GASTROINTESTINAL DISORDERS: A FOCUS ON ACID-SUPPRESSIVE AGENTS

Brian Hemstreet
University of Colorado School of Pharmacy, Anschutz Medical Campus, Aurora, Colorado

1 INTRODUCTION

During the late nineteenth century many theories were conceived within the medical community that development of some gastric disorders, particularly gastric ulceration, was somehow related to the secretion of gastric acid [1]. Hypersecretion of gastric acid was thought to be the main underlying defect leading to not only gastric ulceration but also in the development of erosive lesions within the esophagus. Subsequent research into the physiology of gastric acid secretion helped to delineate the main stimuli for acid secretion, and much interest was focused on gastrin as the main target for attenuation of acid secretion, while others touted histamine as the major contributor and next potential drug target [2]. An infectious etiology of peptic ulcer disease was also proposed at this time but received little interest from a research standpoint until later in the twentieth century.

Early attempts at treating acid-related disorders focused on neutralization of gastric acid with alkaline substances, such as milk, sodium bicarbonate, calcium carbonate, or bismuth. Dietary interventions were implemented as additional adjunctive treatments and often included ingestion of bland foods and use of smaller more frequent meals [1–3]. Alternatively, surgical gastrectomy or vagotomies were also less favorable options for patients unresponsive to these interventions. As more research into the physiology of gastric secretion accumulated, the focus of drug development turned more toward inhibition of the production and secretions of gastric acid.

The production and secretion of gastric acid is facilitated by the presence of greater than one billion parietal cells located in the mucosa of the stomach. These parietal cells secrete hydrochloric acid in response to various neuronal and hormonal stimuli [4]. The main external stimulus for gastric acid secretion is oral intake of food. Following stimulation, gastric acid secretion occurs in three phases. The cephalic phase is triggered by sight and smell of food, while the gastric and intestinal phases are regulated mainly by distention of the stomach, and breakdown products of protein and other ingested nutrients. At the level of the parietal cell, the three primary molecular mediators of acid secretion are acetylcholine, histamine, and gastrin [5, 6]. Gastrin, stored in antral G cells, is released into the bloodstream in response to food intake or increases in gastric pH [4]. As mentioned previously, cholinergic input resulting from innervation of the stomach by the vagus nerve leads to local release of acetylcholine and stimulation of muscarinic M_3 receptors on the basolateral membrane of the parietal cell. Stimulation of the cholycystokinin$_B$ (CCK_B) receptor by gastrin, or the M_3 receptors by acetylcholine receptor on the parietal cell, ultimately results in increased cytosolic concentrations of calcium. This in turn leads to stimulation of histamine release from enterochromaffin-like (ECL) cells. Histamine stimulates the H_2 receptor on the parietal cell, leading to increases in cytosolic cyclic

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad