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Events in the Stomach

What are the functions of the stomach?

The stomach has both motor and secretory functions which are as follows. (i) **Reservoir functions**. The stomach relaxes to accommodate large volumes of food. (ii) **Grinding**. It grinds food to optimal sized particles. (iii) **Mixing**. It mixes the bolus with the gastric juice and converts the bolus into a soup-like *chyme*. (iv) **Partitioning**. It retains the solid portion of the meal until most of the liquid has emptied. (v) **Sieving**. It retains larger particles, permitting more time for their further breakdown. (vi) **Regulating delivery**. It regulates the amount of chyme delivered to the intestine. (vii) **Secretion** of HCl which disinfects the food. (viii) Initiation of protein **digestion**.

What are MMCs? How are they related to BER?

Migrating motor complexes (MMC) are contraction waves *present in the empty gastrointestinal tract*. They are produced by the electrical activity of the single-unit smooth muscle of the gastrointestinal tract that is called the **basal electrical rhythm** (**BER**). This electrical activity originates in pacemaker cells located in the outer circular muscle layer near the myenteric plexus. There is a close correlation of the BER with the MMC. When there are no MMC, the BER consists of rhythmic oscillation of the RMP between about -65 and -45 mV. The oscillations occur due to rhythmic changes in Ca^{2+} and K^+ permeabilities. During the MMC, the electrical oscillations are superimposed with spikes. MMCs occur in a cyclical pattern, each cycle lasting 90 min. It shows three phases. **Phase-I** is the phase of quiescence in which there are no contractions, and no spike potentials on the underlying BER. It is the longest phase, lasting about 80 minutes. **Phase-II** is associated with irregular spikes on the BER and irregular contractions. It lasts about 6 minutes. **Phase-III** is associated with regular contractions and regular spike potentials on the BER. It lasts about 3 minutes. The phase-III MMC is associated with a rise in plasma motilin level (Fig. 83.1).

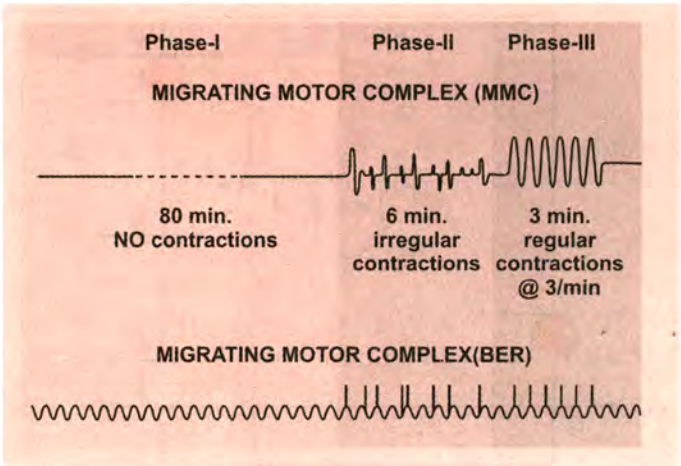

Fig. 83.1

MMCs are of two types. Some originate in the stomach. The phase III of these MMCs have a frequency of 3/min. Others originate in the duodenum. The phase III of these MMCs have a frequency of 11/min. Most MMCs pass along the entire bowel to the terminal ileum with a velocity of 5 cm/min. As soon as one complex reaches the terminal ileum, another starts in the stomach or duodenum.

During MMC, there is an increase in gastric secretion, bile flow and pancreatic secretion. They clear the stomach and small intestine of luminal contents in preparation for the next meal. Hence, they have been called the *interdigestive housekeepers*. MMCs are probably responsible for the hunger contractions.

Describe the motility of the fed stomach.

When food enters the stomach, the fundus and upper part of its body relax to accommodate the food with little increase in pressure. This is called **receptive relaxation**. Receptive relaxation is vagally mediated and is synchronized with the primary peristaltic waves in the esophagus.

