GIT

Medical Biochemistry 3rd year

Carbohydrate Digestion & Absorption

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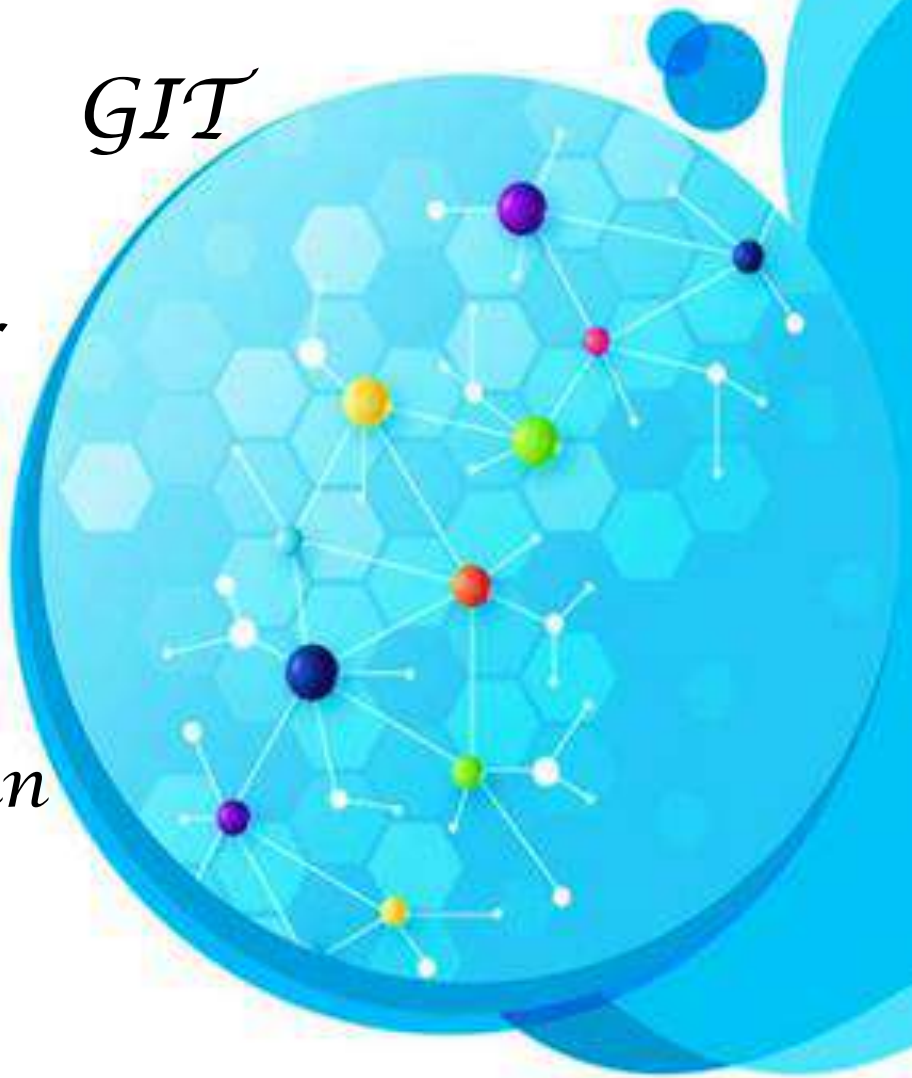
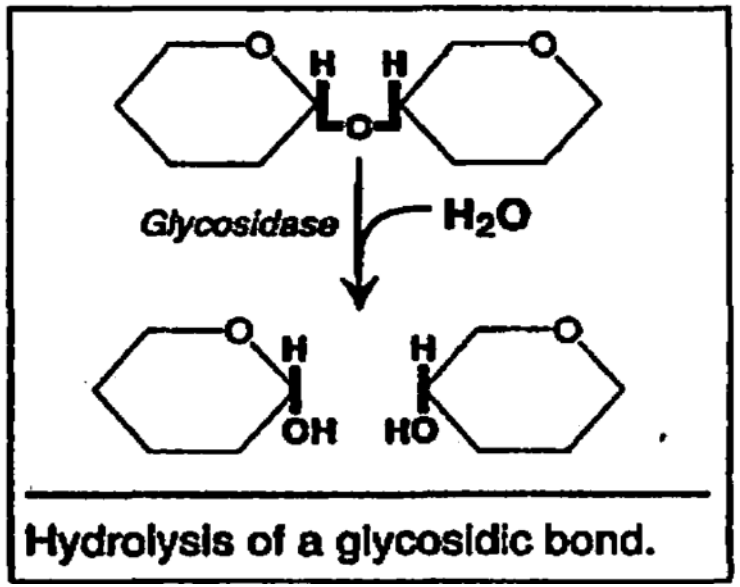


