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Gastroesophageal Reflux Disease (GERD): Is There More to the Story?

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Gastroesophageal reflux disease (GERD) affects both men and women worldwide, with the most common symptom of GERD being frequent heartburn. If left untreated, more serious diseases including esophagitis and/or esophageal cancer may result. GERD has been commonly held to be the result of gastric acid refluxing into the esophagus. Recent work, however, has shown that there are acid-producing cells in the upper aerodigestive tract. In addition, acid-producing bacteria located within the upper gastrointestinal tract and oral cavity may also be a contributing factor in the onset of GERD. Proton pump inhibitors (PPIs) are commonly prescribed for treating GERD; these drugs are designed to stop the production of gastric acid by shutting down the H^+/K^+-ATPase enzyme located in parietal cells. PPI treatment is systemic and therefore significantly different than traditional antacids. Although a popular treatment choice, PPIs exhibit substantial interpatient variability and commonly fail to provide a complete cure to the disease. Recent studies have shown that H^+/K^+-ATPases are expressed in tissues outside the stomach, and the effects of PPIs in these nongastric tissues have not been fully explored. Likewise, acid-producing bacteria containing proton pumps are present in both the oral cavity and esophagus, and PPI use may also adversely affect these bacteria. The use of PPI therapy is further complicated by the two philosophical approaches to treating this disease: to treat only symptoms or to treat continuously. The latter approach frequently results in unwanted side effects which may be due to the PPIs acting on nongastric tissues or the microbes which colonize the upper aerodigestive tract.

1. Introduction

Gastroesophageal reflux disease, or GERD, is a clinically diagnosed condition in which stomach acid is thought to reflux into the esophagus. GERD is a chronic disorder that affects men, women, and children, and the most common symptoms of the disease include heartburn and the regurgitation and/or irritation associated with large meal volumes.[1] Additional symptoms include chest pain, dysphagia, and coughing.[2] Weekly episodes of heartburn and/or acid regurgitation have been found in nearly 20% of Americans and roughly 15% of the worldwide population.[3,4] The prevalence of GERD has increased in the last several decades, and recent epidemiological studies suggest that these numbers will continue to increase in the future.[5–7]

In mild cases, GERD is often self-diagnosed and treated. However, as symptoms persist and/or worsen, clinical evaluation may be necessary. Upper gastrointestinal endoscopy is the most commonly used technique in the detection of GERD; however, radiographic examinations utilizing contrast dyes, as well as catheters and capsules measuring intraesophageal pH, are also used.[2]

Patients suffering from the symptoms of GERD are typically classified into one of two groups: nonerosive reflux disease (NERD) or erosive esophagitis.[6] NERD is defined as the exhibition of GERD symptoms without detection of mucosal injury by upper endoscopy.[6] Erosive esophagitis is characterized by swelling and inflammation of the esophagus, and includes a condition known as Barrett's esophagus—often a precursor to esophageal cancer.[8] Research has shown that a number of risk factors (including tobacco and alcohol use, high body mass index, and diets low in fruit) may be linked to the progression from Barrett's esophagus to esophageal cancer.[9,10]

A number of treatment options are available for patients suffering from GERD, and the chosen treatment plan is usually dependent upon the severity of the presenting symptoms. In very minor cases, simple dietary and lifestyle modifications

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may be enough to relieve symptoms, whereas in very severe cases, surgery may be necessary. However, one of the most commonly utilized treatment options is medication with proton pump inhibitors (PPIs). These drugs are designed to target gastric acid secretion/transport in an effort to relieve symptoms and heal esophageal damage, and are described in detail in Section 3.

Once diagnosed, patients face two general treatment options. The first is to treat only when symptoms are present. Although current therapies are rather effective for the short-term elimination of symptoms, a permanent cure for the disease has yet to be found, and therefore recurrence of the disease is common. The second approach is to treat continuously; however, this puts the patient at risk for long-term side effects. Furthermore, with the recent report of acid-producing cells in nongastric tissues, the continuous use of PPIs needs to be reevaluated. Additionally, changes in the normal microbial flora within the gastrointestinal tract and oral cavity may be affected by the PPIs. As a result of the problems associated with both short-term and long-term treatment options, new therapies are currently being explored, and work is still being carried out in an effort to completely understand GERD.

