cells, D cells, and ECL cells. In addition, the endings of the vagus nerve (CN X) and the intramural nervous plexus in the digestive tract also significantly influence secretion. Nerve endings in the stomach secrete two stimulatory neurotransmitters: acetylcholine and GRP. Their action is both direct on parietal cells and mediated through the secretion of gastrin from G cells and histamine from ECL cells. Gastrin acts on parietal cells directly and indirectly too, by stimulating the release of histamine. The release of histamine is the most important positive regulatory mechanism of the secretion of gastric acid in the stomach. Its release is stimulated by gastrin and acetylcholine and inhibited by somatostatin.

Neutralization of Gastric Acid

In the duodenum, gastric acid is neutralized by sodium bicarbonate secreted from the pancreas, the liver, and Brunner's glands of the duodenum. This also blocks gastric enzymes that have their pH optima in the acid range. The secretion of sodium bicarbonate from the pancreas is stimulated by secretin. This polypeptide gets activated and secreted from S cells in the mucosa of the duodenum and jejunum when the pH in the duodenum falls below 4.5–5. This neutralization is described by the equation:

$$HCL + NaHCO_3 \leftrightarrow NaCl + H_2CO_3$$

This carbonic acid instantly decomposes into carbon dioxide and water and is eliminated through the kidneys in urine.

Role of Gastric Acid in Disease

In hypochlorhydria and achlorhydria, there is low or no gastric acid in the stomach, potentially leading to problems as the disinfectant properties of the gastric lumen are decreased. In such conditions, there is greater risk of infections of the digestive

tract (such as infection with *Helicobacter* bacteria). In Zollinger-Ellison syndrome and hypercalcemia, there are increased gastrin levels, leading to excess gastric acid production, which can cause gastric ulcers. Reflux of gastric acid into the esophagus (gastroesophageal reflux, GER) and more proximally into the laryngopharynx (laryngopharyngeal reflux, LPR) and other extra-esophageal sites (extra-esophageal reflux, EER) also causes significant injury and disease.

Pharmacology

Acid secretion is mediated principally by acetylcholine and gastrin inducing increased cytosolic calcium and histamine activating adenylate cyclase and producing cAMP. All these hormones regulate the activity of the H^+/K^+ ATPase pumps on the parietal cells to control gastric acid production. Extensive research on the mechanism of the production of gastric acid and the discovery of specific receptor subtypes allowed the creation of potent drugs that efficiently inhibit gastric acid secretion. The receptors targeted by competitive inhibitors are muscarinic M1-3-receptors and histamine H_2 receptors, and the receptors targeted by non-competitive inhibitors are H^+/K^+ ATPase enzymes [4].

H_2-Receptor Antagonists

H_2 inhibitors such as cimetidine, famotidine, ranitidine, and nizatidine are used as first-line therapy in peptic ulcer disease and also used for situational relief of reflux symptoms induced by certain activities, for example, in patients who experience heartburn during running. It is recommended that H_2-receptor antagonists are taken 1 hour prior to the activity that causes reflux symptoms. While they are effective in up to 80% of GERD patients [5], they are only effective in approximately 50% of LPR patients [6]. This is because H_2-receptor antagonists merely reduce acid production by blocking stimulation of the parietal cell. The laryngeal epithelium is more sensitive to injury from gastric acid compared to the esophagus, and thus more complete acid suppression is required [7, 8].

M1-Receptor Antagonists

M1-receptor antagonists such as pirenzepine and telenzepine are used to treat peptic ulcer disease and reflux esophagitis. They suppress acid production by inhibiting the release of stimulatory neurotransmitters. Other antimuscarinic antagonists such as atropine, methylscopolamine, and propantheline are potent antagonists of gastric acid secretion; however, they are not often used in treatment of GER or LPR due to

side effects such as photophobia, mydriasis, tachycardia, ileus, blurred vision, and urinary retention [9].

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) such as omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, and dexlansoprazole irreversibly inhibit H^+/K^+ATPase enzyme. By targeting the terminal step in production, they prevent secretion of HCl and thus are potent gastric acid-suppressing agents, which are effective for the treatment of GERD. Although PPIs remain the mainstay for treatment of GERD, there is poor evidence for their efficacy in the treatment of airway reflux-mediated disease including LPR [10]. It is widely believed that the upper airway is more sensitive to reflux than the esophagus and hence that higher-dose PPIs are necessary for the control of LPR-related symptoms [11–13]. At this time, placebo-controlled studies have by and large not shown a significant therapeutic benefit to PPI used in LPR [14–19]. Although some studies have noted evidence of symptomatic improvement with PPI therapy [20, 21], upon review of these two studies, it has been argued that the affected patients only had significant improvement of gastroesophageal reflux symptoms, rather than improvement of upper airway symptoms [18]. Arguments can be made that these studies were done prior to the era of combined hypopharyngeal-esophageal impedance with dual pH probe testing and that the diagnosis of non-acid reflux was incomplete. In light of the poor data for the efficacy of acid suppression in treatment of EER, the American Gastroenterological Association has specifically recommended against the empiric use of PPIs for suspected LPR unless there are concomitant symptoms of GERD [22]. Likely as a result of the paucity of alternative effective therapies, however, PPIs continue to be used for LPR [18, 23], and indeed the American Academy of Otolaryngology–Head and Neck Surgery has recommended empiric use of high-dose PPI therapy for suspected LPR, with laparoscopic fundoplication proposed as an alternative to medical management [12]. A survey from the American Bronchoesophagological Association reported that the twice-daily PPIs remain a popular first-line therapy for LPR [24].

Prokinetic Agents

Prokinetic agents such as metoclopramide and cisapride are used in reflux patients who have dyspeptic symptoms such as nausea, vomiting, and abdominal bloating. These drugs increase lower esophageal sphincter pressure and accelerate esophageal acid clearance and gastric emptying. Their use has fallen out of favor in recent [25]. Problems with cardiac arrhythmias and drug-associated deaths led to removal of cisapride from the US market in 2000 [26]. Their results as single-agent therapy for GER or LPR have been disappointing. Some patients are intolerant of the medicines' side-effect profiles including diarrhea or cramping, and treatment success with acid suppression has been variable and limited.

Sucralfate

Sucralfate is used in the treatment of GER and stress ulcers and may be useful in the treatment of LPR. Sucralfate is a locally acting substance that reacts with HCl to form a cross-linking viscous material that acts as an acid buffer for up to 8 hours. It attaches to proteins on the surface of ulcers, such as albumin and fibrinogen, to form stable and insoluble complexes, creating a barrier against gastric refluxate. In addition, it prevents back diffusion of hydrogen ions and absorbs both pepsin and bile acids further preventing damage by reflux.

Alginate

Alginate anti-reflux preparations are widely used for the treatment of GER. They react with stomach acid to form a gel raft which floats on top of the stomach, helping to keep gastric contents in the stomach and preventing GER. Several studies have shown the efficacy of Gaviscon Advance (Reckitt Benckiser, Kingston-upon-Thames, UK) in the treatment of LPR. This alginate preparation is licensed in the UK for the treatment of LPR but is not currently available in the USA. Treatment with Gaviscon Advance, either alone or in conjunction with a PPI, was found to be significantly beneficial in improving symptoms, laryngeal findings, and patient quality of life compared to control [27].

