



MEDICINE 438's

GIT PHYSIOLOGY

LECTURE III: Physiology of the Stomach and
Regulation of Gastric Secretions

EDITING FILE

IMPORTANT

MALE SLIDES

EXTRA

FEMALE SLIDES

LECTURER'S NOTES

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.

Functional Anatomy of the Stomach:

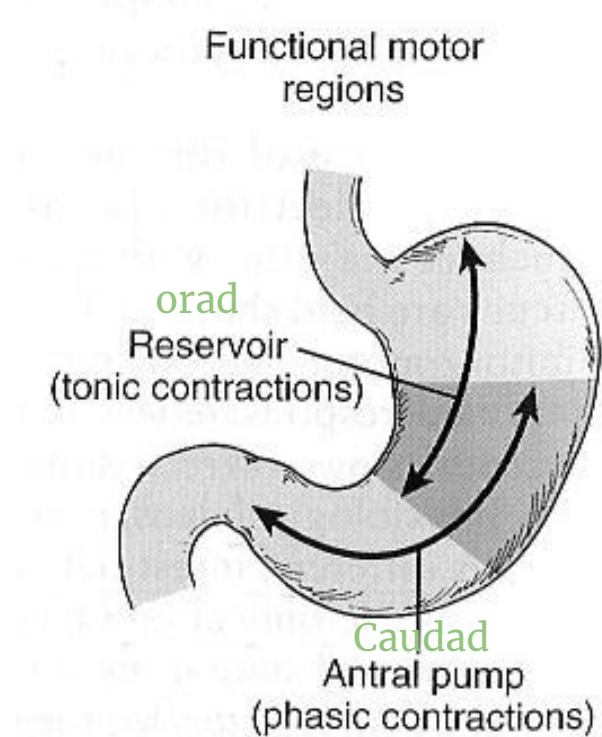
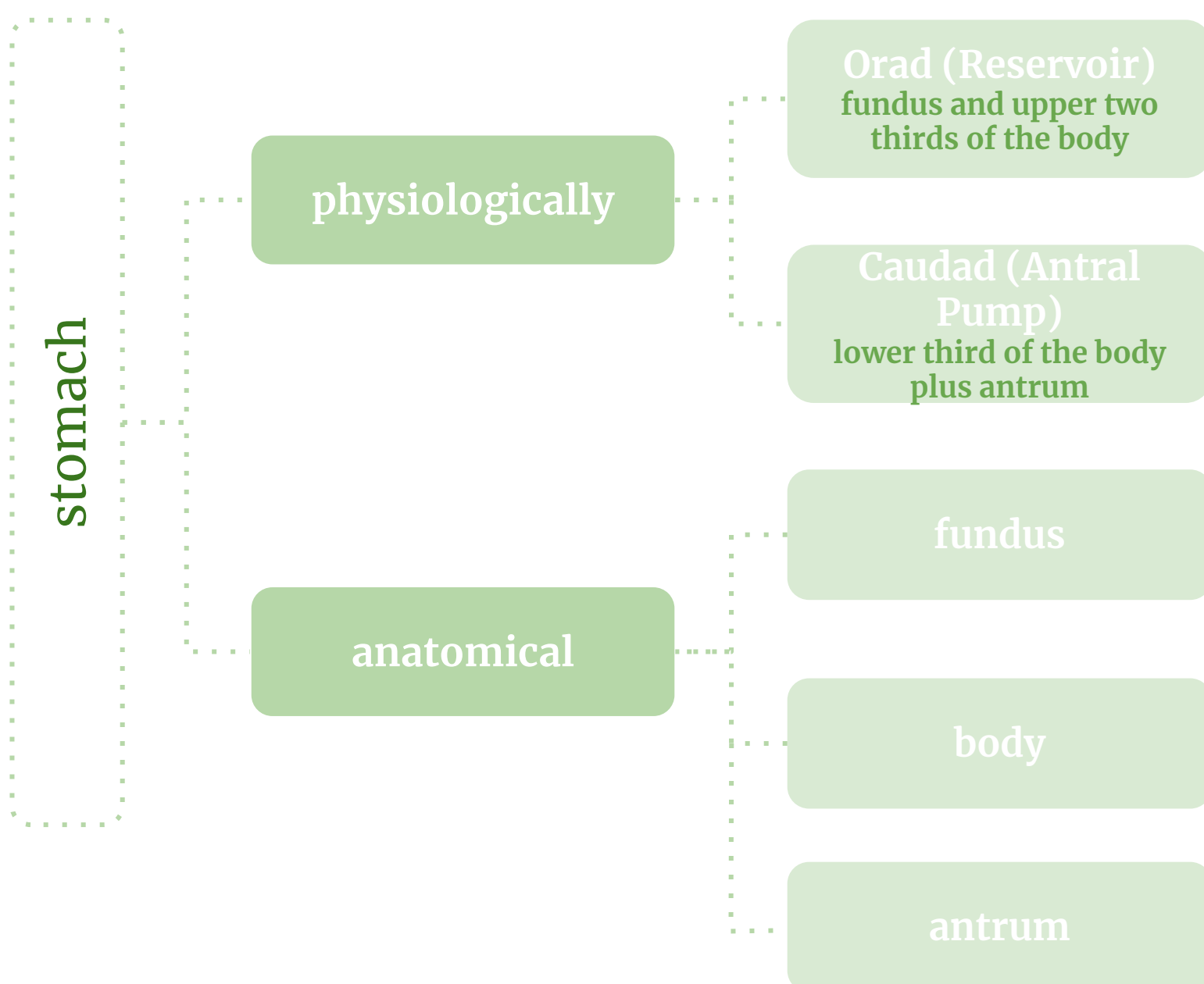


Figure 3-1

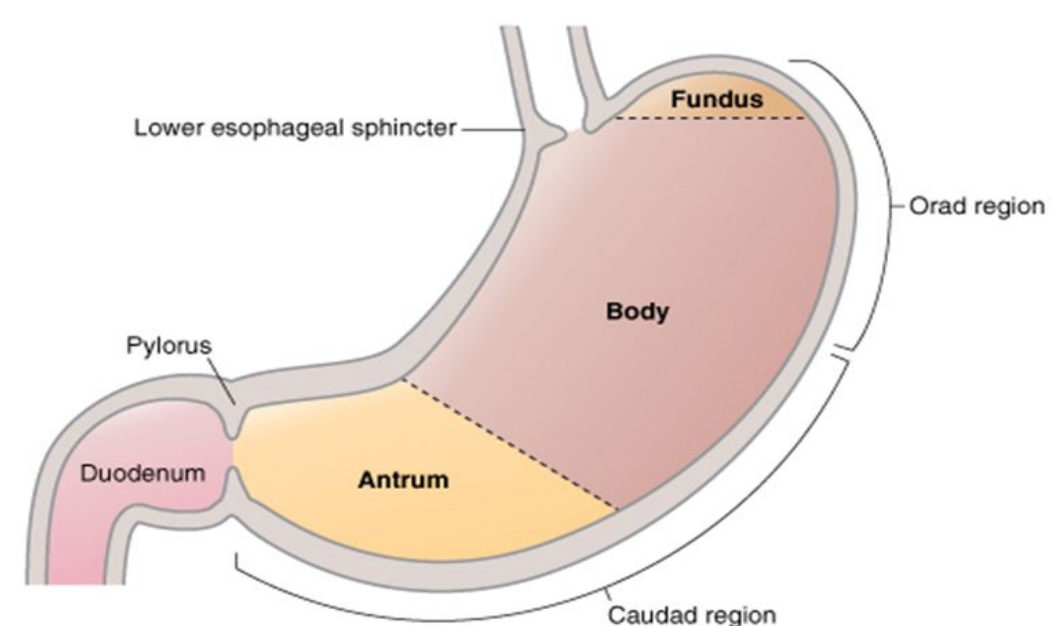


Figure 3-2

- Gastric mucosa is formed of columnar epithelium that is folded into “pits”.
- The pits are the opening of gastric glands.
- There are several types of gastric glands in the stomach and are distributed differentially in the stomach.

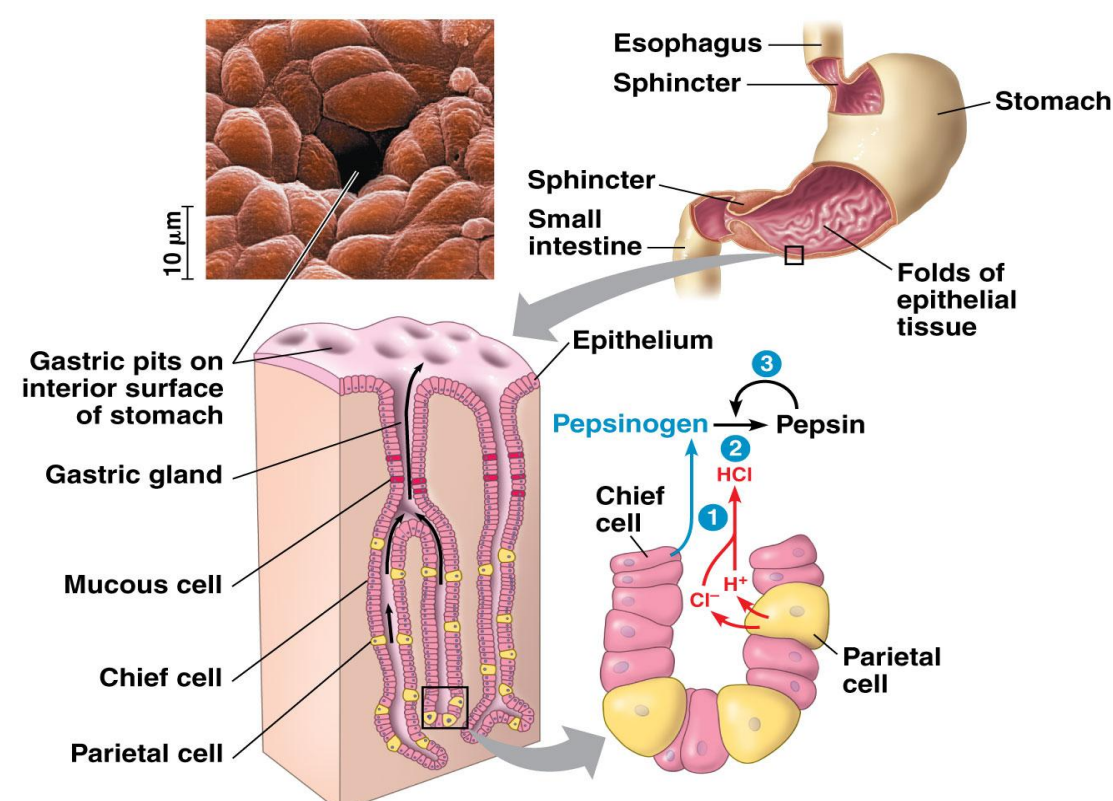


Figure 3-3

Types of Gastric Glands:

	Mucus secreting glands (cardiac glands)	oxyntic(parietal)glands (most abundant glands)	Pyloric glands
Types of cells	-	Mucus neck cells Peptic (Chief) cells Parietal cells (Oxyntic cells)	Many G cells
secrete	Mucus HCO ₃ ⁻	HCl Pepsinogen IF Mucus	Gastrin Mucus
Found in	Cardia	Body & fundus (above the notch) <i>Proximal 80% of stomach</i>	Antrum (below the notch) <i>Distal 20% of stomach</i>

Structure of a Gastric Oxyntic Gland:

- ★ HCl is secreted across the parietal cell microvillar membrane and flows out of the intracellular canaliculi into the oxyntic gland lumen.
- ★ The surface mucous cells line the entire surface of the gastric mucosa and the openings of the cardiac, pyloric, and oxyntic glands.
 - These cells secrete mucus and HCO₃⁻ to protect the gastric surface from the acidic environment of the stomach.

The distinguishing characteristic of a surface mucous cell is the presence of numerous mucus granules at its apex.

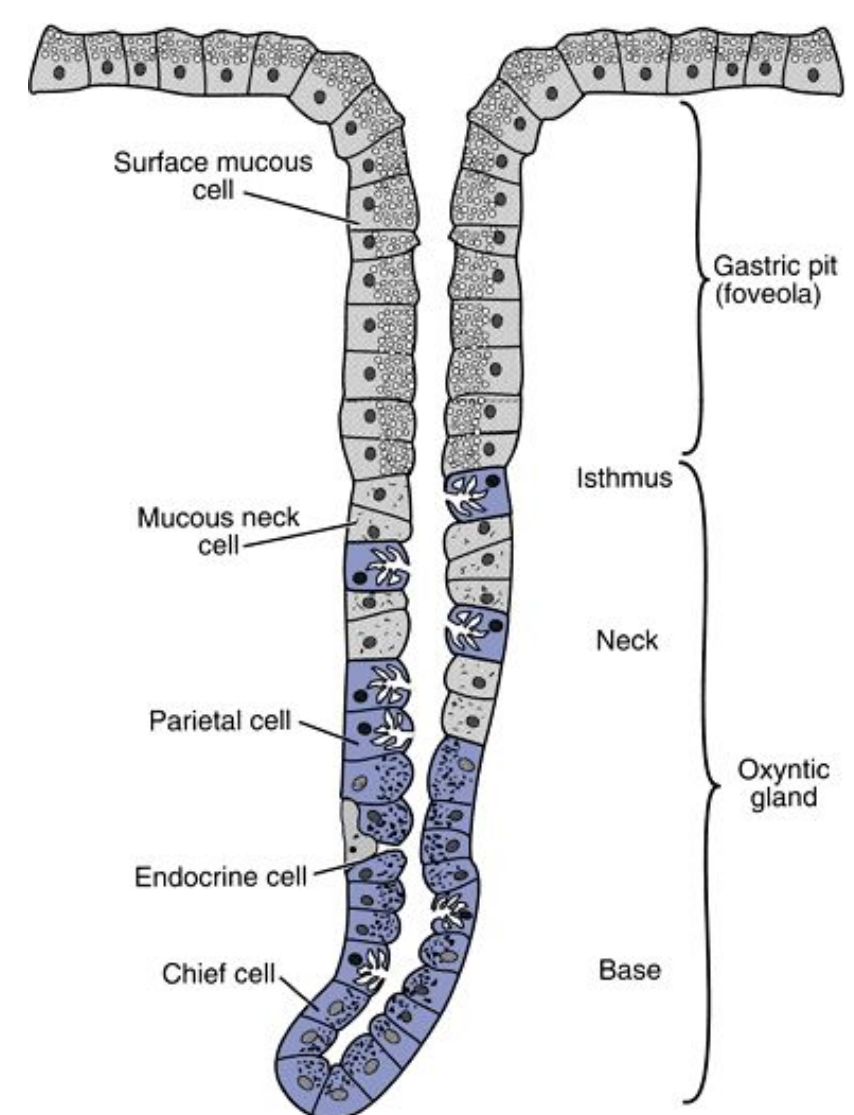


Figure 3-4

Types of Cells Present in Gastric Glands:

Cell type	Secretion	location
Oxyntic (parietal) cell	HCl & IF (intrinsic factor)	Body most distinctive cells in stomach
Peptic (chief) cell	Pepsinogen	Body
Mucus (neck) cells	Mucus, HCO ₃ ⁻	antrum
Enterochromaffin-like cells	Histamine	-
G cells	Gastrin (increases HCl secretion from Parietal cells)	antrum
D Cells (decreases HCl secretion)	Somatostatin	antrum

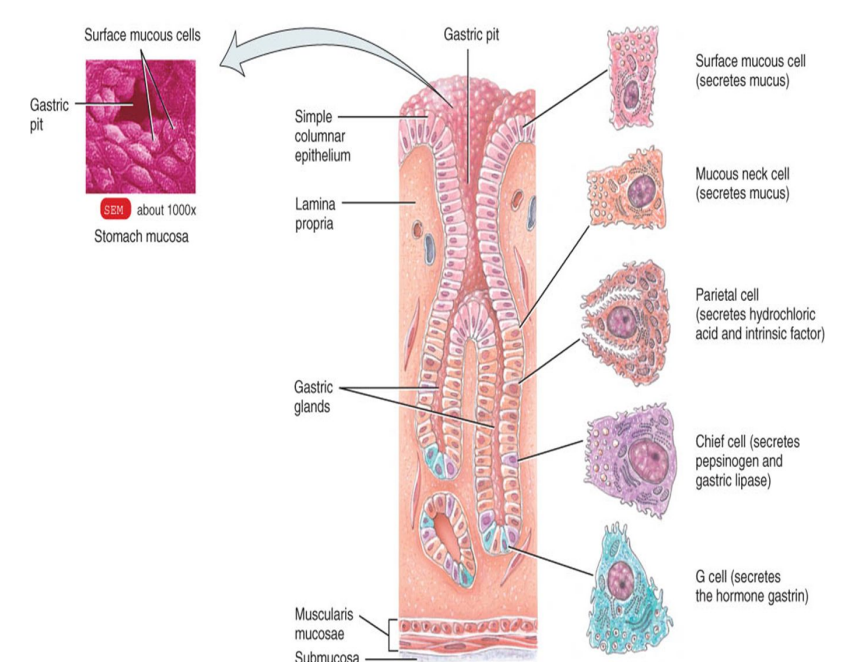


Figure 3-5

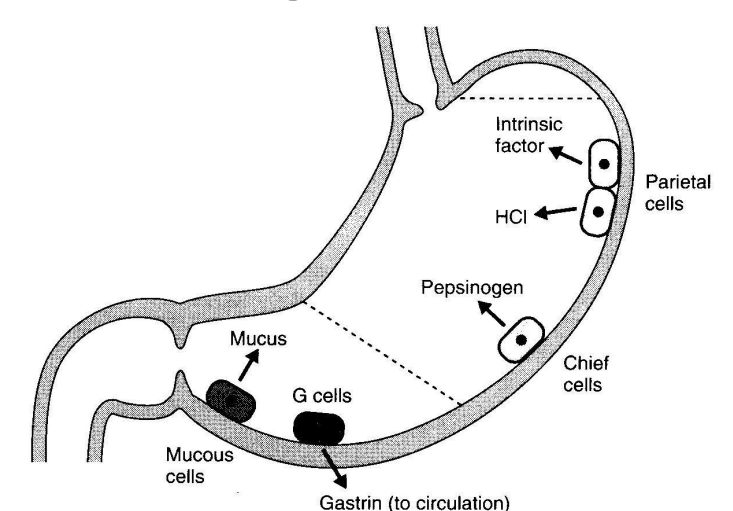


Figure 3-6

Gastric juice is composed of:

- ★ HCL.
- ★ Pepsinogen.
- ★ Electrolytes.
- ★ Intrinsic factor.
- ★ Mucus (mucus gel layer).

Mechanism of HCl Secretion by Parietal Cells:

1. Cl^- is actively transported from the cytoplasm of the parietal cell into the lumen of the canaliculus¹.
2. Na^+ are actively transported out of the canaliculus into the cytoplasm of the parietal cell.
3. Water becomes (because it is a weak acid) dissociated into H^+ and OH^- in the cell cytoplasm. The H^+ are then actively secreted into the canaliculus in exchange for K^+ .
4. 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 HCO_3^- .
5. HCO_3^- then diffuse out of the cell cytoplasm into the extracellular fluid in exchange for Cl^- that enter the cell.