2. Gastric acid secretion

The human body uses gastric acid for a number of activities, including protein digestion, absorption of vitamins and minerals, and preventing intestinal infection and bacterial overgrowth.[11]

Acid production and regulation

The production and regulation of gastric acid is a complex physiological process controlled by a series of hormonal, neuronal, and paracrine pathways working together within the stomach, using both central and peripheral mechanisms.[12,13] Gastric acid is produced in the parietal cells found along the lining of the stomach, and direct stimulation of the parietal cells by the vagus nerve accounts for nearly 50% of the overall acid that is produced during digestion.[14] Peripheral mechanisms involving a number of endocrine cells—including G cells, D cells, and enterochromaffin-like (ECL) cells—are needed to stimulate further acid production (Figure 1).

The basolateral membrane of parietal cells house a number of receptors which can be triggered by physiological stimuli to begin gastric acid production. Gastrin, histamine, and acetylcholine are the best known stimulants, and each binds to a specific receptor. Gastrin is produced by G cells in the antrum and, via the blood, is carried to ECL cells where it binds to cholecystokinin$_2$ (CCK_2) receptors, triggering the release of histamine.[12,13,15,16] Acetylcholine (Ach), a peptide released from postganglionic enteric neurons, is thought to bind either to M_3 receptors on parietal cells, thereby directly stimulating acid secretion, or to M_3 receptors on ECL cells, resulting in histamine release.[11,13] Histamine, once released, is able to bind to H_2 receptors on the parietal cells. The ligand–receptor binding activities of these various stimulants activate signal transduction

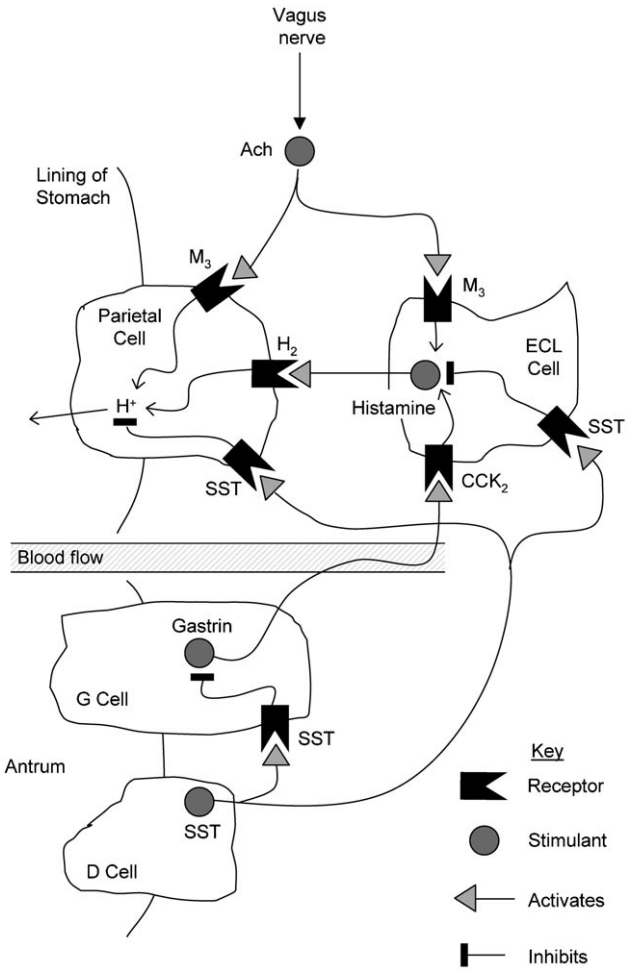


Figure 1. Diagram outlining the pathways involved in the production and regulation of gastric acid.

pathways which lead to an increase in the concentration of intracellular calcium and/or cyclic adenosine monophosphate (cAMP). The increased levels of Ca^{2+} and cAMP result in morphological changes that transfers the enzyme H^+/K^+-ATPase from cytosolic tubulovesicles into the apical membrane of the parietal cell. It is the activation of this gastric H^+/K^+-ATPase that serves as the final step in acid secretion.[12,13,17]

