Chapter 25

## Overview of Gastrointestinal Function & Regulation

The primary function of the gastrointestinal tract is to serve as a portal whereby nutrients and water can be absorbed into the body. The meal is mixed with a variety of secretions that arise from both the gastrointestinal tract itself and organs that drain into it, such as the pancreas, gallbladder, and salivary glands.

The parts of the gastrointestinal tract that are encountered by the meal or its residues include, in order, the mouth, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, and anus. Throughout the length of the intestine, glandular structures deliver secretions into the lumen, particularly in the stomach and mouth.

Also important in the process of digestion are secretions from the pancreas and the biliary system of the liver. The intestine itself also has a very substantial surface area, which is important for its absorptive function.

Gastrointestinal Secretions:

1- SALIVARY SECRETION :The first secretion encountered when food is ingested is saliva. Saliva is produced by three pairs of salivary glands (the parotid, submandibular, and sublingual glands) that drain into the oral cavity. It has a number of organic constituents that serve to initiate digestion (particularly of starch, mediated by amylase) and which also protect the oral cavity from bacteria .(such as immunoglobulin A and lysozyme

Salivary glands

Parotid gland

Sublingual gland

Submandibular gland

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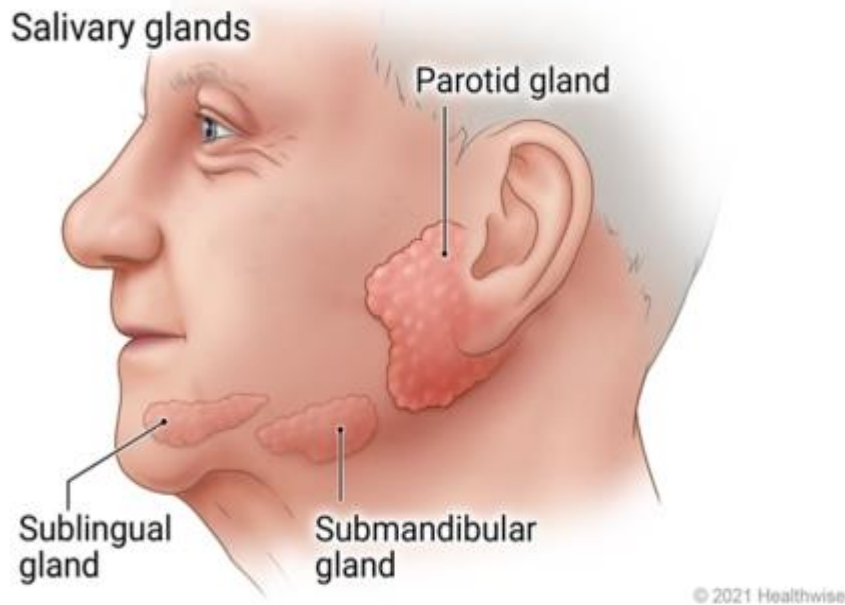
Secretions of the three glands differ in their relative proportion of proteinaceous and mucinous components, which results from the relative number of serous and mucous salivary acinar cells, respectively. Saliva is also hypotonic compared with plasma and alkaline; the latter feature is important to neutralize any gastric secretion that reflux into the esophagus.

