بسم الله الرحمن الرحيم

السلام عليكم ورحمة الله وبركاته

Gastrointestinal Physiology
Lecture 4

Physiology of the Stomach and Regulation of Gastric Secretions

Chapter 63; pages 765-768

Chapter 64; pages 777-780

Dr. Hayam Gad

Learning Objectives

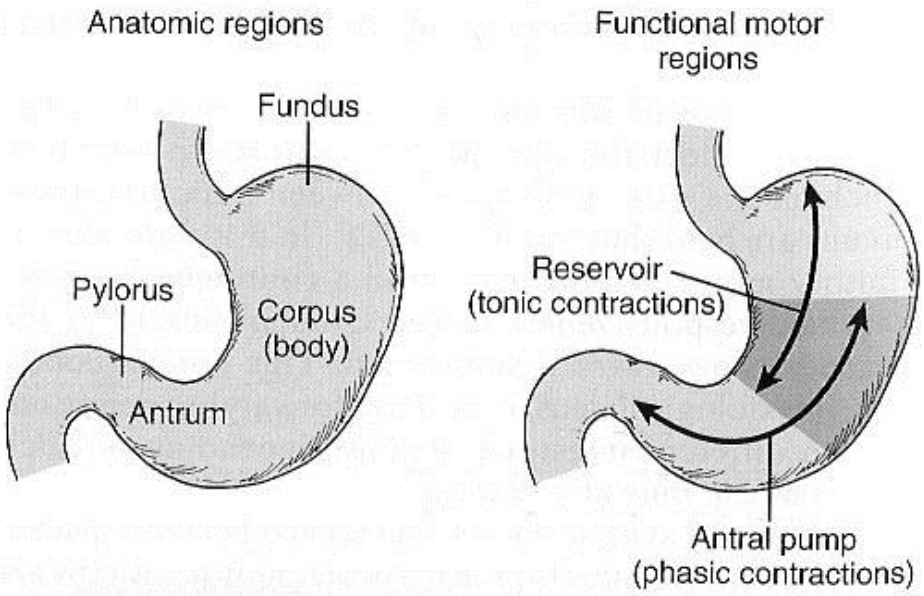
- Functions of stomach
- Gastric secretion
  - ✓ Mechanism of HCl formation
  - ✓ Gastric digestive enzymes
  - ✓ Neural & hormonal control of gastric secretion
  - ✓ Phases of gastric secretion
- Motor functions of the stomach
- Stomach Emptying
  - ✓ Gastric factors that promote stomach emptying
  - ✓ Duodenal factors that inhibit stomach emptying

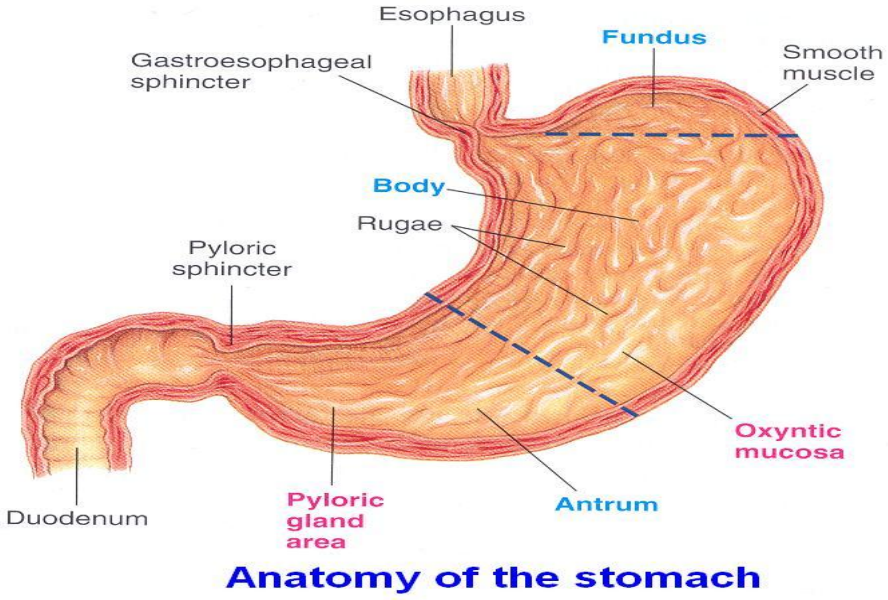
Anatomical and Physiological Divisions of the Stomach

Anatomically the stomach is composed of the fundus, body and the antrum.

Physiologically, it is composed of :

- **The orad portion** (fundus and upper two thirds of the body)- Reservoir part (tonic contraction)
- **The caudal** (lower third of the body plus antrum)- Antral pump (phasic contraction).





Anatomy of the stomach

Functions of stomach

1- It stores food & regulates its passage to small intestine.

2- It secretes juice that liquefies & partly digests food.

3- It produces intrinsic factor necessary for vitamin B_{12} absorption.

4- Gastric HCl:

- ✓Kills ingested bacteria.
- ✓Is necessary for iron & Ca^{++} absorption.
- ✓Catalyzes cleavage of inactive pepsinogen into active pepsin.

7- Absorption of water and lipid-soluble substances (alcohol and drugs).

8- It has endocrine function, e.g. It produces gastrin and somatostatin.

Gastric Secretion

Histologically gastric mucosa is divided into 3 areas:-

1- The cardiac area (10 % of mucosa)

Most of cells secrete mucus.

2- The main gastric area (70-80 %)

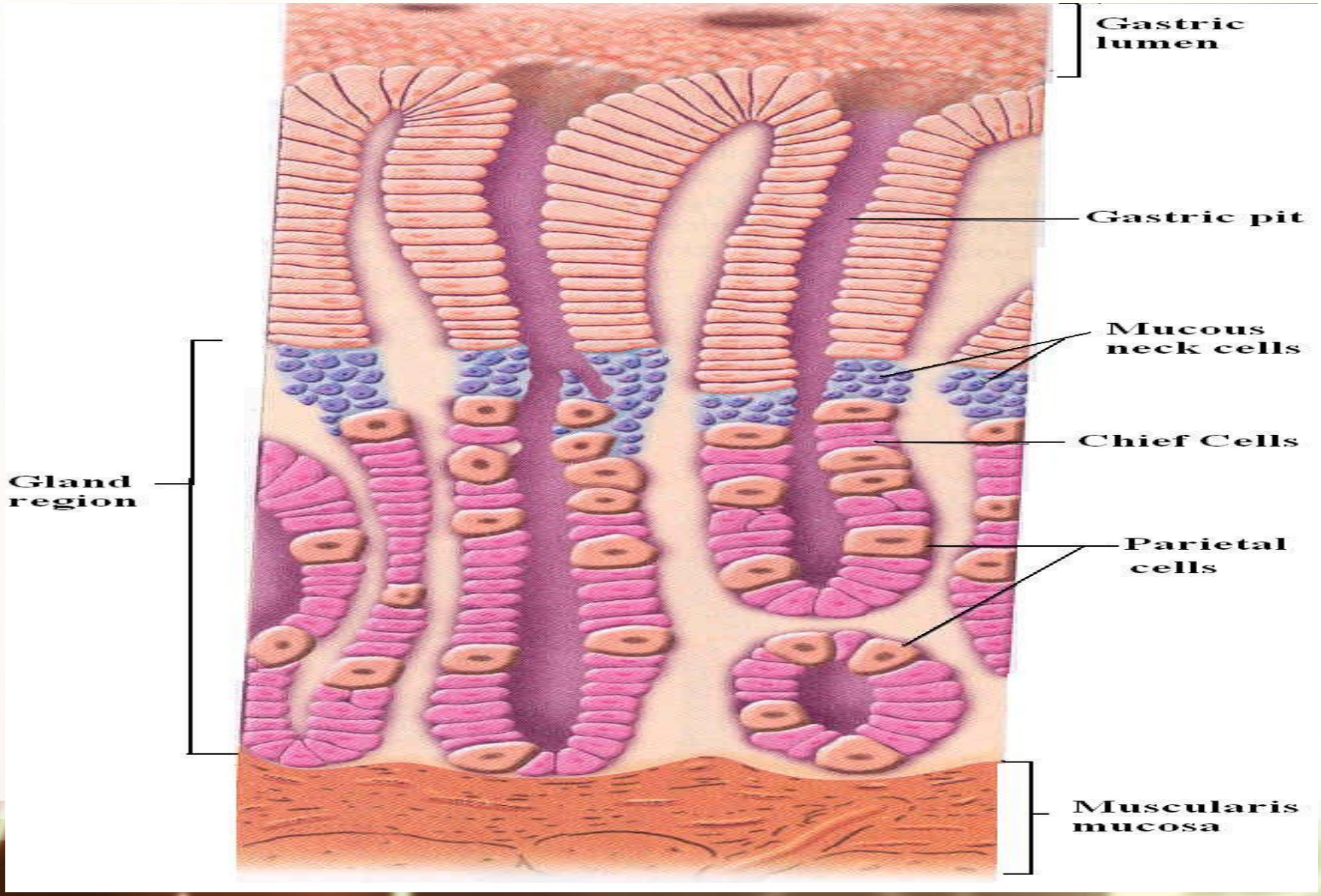
Includes mucosa of fundus & body. Its oxyntic glands secrete all constituents of gastric juice.

- Parietal (oxyntic) cells secrete HCl & intrinsic factor.
- Peptic (chief) cells secrete pepsinogen.
- Mucous neck cells secrete mucus & HCO_3^-.

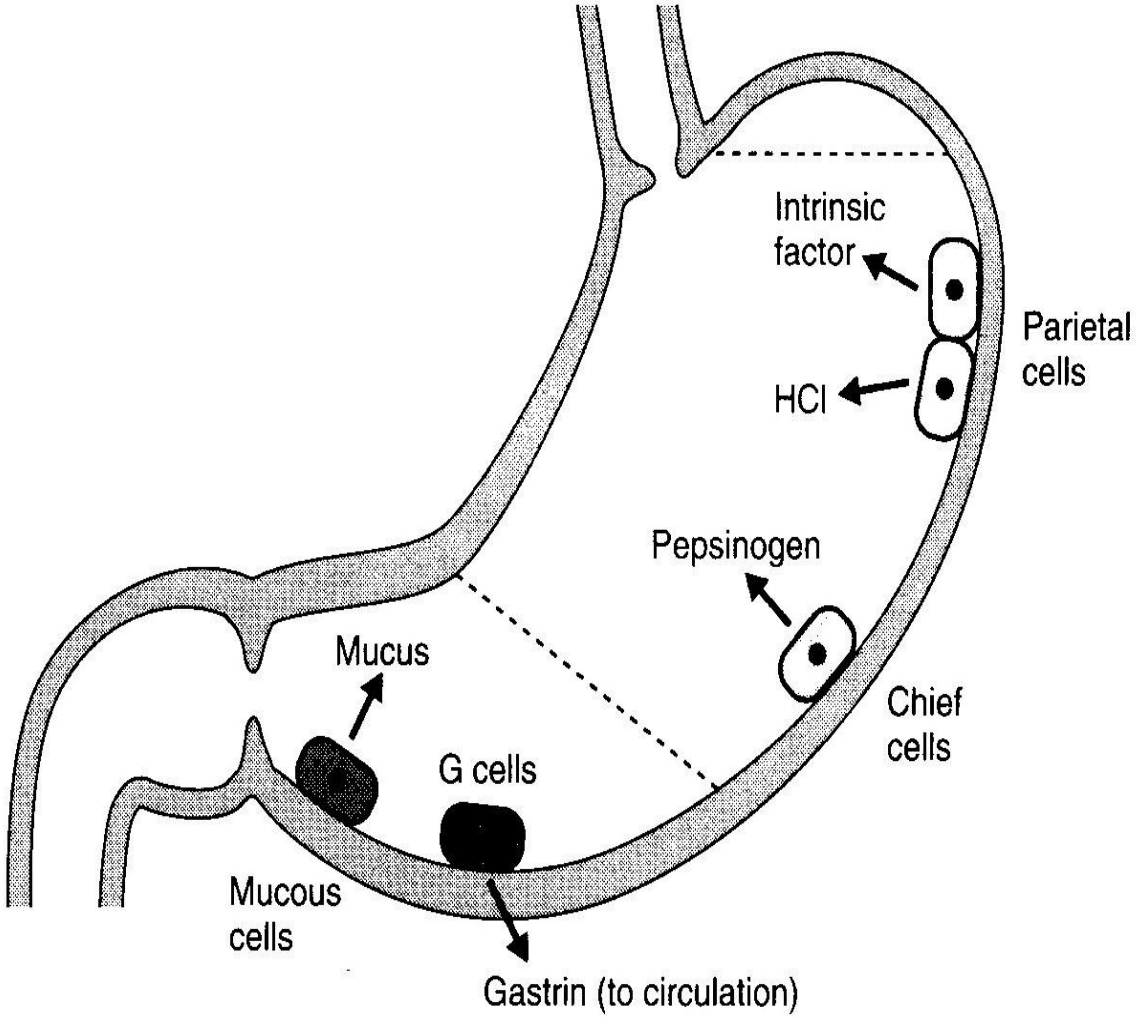
3- The pyloric area (15 %)

Most of its cells are mucous cells. Contains G- cells that secrete gastrin.