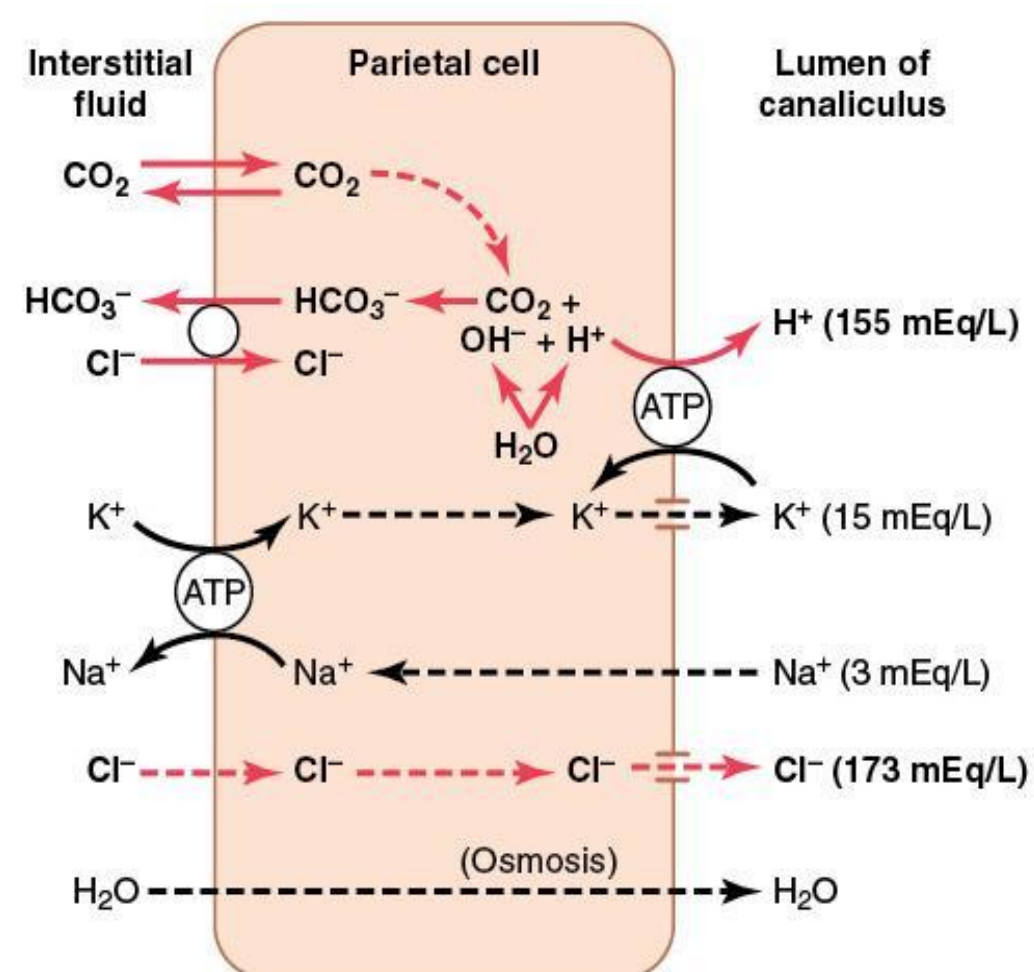


Figure 3-7

Mechanism of HCl production:

- ★ Depends on H/K ATPase. (H/K ATPase pump depends on [K]out)
- Inhibited by: omeprazole
- ★ [HCl] drives water into gastric content to maintain osmolality
- ★ During gastric acid secretion: amount of HCO_3^- in blood = amount of HCl being secreted
- ★ Alkaline tide¹.

Control of HCL secretion :

HCL secretion control

Neural

direct

Ach act on parietal cells → increases HCL secretion

indirect

Act on G cells by releasing **Gastrin releasing peptide (GRP)** → secrete gastrin which act on CCK_B receptor⁴ of parietal cells → increases HCL secretion

Hormonal

Gastrin
(Endocrine secretion)³

Act on **enterochromaffin like cells (ECL)** which secrete histamine → act on H_2 receptor of parietal cell → increases HCL secretion.

Paracrine

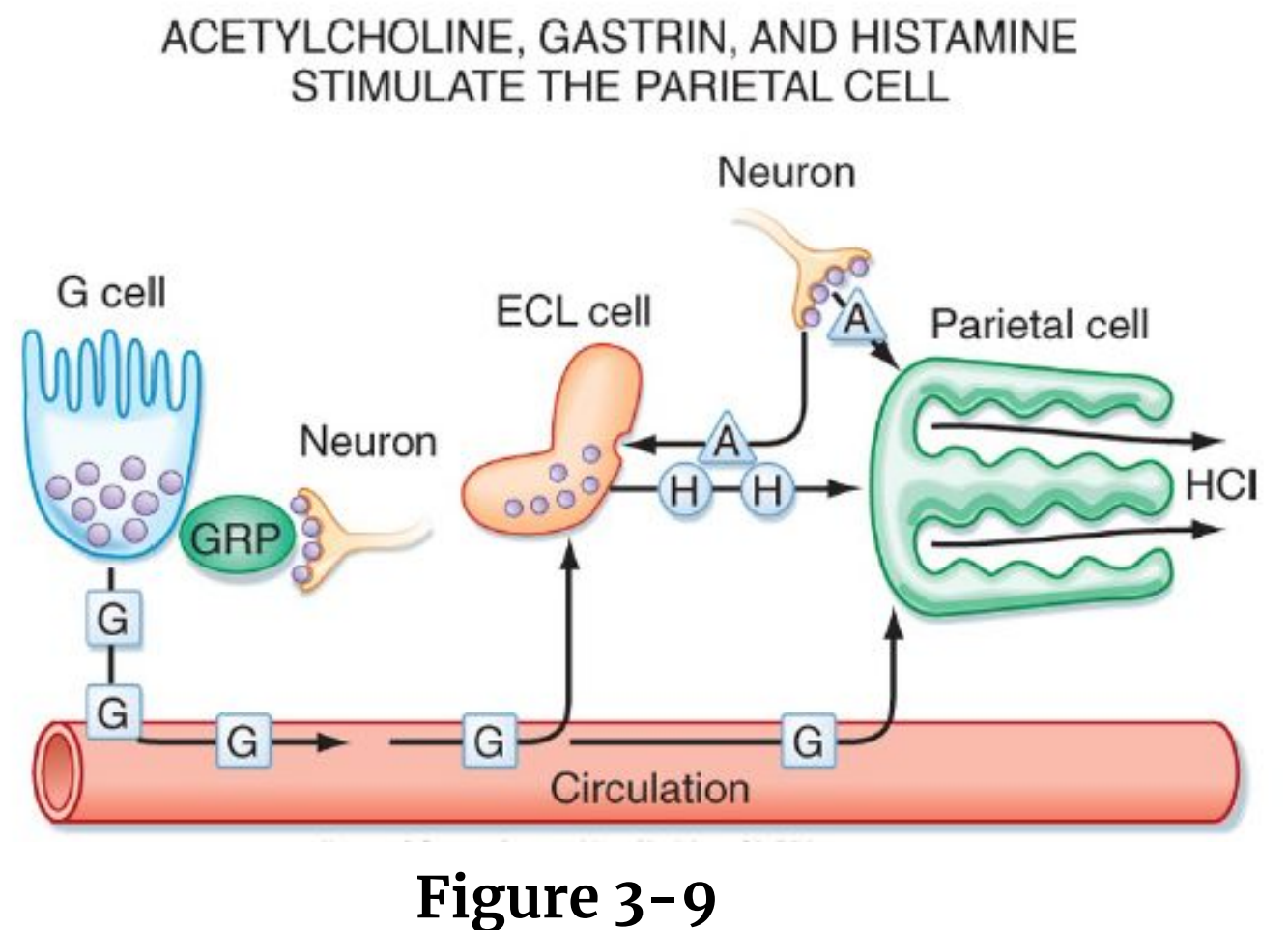
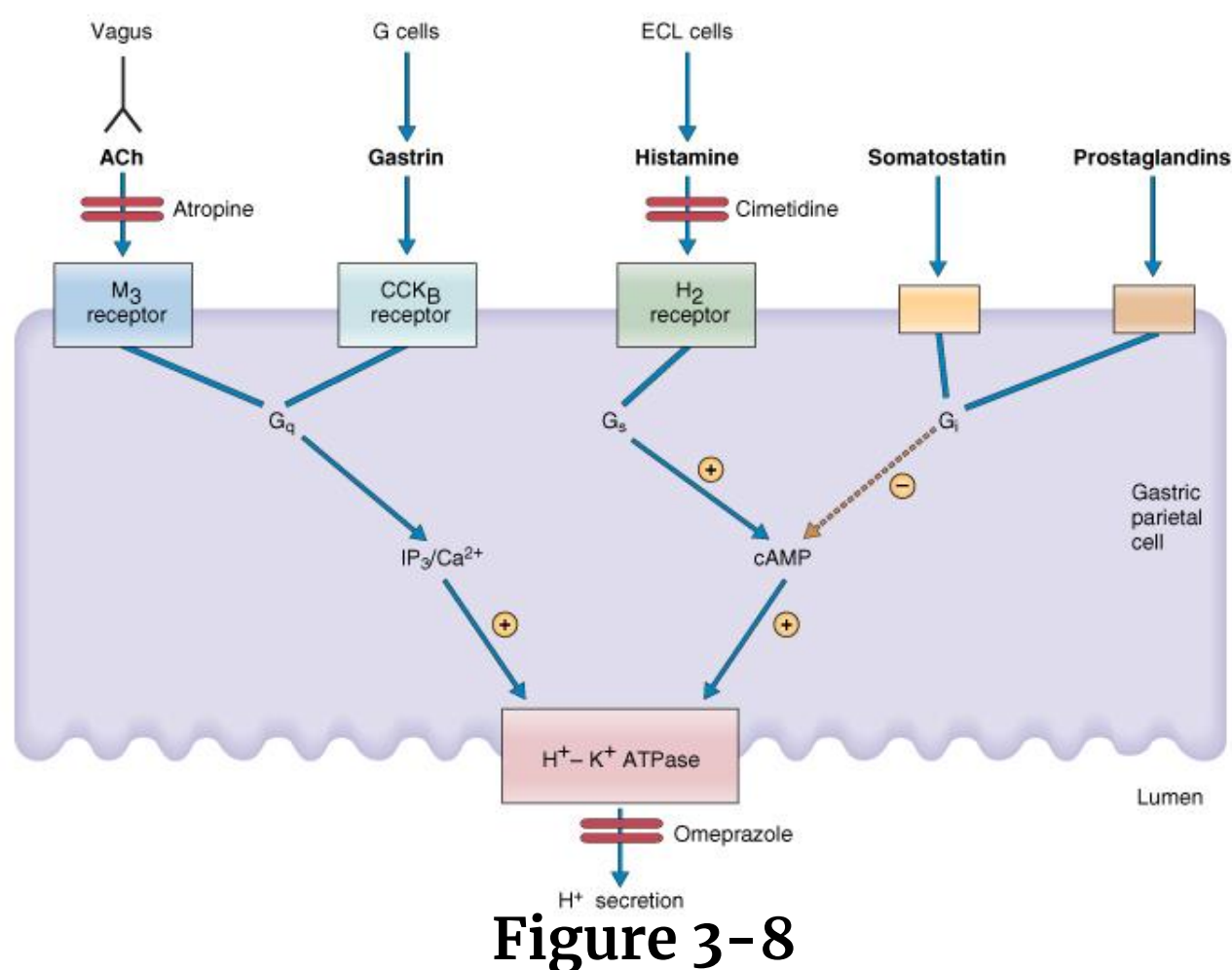
histamine

Histamine activate H_2 receptor on parietal cells thus increase HCL secretion.

