

OVERVIEW ON GASTROINTESTINAL PHARMACOLOGY

Stefano Evangelista

Menarini Ricerche spa, Firenze, Italy

Keywords: antacids, antiemetics, dopamine (D) receptor, gastroesophageal reflux disease (GERD), *helicobacter pylori*, histamine-2 receptor antagonists, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), laxatives, non-ulcer dyspepsia, proton pump inhibitors (PPIs), prokinetics, serotonin or 5-hydroxytryptamine (5-HT) receptor, spasmolytics

Contents

1. Introduction
 2. Drugs that control gastric acid secretion and treat peptic ulcers
 - 2.1. Antacids
 - 2.2. Histamine (H₂) Receptor Antagonists
 - 2.3. Proton Pump Inhibitors (PPIs)
 - 2.4. *Helicobacter pylori* (H. pylori) Therapy
 3. Drugs stimulating gastrointestinal motility
 - 3.1. Dopamine D₂-receptor Antagonists
 - 3.2. Serotonin 5-HT₄ Receptor Agonists
 - 3.3. Macrolides
 4. Drugs to treat constipation
 - 4.1. Laxatives
 5. Drugs to treat diarrhea
 - 5.1 Antidiarrheal Agents
 6. Drugs to treat emesis
 - 6.1. Antiemetic Agents
 7. Drugs to treat Irritable Bowel Syndrome
 - 7.1. Spasmolytics
 - 7.2. Serotonin Compounds: 5-HT₃ Receptor Antagonist and 5-HT₄ Receptor Agonists
 8. Drugs to treat Inflammatory Bowel Disease
 - 8.1. Anti-IBD Therapies
- Glossary
Bibliography
Biographical Sketch

Summary

Gastrointestinal (GI) pharmacology deals with the properties and actions of drugs affecting gastrointestinal system function. These drugs normalize impaired function in the GI tract.

From a historical viewpoint, successful GI drugs include antisecretory compounds, the histamine (H₂) receptor antagonists and proton pump inhibitors (PPIs), the discovery and development of which revolutionized the treatment of gastric ulcers, reducing the need for surgical intervention and leading to the first blockbuster drugs and a Nobel

Prize in medicine for Sir James Black. The subsequent association of *H pylori* with gastritis and peptic ulcer formation and the use of antibiotic regimens in conjunction with H₂ antagonists and PPIs as an even more effective means of ulcer therapy led to another Nobel Prize in the area to Barry Marshall and Robin Warren.

Antisecretory compounds are also used in the treatment of gastroesophageal reflux disease (GERD), as are prokinetics such as dopamine (D)₂ receptor antagonists and 5-HT₄ and motilin receptor agonists. Some of these compounds are also used as antiemetics as both 5-HT and dopamine are involved in the gastric motor reflexes and emetic signals of vomiting. In this area, 5-HT₃ receptor antagonists have been successful treatment modalities. Prokinetics and laxatives are used in constipation while different forms of diarrhea require specific treatments. Mild to moderate diarrhea is usually treated not specifically with opioid agonists such as loperamide.

Other gastrointestinal diseases include irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and colorectal cancer. IBS, a chronic dysregulation of brain-gut relationships is reflected in altered gut motility and defecation and can be treated with spasmolytics, psychotropic agents and new 5-HT receptor agonists or antagonists, the latter, albeit, with suboptimal therapeutic indices. IBD, reflected as ulcerative colitis and Crohn's disease, represents several idiopathic chronic disorders that are currently treated with aminosalicylates, corticosteroids or immunosuppressive drugs. Both IBS and IBD represent areas of significant unmet medical need from a pharmaceutical perspective.

1. Introduction

Gastrointestinal pharmacology studies the properties and actions of drugs affecting the gastrointestinal system, which is responsible for:

- Providing the body with essential nutrients;
- Maintaining adequate levels of all essential nutrients in the bloodstream to facilitate normal activity;
- Eliminating wastes derived from the diet, and some products of the body's metabolism, in order to avoid toxic waste inside the body.