Surgical Management of Reflux

Laparoscopic fundoplication and magnetic ring procedures are well-established, reliable options for the surgical management of GERD. In contrast to the predictable improvement seen in the treatment of GERD, research on the efficacy of anti-reflux surgery in the treatment of LPR is mixed, with various studies showing resolution of symptoms ranging from 63% up to 85% of patients [28–30]. Hypotheses for this variance range from differences in surgical technique to differences in patient selection criteria. In particular, it has been observed that patients with more severe stereotypical GERD symptoms are more likely to benefit from anti-reflux surgery [28, 31], and in particular patients with preoperative heartburn and pH < 4 for over 12% of a 24-hour period have been found to have a 90% probability of symptomatic improvement [31].

Pepsin

History

Pepsin is the principal proteolytic enzyme in the stomach. It is found in all vertebrates studied like mammals and fishes. Pepsin was the first enzyme to be discovered. It was discovered in 1836 by German physiologist Theodor Schwann named

pepsin from the Greek word pepsis, meaning "digestion." In 1930, pig pepsin, after urease, became the second enzyme to be crystallized by American biochemist John H. Northrop using dialysis, filtration, and cooling. The crystallization of these enzymes was important in demonstrating that enzymes were proteins with a defined structure [32].

Structure

Pepsin's primary structure is composed of 326 amino acid residues and has a molecular weight of around 35,000 daltons. Its secondary structure is a single-chain peptide consisting mainly of beta sheets (Fig. 4.1). Pepsin is composed of two homologous domains (N-terminal and C-terminal domains) that fold to create a tertiary structure made of two nearly identical and symmetrical lobes. Each lobe is made of two beta-sheets and two short alpha-helices. A six-stranded, antiparallel beta-sheet connects the two lobes and allows the formation of the catalytic site in a deep cleft. The catalytic site is made of two aspartate residues (Asp32 and Asp 215) and activated when one aspartate is protonated and the other is deprotonated [32]. Pepsin is created in the chief cells of the stomach mucosa. It has multiple isoenzymes with the most common isoenzymes named isoenzymes 1–6. Isoenzyme 3 makes the largest proportion of total pepsin at 80%, with isoenzymes 3B making 70% of total enzyme activity. Isoenzymes 1 and 2 makes less than 6% proportion of total pepsin; pepsin 4 is not active; pepsin 5 makes 6–7% of enzyme activity; and

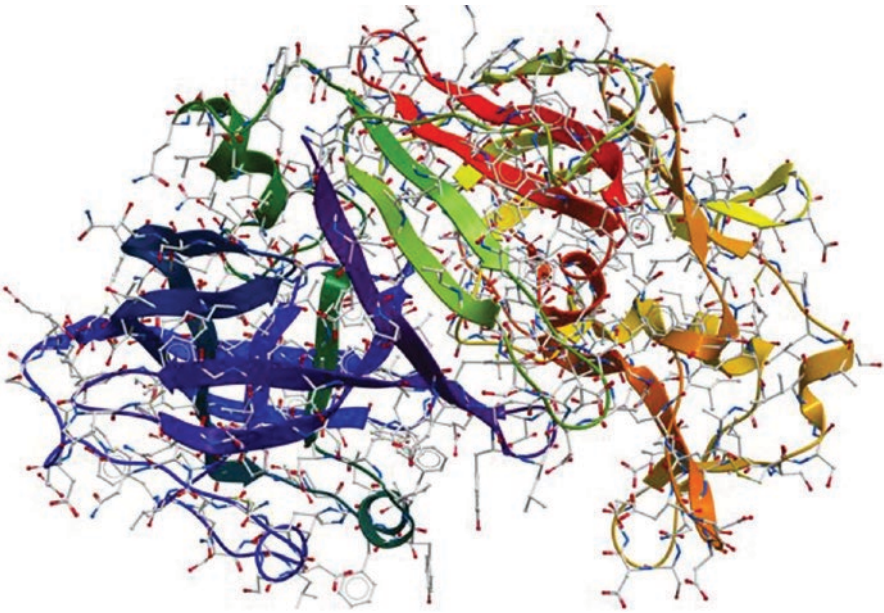

Fig. 4.1 Secondary structure of pepsin (https://sciencestruck.com/pepsin-enzyme-structure-function-important-facts)