Upon stimulation, the parietal cells release hydrochloric acid (HCl) into the lumen of the stomach via the H^+/K^+-ATPase (Figure 2). H^+ is transported across the apical membrane and into the canaliculi of the parietal cells in exchange for K^+; to maintain neutrality, Cl^- is also simultaneously transferred during this process by Cl^- channels in the apical membrane. Potassium channels located in the apical membrane recycle K^+ from the cytoplasm into the canaliculi, and the cytoplasmic concentration of K^+ is further regulated by a Na^+/K^+-ATPase located on the basolateral membrane. For every H^+ transferred into the canaliculi by the H^+/K^+-ATPase, an HCO_3^- ion is also released from the parietal cell cytoplasm by a basolateral Cl^-/HCO_3^- exchanger. This process also transfers a Cl^- ion into the cytoplasm.[12,13,16,17]

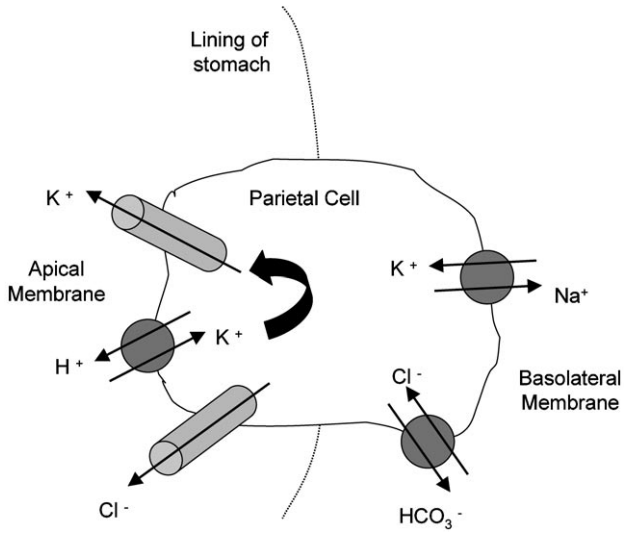


Figure 2. Diagram outlining the ion exchange that occurs in parietal cells during gastric acid secretion.

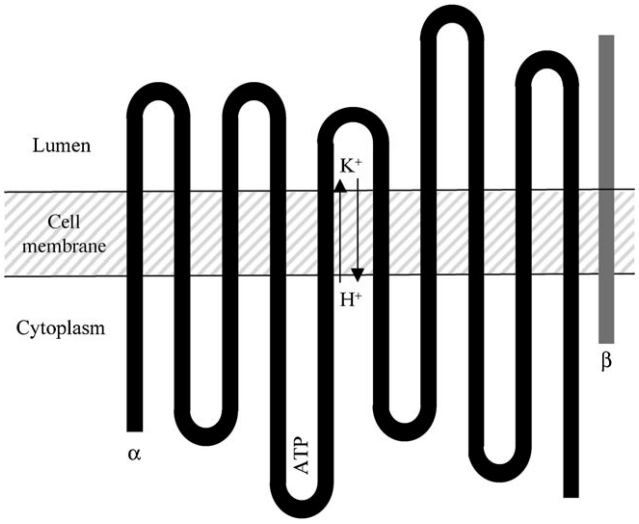


Figure 3. A simplified diagram of the gastric H^+/K^+-ATPase, showing the α (black) and β (gray) subunits.

The accumulation of H^+ in the canaliculi of the parietal cells results in a pH of 1.0 or lower, compared with a pH of approximately 7.4 in the cytoplasm of the parietal cell.[17,18] Once the intragastric pH decreases to a sufficient level, somatostatin (SST) is released from antral D cells to stop acid secretion (Figure 1). SST is a peptide that can directly inhibit acid secretion by acting directly on parietal cells or indirectly by inhibiting the release of histamine and gastrin in ECL and G cells, respectively.[14] Secretin (another peptide) and endogenous prostaglandins have also been found to play a role in acid suppression. These pathways work together to shut down the H^+/K^+-ATPase.[16]

Gastric H^+/K^+-ATPase structure and properties

The ion transport of H^+/K^+-ATPase is coupled to a cycle of phophorylation and dephosphorylation, making this enzyme a member of the ion-motive-phosphorylating, or P-type, ATPase family.[13,17] H^+/K^+-ATPase is a heterodimer consisting of α and β subunits (Figure 3), with each subunit being responsible for different functions. The catalytic and transport site of the enzyme is found on the α subunit, which is comprised of ten helical transmembrane segments and located mostly within the cytoplasm. The binding sites for ATP, H^+, and K^+ are all located on the α subunit.[14,17] The β subunit, which is smaller and predominately extracellular, helps to stabilize the α subunit and is responsible for directing the heterodimer to membrane destinations within the cell. Possessing only a single transmembrane segment, the β subunit contains seven N-linked oligosaccharides that protect the H^+/K^+-ATPase from the highly acidic environment of the apical lumen.[14]