 Salivary secretion is almost entirely controlled by neural influences, with the parasympathetic branch of the autonomic nervous system playing the most prominent role. Sympathetic input slightly modifies the composition of saliva (particularly by increasing proteinaceous content), but has little influence on volume.
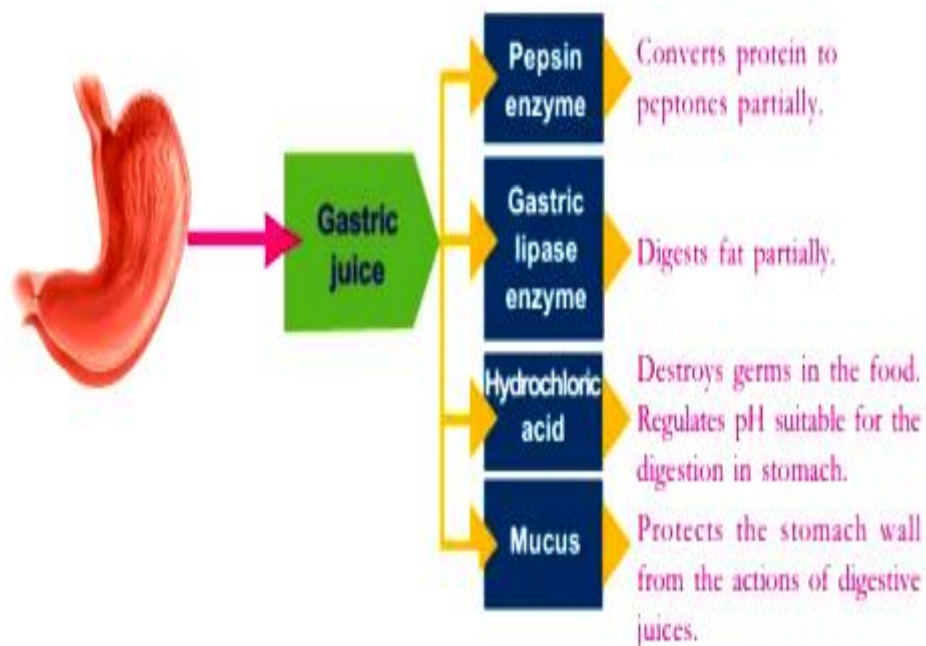
Saliva performs a number of important functions: it facilitates swallowing, keeps the mouth moist, serves as a solvent for the molecules that stimulate the taste buds, aids speech by facilitating movements of the lips and tongue, and keeps the mouth and teeth clean.
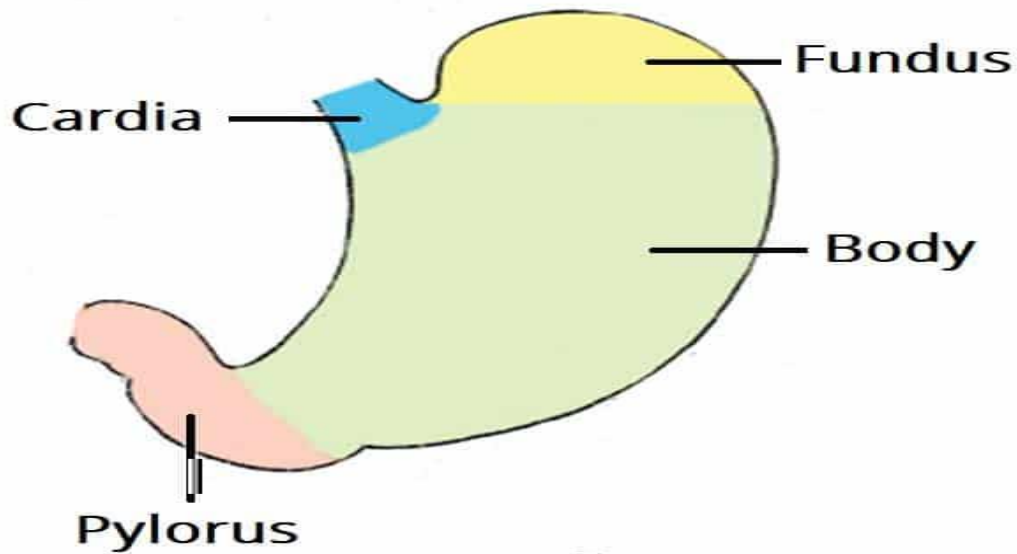
 2- GASTRIC SECRETION: Food is stored in the stomach; mixed with acid, mucus, and pepsin; and released at a

controlled, steady rate into the duodenum. The stomach also adds a significant volume of digestive juices to the meal. Like salivary secretion, the stomach readies itself to receive the meal before it is actually taken in, during the so-called cephalic phase that can be influenced by food preferences .