Structure of a Gastric Oxyntic Gland



The Normal Locations of Gastric Cells



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

Gastric Juice

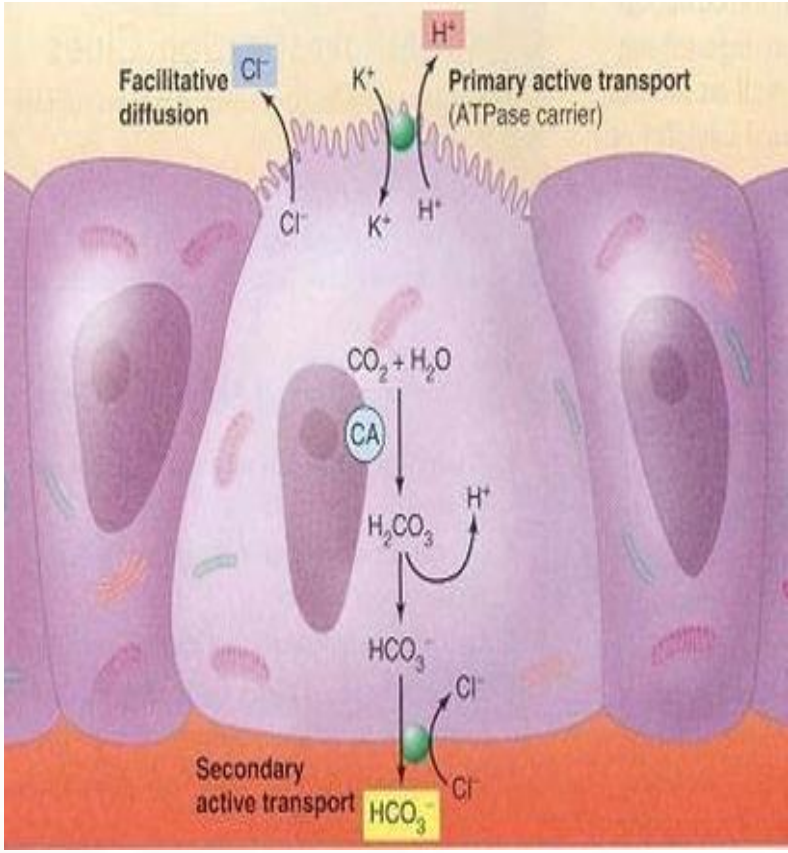
Volume about 2-3 L/day

Main constituents are:

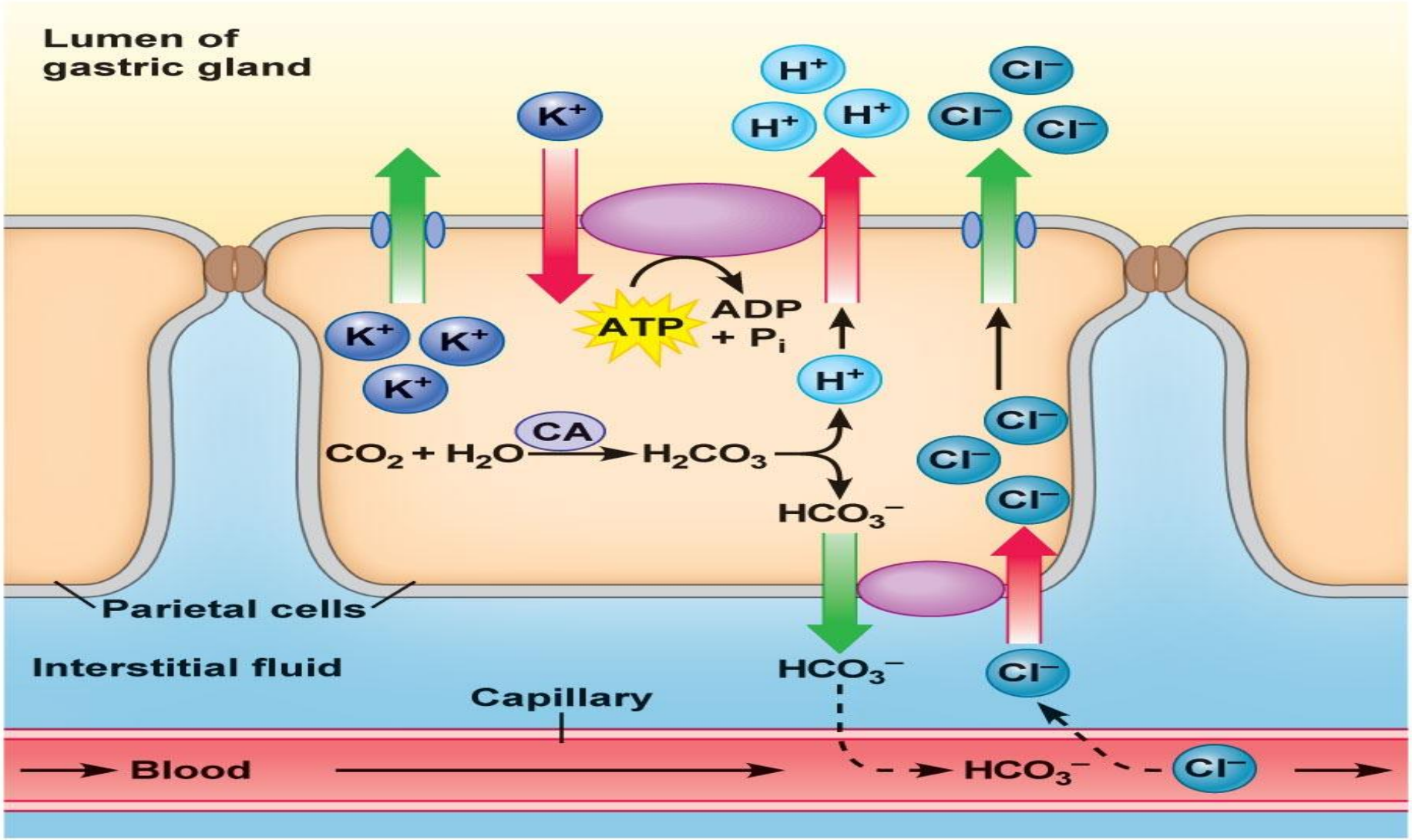
- HCl
- Digestive enzymes (Pepsinogen)
- Mucus (mucus gel layer)
- Electrolytes
- Intrinsic factor.

Gastric HCL

- Secreted by **parietal cells**, the most distinctive cells in the stomach.
- They are pyramidal in shape.
- Their structure is unique in that they have an abundance of mitochondria and intracellular canaliculi that are continuous with the lumen of the oxyntic gland.
- HCl is secreted across the parietal cell microvillar membrane and flows out of the intracellular canaliculi into the oxyntic gland lumen.



Mechanism of HCl formation



- ✓ Cl^- is actively transported from cytoplasm into luminal canaliculi. This create –ve potential which causes passive diffusion of K^+ from cytoplasm into canaliculi. Thus K^+ & Cl^- enters canaliculi.
- ✓ Intracellular H_2O dissociates into H^+ & OH^-.
- ✓ H^+ is actively transported across canalicular membrane against concentration gradient by H^+-K^+ ATPase which exchange H^+ with K^+. It can be inhibited by omeprazole (proton pump inhibitors).
- ✓ CO_2, either formed during metabolism in the cell or entering the cell from the blood, combines under the influence of carbonic anhydrase with the OH^- to form $HCO3^-$.
- ✓ HCO_3^- diffuses from the cell to plasma (Alkaline tide) and CL^- enters via a carrier mechanism that facilitates exchange between the 2 ions.

Gastric digestive enzymes

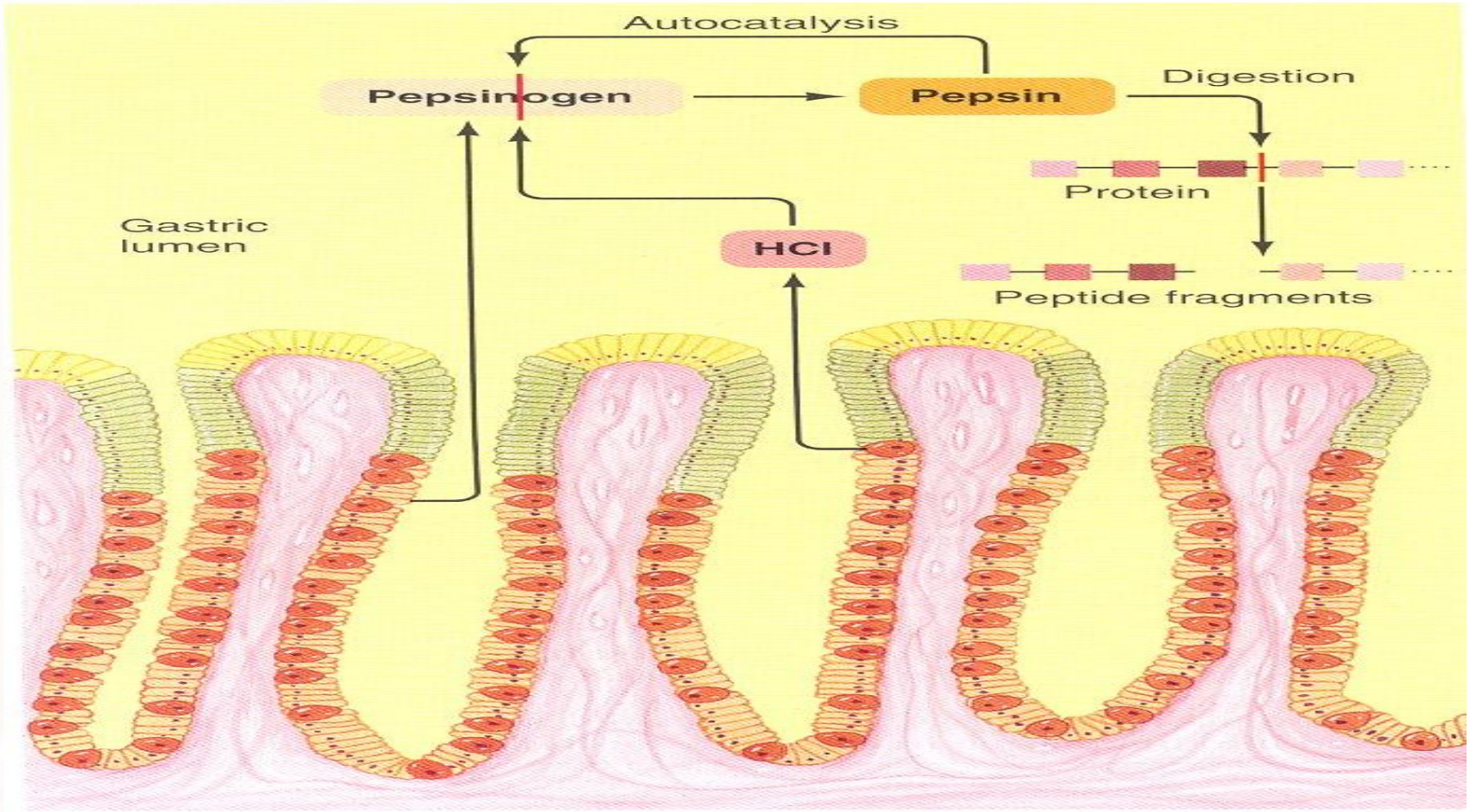
Pepsin enzyme

Several types of pepsinogen secreted from chief cells. They are activated by HCl into pepsin and once activated, they can activate more pepsinogen. The optimum pH is 1.5-3.5. Pepsin breaks down proteins into peptones & polypeptides. Pepsinogen secretion is stimulated by Ach, acid, gastrin, secretin & CCK.