The gastrointestinal tract is usually divided into two main parts:

- The upper tract, which consists of structures that aid in the ingestion and digestion of food such as the mouth, esophagus, stomach and duodenum. Digestion of food is the extraction of essential nutrients from ingested food. It begins in the mouth with the mechanical breakdown of food. The best environmental conditions for the treatment of various food components are produced by the secretory activity of the coating epithelium, the intramural glands and extramural exocrine glands, such as the salivary glands, the liver and the pancreas, which produce digestive enzymes and hormones to facilitate the breakdown of food particles.
- As the bolus of food moves to the esophagus, it progresses through to the lower tract, which consists of the small and large intestine. Digestion of food is completed in the small intestine, where most of the nutrients are absorbed. The

large intestine primarily serves to absorb water and electrolytes and to eliminate the waste products of digestion. Indigestible food particles are stored in the sigmoid colon until they are eliminated through the rectum.

An integrated pattern of motility is very important for the digestion and elimination of food. It should be noted that between the inner part of the gut (mucosal surface devoted to absorption) and the outer part (serosal surface) lie the muscular structures, some of which are in a circular arrangement (circular muscle) that are able to narrow or restrict the lumen. Other muscles are arranged lengthwise (longitudinal muscles) and their constriction causes the shortening of the intestine. In some parts, the circular muscles form valves, called sphincters, whose constriction determines the closure of a passage or a natural opening. The circular and longitudinal muscles constrict and release in coordinated waves, called peristaltic waves, thus mixing the contents of the intestine and allowing the progression of food from the mouth to the anus.

Pathologies of the gastrointestinal tract are due to impairment of one or more of these simple functions (secretion, absorption, motility) and are divided into functional types (e.g. irritable bowel syndrome (IBS), dyspepsia) or organic (e.g. inflammatory bowel disease (IBD), peptic ulcer, gastroesophageal reflux disease (GERD)), depending on the diagnosis based on the symptoms only or with the aid of precise clinical tests.

Several classes of drugs that are able to efficiently treat some of these diseases have been developed.

2. Drugs that Control Gastric Acid Secretion and Treat Peptic Ulcers

From a historical point of view, this class of drug is the most important for gastrointestinal diseases. In fact, the introduction of antisecretory compounds, firstly histamine (H₂) receptor antagonists and then proton pump inhibitors (PPIs), has led to the reduction of surgical interventions (see peptic ulcer characteristics in Table 1).

Factors involved in ulcer formation:
<p>Imbalance between aggressive factors (gastrin, acid and <i>helicobacter pylori</i>) and defensive ones (bicarbonate, mucus and prostaglandins)</p> <ul style="list-style-type: none"> • Breakdown of mucosal barrier due to: <ul style="list-style-type: none"> --alcohol --high salt concentrations --bile acids • Excess acid secretion <p>Drugs, especially non-steroidal antinflammatory drugs</p>

Table 1: Summary of the characteristics of peptic ulcer disease

Gastric acid secretion originates with an energy-requiring hydrolysis of water into hydrogen and hydroxyl ions in oxyntic (parietal) cells. The hydrogen ions, as well as chloride ions, are actively secreted into the stomach lumen to form isosmotic hydrochloric acid (see Figure 1). The hydroxyl ions are converted to bicarbonate ions by

carbonic anhydrase and passively enter the gastric venous blood, raising its pH. Acid is essential for activation of the protease pepsin to initiate protein digestion. The oxyntic cells also secrete gastric intrinsic factor, which is necessary for absorption of vitamin B₁₂ and normal erythropoiesis. Damage to the gastric mucosa by acid and various ingested and secreted products is prevented by mucosal barriers. Adherent mucus physically and chemically protects the underlying mucosa. The gastric mucosa is normally a tight epithelium, relatively impermeable to hydrogen ions. Finally, the active secretion of hydrogen ions removes them from the mucosa where damage would otherwise result.

Acid secretion can be regulated by three major pathways: neural stimulation via the vagus nerve, endocrine stimulation via gastrin released from antral G cells, and paracrine stimulation by the local release of histamine from enterochromaffin-like cells.