3. Drugs used to treat GERD

As discussed above, the production of gastric acid is a complex process involving many different physiological pathways. To this end, both the H^+/K^+-ATPase enzyme and many of the cell receptors have been investigated as targets in the search for potential drugs to treat GERD. Currently, both over-the-counter (OTC) and prescription drugs are commercially available to patients, including antacids and alginates, prokinetics, histamine H_2-receptor antagonists (H_2RAs), and proton pump inhibitors (PPIs). Additionally, two potentially new classes of drugs—cholecystokinin$_2$ (CCK_2) receptor antagonists and potassium-competitive acid blockers (P-CABs)—are currently being evaluated in clinical trials.

Antacids and alginates

Both antacids and alginates are OTC drugs which offer limited, local, rapid, short-term relief from heartburn and are commonly used by patients without prior consultation with a physician. Antacids locally raise the pH of the stomach and esophagus. Alginates are usually formulated with antacids and provide a barrier at the top of the stomach, which prevents acid from entering into the esophagus.[19] Examples of antacids and alginates include aluminum hydroxide, magaldrate, and hydrotalcite. As only very small amounts of the drugs enter into circulation, both antacids and alginates lack major side effects.[20] However, whereas these drugs are sometimes useful in treating minor cases of GERD, frequent dosing is often necessary, and they are not useful in healing erosive esophagitis.[19]

Prokinetics

Many patients suffering from GERD exhibit delayed esophageal clearance;[21] the prokinetic drugs (such as metoclopramide, domperidone, and cisapride—Figure 4) attempt to increase esophageal peristalsis and release the contents of the stomach by either acting directly on dopaminergic receptors and/or activating serotonin (5-HT_4) receptors in the gut to agonistically release acetylcholine.[19,22] Treatment using prokinetics results

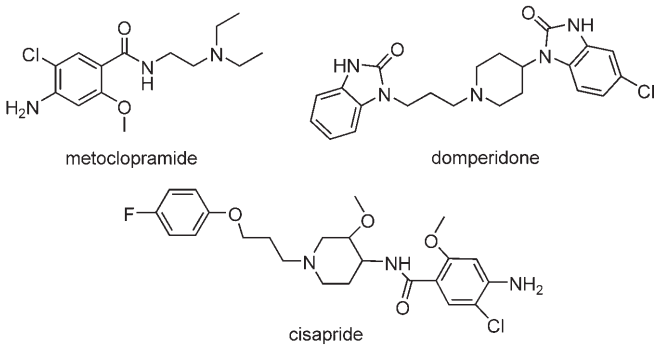


Figure 4. Chemical structures of the prokinetics.

in nearly a 70% acid suppression. However, the onset of relief is much slower than that found with antacids, and relief typically lasts for only 4–8 h.[19] Thus, many patients need to take two doses per day. Additionally, due to a large number of side effects—including fatigue, tremor, parkinsonism, tardive dyskinesia, and cardiac events—prokinetics are not routinely prescribed.[19,20] These drugs have not been shown to effectively improve the healing of high-grade esophagitis and are therefore limited in use to patients suffering from only minor cases of GERD.

Histamine H_2-receptor antagonists

Parietal cell H_2-receptors are one of the stimulants used by the body to produce acid. The H_2RAs (including ranitidine, famotidine, cimetidine, and nizatidine—Figure 5) reversibly block

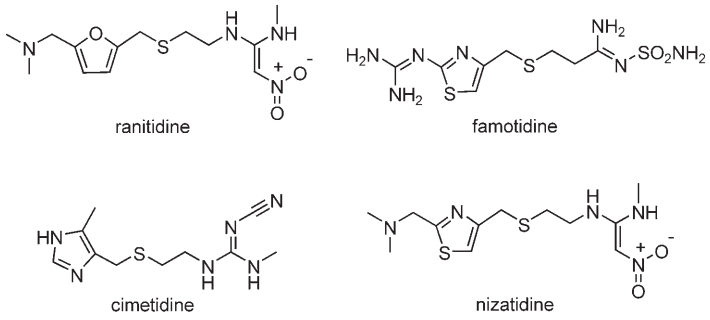


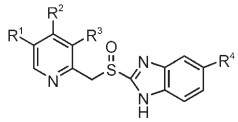
Figure 5. Chemical structures of the H_2RAs.