Entry of food in the stomach is associated with *immediate cessation of MMC* although the BER continues as before. In its place appear **peristaltic contractions** that resemble the Phase-II of the interdigestive MMC. Unlike the Phase-II of the interdigestive MMC, these peristaltic waves occur as long as food is present in the stomach and also, these peristaltic waves retain the large particles in the stomach. In contrast, the Phase-III of the interdigestive MMC sweeps out even the large food particles into the duodenum are comparatively weaker.

The peristaltic waves begin near the middle of the body of the stomach and sweep downwards towards the pyloric sphincter. As the wave approaches the pylorus, the sphincter closes. Hence, only a small amount of liquefied chyme squirts through the sphincter into the duodenum, while most of the chyme bounces back off the closed sphincter.

Describe the factors affecting gastric emptying.

Gastric emptying is regulated mainly from the duodenum through the **enterogastric reflex**. A number of factors initiate this reflex by stimulating duodenal receptors. The reflex is mediated either by local neural circuits or by gastrointestinal hormones. The enterogastric reflex ensures that the gastric chyme does not enter the duodenum too fast. The reflex is initiated by the following

factors: (i) **Acid in the duodenum**. It stimulates the release of secretin which reduces gastric motility and increases pyloric sphincteric tone. (ii) **Products of fat digestion**. These stimulate the releases of a number of gastrointestinal hormones like CCK, GIP, VIP and peptide YY, all of which reduce gastric motility. Even before these hormones were identified, the presence of a hormonal mediator was suspected and was provisionally named **enterogastrone**, a term which is obsolete today. (iii) **Products of protein digestion**. These stimulate the release of gastrin, CCK and GIP, all of which slow gastric emptying. (iv) **Osmolarity of the duodenal chyme**. Entry of hyperosmolar chyme into the duodenum reflexly slows gastric emptying. The hormonal mediator of the reflex has not been identified yet. (v) **Mechanical distention of duodenum**. It retards gastric emptying through neural mechanism. (vi) Fats are very effective in inhibiting gastric emptying. Some people consume fats before a cocktail party. The fat keeps the alcohol in the stomach longer, slowing its absorption and reducing the chances of getting intoxicated.

Other factors also affect gastric emptying. (vii) Liquids leave the stomach much faster, flowing around the solid food in the stomach. (viii) Solids with smaller particles leave the stomach faster than solids with larger particles. (ix) Vagotomy slows gastric emptying and cause gastric atony and distention. (x) Excitement speeds up gastric emptying, and fear retards it.

What are the different types of cells in a gastric gland and what do they secrete?

The gastric mucosa contains several gastric glands. Several of the glands open on a common chamber (gastric pit) that opens in turn on the surface of the mucosa. Mucus and HCO_3^- are secreted by **mucus cells** on the surface of the epithelium between glands. In the body of the stomach, including the fundus, the glands contain **parietal (oxyntic) cells**, which secrete hydrochloric acid and intrinsic factor, and **chief (peptic) cells**, which secrete pepsinogens (Fig. 83.2).

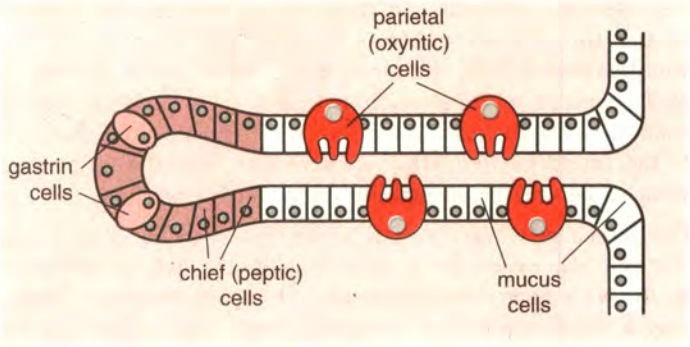

Fig. 83.2

About 2.5 L of gastric juice is secreted into the lumen daily. It contains **pepsin** (from chief cells), **acid** (from parietal cells), **mucus** (from mucus cells) and **intrinsic factor** (from parietal cells). Gastric gland also secretes a hormone **gastrin** which is secreted by the **G-cells**.

What are the functions of gastric acid?