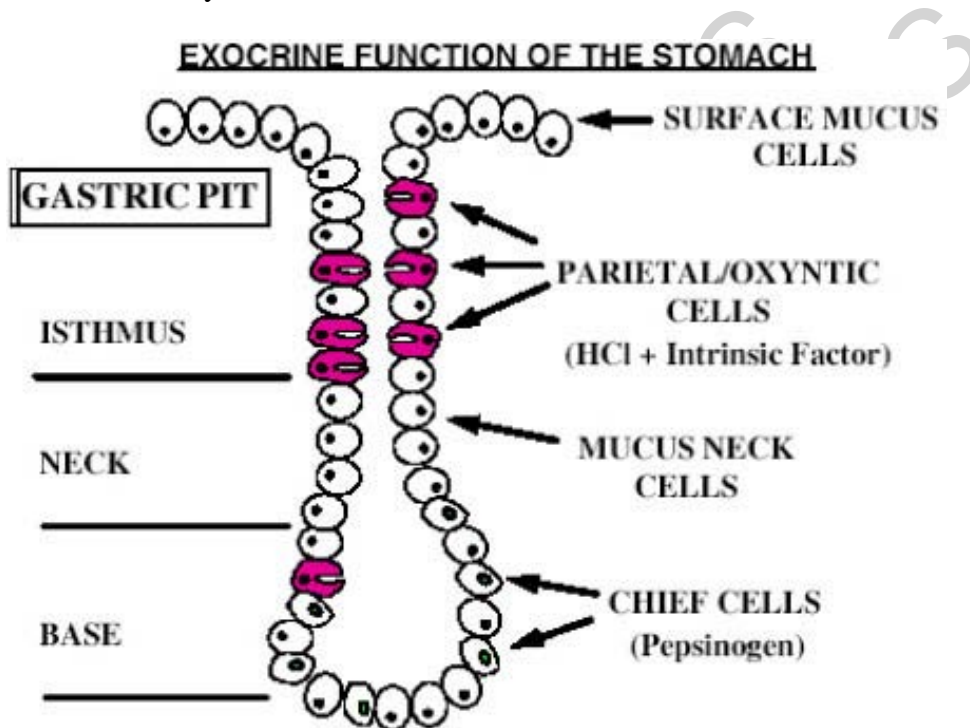


Figure 1: A representation of a gastric pit divided into isthmus, neck and base and with chief, mucus and parietal cells. Each of them is specialized to secrete a different substance inside the lumen.

2.1. Antacids

The famous theory “no acid, no ulcer” of the early years of the past century, led to the identification of this class of drugs during the 60’s (Table 2). The principal target of this class of drugs is the neutralization of the acid secreted by parietal cells, maintaining the pH of the stomach at values greater than or equal to 4. The antacid composition varies with constituents and acid-neutralizing capability. The most common are hydroxide of magnesium and aluminum but also sodium bicarbonate and calcium carbonate are used as well. The activity of antacids depends on their dissolution, water solubility and presence of food in the stomach that can prolong their effects. Compensatory increase in

pepsin and gastrin is usually recorded when the pH reaches 5 and is balanced by autoregulatory mechanisms involving pepsinogen. Alkalinization of the gastric content increases the gastric motility through the action of gastrin. The main adverse effect of antacids is due to alkalinization of urine and gastric media that can alter the pharmacokinetics of some drugs, leading to potential significant drug interactions. Antacids are nowadays used for gastritis and duodenal ulcers, but their use for gastric ulcers and GERD has been superseded by the introduction of antisecretory agents, because antacids only partially neutralize the gastric acid that has already been secreted, and therefore symptom control and ulcer healing rates are unsatisfactory after their administration.

Antacids neutralize HCl to form a salt and water	
Generally, large doses are needed (e.g. 7X daily)	
Antacids are basic compounds, composed of a metal ion and a base	Metal ion: Al ³⁺ , Mg ²⁺ , Ca ²⁺ , Na ⁺
	Bases: hydroxide, carbonate, bicarbonate, citrate, trisilicate
Therapeutic uses of antacids	Gastric Ulcer and Duodenal Ulcer
	Gastroesophageal Reflux Disease (GERD)
	Prophylaxis of stress ulcerations
	Gastritis

Table 2: Pharmacological agents for treatment of peptic ulcer disease: Antacids

2.2. Histamine (H₂) Receptor Antagonists

Acid secretion can be stimulated by three principal “secretagogues”: histamine, acetylcholine and gastrin. The action of these three substances is synergistic in that a small dose of one potentiates the response brought about by a small dose of another. Each has a specific receptor site on the basolateral membrane of the oxyntic/parietal cell (Figure 2). Vagal stimulation and gastrin released by G cells stimulate the release of histamine from enterochromaffin-like, or mast, cells. Histamine activates parietal cell H₂ receptors, known to be linked to the stimulation of adenylate cyclase by cAMP pathway activation (Figure 2).