Subsequently, there is a gastric phase of secretion that is quantitatively the most significant, and finally an intestinal phase once the meal has left the stomach. Each phase is closely regulated by both local and distant triggers .
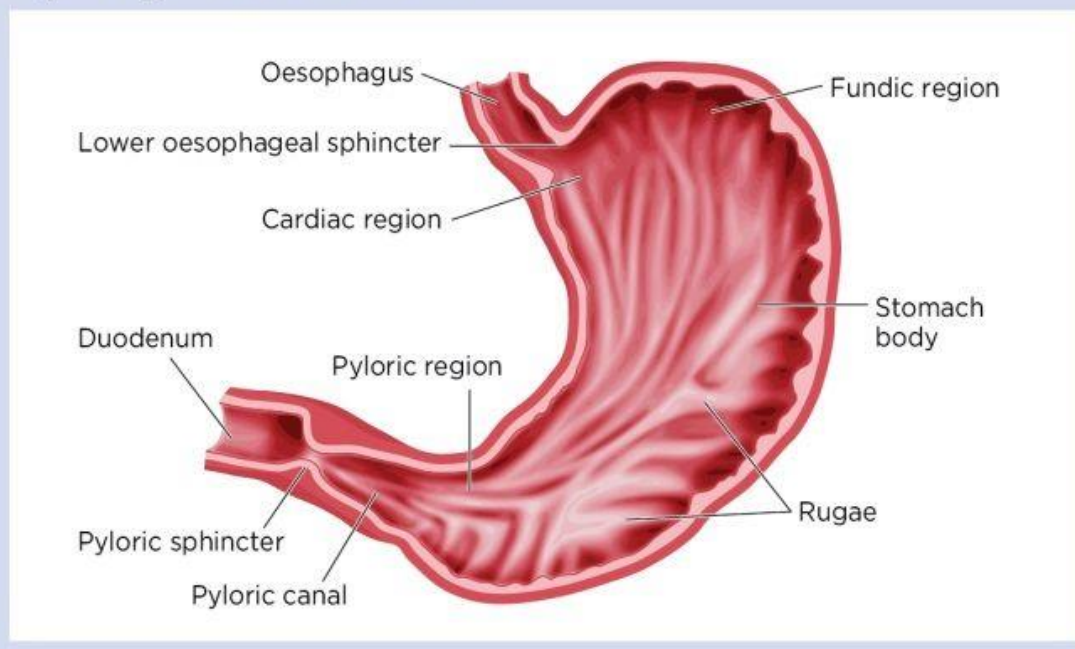
The gastric secretions arise from glands in the wall of the stomach that drain into its lumen, and also from the surface cells that secrete primarily mucus and bicarbonate to protect the stomach from digesting it self . . Gastric secretion adds about 2.5 L/day to the intestinal contents.

Fundus
Cardia
Body
Pylorus

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Fig 1. **Regions of the stomach**

Oesophagus
Lower oesophageal sphincter
Cardiac region
Duodenum
Pyloric region
Pyloric sphincter
Pyloric canal
Fundic region
Stomach body
Rugae

The most characteristic secretions derive from the glands in the fundus or body of the stomach. These contain the distinctive parietal cells, which secrete hydrochloric acid and intrinsic factor; and chief cells, which produce pepsinogens and gastric

lipase The acid secreted by parietal cells serves to sterilize the meal and also to begin the hydrolysis of dietary macromolecules. Intrinsic factor is important for the later absorption of vitamin B12, or cobalamin. Pepsinogen is the precursor of pepsin, which initiates protein digestion. Lipase similarly begins the digestion of dietary fat

There are three primary stimuli of gastric secretion, each with a specific role to play in matching the rate of secretion to functional requirements:

1- Gastrin is a hormone that is released by G cells in the antrum of the stomach both in response to a specific neurotransmitter released from enteric nerve endings, known as gastrin-releasing peptide (GRP).