H_2 blockers are used for the treatment of peptic ulcer disease or gastroesophageal reflux disease. (e.g. Cimetidine)

FOOTNOTES

1. A canaliculus is an adaptation found on gastric parietal cells. It is a deep infolding, or little channel, which serves to increase the surface area, e.g. for secretion.
2. **Alkaline tide** refers to a condition, normally encountered after eating a meal, where during the production of hydrochloric acid by parietal cells in the stomach, the parietal cells secrete bicarbonate ions across their basolateral membranes and into the blood, causing a temporary increase in pH.
3. Forms of chemical signaling:
 - Autocrine: act on the cells which produce them, e.g. cytokines.
 - Paracrine: act on the cells that are in close proximity to the cells that produce them, e.g. histamine.
 - Endocrine: a cell target a distant cell through the bloodstream
4. Gastrin can act on CCK receptors because they are members of the same family of peptide hormones known as the gastrin family.



Other Gastric Secretions-Mucus:

- Bicarbonate rich mucus layer protects the stomach mucosa. (Mucus is a protein, so it needs to be produced continuously because it gets degraded by pepsin).

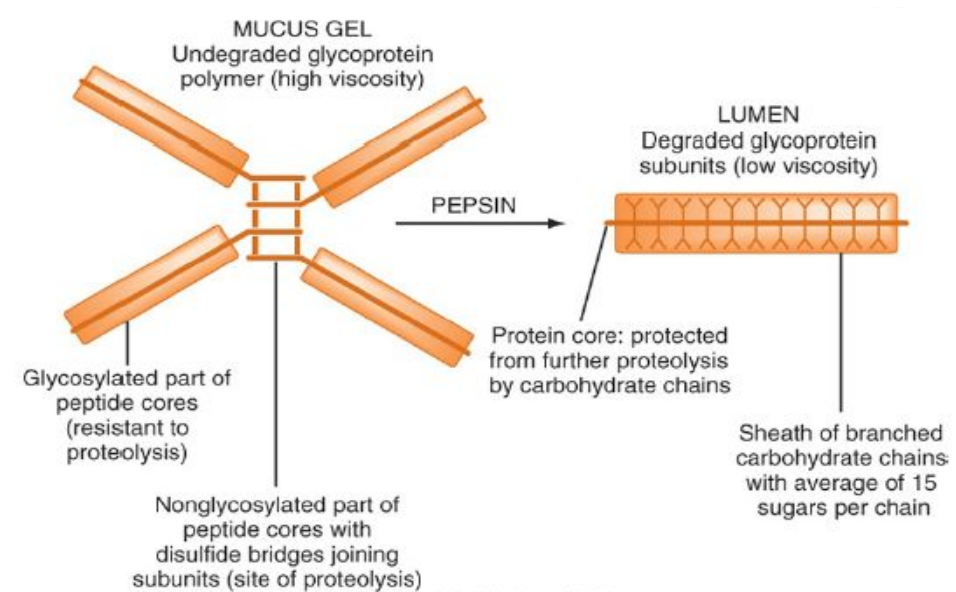


Figure 3-10

Other Gastric Secretions-Pepsin:

- Several types of pepsinogen secreted from chief cells. They are activated by HCl into pepsin and once activated, they can activate more pepsinogen. These amino acids or peptides activate G cells to secrete Gastrin thus increasing HCL secretion.
- The optimum pH is (1.5-3.5) (1.8-3.5).
- Pepsin breaks down proteins into peptones & polypeptides.
- pH > 5 inactivates pepsin
- Pepsinogen secretion is stimulated by Ach, acid, gastrin, secretin & CCK.

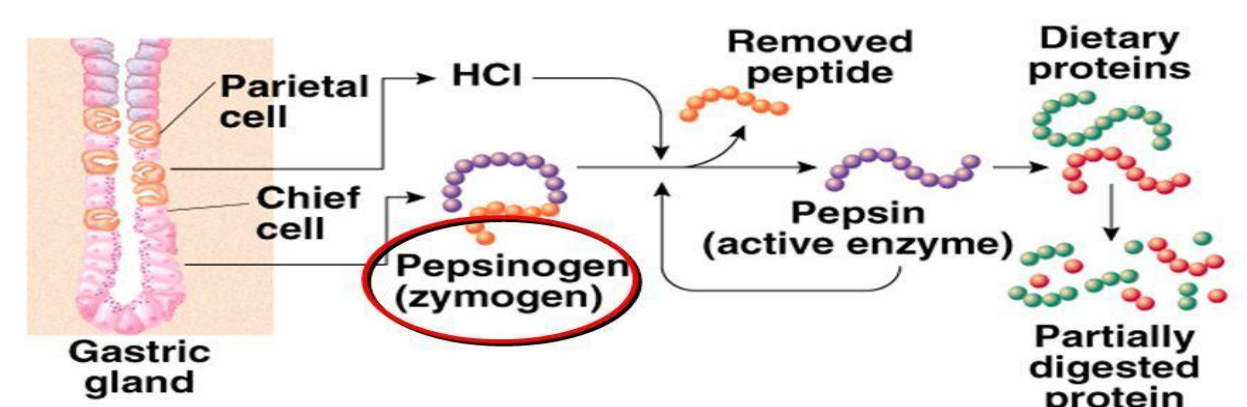


Figure 3-11

Other Gastric Secretions-Intrinsic Factor:

- It is a glycoprotein secreted by parietal cells.
- It is the only essential function of stomach as it is essential for vitamin B₁₂ absorption.
- Atrophy of gastric mucosa leads to pernicious anemia.

The Rate of Secretion Modify the Composition of Gastric Juice:

- At a low secretion rate, gastric juice contains high concentrations of Na^+ and Cl^- and low concentrations of K^+ and H^+ .
- When the rate is increased:
 - Na^+ concentration decreases.
 - H^+ concentration increases significantly.
 - Cl^- concentration increases.
- Gastric juice is derived from the secretions of **two major sources**:
- ★ **Parietal cells**: its secretion (HCl secretion) contributes mainly to the changes in electrolyte composition with higher secretion rates.
- ★ **Nonparietal cells**: constant secretion, thus having little contribution to the electrolyte changes

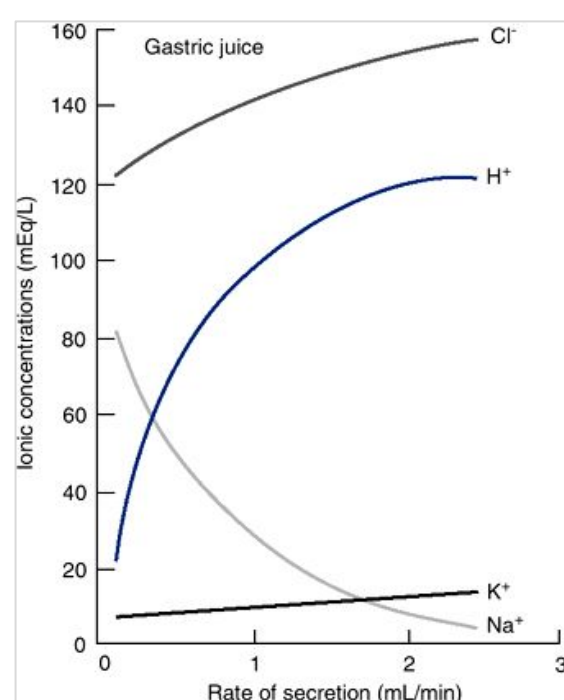


Figure 3-12

- Low secretion rate (between meals): high NaCl .
- High secretion rate (after a meal): high HCl .
- Always isotonic.

Salivary secretion is the opposite (at high secretion rates there is high NaCl concentration)

Gastric Secretion Phases :

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

1 Cephalic phase

- 30% of HCl is secreted in this phase.
- Before food arrives at stomach.
- Stimuli → (Smelling, taste, Chewing and swallowing).
- Mechanism:
 - ★ CNS send impulses via the vagus nerves, The nerve endings release ACh , which directly stimulates acid secretion from parietal cells.
 - ★ CNS send impulses via the vagus nerves, nerves also release gastrin-releasing peptide (GRP), which stimulates G cells to release gastrin, indirectly stimulating parietal cell acid secretion.