Carbohydrate from Diet

- More than 60% of our foods are carbohydrates

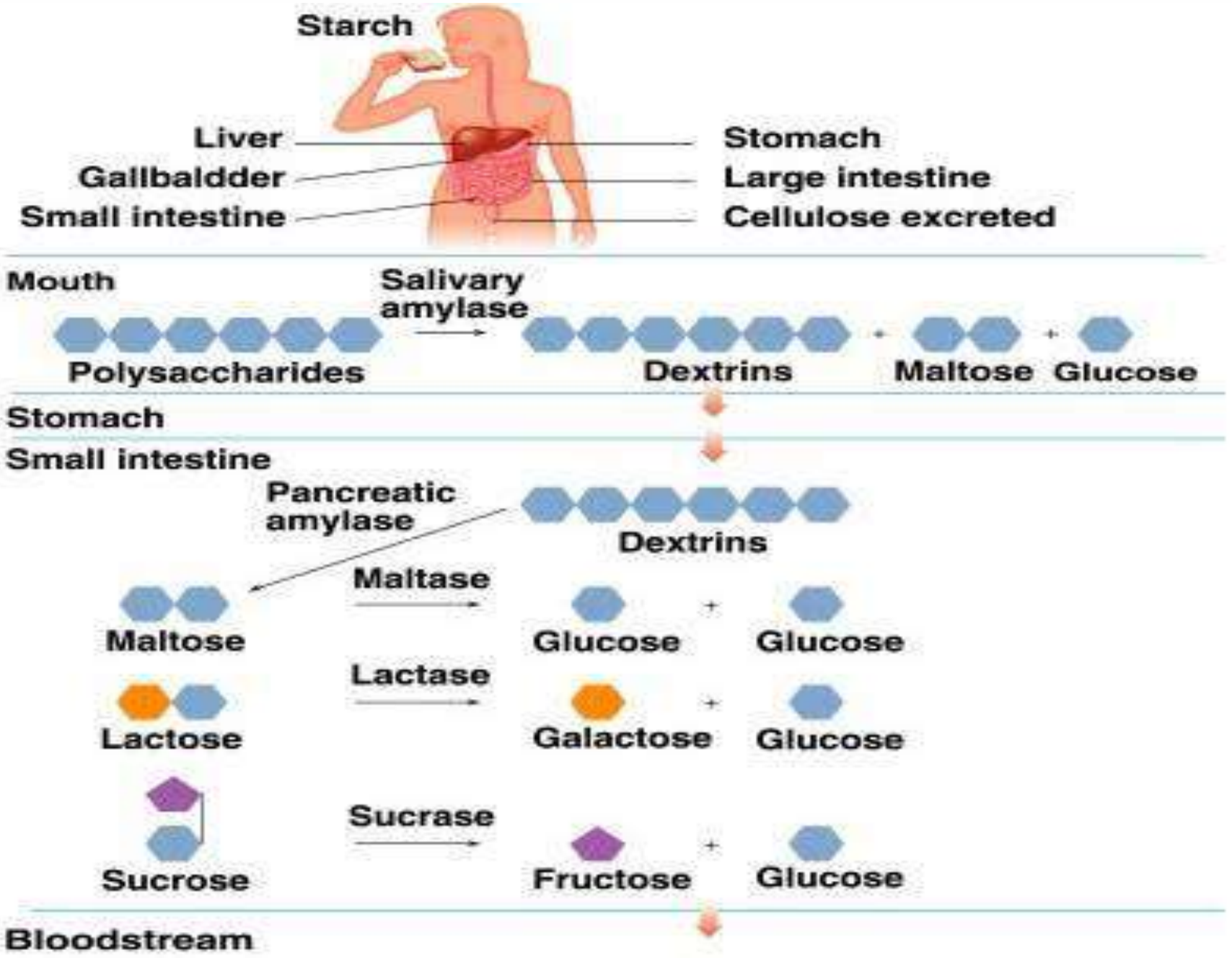
1. Large amounts of:
   - Starch (Homopolysaccharides): polymers of glucose (Amylose & Amylopectin).
   - Maltose (disaccharides): glucose + glucose
   - Sucrose (disaccharides): glucose + fructose.
   - Lactose (disaccharides): glucose + galactose.
2. Small amount of pure glucose.



Hydrolysis of a glycosidic bond.

Digestion

1. In the mouth:
   - Salivary amylase hydrolyzes α-glycosidic bonds in polysaccharides to give smaller polysaccharides (dextrins), maltose, and some glucose.
2. In the small intestine:
   - Pancreatic amylase hydrolyzes dextrins to maltose and glucose.
   - The disaccharides maltose, lactose, and sucrose are hydrolyzed to monosaccharides.
   - Disaccharidases are present over brush border of enterocytes.


Starch
Liver
Gallbaldder
Small intestine
Stomach
Large intestine
Cellulose excreted
Mouth
Salivary amylase
Polysaccharides
Dextrins
Maltose
Glucose
Stomach
Small intestine
Pancreatic amylase
Dextrins
Maltase
Maltose
Glucose
Glucose
Lactase
Lactose
Galactose
Glucose
Sucrase
Sucrose
Fructose
Glucose
Bloodstream

Digestion of cellulose

- Human cannot digest (hydrolyze) cellulose due to absence of digestive hydrolase enzyme that attacks β-linkage.
- The presence of cellulose in diet is important because it:

1. increases the bulk of stool.
2. This stimulates intestinal movement and prevents constipation.