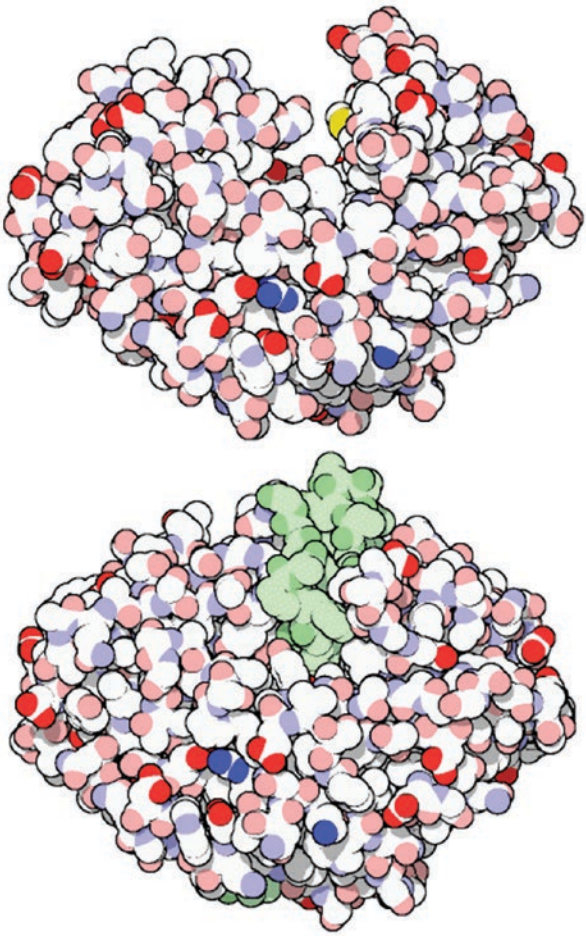

Fig. 4.2 Tertiary structure of pepsin (top) and pepsinogen (bottom). (Image from the RCSB PDB December 2000 Molecule of the Month feature by David Goodsell)

pepsin 6 is the remainder of the zymogen [33]. Pepsin is made initially as an inactive pre-proenzyme. The pre-proenzyme is made of signal protein, activation peptide, and active enzyme. As the molecule is inserted in the rough endoplasmic reticulum, the signal peptide is cleaved, creating the proenzyme, pepsinogen (Fig. 4.2). Pepsinogen is transported to the Golgi apparatus, where it is stored in secretory granules and released in the stomach lumen by exocytosis. Pepsinogen's primary structure has an additional of 44 amino acids that occlude the active site groove. In the stomach lumen, the chief cells secrete pepsinogen, which is hydrolyzed by HCl, creating its active protein, pepsin (Fig. 4.2).

Pepsin Physiology and Role in Digestion

Pepsin is the main digestive enzyme in the stomach. Its principal role is digesting protein in the stomach. It is released from chief cells as pepsinogen, its inactive form, to prevent digestion of protective proteins in the gastric mucosa. Pepsin release is activated by the same neural and hormonal modulators that stimulate gastric acid release. Gastrin, acetylcholine, and histamine stimulate parietal cells to secrete chloride and hydrogen ions via the H^+/K^+ ATPase pump to form HCl. Similarly, in chief cells, gastrin and acetylcholine from vagus nerve activation induces the release of pepsinogen. The presence of HCl in the lumen creates the acidic environment that allows pepsinogen to unfold and cleave itself in an autocatalytic fashion, thereby generating pepsin (Fig. 4.3). Pepsin then cleaves the 44 amino acids from pepsinogen creating more pepsin. Pepsin will digest up to 20% of ingested protein's amide bonds by cleaving preferentially after the N-terminal of amino acids (Fig. 4.4), especially aromatic amino acids such as phenylalanine, tryptophan, and tyrosine. Pepsin exhibits preferential cleavage for hydrophobic, preferably aromatic, residues in P1 and P1' positions. Increased susceptibility to hydrolysis occurs if there is a sulfur-containing amino acid close to the peptide bond, which has an aromatic amino acid. For example, pepsin cleaves Phe-Val, Gln-His, Glu-Ala, Ala-Leu, Leu-Tyr, Tyr-Leu, Gly-Phe, Phe-Phe, and Phe-Tyr bonds in the B chain of insulin. Peptides may be further digested by other proteases in the duodenum and eventually absorbed in the intestine. Pepsin is stored as pepsinogen so it will only be released when needed and does not digest the body's own proteins in the stomach's lining.