Lipase enzyme

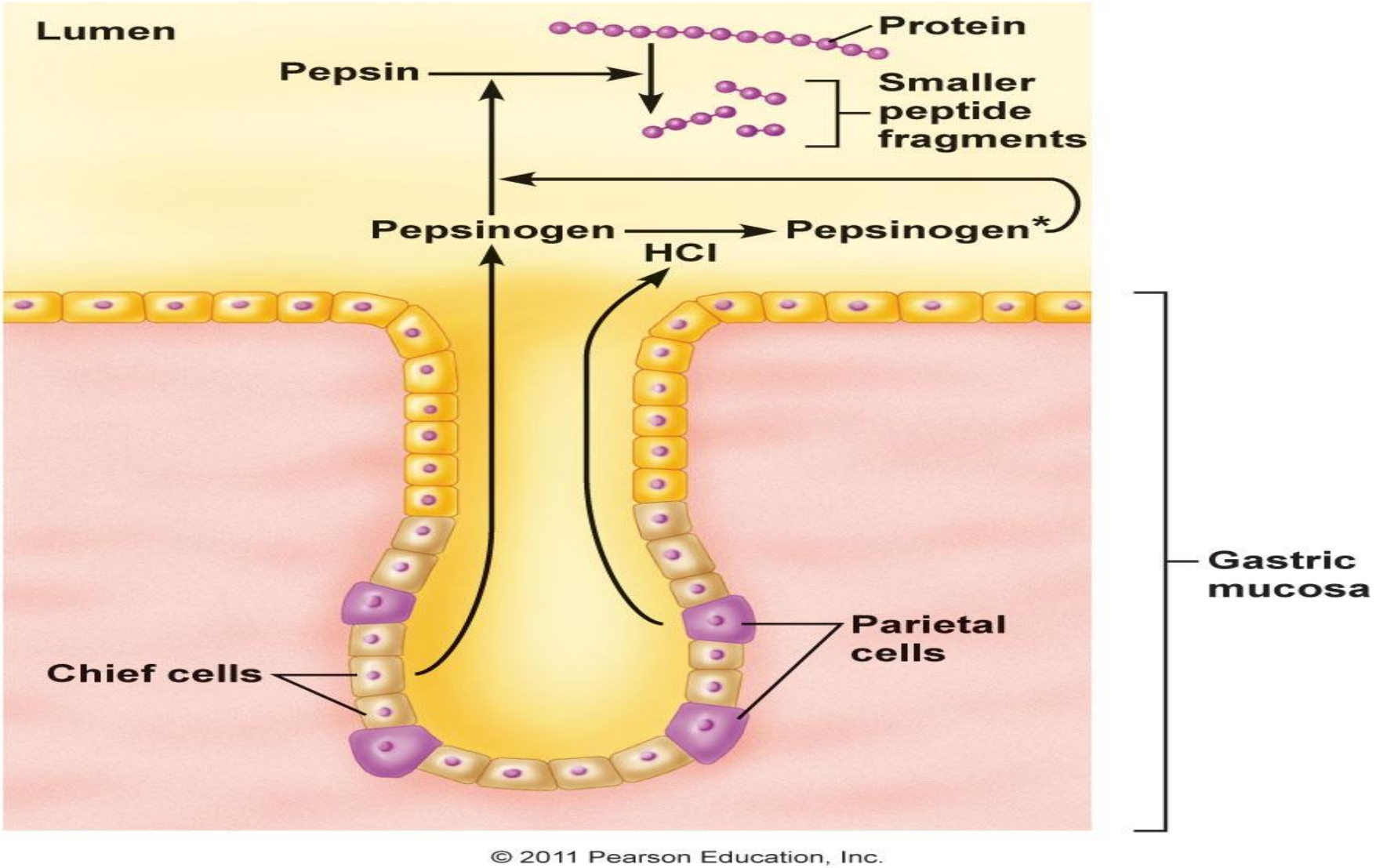
Secreted from fundic mucosa. It hydrolyses TG into MG & FA. Its activity is less than pancreatic lipase.

Pepsin enzyme



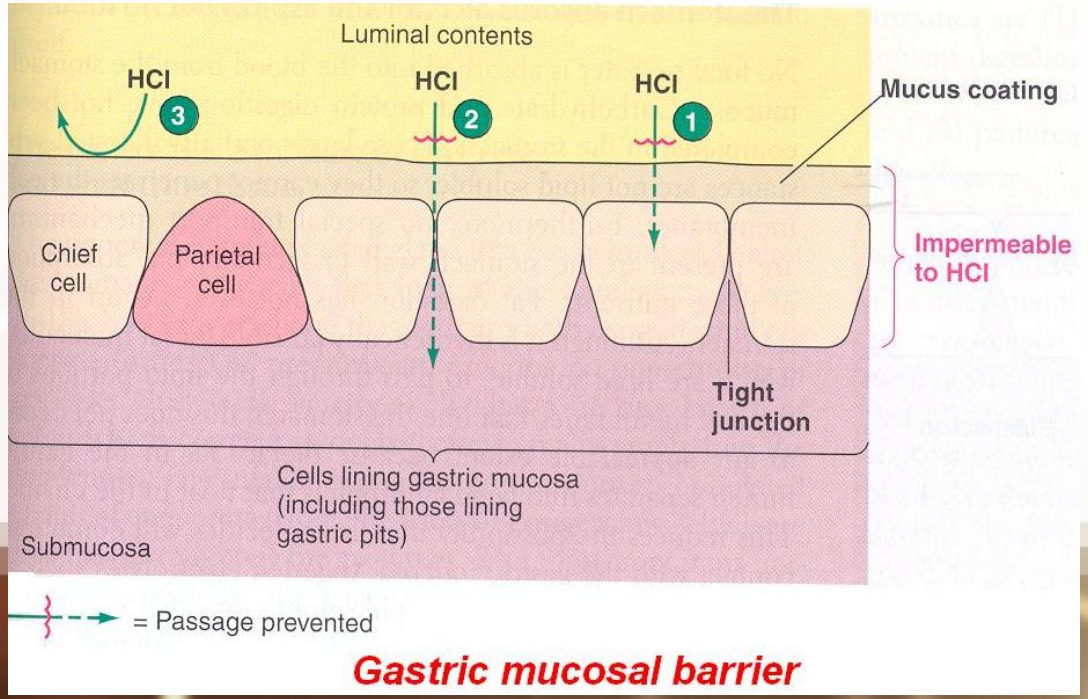
Pepsinogen activation in the stomach lumen

Pepsinogen activation in the stomach lumen



Gastric mucus

- It is glycoprotein. Its secretion is stimulated by mechanical & chemical irritation of mucosa.
- It is about 0.2 mm thick and separate surface epithelial cells from acidic contents thus it allows neutral pH at epithelial cells despite luminal pH about 2.



Gastric mucosal barrier

Functions:-

1. It protects the mucosa against mechanical injury by lubricating of chyme.
2. It protects the mucosa against chemical injury by acting together with HCO_3^- as a barrier to HCl & pepsin. It also neutralize HCl and arrest action of pepsin.

   Aspirin & nonsteroidal anti-inflammatory agents inhibit secretion of both mucus & HCO_3^-. Prolonged use of these drugs may produce gastritis or ulcer.

Intrinsic Factor

- It is glycoprotein secreted by **parietal cells**.
- It is the only essential function of stomach as it is essential for vitamin B_{12} absorption.
- Atrophy of gastric mucosa leads to pernicious anemia.

Neural & Hormonal Control of Gastric Secretion

- ☑ Vagus nerve (neural effector) either by releasing Ach (direct activation of parietal cells) or by releasing gastrin releasing peptide, GRP (indirect activation).
- ☑ Gastrin (hormonal effector)
- ☑ Enterochromaffin-like cells release Histamine→ activates H_2 receptor (parietal cells) → increases acid secretion

Gastric Secretion Occurs in Three Phases

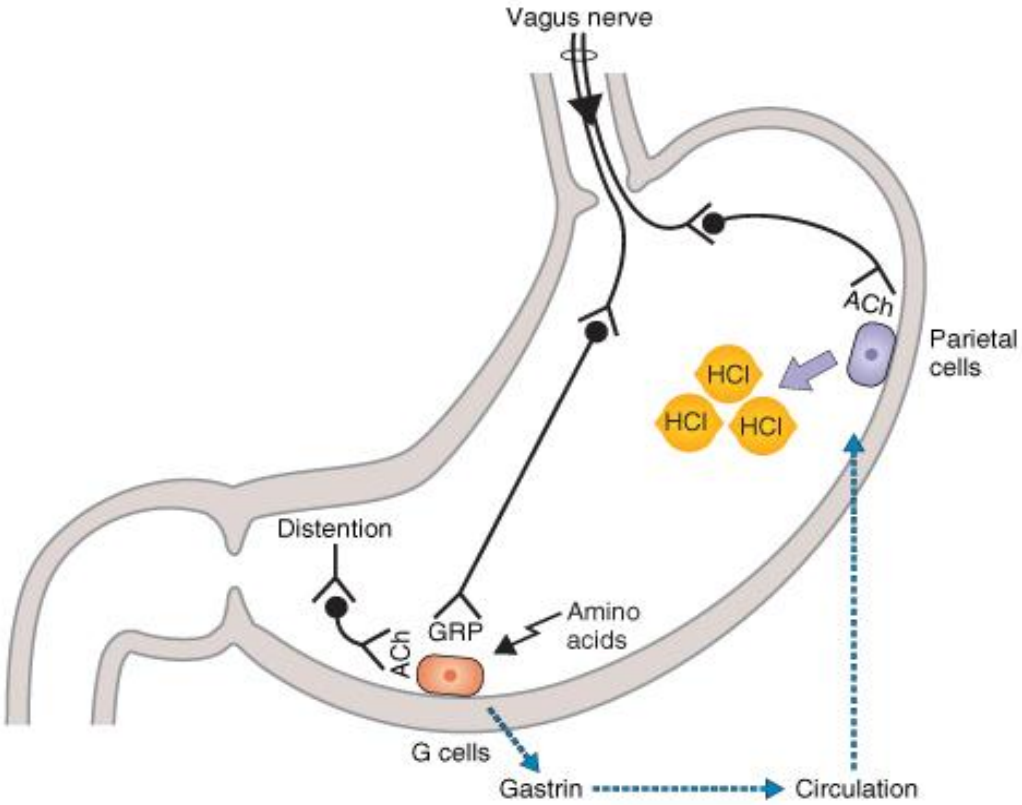
The stimulation of acid secretion resulting from the ingestion of food can be divided into three phases:

1. Cephalic phase(30%):
   Smelling, Chewing and swallowing
   Stimulates parietal G-Cells
   GRP

2. Gastric phase (60%):
   Gastric distention
   proteins

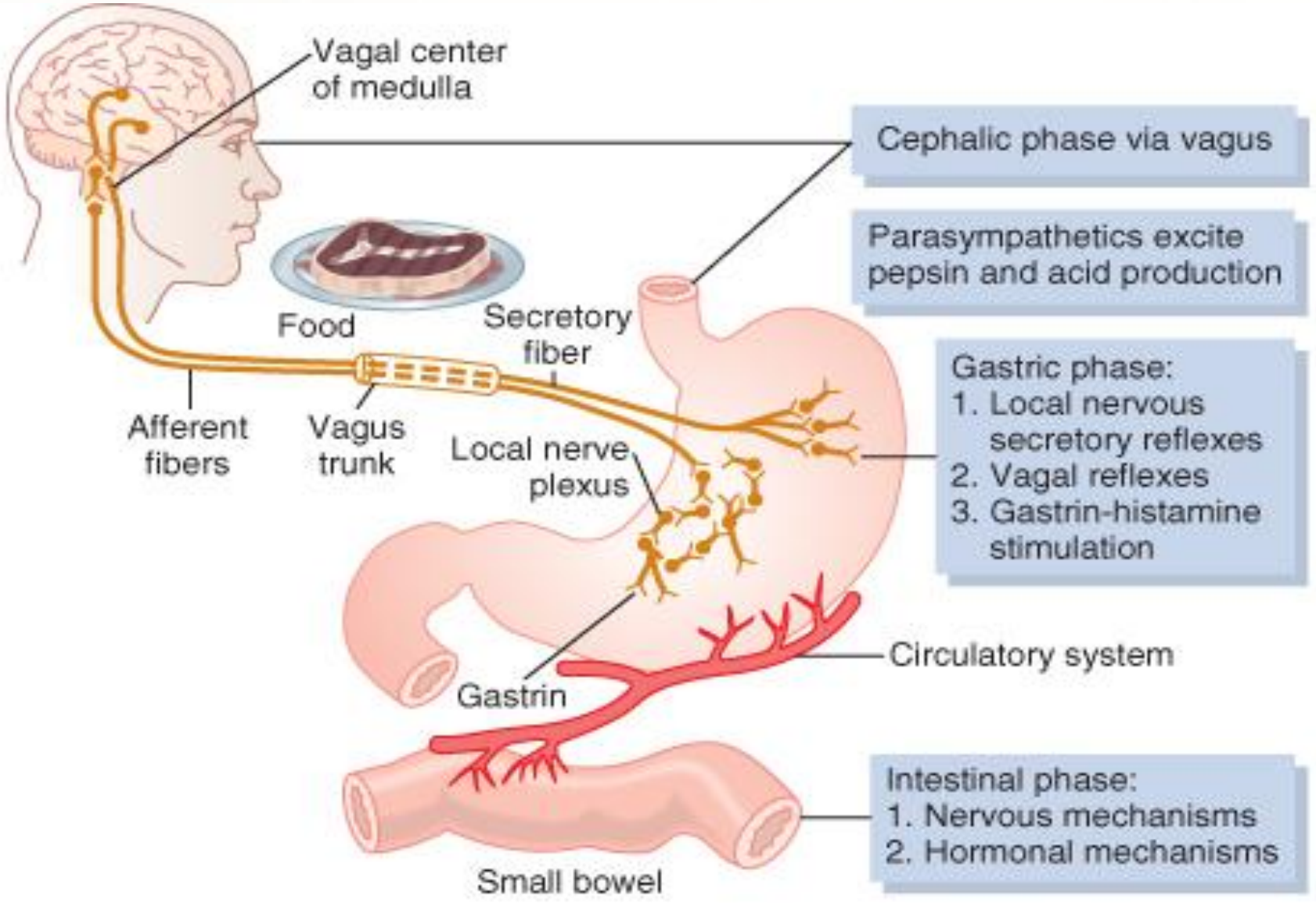
3. Intestinal phase (10%):
   Digested proteins

REGULATION OF HCl SECRETION



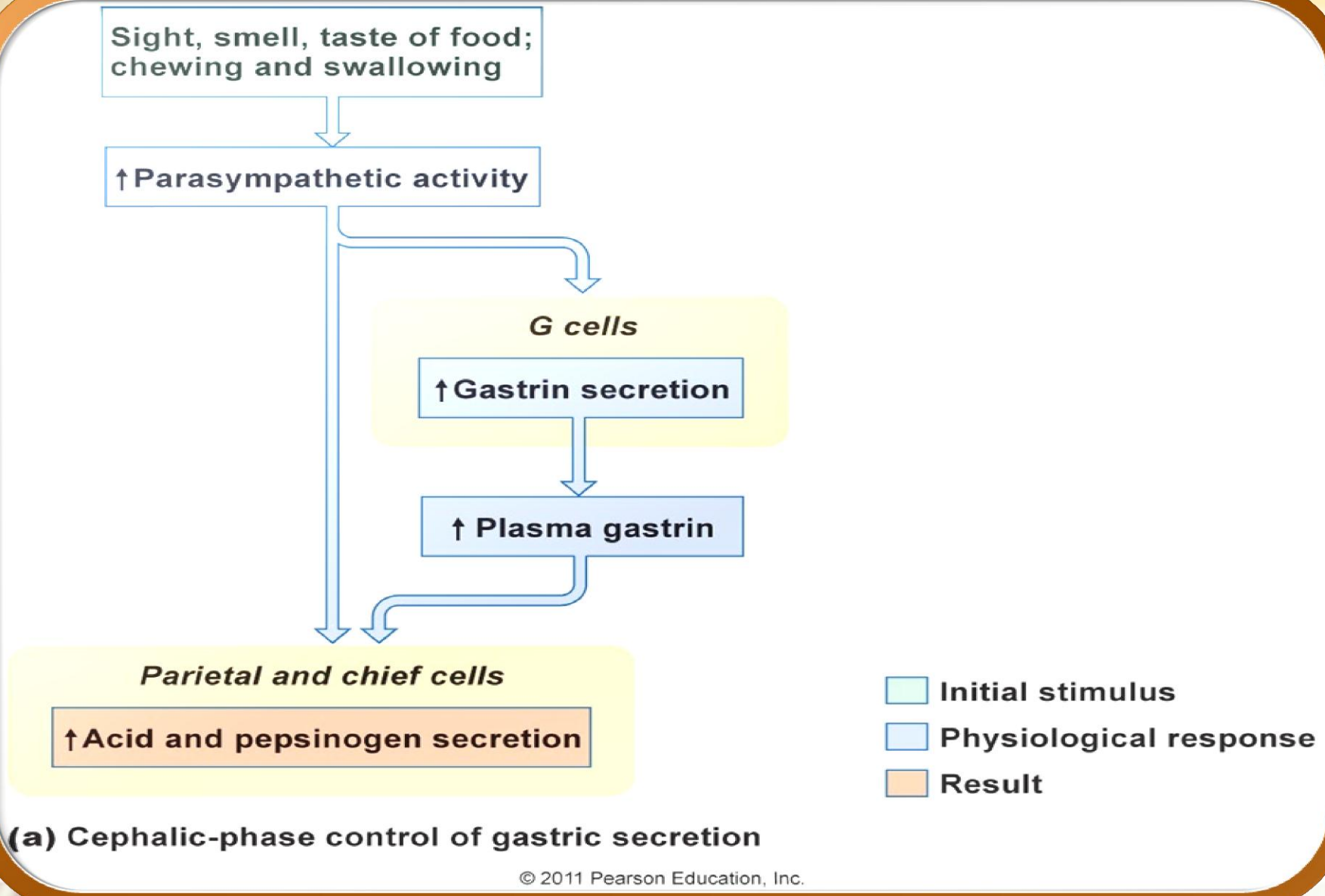
Phase	% of HCl Secretion	Stimuli	Mechanisms
Cephalic	30%	Smell, taste, conditioning	Vagus → parietal cell Vagus → gastrin → parietal cell
Gastric	60%	Distention	Vagus → parietal cell Vagus → gastrin → parietal cell
		Distention of antrum	Local reflex → gastrin → parietal cell
		Amino acids, small peptides	Gastrin → parietal cell

Phases of Gastric Secretion



1. The Cephalic Phase

- It involves the central nervous system. Seeing, smelling, thinking of appetizing food, chewing, and swallowing food send afferent impulses to vagal nucleus which sends impulses via the vagus nerves to the parietal and G cells in the stomach.
- The nerve endings release ACh, which directly stimulates acid secretion from parietal cells.
- The nerves also release gastrin-releasing peptide (GRP), which stimulates G cells to release gastrin, indirectly stimulating parietal cell acid secretion.



(a) Cephalic-phase control of gastric secretion

2. The gastric Phase

It is mediated by nervous & hormonal mechanisms. It is elicited by presence of food in stomach. The stimuli are distension of stomach and presence of amino acids & peptides.

a. Nervous mechanism

Distension of either body or antrum of stomach stimulates mechanoreceptors in gastric wall. Gastric secretion occurs by long vagovagal reflex and also by short intramural cholinergic reflexes.

b. Hormonal mechanism (Gastrin hormone)

- Gastrin is secreted from G cells in antrum, enters the blood and then stimulates gastric glands.

- Stimuli of gastrin release:

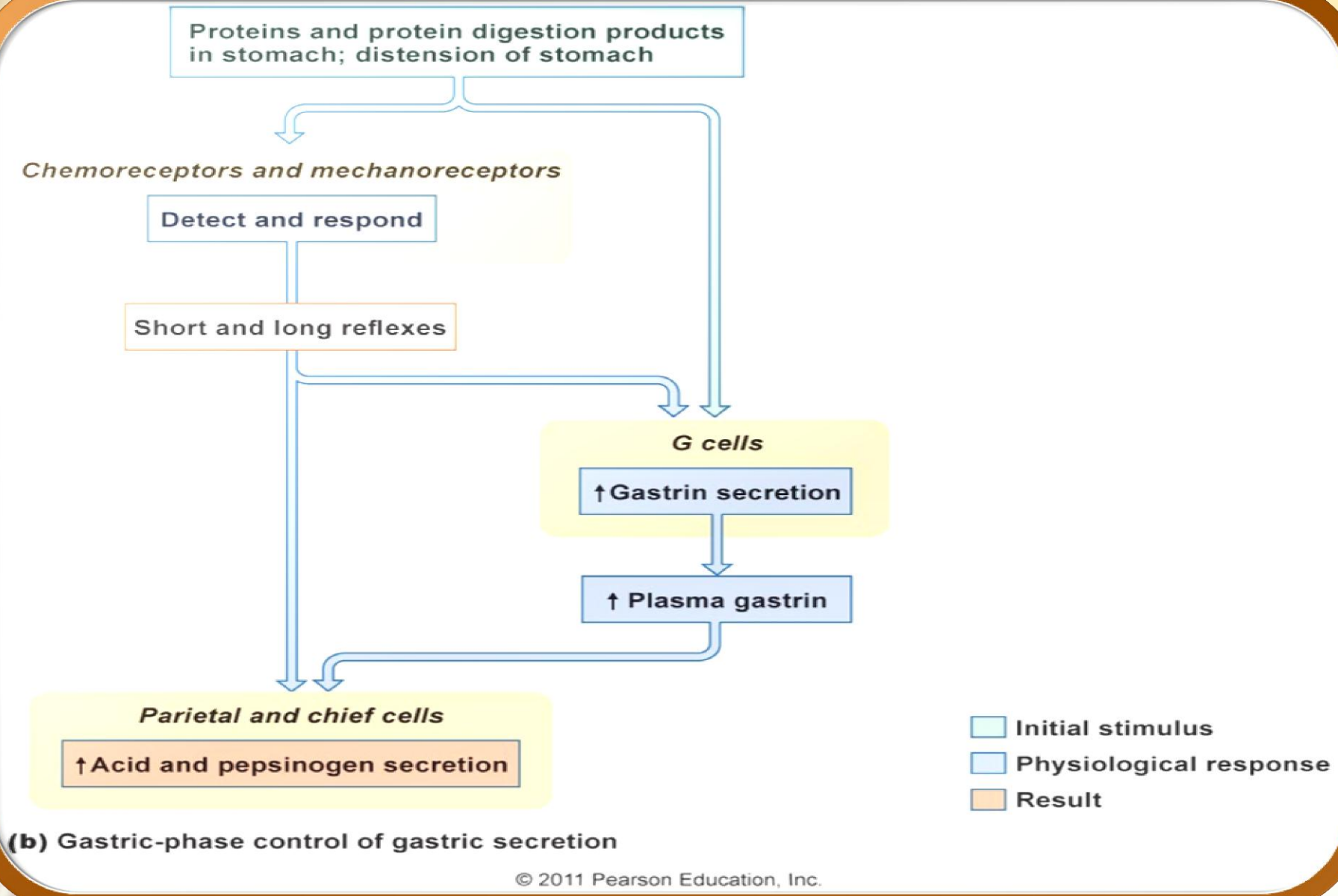
  1- The presence of amino acids & peptides.