Carbohydrate Absorption

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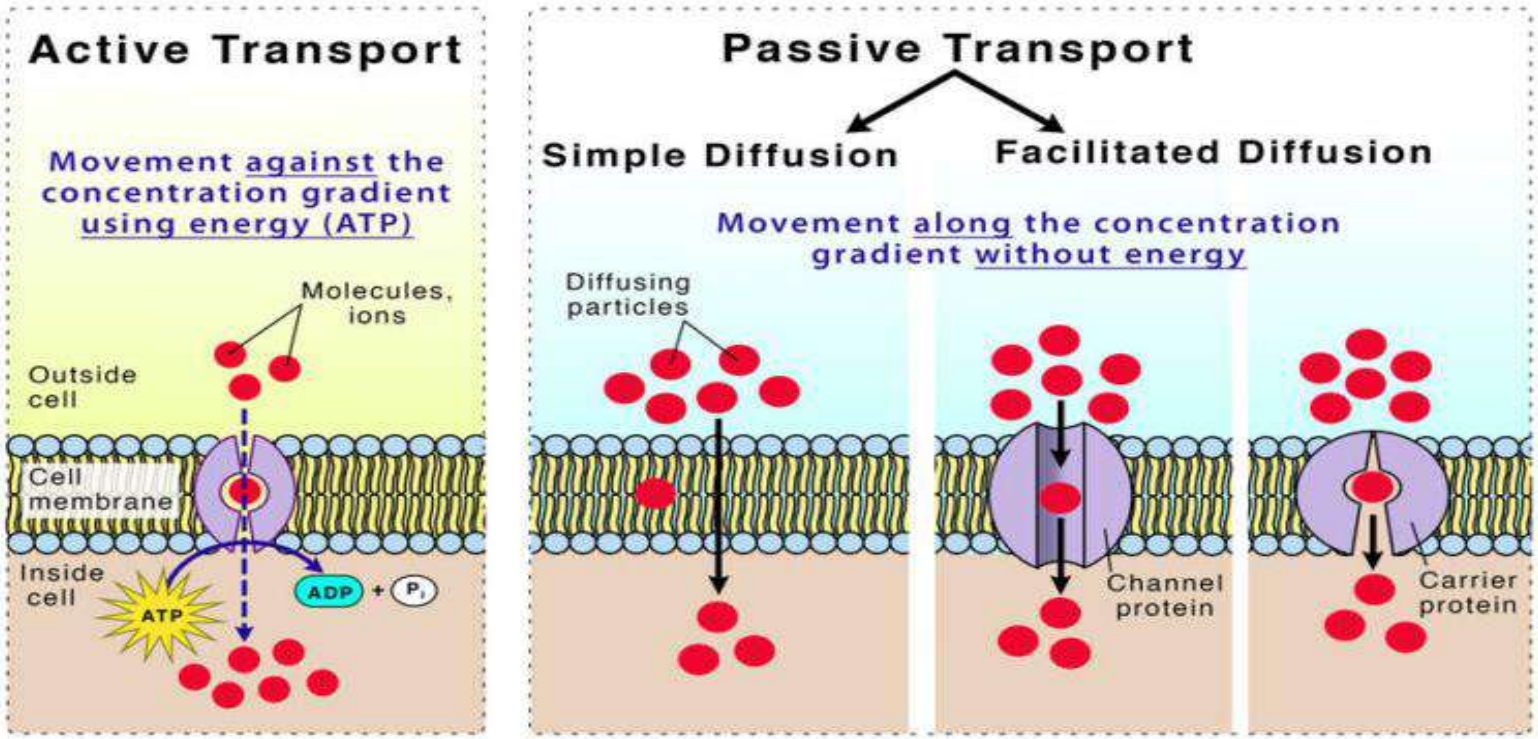
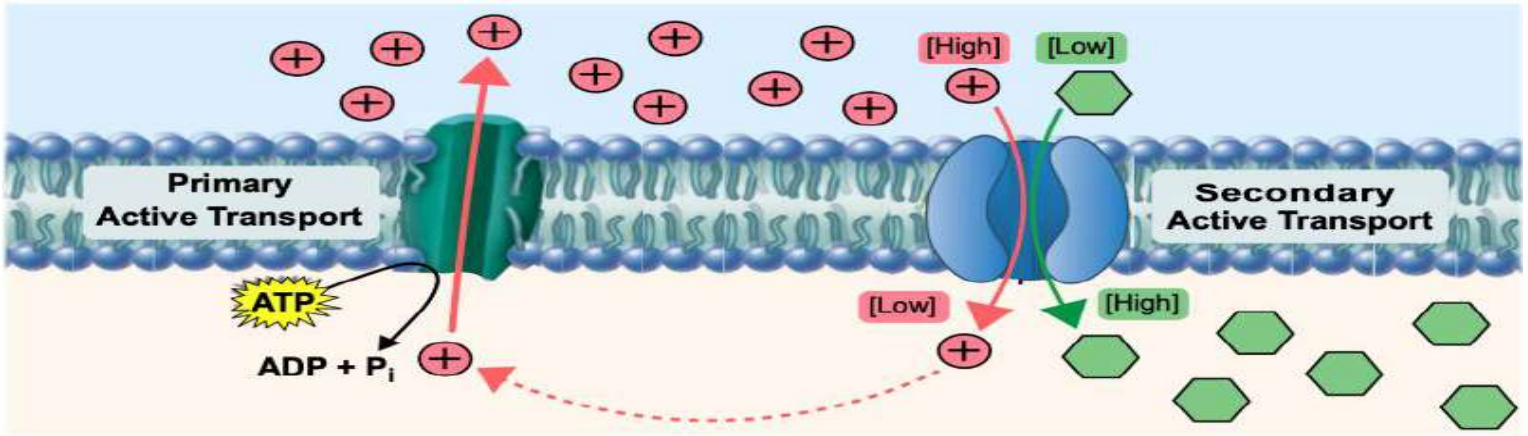
Active VS Passive Transport



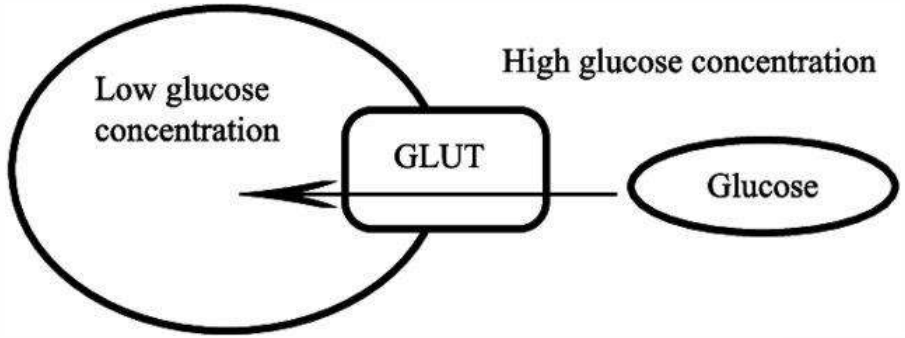


Carbohydrate Absorption: Introduction:

- The end products of carbohydrate digestion are monosaccharides: glucose, galactose and fructose.
- They are absorbed from the jejunum to portal veins to the liver, where fructose and galactose are transformed into glucose.
- Two mechanisms are responsible for absorption of monosaccharides: active transport and passive transport

A- Passive Transport [Apical (Luminal) Absorption]

1. Initially, after the breakdown of dietary carbohydrates into glucose, the concentration of glucose in the lumen of the small intestine is higher than in the enterocytes. So, glucose moves from the lumen into the enterocytes through facilitated diffusion facilitated by Glucose transporter type 2 (GLUT2).
2. This transport process occurs until the concentration of glucose inside the enterocytes reaches a certain level, at which point passive diffusion alone cannot maintain an efficient uptake of glucose.