these receptors, thereby inhibiting acid secretion.[23] The H_2RAs have efficacies similar to that of the prokinetics: the drugs have a slower onset of action than the antacids and provide only temporary relief.[24] Available as both OTC and prescription drugs, H_2RAs are commonly used to treat isolated incidents of heartburn. Long-term treatment using H_2RAs is not recommended, as the body quickly develops a pharmacological tolerance to the drug (within 1–2 weeks)[25] and does not promote mucosal healing in cases of esophagitis.[20]

Proton pump inhibitors

PPIs are the most common form of treatment for moderate-to-severe cases of GERD. These drugs work by blocking the gastric acid pump (H^+/K^+-ATPase) of acid-producing cells in the stomach. The PPIs are formulated as weak bases which accumulate in the parietal cells and react with the secreted acid to give rise to the thiophilic form of the drug; this active form of the drug then binds directly with cysteine residues of the gastric acid pump via disulfide bonds, thereby blocking acid transport.[13,26] A number of PPIs are currently commercially available in tablet form, including omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole.[20,27] The general structures of the PPIs are shown in Table 1; esomeprazole (not shown) is the *S*-enantiomer of omeprazole.[16,28] In 2002, Protonix© (pantoprazole) became the first PPI clinically approved for intravenous use in the United States.[29] Since that time, both Prevacid© (lansoprazole) and Nexium© (esomeprazole) have also been approved.[30]

Table 1. Chemical structures of the PPIs.



PPI	R^1	R^2	R^3	R^4
Omeprazole	CH_3	OCH_3	CH_3	OCH_3
Lansoprazole	H	OCH_2CF_3	CH_3	H
Rabeprazole	H	$O(CH_2)_3OCH_3$	CH_3	H
Pantoprazole	H	OCH_3	OCH_3	$OCHF_2$

The onset of relief is typically faster for PPIs than for either the H_2RAs or prokinetics, and PPIs have been shown to significantly improve the healing of the esophagus with long-term treatment.[19] Furthermore, PPIs are usually taken only once per day, thus making them a more popular option for patients. Although more effective than other current commercially available treatment methods, the use of PPIs can result in a number of known rare side effects, including nausea, diarrhea, headache, insomnia, and anaphylaxis.[27,31,32] The first-generation PPIs that are currently used have also shown significant interpatient variability and in many cases may adversely interact with other drugs.[16]

Cholecystokinin$_2$ receptor antagonists

The CCK_2 receptor antagonists (Figure 6) are a new class of drugs designed to block the CCK_2 receptors, thereby inhibiting gastric acid secretion.[15,16] The majority of these compounds, such as spiroglumide and YF476, were shown to reduce acid secretion in initial clinical trials, but have since been discontinued because of either a lack of potency or development of tolerance.[17] A number of second-generation candidates, including itriglumide and Z-360, have shown improvement over their first-generation counterparts and are still being evaluated in

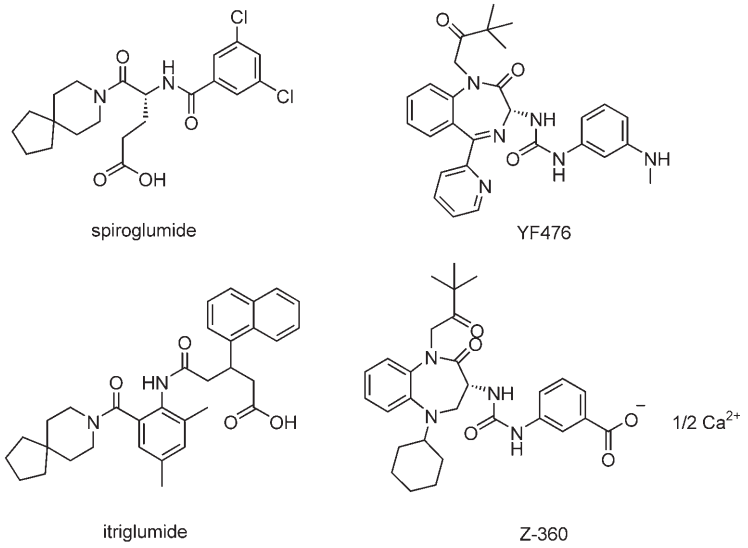


Figure 6. Chemical structures of the CCK_2 receptor antagonists.