Gastric juice serves the following functions: (i) The acidic gastric juice acts as a good solvent that dissolve iron compounds and other foodstuffs that are not soluble in water. (ii) An acidic pH is required for activation of gastric enzyme pepsin. (iii) Acid is a strong disinfectant, killing bacteria and other microorganisms in the ingested food. (iv) Acid stimulates the duodenum to secrete hormones to release bile and pancreatic juices.

What are the functions of the gastric enzymes?

The *stomach secretes two enzymes*: pepsin, which digests proteins and gastric lipase, which digests fats. **Gastric lipase** is of little importance in fat digestion except in pancreatic insufficiency. **Pepsin** cleaves food *proteins,* forming small *peptides.* When secreted by the chief *(zymogen)* cells, pepsin is in its inactive form, a larger protein called *pepsinogen*. Acid in the lumen promotes conversion of pepsinogen to pepsin. Pepsin, once formed, also attacks pepsinogen, producing more pepsin molecules *(autocatalysis).*

Describe the mechanism of HCl secretion by the parietal cells.

Gastric glands secrete a concentrated solution of *hydrochloric acid*, which has a pH of approximately 1.0. Its secretion involves the secretion of H^+ ions and the secretion of Cl^- ions. **Secretion of H^+ ions** occurs in the following steps (Fig. 83.3). (1) H^+ ions are produced inside the cell from metabolic CO_2 through the following reaction which is catalyzed by the enzyme *carbonic anhydrase* that is present in the parietal cells in large amounts, i.e., $CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^-$. (2) The hydrogen ions are secreted by the parietal cell through its apical membrane by a *primary active transport* with coupled antiport of K^+ ions. The H^+-K^+ exchange is obviously electroneutral. (3) The *bicarbonate* (HCO_3^-) ions produced is transported out of the parietal cell at the serosal border through *primary active transport* with coupled antiport of *chloride ions* into the cell. The HCO_3^--Cl^- exchange is again electroneutral. The HCO_3^- transported out of the parietal cells enters the blood stream and increases the blood pH (the *postprandial alkaline tide*). The **secretion of Cl^- ions** occurs in the following steps. (4) The Na^+-K^+ pump located on the basolateral membrane of the parietal cell pumps out three Na^+ for every two K^+ pumped in. The inside of the parietal cell therefore becomes

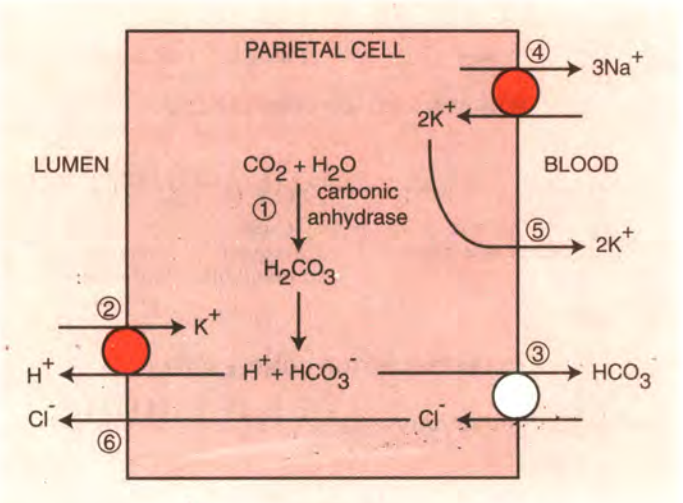

Fig. 83.3

negative. (5) The K^+ ions that are pumped in diffuse out through the K^+ channels present on the basolateral as well as apical membranes. This diffusion further increases the intracellular negativity of the parietal cell. (6) *The high intracellular negativity forces out Cl^- ions* through the Cl^- channels located on the apical membrane.