Active Transport [Apical (Luminal) Absorption]

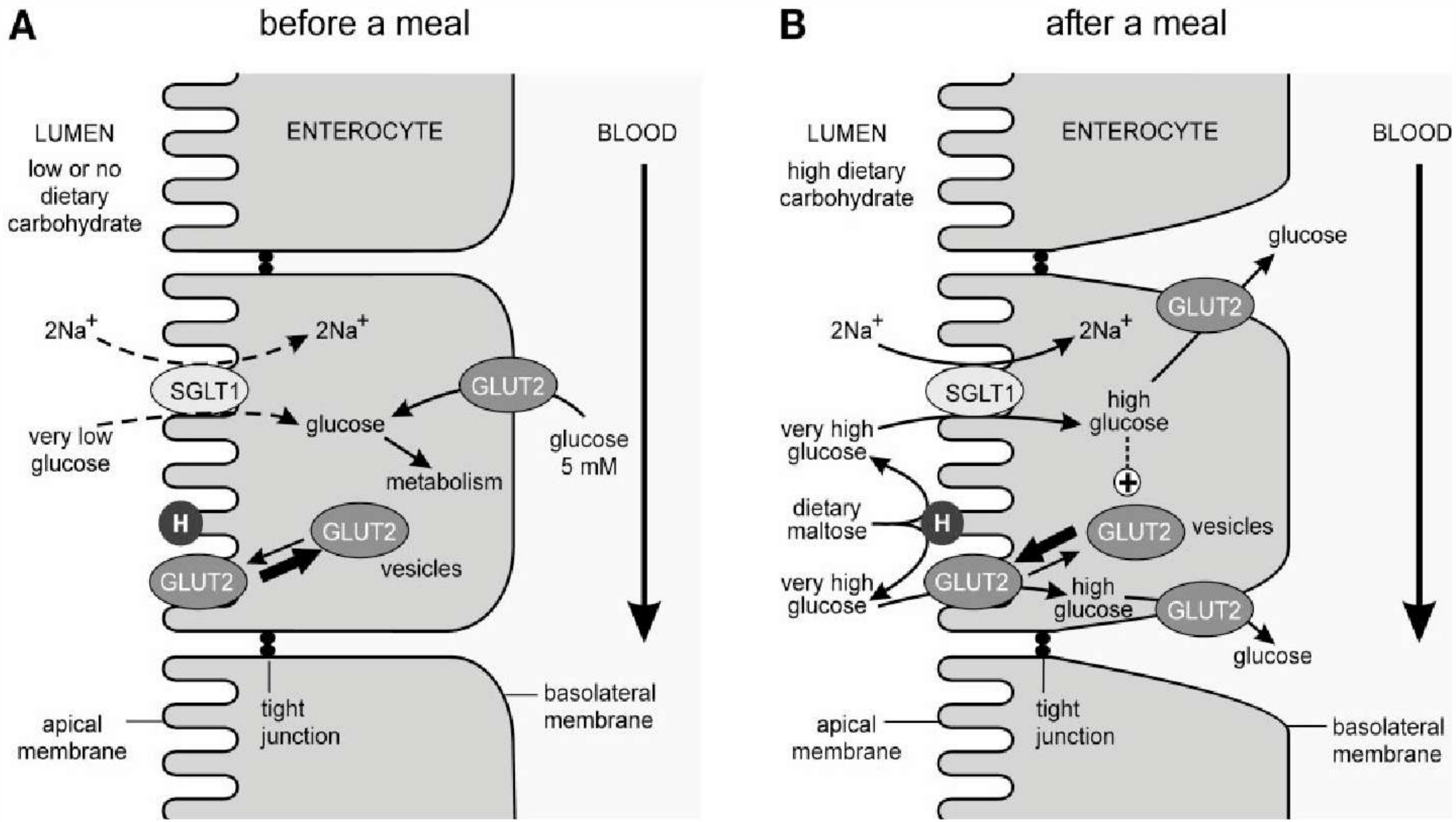
2.Later, once the concentration of glucose inside the enterocytes increases, active transport mechanisms come into play to ensure efficient glucose absorption.

- The sodium-glucose cotransporters (SGLTs), which is responsible for actively transporting glucose into the enterocytes.

Active Transport [Apical (Luminal) Absorption]

2.SGLT1 couples the transport of glucose with sodium ions (Na+) in a process known as secondary active transport.

- The sodium gradient across the apical membrane, which is established by the sodium-potassium ATPase pump, provides the energy needed for SGLT1 to transport glucose against its concentration gradient. As sodium ions move into the enterocytes, glucose molecules bind to into the enterocytes.


A
before a meal
LUMEN
low or no dietary carbohydrate
ENTEROCYTE
BLOOD
2Na+
2Na+
SGLT1
very low glucose
glucose
GLUT2
glucose 5 mM
metabolism
H
GLUT2
GLUT2
vesicles
apical membrane
tight junction
basolateral membrane
B
after a meal
LUMEN
high dietary carbohydrate
ENTEROCYTE
BLOOD
glucose
GLUT2
2Na+
2Na+
SGLT1
high glucose
very high glucose
dietary maltose
H
GLUT2
vesicles
very high glucose
GLUT2
high glucose
GLUT2
glucose
apical membrane
tight junction
basolateral membrane

Basolateral Absorption:

- After entering the enterocytes, glucose is then transported across the basolateral membrane to reach the bloodstream.
- The transporter responsible for this step is GLUT-2 (Glucose transporter type 2), which is a sodium-independent transporter.
- GLUT-2 allows facilitated diffusion of glucose from the enterocyte into the bloodstream (portal circulation).