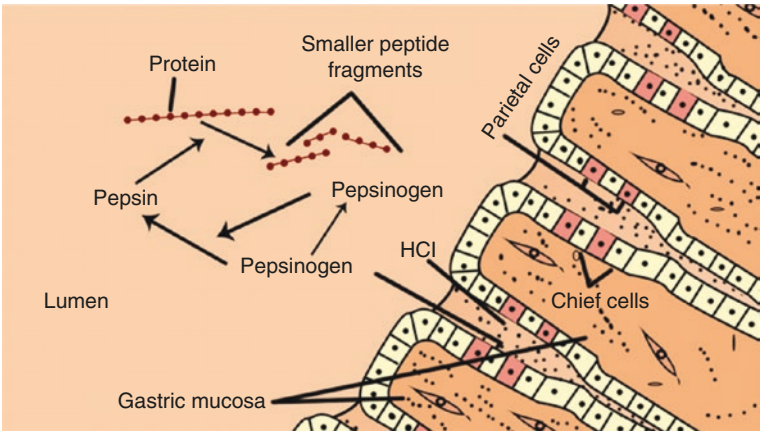

Fig. 4.3 Process involved in the cleavage of pepsinogen to pepsin (https://sciecestruck.com/pepsin-enzyme-function-important-facts)

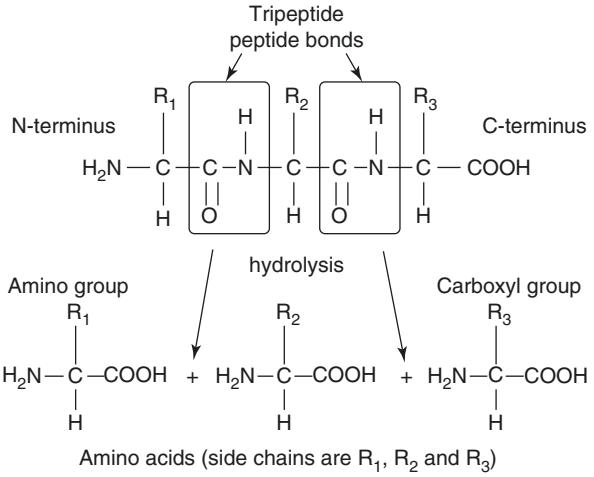

Fig. 4.4 Reaction involved in the cleavage of peptide bonds in amino (https://sciencestruck.com/pepsin-enzyme-structure-function-important-facts)

Pepsin is maximally active at pH 1.5–2.5 but has activity up to pH 6.5. While inactive at pH 6.5 and above, it remains stable to pH 8. The enzyme is not irreversibly inactivated (denatured) until pH 8. While the stomach is designed to resist damage by pepsin, reflux of pepsin into the esophagus and laryngopharynx causes damage even above pH 4. Pepsin is considered an important etiological factor in reflux disease of the aero-digestive tract and a biomarker for reflux, whose levels and acidity can be related to the severity of damage.