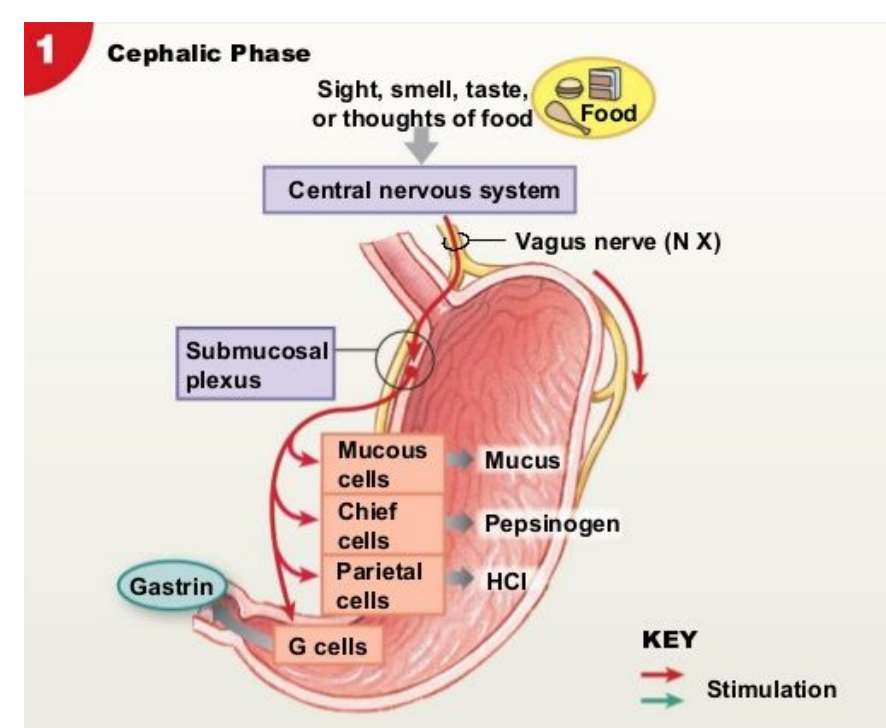


Figure 3-13

2 Gastric phase

- 60% of HCl is secreted in this phase.
- when food enters the stomach.
- Stimuli → (distention, amino acid, small peptides).
- Mechanism:
 - ★ **Distention of the stomach stimulates mechanoreceptors**, which stimulate the parietal cells directly through short local (enteric) reflexes and by long vago-vagal reflexes.
 - ★ **Digested proteins in the stomach are also potent stimulators of gastric acid secretion**, an effect mediated through gastrin release. Several other chemicals, such as alcohol and caffeine, stimulate gastric acid secretion through mechanisms that are not well understood.

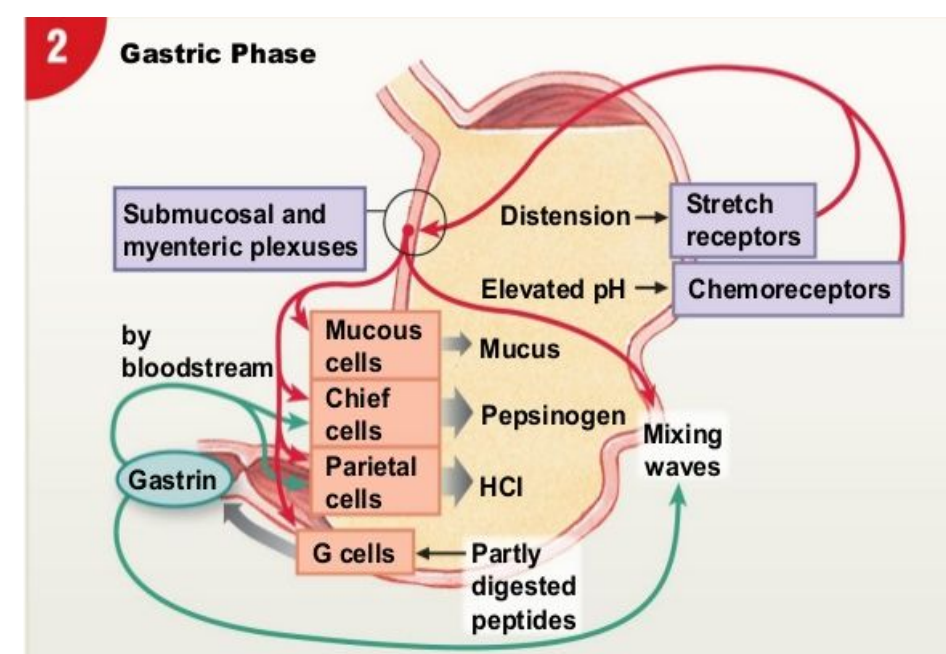


Figure 3-14

3 intestinal phase

- 10% of HCL is secreted in this phase.
- when chyme enters duodenum.
- Stimuli → (protein digestion products in the duodenum).
- Mechanism :-
 - protein digestion products in the duodenum stimulate gastric acid secretion through the action of the circulating amino acids on the parietal cells.
 - Distention of the small intestine, probably via the release of the hormone entero-oxyntin from intestinal endocrine cells, stimulates acid secretion.

- **Inhibitory hormones (Enterogastrones):**

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

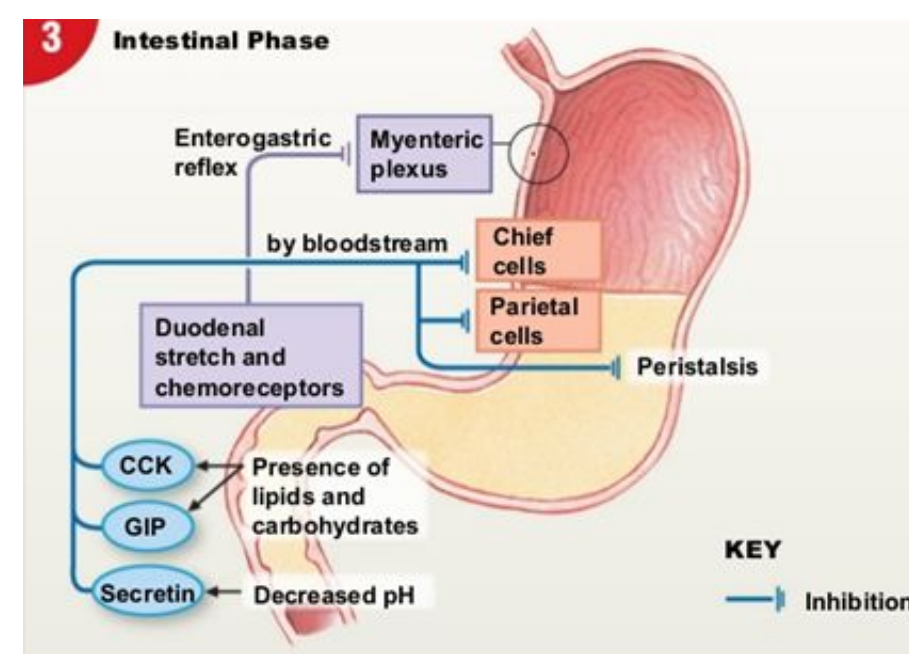


Figure 3-15

Hormones summary :

Hormone	Site of Secretion	Stimuli for Secretion	Actions
Gastrin	G cells of the: → Antrum → Duodenum → jejunum	★ Protein ★ Distention of the stomach ★ Vagal stimulation ★ Gastrin releasing peptide (GRP) (Acid inhibits release)	Stimulates: - Gastric H ⁺ secretion - Growth of gastric mucosa
Cholecystikinin (CCK)	I cells of the: → Duodenum → Jejunum → ileum	★ Protein ★ Fatty acids ★ Acids	Stimulates: - Pancreatic enzyme secretion - Pancreatic HCO ₃ ⁻ secretion - Gallbladder contraction - Growth of the exocrine pancreas - Relaxation of the sphincter of Oddi Inhibits: Gastric emptying
Secretin	S cells of the: → Duodenum → jejunum → ileum	★ Acids ★ Fat (in the duodenum)	Stimulates: - Pepsin secretion - Pancreatic HCO ₃ ⁻ secretion - Biliary HCO ₃ ⁻ secretion - Growth of the exocrine pancreas Inhibits: Gastric H ⁺ secretion
Glucose-Dependent Insulinotropic Peptide (GIP)	K cells of the: → Duodenum → jejunum	★ Protein ★ Fatty acids ★ Oral glucose	Stimulates: Insulin secretion from pancreatic β cells Inhibits: Gastric H ⁺ secretion
Motilin	M cells of the: → duodenum → jejunum	★ Fat ★ Acid ★ Nerve	Stimulates: Gastric motility Intestinal motility

Function Of Stomach Movement:

1 Storage of food:

- When the stomach is stretched by food, 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 which allows storage. Stomach can store 0.8–1.5 L of food.
- Gastric contents may remain unmixed for 1 hour in the corpus (body of stomach).
- The pressure in the stomach remains low until the volume reaches ~1.5 L of food. This function is regulated by Relaxation Reflexes:

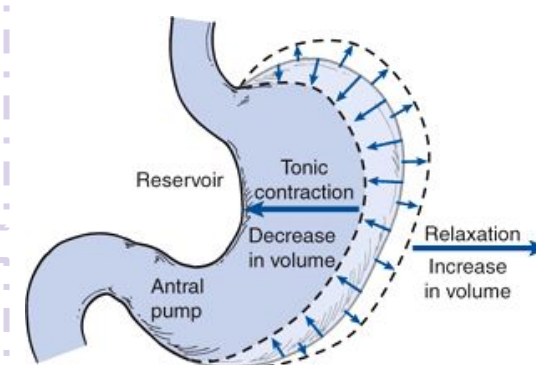
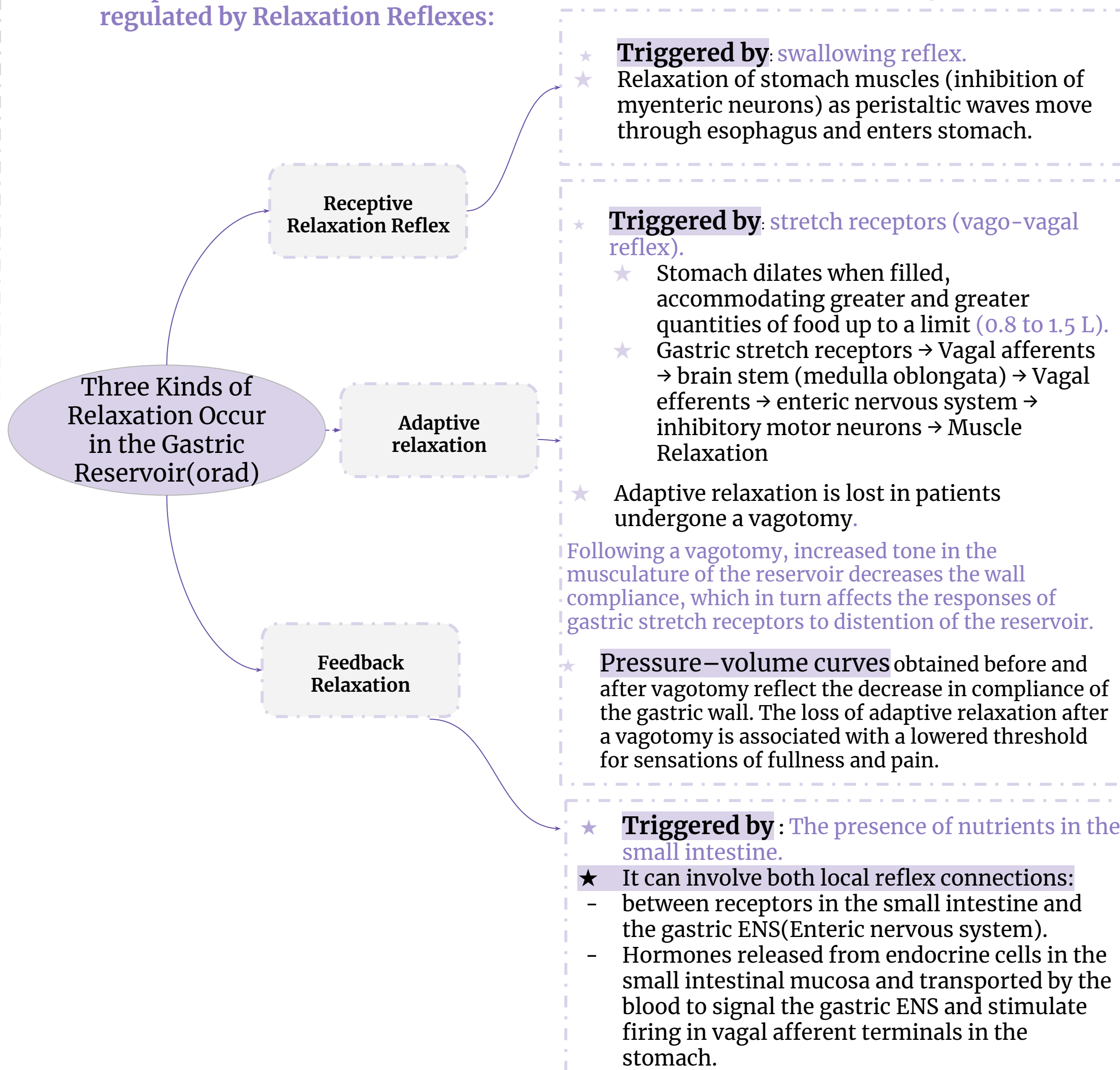


Figure 3-16

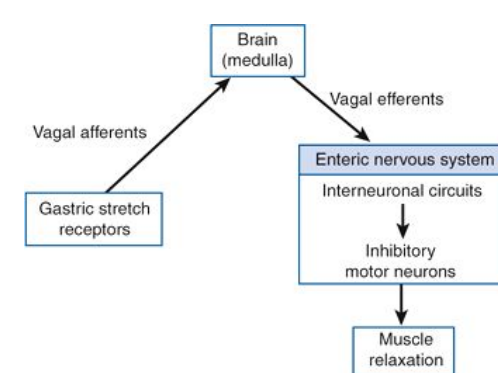


Figure 3-17

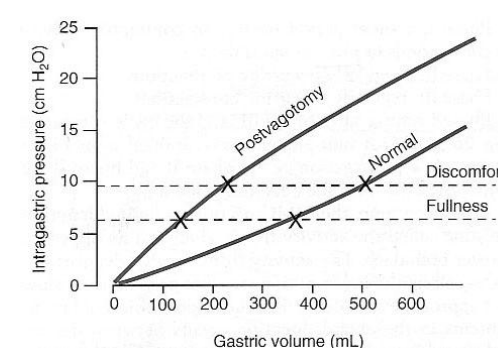


Figure 3-18

2 Mixing Of Food :

- ★ Major mixing activities take place in the antrum (antral pump region, phasic contraction).
- ★ The Basic Electrical Rhythm of the Stomach Wall. The digestive gastric juices come in contact with the food lying against the mucosal surface of the stomach.
- ★ The presence of food causes weak peristaltic constrictor waves called mixing/constrictor waves once every 15–20 seconds. It's initiated by the basic electrical rhythm of the slow spontaneous electrical waves of the gut wall.
- ★ 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.
- ★ Retropulsion results when it move against a tight pylorus.

3

Regulate emptying of the chyme from the stomach into the small intestine (duodenum):

- ★ Chyme is a murky semi-fluid or paste composed of food that is thoroughly mixed with gastric secretions.
- ★ Movement of chyme into duodenum is achieved by "Pyloric pump"

Each time a peristaltic wave passes from the antrum to the pylorus, few millimeters of antral content move into the duodenum through the pyloric sphincter.

4

Hunger Contraction:

- ★ Rhythmical peristaltic contractions that can become very strong and fuse to form a continuing tetanic contraction lasting sometimes 2-3 minutes.
- ★ It's intense in young healthy people and **increase by** low blood glucose levels.
- ★ Hunger pain can begin after 12-24 hr of last food ingestion.

5

The main functions of the upper part of the stomach (Reservoir part):

- ★ To maintain a continuous compression.
- ★ To accommodate the received food without significant gastric wall distention or pressure (Storage of food).

6

Absorption of water and a few highly-lipid soluble substances (alcohol and Aspirin):

Stomach is a poor absorptive area of GIT:

- ★ It lacks the villous type of absorptive membrane.
- ★ It has tight junctions between epithelial cells.

Retropulsion Phenomena:

As the trailing contraction (explained in the next page) approaches the closed pylorus, the gastric contents are forced into an antral compartment of ever-decreasing volume and progressively increasing pressure.

Results in

Jet-like retropulsion through the orifice formed by the trailing contraction (discussed in the next page). Repetition at 3 cycles/min reduces particle size to the 1-mm to 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 to 50-70 cm of H₂O (compared to a pressure of ~10 cm of H₂O during the mixing peristaltic contractions).

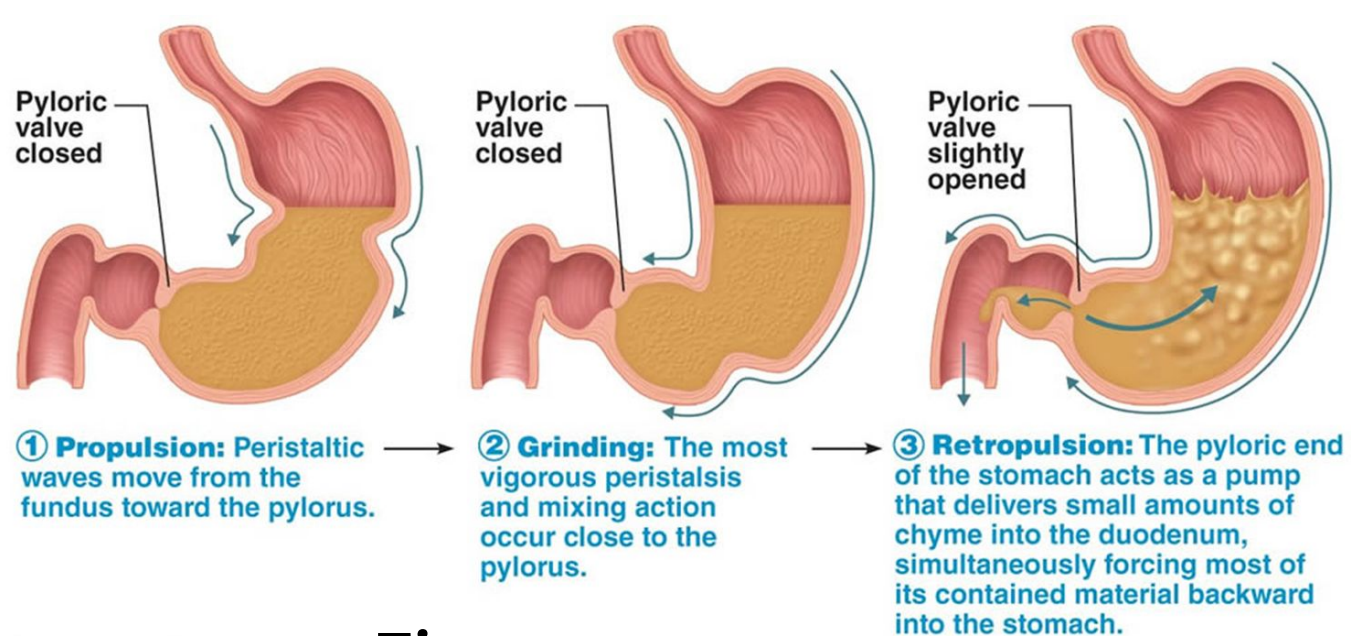


Figure 3-19

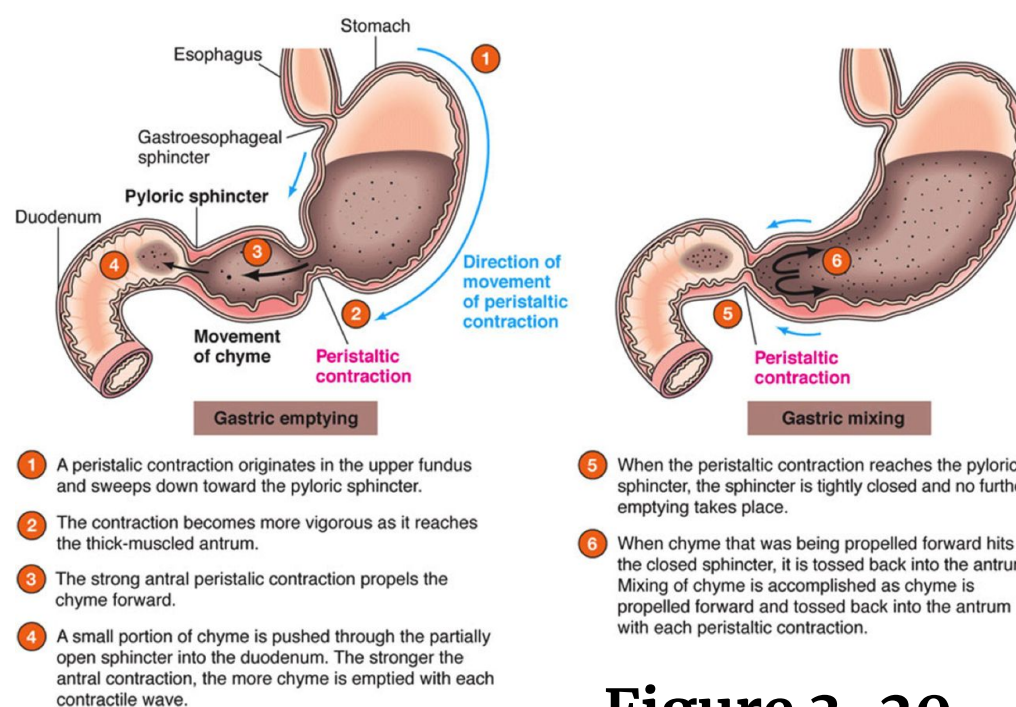


Figure 3-20

Motor Behavior of the Antral Pump Is Initiated by a Dominant Pacemaker (Motility in the Antrum):