clinical trials; however, despite these somewhat promising advancements, it is anticipated that the CCK_2 receptor antagonists will not be useful as a stand-alone treatment but, rather, will only be beneficial when used in combination with the PPIs.[16]

Potassium competitive acid blockers

Like the PPIs, the potassium competitive acid blockers target the H^+/K^+-ATPase of parietal cells. But whereas the PPIs chemically interact with the H^+/K^+-ATPase, P-CABs exhibit a structural specificity for the K^+-binding region of the H^+/K^+-ATPase to disrupt acid secretion.[16] Four different classes of P-CABs exist: imidazopyridines, quinolines, pyrimidines, and imidazonaphthyridine (Figure 7A); each class differs in its chemical structure, but all four utilize the same acid-blocking mechanism.[17,33] Early clinical results suggest that these drugs are fast-acting, achieving full acid inhibition upon the first dose.[16] Furthermore, development of tolerance has not been detected with any of the P-CABs currently undergoing clinical trials.[17] However, one agent, AZD0865, was dropped from consideration following phase II clinical trials after it was found to exhibit similar potency to that of the PPI esomeprazole. Three other agents are still in clinical development, with the most promising of these being revaprazan, a pyrimidine currently in Phase III clinical trials (Figure 7B).[16]

4. Long-term effects of PPI use

Whereas short-term use of PPIs has been found to help heal esophagitis, relapse is observed in nearly 80% of patients within 30 weeks of discontinuing treatment.[34] Two main factors contributing to this phenomenon are: 1) current medications are unable to reverse the underlying pathophysiological changes (such as the lack of effective esophageal clearance), and 2) rebound acid hypersecretion is common upon withdrawal of PPI use.[20] Therefore, continuous treatment is usually necessary to maintain success in patients, even after the disappearance of symptoms. Despite the need for continuous treatment, however, relatively little is known about the lasting biological effects that long-term PPI use might induce.

When PPIs are introduced into the stomach, the resulting increase in pH leads to significant changes in the intragastric environment. The normally low pH level of gastric acid sometimes serves as a protective force against microorganisms; PPI use can lead to sharp increases in the pH level that compromise this defense mechanism.[35] For example, studies have suggested that patients using PPIs are exposed to a greater risk of infection from *Clostridium difficile*, a bacteria commonly found in the environment—and more prevalently in hospitals and nursing homes—that is responsible for nosocomial diarrhea.[36]

It is also believed that the increased pH brought about by PPI use adversely affects the immune and inflammatory response of the gastric mucosa. To this end, a recent study showed that PPI use in rats induced transcriptional changes in the apoptosis, inflammatory, immune, and stress responses of the gastric mucosa.[37] Previous studies in rats have also suggested that PPIs increase mucosal thickness and ECL cell density, possibly leading to the development of gastric tumors.[38,39] This preliminary work suggests that PPI use may cause a number of previously unknown biological changes, but more research is needed to fully understand the effects of long-term PPI use at the molecular level.

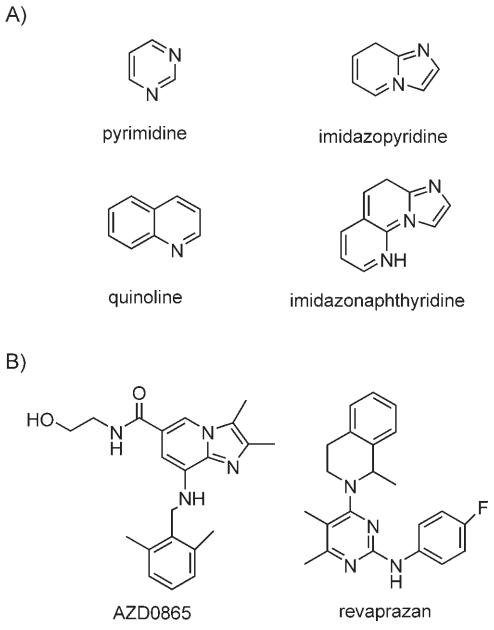


Figure 7. A) The four classes of P-CABs. B) Chemical structures of clinically tested P-CABs.

Additionally, changes in extracellular pH are known to alter intracellular pH; these pH changes, in turn, can affect the amount of internally-bound Ca^{2+}.[40,41] As intracellular calcium levels are altered, changes in gene expression may result, potentially contributing to tumor progression.[42–44] Thus, the possibility exists that PPI use may trigger unwanted changes in gene expression. The clinical significance of altered cellular gene expression resulting from long-term PPI use has yet to be determined.