Physiologic Agonists and Antagonists

Secretion of pepsinogen is mediated mainly by stimulators of cAMP synthesis such as secretin, histamine, and vasoactive intestinal peptide or agents that increase cytosolic calcium concentration such as gastrin and cholecystokinin (CCK) [34]. Additionally, vasoactive intestinal peptide, CCK, and secretin's stimulation of pepsin release is independent of gastric acid secretion. Secretin and CCK stimulate chief cells to release pepsinogen [34].

The primary physiologic inhibitor of pepsin is somatostatin. Excess gastric acid in the stomach induces somatostatin release from D cells throughout the gastric mucosa. Somatostatin directly inhibits parietal cells to reduce acid secretion and indirectly inhibits acid production by blocking histamine release from ECL cells and mast cells and gastrin secretion, as a consequence, decreasing pepsin release [35].

Plant-Based Versus Animal-Based Digestion

Proteins are hydrolyzed to smaller peptide units by pepsin in the gastric lumen before complete degradation to individual amino acids in the small intestines. All proteins are not degraded equally. Some proteins are harder to digest than others

and can survive fully intact or partially degraded to the large intestines. The level of digestion depends on the source (plant-based vs animal-based proteins) and the processing conditions of the proteins altering proteins' digestive susceptibility. Animal-based proteins are more easily digestible (>90%) than plant-based proteins (70–90%) [36]. This difference in digestibility may be due to some antinutritional factors present in some plant proteins. Legumes, cereals, potatoes, and tomatoes have proteins that inhibit proteolysis by pepsin and other gastrointestinal proteases. Tannins (polyphenols) found in vegetables, grains, and fruits decrease activity of gut enzymes by binding to proteases and dietary proteins and inhibiting hydrolysis through allosteric inhibition of proteases or destabilization of the enzymes' structures [36, 37]. Phytic acid, also found in plants and grains, is shown to inhibit digestibility. Many plants contain complex carbohydrates that surround their proteins and prevent enzymes from protein degradation by digestive enzymes [36, 38]. There is lack of data on the effect of plant protein on gastrin secretion; however, in 1988, Mcarthur et al. performed a study comparing the effect of soy proteins versus beef proteins on gastrin release in ten normal subjects. The results showed that there was about 30–40% less acid secretion and 65–75% less gastrin secretion when individuals consumed soy proteins versus beef proteins [39]. Less gastric acid and gastrin stimulation may also decrease the secretion of pepsin and, thus, be beneficial for relief of reflux symptoms in patients with LPR and GERD. In essence, the presence of protein inhibitors in plant-based proteins may be important in the use of Mediterranean diet style as therapy for GER or LPR. Martinucci et al., in a clinical study, measured the multichannel intraluminal impedance and pH (MII-pH) in 165 patients with heartburn after a 1-day consumption of Mediterranean diet and animal protein divided into 2 separate meals [40]. The results revealed that consumption of animal proteins raised acid about three times higher compared to vegetable proteins (acid exposure time (AET) −1 h, 3.3 +/− 2.7% vs 0.9+/− 1.4%); furthermore, patients who consumed animal proteins experienced higher reflux events to those who consumed plant proteins (total reflux events: 12.4+/− 9 vs 6.3+/− 3.9) [40]. Similarly, Zalvan et al. compared the efficacy of alkaline water and Mediterranean diet versus PPI therapy in the treatment of LPR through a retrospective study from 2010 to 2015 [41]. Utilizing a six-point reduction or improvement in Reflux Symptom Index (RSI) score, the study results showed no statistically significant difference in the number of six-point reduction in RSI score in patients on PPI therapy to those on the Mediterranean style diet; 54% and 62.6%, respectively, attained a six-point reduction in RSI score. Notably, patients on Mediterranean style had a statistically higher mean percent reduction in RSI compared to patients on PPI therapy, 39.8% and 27.2%, respectively [41]. In conclusion, the study demonstrated that there is no statistically significant difference in the efficacy of PPIs versus Mediterranean diet style in the treatment of LPR; moreover, other studies clearly show the advantage of vegetal proteins in the treatment of GERD and LPR symptoms.

