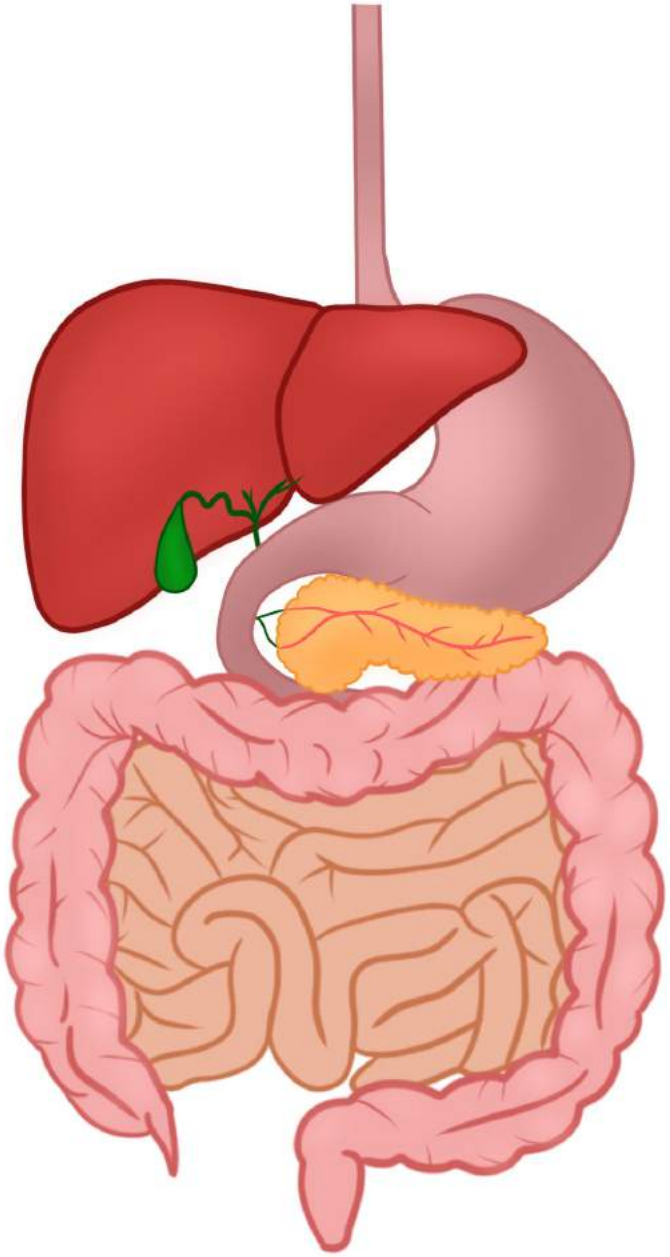

GASTROINTESTINAL PHYSIOLOGY

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Booklet Disclaimer

About StudyAid

StudyAid is a student organization at the Jagiellonian University in Krakow. Throughout the academic year we host seminars in the major theoretical subjects: anatomy, physiology, biochemistry, immunology, pathophysiology, supplementing the lectures provided by the university. We are a group of 25 tutors, who are students at JU, each with their own field of specialty. To make our seminars as useful and relevant as possible, we teach in an interactive manner often using drawings and diagrams to help students remember the concepts. In addition to most seminars we create booklets, on which the seminars are based to aid the students in following the presentations. If you have any questions, do not hesitate to contact StudyAid at www.studyaid.no, we are always happy to answer any questions you may have academically related or not.

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How to use this booklet

This booklet is only meant as a SUPPLEMENTARY tool in your studies for the final exam. We absolutely recommend you to use other sources as well. We have tried to focus on exam relevant materials, but there is no guaranty that this will cover everything.

In this booklet we have tried to break down the material of GI physiology. You will find summarizing tables, illustrations and flow charts. Use them as a supplement as you go through other materials.

Last in each section there is a set of questions, made so that you can review the material. Try to answer by yourself before you check the answer sheet. A suggestive answer sheet is provided in an additional document.

Abbreviations

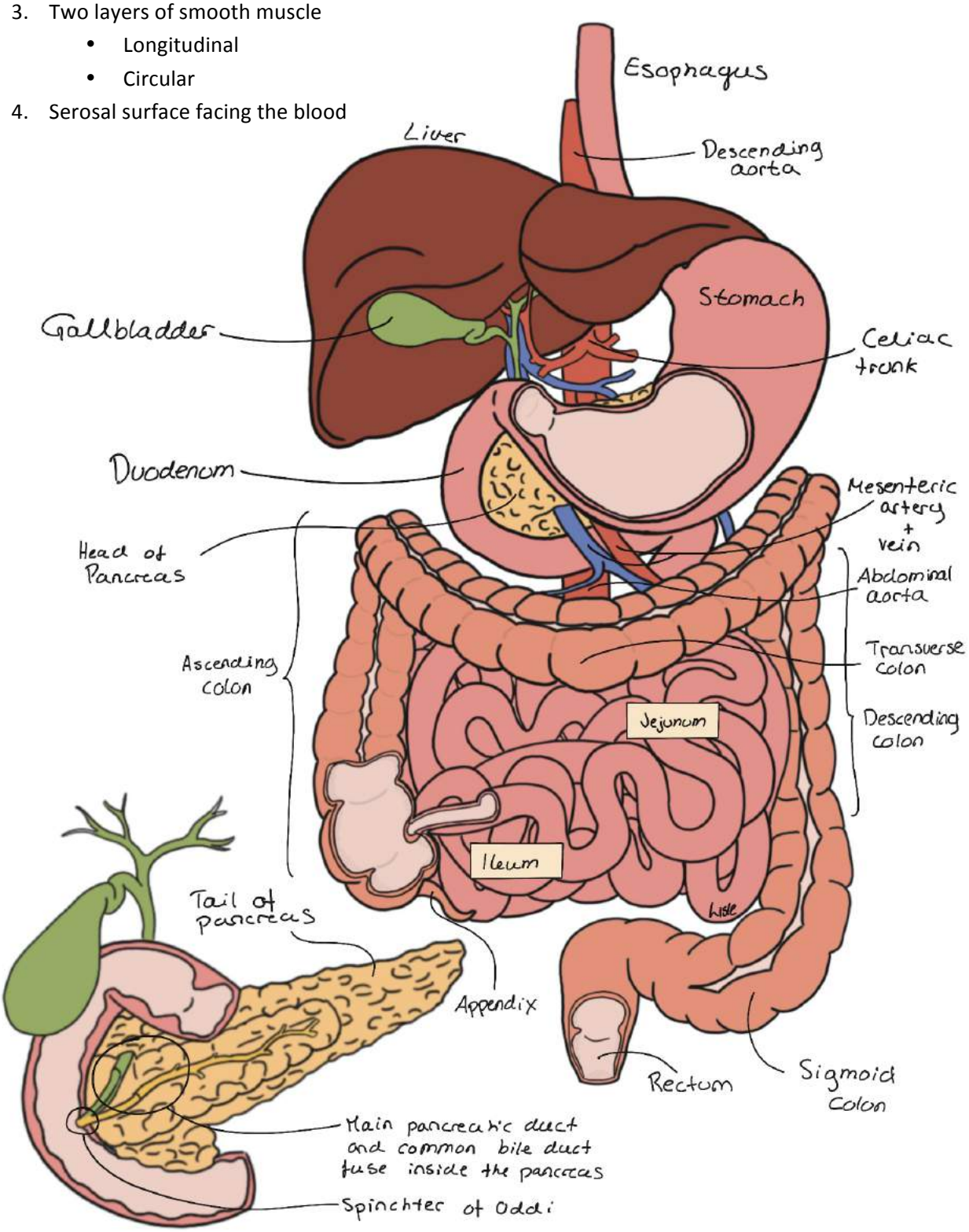
On the exams there will be used abbreviations, so make sure you know them.

Structures	
ENS	Enteric Nervous System
ECL cell	Enterochromaffin-like Cell
GIT	Gastrointestinal Tract
GI	Gastrointestinal
MMC	Migratory Myoelectrical Complex
LES	Lower Esophageal Sphincter
UES	Upper Esophageal Sphincter
PNS	Parasympathetic Nervous System
SNS	Sympathethic Nervous System
Substances	
ACh	Acetylcholine
GIP	Glucose-Dependent Insulinotropic peptide
GRP	Gastrin-Releasing Peptide
GLP-1	Glucagon-like peptide-1
NE	Norepinephrine
POMC	Pro-melanocortin
VIP	Vasoactive Intestinal Peptide

Section 1 – Structure of the Gastroint estinal Tract

The wall of the GI tract consists of multiple layers:

1. Mucosal surface facing the lumen
    - Epithelial cells
    - Lamina propria (connective tissue, lymph and blood vessels)
    - Muscularis mucosae (contraction changes the **epithelial cell layer**)
2. Submucosal layer (glands, blood vessels)
3. Two layers of smooth muscle
    - Longitudinal
    - Circular
4. Serosal surface facing the blood



Section 2 – Innervation of the Gastrointestinal Tract

2.0 – Extrinsic innervation of the gastrointestinal tract

2.1 – Intrinsic innervation of the GIT

2.3 – Reflexes

2.4 – Test yourself

Definition

The gastrointestinal tract is partly regulated by the autonomic nervous system. The autonomic nervous system is divided into extrinsic and intrinsic parts.

1. Extrinsic = Sympathetic and parasympathetic nervous system
2. Intrinsic = Enteric nervous system

Together these parts cooperate extensively to regulate the gastrointestinal tract.

2.0 – Extrinsic Innervation of the Gastrointestinal Tract

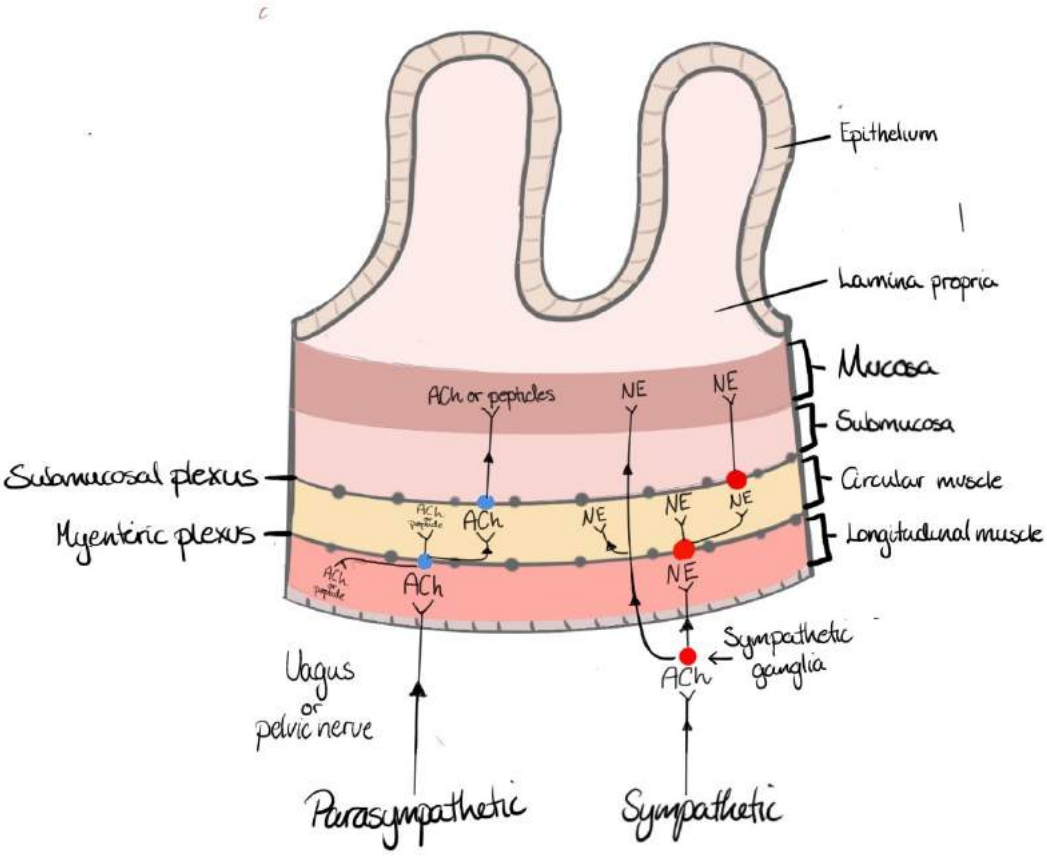


Illustration of how the parasympathetic and sympathetic nerves interact with the enteric nervous system.

	Parasympathetic *"Rest and digest"*	**Sympathetic** **"***Fight or flight"*
Anatomy of pathway	Long ***preganglionic*** fibers synapse in ganglia *lo*cated in the walls of the gastrointestinal tract, within the submucosal and myenteric plexuses. Information from the parasympathetic nerves are then passed on to the smooth muscle, secretory and endocrine cells	***1. Preganglionic*** fibers are short. Synapse in ganglia *outside* the GI tract. The ganglia associated wit the GIT is: • Celiac • Superior mesenteric • Inferior mesenteric • Hypogastric ***2.*** Long ***postganglionic*** fibers synapse on ganglia in the myenteric and submucosal plexuses, or directly innervate smooth muscle, endocrine or secretory cells.
Neurotransmitter	***1. Preganglionic:*** • Acetylcholine (ACh) ***2. Postganglionic*** cholinergic or peptidergic neurons: • Cholinergic ○ Acetylcholine (ACh) • Peptidergic • Substance P • VIP *Some peptides have not yet been identified.*	***1. Preganglionic***: • Acetylcholine ***2. Postganglionic*** – adrenergic: • Norepinephrine (NE)
Innervation	Vagus innervates upper gastrointestinal tract • Striated muscle of the upper part of the esophagus • Wall of the stomach • Small intestine • Ascending colon Pelvic nerve innervates lower gastrointestinal tract • Striated muscle of the external anal canal • Wall of the transverse, descending and sigmoid colons.	Innervates either the myenteric or submucosal plexus, or directly the endocrine, secretory or smooth muscle cells.

2.1 – Intrinsic Innervation of the Gastrointestinal Tract

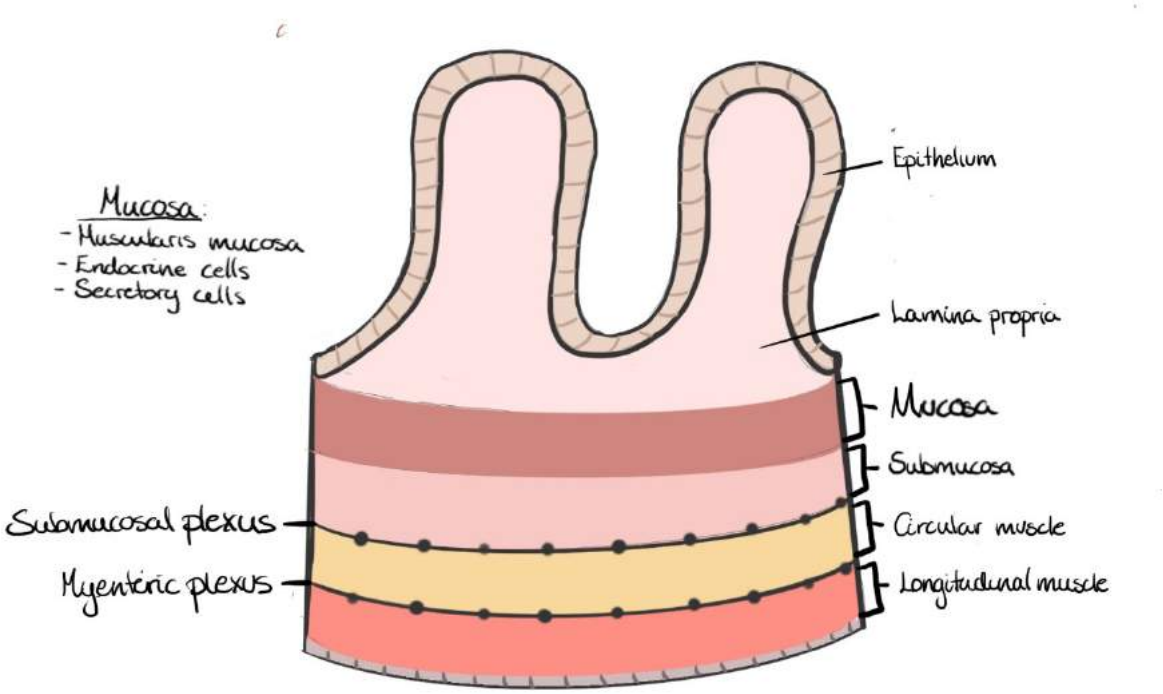
Definition

Intrinsic (enteric) nervous system is not dependent on the autonomic nervous system to direct the functions of the gastrointestinal tract.

It is located in the myenteric and submucosal ganglia.

I. **Myenteric plexus (Auerbach's plexus)**
   - Located between longitudeal and circular muscle.
   - Mostly control motor activity.

II. **Submucosal plexus (Meissner's plexus)**
   - Located between the submucosa and circular muscle.
   - Innervates myocytes, glandular epithelium, blood vessels, endocrine and exocrine cells.
   - Mainly responsible for regulation of absorption and secretion.



2.2 – Neurotransmitter and Neuromodulators Regulating the GIT

Substance	Source	Action
Acetylcholine *Main neurotransmitter of parasympathetic nervous system.*	Cholinergic neurons	- Contraction of smooth muscle in wall - Relaxation of sphincters - ↑ Salivary secretion - ↑ Gastric secretion - ↑ Pancreatic secretion
Norepinephrine *Main neurotransmitter of sympathetic nervous system.*	Adrenergic neurons	- Relaxation of smooth muscle - Contraction of sphincters - ↑ Salivary secretion
Vasoactive Intestinal Peptide (VIP)	Neurons of mucosa and smooth muscle	- Relaxation of smooth muscle - ↑ Intestinal secretion - ↑ Pancreatic secretion
Gastrin-Releasing Peptide (GRP)	Neurons of gastric mucosa	- ↑Gastrin secretion
Enkephalins (opiates)	Neurons of mucosa and smooth muscle	- Contraction of smooth muscle - ↓ Intestinal secretion
Neuropeptide Y	Neurons of mucosa and smooth muscle	- Relaxation of smooth muscle - ↓ Intestinal secretion
Substance P	Cosecreted with ACh	- Contraction of smooth muscle - ↑ Salivary secretion

2.3 – Reflexes

Selected reflexes of the GIT

Gastroileal reflex	Stomach signals to the ileocecal valve to relax and increase passage of chyme as food leaves the stomach.
Gastrocolic reflex	Stomach signals to evacuate the colon.
Enteric gastric reflexes	Intestines signal to stop gastric motility and secretions
Colonoileal reflex	Colon signals to stop empting of ileum into the colon.
Vomiting reflex	Vomiting center in medulla recieves information from the vestibular system, back of the throat, the GIT and chemoreceptors in the trigger zone of the fourth ventricle and initiates a vomiting response.
Defecation reflexes i.e. rectosphincteric reflex.	Rectum contracts and internal anal sphincter relaxes as the rectum relaxes. Defacation does not occur before external anal sphincter is relaxed.

2.3.1 – Vagovagal reflexes

I. **Mechanism**

The vagus nerve has both mechano- and chemoreceptors in the gastrointestinal mucosa that relay information to the CNS, triggering reflexes with an efferent limb also in the vagus nerve. When the vagus nerve participates in both the afferent and the efferent limb, the reflex is referred to as the vasovagal reflex.

II. **Examples**

- Receptive relaxation
- Potentiation CCK action on enzymatic secretion from acinar cells
- Amplification of gastric secretions

CLINICAL CORRELATION

Resection of the vagus nerve

Damage to the vagus nerve will affect the GIT in many ways. The effects are:

- Trouble opening the LES as the vagus nerve mediates the opening
- Absence of receptive relaxation
- Irregular and chaotic peristalsis of the stomach

2.4 – Test Yourself

1. **The extrinsic nervous system is comprised of…?**

2. **The submucosal plexus is located between which layers in the intestinal wall?**

3. **What is the main function of Myenteric (Auerbach's) plexus?**

4. **Short preganglionic, and long postganglionic fiber fit the descriptions of fibers from…?**

5. **What is the main neurotransmitter released from cholinergic neurons?**

6. **Which structures in the GIT is innervated by the vagus nerve?**

7. **What are the actions of Norepinephrine?**

8. **What is the action of Enkephalins?**

9. **What is the function of the gastroileal reflex?**

10. **The term ”Vagovagal reflex” means…?**

Section 3 – Gastrointestinal Regulatory Substances

3.0 – Classification of gastrointestinal substances.

Gastrointestinal peptides are classified as paracrines, neurorcines or hormones.

- **Hormones**
  - Peptides released from endocrine cells (here in the GIT) into the systemic circulation.
  - Can have an effect locally, or further away from it's origin.
  - Gastrin, CCK, Secretin and GIP are gastrointestinal peptides classified as hormones.

- **Paracrines**
  - Secreted by endocrine cells
  - In contrast to hormones, paracrines work locally within the tissues that secretes them as they diffuse through the interstitial tissue to their target.
  - Somatostatin is the major gastrointestinal paracrine. Histamine is classified as a paracrine as well, but histamine is *not* a peptide.

- **Neurocrines**
  - Synthesized in the neurons and released following an action potential. It is released into the synapse where it diffuses across and acts on its target cell.
  - Neurocrine of the GIT include ACh, NE, VIP, GRP, Enkephalins, Neuropeptide Y and substance P.

3.1 – Gastrointestinal hormones

3.1.1 – Gastrin

I. Stimulation of gastrin stimulation

Gastrin is released from G-cells located in the antrum of the stomach. The three primary stimuli for gastrin secretion is:

1. The presence of **proteins** in the gastric lumen (Phenylalanine and Tryptophan is the most potent stimuli for gastrin release amongst the products of protein digestion)
2. Gastric **distension** – which stimulates vagal response
3. Direct **vagal stimuli** via the release of a specific neurotransmitter, Gastrin Releasing Peptide (GRP/bombesin).

II. Inhibition of gastrin release

The release of gastrin is inhibited by the presence of acid in the lumen (low pH) and *somatostatin*.

III. Main function of gastrin

The main function of gastrin is to stimulate secretion of gastric acid. When released, gastrin travels through the blood stream to the fundic glands, where it binds to receptors on parietal cells and ECL cells (and likely; chief cells). Stimulation of parietal cells activates secretion of gastric acid, while activation of ECL cells causes the release of *histamine.* Histamine potentiates the secretion of gastric acid by binding to H_2 receptors (histamine receptors) on the parietal cells.