5. Nongastric acid production

The treatment options discussed above in Section 3 are all designed to act upon the acid-producing cells of the stomach, with the PPIs and P-CABs specifically designed to target the gastric proton pump. However, a number of recent studies have provided evidence that the H^+/K^+-ATPase enzyme located in the stomach is also present in a number of other locations throughout the body. Likewise, a number of acid-producing bacterial species have been found within the upper gastrointestinal tract and oral cavity. These two important discoveries may help to explain both the onset of GERD, as well as the long-term side effects that result from PPI use. The possibility exists that these bacteria are directly producing acid that contributes to the onset of GERD. Furthermore, in terms of treatment, the potential effects of the acid-producing species are twofold: 1) the current drugs used to treat GERD might be affecting areas outside of the stomach, resulting in unwanted side effects, and 2) microbes may play a central role in the side effects observed during PPI treatment.

Nongastric H^+/K^+-ATPases

As mentioned above, the gastric H^+/K^+-ATPase is a member of the P-type ATPase family. Nongastric H^+/K^+-ATPases and the well-documented Na^+/K^+-ATPase, found in muscle and nerve cells, are also members of this family. Like their gastric counterparts, the nongastric H^+/K^+-ATPases are made up of an α and β subunit, in which the α subunit serves as the catalytic site, and the β subunit is thought to help stabilize the heterodimer.[45,46] Although the subunit composition and functional properties of these enzymes have not been fully characterized yet, it is believed that the nongastric H^+/K^+-ATPases are involved with maintaining the K^+ homeostasis in K^+- and Na^+-deficient environments.[46]

In addition to the stomach, H^+ ion-exchange pumps have been identified in rat and cockroach salivary glands,[47–49] rat colon,[50] rat kidney,[51] rabbit and human esophagus,[52,53] and human lung cells.[54] Our laboratory has also used immunohistochemical staining to positively identify the presence of both the α and β subunits of H^+/K^+-ATPase in human tissues of the larynx[55,56] and lung,[57] respectively. We have recently extended these studies to include human tissues of the salivary glands, sinus, and tongue (Figure 8); the positive staining observed in the immunohistochemistry results suggests that all three of these locations also express the H^+/K^+-ATPase enzyme.

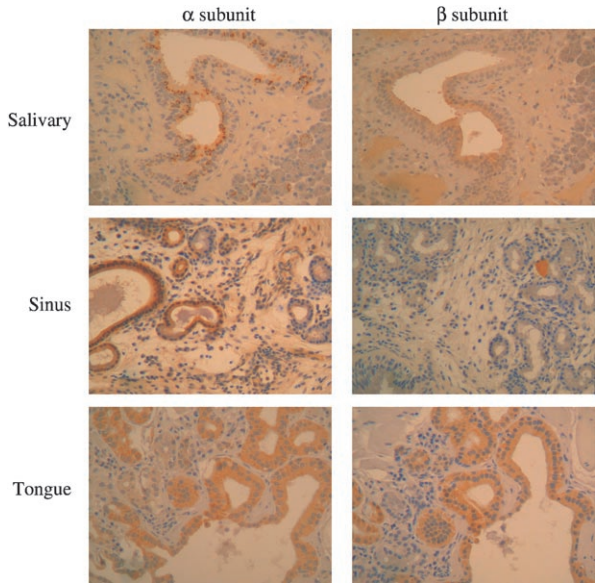


Figure 8. Immunohistochemical staining of human salivary, sinus, and tongue mucosa for the proton pump alpha (left column) and beta (right column) subunits. Images shown at 20x original magnification. Positive immunohistochemical staining is brown. Staining was carried out analogously to previously published methods.[56]

Preliminary studies of the nongastric H^+/K^+-ATPases described above suggest that they might play a crucial role in the treatment of GERD. Studies involving the rat submandibular gland demonstrated that acid-base disturbances lead to adaptive changes of the enzyme, in particular causing an 'activated state' of the H^+/K^+-ATPase upon metabolic acidosis.[49] The Na^+/H^+ antiport of the human esophagus might also serve as a defense against high levels of acid, particularly contents of the stomach being refluxed into the esophagus.[52] More studies are still needed, but the initial results suggest that the nongastric H^+/K^+-ATPases might serve as direct sites for PPI and potassium-competitive acid blocker pharmacotherapy.