2- Histamine is also a trigger of parietal cell secretion, via binding to H2- receptors

3- Finally, parietal and chief cells can also be stimulated by acetylcholine, released from enteric nerve endings in the fundus.

Gastric secretion that occurs during the cephalic phase is defined as being activated predominantly by

vagal input. Once the meal is swallowed, on the other hand, meal constituents trigger substantial release of gastrin and the physical presence of the meal also distends the stomach and activates stretch receptors, which provoke a "vago-vagal" as well as local reflexes that further amplify secretion during the gastric phase

The presence of the meal also buffers gastric acidity that would otherwise serve as a feedback inhibitory signal to shut off secretion secondary to the release of somatostatin, which inhibits both G and ECL cells as well as secretion by parietal

cells themselves. This probably represents a key mechanism whereby gastric secretion is terminated after the meal moves from the stomach into the small intestine The Gastric parietal cells are packed with mitochondria that supply energy to drive the apical H+,K+-ATPase, or proton pump, that moves H+ ions out of the parietal cell against a concentration gradient of more than a million-fold. The secretion of protons is also accompanied by the release of equivalent numbers of bicarbonate ions into the bloodstream , which are later used to neutralize gastric acidity once its functions its complete

3- PANCREATIC SECRETION: The pancreatic juice contains enzymes that are of major importance in digestion . Its secretion is controlled in part by a reflex mechanism and in part by the gastrointestinal hormones secretin and cholecystokinin (CCK). Granules containing the digestive enzymes (zymogen granules) are formed in the cell and discharged by exocytosis from the apexes of the cells into the lumens of the pancreatic ducts. About 1500 mL of pancreatic juice is secreted per day. Bile and intestinal juices are also neutral or alkaline, and these three secretions neutralize the gastric acid, raising the pH of the duodenal contents to 6.0–7.0. The pancreatic juice also contains a range of digestive enzymes, but most of these are released in

inactive forms and only activated when they reach the intestinal lumen. The enzymes are activated following proteolytic cleavage by trypsin, itself a pancreatic protease that is released as an inactive precursors (trypsinogen) . The potential danger of the release into the pancreas of a small amount of trypsin is apparent; the resulting chain reaction would produce active enzyme that could digest the pancreas. It is therefore not surprising that the pancreas also normally secretes a trypsin inhibitor. Secretion of pancreatic juice is primarily under hormonal control

4. SECRETION BILIARY

An additional secretion important for gastrointestinal function, bile, arises from the liver. The bile acids contained therein are important in the digestion and absorption of fats. Bile is also the only route by which the body can dispose of cholesterol—either in its native form, or following conversion to bile acids. Bile is made up of the bile acids, bile pigments, and other substances dissolved in an alkaline electrolyte solution that resembles pancreatic juice. About 500 mL is secreted per day. Some of the components of the bile are reabsorbed in the intestine and then excreted again by the liver (enterohepatic circulation). The glucuronides of the bile pigments, bilirubin and biliverdin, are responsible for the golden yellow color of bile.

When considering bile as a digestive secretion, it is the bile acids that represent the most important components. They are synthesized from cholesterol and secreted into the bile .

Gastro intestinal regulation

The various functions of the gastrointestinal tract, including secretion, digestion, and absorption , and motility must be regulated in an integrated way to ensure efficient assimilation of

nutrients after a meal. There are three main modalities for gastrointestinal regulation that operate in a complementary fashion to ensure that function is appropriate .

First, endocrine regulation is mediated by the release of hormones by triggers associated with the meal. These hormones travel through the bloodstream to change the activity of a distant segment of the gastrointestinal tract, an organ draining into it (eg, the pancreas), or both.

Second, some similar mediators are not sufficiently stable to persist in the bloodstream, but instead alter the function of cells in the local area where they are released in a paracrine fashion .