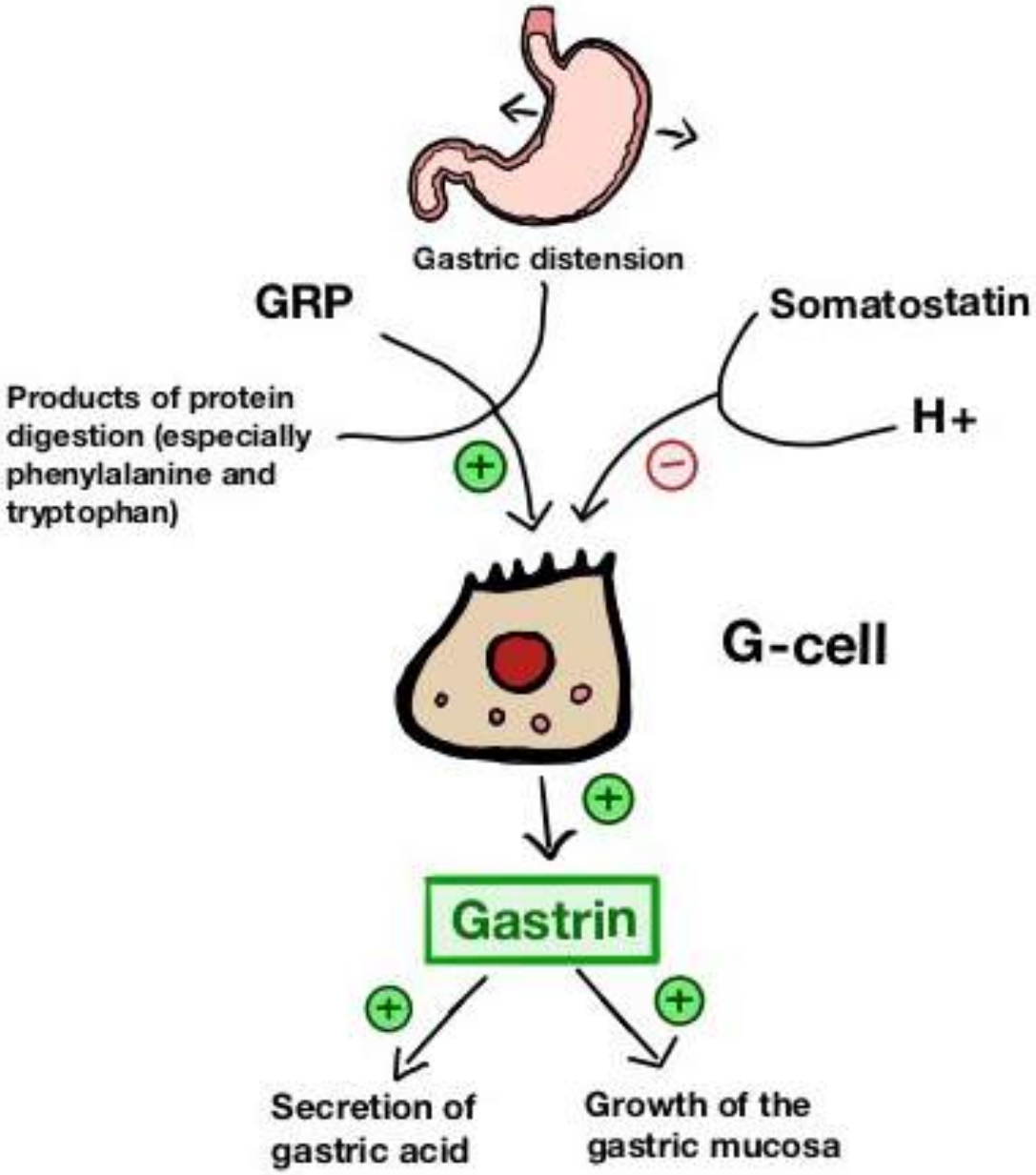
CLINICAL CORRELATION

Zollinger-Ellison syndrome

Excess of gastrin - Caused by a gastrin-secreting tumor (gastrinoma)

Signs and symptoms include

- Increased H^+ secretion by parietal cells
- Hypertrophy of the gastric mucosa
- Duodenal ulcers – due to the increased H^+
- Decreased fat digestion due to inactivation of pancreatic lipase – leading to steatorrhea.


Gastric distension
GRP
Somatostatin
Products of protein digestion (especially phenylalanine and tryptophan)
H+
G-cell
Gastrin
Secretion of gastric acid
Growth of the gastric mucosa

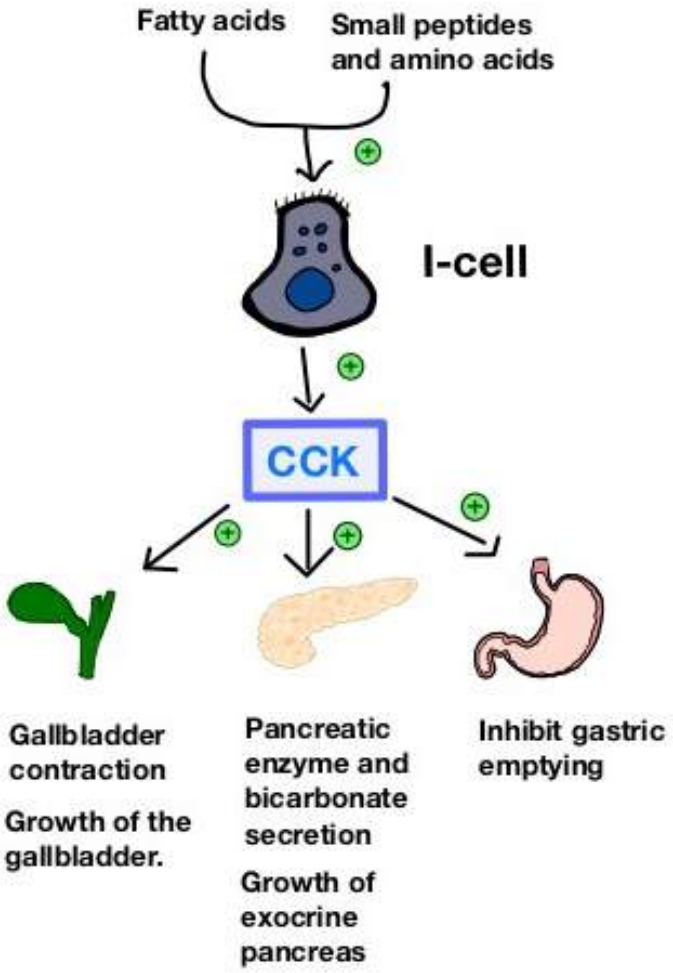
3.1.2 – Cholecystokinin (CCK)

I. Stimuli and secretion

CCK is secreted by I-cells in the duodenum and jejunum. The secretion is stimulated by fatty acids, and small peptides and amino acids. In other words CCK is secreted in response to a meal containing fat and protein. Main function of CCK is to promote fat digestion and absorption.

II. **Major actions of CCK**

1. **Contraction of the gallbladder**
    a. With simultaneous relaxation of sphincter of Oddi, causes ejection of bile.
2. **Secretion of pancreatic enzymes**
    a. Pancreatic lipases digest ingested lipids.
    b. Pancreatic amylase digests carbohydrates.
    c. Pancreatic proteases digest proteins.
3. **Secretion of pancreatic bicarbonate** (HCO_3^-)
4. **Growth of exocrine pancreas and gallbladder.**
5. **Inhibition of gastric emptying**
    a. Critical for proper digestion and absorption of fat, as it provides the time needed.



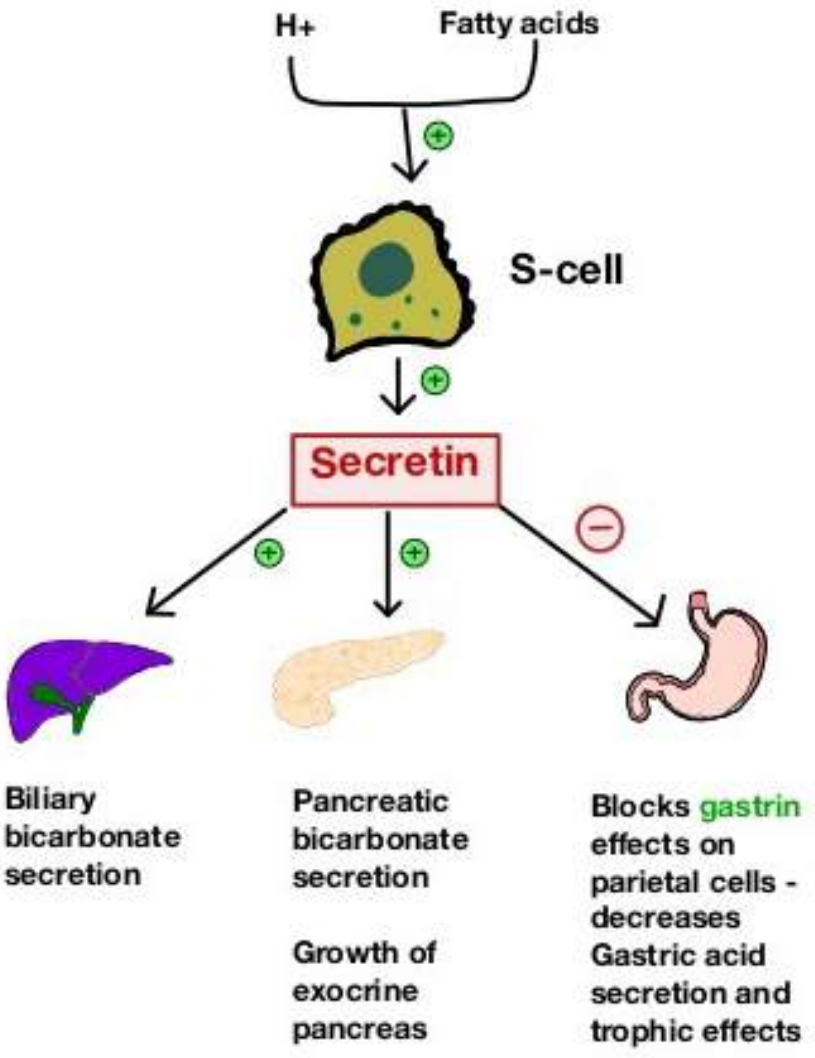
3.1.3 – Secretin

I. Stimuli and secretion

Secretin is secreted by S-cells in the duodenum. Secretion is stimulated by H^+(low pH) and fatty acids in the lumen of the small intestine.

II. Main functions

Secretin promotes secretion of pancreatic and biliary bicarbonate to neutralize the acid, which is essential for fat digestion. An additional ability of secretin is the inhibition of the effects of gastrin on parietal cells.



3.1.4 – Glucose-Dependent Insulinotropic Peptide (GIP)

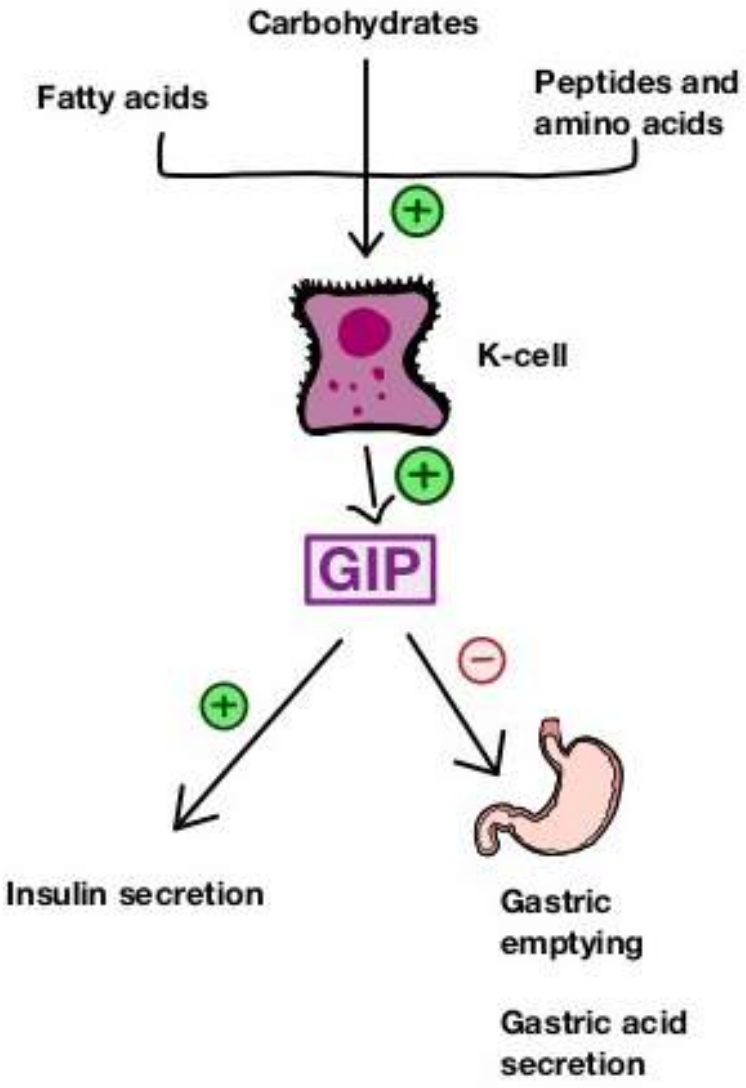
I. Stimuli and secretions

GIP is secreted by K-cells in the duodenum and jejenum in response. GIP is the only GI hormone that is stimulated by all the nutrients: glucose, fatty acids and amino acids.

II. Main functions

Major function of GIP is stimulation of insulin secretion. This is the explanation of why oral glucose is taken up more rapidly by the cells, than the same amount of intravenously administered glucose. Intravenously administered glucose stimulates insulin secretion only by direct action on the β cells, while oral glucose activates GIP.

GIP also inhibits gastric H^+secretion and gastric emptying.



3.2 – Overview of gastrointestinal regulatory substances

3.2.0 – True hormones

Regulatory substance	Physiologic action	Site of release	Stimuli causing release
Gastrin *Gastrin-CCK family*	Increases gastric acid secretion from parietal and ECL cells Stimulates growth of gastric gland mucosa.	G-cells in the gastric antrum (and duodenum)	3 primary stimuli for release 1. Neurotransmitter **GRP(bombesin**) from enteric nerves 2. Presence of **proteins** in the lumen 3. **Distension** of the gastric lumen. **NB!** The presence of acid in the lumen inhibits the secretion of gastrin
CCK *Gastrin-CCK family*	Stimulates 1. Gallbladder contraction and relaxation of the sphincter of Oddi 2. Pancreatic enzyme secretion 3. Pancreatic bicarbonate (HCO_3^-) secretion 4. Growth of exocrine pancreas and gallbladder Also it inhibits gastric emptying.	Released by I-cells of the duodenum and jejenum	Release is mainly stimulated by the presence of **fat** and **protein** in the lumen of the duodenum.
Secretin *Secretin-glucagon family*	Stimulates 1. Pancreatic bicarbonate secretion 2. Biliary bicarbonate secretion Inhibits 3. Effects of gastrin (gastric acid secretion & trophic effects on gastric mucosa)	Secreted by S-cells in the duodenum.	Release is stimulated by the presence of **acid (H^+)** and **fat** in the duodenum.
GIP *Secretin-glucagon family*	**Stimulates** insulin **Inhibits** gastric acid secretion and slows gastric emptying.	Secreted by K-cells in the duodenum and jejenum	Release is stimulated by **glucose, protein** and **fat**. ★ This hormone is the only hormone stimulated by all types of nutrients (glucose, amino acids and fatty acids)

3.2.1 – Candidate hormones

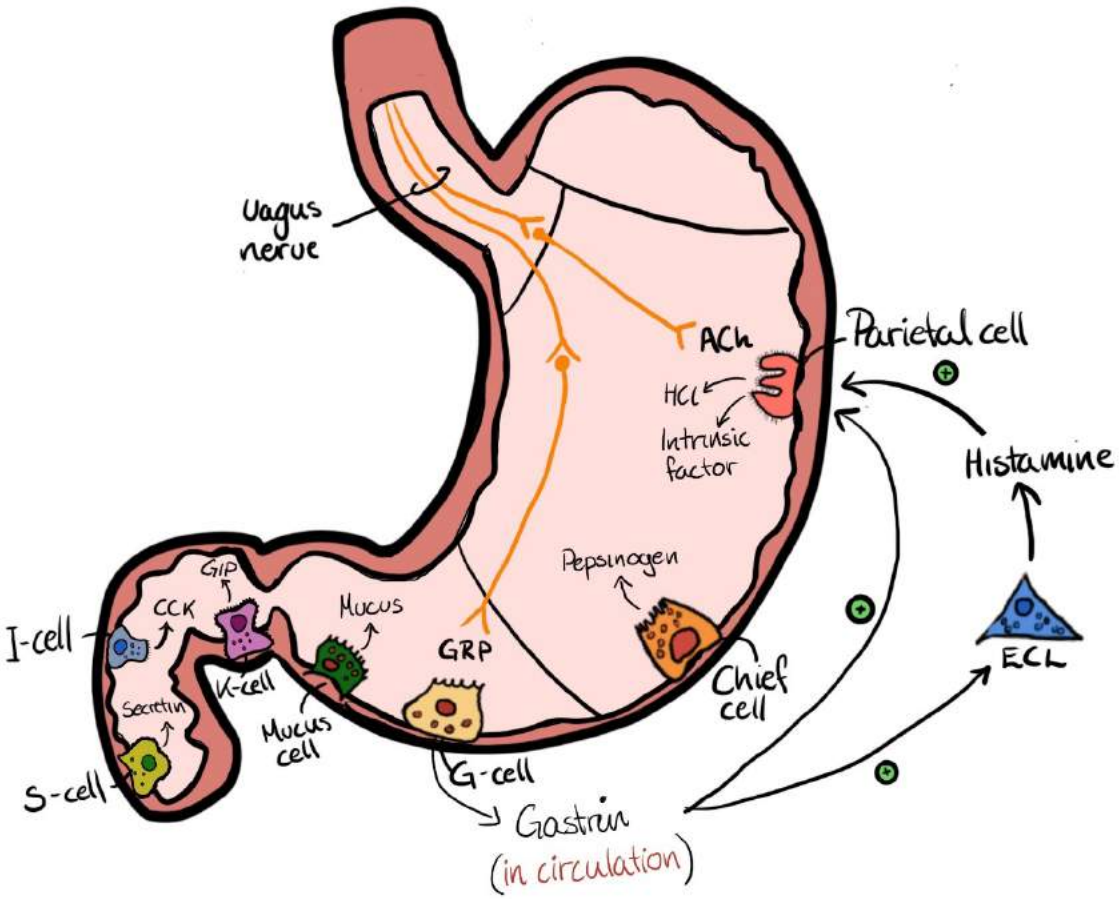
Regulatory substance	Physiologic action	Site of release	Stimuli causing release
Motilin	Believed to stimulate gastric and duodenal motility – specifically to initiate **interdigestive myoelectric complexes**	Released in the duodenum and jejenum	The stimuli for release of motilin in currently unknown
Pancreatic polypeptide	Inhibits pancreatic bicarbonate and enzyme secretion.	Pancreatic islets of Langerhans	Release is stimulated by the presence of **protein, carbohydrates** and **lipids.**
Enteroglucagon	Directs liver to increase glycogenolysis and gluconeogenesis	Released from intestinal cells	Release is stimulated by decrease in blood glucose concentration
Glucagon-like peptide-1 (GLP-1)	1. Stimulates insulin secretion by binding to receptors in pancreatic β cells 2. Increases β cells sensitivity to glucose 3. Inhibits glucagon secretion 4. Decreases gastric emptying 5. Inhibits appetite	Synthesized and secreted by L cells of the small intestine	Orally ingested glucose.

3.2.2 – Paracrines

Regulatory substances	Physiologic action	Site of release	Stimuli causing release
Somatostatin	Inhibits release of most other gastrointestinal hormones. ***Inhibits:*** • Secretion of gastric acid $(H^+)$and pepsinogen secretion • Pancreatic and small intestine fluid secretion • Gallbladder contraction • Insulin and glucagon release	Released by D-cells in the GIT mucosa, and by Delta (δ) cells in the pancreatic islets of Langerhans. (Also secreted by the hypothalamus)	Release is stimulated by **decreased pH** in the lumen. Inhibited by vagal stimuli.
Histamine	Stimulates to parietal cells to secrete gastric acid.	Released by ECL cells in the gastric glands.	Release is stimulated by **gastrin**, and also other unknown causes.

3.2.3 – Neurocrines

Regulatory substances	Physiologic action	Site of release	Stimuli causing release
VIP	Relaxes sphincter and gut circular muscles Stimulates intestinal and pancreatic secretion	Released by enteric nerve endings in mucosa and smooth muscle of the GIT.	Release is stimulated by the Enteric nervous system (ENS)
GRP/ Bombesin	Stimulates the release of gastrin	Released by enteric nerve endings in the gastric mucosa.	Release is stimulated by the ENS
Enkephalins	Stimulate smooth muscle contraction Inhibits intestinal secretion	Released by enteric nerve endings in mucosa and smooth muscle of the GIT.	Release is stimulated by the ENS



Place of secretion of some gastrointestinal regulatory substances.

3.3 – Appetite and Satiety

I. Control centers

Appetite and satiety is controlled by the hypothalamus.

- **Ventromedial nucleus (VPN)** is the satiety center.
- **Lateral hypothalamic area (LHA)** is the feeding center

II. Influencing appetite and satiety

The **arcuate nucleus** provides information via neurons that project into the satiety and feeding centers. The neurons can either be

1. **Anorexigenic neurons**
   - Releasing POMC which causes an ↓ appetite (↑ satiety)
2. **Orexigenic neurons**
   - Releasing neuropeptide Y which causes an ↑ appetite (↓ satiety)

Several substances have the ability to influence appetite and satiety by acting on the anorexigenic and orexigenic neurons. Substances increasing appetite include Ghrelin. Substances inhibiting appetite include leptin, Insulin, GLP-1 and peptide YY.

3.3.0 – Substances influencing appetite and satiety

Regulatory substance	Physiologic action	Site of release	Stimuli of release
Decreasing appetite - Stimulates anorexigenic and inhibits orexigenic neurons.			
Leptin	Chronic (*long-term*) effect to decreases appetite.	Secreted by fat cells in proportionally to the amount of fat stored in adipose tissue.	Is stimulated by the presence of body fat.
Insulin	Short-term regulation of appetite.	Secreted by βcells of the endocrine pancreas.	Levels fluctuate during the day in response to increases in blood glucose levels.
GLP-1	*See table in section 3.2*		
Peptide YY	Acts directly on hypothalamus to decrease appetite, but also inhibits ghrelin secretion.	Secreted by intestinal L cells.	Secreted following a meal.
Increasing appetite – Stimulates orexigenic and inhibits anorexigenic neurons.			
Ghrelin	Increases appetite and food intake.	Secreted by gastric cells before the ingestion of a meal.	Strongly stimulated by periods of starvation and weight loss.