  2- Gastric distension,

  3- Alcohol & caffeine.

  4- Vagal excitation.

  5- Rising of pH of gastric juice.



(b) Gastric-phase control of gastric secretion

Actions of gastrin:

1- It stimulates gastric acid secretion, secretion of pepsin and intrinsic factor.

2- It stimulates intestinal secretion.

3- It stimulates pancreatic secretion of enzyme & HCO_3^-.

4- It stimulates biliary secretion of HCO_3^- & H_2O.

5- It stimulates gastric motility.

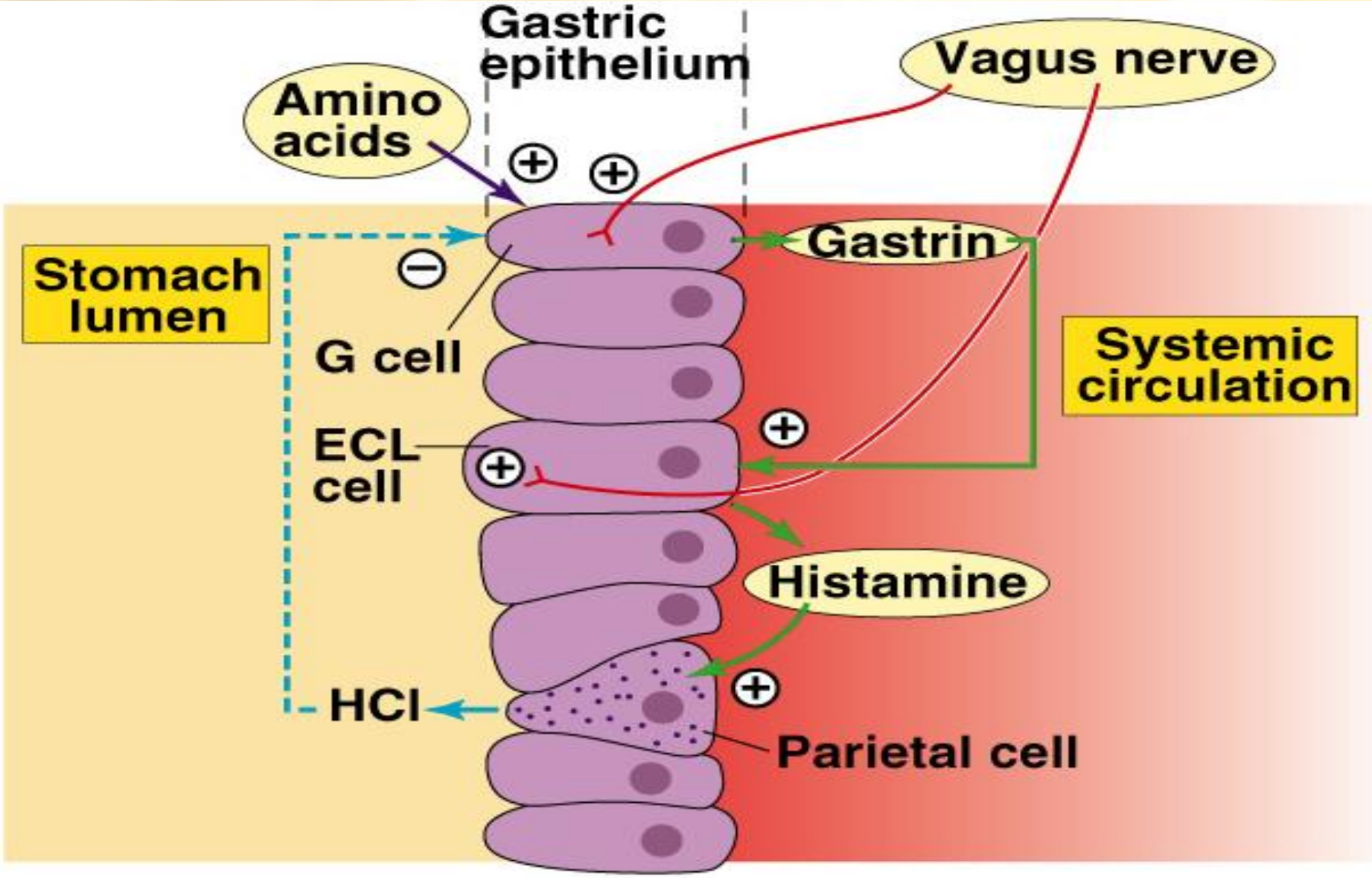
6- It stimulates intestinal motility & relaxes ileocaecal sphincter.

7- It contract LES.

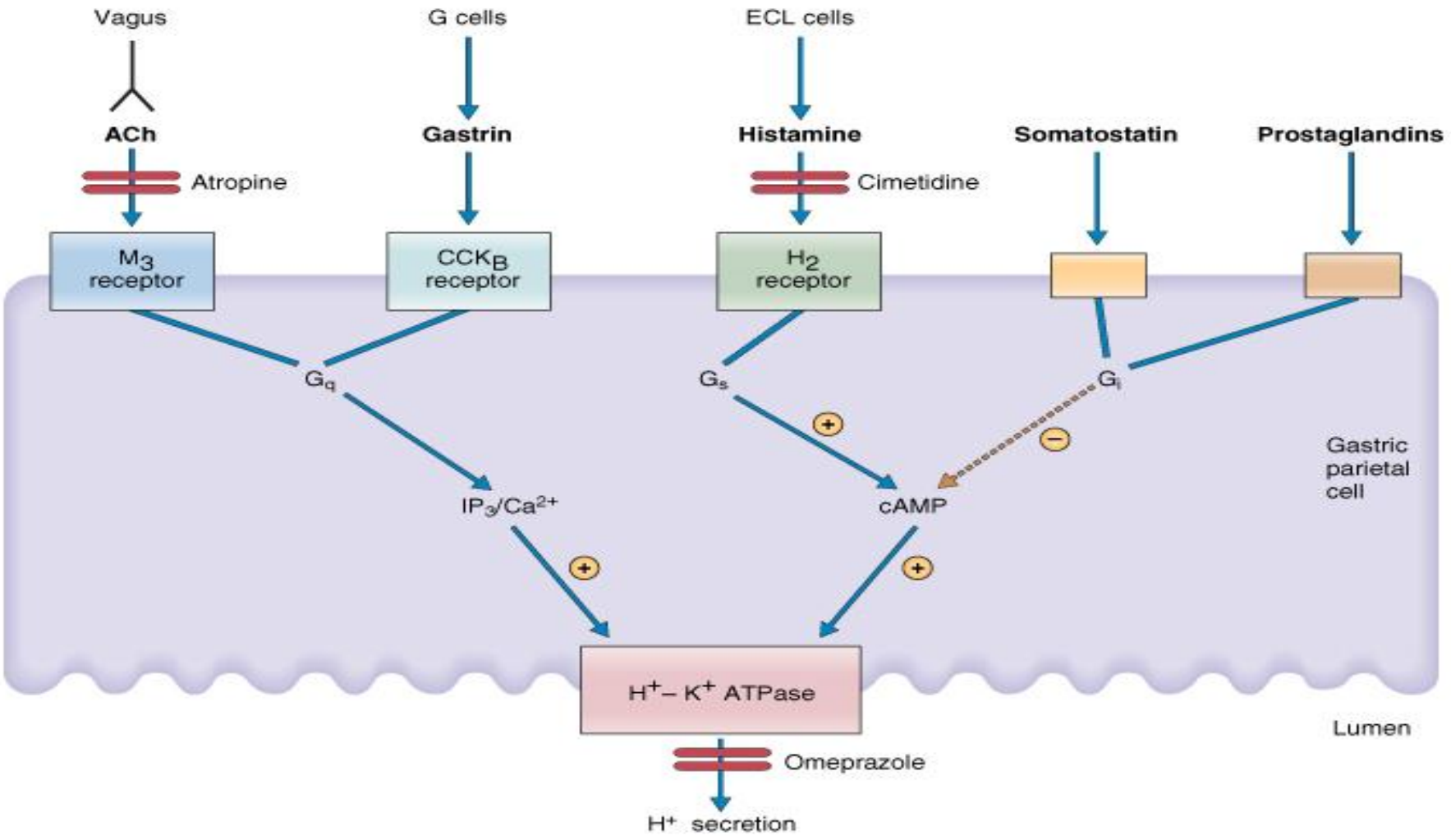
8- It has trophic effect on gastric mucosa.