Finally, the intestinal system is endowed with extensive neural connections. These include connections to the central nervous system (extrinsic innervation), but also the activity of a largely autonomous enteric nervous system that comprises both sensory and secret motor neurons.

HORMONES PARACRINS

Biologically active polypeptides that are secreted by nerve cells and gland cells in the mucosa act in a paracrine fashion, but they also enter the circulation. Measurement of their concentrations in blood after a meal has shed light on the roles these gastrointestinal hormones play in the regulation of gastrointestinal secretion and motility .

GASTRIN: Gastrin is produced by cells called G cells in the antral portion of the gastric mucosa. Gastrin has a variety of actions, but its principal physiologic actions are stimulation of gastric acid and pepsin secretion and stimulation of the growth of the mucosa of the stomach and small and large intestines (trophic action).

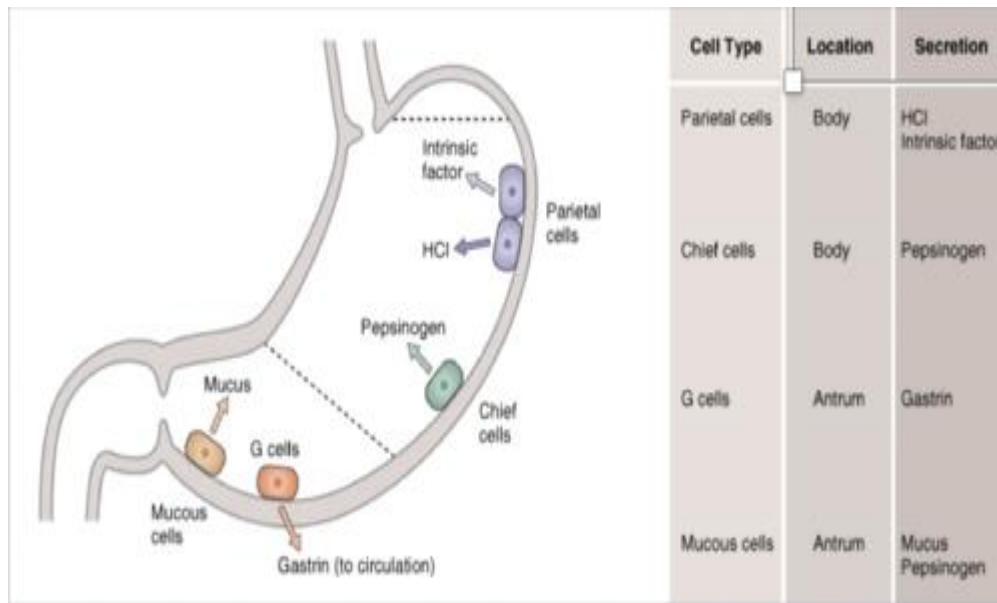Gastrin secretion is affected by the contents of the stomach, the rate of discharge of the vagus nerves, and blood borne factors. Gastrin secretion is also increased by the presence of the products of protein digestion in the stomach, particularly amino acid which act directly on the G cell