- Gastric action potentials determine the duration and strength of the phasic contractions of the antral pump.
- They are initiated by a dominant pacemaker (ICC) (interstitial cells of Cajal).

1

The action potentials (AP) propagate rapidly around the gastric circumference and trigger a ring-like contraction

2

The AP 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 from the pacemaker site to the gastroduodenal junction.
- The pacemaker region in humans generates AP and associated antral contractions at a frequency of three per minute.
- The gastric action potential lasts about 5 seconds, it has:

- ★ Rising phase (depolarization)
- ★ Plateau phase
- ★ Falling phase (repolarization)

- Electrical action potentials in gastrointestinal muscles occur in four phases, determined by specific ionic mechanisms:

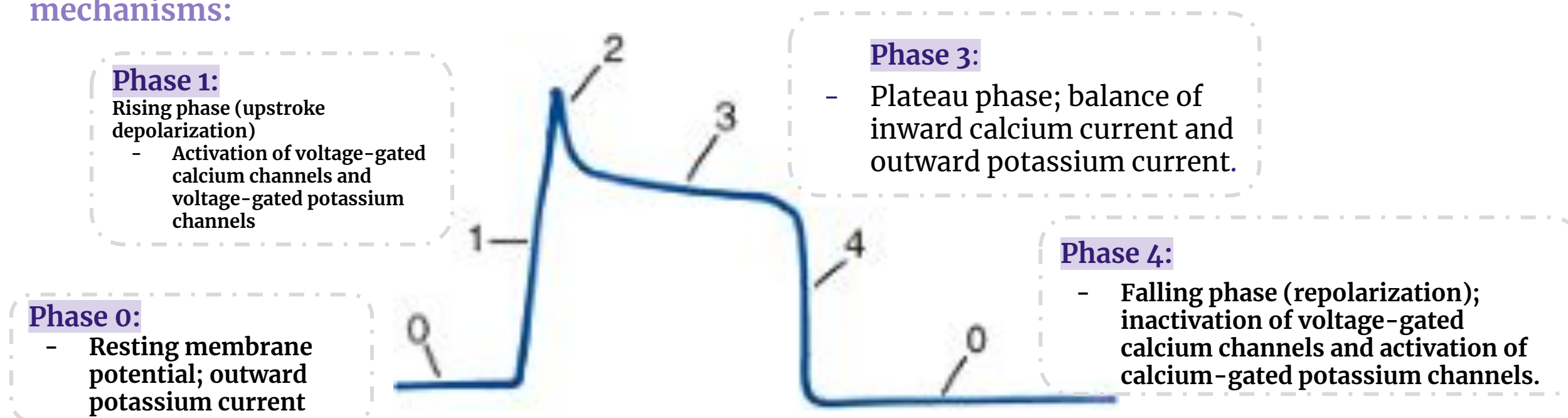


Figure 3-21

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:

Leading contraction

- ★ It has a relatively constant amplitude.
- ★ Associated with the rising phase of the action potential.

Trailing contraction

- ★ Variable amplitude
- ★ Associated with the plateau phase.

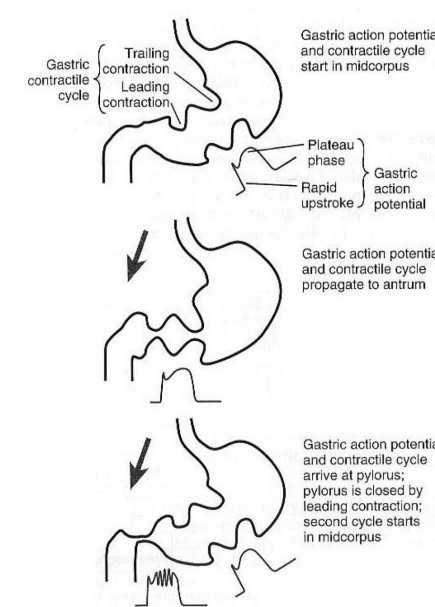


Figure 3-22

- The leading contractions have negligible amplitude as they propagate to the pylorus. As the rising phase reaches the terminal antrum and spreads into the pylorus, contraction of the pyloric muscle closes the orifice between the stomach and duodenum.
- The trailing contraction follows the leading contraction by a few seconds.

Stomach emptying:

- ★ Stomach emptying is the result of intense peristaltic antral contractions against resistance to passage of chyme at the pylorus.
- ★ **The pyloric sphincter** is characterized by strong circular muscle (as compared to the antrum) and remains tonically contracted most of the time. However, during pyloric constriction, watery chyme can still pass through the pylorus into the duodenum, but not food particles.
- ★ Pyloric constriction is determined by:
 - Nervous reflex signals
 - Humoral reflex signals (from the duodenum and stomach).
- ★ The rate of stomach emptying is controlled by signals from the stomach and duodenum, with the latter being far stronger and controls emptying of the chyme at a rate that allows the proper digestion and absorption in the small intestines.

Factors that regulate gastric emptying:

Gastric Factors that Promote Stomach Emptying

Powerful Duodenal Factors That Inhibit Stomach Emptying.

1 Effect of Gastric Food Volume on Rate of Stomach Emptying.

- Increased gastric food volume → increased stretch in the stomach wall (which elicits local myenteric reflexes) → increased pyloric pump activity & the tonic contraction of the pyloric sphincter gets inhibited, leading to increased stomach emptying.

2 Effect of the Hormone Gastrin on Stomach Emptying.

- Gastrin is released from the antral mucosa in response to the presence of digestive products of meat.
- It promotes the secretion of acidic gastric juices (e.g. HCl) by the stomach gastric glands (or oxyntic glands) located on the inside surface of the body and fundus of the stomach; (i.e. proximal 80% of the stomach).
- It also enhances the activity of the pyloric pump and motor stomach function (moderate effect) and probably promotes stomach emptying.

Factors that regulate gastric emptying:

Gastric Factors that Promote Stomach Emptying

Powerful Duodenal Factors That Inhibit Stomach Emptying.

1 Inhibitory Effect of 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:

- ★ Directly from the duodenum to stomach through the **ENS** (enteric nervous system) in the gut wall.
- ★ Through extrinsic nerves that go to the prevertebral sympathetic ganglia and then back through inhibitory sympathetic nerve fibers to the stomach.
- ★ Through the vagus nerves reflex (to a slight extent) → the brain stem → 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 include:

- Duodenal **distention**.
- Duodenal **irritation**.
- Duodenal **acidity**.
- **Osmolality of the chyme** in the duodenum.
- **Protein** (and may be fat) content of the chyme in the duodenum.

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** (probably a receptor mediated mechanism) **the release of:**
- ★ **cholecystokinin (CCK)** , acts as an inhibitor to block increased stomach motility caused by gastrin.
- ★ other inhibitory hormones such as (**secretin** and gastric inhibitory peptide (**Glucose-dependent insulinotropic peptide GIP**) from the epithelium of the duodenum and jejunum.)

Release of CCK, secretin, and GIP: they circulate and inhibit the pyloric pump and increase the tone of the pyloric sphincter thus decreasing stomach emptying.