Acid-producing bacteria

Prior to the discovery of the bacteria *Helicobacter pylori* in 1980, it was originally believed that bacteria could not survive in the harsh acidic conditions of the stomach. Until recently, it was similarly believed that bacteria could not live in the esophagus; however, species of bacteria have been found in the upper gastrointestinal tract.[58] Many of these species are acid-producing bacteria, such as *Streptococcus* and *Lactobacilli*, and a number of these strains have also been observed in the oral cavity and gastrointestinal tract.[59] Some of these bacteria are part of the natural human flora, whereas others can be acquired through the consumption of dairy products and other fermented foods.

Since the discovery of *H. pylori*, which is known to cause inflammation of the gastric mucosa, numerous studies have been carried out to determine if a correlation exists between *H. pylori* and GERD. Results have been inconclusive, and a

direct relationship between the two has not been found.[60,61] Furthermore, the presence of *H. pylori* has not been found to affect the performance of currently available PPIs.[62]

Unlike the bacteria recently found in the oral cavity and upper gastrointestinal tract, however, *H. pylori* does not produce acid and subsequently does not contain a proton pump. Given the rather recent discovery of the acid-producing species outside of the stomach, little is currently known if, and to what extent, these bacteria play a role in GERD onset and treatment.[63] Thus, the possibility exists that the bacterial species present in the esophagus and oral cavity may be producing acid, thereby directly contributing to the onset of GERD. On the other hand, these bacteria may also be affecting GERD treatment, by indirectly serving as an extrinsic site of action for the targeted therapies. In particular, the use of PPIs to treat GERD might be affecting the growth and survival of bacteria naturally found in the upper aerodigestive and gastrointestinal tracts, given the similarity in structure among bacterial proton pumps and proton pumps in human tissue, and the similar mechanism used to shut down these pumps. Clearly more research is needed in this area to understand the role of the bacterial biota as it relates to GERD.

Summary

Gastroesophageal reflux disease is a chronic disease affecting both men and women of all ages. Symptoms most commonly include heartburn and can range from mild to severe in nature. If left untreated, GERD can lead to more serious diseases including esophagitis, Barrett's esophagus, and esophageal cancer. A number of different treatment options are currently available, with proton pump inhibitors (PPIs) being the most popular choice. PPIs are designed to target the gastric H^+/K^+-ATPase enzyme—the last step of the acid production pathway—but often fail to provide a complete cure to the disease, as recurrence is common in cases of GERD. Recent evidence has shown that H^+/K^+-ATPases also exist in areas outside the stomach and that acid-producing bacteria containing these proton pumps are present in both the oral cavity and esophagus. Further studies need to be carried out to determine if these bacteria are a causal factor of GERD (by directly producing acid) and/or if the treatment of GERD by pharmaceuticals is indirectly disturbing the natural human bacterial flora and nongastric tissues expressing H^+/K^+-ATPases (by shutting down their proton pumps). Understanding the role that these acid-producing species play in GERD may possibly lead to better long-term care of the patient and/or a complete cure to the disease.

Outlook

The number of GERD cases, and subsequently Barrett's esophagus and esophageal cancer, has risen in recent years and is likely to continue to increase in the future. Whereas a number of treatment choices are currently available, it appears that the proton pump inhibitors will continue to remain the number one option in controlling symptoms for the foreseeable future. However, the substantial interpatient variability and high relapse rates suggest that current strategies used to treat GERD can be improved. Furthermore, the recent discovery of acid-producing bacteria in the oral cavity and esophagus, and the discovery of nongastric H^+/K^+-ATPases, has opened the door to further research that may potentially help to more completely explain the origins and/or side effects of GERD. The effect that current GERD therapies, particularly PPIs, play on the nongastric tissues expressing H^+/K^+-ATPase and the bacterial species located in the oral cavity and upper GI tract still needs to be determined. Furthermore, should these newly discovered bacteria be found to induce GERD, a new treatment option—antibiotics—would become available, one that would likely provide long-term relief from the disease. Thus, in addition to the work being done to improve the formulations of currently available pharmaceuticals and to fully understand their biological consequences, it is imperative that future research in this area also sufficiently addresses the role microbes play in this disease.

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Keywords: bacteria · biological activity · gastroesophageal reflux disease (GERD) · proton pump inhibitors (PPIs) · toxicology

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