

Regulation of gastric acid secretion



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The stomach is a J-shaped enlargement of the gastrointestinal tract just lies below the diaphragm; the digestive tube dilates into an elongated pouchlike structure, the size of which varies according to several factors, notably the amount of distention. For sometime after a meal, the stomach is enlarged because of distention of its walls, but, as food leaves, the walls partially collapse, leaving the organ about the size of a large sausage. In adults the stomach usually holds a volume upto 1. 0 to 1. 5L.

ANATOMY OF STOMACH

1. 1. 1 Divisions of the stomach:

The fundus, body and the pylorus are the three divisions of the stomach. The fundus is the enlargement portion of the left and above opening of the oesophagus into the stomach. The body is the central part of the stomach, and the pylorus is its lower portion.

1. 1. 2 Curves of the stomach:

The curve formed by the upper right surface of the stomach is known as the lesser curvature; the curve formed by the lower left surface is known as the greater curvature.

1. 1. 3 Sphincter muscles:

Sphincter muscles guard both stomach openings. A sphincter muscle consists of circular fibres so arranged that there is an opening in the centre of them (like the hole in a doughnut) when they are relaxed and no opening when they are contracted.

The cardiac sphincter controls the opening of the oesophagus into the stomach, and the pyloric sphincter controls the opening from the pyloric portion of the stomach into the first part of the small intestine.

1. 1. 4 Stomach wall:

Gastric mucosa

The epithelial lining of the stomach is thrown into folds, called rugae, and marked by depressions called gastric pits. Numerous coiled tubular- type glands, gastric glands, are found below the level of the pits, particularly in the fundus and body of the stomach. The glands secrete most of the gastric juice, a mucous fluid containing digestive enzymes and hydrochloric acid.

1. 1. 5 Functions of the stomach:

The stomach carries on the following the functions:

- It serves as a reservoir, storing food until it can be partially digested and moved further along the gastrointestinal tract.
- It secretes gastric juice, containing acid and enzymes, to aid in the digestion of food.
- It carries on the limited amount of absorption – of some water, alcohol, and certain drugs.
- It produces the hormone gastrin, which helps regulation of digestive functions.
- It helps to protect the body by destroying pathogenic bacteria swallowed with food or with mucous from the respiratory tract.

1. 2 Regulation of gastric acid secretion:

The mechanisms operating at the gastric parietal cells as summarized in the above figure. The terminal enzyme H⁺K⁺ATPase (proton pump) which secretes H⁺ ions in the apical canaliculi of parietal cells can be activated by histamine, Ach and gastrin acting via their own receptors located on the basolateral membrane of these cells. Out of the three physiological secretagogues, histamine, acting through H₂ receptors, plays the dominant role, because the other two, gastrin and Ach act partly directly by releasing histamine from paracrine enterochromaffin like cells called “ histaminocytes” located in the oxyntic glands. While H₂ receptors activate H⁺K⁺ATPase by generating cAMP, muscarinic and gastrin receptors appear to function through the phospholipaseC -IP₃-DAG pathway that mobilizes intracellular Ca⁺. The cAMP mediated proton pump activation also involves Ca⁺. The secretomotor response to gastrin and cholinergic agonists is expressed fully only in the presence of cAMP generated by H₂ activation. As such, histamine participates in the acid response to gastrin and Ach at more than one levels, and H₂ antagonists suppress not only histamine but also Ach, pentagastrin and in fact any gastric acid secretory stimulus.

Gastrin is secreted from the antrum in response to rise in antral pH, food constituents and vagally mediated reflexes. The dominant muscarinic receptor mediating vagal responses is of M₁ subtype. Its location on the ganglion cells of the intramural plexuses has been confirmed. The parietal cell muscarinic receptor is of the M₂ subtype but the subtype of muscarinic receptor on histaminocytes has not been defined. Vagus releases Ach in

dose proximity to histaminocytes and gastrin secreting cells, but apparently at a distance from the parietal cells.

Prostaglandins have been ascribed a “ cytoprotective” role in the gastric mucosa by augmenting mucus and bicarbonate secretion, as well as other actions. PGE₂, produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation and gastrin release.

CONTROL OF GASTRIC ACID IN STOMACH:

1. 3 Peptic Ulcer

Peptic ulcers disease refers to a group of disorders characterized by circumscribed lesions of the mucosa of the upper gastrointestinal tract (especially of the stomach and duodenum). The lesions occur in regions exposed to gastric juices. When the stomach’s natural protections from acid stop working ulcers will occur. Duodenal ulcers almost always develop in the duodenal bulb (the first few centimetres of the duodenum). A few, however, arise between the bulb and the ampulla. Gastric ulcers form most commonly in the antrum or at the antral-fundal junction. Nearly 80 % of peptic ulcers are duodenal the others are gastric ulcers. Most duodenal ulcers appear in people between ages 20 and 50 years, while gastric ulcer usually occurs between ages 45 and 55 years. Duodenal ulcer is twice as common in men as in women and gastric ulcers affect men and women equally.