3.4 – Test Yourself

1. **What is the definition of paracrines?**

2. **Gastrin secretion is stimulated by what factors?**

3. **What is the cause of Zollinger-Ellison syndrome?**

4. **What are the 5 main functions of CCK?**

5. **Why is oral glucose taken up more rapidly than intravenously administered glucose?**

6. **What are the actions of somatostatin?**

7. **In what region of the stomach is Gastrin produced?**

8. **Which cell release histamine?**

9. **The vagus nerve increase secretions from two type of cells, which two?**

10. **What is the effect and mechanism of orexigenic neurons?**

Section 4 – Gastorintestinal Motility

- **Definition**
  The motility of the GIT refers to the contraction and relaxation of the walls and sphincter. The main function of the motility is to mix and grind the ingested food so that it can be easily absorbed and digested.

4.0 – Muscle and Contractile Tissue in GIT

The different contractile tissue of the GIT	Almost all of the contractile tissue in the GIT is smooth muscle, striated muscle tissue is only found in: • Muscles of the pharynx • Muscles of the upper 1/3 of the esophagus • External anal sphincter The smooth muscle of the GIT is unitary smooth muscle, and the cells are connected with **gap-junctions**. The gap-junctions allow for rapid spread of action potentials.
Different muscle with different function	**Circular** • Contraction decreases diameter of the segment **Longitudinal** • Contraction decreases length of the segment
Different states of muscle tone in the GIT	**Phasic** - Periodic contractions, followed by relaxation - Found in areas of the GI involved with mixing and grinding. **Tonic** - Continous contraction tone – with no regular periods of relaxation. - Typically found in the sphincters: Lower esophageal sphincter (LES), ileocecal sphincter, and internal anal sphincter. - Also found in the orad – the upper region of the stomach.

4.1 – Slow waves

A unique feature of the GI smooth muscle.

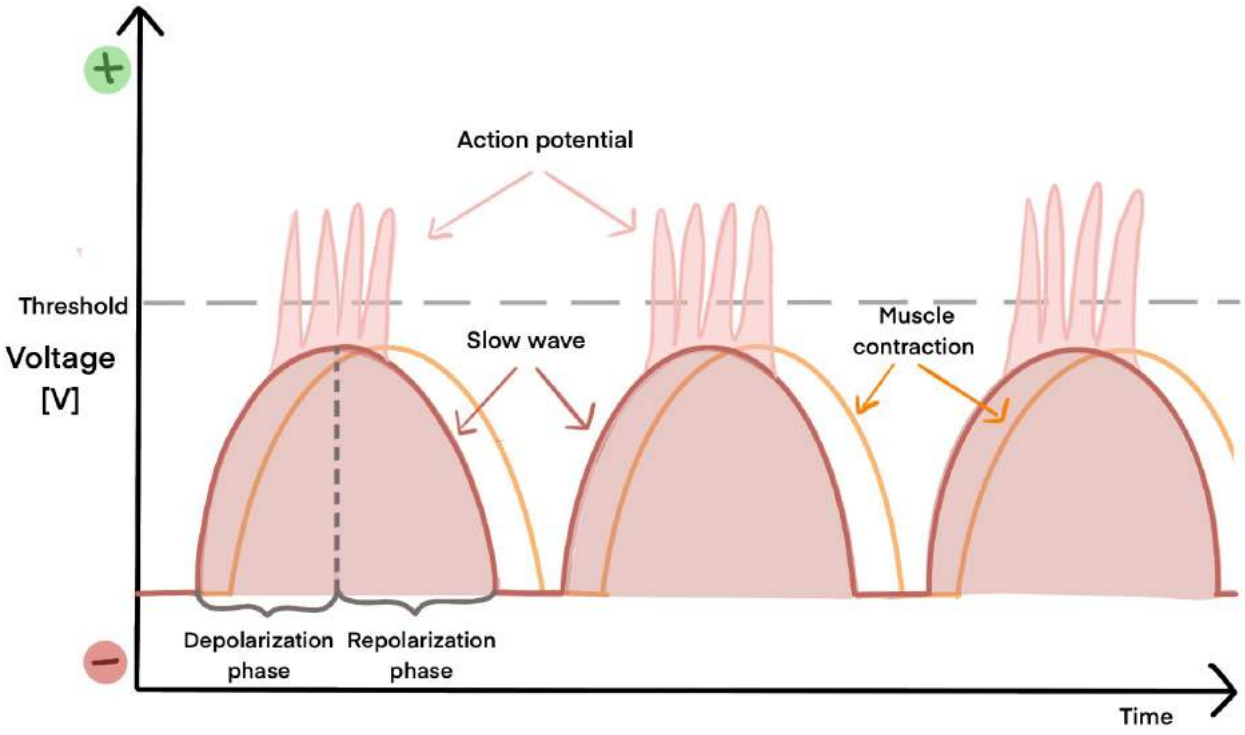
I. Phases of slow waves

Slow waves can be can be described as oscillating depolarization and repolarization of the membrane potential in the smooth muscle cells of the GI tract.

1. **Depolarization phase:** membrane potential becomes less negative and moves toward threshold. Caused by cyclic opening of Ca^+ channels, which produces an inward current that depolarizes the membrane.
2. **Plateau phase:** action potentials can occur, if slow wave is depolarized to threshold. Caused by maintaining the Ca^+ channels open, so the onward current can continue.
3. **Repolarization phase:** membrane potential becomes more negative, and moves away from the threshold. Caused by opening of K^+ channels producing an outward flow of K^+, which repolarizes the membrane.

II. Action potentials

An **action potential** will occur at the peak of the slow wave if it is depolarized all the way to the threshold. Following the electrical impulse, the muscles will contract (tension will increase). The greater the number of action potentials, the greater the contraction. Contraction will also occur with a slow wave that does not reach threshold, but this



contraction will be weak.

III. Interstitial cells of cajal

In the myenteric plexus, there is abundance of a cell called **interstitial cells of cajal**. These cells are believed to be the origin of slow waves. Cyclic depolarization and repolarization occur spontaneously in the interstitial cells of cajal and spread rapidly to adjacent smooth muscle via low-resistance gap junctions. They can be thought of as the **pacemaker** for the GI smooth muscle.

III. **Frequency**

- Frequency of slow waves varies along the GIT
    1. Lowest rate: Stomach – 3 waves/min
    2. Ileum – 9 waves/ min
    3. Highest rate: Duodenum – 12 waves/min
- Frequency of action potentials (and therefor contractions) is determined by the frequency of the slow waves.
- Neural and hormonal activity cannot modulate the slow waves, but they modulate the production of action potentials and the strength of the contractions.

4.2 – Chewing and swallowing

4.2.0 – Chewing

- Mix food with saliva
- Reduce size of food particles
- Mix carbohydrates with salivary amylase – starting carbohydrate digestion
- Can be both voluntarily and involuntarily
    1. **Involuntary** chewing is activated when reflexes in the mouth are stimulated by the presence of food.
    2. **Voluntary** chewing can at any time override the involuntary chewing.

4.2.1 – Swallowing

- Is voluntarily initiated, but is taken over by involuntary or reflex control.
    - Involuntary swallowing is controlled by the swallowing center in the medulla
- The different elements of swallowing is divided into 3 phases
    1. Oral phase
    2. Pharyngeal phase
    3. Esophageal phase.

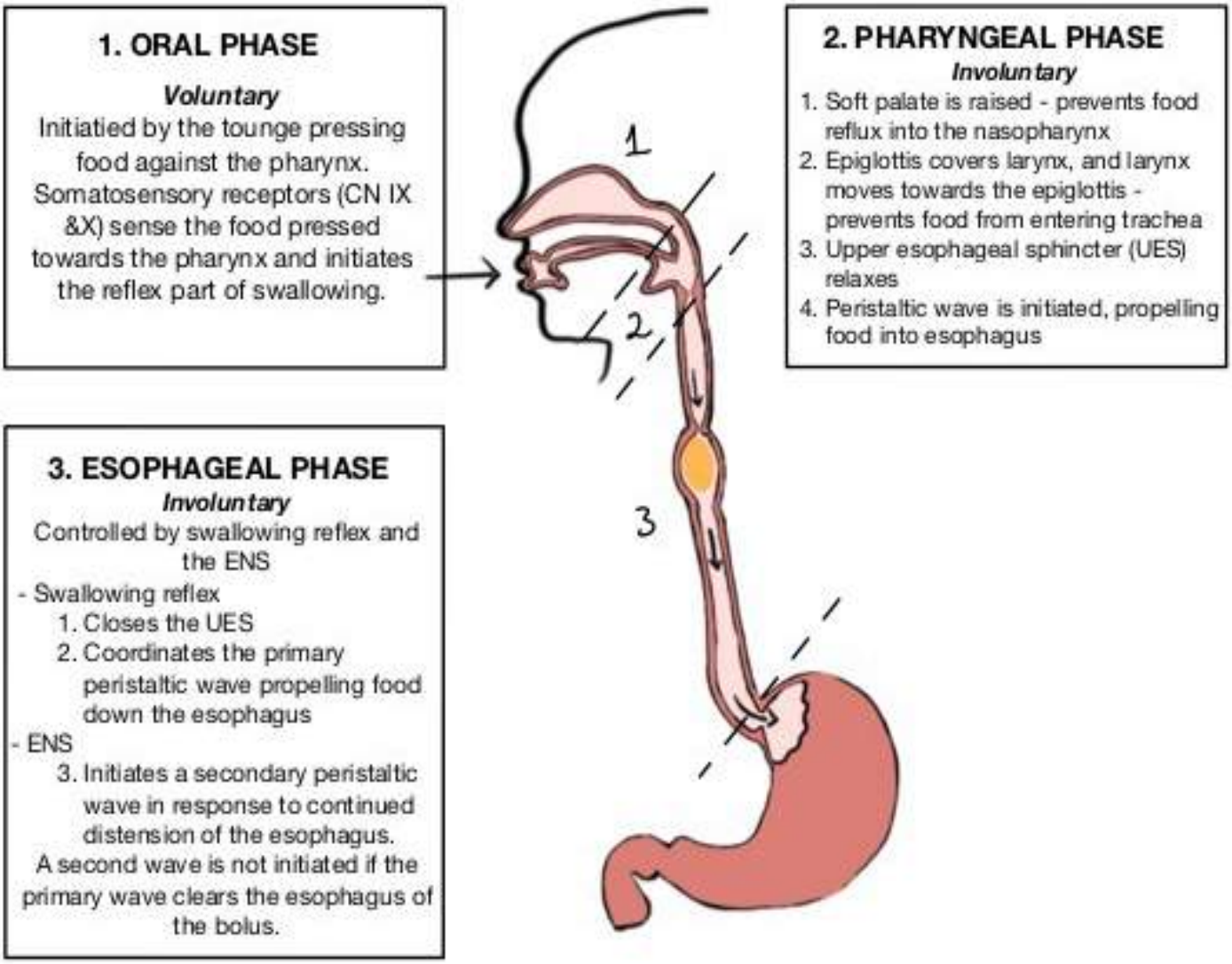


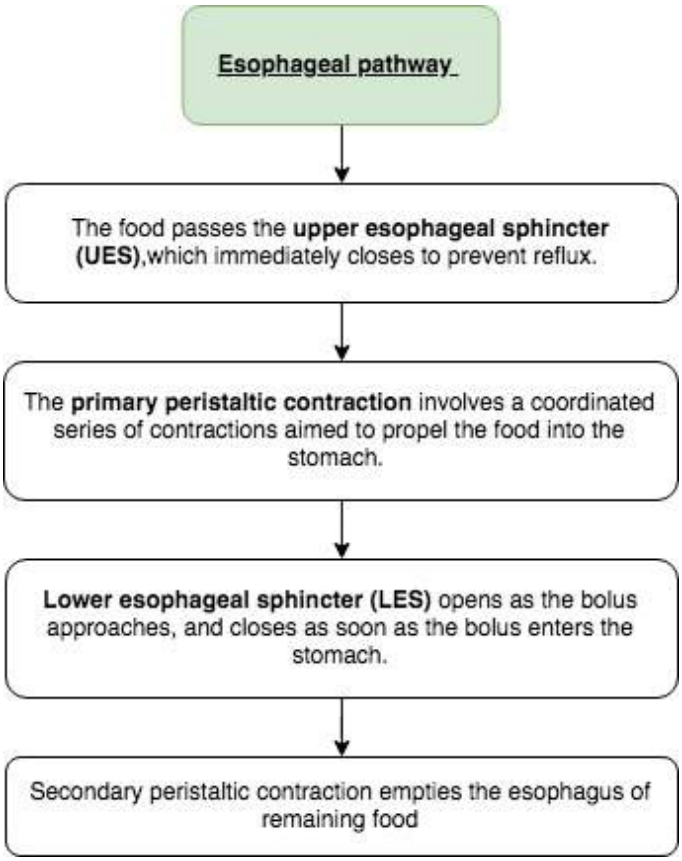
Illustration explains the three phases of swallowing

4.3 – Esophageal Motility

4.3.0 – Esophageal pathway

I. Function

Function of the esophageal motility is to transport the food from the pharynx to the stomach.



II. **Esophageal pathway**

1. The food passes the upper esophageal sphincter (UES), which immediately closes to prevent reflux.
2. The **primary peristaltic contraction** involves a coordinated series of contractions aimed to propel the food into the stomach. This works by administering high pressure behind the bolus through contraction. Gravity will help the bolus move towards the stomach if the person is sitting/standing.
3. Lower esophageal sphincter (LES) opens as the bolus approaches. This opening is mediated by the **vagus nerve** via release of **VIP**. As soon as the bolus enters the stomach, LES returns to it's tonic contraction state. The high pressure of the sphincter prevents reflux into the esophagus.
    - As the LES relaxes, so does the orad region of the stomach. This is called **receptive relaxation.** The physiologic function of the receptive relaxation is to promote movement of the bolus in the stomach.
4. Secondary peristaltic contraction empties the esophagus of remaining food. The wave begins at the point of distension (where the food is) and goes downward.

4.3.1 – Pressure of the esophagus

I. Esophageal pressure

Most of the esophagus is placed in the thorax, which means that the pressure of the esophagus has to be equal to the intrathoracic pressure not to collapse. Intrathoracic pressure is lower than atmospheric pressure, and so is intraesophageal pressure. The pressure in esophagus is also lower than the intraabdominal pressure.

CLINICAL CORRELATION

Gastroesophageal reflux
Conditions with increased intrabdominal pressure may lead to gastroesophageal reflux, where contents of the stomach pass back into the esophagus.

Examples of such conditions are pregnancy, morbid obesity or tumors.

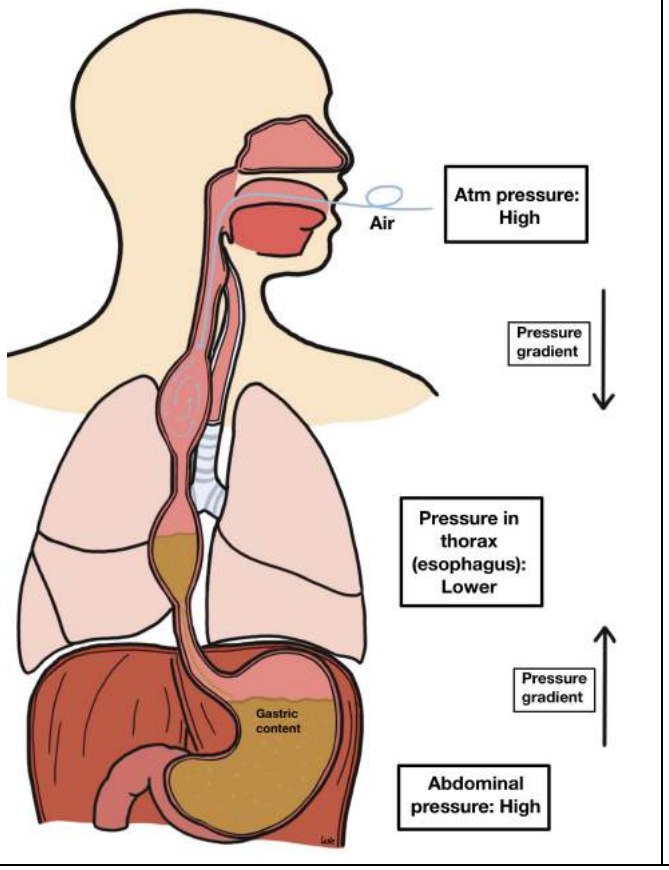
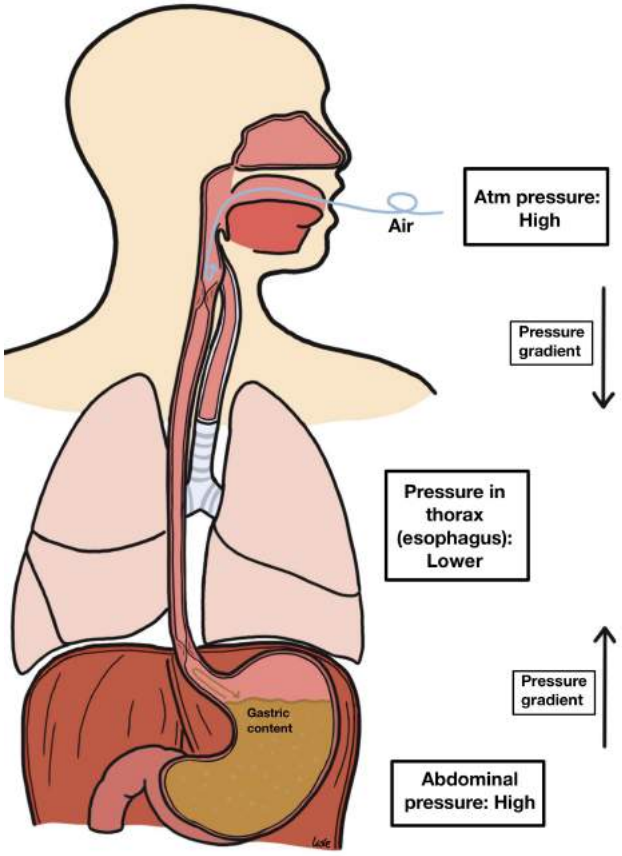
II. Function of esophageal sphincters

The low pressure in the esophagus creates two problems:

1. Keeping air out in the upper end
2. Keeping gastric contents out at the lower end

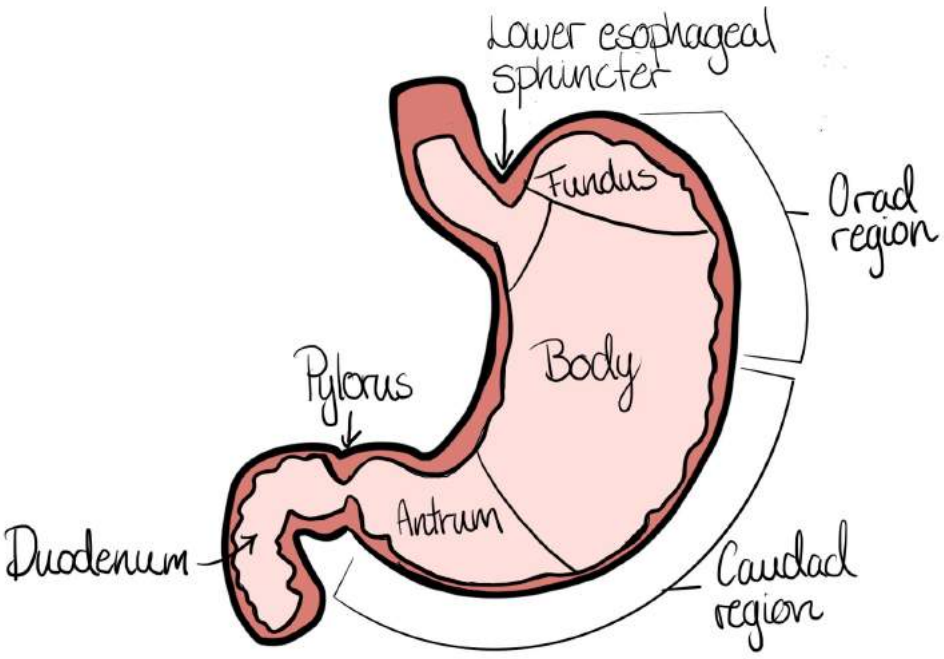
The upper and lower esophageal sphincters solve these problems. They remain closed at all times, except when food is passing.

What would happen if we didn't have esophageal sphincters?

Esophagus without sphincters	Esophagus with sphincters
	
Because the atmospheric and abdominal pressures are higher than the intrathoracic pressure, the **pressure gradient** is from high-pressure outside/abdomen **into the low-pressure thorax** (esophagus)	
No sphincters: Air and gastric content would fill the esophagus	**Sphincters:** No air or gastric content in esophagus

4.4 – Gastric Motility

4.4.0 – Structure and Innervation of stomach



I. Structure

- **3 muscle layers**
    1. Outer longitudinal layer
    2. Middle circular layer
    3. Inner oblique layer – unique for the stomach
- Thickness of the wall increases from proximal (top) to the dital end (bottom).

II. Innervation

- Innervated by both the intrinsic and extrinsic nervous system.
- Myenteric plexus receives parasympathetic innervation from the vagus nerve and sympathetic innervation via fibers from the celiac ganglion.

III. Divided into regions based on differences in motility

1. **Orad – proximal**
    - Thin walled – weaker contractions
    - Receptive relaxation when LES relaxes and bolus enter the stomach.
2. **Caudad – distal**
    - Thick walled – stronger contractions.
    - Contractions mix the food and pass it on to the duodenum.

4.4.1 – Receptive relaxation

I. Mechanism

Receptive relaxation occurs as the lower esophageal sphincter relaxes. This reduces the pressure and increases the volume of the orad region.