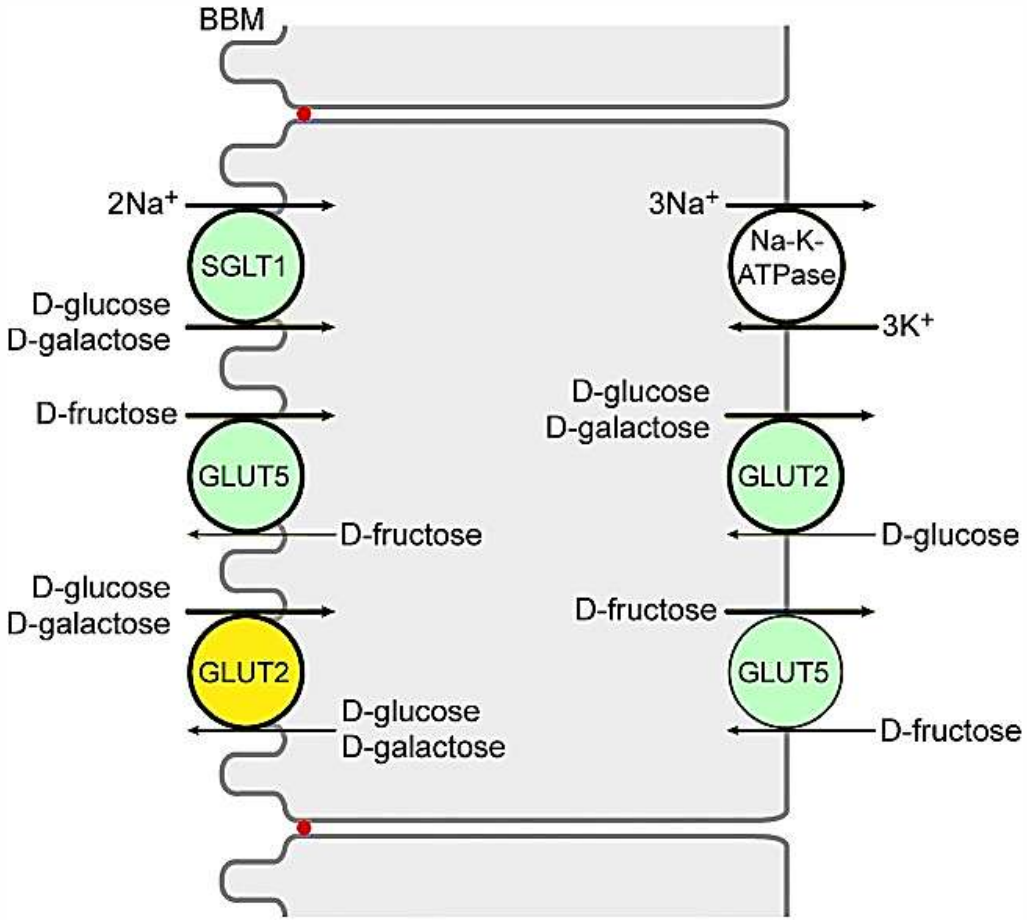
Very Important N.B

- SGLT1 is relevant for the absorption of galactose.
- SGLT2, located in the kidney, is essential for the reabsorption of glucose, transporting glucose back into the blood.

✓ Gliflozin is an SGLT2 inhibitor that reduces the reabsorption of glucose, thereby lowering blood sugar. It is used to treat hyperglycemia in people with type II diabetes.

- GLUT-5 (Na+-independent) is relevant for the absorption of fructose.