The discovery of the first H₂ receptor antagonists (Table 3) by Black and Duncan in 1972 was a very important breakthrough. Peptic ulcer patients were at that time subjected to surgical operations or to unsatisfactory therapy with antacids. The first H₂ receptor antagonist developed was burimamide, followed by metiamide. With minimal structural alteration, cimetidine was developed and had considerable marketing success. The modification of the chemical structure of cimetidine with the substitution of the imidazole ring with a furan led to ranitidine whose pharmacokinetic characteristics allowed a better patient compliance. These drugs provided effective inhibition of production and release of gastric acid via a pharmacologically proven mechanism and became the gold standard therapy for peptic ulcers during the 1980's, leading to a marked improvement of the quality of life for a large number of patients. A further chemical modification was the insertion of thiazole in place of the imidazole ring, and this led to famotidine and nizatidine, whose market impact was less than that obtained by cimetidine and ranitidine.

H₂ receptor antagonists are highly selective. Although H₂ receptors are found in other tissues such as vascular and bronchial smooth muscle, they do not interfere with functions other than gastric acid secretion. The inhibition of the H₂ receptor is competitive and linked to the plasma concentration attained by the drug. This class of drug is able to reduce gastric acid secretion stimulated by gastrin, food, and sham feeding, fundic distention and by several pharmacological/chemical agents. They decrease H⁺ concentration in the gastric lumen as well the volume of acid secretion, along with pepsin secretion from chief cells. Some effects of H₂ receptor antagonists were reported on gastric emptying, pressure of lower esophageal sphincter and pancreatic secretions. Experimental evidence showed that they protect the stomach from gastric ulceration induced by pyloric ligation, stress, NSAIDs, aspirin and H₂ receptor agonists. The tolerability of H₂ receptor antagonists is very good and they can be administered at doses exceeding that required to inhibit gastric acid secretion and therefore, despite their short half-lives, are given in relatively large quantities to allow an effective therapy.

However, H₂ receptor antagonists do not block parietal cell stimulation by agonists other than histamine (e.g. vagal acetylcholine interacting with parietal cell muscarinic M₃ receptors is only partially inhibited). They also develop rapid tolerance during therapy due to the elevation of cAMP in parietal cells and are more effective in inhibiting nocturnal than day-time acid secretion.

H ₂ -antagonists are selective for H ₂ receptors and block the effect of histamine on the parietal cell	
Cimetidine	Effective dose is 400 mg bid or 800 mg nightly; antisecretory effect lasts 6-8 hours
	<p>All in all is a safe drug, however some important side effects are:</p> <ul style="list-style-type: none"> • Antiandrogenic activity: gynecomastia, impotence • Disturbances in CNS function, especially in the elderly due to passage across the blood brain barrier • Interferences with drug metabolism by binding to cytochrome P-450. It inhibits oxidative metabolism of warfarin, phenytoin, theophylline, phenobarbital, diazepam, propranolol, imipramine

Ranitidine	Effective dose is 150 mg bid or 300 mg nightly
	Pharmacologically very similar to cimetidine but more potent (5-10 X)
	Pharmacokinetics similar to cimetidine; therapeutic effect lasts longer
	Fewer side effects at therapeutic doses
Famotidine and Nizatidine	Pharmacologically very similar to other H ₂ antagonists
	They do not increase blood alcohol

Table 3: Pharmacological agents for treatment of peptic ulcer disease: Histamine (H₂)-receptor antagonists

2.3. Proton Pump Inhibitors (PPIs)

As described previously, the three major secretagogues are histamine, acetylcholine and gastrin and each is able to specifically interact with their own receptor on the basolateral membrane of the parietal cell (Figure 2). This activation by the cAMP pathway for histamine or by calcium sensitive pathways for muscarinic and gastrin receptors triggers the H⁺/K⁺ ATPase pump, and through an active transport mechanism, is able to increase the hydrogen ion concentration into the lumen of the stomach in terms of 20-40 mEq per hour.