Control of HCl secretion at the level of parietal cells

- ☆ Gastrin reaches parietal cells via blood stream to stimulate HCl secretion **(endocrine action)**.
- ☆ Ach is released near parietal cells by cholinergic nerve endings to stimulate HCl secretion **(neurocrine action)**.
- ☆ Histamine is released from enterochromaffin cells in gastric mucosa and diffuses to parietal cells to act on H_2 receptors to stimulate HCl secretion **(paracrine action)**.
- Cimetidine & ranitidine are H_2 receptor blockers and potent inhibitor of gastric acid secretion and both are used for treatment of peptic ulcers and gastroesophageal reflux


Gastric epithelium
Vagus nerve
Amino acids
Gastrin
Stomach lumen
G cell
Systemic circulation
ECL cell
Histamine
HCl
Parietal cell

Agents that stimulate and inhibit H^+ secretion by gastric parietal cells



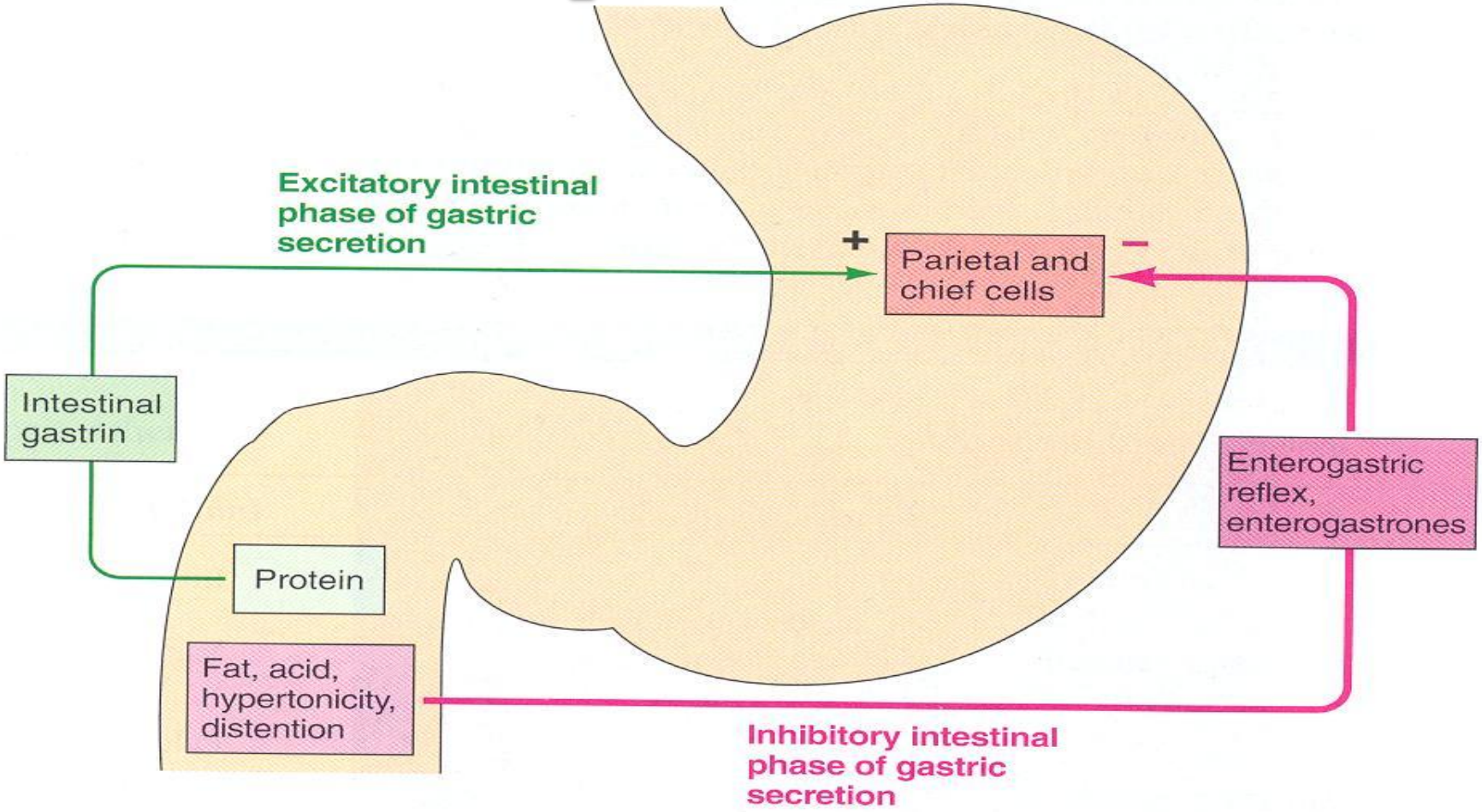
Inhibition of Acid Secretion

Inhibitory hormones **(Enterogastrones)**:

- Somatostatin (D-cells) in antrum
- Secretin (S-cells) in duodenum
- Glucose-dependent insulinotropic peptide (GIP) in duodenum

Hormone	Site of Secretion	Stimuli for Secretion	Actions
Gastrin	G cells of the stomach	Small peptides and amino acids Distention of the stomach Vagal stimulation (GRP)	↑ Gastric H^+ secretion Stimulates growth of gastric mucosa
Cholecystokinin (CCK)	I cells of the duodenum and jejunum	Small peptides and amino acids Fatty acids	↑ Pancreatic enzyme secretion ↑ Pancreatic HCO_3^- secretion Stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi Stimulates growth of the exocrine pancreas and gallbladder Inhibits gastric emptying
Secretin	S cells of the duodenum	H^+ in the duodenum Fatty acids in the duodenum	↑ Pancreatic HCO_3^- secretion ↑ Biliary HCO_3^- secretion ↓ Gastric H^+ secretion Inhibits trophic effect of gastrin on gastric mucosa
Glucose-Dependent Insulinotropic Peptide (GIP)	K cells of the Duodenum and jejunum	Fatty acids Amino acids Oral glucose	↑ Insulin secretion from pancreatic β cells ↓ Gastric H^+ secretion
Motilin	M cells of the duodenum and jejunum	Fat Acid Nerve	Stimulates: Gastric motility Intestinal motility

3. The intestinal phase



Excitatory and inhibitory components af intestinal phase of gastric secretion

The presence of chyme in duodenum causes neural & hormonal responses that first stimulates & later inhibits gastric acid secretion.

Gastric secretion is enhanced by:-

i. Distension of duodenum stimulates G.A. secretion by means of vagovagal reflex and the release of the hormone entero-oxyntin from intestinal endocrine cells that stimulates parietal & G- cells.

ii. Presence of protein digestive products in duodenum stimulates G- cells in duodenum & proximal jejunum to release gastrin.

The inhibitory mechanisms that limit G.A secretion

1. The presence of food in small intestine initiates enterogastric reflex, transmitted through ENS & autonomic NS that inhibits G.A secretion.

2. Drop the pH in pyloric antrum to < 2.5 reduces G.A secretion via release of somatostatin from antral & duodenal D-cells.

3. The presence of acid, fat, protein digestive products, hypertonic solution in upper intestine inhibits G.A secretion. These effects are mediated mainly by hormonal mechanisms.

Enterogastrones

Are hormones released from intestine and affect G.A secretion as:-

1) Bulbogastrone
2) Gastric inhibitory peptide.
3) Secretin & CCK.
4) Pancreatic glucagone.
5) Other peptides as VIP, somatostatin, and certain types of prostaglandins.

The functional purpose of the inhibition of G.A secretion by intestinal factors is to slow the release of chyme from stomach when the small intestine is already filled.

Motor Functions of the Stomach

I- Motor Behavior of the upper part of the stomach (Reservoir part)

The main functions of the upper part of the stomach:

1. To maintain a continuous compression (tonic contraction)
2. To accommodate the received food without significant gastric wall distention or pressure (Storage of food).

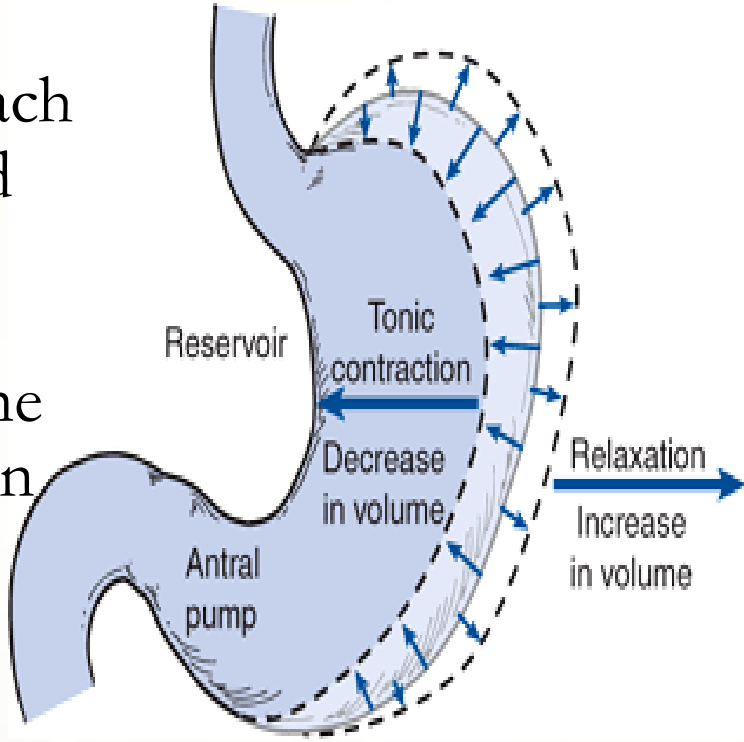
The stomach can store 0.8-1.5 L of food. Gastric contents may remain unmixed for 1hour in the corpus.

Relaxation Reflexes in Gastric Reservoir Part

Three Kinds of Relaxation Occur in the Gastric Reservoir:

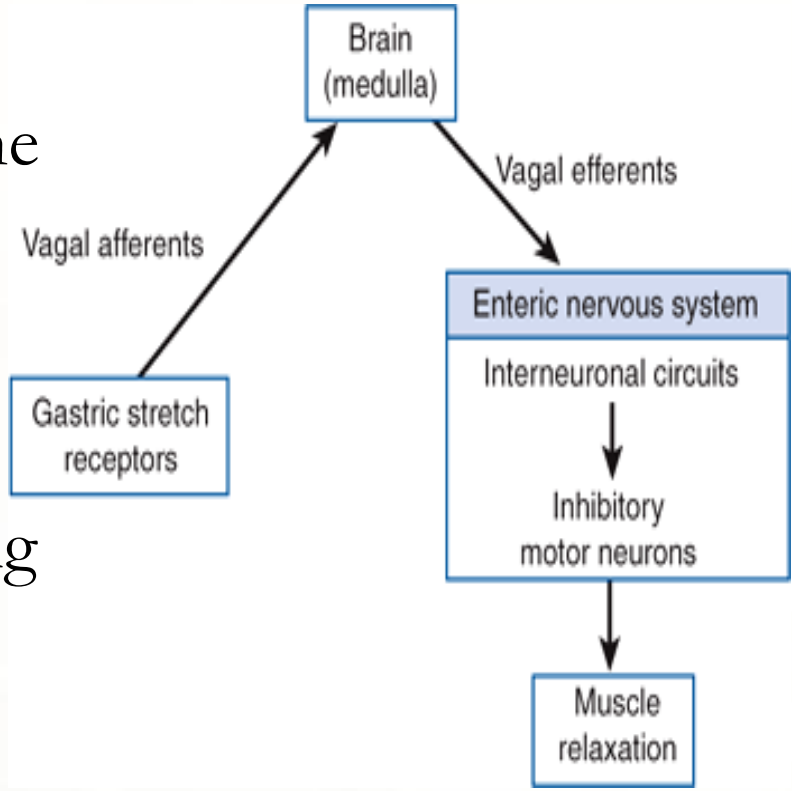
A- Receptive Relaxation Reflex:

- Triggered by swallowing reflex.
- When the esophageal peristaltic waves reach the stomach, a vagovagal reflex is initiated from the stomach to the brain stem and back to the muscular wall of the stomach resulting in reduction in muscular wall tone and the stomach relaxes through inhibition of myenteric neurons which prepares the stomach to receive the food.
- The pressure in the stomach remains low until the volume reaches ~1.5 L of food.



B- Adaptive relaxation:

- Triggered by stretch receptors (vago-vagal reflex).
- Normally, when food stretches the stomach, a "vagovagal reflex" from the stomach to the brain stem and then back to the stomach reduces the tone in the muscular wall of the body of the stomach so that the wall bulges progressively outward, accommodating greater and greater quantities of food up to a limit (0.8 to 1.5 L).
- This reflex is lost in vagotomy.



