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Potassium-competitive acid blockers: Advanced therapeutic option for acid-related diseases

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ABSTRACT

Acid-related diseases (ARDs), such as peptic ulcers and gastroesophageal reflux disease, represent a major health-care concern. Some major milestones in our understanding of gastric acid secretion and ARD treatment reached during the last 50 years include 1) discovery of histamine H_2-receptors and development of H_2-receptor antagonists, 2) identification of H^+,K^+-ATPase as the parietal cell proton pump and development of proton pump inhibitors (PPIs), and 3) identification of *Helicobacter pylori* (*H. pylori*) as the major cause of peptic ulcers and development of effective eradication regimens. Although PPI treatments have been effective and successful, there are limitations to their efficacy and usage, i.e. short half-life, insufficient acid suppression, slow onset of action, and large variation in efficacy among patients due to CYP2C19 metabolism. Potassium-competitive acid blockers (P-CABs) inhibit H^+,K^+-ATPase in a reversible and K^+-competitive manner, and exhibit almost complete inhibition of gastric acid secretion from the first dose. Many pharmaceutical companies have tried to develop P-CABs, but most of their clinical development has been discontinued due to safety concerns or a similar efficacy to PPIs. Revaprazan was developed in Korea and was the first P-CAB approved for sale. Vonoprazan, approved in 2014 in Japan, has a completely different chemical structure and higher pKa value compared to other P-CABs, and exhibits rapid onset of action and prolonged control of intragastric acidity. Vonoprazan is an effective treatment for ARDs that is especially effective in healing reflux esophagitis and for *H. pylori* eradication. P-CABs, such as vonoprazan, promise to further improve the management of ARDs.

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1. Introduction

Gastric acid is important for the sterilization of food and water and for digestion. Gastric acid secretion is a complex process that involves neuronal, hormonal, and endocrine pathways, all of which have one common target: the parietal cell. The parietal cell is responsible for secreting concentrated hydrochloric acid into the gastric lumen. The empirical realization that peptic ulcer disease (PUD) only occurred in the presence of gastric acid (Schwartz, 1900) led to the dictum of "no acid, no ulcer". Acid is also considered of central importance in the initiation and continuation of gastroesophageal reflux disease (GERD), nonsteroidal anti-inflammatory drug (NSAID) associated upper gastrointestinal damage, and ulceration in hypersecretory conditions such as Zollinger–Ellison syndrome. Many patients with these diseases benefit from acid-suppressive therapy, supporting the importance of gastric acid in the pathogenesis of these diseases.

Since the isolation of *Helicobacter pylori* (*H. pylori*) more than 30 years ago (Marshall & Warren, 1984), our understanding of the pathogenesis of gastroduodenal diseases has changed dramatically. Many diseases related to *H. pylori*, such as peptic ulcer and mucosal associated lymphoid tissue lymphoma, are curable, and gastric cancer might even be preventable, by the implementation of *H. pylori* eradication therapy (Malfertheiner et al., 2014). The incidence of PUD in the Western hemisphere and Japan has decreased in the past few decades, probably due to decreased infection rates with *H. pylori*. However, over the same period, the incidence of GERD has increased dramatically and GERD has become a major gastric acid-related disease (ARD).

The healing of duodenal ulcers, gastric ulcers and GERD with acid suppressants is highly correlated with control of gastric acid secretion (Burget et al., 1990; Howden et al., 1991; Bell et al., 1992). The goals of treatment for these diseases are to heal established lesions, relieve symptoms, and to prevent recurrence and complications. A meta-analysis has shown that maintaining intragastric pH at 3 or above for 18 to 20 h a day is optimal for healing duodenal ulcer (Howden et al., 1994). In patients with reflux esophagitis, an intragastric pH of 4 or

Abbreviations: ARD, acid-related disease; CCK_2R, cholecystokinin-2 receptor; ECL, enterochromaffin-like; H_2RA, histamine H_2 receptor antagonist; *H. pylori*, *Helicobacter pylori*; GERD, gastroesophageal reflux disease; M_3R, muscarinic M_3 receptor; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

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above has been shown to be the standard target for treatment (Hunt, 1999). Current *H. pylori* eradication therapy uses at least 2 antibiotics, such as amoxicillin and clarithromycin, and also requires administration of acid suppressant to elevate intragastric pH to 5 or above to promote *H. pylori* transition from a stationary phase to a growth phase, which leaves the bacteria susceptible to antibiotics (Sachs et al., 2011). The quest for better therapies has pushed research towards new acid-suppressive agents and formulations (Scarpignato & Hunt, 2015). This review examines the development and issues associated with current ARD treatments, with a particular focus placed on potassium-competitive acid blockers (P-CABs) which promise to be the most effective acid suppressant to date.