Approximately 10 to 20 % of gastric ulcer patients also have a concurrent duodenal ulcer.

Gastric ulcer is often a chronic disease and may persist for 10 to 20 years characterized by repeated episodes of healing and re-exacerbation. Peptic

ulcers occur when there is an imbalance between offensive factors and defensive mucosal factors (Goel and Bhattacharya, 1991). Ulceration in the mucosa can be because of either breakdown of mucosa with the development of surface defects or failure of restitution of mucosal integrity resulting in retardation or failure of healing of the ulcers. No apparent causal factor is sufficiently uniquely associated with peptic ulcers to warrant unequivocal implication in pathogenesis of the ulceration. The mechanism of defensive action consists of humoral, functional and neuronal factors. All these factors are responsible for the mucosal protection.

The precise biochemical changes during ulcer generation are not clear yet, although various hypotheses have been proposed from time to time.

Increased gastric motility, vagal over activity, mast cell degranulation decreased gastric mucosal blood flow and decreased prostaglandin level during stress condition is thought to be involved in ulcer generation.

Similarly role of oxygen derived free radicals have been shown to play a role in experimental gastric damage induced by ischemia and reperfusion, hemorrhagic shock and ethanol administration. *Helicobacter pylori* a pathogen is now known to be the most common and important causes of gastric ulcer in humans (Davies et al., 1994), exhibits active inflammation with epithelial damage accompanied by neutrophil migration.

Although the currently used drugs for ulceration are broadly classified into two, those that decrease or counter increase in acid-pepsin secretion and those that afford cytoprotection by virtue of their effects on mucosal defensive factors. Ulcer treatment can be carried out by reducing the action of aggravating factors. Since gastric acid is one of the major aggressive

factor contributing to peptic ulcer disease, the reduction of gastric acid either by surgical or pharmacological intervention has been used to promote ulcer healing. However, not all patients, with gastric or duodenal ulcer have high acid secretion. In fact, only 30%-40% of cases with duodenal ulcer have hypersecretion of gastric acid and, in patients with gastric ulcer, acid secretion is either normal or low (Gupta et al., 1980). In these cases, decreased mucosal resistance might be the dominant factor.

The neutralization of gastric acid can be done by antacid administration, but their effectiveness is only for a brief period. Muscarinic antagonists such as pirenzepine or telenzepine are effective inhibitors of acid production. The histamine H₂-receptor antagonists (H₂RA) like cimetidine, ranitidine, famotidine etc. act as potent inhibitors of acid secretion. Complete inhibition of parietal cells acid secretion by receptor antagonist is difficult because of complexity of known receptors on parietal cells and a variety of second messenger signaling system coupled to these receptors, which involve adenylate cyclase coupled with histamine receptor and intracellular Ca⁺² with acetylcholine receptors. Thus, the most successful and desirable therapy is to inhibit the enzyme responsible for acid secretion. Moreover, H₂RA have been reported to have some adverse reactions ranging from gastric carcinoid to tolerance and rebound acid secretion. Inhibition of gastric H⁺/K⁺ -ATPase of the parietal cell by drugs such as by proton pump inhibitors (PPIs) like omeprazole, lansoprazole, timoprazole, etc. has been shown to be effective in the treatment of peptic ulcer disease. However, such agents irreversibly inactivate the ATPase and the return of acid secretion following such inhibition requires de novo synthesis of new pump.

Although these drugs have brought about remarkable changes in ulcer therapy, the efficiency of these drugs is still debatable. Reports on clinical evaluation of these drugs shows that there are incidences of relapses and adverse effects and danger of drug interactions during ulcer therapy.

Further, in the developing countries, like India, most of the population is living in rural areas and depending on their indigenous system of drugs because of expensive modern treatment. Hence, the search for an ideal anti-ulcer drug continues and has also been extended to herbal drugs in search for new and novel molecules, which afford better protection, decrease the incidence of relapse and decrease the cost of the treatment.