C- Feedback Relaxation:

- The presence of nutrients in the small intestine triggers feedback relaxation.
- It can involve both local reflex connections between receptors in the small intestine and the gastric ENS or hormones that are released from endocrine cells in the small intestinal mucosa and transported by the blood to signal the gastric ENS and stimulate firing in vagal afferent terminals in the stomach

II- Motor Behavior of the Antral Pump region, (phasic contraction)

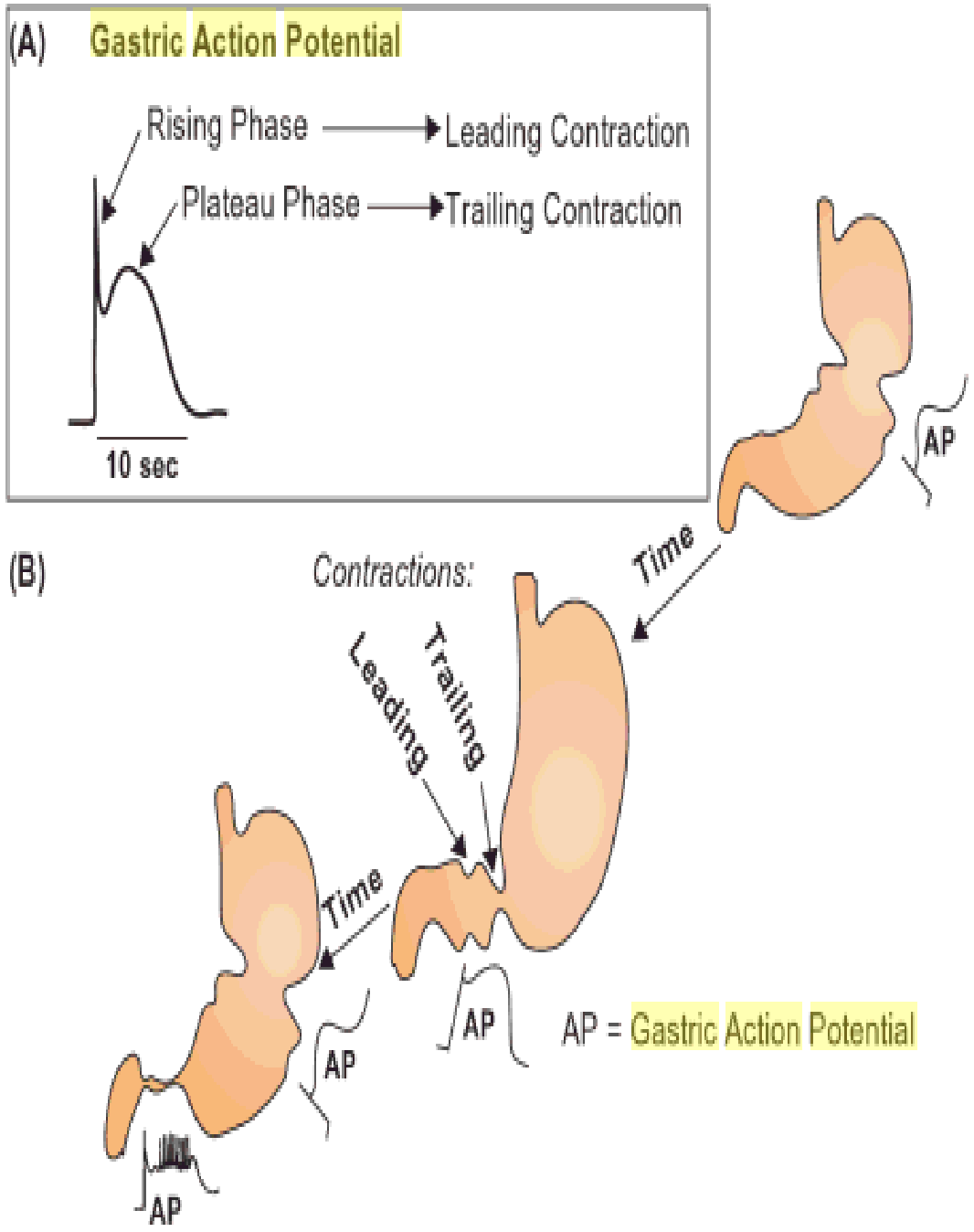
Major mixing activities take place in the antrum

- Contact of gastric chyme with the mucosal surface of the stomach, causes weak peristaltic constrictor waves called mixing waves once every 15-20 sec.
- These waves are initiated by the gut wall basic electrical rhythm of the slow spontaneous electrical waves.
- These waves progress from the body to the antrum and become intense forcing the chyme to mix and move under high pressure from the antrum toward the pylorus.
- Each time a peristaltic wave passes from to the antrum to the pylorus, few millimeters of antral content move into the duodenum through the pyloric sphincter.

Gastric action potentials

- Gastric action potentials are initiated at a frequency of 3/min and lasts about 5 seconds . They propagate rapidly around the gastric circumference and trigger a ring-like contraction.
- The action potentials and associated ring-like contraction then travel more slowly toward the gastroduodenal junction.
- Electrical syncytial properties of the gastric musculature account for propagation of the action potentials to the gastroduodenal junction.

Gastric Action Potentials are characterized by an initial rapidly rising upstroke, followed by a plateau phase, and then a falling phase back to the baseline membrane potential

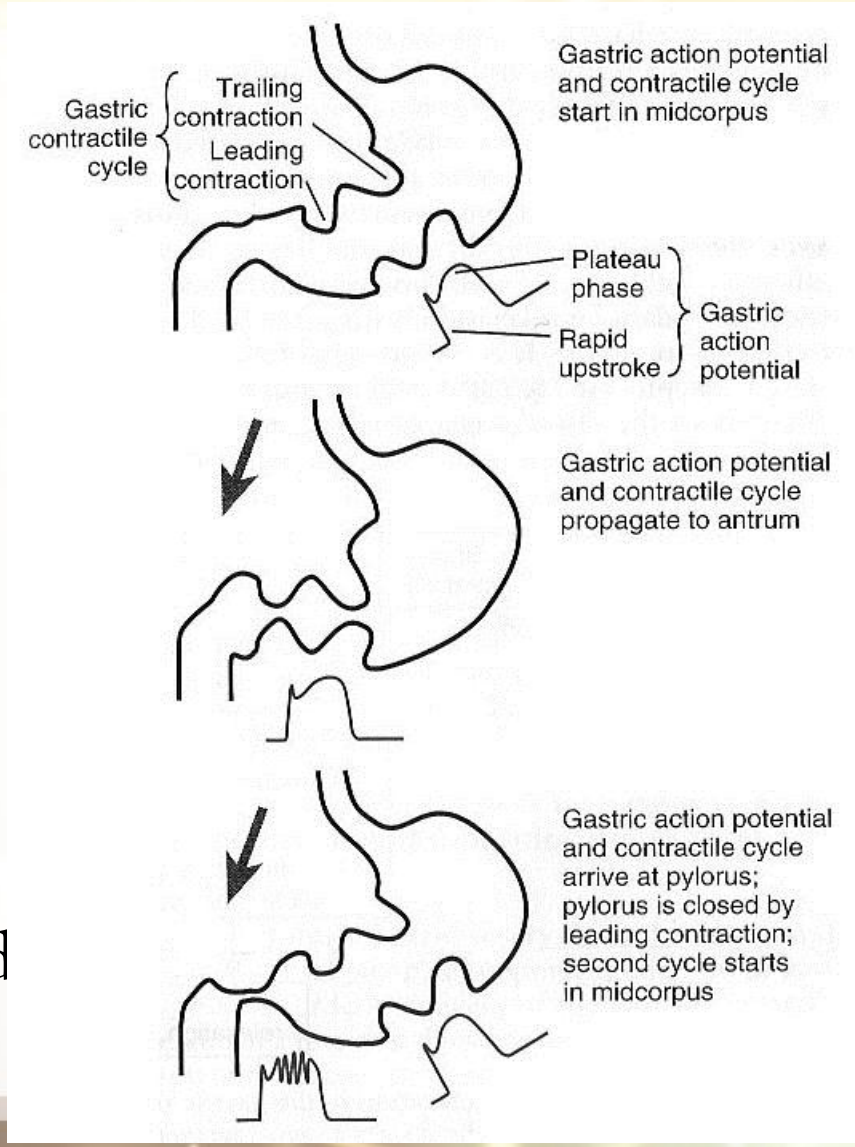


The Gastric Action Potential Triggers Two Kinds of Contractions

The gastric action potential is responsible for two components of the propulsive contractile behavior in the antral pump.

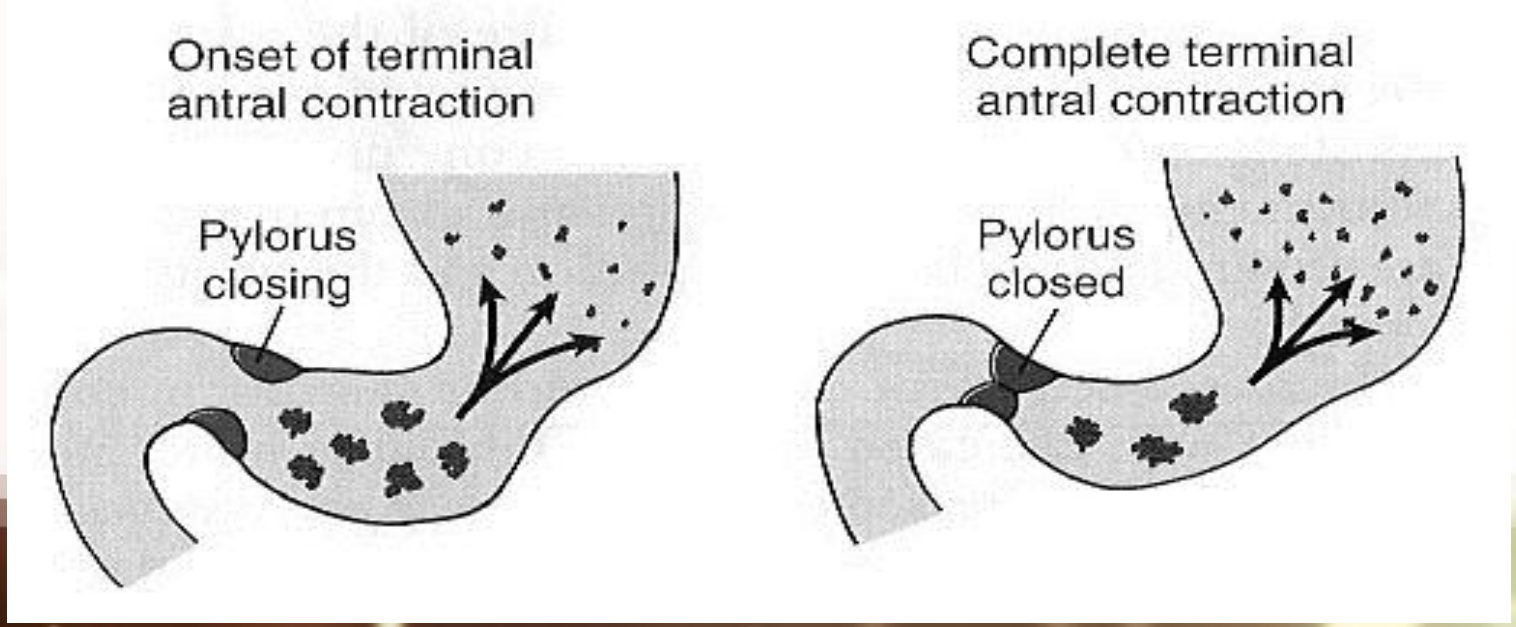
(1) A leading contraction, which has relatively constant amplitude, is associated with the rising phase of the action potential