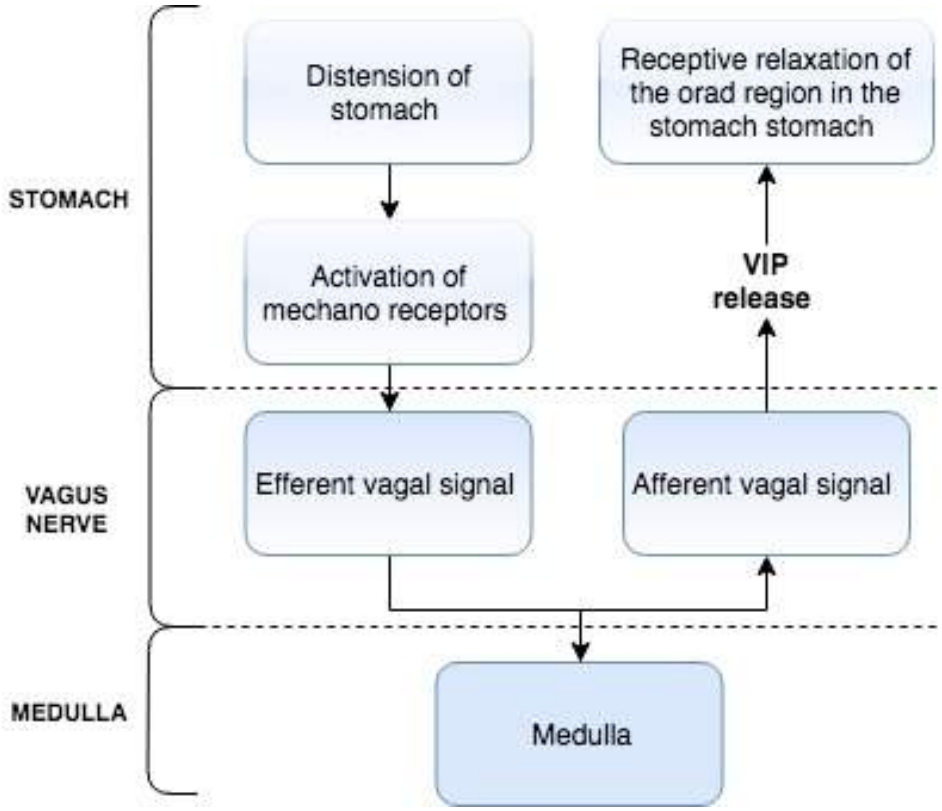
II. Reflex pathway

Receptive relaxation is a **vagovagal reflex** - both afferent and efferent limb lies within the vagus nerve. The distension of the stomach is detected by mechanoreceptors and passes the information to the CNS via the sensory nerves (afferent limb). Signals are then sent via neurons to relax the orad stomach (efferent limb). The neurotransmitter released from the neurons is **VIP.**

CLINICAL CORREOLATION

Vagovagal reflex

As this is a vagovagal reflex, receptive relaxation will be eliminated by a vagotomy. This will increase intrabdominal pressure, and can lead to vomiting due to inability of the orad stomach to relax.



4.4.2 – Contractions

I. Mechanism of contractions

- Mixing and digestion mostly happens in the caudad region. Wall is thicker and produces contractions strong enough. Contractions begin in the middle of the body, and move down. They increase in strength closer to the pylorus.
- Periodically gastric content is propelled through the pylorus into the duodenum. Wave of contraction also closes the pylorus controlling the amount of chyme injected into the duodenum. Food not injected into the duodenum goes back into the stomach to get churned and mixed some more, this is called **retropulsion.**
- Slow waves = 3-5/ min in caudad stomach which means that contractions are 3-5/ min

II. Regulation of contraction

- Parasympathetic stimuli, gastrin and motilin increase frequency of **action potentials** and the force of contraction.
- Sympathetic stimuli, secretin and GIP decrease frequency of **action potentials** and the force of contraction.

III. Motilin

Regulates the **migrating myoelectric complexes,** which are periodic gastric contractions occurring at 90-minute intervals and functions to cleat the stomach of remaining food.

4.4.3 – Gastric emptying

1. Gastric emptying must be regulated to ensure enough time for:
    - Proper digestion and absorption
    - Neutralization of acids in the duodenum.
2. Presence of fat and acid in the duodenum will decrease the rate of gastric emptying.
    - Presence of fat stimulates release of CCK that inhibits gastric emptying.
    - Presence of acid stimulates H^+ sensitive reflexes of the ENS, which detects the acidic environment in the duodenum and slows down the gastric emptying.
3. Fluids will leave the stomach faster than solids, and isotonic content will leave faster than hypotonic or hypertonic contents.
4. Due to the effects of CCK, the rate of emptying also depends on the types of food ingested.
    a. Carbohydrates empty the fastest
    b. Protein 2nd fastest
    c. Fats take the longest to leave the stomach.

CLINICAL CORRELATION

Sport drinks

The producers of sports drinks, such as *Powerade*, have used knowledge of gastric emptying in their production. By making their drinks isotonic they can be taken up by the bloodstream much faster than hypotonic or hypertonic drinks. This is useful when fluids needs to be replaced fast, such as when practicing sports.

I. Substances affecting the rate of gastric emptying

Decreasing (↓) the rate of gastric emptying
CCK
GLP-1
GIP
H^+ sensitive reflexes of the ENS

4.5 – Intestinal motility

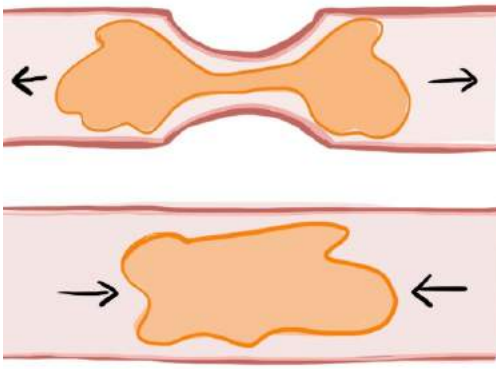
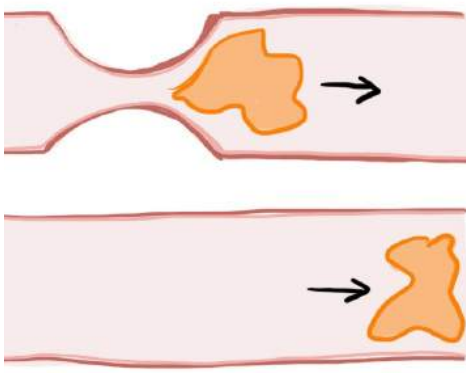
4.5.0 – Small intestine

- Responsible for digestion and absorption of nutrients
    - Motility serves to mix chyme with digestive enzymes and expose nutrients to intestinal mucosa.
- **Migratoring myoelectrical complexes (MMC)** occur every 90 min to empty intestine of residues.

I. Innervation

Parasympathetic innervation	Sympathetic innervation
Increases (↑) contraction of smooth muscle	**Decreases** (↓) contraction of smooth muscle
Via vagus nerve	Via fibers originating in the celiac and superior mesenteric ganglia.
Neurocrines transmitted in addition to ACh include VIP, enkephalins and motilin.	

II. Patterns of contraction – coordinated by ENS

Segmentation contraction	Peristaltic contraction
Serve to mix the chyme with digestive enzymes, but do not move the chyme forward.	Serve to propel the chyme forward. Initiated by stretching of the gut wall Can be increased by PS stimuli, and decreased by sympathetic stimuli, but function without extrinsic innervation.
Chyme is moved back and forth back contractions splitting up the bolus, and the bolus merging back when the intestines relax.	Contraction behind the bolus, and relaxation in front pushes the bolus forward, down the intestinal tract. These contractions are repeated down the entire small intestine. The circular and longitudinal muscles contracts at opposite times to make the peristaltic movement. They are reciprocally innervated, so that they do not contract at the same time.
	

4.5.1 – The large intestine

- Material in large intestine is destined for excretion.
- Contents enter through the ileocecal sphincter, which contracts to prevent reflux.
- In the cecum and proximal colon segmentation contractions occur in the same way as in the small intestine
- Water is absorbed in the distal colon.

I. Mass movements

- Function to move contents over longer distances
- Occur 1-3 timer per day
- Final mass movements move fecal content into the rectum, where they are stored until defecation.

4.5.2 – Defecation

I. Gastrocolic reflex

- Distension of the stomach increases motility of colon, and the frequency of mass movements.
- Parasympathetic nervous system mediate the afferent limb in the stomach.
- CCK and gastrin mediate efferent limb, which causes increased motility.

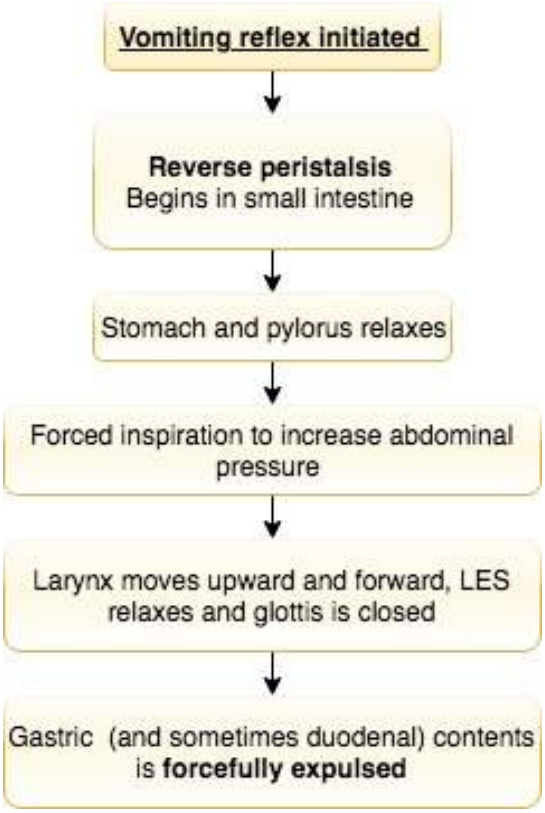
II. Rectosphincteric reflex

- Rectum contracts, and internal anal sphincter relaxes as rectum fills with feces.
- External anal sphincter is tonically contracted and under voluntary control. Defecation will not occur until appropriate.

4.5.3 – Vomiting

I. Vomiting reflex

- Triggered from signals in from the gastrointestinal tract, back of the throat, vestibular system and chemoreceptors in the trigger zone of 4th ventricle s
- These signal sends afferent information to the vomiting center in the medulla activating the vomiting reflex.



4.6 – Test Yourself

1. **What is the function of the circular smooth muscles?**

2. **During the slow waves, when and how can an action potential occur?**

3. **Where is the frequency of slow waves the highest?**

4. **Which phase of swallowing is voluntary?**

5. **What element of swallowing does the ENS control?**

6. **Explain the mechanism and function of receptive relaxation**

7. **What is the main problem with a dysfunctional Upper esophageal sphincter?**

8. **What are the factors increasing action potentials and force of contraction in the stomach?**

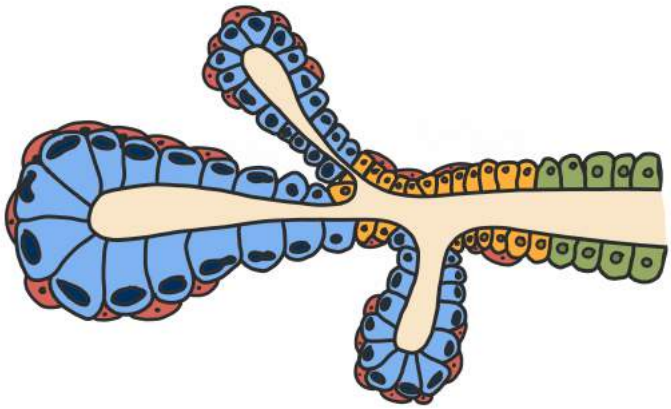
9. **Which two factors are the main regulators of the rate of gastric emptying?**

10. **What is the function of MMC, and how often does it occur?**

Section 5 – Secretion

5.0 – Salivary glands

I. Structure and function of cells in the salivary glands



Acinar cells	Produce the saliva
Myoepithelial cells	Helps move the saliva into ducts
Intercalated ducts	Modify the saliva
Striated ducts	

II. Composition of saliva

- Water, ions, enzymes and mucus
- Initial saliva: Similar to plasma (isotonic)

III. Production of saliva

- Ductal cells are impermeable to water
- Modified saliva:
  1. Hypotonic compared to plasma
  2. More K^+ and HCO_3^- and less Na^+ and Cl^-

Action of ductal cells	Compounds involved
Absorption	Na^+ and Cl^-
Secretion	K^+ and HCO_3^-, organic compounds: enzymes (e.g. amylase), mucin glycoproteins, IgA and kallikrein[1]

[1]Kallikrein activates bradykinin → vasodilation → increased blood flow during periods of high salivary activity

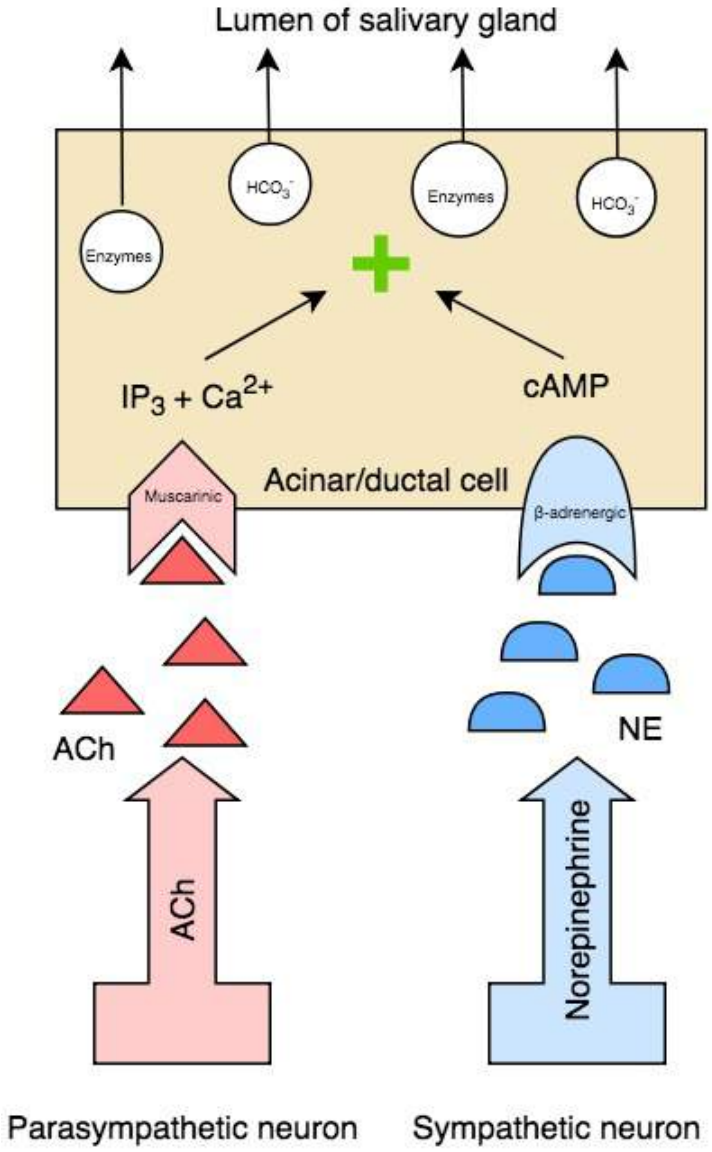
Flow rate and saliva composition: The “contact-time” explanation

1. **High** flow rate of saliva → less time for modification → saliva stays **similar to plasma**
2. **Low** flow rate of saliva → more time for modification → saliva is **hypotonic** compared to plasma

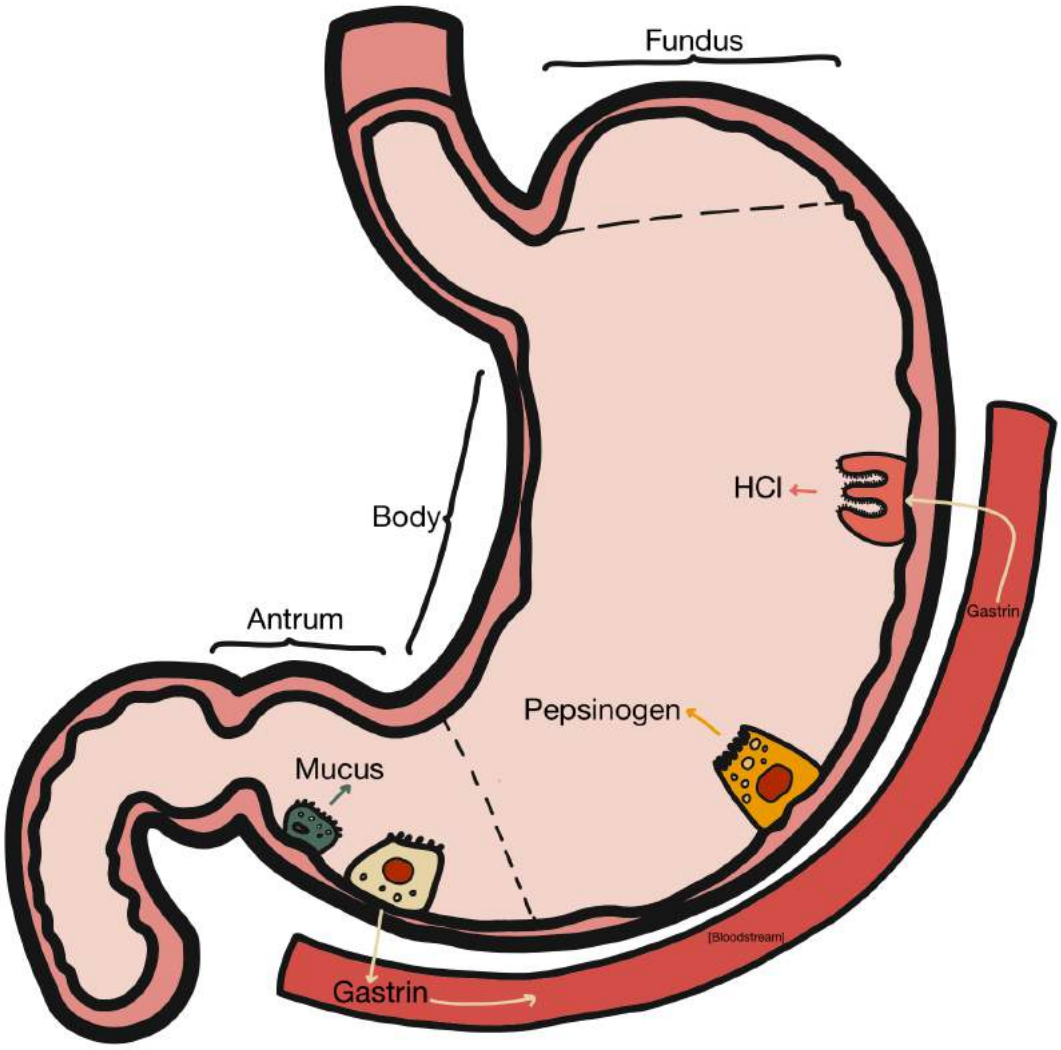
> **HCO_3^- secretion:**
> Selectively stimulated by parasympathetic stimulation and its concentration will be high at high flow rates.

IV. Regulation of secretion

- Secretion of saliva is stimulated by both sympathetic and parasympathetic nerves, but the parasympathetic stimulation dominates.



5.1 – The Stomach

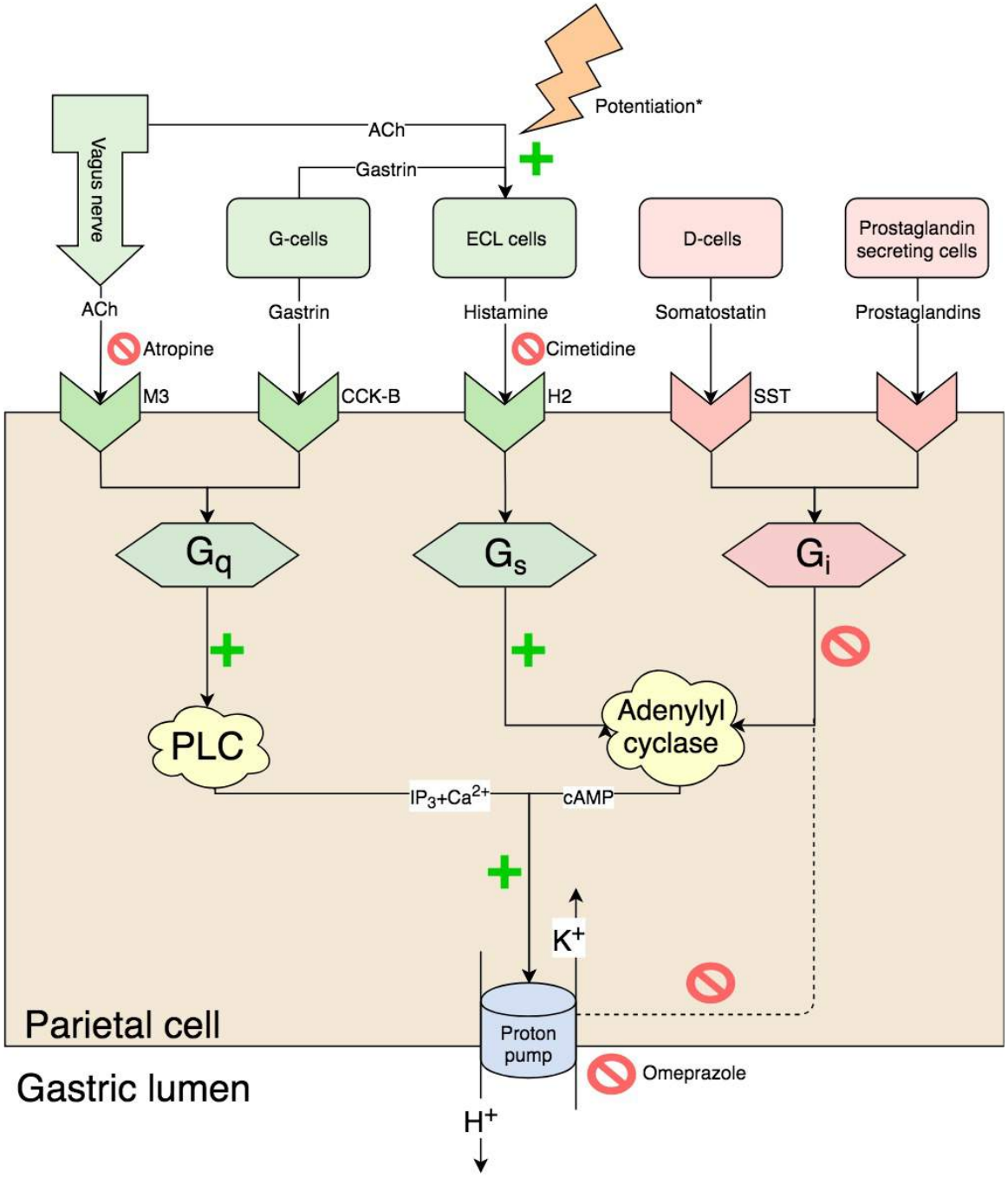


Location	Cells	Secretions
Fundus, Body	Parietal cells	HCL, intrinsic factor
	Chief cells	Pepsinogen
Antrum	G-Cells	Gastrin (to circulation)
	Mucous cells	Mucus, pepsinogen
	D-cells (not in picture)	Somatostatin

I. Gastric acid secretion

- Carbonic anhydrase produces H^+ and HCO_3^- from CO_2 and water
- H^+ is **secreted** into the lumen by K^+, H^+-ATPase
- HCO_3^- is **absorbed** into the blood via a Cl^-, HCO_3^- exchanger. The Cl^- that enters the parietal cell when HCO_3^- is absorbed diffuses into the lumen through Cl^- channels, following the H^+.
- Substances that regulates parietal cells and alters acid secretion:

Alkaline tide:
The increased pH observed in gastric venous blood after a meal. Caused by increased acid secretion which increases bicarbonate absorption.