Acid in the antrum inhibits gastrin secretion, partly by a direct action on G cells and partly by release of somatostatin, a relatively potent inhibitor of gastrin secretion. The effect of acid is the basis of a negative feedback loop regulating gastrin secretion. Increased secretion of the hormone increases acid secretion, but the acid then feeds back to inhibit further gastrin secretion.
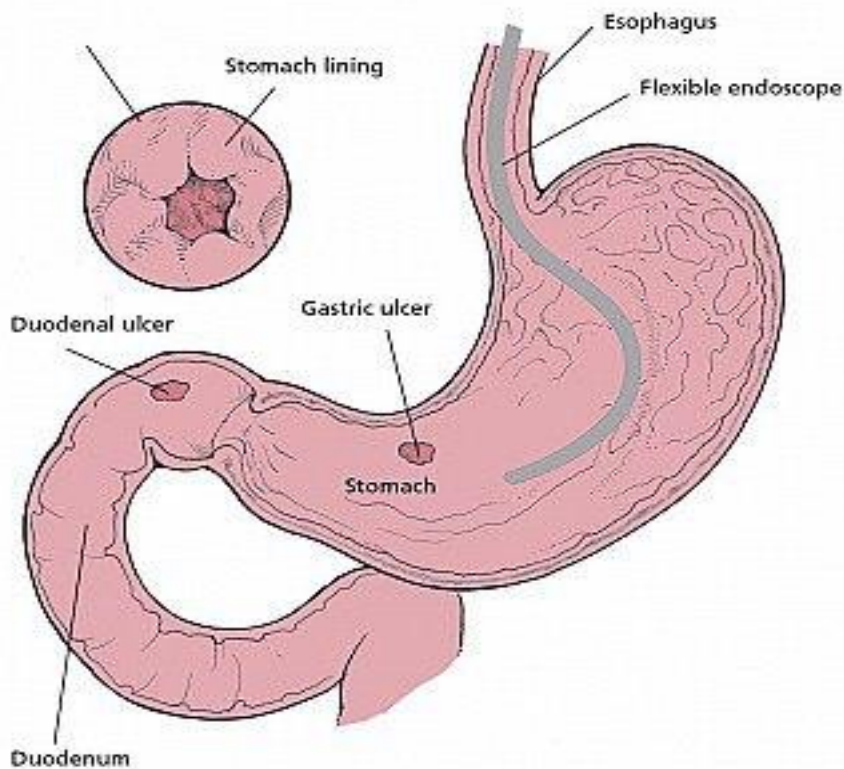
Cholecystokinin(CCK): is secreted by endocrine cells known as I cell in the mucosa of the upper small intestine. The most important action is to be the stimulation of pancreatic enzyme secretion; the contraction of the gallbladder (the action for which it was named); and relaxation of the sphincter of Oddi, which allows both bile and pancreatic juice to flow into the intestinal lumen. In addition to its secretion by I cells, CCK is found in nerves in the distal ileum and colon. It is also found in neurons in the brain, especially the cerebral cortex, and in nerves in many parts of the body.

In the brain, it may be involved in the regulation of food intake, and it appears to be related to the production of anxiety and analgesia. In addition to its primary actions, CCK augments the action of secretin in producing secretion of an alkaline pancreatic juice. It also inhibits gastric emptying, exerts a trophic effect on the pancreas, and may enhance the motility of the small intestine and colon. The secretion of CCK is increased by contact of the intestinal mucosa with the products of digestion, particularly peptides and amino acids. Because the

bile and pancreatic juice ==that enter the duodenum in response to CCK enhance the digestion of protein and fat==, and the products of this digestion stimulate further CCK secretion, a sort of positive feedback operates in the control of CCK secretion

Cell Type	Location	Secretion
Parietal cells	Body	HCl Intrinsic factor
Chief cells	Body	Pepsinogen
G cells	Antrum	Gastrin
Mucous cells	Antrum	Mucus Pepsinogen