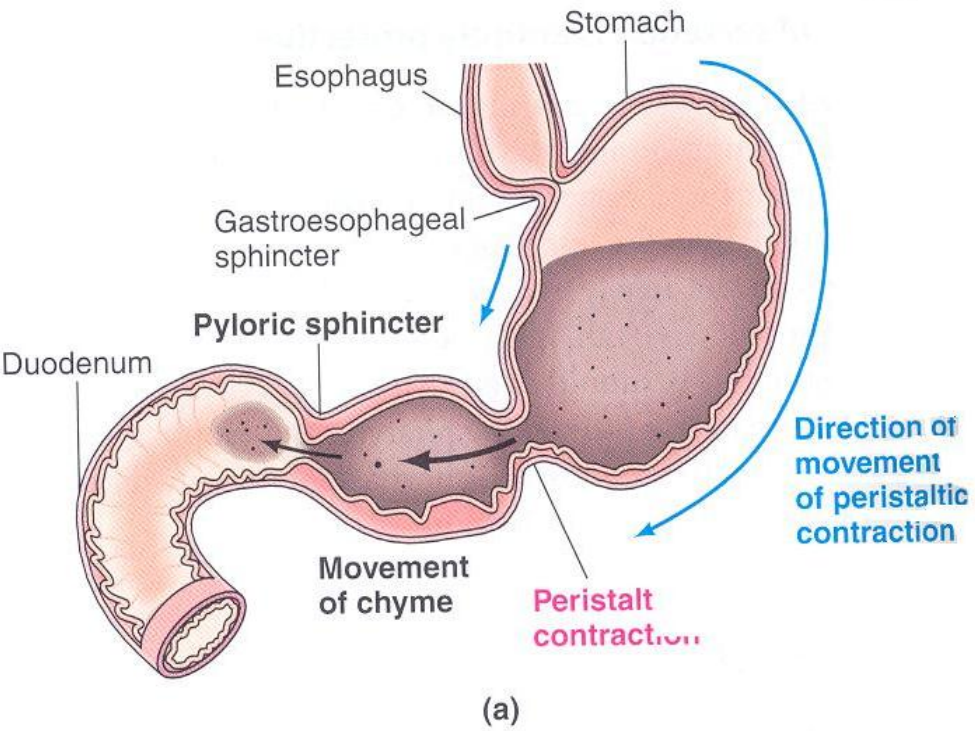
(2) A trailing contraction, of variable amplitude, is associated with the plateau phase.

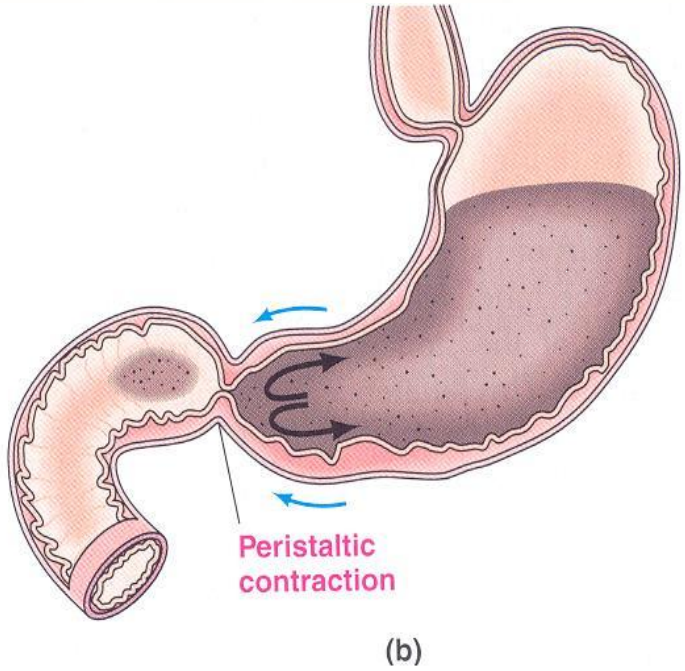


Retropulsion Phenomena

- As the trailing contraction approaches the closed pylorus, the gastric contents are forced into the antral compartment of ever-decreasing volume and progressively increasing pressure. This results in jet-like retropulsion through the pyloric orifice. Repetition at 3 cycles/min reduces particle size from 1-7 mm range that is necessary before a particle can be emptied into the duodenum. These intense peristaltic contractions that cause emptying increase the pressure in the stomach.



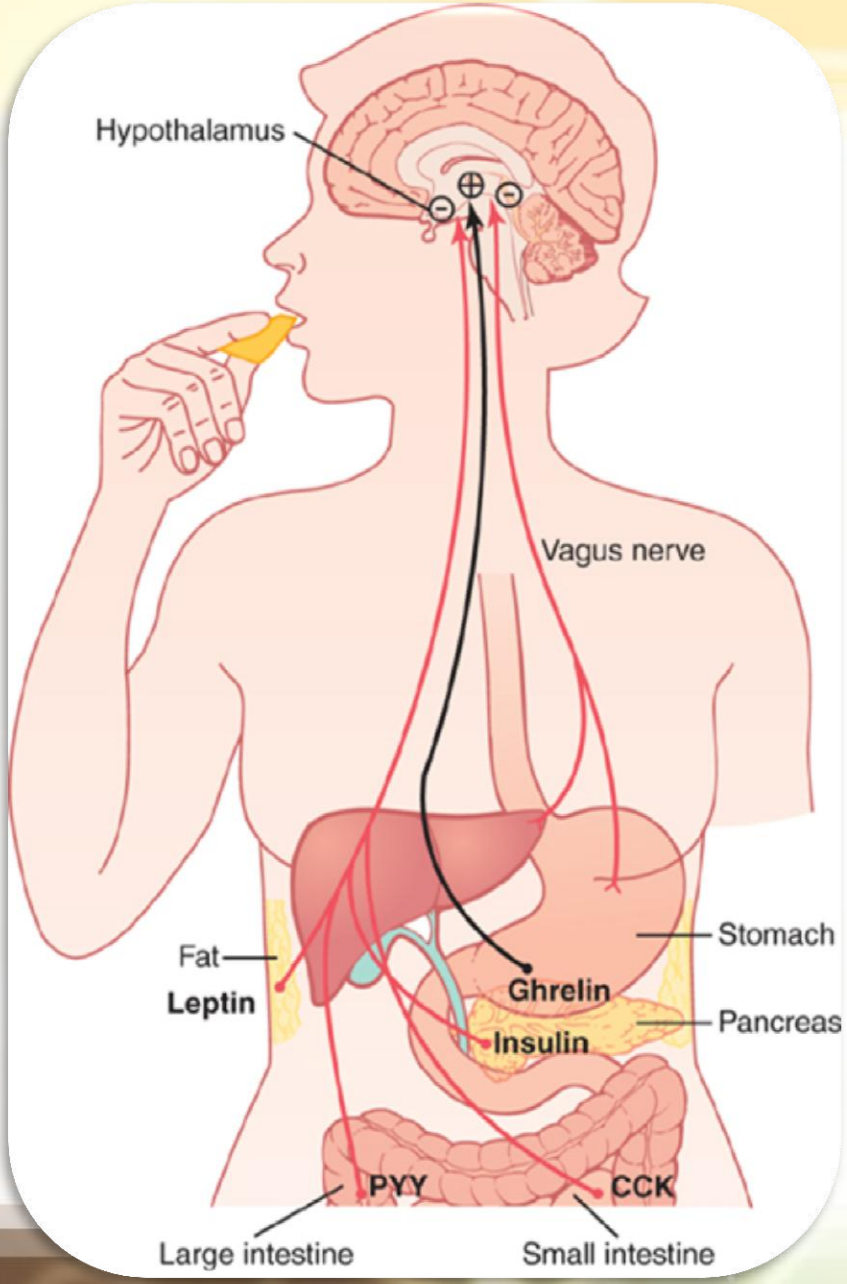




Gastric emptying and mixing as a result of antral peristaltic contraction

Hunger Contractions:

- ✓ Hunger contractions occur when the stomach has been empty for several hours.
- ✓ These are rhythmical peristaltic contractions that can become very strong and fuse to form a continuing tetanic contraction lasting 2-3 minutes.
- ✓ Hunger contractions are intense in young healthy people and increase by low blood glucose levels.
- ✓ Hunger pain can begin after 12-24 hr of last food ingestion.



The migrating motor complex

- It is bursts of depolarization accompanied by peristaltic contraction that occur in empty stomach during interdigestive period.
- MMC moves on a long whole length of small intestine to reach ileocaecal valve after 1.5-2 h where it disappears. A new wave of MMC starts.
- The activity of MMC terminates as soon as food is ingested.
- The function of MMC is to sweep remnants in stomach & small intestine into colon.

Stomach Emptying

Results from intense peristaltic antral contractions against resistance to passage of chyme at the pylorus.

- **Role of the Pylorus in Controlling Stomach Emptying:**
  The pyloric sphincter is characterized by strong circular muscle (as compared to the antrum) and remains tonically contracted most of the time.

  Pyloric constriction is determined by nervous and humoral reflex signals from the stomach and the duodenum.

  However, during pyloric constriction, watery chyme can still pass through the pylorus into the duodenum, but not food particles.

Regulation of Stomach Emptying

- The rate of stomach emptying is controlled by signals from the duodenum and stomach.
- The signals from the duodenum are far stronger and control emptying of chyme at a rate that allows the proper digestion and absorption in the small intestines.

Gastric Factors that Promote Stomach Emptying

1. **Gastric Food Volume:** An increase in gastric food volume results in increased stretch in the stomach wall which elicits local myenteric reflexes that increase the activity of the pyloric pump and inhibit the tonic contraction of the pyloric sphincter leading to increased stomach emptying.

2. **Gastrin Hormone:** Gastrin is released from the antral mucosa in response to the presence of digestive products of meat. Gastrin promotes the secretion of acidic gastric juices from gastric glands located on the inside surface of the body and fundus of the stomach. Gastrin also increases the activity of the pyloric pump and motor stomach function (moderate effect) and probably promotes stomach emptying.

Duodenal Factors That Inhibit Stomach Emptying

1. Enterogastric Nervous Reflexes from the Duodenum

When food enters the duodenum, multiple nervous reflexes are initiated from the duodenal wall and pass back to the stomach to regulate stomach emptying depending on the volume of chyme in the duodenum.

These duodenal reflexes are mediated by three routes:

(1) Directly from the duodenum to stomach through the enteric nervous system in the gut wall

(2) Through extrinsic nerves that go to the prevertebral sympathetic ganglia and then back through inhibitory sympathetic nerve fibers to the stomach

(3) Through the vagus nerves reflex to the brain stem to inhibit the normal excitatory signals that are transmitted to the stomach through the vagus nerves.

These reflexes inhibit the pyloric pump and increase the tone of the pyloric sphincter thus decreasing stomach emptying.

The duodenal factors that can initiate the enterogastric inhibitory reflexes and inhibit stomach emptying include:

(1) Duodenal distention

(2) Duodenal irritation

(3) Duodenal acidity activates S cells to release Secretin which constricts the antrum

(4) Hyperosmotic chyme in the duodenum

(5) Protein content of the chyme in the duodenum.

(6) Fat (monoglycerides) in the duodenum activates different cells to produce CCK and GIP that delay gastric emptying

2. Hormonal Feedback from the Duodenum Inhibits Gastric Emptying – Role of Fats and the Hormone Cholecystokinin.

- Fat entering the duodenum or acidity of chyme or excess quantities of chyme causes the release of cholecystokinin (CCK), and probably other inhibitory hormones such as secretin and gastric inhibitory peptide, (GIP) from the epithelium of the duodenum and jejunum.

- When released, CCK (and probably secretin and GIP) circulates and inhibit the pyloric pump and increase the tone of the pyloric sphincter thus decreasing stomach emptying. CCK also acts as an inhibitor to block increased stomach motility caused by gastrin.

Summary
Constriction of Pyloric Sphincter

- Hormones
  1. Cholecystokinin (CCK)
  2. Secretin
  3. Glucose-dependent insulinotropic peptide (GIP)
- Sympathetic innervation


Thank You