Of late the search for new safe alternative drugs have rekindled the interest in cytoprotective drugs, which protects the mucosal layer from inducing agents. Cytoprotection has been defined as the ability of pharmacological agents-originally prostaglandins to prevent or reduce gastric, duodenal, or intestinal mucosal injury by mechanisms other than inhibition of gastric acid secretion. Although few drugs like sucralfate and prostaglandin analogs are recognized as cytoprotective agents (Vergin and Kori-Lindner, 1990), many natural drugs have been reported to possess this activity viz. plantain banana (*Musa sapientum* var *Paradisiaca*), *Tectona grandis*, *Azadirachta indica* and rasayana drugs like *Centella asiatica*, *Asparagus racemosus*, *Convolvulus pluricaulis*, *Emblica officinalis*, *Bacopa monniera* and *Withania somnifera*, etc. (Goel and Sairam, 2002).

India is one of the country rich in medicinal plants which were used by our ancestors. Traditionally, plants were used as medicine in a traditional way such as Ayurveda, Naturopathy, Siddha and Unani. After knowing the used of <https://assignbuster.com/regulation-of-gastric-acid-secretion/>

plants in medicine, synthetic drugs were now started replacing by herbal products.

Humans have used plant materials since prehistoric times and in some countries such as China documentary evidence shows that herbal medicines have been used for at least 7000 years. In Europe there is a rich history in the use of herbal medicines and these have been well documented in medieval herbals such as Culpeper's and Gerard's materia medica. Nowadays many countries are having interest in using Indian medicinal plants as it can cure many diseases and other purposes.

Herbal medicines differ from synthetic drugs in several attributes. Though, herbal medicines are mixed chemical compounds, all have not been isolated, characterized and quantified. When an extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substances or new chemical entity. The same type of acute, subacute and chronic toxicity data has to be generated.

Majority of medicinal herbs contain dozens of different compounds, often of great complexity, flavonoids, saponins, glycosides, alkaloids, mucilage, tannins, polysaccharides, etc., that buffer, modulates and modify the effect of any " active principles". Study after study has shown that administering of isolated purified constituents of the whole or part of the plant cannot mimic effects produced by extracts of same part of the plant.

1. 3. 1 Pathophysiology of Peptic Ulcer

Peptic ulcer generally occurs when aggravating factors are higher than defensive mucosal factors (Goel & Bhattacharya, 1991). The peptic ulcer can be treated by reducing the activity of aggravating factors thereby increasing the activity of defensive factors.

H. Pylori

H. Pyloric is a Gram -ve spiral-shaped bacterium. H. Pyloric is the most common cause of non-NSAID associated peptic ulcer disease. H. Pyloric has been found in the gastric antrum of a significant number of patients with duodenal ulcers and gastric ulcers.

H. Pyloric lives in the acidic environment of the stomach. The initial infection is transmitted by the oral route. H. Pyloric attaches to adhesion molecules on the surface of gastric epithelial cells. In the duodenum, H. Pyloric attaches only to areas containing gastric epithelial cells that have arisen as a result of excess and damage to the duodenal mucosa. H. Pyloric is able to live in such a hostile environment partly because of its production of the enzyme urease, which converts urea to ammonia. The ammonia buffers the H⁺ and forms ammonia OH creating an alkaline cloud around the bacteria and protecting it from the acidic environment of the stomach. It causes inflammation and epithelial cell damage (Golan, and Arman).

NSAIDs

More than 100,000 patients are hospitalised each year for NSAID-associated gastro-intestinal complications and gastrointestinal bleeding has a 5% to 10% mortality rate in these patients.

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NSAID-associated gastrointestinal damage is attributable to both topical injury and systemise effects of the NSAID. Most NSAIDS are weak organic acids. In the acidic environment of the stomach, these drugs are neutral components that can cross the plasma membrane and enter gastric epithelial cells. In the neutral intracellular environment, the drugs are recognized and trapped. The resulting intracellular damage is responsible for the local gastrointestinal injury associated with NSAID use.

Gastric acid secretion

Inhibition of cyclooxygenase prostaglandins Bicarbonate/ Mucous

Production

Blood flow

NSAIDS

Neutrophil adherence Mucosal dama-

Expression of intercellular vascular endothelial ge due to neutro-

Adhesion molecules in gastric cells phil free radicals

Vascular endothelium and proteases.

Acid hypersecretion

Acid hypersection is an important causative factor in some patients with peptic ulcer disease. Zollinger-Ellison Syndrome(Z-E-S)are two clinical examples in which hyperacidity leads to peptic ulcer disease. In Z-E-S, a gastrin-recreting tumor of the non-beta cells of the endrocrine pancrease <https://assignbuster.com/regulation-of-gastric-acid-secretion/>

lead to increased acid secretion. In lusting ulcer, seen in patients with reverse head injuries, heightened vagal tone causes gastric hyperacidity.

Figure is showing the interactions among an enterochromaffin-like (ECL) cell that secretes histamine, a parietal cell that secretes acid, and a superficial epithelial cell that secretes cytoprotective mucus and bicarbonate.