Mediator of Cell Damage and Role in Disease

In vitro studies have shown that via receptor-mediated endocytosis, non-acid pepsin can enter the epithelium of the hypopharynx and larynx [42, 43]. Following endocytosis, receptors and ligands are sorted within weakly acidic late endosomes and the trans-reticular Golgi (TRG) raising the possibility of pepsin transport via these pathways. Immuno-electron microscopic findings have supported this notion, having identified co-localization of pepsin with the late endosome marker Rab-9 and the TRG marker TRG-46 [44]. The TRG has a weakly acidic pH (pH 5), at which pepsin has roughly 40% of its maximal activity [42, 45]; as such, inactive pepsin might potentially be taken up by laryngeal epithelial cells and be activated within intracellular compartments of low pH, setting the stage for intracellular damage. Exposure of hypopharyngeal cells to pepsin at pH 7 has been shown to induce the expression of several pro-inflammatory cytokines and receptors, including IL-1α, the neutrophil chemoattractant IL-8, and the eosinophil colony-stimulating factor IL-5 [43]. Conversely, exposure of laryngeal epithelium to pepsin has been shown to deplete protective proteins such as Sep70 and carbonic anhydrase-III, implying multiple pathways by which pepsin-mediated cell damage might contribute to ongoing inflammation and the endoscopic findings of LPR disease [42]. Moreover, the aforementioned pro-inflammatory cytokine profile, induced in hypopharyngeal tissues independent of acidic refluxate, is similar to that expressed in reflux esophagitis and which is known to contribute to ongoing inflammation in the pathophysiology of GERD [43].

The above research identifies a novel mechanism by which pepsin might induce cellular injury and inflammation irrespective of the acidity of the extracellular environment, potentially proffering an explanation for the persistence of chronic mucosal inflammation, symptoms, and endoscopic findings in many patients with reflux-attributed laryngeal pathology in spite of therapy with high-dose acid suppression. While pepsin has long been known to play an etiologic role in GERD due to its proteolytic activity in the low-pH environment induced by GER episodes, the finding of potentially active intracellular pepsin and induction of a pro-inflammatory response suggests a role for pepsin in reflux-mediated disease of the airway where pH may be less clinically relevant. The receptor-mediated uptake of nonacid pepsin, as can occur following LPR, and any inflammatory or neoplastic changes which may occur as a result [46–48], cannot be prevented by PPIs, which only address acid production in gastric mucosa. As the role of pepsin in LPR-mediated mucosal damage seems to involve its activation within more acidic intracellular compartments or through dysregulation or activation of cell signaling cascades [44], the amelioration of the acidic environment of gastric refluxate with PPI or H_2-receptor antagonists may not adequately address pepsin-mediated inflammatory changes.

Therapeutic Target

As discussed above, PPIs continue to be commonly used in clinical practice for the treatment of airway reflux disease including LPR in spite of poor evidence for their efficacy [14–19], with approximately $26 billion spent yearly for this indication [49]. In light of the inefficacy of PPI therapy for LPR and its associated costs and potential risks, there is substantial interest in an alternative modality for the treatment of LPR [33, 50, 51]. Pepsin represents an exciting potential novel target for future therapies, particularly for patients who experience symptoms refractory to PPI therapy in light of its role in nonacid LPR [33, 44]. Two mechanisms by which pepsin might be targeted have been identified: irreversible inactivation and via receptor antagonism [33, 44]. While the first of these would prevent pepsin's reactivation within the acidic environment of intracellular compartments, the latter would prevent its endocytosis. Although pepstatin A is a potent inhibitor of pepsin activity and is currently commercially available, its poor pharmacokinetics and water-soluble characteristics make it a poor candidate for the purpose of treating LPR. As such, novel agents targeting pepsin are currently in development and represent an exciting potential avenue for the treatment of reflux-mediated disease including LPR.

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