2. Mechanisms of gastric acid secretion

The parietal cell of the gastric gland is a highly differentiated cell responsible for secreting concentrated hydrochloric acid into the gastric lumen. Gastric acid secretion can occur upon ingestion of food or drink, or be stimulated by the thought, smell, or taste of food. Such direct and indirect parietal cell stimulation is mediated by 3 types of receptor: cholinergic muscarinic M_3 receptors (M_3R), histamine H_2-receptors (H_2R), and cholecystokinin-2/gastrin receptors (CCK_2R). Histamine, produced in enterochromaffin-like (ECL) cells by the decarboxylation of L-histidine by histidine decarboxylase, is thought to play a central role as a stimulant of gastric acid secretion by binding to H_2R. H_2R activation causes an increase in intracellular cyclic AMP levels, which serves as a second messenger that transfers the signal to the final step of acid secretion, i.e. H^+,K^+-ATPase (Ganser & Forte, 1973; Soll & Wollin, 1979). In contrast, stimulation of either M_3R by acetylcholine or CCK_2R by gastrin results in a signal mediated by an intracellular increase in free Ca^{2+} ions. Gastrin mediates acid secretion primarily by stimulating the release of histamine from neuroendocrine ECL cells after binding to CCK_2R. There has been some debate over whether activation of the parietal cell CCK_2R leads to acid secretion (Hinkle et al., 2003; Dufresne et al., 2006), and it seems the intracellular concentration of cyclic AMP must first be above a threshold level before gastrin can directly stimulate the parietal cell (Soll, 1982; Geibel et al., 1995). Activation of these receptors stimulates H^+,K^+-ATPase (Sachs et al., 2014).

H^+,K^+-ATPase belongs to the family of P_2-type ATPases, which includes the ubiquitous Na^+,K^+-ATPase and sarcoplasmic reticulum Ca^{2+}-ATPase. H^+,K^+-ATPase assembles as a heterodimer comprised of one catalytic α and one β subunit, which share a significant degree of sequence homology with the corresponding subunits of Na^+,K^+-ATPase. The H^+,K^+-ATPase α subunit contains about 1035 amino acids (Maeda et al., 1988) and the β subunit contains about 290 amino acids (Hall et al., 1990; Reuben et al., 1990). The H^+,K^+-ATPase α subunit has 10 transmembrane segments and the β subunit has 1 transmembrane segment. The α subunit contains the catalytic site and is responsible for ion exchange between the gland lumen and parietal cell cytosol, while the β subunit is essential for stabilization of the α subunit. The extracellular domain of the β subunit contains multiple N-glycosylation sites, which are not only necessary for targeted membrane trafficking, but also for correct heterodimer assembly (Asano et al., 2000; Vagin et al., 2003). In the resting parietal cell, H^+,K^+-ATPase is found in smooth-surfaced cytoplasmic tubulovesicles. Upon stimulation, H^+,K^+-ATPase is moved to apical microvilli of the secretory canaliculi of the parietal cell (Yao & Forte, 2003; Forte & Zhu, 2010). Along with H^+,K^+-ATPase, the K^+-channel KCNQ1/KCNE2 complex and a Cl^- channel are also moved (Lambrecht et al., 2005; Nguyen et al., 2013). This morphological change results in a several-fold expansion of the secretory canaliculi (Helander & Hirschowitz, 1972). H^+,K^+-ATPase catalyzes an electroneutral exchange of cytoplasmic protons for extracytoplasmic potassium by means of conformational changes that occur by MgATP-driven phosphorylation and dephosphorylation of the α subunit (Sachs et al., 1976). Activation of K^+ and perhaps Cl^- conductance in the H^+,K^+-ATPase membrane allows K^+ to access the extracytoplasmic face of the pump, which enables dephosphorylation and recycling of the pump (Wolosin & Forte, 1983). H^+,K^+-ATPase conformations that bind ions for outward transport are termed E_1 conformations, and conformations that bind luminal ions for inward transport are termed E_2 conformations. As a member of the P_2-type ATPase family, the H^+,K^+-ATPase enzyme cycle involves switching between E_1 and E_2-P states (Fig. 1). Hydronium ion binding to the cytoplasmic surface of the E_1 form of H^+,K^+-ATPase activates phosphorylation by MgATP to form the intermediate E_1-P, which then converts to E_2-P in the acid transporting step. After release of H_3O^+ and binding of K^+ on the extracytoplasmic surface of the enzyme, the E_2-PK^+ conformation is formed. The E_2-PK^+ conformation then converts to the E_1K^+ conformation after dephosphorylation. The E_1K^+ conformation releases K^+ to the cytoplasmic side, allowing rebinding of H_3O^+ and completing the enzyme cycle. At neutral pH, $2H^+$ are exchanged for $2\ K^+$ per hydrolysis of 1 ATP, but as the luminal pH falls, the exchange stoichiometry becomes $1H^+$ exchanged for $1K^+$ per 1 ATP. This stoichiometry change is explained by the pKa of one of the hydronium binding sites, which remains protonated at luminal pH < 3.0 (Rabon et al., 1982). H^+,K^+-ATPase exists as an $(\alpha\beta)_2$ heterodimeric dimer (Shin & Sachs, 2006).