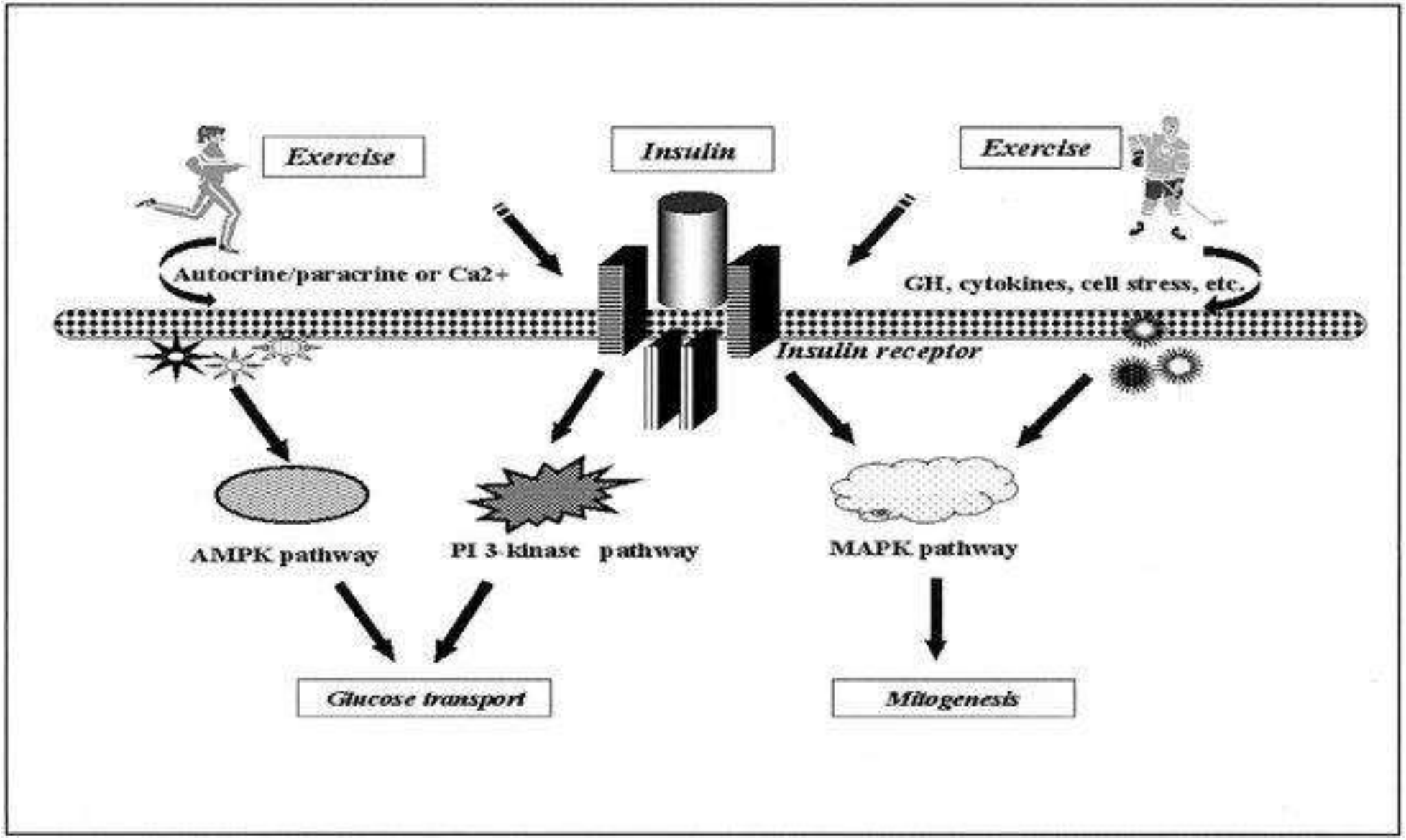
Very Important N.B



Glucose transporters their respective sites of action, and some additional notes:		
Transporter	Site	Note
GLUT 1 & 3	RBCs & Brain	High affinity and Insulin independent, so they are important for glucose uptake even at low glucose concentration.
GLUT2	liver, pancreas, and small intestine	* Has low glucose affinity so, hepatocytes don't uptake glucose except at extremely high concentration for its storage. * In ß cells, it acts as glucose sensor for insulin release.
GLUT4	Skeletal muscle and adipose tissue	* Its expression on cell membrane depends on insulin level. * It's responsible for insulin-dependent glucose uptake.
GLUT5	Small intestine and testes	Specialized for fructose transport, less extend for glucose and galactose

Exercise helps in control of glucose levels in diabetics and decrease the need of anti-DM drugs?

- The expression of GLUT-4 on the surfaces of skeletal muscle cells is also mediated by exercise, induced by high AMP, which activates AMP-activated protein kinase (AMPK) (insulin-independent).
- That's why exercise helps control glucose levels in diabetes and decreases the need for anti-diabetes drugs.


Exercise
Insulin
Exercise
Autocrine/paracrine or Ca2+
GH, cytokines, cell stress, etc.
Insulin receptor
AMPK pathway
PI 3-kinase pathway
MAPK pathway
Glucose transport
Milogenesis

Defects of carbohydrate digestion and absorption

1. LACTASE DEFICIENCY
2. SUCRASE DEFICIENCY

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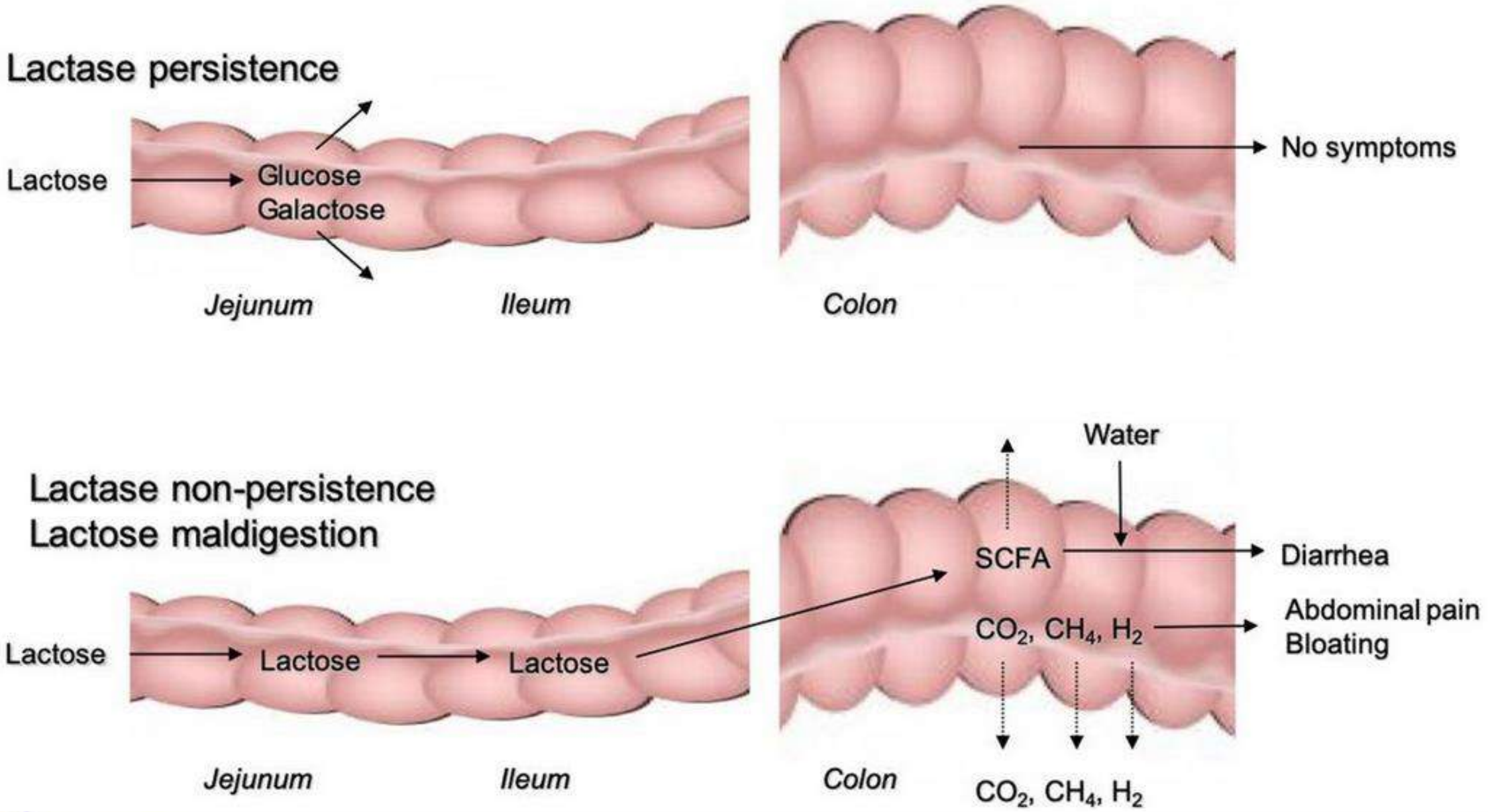
Lactase deficiency

- It also known as lactose intolerance & is a deficiency of lactase enzyme which digest lactose.
- It may be Congenital or Acquired.
- Hereditary (autosomal recessive) mostly in Asians and Africans. 1ry cause.
- Acquired after gastroenteritis due to enterocytes destruction. 2ry cause.