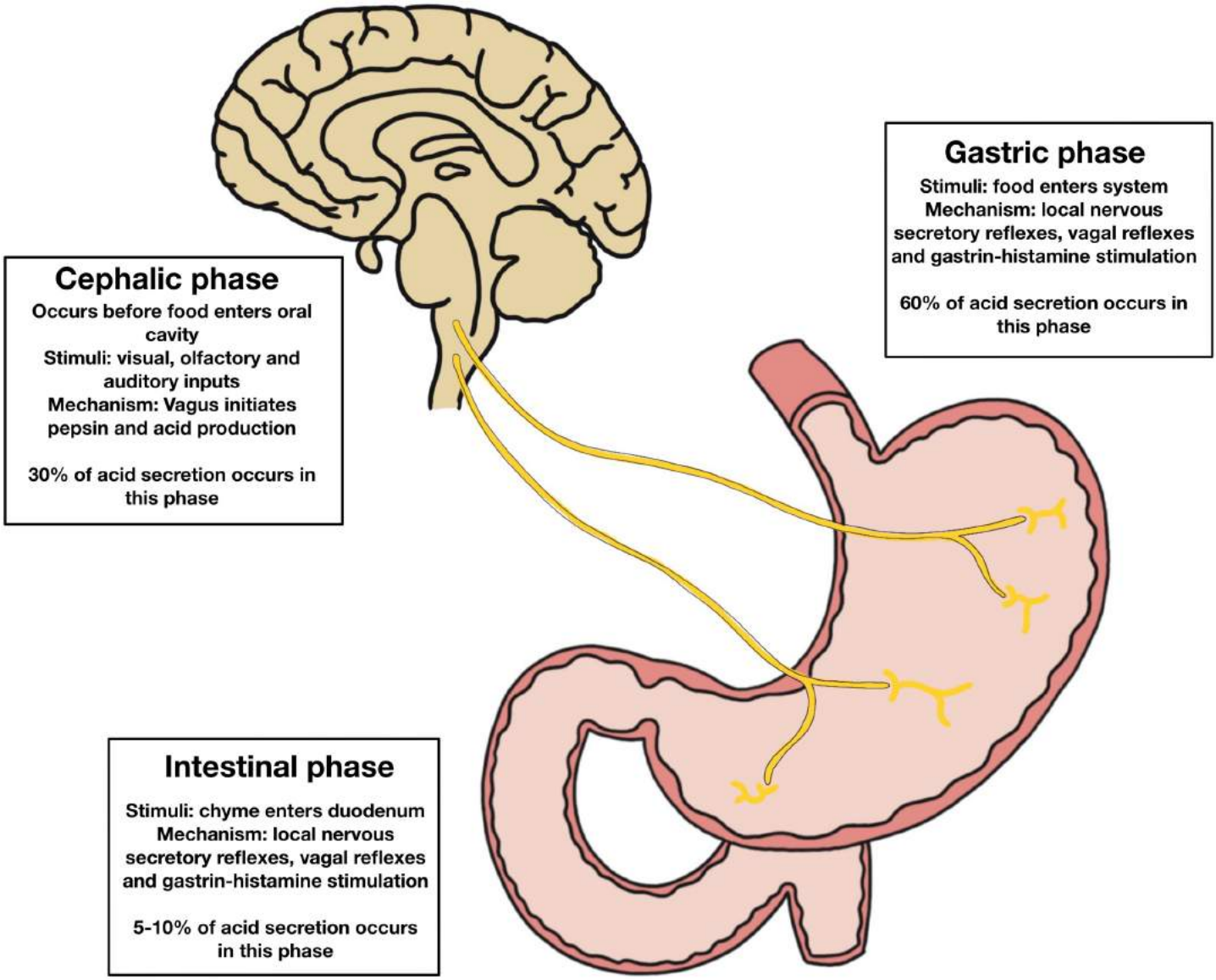


II. Summary of parietal cell regulation:

Source of stimuli	Mediator	Receptor	G-protein	2nd messenger	Result
Vagus nerve	ACh[2]	M3	G_q	IP_3+Ca^{2+}	Increased acid secretion
G-cells	Gastrin	CCK-B			
ECL cells	Histamine	H2	G_s	cAMP	
D-cells	Somatostatin	SST	G_i		Reduced acid secretion
	Prostaglandin				

[2]Atropine can have greater effect on acid secretion than expected due to its indirect inhibition (effect on potentiation) of histamine secretion.

III. Phases of gastric secretion

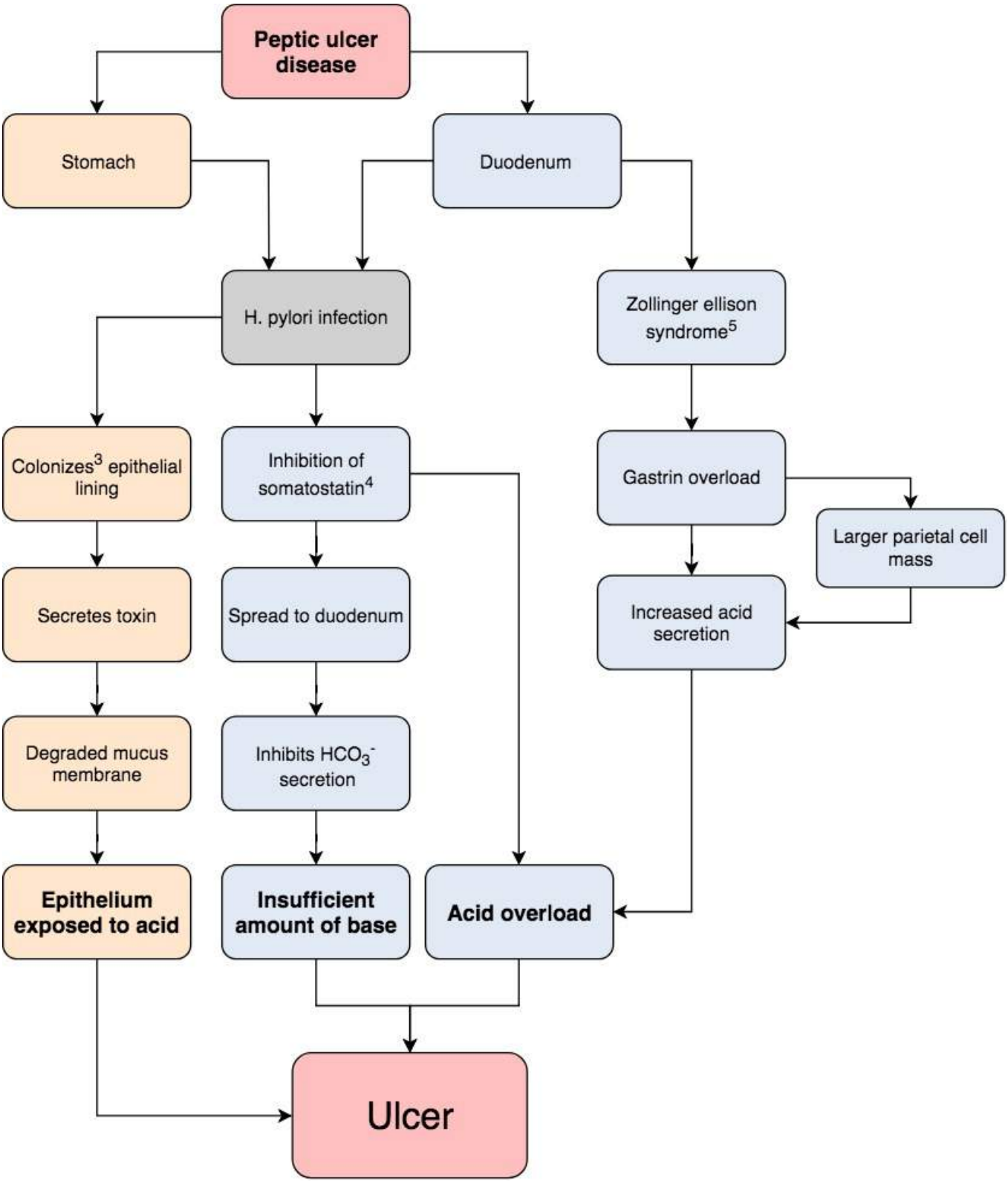


IV. Peptic ulcer disease

- Conditions producing peptic ulcers:
  1. Loss of mucus membrane

     And/or

  2. Excessive acid secretion



V. Summary of peptic ulcer disease:

Location	Cause	Mechanism	
Stomach	Most often H. pylori infection	1. H. pylori colonizes on epithelial lining[3] 2. Secretes toxins degrading the protective mucus barrier 3. Epithelium exposed to acid 4. Ulcer	
Duodenum	Imbalance between acid delivered from stomach and bicarbonate secreted from pancreas	H. pylori	1. Inhibits somatostatin[4] = Acid overload 2. Spread to duodenum and inhibit HCO_3^- secretion = Insufficient amount of base 3. Ulcer
		Zollinger-Ellison syndrome[5] (gastrinoma in pancreas)	1. too much gastrin 2. increased acid secretion + larger parietal cell mass (= even more acid) 3. amount of HCO_3^- in duodenum is insufficient 4. Ulcer Uwaga! Lipase will be inactivated by acid = steatorrhea

[3]H. pylori produces urease, which synthesizes NH_4. NH_4 alkalinizes the environment so the bacteria can survive in the acidic environment in the stomach.

[4]Indirectly inhibits acid secretion (suppress GI hormones)

[5]The symptoms caused by a gastrinoma, most often located in duodenum. A gastrinoma is a gastrin secreting tumor, does not respond to negative feedback.

VI. Pepsinogen secretion

- Secreted by mucous cells and chief cells
- Pepsinogen is converted to pepsin by the low pH in the stomach
- Most dependent on vagal stimulation (distension)

VII. Intrinsic factor secretion

- Only essential secretion in the stomach
- Intrinsic factor is needed for absorption of vitamin B_{12}
- Deficiency causes pernicious anemia

CLINICAL CORRELATION

Pernicious anemia

Intrinsic factor is only secreted by parietal cells in the stomach. Intrinsic factor protects B_{12} from being degraded in the intestines. In situations where the gastric mucosa is damaged and parietal cells are lost, intrinsic factor will not be secreted. The result is disrupted uptake of vitamin B_{12}, and subsequent anemia due to inability to properly produce RBCs.

Examples of situations causing pernicious anemia:

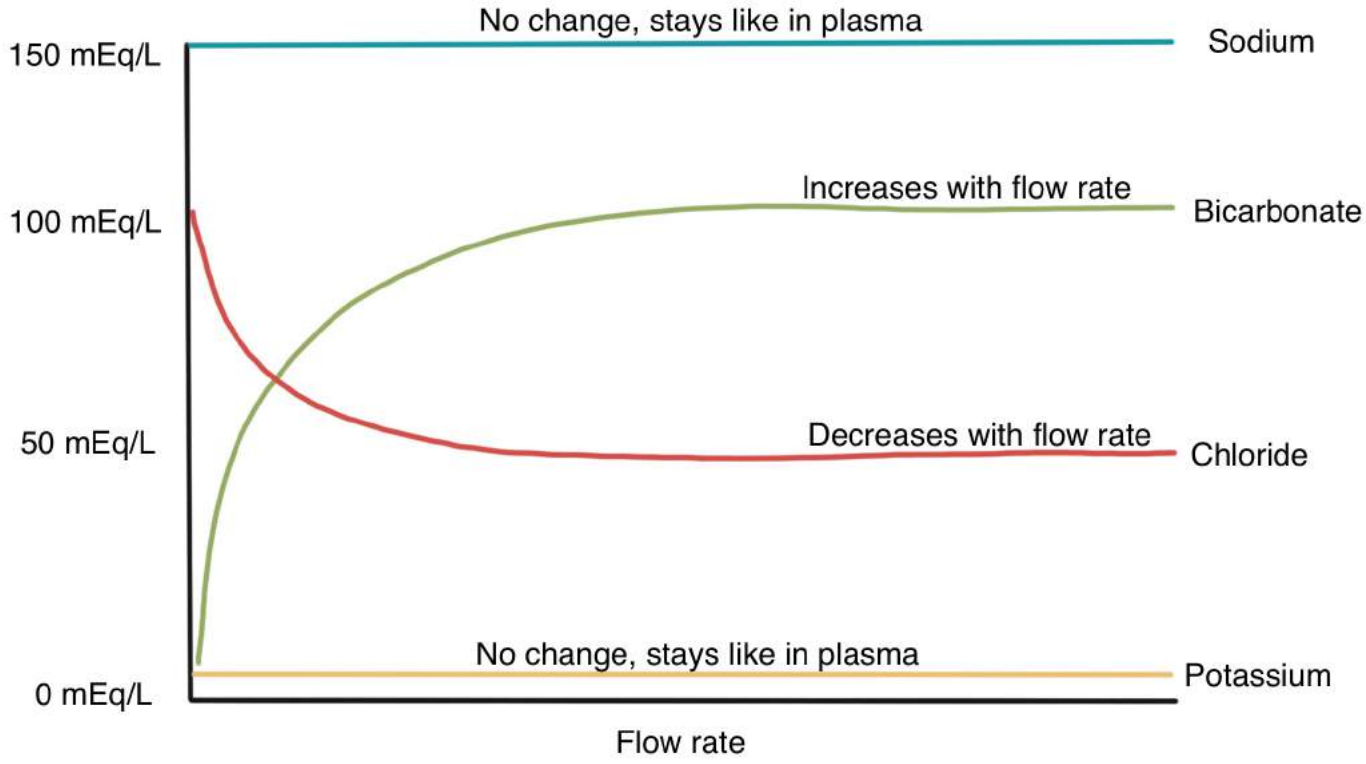
1. Gastric bypass
2. Atrophic gastritis

5.2 – The Pancreas

I. Structure of exocrine pancreas and formation of secretion

Cell type	Component of fluid	Content + function	Production
Acinar	Enzymatic	Enzymes for digestion: Lipase and amylase (active enzymes), inactive proteases	Produced in RER and stored as inactive proteases in zymogen granules until release
Centroacinar + ductal	Aqueous	Na^+, Cl^-, K^+ and HCO_3^- (neutralizes acid from stomach)	**1.** *Reaction catalyzed by carbonic anhydrase:* CO_2 + water → H_2CO_3 **2.** *Next, a spontaneous reaction*: H_2CO_3 → HCO_3^- + H^+ **3.** *HCO_3^-*: Secreted into lumen by a Cl^-/ HCO_3^- exchanger **4.** H^+*:* absorbed into the blood (acidification of pancreatic venous blood after meals)

II. Effect of flow rate on composition



III. Regulation of pancreatic secretion

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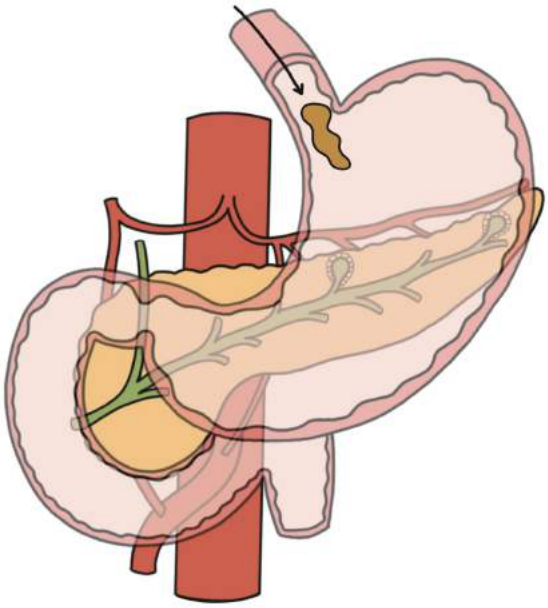
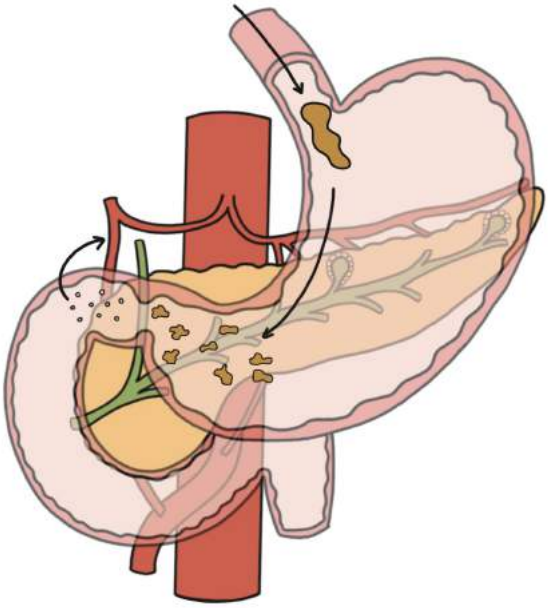
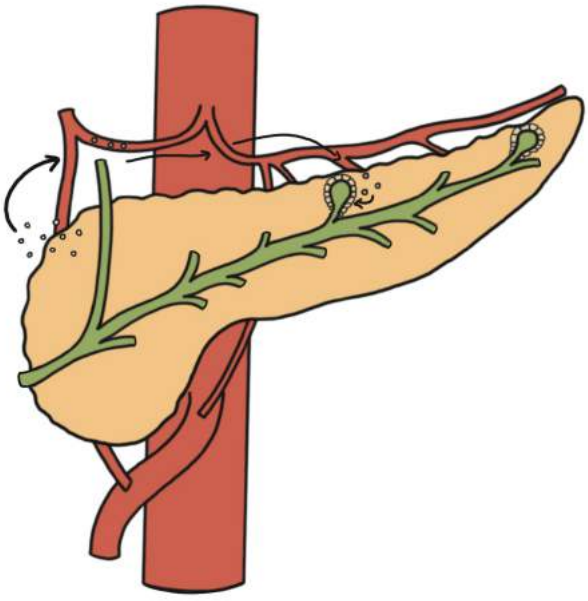
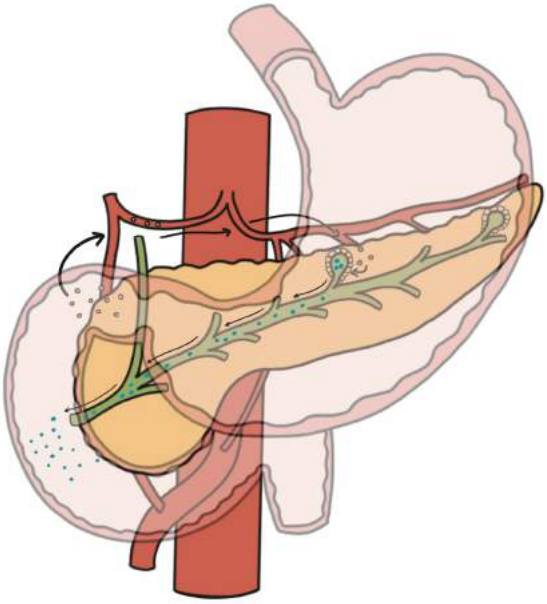
<tr><th colspan="2">Hormonal regulation</th></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>1. Food enters stomach</td><td>2. Stimulation of hormone secretion</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>3. Hormones travel via blood to pancreas</td><td>4. Acini/ducts are stimulated and release their producs</td></tr>
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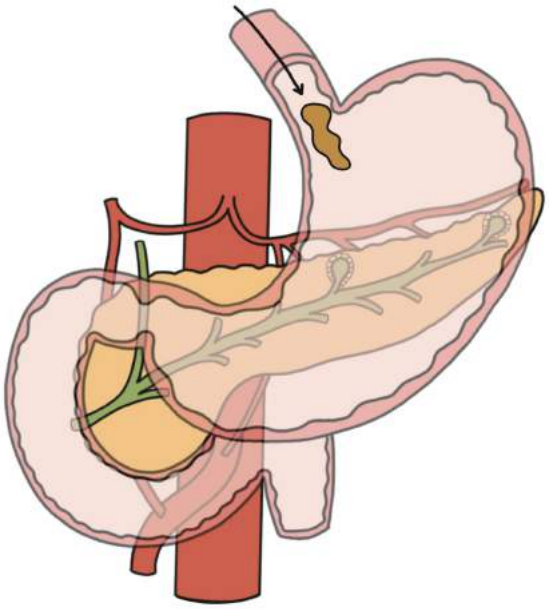
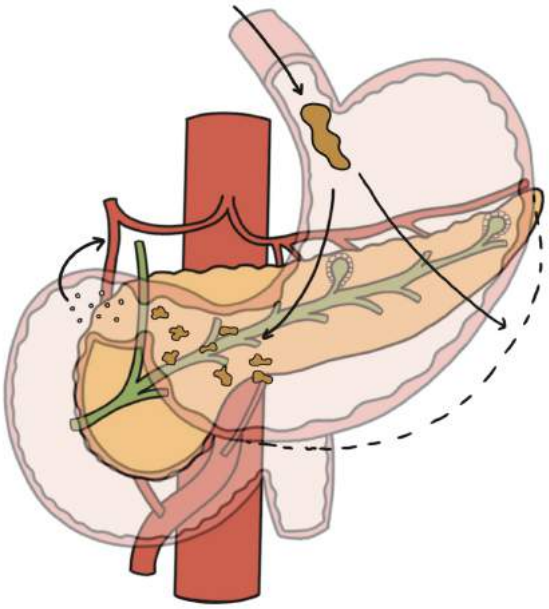
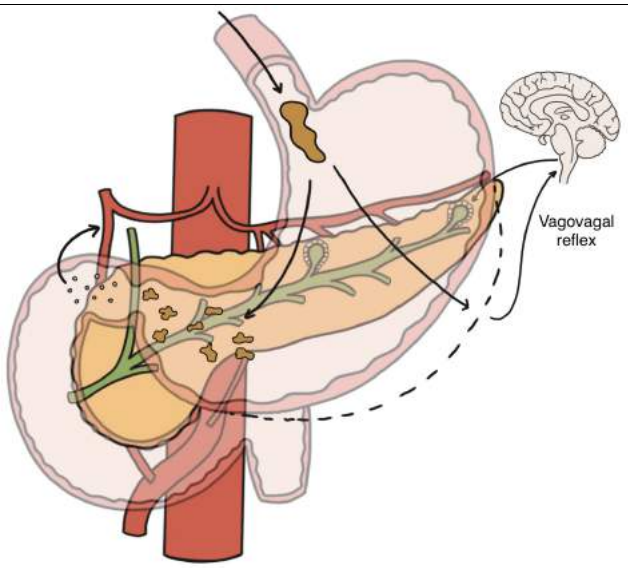
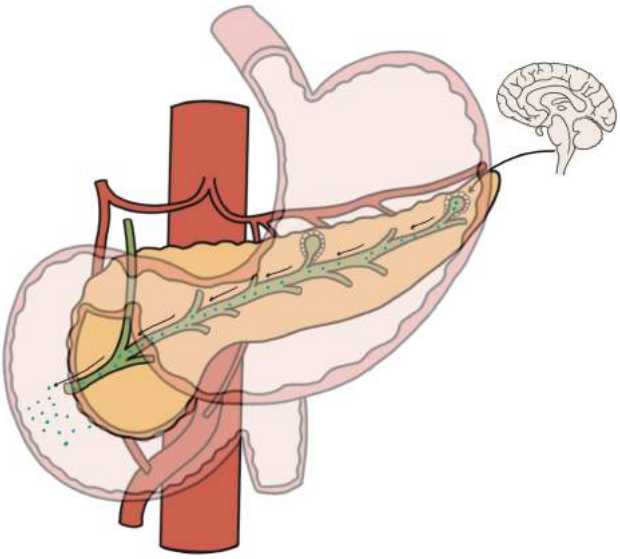
<tr><th colspan="2">Neural regulation</th></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>1. Food enters stomach</td><td>2. Stomach is distended</td></tr>
<tr><td> 
</td><td>  </td></tr>
<tr><td>3. Vagovagal reflex[6]</td><td>4. Acini/ducts are stimulated and release their producs</td></tr>
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[6]Stretch receptors activated → stimulation of afferent vagal fibers → signal travels to medulla → efferent vagal fibers are stimulated and acts on pancreatic acini/ducts.