Peptic ulcer viewed through an endoscope

Treatment of Stomach Ulcers

Avoid irritating foods

Reduce alcohol consumption and smoking

Manage stress

Use acid-reducing drugs, antibiotics, and acetaminophen

Endoscopic or sugerical intervention

Peptic Ulcers

Esophagus

Stomach

H. pylori bacteria

Duodenum
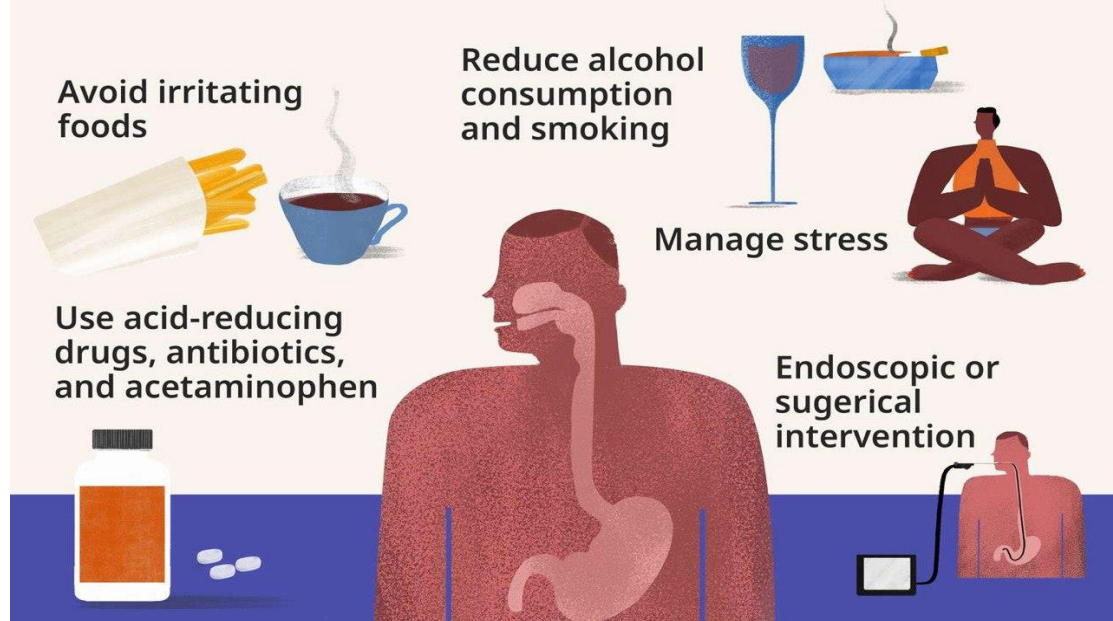
Peptic ulcer
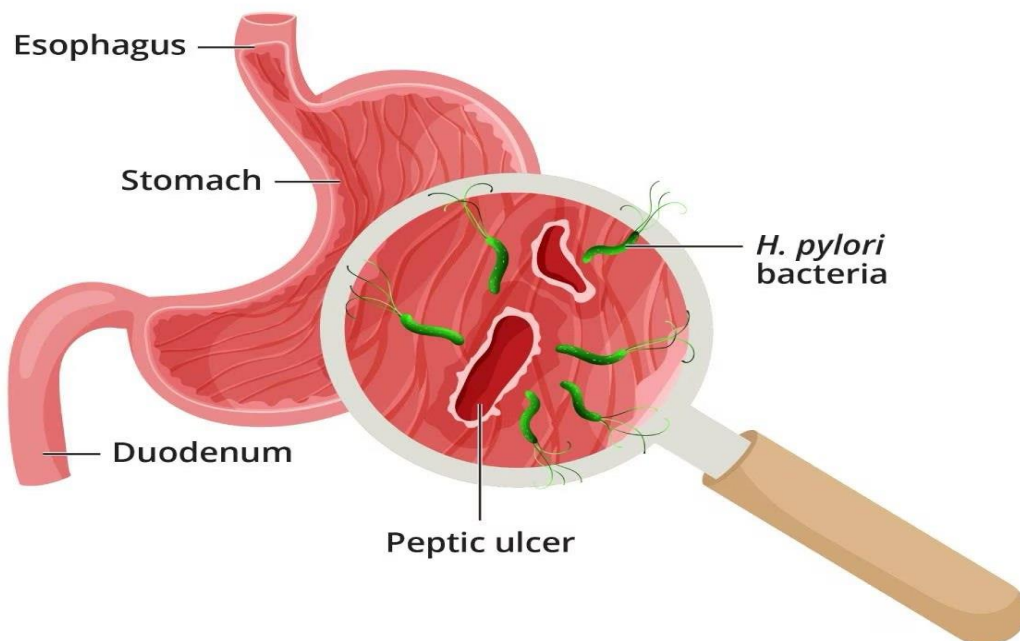
Secretin :

Secretin is secreted by S cells that are located deep in the glands of the mucosa of the upper portion of the small intestine. Only one form of secretin has been isolated, and any fragments of the molecule that have been tested to date are inactive. Its half-life is about 5 min, but little is known about its metabolism

Secretin increases the secretion of bicarbonate by the duct cells of the pancreas and biliary tract. It thus causes the secretion of a watery, alkaline pancreatic juice. It also augments the action of CCK in producing pancreatic secretion of digestive enzymes. It decreases gastric acid secretion and may cause contraction of the pyloric sphincter.