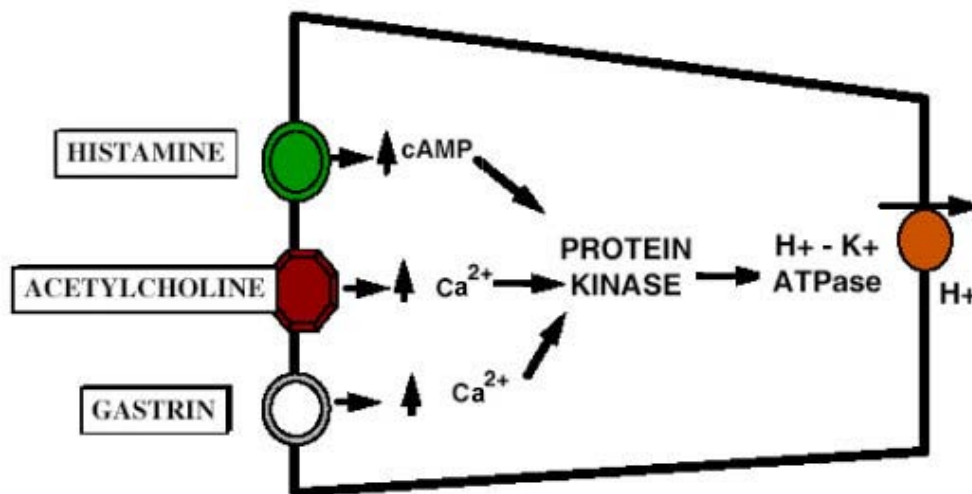


Figure 2: Physiological regulation of gastric acid secretion in oxyntic/parietal cells: the agonist (histamine, acetylcholine or gastrin) interacting with their own receptor leads to the activation of the H⁺/K⁺ ATPase pump, which is able to increase the hydrogen ions into the lumen.

By the selective blocking of this pump, which represents the final step of gastric acid secretion, a novel class of efficient antisecretory agents called proton pump inhibitors (PPIs) has been developed. Their superior antisecretory potency, long-lasting efficacy and pharmacokinetic characteristics have established these compounds as drugs of choice for the therapy of peptic ulcers. In fact the last compound of this class launched

on the market is esomeprazole, the active isomer of omeprazole, which was the 3rd best selling drug worldwide in 2005.

Similarly to the H₂ receptor antagonists, lansoprazole, pantoprazole and rabeprazole were subsequently developed by modifying the chemical structure of omeprazole, the first PPI discovered (Table 4). In contrast to H₂ receptor antagonists, all PPIs possess a common structural element: the benzimidazole ring that is linked to the pyridine ring with a bridge containing a sulfinyl group. At neutral pH, PPIs are weak bases devoid of inhibitory activity but when they reach the secretory canaliculi they became protonated and are trapped.

The protonated molecule is converted from sulfenic to sulfonamide and this latter covalently binds the sulphhydryl groups at the extracellular domain of the membrane-spanning H⁺/K⁺ ATPase pump. The selectivity and specificity of PPIs originate from the selective distribution of the pump, and the requirement for an acidic condition in order to activate, trap and protonate the drugs within the canaliculi close to the target enzyme. The inhibition of acid secretion obtained by PPIs is permanent and it is resumed only after the insertion of new molecules of H⁺/K⁺ ATPase into the luminal membrane.

PPIs produce only small changes in gastric volume, secretion of pepsin and intrinsic factor, and do not affect gastric motility. An increased secretion of gastrin might be the result of the prolonged inhibition afforded by PPIs. In rodents, hyperplasia of parietal cells due to the trophic effect of gastrin has been observed after long-term administration of omeprazole, but in humans no evidence of mucosal proliferation has been found.

PPIs promote healing of ulcers in the stomach, duodenum and esophagus and are particularly effective in patients that do not respond to H₂ antagonist therapy, especially those with Zollinger-Ellison syndrome. In GERD, PPIs are definitively better than H₂ antagonists, are more rapid in producing relief and, in general, they do not show the drawbacks of the H₂ antagonists, such as development of rapid tolerance during therapy, and are without differences in inhibiting nocturnal versus day-time acid secretion.