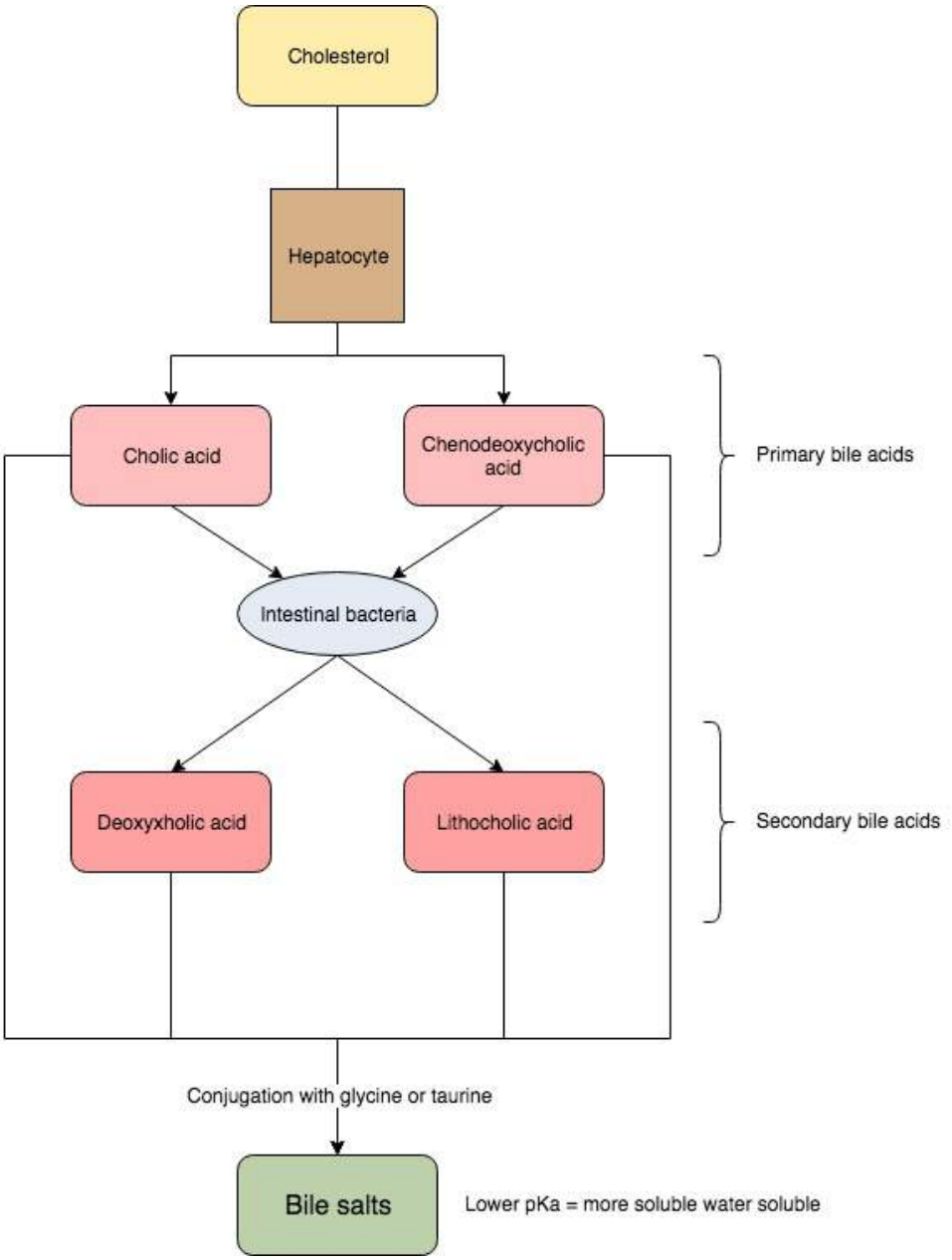
Regulation	System	Trigger	Mediator	Product	Location
Stimulation	PNS	Distension of stomach	Vagus (ACh, Potentiates CCK and Secretin!)	Enzymes + HCO_3^-	Acini + ducts
	Hormones	Fatty acids, some amino acids, small peptides	CCK (from I-cells)	Enzymes	Acini
		H^+ in the lumen	Secretin (from S-cells)	HCO_3^-	Ducts
Inhibition	SNS	Post-ggl. nerves from celiac and superior mesenteric ggl.			

Comment: CCK and vagus mostly stimulates the acini, but has effect on ductal cells too. Compared to secretin the ductal stimulation by CCK and vagus is minor, it only potentiates the effects of secretin.

5.3 – The Gallbladder

- CCK stimulates contraction of gallbladder and relaxation of sphincter of Oddi → Ejection of bile
- Bile salts are recirculated to the liver from the ileum via the enterohepatic circulation
- Bile is concentrated in the gallbladder: water and ions move out and organic compounds remain

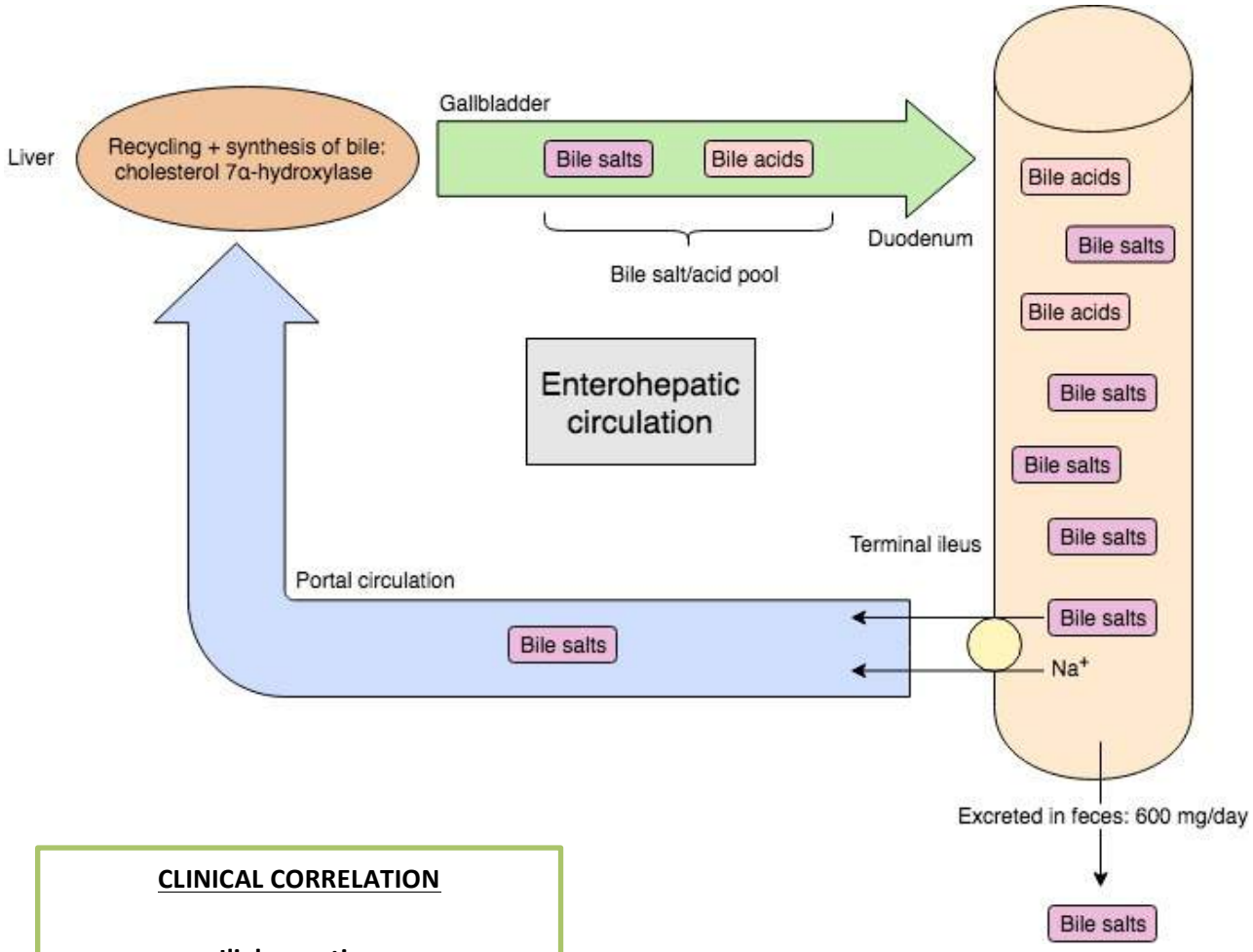
I. Composition of bile



II. The function of bile

- Epithelial cells in gallbladder absorb water and ions isosmotically → More concentrated bile
- Bile is ejected when duodenum is relaxed and the pressure is low
- Bile emulsifies dietary lipids:
    - Bile salts surround the lipid, making droplets. They repel each other, which increases surface area for absorption.
    - Bile salts then form *micelles* with the products of lipid digestion.
- Primary bile salts are more efficient at solubilizing lipids because they have more hydroxyl groups (–OH) than secondary bile salts

III. Enterohepatic circulation



CLINICAL CORRELATION

Ilial resection

- If a patient undergoes Ilial resection, the recirculation of bile salts will be disrupted.
- Large amounts of bile salts will be excreted in the feces, and the liver will be unable to replace the lost bile.
- The result is decreased absorption of fats and steatorrhea (fatty stools).

Choleretic agents

Any agent that stimulates hepatic secretion of bile. The recirculation of bile salts has what we call a "choleretic effect" on the liver.

Recirculation of bile → Secretion of bile

5.4 – Test Yourself

1. **What is the composition of saliva before and after its modified in the salivary gland duct?**

2. **According to the "contact-time" explanation, the bicarbonate concentration in saliva should be low at times when flow rate is high. Why is this not the case?**

3. **Which cells secretes Intrinsic factor?**

4. **Which secretory product from cells in the stomach is not secreted into the stomach? Where is it secreted into?**

5. **What are the roles of gastrin and ACh in histamine secretion by ECL cells? Why is this important to remember when administrating atropine?**

6. **In which phase of gastric secretion is the most gastric acid secreted?**

7. **How does a peptic ulcer develop?**

8. **What is a complication of a gastric bypass?**

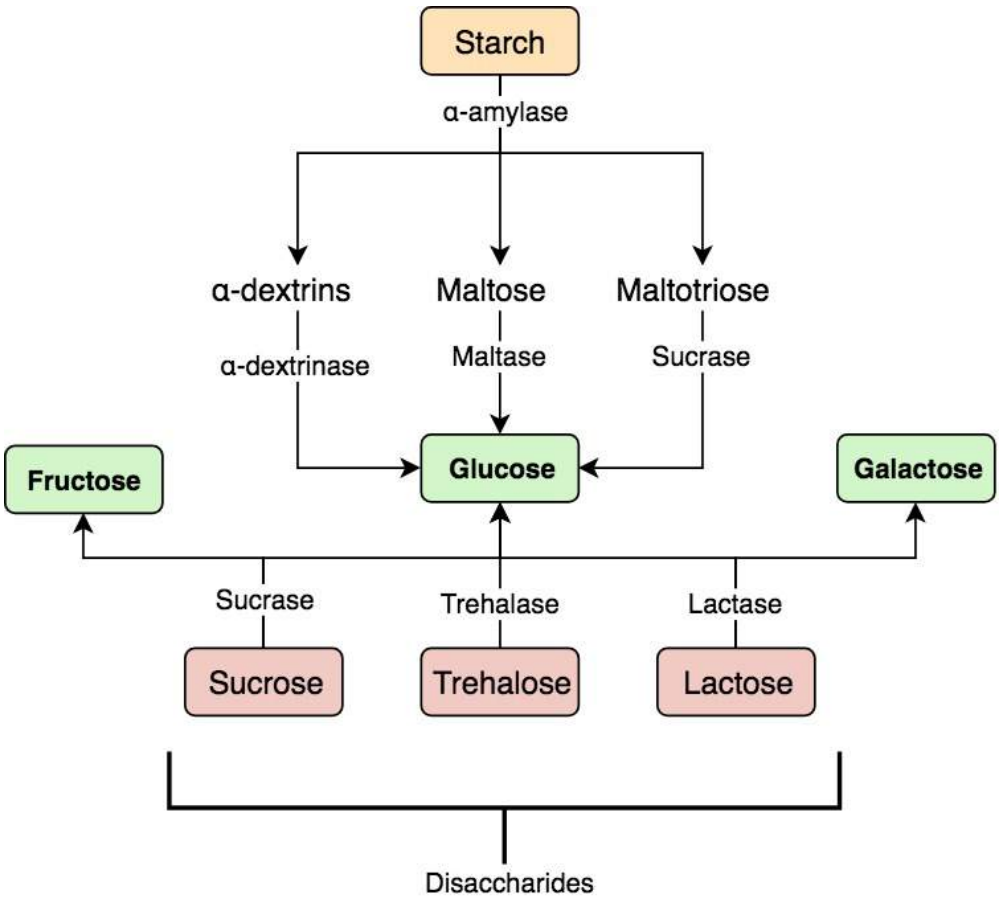
9. **How is the vagus nerve involved in pancreatic secretion?**

10. **What is the function of bile? What can be a complication of an ilial resection?**

Section 6 – Digestion and Absorption

6.0 – Carbohydrates

I. Digestion



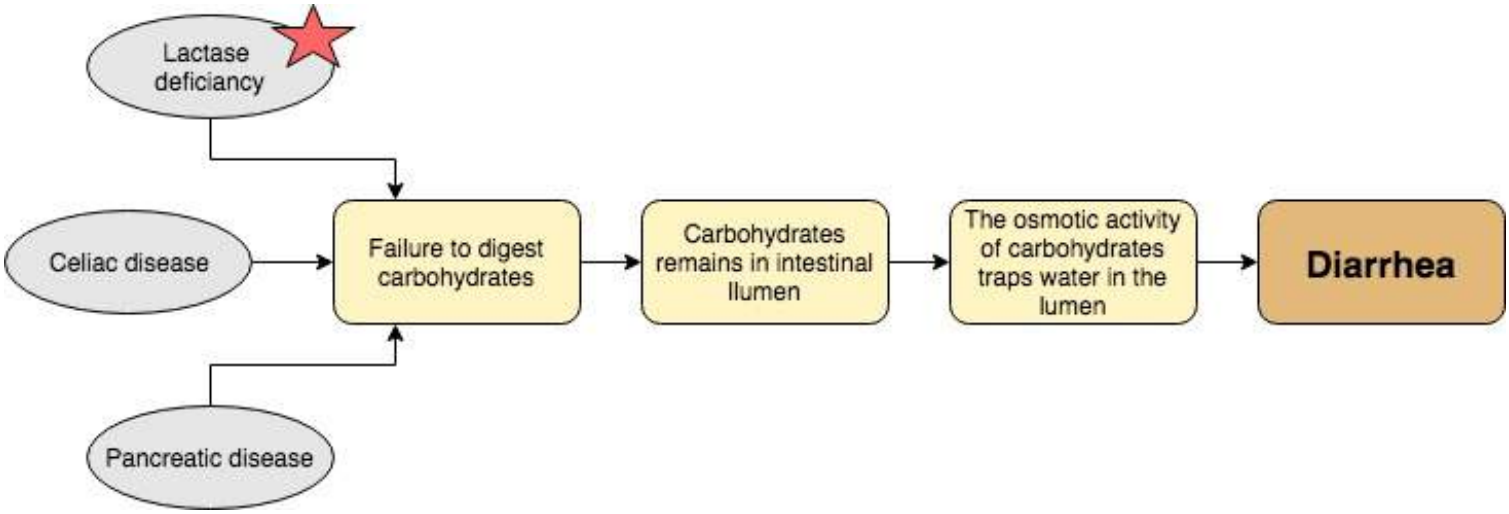
II. Absorption

Disaccharide	Transporter in	Mechanism	Transporter out	Mechanism
Glucose	SGLT 1	Sodium dependent cotransport	GLUT 2	Facilitated diffusion
Galactose				
Fructose	GLUT 5	Facilitated diffusion		

Comment: Intracellular sodium concentration is kept low (ideal for sodium dependent cotransport) by the sodium-potassium pump.

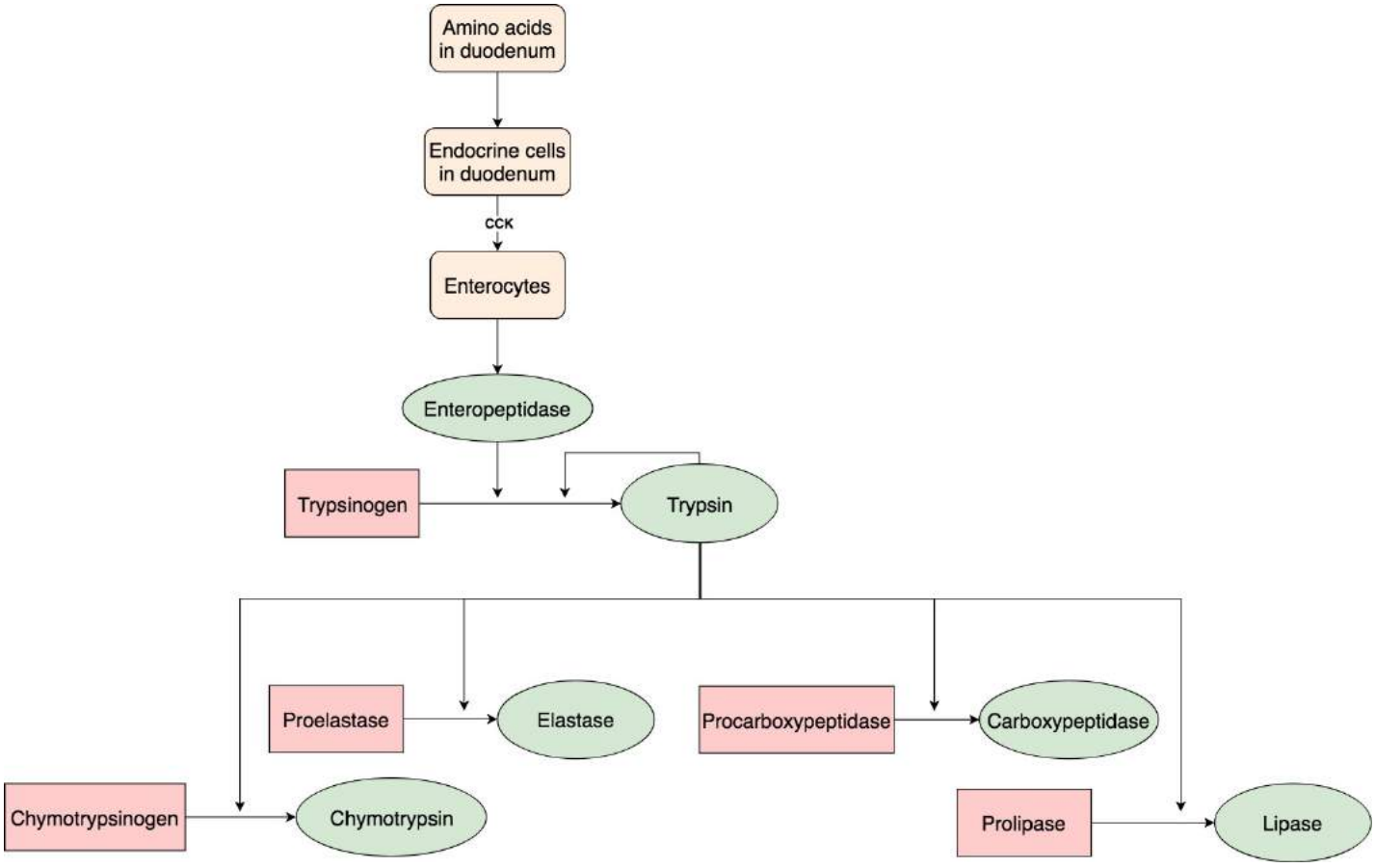
III. Disorders of carbohydrate digestion and absorption

Osmotic diarrhea: Undigested macronutrients in intestinal lumen acts as solutes and "pull" water into the lumen.