Physiological pathways, shown in solid black, may be stimulatory (+) or inhibitory (-). 1 and 3 indicate possible inputs from postganglionic cholinergic fibres, while 2 shows neural input from the vagus nerve. Physiological agonists and their respective membrane receptors include acetylcholine (ACh), muscarinic (M), and nicotinic (N) receptors; gastrin, cholecystinin receptor 2 (CCK2); histamine (HIST), H2 receptor; and prostaglandin E2 (PGE2), EP3 receptor. Drug actions are indicated by dashed lines. A blue X indicates targets of pharmacological antagonism. A light blue dashed arrow indicates a drug action that mimics or enhances a physiological pathway. Shown in blue are drugs used to treat acid-peptic disorders. NSAIDs are nonsteroidal anti-inflammatory drugs and are ulcerogenic.

1. 4 Gastrointestinal Motility:

Laxatives are drugs that either accelerate faecal passage or decrease faecal consistency. They work by promoting one or more of the mechanisms that cause diarrhoea. Because of the wide availability and marketing of OTC laxatives, there is a potential that an appropriate diagnosis will not be sought (Jahangir moini).

Rarely in medicine is there an absolute indication for the use of laxatives. A high fibre, well-balanced diet rich in fruits and vegetables supplemented by bran should be enough to normalize bowel function. The fear of

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auto-intoxication and the constant concern of many patients regarding the frequency and quality of bowel movement make laxatives one of the most popular over-the-counter drugs in the market with serious potential for user abuse. Accepted indications for laxatives and stool softeners include preparation for diagnostic colonic examination (Barium enema, colonoscopy; treatment of anorectal disorders) and prevention of hepatic encephalopathy (Smith and Reynard).

Fibre is defined as the undigested residue of fruits, vegetables, and other foods of plant origin after digestion by the human GI enzymes. Fibre's water holding capacity is the ability of the fibre to hold water and make bulking of faecal materials possible. Fibre's stool bulking capacity is the ability of the fibre to increase the volume of intestinal content because it can absorb and hold water. Bacterial growth in the colon provides additional bulking.

Insoluble fibre speeds GI transit time.

Cholinergic mechanisms are also responsible for modulating motor phenomena in the gut; thus it is not surprising that cholinomimetic agents are effective in promoting gastrointestinal motility. It also has cholinomimetic properties, apparently sensitizing intestinal smooth muscle cells to the action of Acetylcholine rather than acting on acetylcholine receptors. The drug acts to hasten esophageal clearance, raise lower esophageal sphincter pressure, accelerate gastric emptying, and shorten small bowel transit time.

1. 4. 1 Mechanism of Laxative Action: (KD Tripathi, 1999)

- a. By their hydrophilic or osmotic nature, laxative can cause retention of fluids, in the colonic content, as well as increase the mass.
- b. Inhibiting Na⁺K⁺ATPase of villous cells – impairing electrolyte and water absorption.
- c. Stimulating adenyl cyclase in crypt cells – increasing water and electrolyte secretion.
- d. Enhancing PG synthesis in mucosa which increases secretion.
- e. Structural injury to the absorbing intestinal mucosal cells.

1. 4. 2 Classification of Laxatives:-

Many drugs in low doses act as laxative and in larger doses as purgatives

1. Bulk forming 4. Stimulant purgatives

Dietary fibre: Bran (a) Diphenylmethanes

Psyllium Phenolphthalein

Methylcellulose (b) Castor oil

5. Anthraquinones

2. Stool softner Senna, Cascara sagrada

Docusates (DOSS) 6. Osmotic purgatives

3. Lubricant Magnesium, sodium salts

Liquid paraffin Lactulose

1. 4. 3 Anthraquinone Derivatives:-

Senna is obtained from the leaves and pods of *Cassia augustifolia* and contains the anthraquinone glycosides called emodins. In oral dose the sennosides is poorly absorbed, but after removal of the sugar and reduction to anthrol by colonic bacteria, they are absorbed into circulation – excreted in bile to act on small intestine. It takes 6-7 hrs to produce action. The active principle is believed to act on the myentric plexus to increase peristalsis and decrease segmentation. They also inhibit salt and water absorption in the colon. In India, sennosides are usually marketed in combination with stool softeners such as docusates. Side effects observed are nausea, vomiting, diarrhoea, colic, urine discoloration (yellowish brown to red) and melanosis (colonic atony and mucosal pigmentation after a regular use of the drug). It should be used cautiously in women and children bebelow years of age, and after abdominal surgery.

Preparations

GLAXENNA tab. Sennosides (calcium salt)

11. 5 mg.

SOFSENA tab - 12 mg.

PURSENNID tab -18 mg

LAXSENA tab - 12mg, 18mg(forte)