What are the receptors involved in the control of gastric acid secretion

The *second messengers* that activate gastric acid secretion are activated by various receptors present on the membrane of the parietal cell. There are 5 types of receptors of which 3 are stimulatory and 2 are inhibitory. (i) **Acetylcholine (Muscarinic) receptors**. When acetylcholine binds to these receptors, the Gs → phospholipase-C pathway generates high levels of IP_3 and diacylglycerol from membrane phospholipids. IP_3 mobilizes Ca^{2+} from intracellular stores while diacylglycerol activates protein kinases. (ii) **Gastrin receptors**. The second messengers associated with gastrin have not been identified with certainty but is unlikely to be Ca^{2+} or cAMP. (iii) **Histamine receptors**. H_2 receptor stimulation leads to the formation of cAMP through the Gs → adenyl cyclase pathway. The cAMP then activates protein kinase A. (iv) **Prostaglandin (PGE_2)** and (v) **Somatostatin receptors**. Somatostatin and prostaglandin E_2 bind to specific receptors that act via an inhibitory GTP regulatory protein (G_i) in preventing the activation of adenylate cyclase (Fig. 83.4).

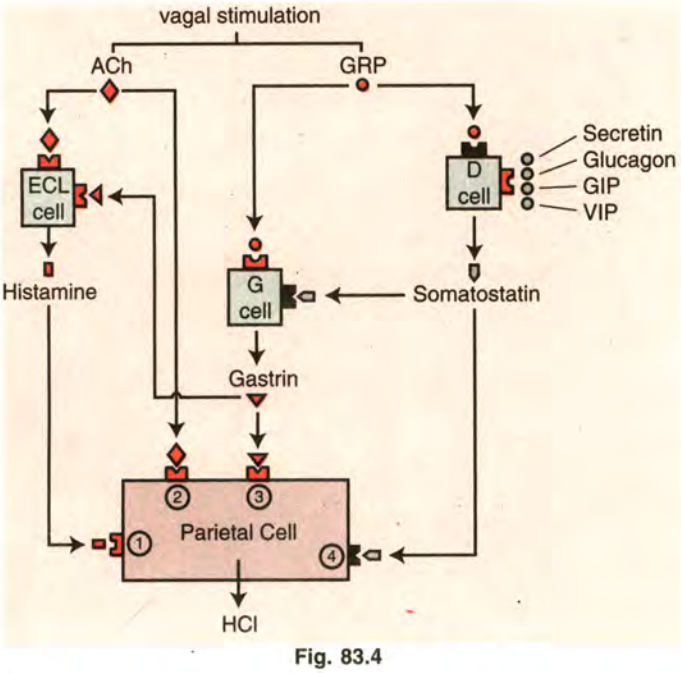

Fig. 83.4

Describe the paracrine cells involved in gastric acid secretion.

The paracrine control of gastric secretion involves the G-cells, D-cells and ECL cells. (i) **G-cells** are located at the base of the gastric glands and are especially abundant in the pyloric gastric glands. It secretes gastrin, which stimulates HCl secretion. Gastrin secretion is *stimulated by GRP* (**Gastrin-releasing peptide**) and *inhibited by somatostatin*. (ii) **D-cells** secrete **somatostatin**, which *inhibits HCl secretion* in two ways: through a direct action on parietal cells and an indirect action by inhibiting gastrin secretion by G-cells. D-cells are located adjacent to the G-cells or the parietal cells. Secretin, enteroglucagon, GIP and VIP – all inhibit gastric secretion by stimulating somatostatin release. (iii) **Enterochromaffin-like (ECL)** cells are found in the oxyntic region of the stomach, in the base of the gastric gland. They secrete histamine. The histamine released stimulates HCl secretion from parietal cells. ECL cells bear both gastrin receptors and ACh receptors. They release histamine in response to both circulating gastrin as well as the ACh released by vagal fibers. Stimulation of ECL cells is an important mechanism through which gastrin stimulates acid secretion.

What is the effect of vagus on gastric secretion?

Vagal fibers to the stomach have two types of neurotransmitters. (i) Some vagal fibers release **gastrin releasing peptide** (GRP). The GRP increases gastrin secretion from G-cells with consequent increase in acid secretion. The GRP also inhibits somatostatin secretion from D cells and thereby disinhibits HCl secretion from parietal cells. (ii) Other vagal fibers release **acetylcholine**, which acts directly on the cells in the glands in the body and the fundus to increase the secretion of acid, pepsin and mucus. Part of the acid secretion is mediated by ECL cells that secrete histamine. Vagotomy does not abolish the secretory response to local stimuli.