6.1 – Proteins

I. Digestion



Summary of protein digestion

Location	Type of enzyme	Inactive enzymes	Activated by	Active enzyme
Stomach	Endoprotease[1]	Pepsinogen	Gastric acid	Pepsin[3]
Small intestine		Trypsinogen	Enteropeptidase/ trypsin	Trypsin
		Chymotrypsinogen	Trypsin	Chymotrypsin
		Proelastase		Elastase
		Prolipase		Lipase
	Exoprotease[2]	Procarboxypeptidase		Carboxypeptidase A + B

[1] Hydrolyze interior peptide bonds

[2]Hydrolyze one amino acid at a time from C-terminal ends of proteins and peptides

[3]Above pH 5, pepsin in inactivated, it has 3 isoenzymes and is not an essential enzyme

II. Absorption

Molecules absorbed	Mechanism
Amino acids	Sodium cotransport[4], 4 types of channels: 1. Neutral 2. Basic 3. Acidic 4. Imino
Dipeptides	Proton di-/tripeptide cotransporter[5]
Tripeptides	

[4]L-amino acids are absorbed with the same mechanism as monosaccharides, sodium cotransport

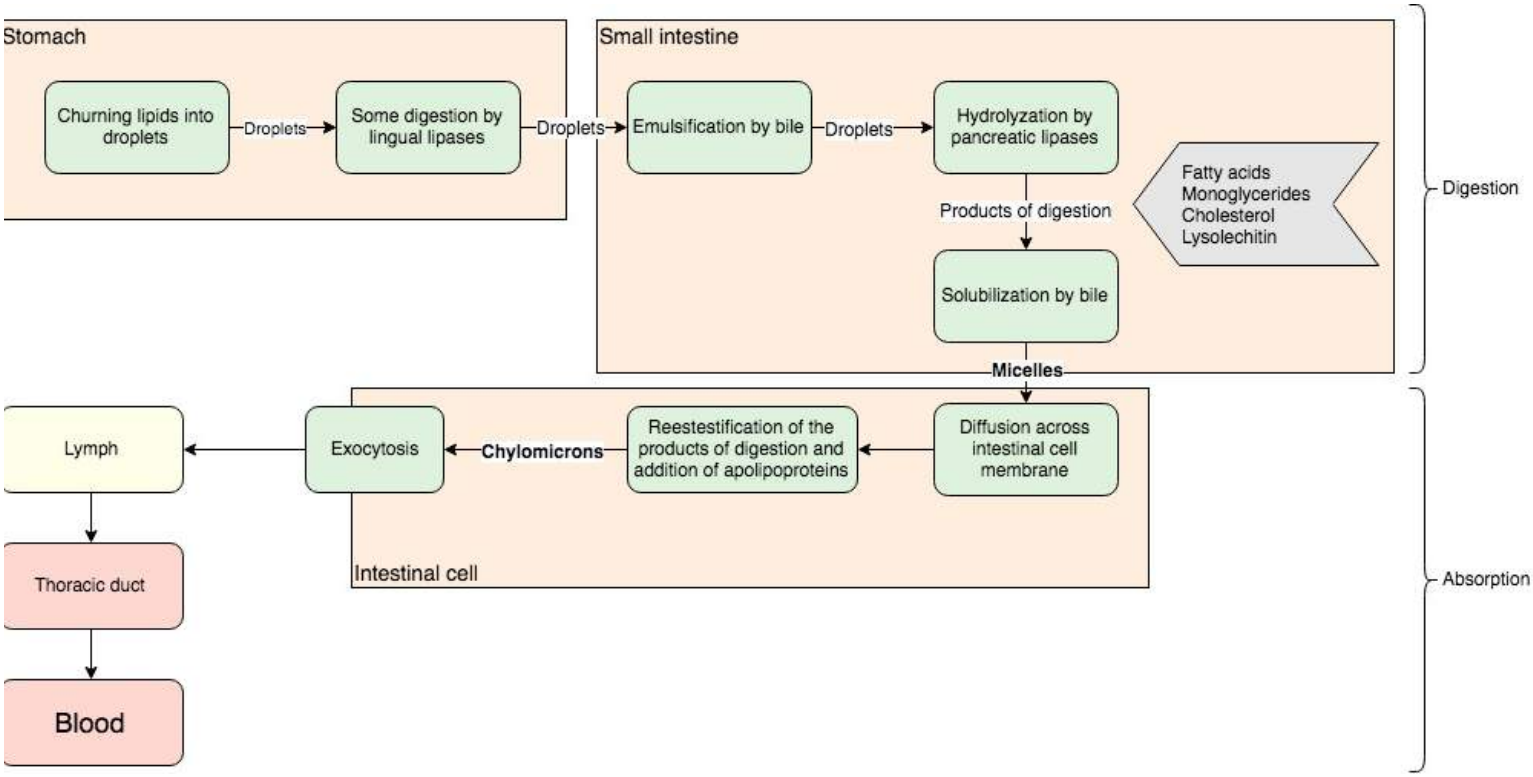
[5]Proton gradient is maintained by proton/sodium antiporters on the apical membrane

III. Disorders of protein digestion

Mechanism	Why is it a problem?	Examples
Pancreatic dysfunction	Absence of trypsin can make it look like all enzymes are missing	Chronic pancreatitis
Transport dysfunction	Impaired absorption of digested material	Cystinuria: Genetic disorder in which the cotransporter for dibasic amino acids in kidneys and intestines is missing or dysfunctional.

6.2 – Lipids

I. Digestion and absorption



The most important action of the stomach in lipid digestion is to slowly release the stomach content to the small intestines. If the content is released too fast, there will not be enough time to digest the lipids. CCK is the hormone responsible for slowing down gastric emptying.

II. Disorders of lipid digestion

Mechanism	Why is it a problem?	Examples
Pancreatic insufficiency	No enzymes or bicarbonate[6]	Cystic fibrosis
Acidity in duodenum	Inactivation of degestive enzymes	Zollinger-Ellison syndrome
Deficiency of bile salts	No production of micelles	Ilial resection
Bacterial overgrowth	Bacteria can deconjugate bile salts[7]	Decreased motility
Fewer intestinal cells	Less surface area = less diffusion[8]	Tropical sprue
Failure to synthesize apolipoproteins	No chylomicrons = no absorption[9]	Malnutrition

[6]No lipase to digest the lipids or bicarbonate to alkalinize stomach content

[7]Bile acids (deconjugated bile salts) are less lipid soluble than bile salts, and are therefore less effective

[8]Rate of diffusion depends on surface area.

[9]Apolipoproteins are essential for the structure and function of chylomicrons

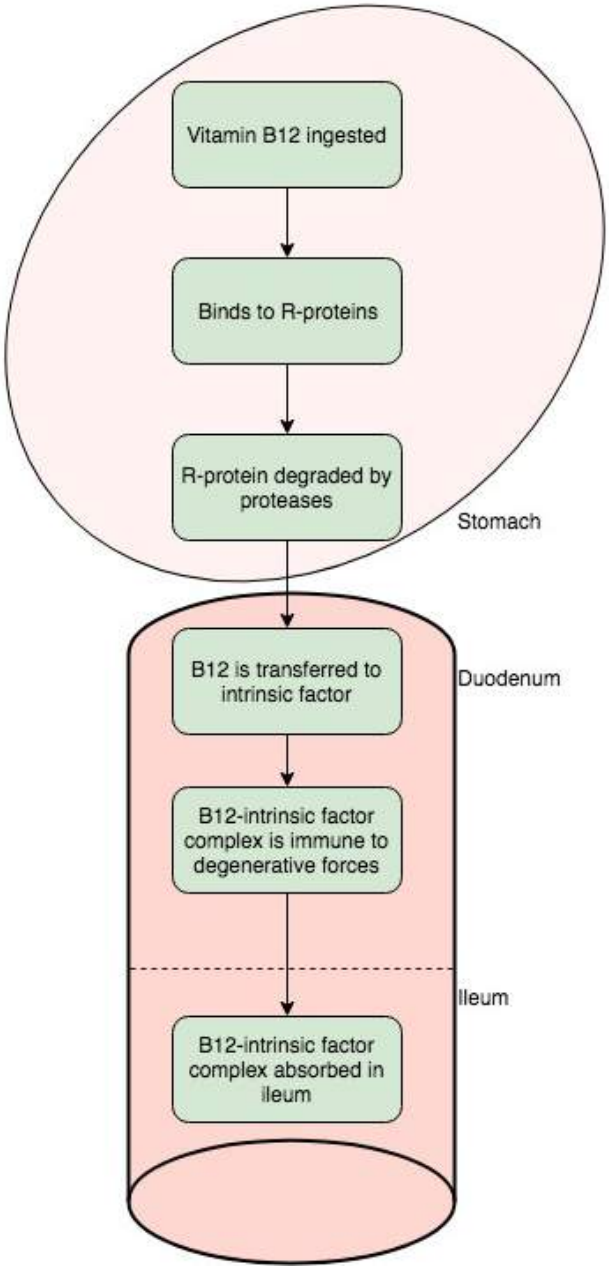
6.3 – Vitamins

I. Lipid soluble

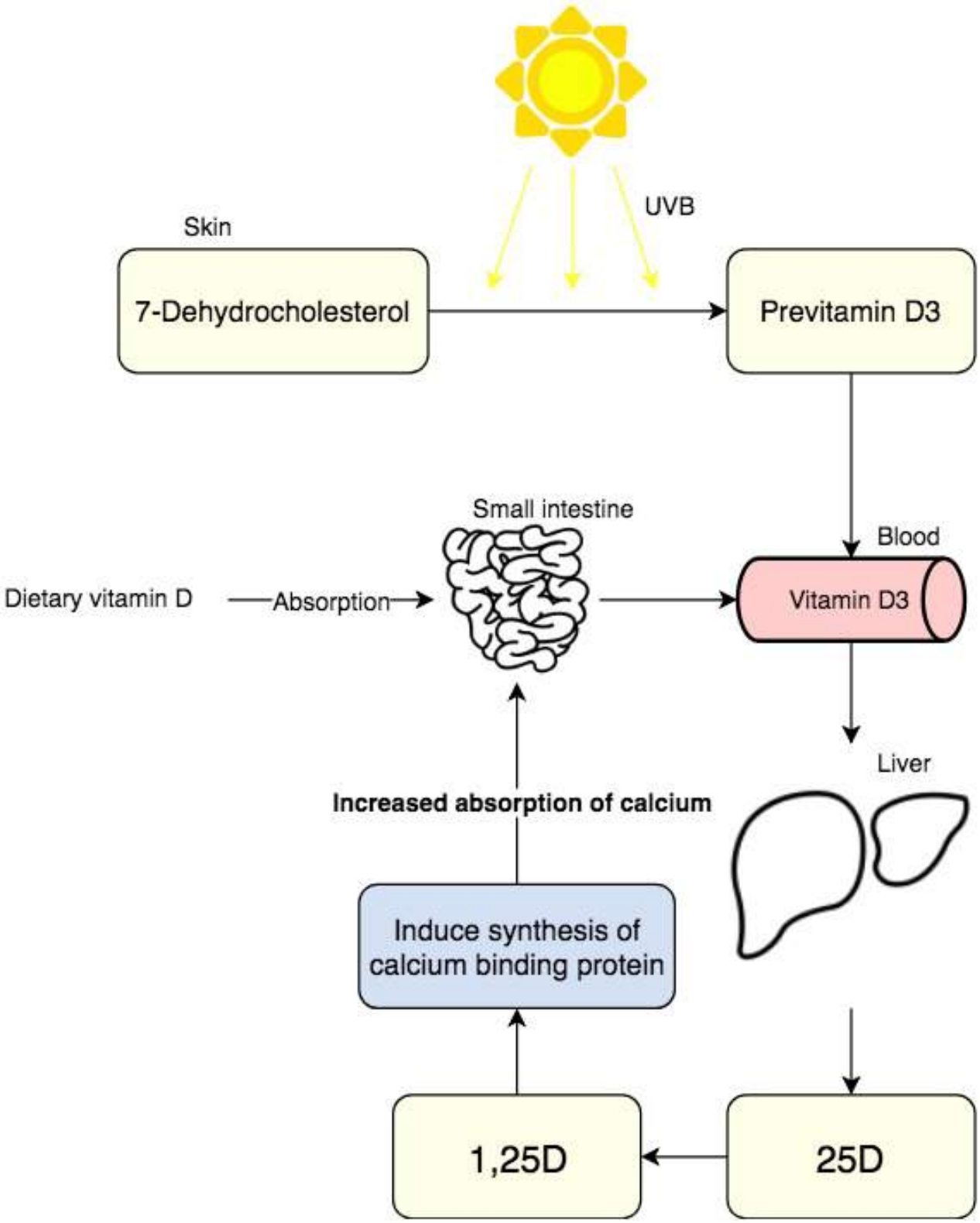
- The lipid soluble vitamins are vitamins A, D, E and K – *ADEK*. Processed like dietary lipids.

II. Water soluble

- Most of them are absorbed with sodium dependent cotransport, except vitaminB_{12} and vitamin D
- **Vitamin B_{12}:**

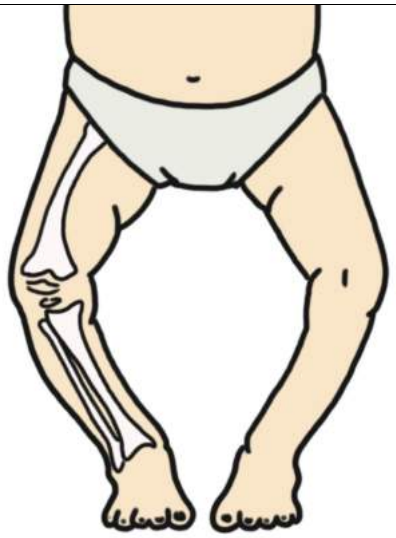
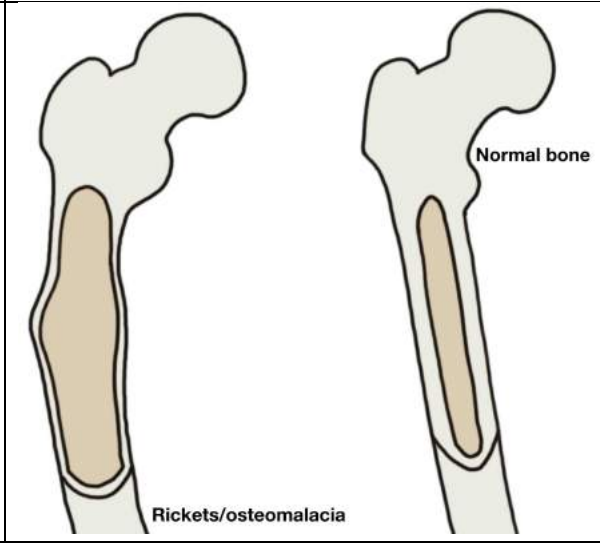


- **Vitamin D:**
  The active form of vitamin D (1,25-dihydroxycholecalciferol) is required for normal absorption of calcium.

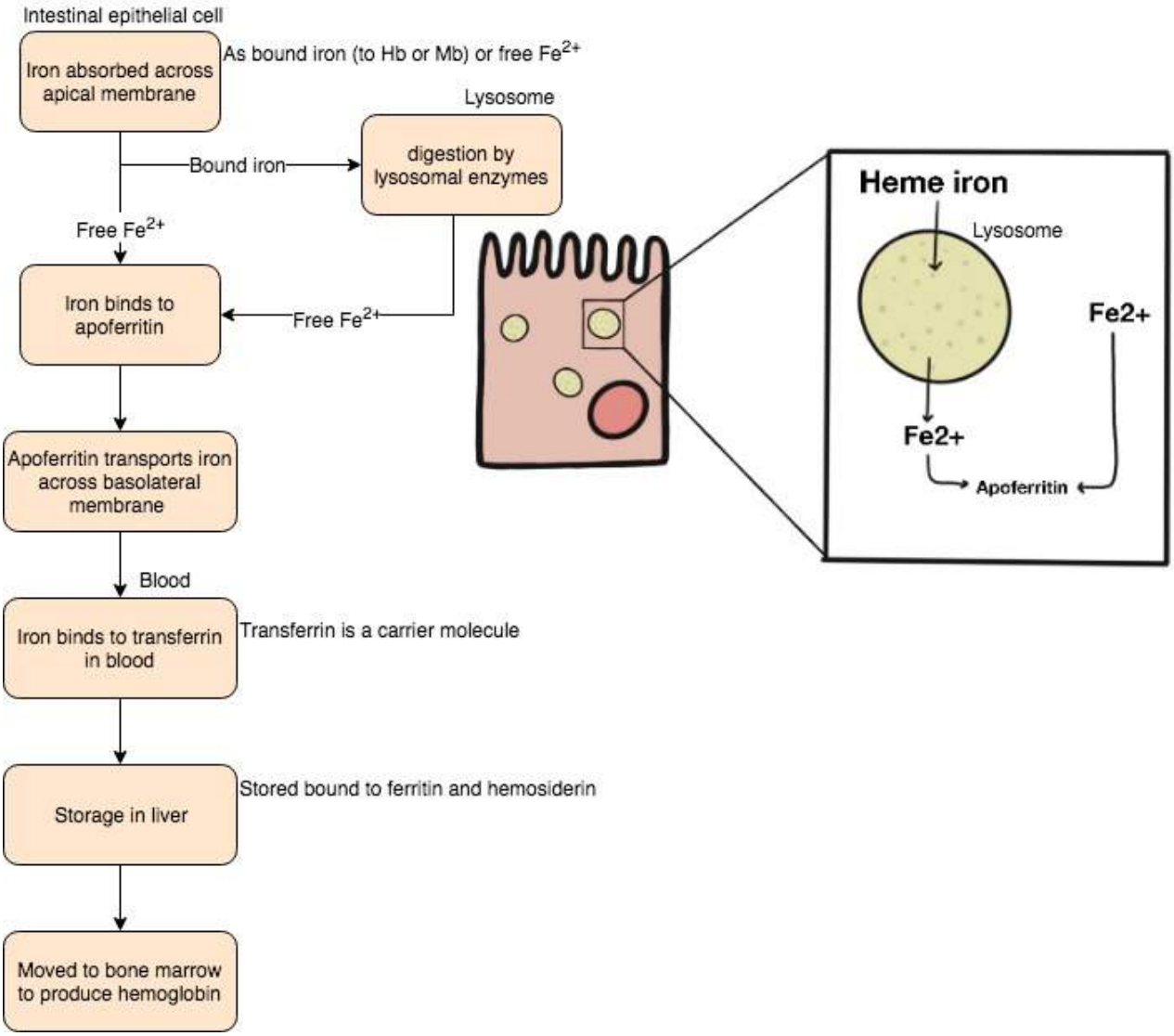


25D: 25-dihydroxycholecalciferol
1,25D: 1,25-dihydroxycholecalciferol

Vitamin D deficiency disorders

Vitamin D deficiency: decreased calcium absorption	
Children: Rickets	**Adults: Osteomalacia**
	

6.4 – Iron


Intestinal epithelial cell
Iron absorbed across apical membrane
As bound iron (to Hb or Mb) or free Fe^{2+}
Lysosome
digestion by lysosomal enzymes
Bound iron
Free Fe^{2+}
Iron binds to apoferritin
Free Fe^{2+}
Apoferritin transports iron across basolateral membrane
Blood
Iron binds to transferrin in blood
Transferrin is a carrier molecule
Storage in liver
Stored bound to ferritin and hemosiderin
Moved to bone marrow to produce hemoglobin
Heme iron
Lysosome
Fe2+
Fe2+
Apoferritin

6.5 – Test Yourself

1. **How are the monosaccharides transported into the intestinal cells?**

2. **What is osmotic diarrhea? When does it occur?**

3. **What is the stimuli that initiates the release of enteropeptidase from enterocytes?**

4. **GLUT2 is a transporter of glucose; from where to where does it transport glucose?**

5. **Where does most of the lipid digestion occur?**

6. **How are lipids transported into blood?**

7. **What is an R-protein?**

8. **What is the major role of vitamin D?**

9. **What happens if a child is deficient of vitamin D vs. If an adult person has a vitamin D deficiency?**

10. **Which forms of iron can be absorbed across the intestinal cell membrane?**

Section 7 – Intestinal Fluid and Electrolyte Transport

7.0 – Fluid Balance

I. Mechanism of fluid absorption

Intestinal epithelial cells lining the intestines absorb large amounts of fluid.

1. First solute is absorbed
2. Then water is absorbed

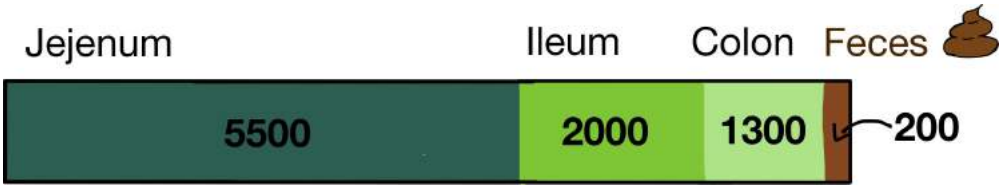
The water and solute absorbed is always isosmotic, in other words they are absorbed in proportion to one another.

II. Daily fluid balance

Every day approximately **9 L** of fluid is absorbed from the GIT. This large volume is composed of

- 2 L of liquids consumed in the diet
- 7 L of gastrointestinal secretions (salivary, gastric, pancreatic, biliary and intestinal secretions)

Between 100-200mL is not absorbed, and is excreted in the **feces**.



Most of the fluid is absorbed by the **epithelial cells** of the small intestine and colon. The largest amounts of fluid is absorbed in the small intestine (approximately 7500ml) .

III. Routes of absorption

The epithelial cells of the small intestine both secrete and absorb electrolytes and fluid. This is done via both cellular and paracellular (inbetween the cells) routes. Whether the fluid and electrolytes moves through the cellular or paracellular routes is decided by the permeability of the tight junctions between the epithelial cells.

- **Small intestine** - tight junctions have little resistance and permit more paracellular movement.
- **Colon** - tight junctions are highly resistant, and do not permit paracellular movement.

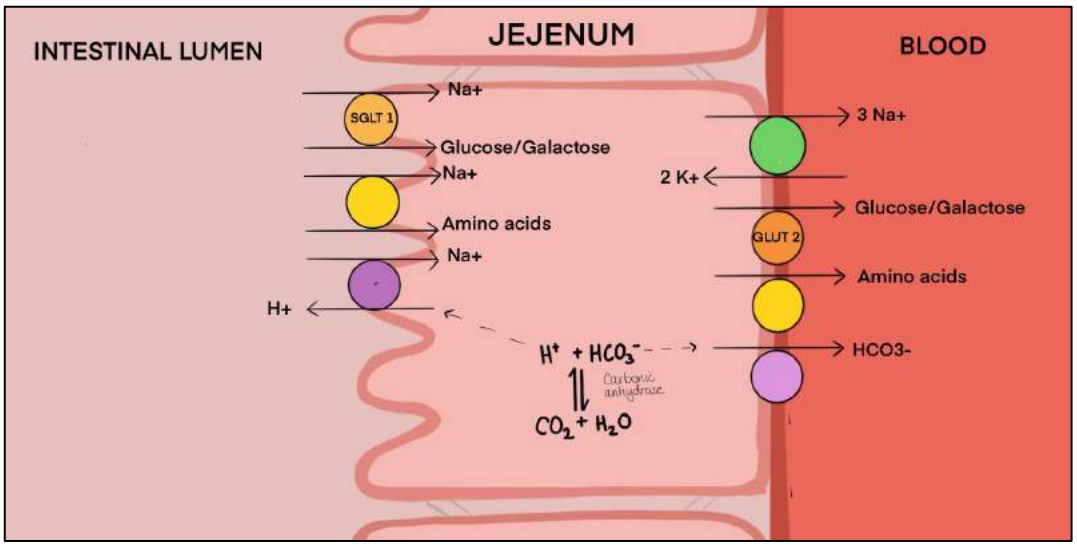
7.1 – Intestinal Absorption

7.1.1 – General

- Mechanisms of absorption vary in the jejunum, ileum and colon.
- Intestinal **absorption = villi**
- Intestinal **secretions = crypts**

7.1.2 – Jejunum

- Net absorption of $Na^+ and\ HCO_3^-$ into the bloodstream.
- Major site of Na+ in small intestine – mechanism similar to early proximal tubule in kidney.