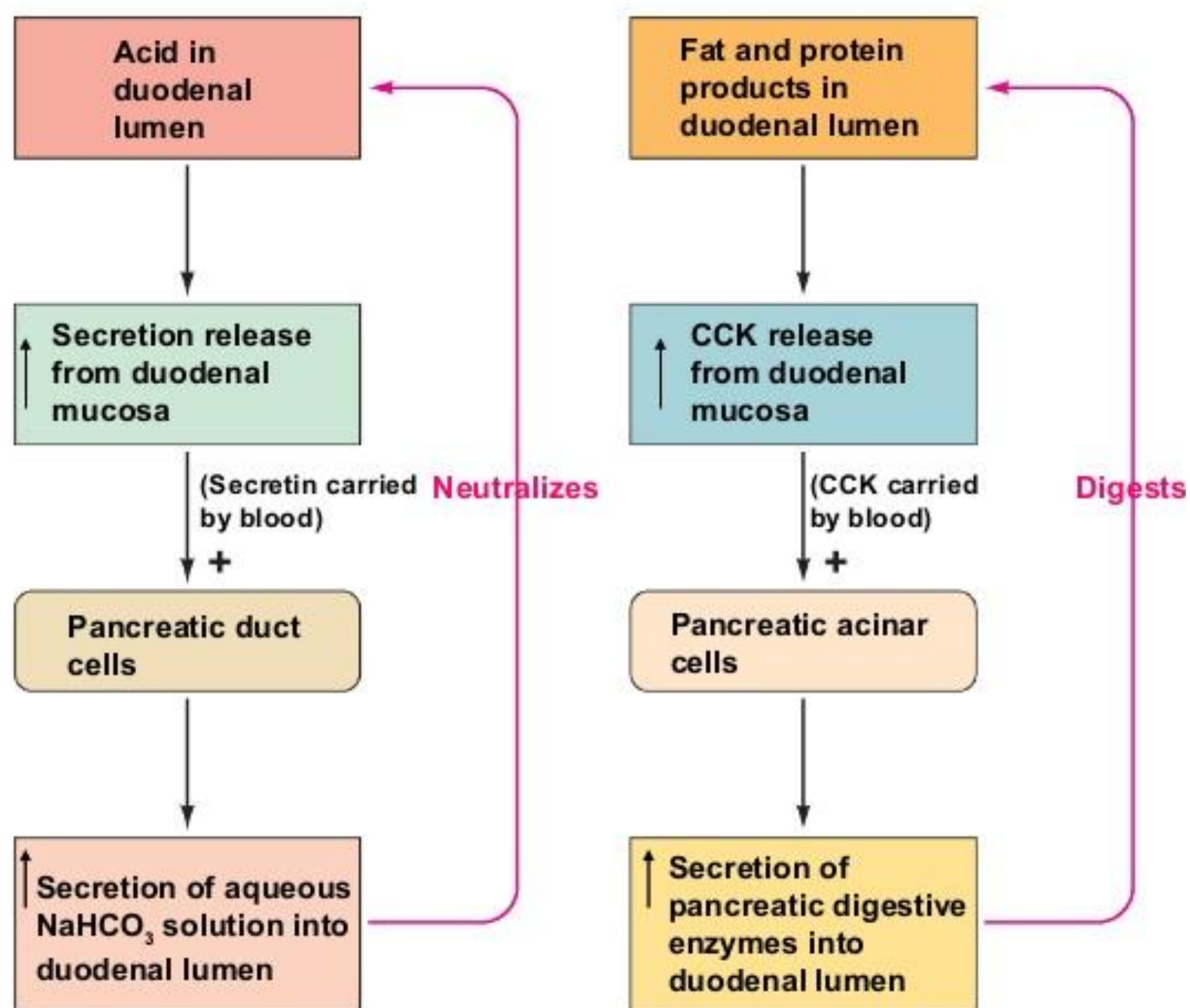


Figure 3-23

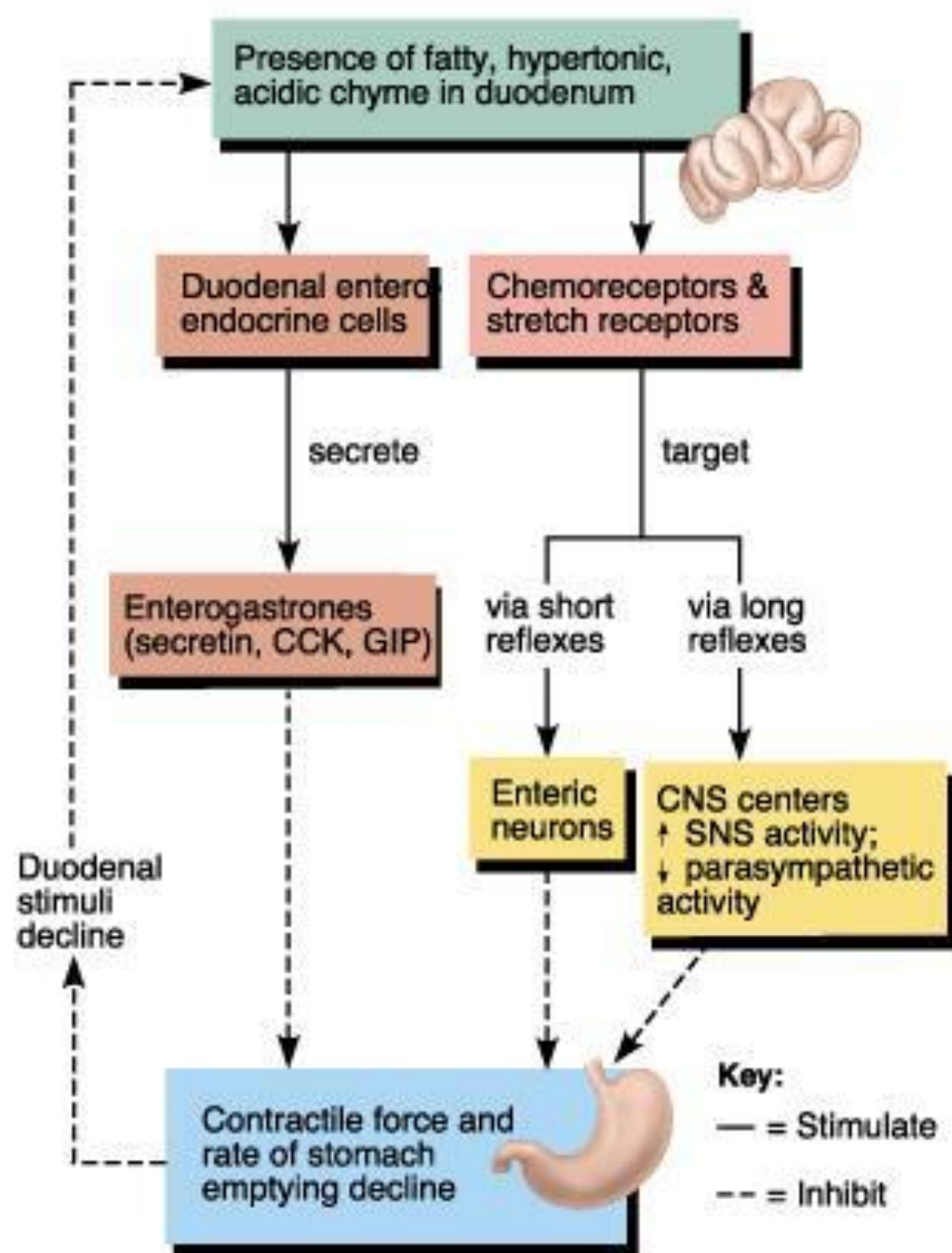


Figure 3-24

FURTHER READINGS

What triggers gastric emptying? The difference between mixing and emptying contractions

- **Action potentials** originate in a region in the body of the stomach, the ICC, which spreads downwards towards the duodenum.
- The rate of firing of ICC is three per minute in the region of the stomach, it is always constant and is not affected by neural or hormonal control.
- **Differences in patterns of contractions (mixing or emptying) seen at different times shouldn't be attributed to frequency of slow waves, since it is always constant**, the differences then must be determined by differences in the intensity of action potential (generated at the peaks of slow wave potentials) which will generate different types of movements.
- The higher the positivity (in millivolts) and the more intense the action potential which will result in a stronger contraction, excitatory signals (hormones, neurotransmitters) cause positive ion influx, and increase the positivity.
- **Mixing contractions:** Usually the movements are of the mixing type, the slow waves of ICC are always generated, however *mixing movements only occur if these slow waves were compounded with excitatory signals triggered most commonly by gastric distension due to the presence of food (mechanoreceptors that stimulate ENS to release ACh, serotonin or substance P and cause contraction of SMCs).*
- **Emptying contractions:** We know that there is a rising wave of a constant amplitude and a plateau phase of a variable amplitude, therefore *any change in the action potential's intensity must be due to signals superimposed on the plateau phase, since the contraction during the rising phase (leading contraction) is always constant, therefore the changes affect the plateau phase and causes the action potential to become more intense.* And in turn causes the mixing movement to be a stronger, emptying movement. With the circular muscles of the stomach generating much higher pressure inside the stomach.
- These excitatory signals that increase the intensity plateau phase can be neurotransmitters, like ACh, serotonin triggered by gastric distension. Or due to lack of inhibitory control, as we know, CCK and Secretin are released in the presence of nutrients in the duodenum and they can inhibit gastric emptying by decreasing the intensity of the plateau phase, therefore the emptying movement remain as mixing movements. This is why hunger contractions are intense and resemble emptying contractions, the duodenum during emptying contractions exerts way less inhibitory effect (through CCK or ENS) on gastric motility (plateau phase).
- In short, there are two types of movement. Mixing, which is triggered by the presence of food and generates enough intensity in the plateau phase to accommodate mixing movements, and emptying movements, which is caused by an increase in the intensity of plateau phase due to lack of inhibitory control (CCK, which can decrease action potential intensity, it binds to nerve endings and causes presynaptic inhibition) or an increase in an excitatory input (vagus nerve due to distension) and prevents the entry of food into a busy small bowel.

QUIZ



1. The gastric motility is stimulated by:
A) Cholecystokinin
B) Distention of the stomach
C) Secretin
D) Peptide YY
2. Histamine stimulates acid secretion by binding with which of the following receptors on parietal cells?
A) CCK-B receptors
B) H₂ receptors
C) H₁ receptors
D) M₃ receptors
3. Pepsinogen is converted to pepsin by:
A) Gastrin
B) HCL
C) Secretin
D) Somatostatin
4. Somatostatin is secreted by:
A) Delta cells
B) Enterochromaffin-like cells
C) Parietal cells
D) Chief cells
5. Major stimulus that causes release of secretin is?
A) Gastrin
B) Cholecystokinin
C) Protein digestion products
D) HCL
6. Deficiency of intrinsic factor is associated with?
A) Steatorrhea
B) Pernicious Anemia
C) Jaundice
D) Protein energy malnutrition

SHORT ANSWER QUESTIONS

Q1: Mention factors that promote stomach emptying?

Q2: Mention the gastric glands and their cell types & secretions?

1. Gastric Factors that Promote Stomach Emptying

- Increased gastric food volume
- Gastrin promotes the secretion of acidic gastric juices, and enhances the activity of the pyloric pump and motor stomach function

2.

- Mucus secreting glands (cardiac glands):
 - Secretes: Mucus, HCO₃⁻
- Oxyntic (parietal) gland:
 - Type of cells: mucus neck cells, peptic cells, parietal cells
 - Secretes : HCL, pepsinogen, Intrinsic Factor, mucus
- Pyloric glands:
 - Type of cells: G cells
 - Secretes: Gastrin & Mucus

ANSWER KEY: B, B, B, A, D, B



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