Describe the phases of gastric acid secretion.

There are four phases of gastric secretion: interdigestive, cephalic, gastric and intestinal. In the **interdigestive phase** (basal acid secretion), acid is continuously secreted by the stomach even between meals and during sleep. A circadian rhythm is seen, with basal secretion reaching its peak around midnight and its lowest around 7 in the morning. Interdigestive phase of gastric acid secretion is vagally mediated. Emotional outbursts, tension and anxiety alter basal acid secretion.

Gastric secretion stimulated by **cephalic factors** accounts for up to 50% of the acid secreted in response to a normal meal. It is vagally mediated and is easily conditioned. The unconditioned stimulus is the presence of food in the mouth. Conditioned stimuli include the sight, smell, and thought of food increase gastric secretion. The conditioned reflex involves activation of the anterior hypothalamus and parts of the adjacent orbital frontal cortex. The cephalic phase of gastric secretion is influenced by psychic states: it is *increased with anger and hostility*, and is *reduced in fear and depression*.

The **gastric phase** of acid secretion comes into play when food makes contact with the gastric mucosa. It accounts for up to 50% of the acid secretion in response to meal. Acid secretion in this phase is brought about by: (i) *gastrin secretion*, brought about by the stimulatory effect of the products of protein digestion, mainly amino acids, and (ii) *stretch of the stomach wall* which activates a local reflex arc that terminates on vagal postganglionic neurons.

The **intestinal phase** begins when food enters the intestine. *Gastric secretion is inhibited* by the same intestinal factors that reduce gastric motility through the enterogastric reflex. Briefly, they are: (i) acid in the duodenum; (ii) product of fat digestion; (iii) osmolarity of the duodenal chyme; and (iv) mechanical distension

of the duodenum. Products of protein digestion, however, have a slight *stimulatory effect on gastric acid secretion*, and accounts for about 5% of the total gastric acid secretion that occurs following a meal. The hormone *enterogastrone* was thought to mediate the inhibition of gastric secretion in the intestinal phase. The candidates for this non-existent hormone, which might mediate the intestinal inhibition of acid secretion, are *secretin*, *CCK*, *prostaglandins*, *somatostatin*, and *peptide YY*.

Several **other factors** are known to affect gastric secretion. Hypoglycemia stimulates central vagal discharge to stimulate acid and pepsin secretion. Other stimulants include alcohol and caffeine, both of which act directly on the mucosa.

Define basal acid output. How is it measured?

Basal acid secretion (BAO) is the rate of acid secretion in the absence of all avoidable stimulations. About 400ml of gastric juice is collected overnight (from 9.00 pm to 9.00 am) through an indwelling nasogastric catheter. The room is made devoid of the physical presence and even the odor of food. Normally, BAO is < 10 mmoles/L in males and < 5 mmoles/L in females.

How is the gastric epithelium protected from the corrosive effect of acid?

The stomach mucus forms a thick protective coat covering the inner linings of the stomach in order to protect it from mechanical damage and the corrosive actions of the acid in the gastric juice. The breakdown of this coat is one of the causes of ulcers. Gastric wall cells' impermeability to acid, as well as the protective action of the alkaline stomach mucus, prevents ulcers from occurring in healthy individuals. The surface membranes of the mucosal cells and the tight junctions between the cells are also part of the **mucosal barrier** that protects the gastric epithelium from damage. Substances that tend to disrupt the barrier and cause gastric irritation include *ethanol, vinegar, bile salts, aspirin* and other *nonsteroidal anti-inflammatory drugs* (**NSAIDs**). Prostaglandins stimulate mucus secretion, and aspirin and related drugs inhibit prostaglandin synthesis. Some of the resistance of the gastric mucosa to autodigestion is also provided by the presence of acid-resistant peptides called **trefoil peptides** in the mucosa.