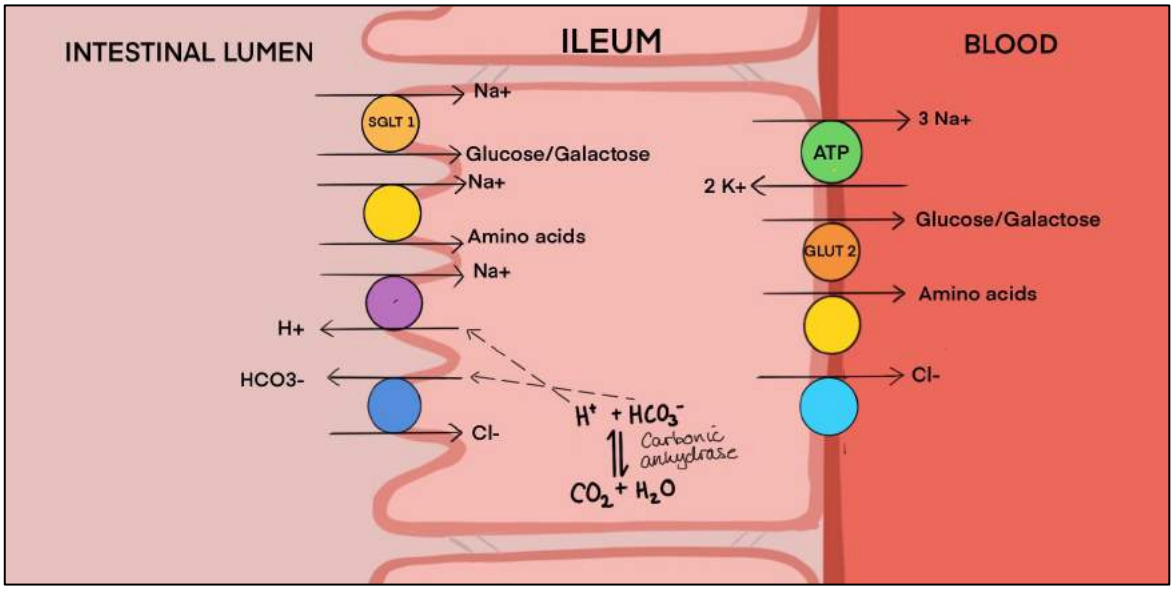
Epithelial cell of the jejunum	
Apical membrane	
Na^+- glucose cotransporter	Both substances are absorbed into the cell.
Na^+- galactose cotransporter	
Na^+- amino acid cotransporter	
$Na^+ - H^+$exchanger	Na^+ is absorbed into the cell, H^+ is secreted into the intestinal lumen[1].
Basolateral membrane	
$Na^+ - K^+$ ATPase	Active transport – 3 Na^+ into blood, 2 K^+ into the cell. Responsible for "housekeeping" - keeping the correct intracellular concentrations of $K^+$and Na^+
GLUT2	Glucose transporter, transports glucose out of the cell and into the blood.
Amino acids transporters	Transports amino acid into the blood.
HCO_3^- transporter	Transports bicarbonate into the blood.

[1] H+ needed for Na+-H+ exchange comes from CO_2 and H_2O which is converted to H^+ and bicarbonate in the presence of carbonic anhydrase. H+ is secreted into the intestine, and HCO_3^- is absorbed into the blood.

$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} HCO_3^- + H^+$.

7.1.3 – Ileum

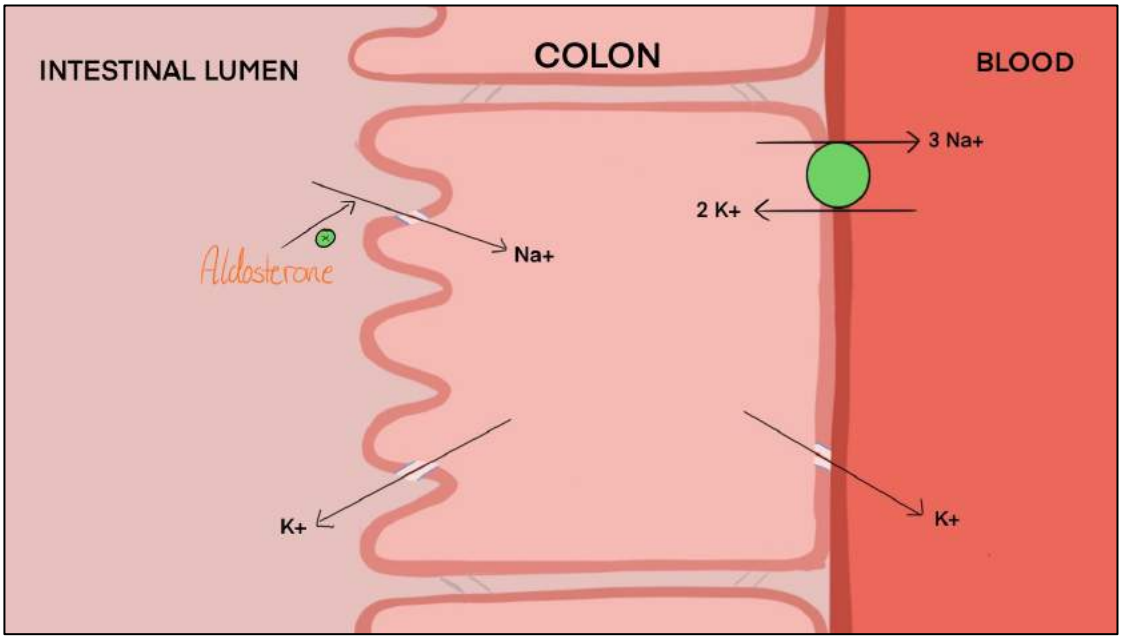
- Net absorption $of\ NaCl$



Contains same transport mechanism as the jejunum, plus:

Epithelial cell of the ileum	
Apical membrane	
Cl^- - HCO_3^- exchanger	HCO_3^- is secreted into the lumen of the intestine (not absorbed to blood as in the jejunum) Cl^- is absorbed into the cell.
Basolateral membrane	
Cl^- transporter	Transports Cl^- into the blood

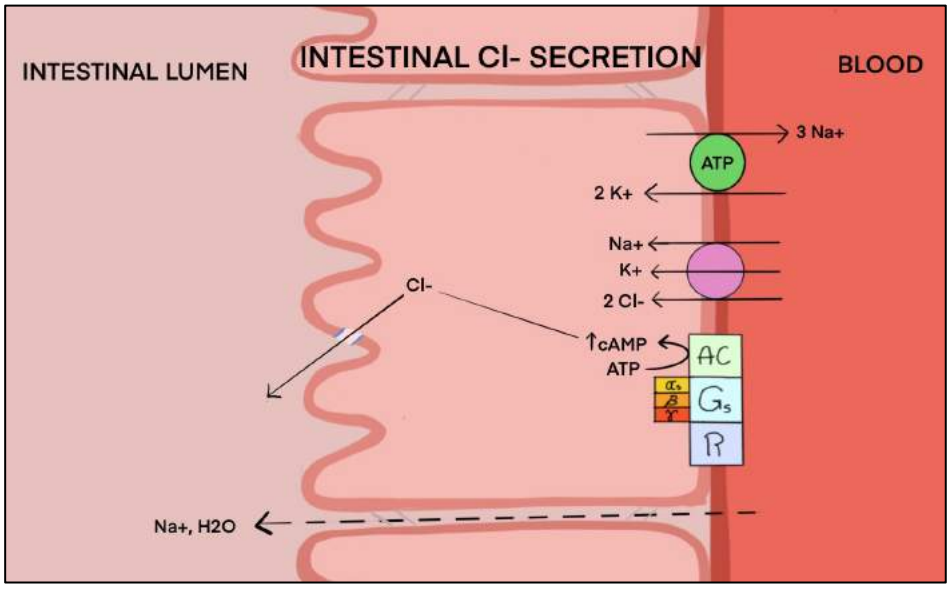
7.1.4 – Colon



Epithelial cell of the colon	
Apical membrane	
Na^+- channel	**Absorbs** Na^+ Produced by aldosterone – leads to increase in Na+ absorption and secondarily to K+ secretion
K^+- channel	K^+ is **secreted** by passive diffusion into the intestinal lumen. The mechanism behind this is that the more Na+ absorbed from fluids, the more K+ is taken into the cell by $Na^+ - K^+$ATPase at the basolateral membrane. K+ will move down it's electrochemical gradient, and with increasing amounts of intracellular K^+more will diffuse into the intestinal lumen[1]. **NB!** Indirectly regulated by aldosterone
Basolateral membrane	
$Na^+ - K^+$ ATPase	Active transport – 3 Na^+ into blood, 2 K^+ into the cell. Responsible for "housekeeping" - keeping the correct intracellular concentrations of $K^+$and Na^+

[1] In diarrhea – high flow rate of intestinal fluid causes increased colonic K^+ secretion, resulting in increased K^+loss via the feces and this may lead to **hypokalemia.**

7.2 – Intestinal Secretion



CLINICAL CORRELATION

Cholera

Cholera, caused by the bacteria Vibrio Cholera, presents with abrupt onset of watery diarrhea, with the loss of up to 1 liter fluid per hour in severe cases. The bacteria attaches to the intestinal epithelial cells and releasing a toxin, which aim to increase intracellular cAMP. Increased cAMP results in active secretion of Na and Cl and other fluids are lost through the osmotic pull from NaCl.

Epithelial cell of intestinal crypts	
Apical membrane	
Cl^--channel	Cl^-diffuses into the intestinal lumen Channel is usually closed. Opens by stimuli from ACh and VIP amongst others. They activate cAMP, which opens the Cl- channels.
Basolateral membrane	
$Na^+ - K^+$ ATPase	Active transport – 3 Na^+ into blood, 2 K^+ into the cell. Responsible for "housekeeping" - keeping the correct intracellular concentrations of $K^+$and Na^+
$Na^+ - K^+ - Cl^-$ cotransporter	Transports 1 Na^+, 1 K^+ and 2 $Cl^-$from blood into the cell.

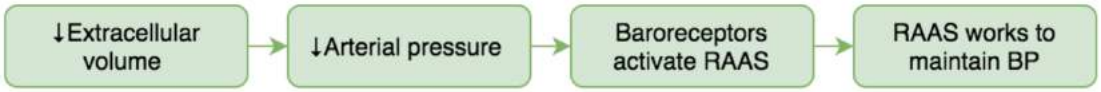
Paracellular diffusion – movement between the cells

- Na^+ diffuses into the intestinal lumen, following Cl^-
- H_2O is secreted following the secretion of NaCl

7.3 – Diarrhea

7.3.1 – Etiology

- Caused by disturbance in the mechanisms controlling absorption.
- The amount of fluids absorb in the GIT each day is about 9 L, in diarrhea all this can be excreted.



7.3.2 – Consequences of diarrhea

I. Fluid loss

- Diarrhea can in severe cases lead to serious illness or death due to rapid loss of large amounts of extracellular volume.
- Loss of extracellular fluid leads to decreased intravascular volume and **decreased arterial pressure.**

II. Compensatory mechanism

- Fluid loss is sensed by baroreceptors that activates **renin-angiotensin II-aldosterone system** (RAAS). Activation of RAAS is an attempt to restore blood pressure, but this will not be sufficient if the lost volume is to great, or if it happens too fast.

III. Electrolyte disturbances

- $\boldsymbol{HCO_3^-}$ is an important component of salivary, pancreatic and intestinal juices, and will be excreted I large amounts in diarrhea. A relative loss of HCO_3^- compared to levels of Cl^- (meaning that more HCO_3^- than Cl^- is lost) will cause **hyperchloremic metabolic acidosis with normal anion gap.**
- $\boldsymbol{K^+}$ moves down it's electrochemical gradient, and with high flow rate increasing amounts will be secreted into the intestinal lumen, and also excreted in feces. If extensive amounts are lost, **hypokalemia** can occur.

7.3.3 – Types of diarrhea

Type of diarrhea	Mechanism	Example of causes
Decreased surface for absorption	Diseases who decrease the absorptive surface area cause decreased absorption of fluid causing diarrhea.	Infection and inflammation of the small intestine
Osmotic diarrhea	Nonabsorbable solutes in the lumen of the intestines retain fluids and cause osmotic diarrhea.	Lactase deficiency
Secretory diarrhea	Caused by excessive secretion of fluid by crypt cells. The volume of fluid secreted is larger than the absorptive capacities and massive diarrhea occurs.	Bacterial infections - Vibrio cholera - Escherichia coli

7.4 – Test yourself

1. **Approximately how much fluid is each day excreted in feces?**

2. **In what part of the small intestine is most of the fluid absorbed?**

3. **What is the function of $\mathbf{Na^+ - K^+ ATPase}$ at the basolateral membrane in the intestinal epithelial cells?**

4. **GLUT2 is a transporter of glucose; from where to where does it transport glucose?**

5. **What is the function of carbonic anhydrase?**

6. **What is the mechanism of K^+ secretion?**

7. **What causes secretion of Cl^-?**

8. **How is water secreted into the intestines?**

9. **Why can diarrhea be lethal?**

10. **What is the difference between secretory and osmotic diarrhea?**

Section 8 - Metabolic Functions of the Liver

8.0 – Introduction

The focus of this section will be to introduce you to the most important functions of the liver. We will not go into the anatomy.

I. Functions of the liver

The liver is a fascinating organ. It is the largest organ in the body located in the abdominal cavity. It receives blood from numerous organs *(stomach, pancreas, small and large intestines and spleen)* through the portal vein, and with this you could guess the liver must have many different functions, including:

1. Filtration and storage of blood
    a. The liver filtrates about 1000 ml of blood every minute and can store up to ≈ 500 ml with an additional 0.5-1L more if needed
2. Metabolism of carbohydrates, protein, fats, hormones and foreign chemical
3. Storage for vitamins and irons
4. Formations of coagulations factors
5. Formation of bile

If you keep on reading, you will learn all about it.

8.1 – Carbohydrate Metabolism

I. Role of liver in carbohydrate metabolism

- The liver is very important for maintaining a normal blood glucose level.
    1. When the glucose level is increased, the liver stores the excess glucose is in the form of glycogen
    2. When the glucose level is decreased, gluconeogenesis *(Amino acids and glycerol are converted into glucose)* is essential.

8.2 – Protein Metabolism

I. **Role of liver in protein metabolism**
   1. **Deamination of amino acids**
      a. Which is needed before you can use the proteins for energy
   2. **Formation of urea** for removal of ammonia from the body
   3. **Synthesizes nonessential amino acids**
      a. Mnemonic to remember the non-essential amino acids**: PVT TIM HALL**
   4. **Synthesizes most plasma proteins**
      a. I.e. Albumin=Major transport protein in the body

CLINICAL CORRELATION

Liver failure

Without the protein metabolism you could be dead within days. Sounds crazy? But this is why. Deamination of amino acids, produce a lot of ammonia as a byproduct. In a normal functioning liver, ammonia will be converted to urea, which can then be excreted in the urine. But if you have liver failure, ammonia will increase. This product is toxic for your body and especially your brain, which can lead to coma and death.

8.3 – Fat Metabolism

Most cells in the body can metabolize fat, but some aspects occur mainly in the liver.

I. **Fatty acid oxidation.**
   - In other words the fat is split and then beta-oxidized, which produces acetyl-CoA that enters the citric acid cycle, which gives us a lot of energy (ATP) for other body functions.

II. **Synthesis of large quantities of**
   - Cholesterol
      a. Important for bile formation, which helps us digest and absorb lipids.
   - Lipoproteins
      a. Primary purpose is to transport hydrophobic lipids
   - Phospholipids
      b. Tree types: Lecithin, cephalins and sphingomyelin.
      c. Has many purposes, but the most important is participation in cell and intracellular membranes

III. **Synthesis of fat** from carbohydrates and protein *(Stored in adipose tissue)*

8.4 – Other Metabolic Functions

I. **Vitamin storage: A, B_{12} and D**
   - Quantity: Vit A > B_{12} and D
   - Storage time A: 10 months, $B_{12:}$ 1 year and D: 10 months

II. **Storage of iron** in the liver is in the form of ferritin

III. **Formation of coagulation factors**
   - Vitamin K dependent ones: 2(Prothrombin),7, 9 and 10, but also fibrinogen can be made by the liver.

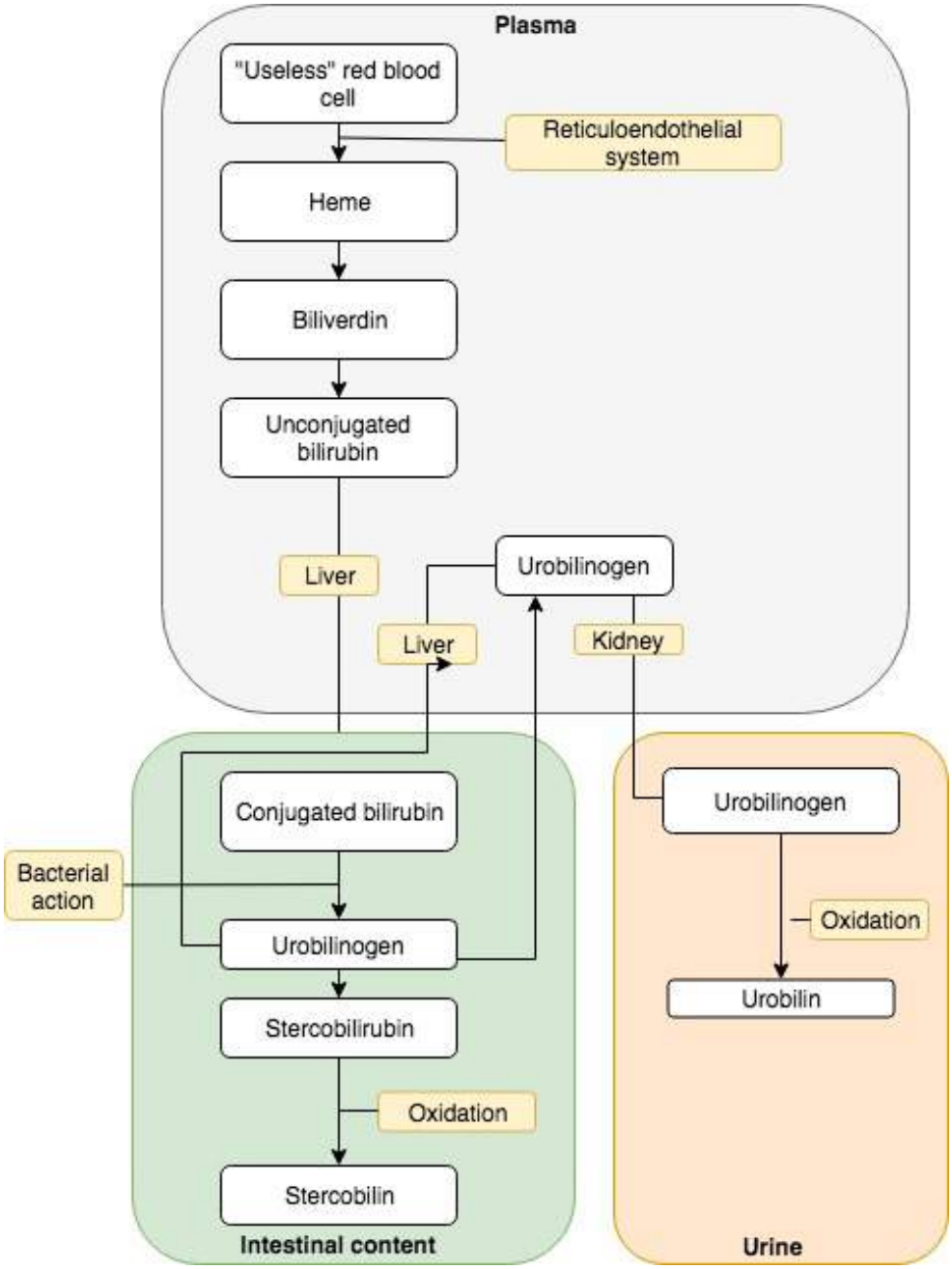
IV. **Detoxification of many drugs** *(ex. Antibiotics),* **and hormones** *(ex. Estrogen, cortisol)*

V. **Formation of bile**
   - Composed of: Bile pigment (Bilirubin), bile salts, phospholipids and cholesterol

8.4.1 – Bilirubin formation and excretion

See *5.3 – Gallbladder* for information about the enterohepatic circulation and composition of bile.

Formation	**Plasma (blood)**	Red blood cells, with their life span of 100-120 days, are continuously broken down by the Reticuloendothelial system. A byproduct of this breakdown is Biliverdin (green color). Biliverdin is converted to bilirubin (yellow color), which is bound to albumin in blood. Albumin transports bilirubin to the liver.
	Liver	Bilirubin (also called unconjugated bilirubin) is converted to **conjugated bilirubin** by the enzyme **UDP glucuronyl transferase**. Conjugated bilirubin is water-soluble and some is excreted in the urine, the rest is secreted in bile to the duodenum.
Excretion	**Intestines**	Conjugated bilirubin travels through the small intestine to the terminal ileum and colon. Here bacteria metabolize conjugated bilirubin to urobilinogen. Urobilinogen has three possible fates: 1. Reuptake via the enterohepatic circulation and delivered back to the liver 2. Taken up into blood and delivered to the kidneys, where it is converted to **urobilin** and excreted in the urine. 3. Converted to **stercobilin** in the intestine and excreted in feces.



Illustrates the production and fate of bilirubin

CLINICAL CORRELATION

Jaundice

Jaundice is a yellow discoloration of the skin and sclera of the eyes due to accumulation of either unconjugated or conjugated bilirubin. Jaundice can occur when there is increased destruction of red blood cells, obstruction of bile ducts or with liver disease.

Physiologic jaundice of the newborn is a physiological condition that occurs about 2-3 days after birth, as the fetal hemoglobin is converted to adult hemoglobin.

8.5 – Test yourself

1. **What is the function of the liver in regards to carbohydrate metabolism?**

2. **Why is the formation of urea essential for life?**

3. **What is the product of beta-oxidation?**

4. **What is synthesized in the liver?**

5. **What is the name of the enzyme converting unconjugated bilirubin to conjugated**