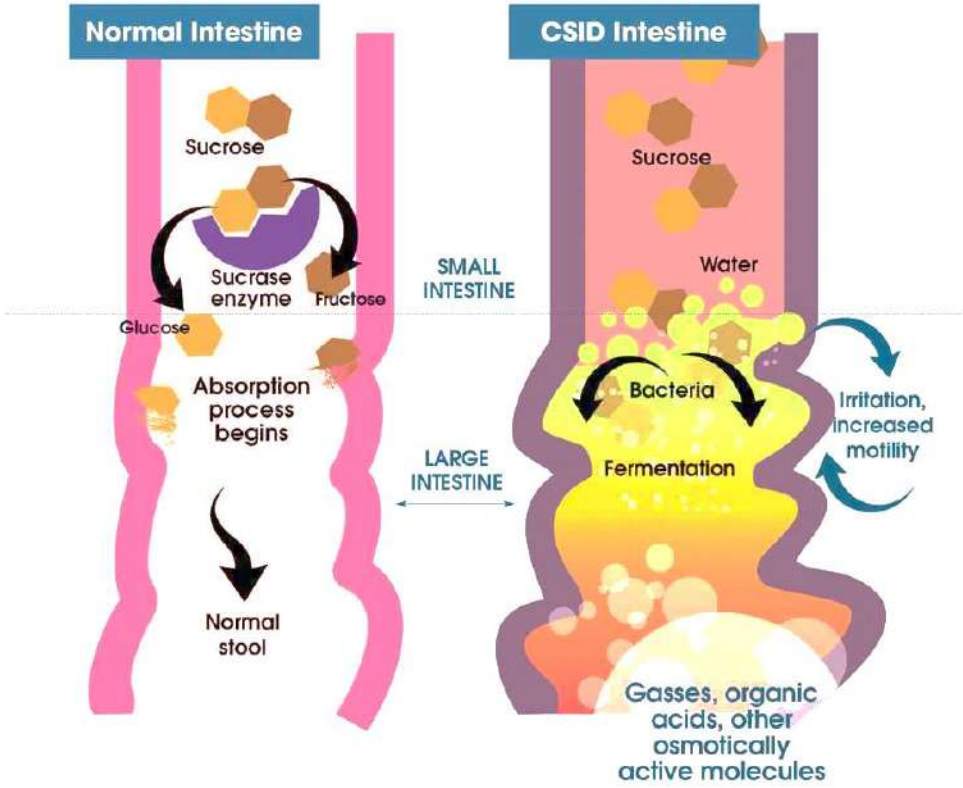

Lactase persistence
Lactose
Glucose
Galactose
No symptoms
Jejunum
Ileum
Colon
Lactase non-persistence
Lactose maldigestion
Water
SCFA
Diarrhea
Abdominal pain
Bloating
CO_2, CH_4, H_2
Lactose
Lactose
Lactose
Jejunum
Ileum
Colon
CO_2, CH_4, H_2

Lactase deficiency

- The presence of lactose in intestine causes:
  - Increased osmotic pressure: So water will be drawn from the tissue (causing dehydration) into the large intestine (causing diarrhea).
  - Increased fermentation of lactose by intestinal bacteria and produce CO_2 gas (distention and abdominal cramps).
  - Investigation: +ve H2 breath test after lactose administration.
- Treated by removing lactose from diet (free lactose milk) or lactase pills.

Sucrase deficiency:

- A rare condition, showing the signs and symptoms of lactase deficiency.
- It occurs early in childhood



Thank You

End of Part I

Medical Biochemistry

Lipid absorption & digestion

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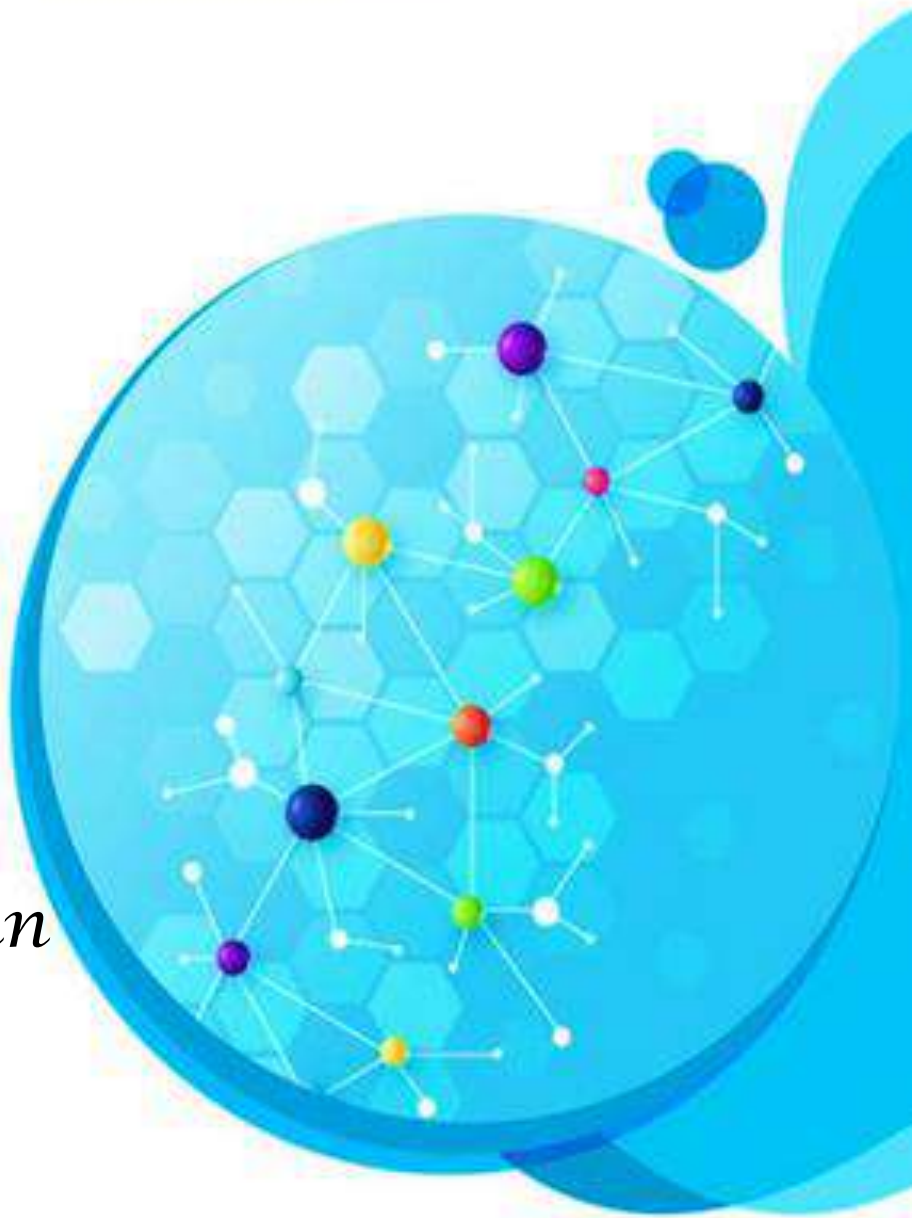