The secretion of secretin is increased by the products of protein digestion and by acid bathing the mucosa of the upper small intestine. The release of secretin by acid is another example of feedback control: Secretin causes alkaline pancreatic juice to blood into the duodenum, neutralizing the acid from the stomach and thus inhibiting further secretion of the hormone.

Gastric Inhibitory Peptide(GIP):

is produced by K cells in the mucosa of the duodenum and jejunum. Its secretion is stimulated by glucose and fat in the duodenum, and because in large doses it inhibits gastric secretion and motility, it was named gastric inhibitory peptide.

In the meantime, it was found that GIP stimulates insulin secretion. Gastrin, CCK, secretin, and glucagon also have this effect, but GIP is the only one of these that stimulates insulin secretion when administered at blood levels comparable to those produced by oral glucose. For this reason, it is often called glucose-dependent insulinotropic peptide.

MOTILIN:

Motilin is a polypeptide containing 22 amino acid residues that is secreted by enterochromaffin cells and Mo cells in the stomach, small intestine, and colon. It acts on G-protein–coupled receptors on enteric neurons in the duodenum and colon and produces contraction of smooth muscle in the stomach and intestines in the period between meals .

SOMATOSTATIN:

Somatostatin, the growth hormone–inhibiting hormone originally isolated from the hypothalamus, is secreted as a paracrine by D cells in the pancreatic islets and by similar D cells in the gastrointestinal mucosa. It exists in tissues in two forms, somatostatin 14 and somatostatin 28, and both are secreted. Somatostatin inhibits the secretion of gastrin, VIP, GIP, secretin, and motilin.

Its secretion is stimulated by acid in the lumen, and it probably acts in a paracrine fashion to mediate the inhibition of gastrin secretion produced by acid. It also inhibits pancreatic exocrine secretion; gastric acid secretion and motility; gallbladder contraction; and the absorption of glucose, amino acids, and triglycerides

Other gastrointestinal peptides

Ghrelin is secreted primarily by the stomach and appears to play an important role in the central control of food intake . It also stimulates growth hormone secretion by acting directly on receptors in the pituitary .

Substance P is found in endocrine and nerve cells in the gastrointestinal tract and may enter the circulation. It increases the motility of the small intestine.

The enteric nervous system

Two major networks of nerve fibers are intrinsic to the gastrointestinal tract: the myenteric plexus (Auerbach plexus), between the outer longitudinal and middle circular muscle layers, and the sub mucous plexus (Meissner plexus), between the middle circular layer and the mucosa . Collectively, these neurons constitute the enteric nervous system

 The system contains about 100 million sensory neurons, interneurons, and motor neurons in humans as many as are found in the whole spinal cord that is concerned with the regulation of gastrointestinal function. It is sometimes referred to as the "little brain" for this reason. It is connected to the CNS by parasympathetic and sympathetic fibers but can function autonomously without these connections The myenteric plexus innervates the longitudinal and circular smooth muscle layers and is concerned primarily with motor control, whereas the sub mucous plexus innervates the glandular epithelium, intestinal endocrine cells, and submucosal blood vessels and is primarily involved in the control of intestinal secretion.

The neurotransmitters in the system include acetylcholine, the amines norepinephrine and serotonin, the amino acid γ-aminobutyrate (GABA), the purine adenosine triphosphate (ATP), the gases NO and CO, and many different peptides and polypeptides. Some of these peptides also act in a paracrine fashion, and some enter the blood stream becoming hormones