<ul style="list-style-type: none"> • Interfere with the final step of acid secretion by the irreversible inhibition of gastric proton pump H⁺/K⁺ ATPase on parietal cell
<ul style="list-style-type: none"> • Indicated in duodenal ulcer (e.g. 95-100% healing after 4 weeks, even in patients resistant to H₂ receptor antagonists), gastric ulcer, NSAIDs induced gastropathies, GERD and Zollinger-Ellison syndrome
<ul style="list-style-type: none"> • First compound developed was omeprazole, others PPIs are lansoprazole, pantoprazole, rabeprazole, esomeprazole that are characterized by a partially improved pharmacokinetic profile and higher tissue selectivity; but these elements do not differentiate the individual PPIs in their clinical use

Table 4: Pharmacological agents for treatment of peptic ulcer disease: Proton Pump inhibitors (PPIs)

-
-
-

TO ACCESS ALL THE 21 PAGES OF THIS CHAPTER,
Visit: <http://www.eolss.net/Eolss-sampleAllChapter.aspx>

Bibliography

Aihara T., Nakamura E., Amagase K., Tomita K., Fujishita T., Furutani K., Okabe S. (2003). Pharmacological control of gastric acid secretion for the treatment of acid-related peptic disease: past, present, and future. *Pharmacol. & Ther.* **98**, 109-127. [This review describes the history and the techniques utilized for the development of antisecretory compounds].

Drossman DA, Camilleri M, Mayer EA, Whitehead WE. (2002). AGA technical review on irritable bowel syndrome. *Gastroenterology* **123**, 2108-2131. [This review describes the pathophysiology and the management of irritable bowel syndrome].

Evangelista S. (2004). Quaternary ammonium derivatives as spasmolytics for irritable bowel syndrome. *Curr Pharm Des* **10**, 3561-3568. [A comprehensive review on this class for IBS treatment describing differences from the chemistry to the clinic characteristics of these compounds].

Gershon MD. (2004). Review article: serotonin receptors and transporters-roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* **20 Suppl 7**, 3-14. [This review reports the role of new classes of 5-HT receptor agonists or antagonists in gut motility disorders].

Hanauer SB, Present DH. (2003). The state of the art in the management of inflammatory bowel disease. *Rev Gastroenterol Disord.* **3**, 81-92. [This is an update concerning the IBD treatment].

Johanson JF. (2004). Options for patients with irritable bowel syndrome: contrasting traditional and novel serotonergic therapies. *Neurogastroenterol Motil* **16**, 701-711. [A paper concerning the comparison between new and old treatments for IBS].

Marshall B.J., Warren J.R. (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* **i**, 1311-1314. [This is the historical paper describing for the first time the discovery of colonization of *H pylori* in the stomach].

Ramkumar D., Rao SS. (2005). Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol* **100**, 936-971. [This is an updated review on constipation treatment].

Stanghellini V., De Ponti F., De Giorgio R., Barbara G., Tosetti C., Corinaldesi R. (2003). New developments in the treatment of functional dyspepsia. *Drugs* **63**, 869-892. [This is an updated review on dyspepsia treatment].

Tonini M., De Giorgio R., De Ponti F. (2004). Progress with novel pharmacological strategies for gastro oesophageal reflux disease. *Drugs* **64**, 374-361. [This is an updated review on GERD treatment].

Biographical Sketch

Dr. Stefano Evangelista has a long history of research in gastrointestinal pharmacology at both academic and private institutes of research.

He has successfully contributed to the characterization of the role of several neuropeptides in GI function and participated to the development of tachykinin antagonists. He belongs to a group developing basic research of the field of capsaicin-sensitive neurons with pioneering inputs in the recognition of the function of neuropeptides such as CRGP, SP, neurokinin A in the GI tract.

Working in a pharmaceutical company in the discovery, and then development, sections, he has strongly participated in the advancement of knowledge on the mechanisms of the actions of drugs from molecular pharmacology to the clinical stage. He is author of 120 full papers and from 1993 until now has been a referee for 20 International Journals.

Dr Evangelista is presently working in the preclinical development of Menarini Ricerche. He has numerous collaborations with academic groups and is particularly involved in exploratory pharmacology to find a new relevant target for the treatment of IBS.