When active acid secretion ceases, parietal cells revert to a resting conformation to prepare for the next stimulation (Forte et al., 1977). Based on the membrane recruitment and recycling hypothesis, withdrawal of stimulus leads to a progressive resequestration of the expanded apical membrane and H^+,K^+-ATPase is taken back into the cytoplasmic tubulovesicles. The proton pump protein has a half-life of about 54 h in rats (and probably similar in humans), thus about 20% of pumps are synthesized anew over 24 h (Shin & Kim, 2013).

It has been suggested that gastric H^+,K^+-ATPase is present at sites other than the stomach e.g., the cortical collecting duct of the kidney (Kraut et al., 2001), rat vascular smooth muscle cells (McCabe & Young, 1992), human leukocytes (Ritter et al., 1998), and rat cardiac myocytes (Beisvag et al., 2003). However, Herrmann et al. (2007) clearly demonstrated, using quantitative mRNA analysis, western blot, and immunohistochemistry, that the stomach is the only organ in humans that expresses significant levels of mRNA and protein of both the α- and β-subunits of gastric H^+,K^+-ATPase.

3. Antacids and receptor antagonists

Pharmacotherapy for PUD has comprised largely ineffective approaches that included antacids and anticholinergics. Antacids, such as sodium bicarbonate, aluminum hydroxide, magnesium hydroxide and calcium carbonate, have come into widespread use, especially in association with a strict Sippy-type bland diet (Sippy, 1983). Antacids provide a degree of symptom relief by neutralizing intragastric acid, but their

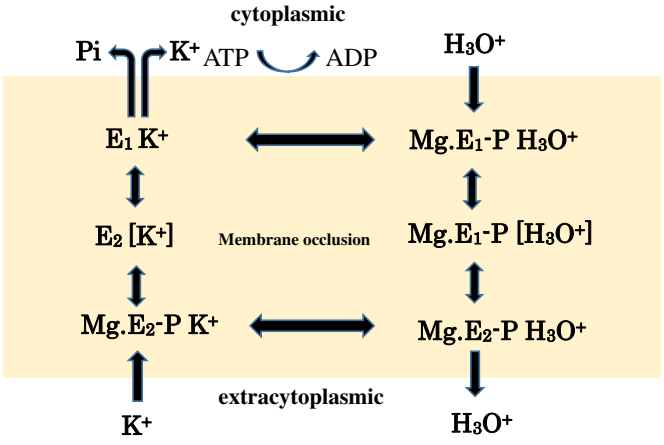

Fig. 1. The catalytic cycle of gastric H^+,K^+-ATPase.

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