Digestion and absorption of Lipids

Digestion of dietary lipids is cleavage of ester bonds present in various unabsorbable lipid forms by lipases enzymes in different parts of GIT.

Dietary Lipids

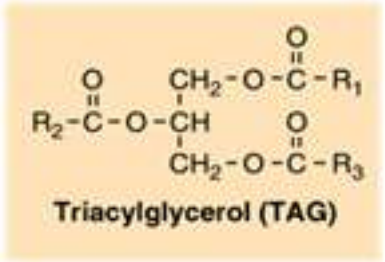
- Dietary lipids intake is:

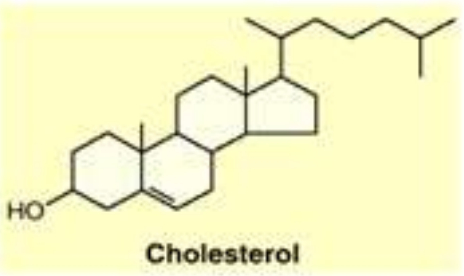
  1. Triacylglycerol (mainly ~ 90%)

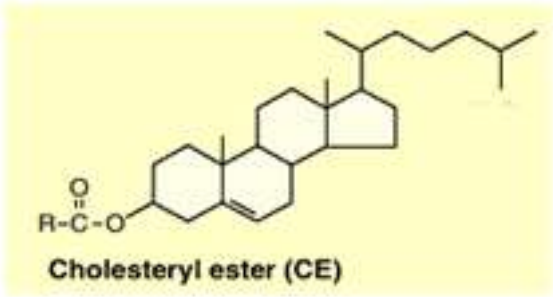
  2. The remainder (10%): includes

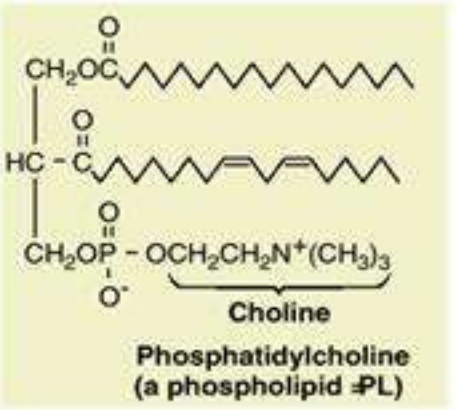
     - Cholesterol & Cholesterol ester

     - Phospholipids, Glycolipids and F.A.









The immiscibility of lipids with water presents a major challenge for lipid digestion.

1. Lipid Insoluble in Water: Dietary lipids are hydrophobic, so they don't dissolve in water, which is the primary component of digestive juices and the environment within the small intestine.

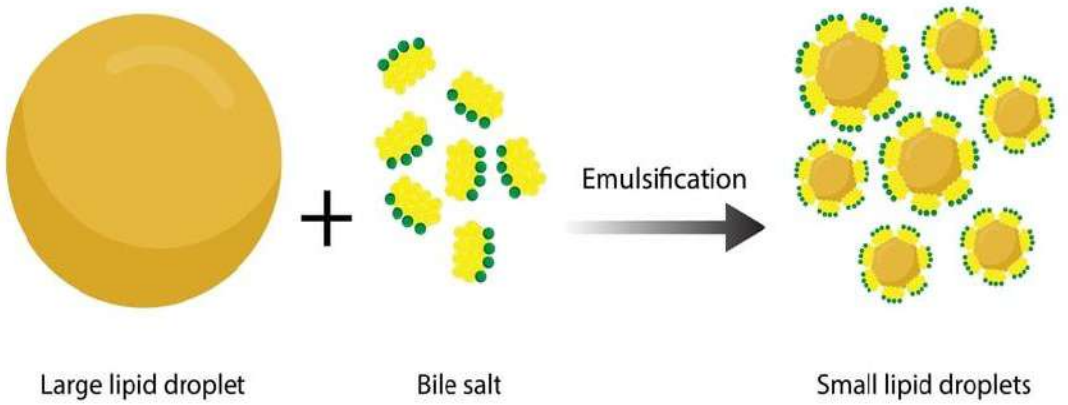
2. Conversely, digestive enzymes, including lipases, are water-soluble and they require an aqueous environment to function effectively

Emulsification of Dietary Lipids in duodenum

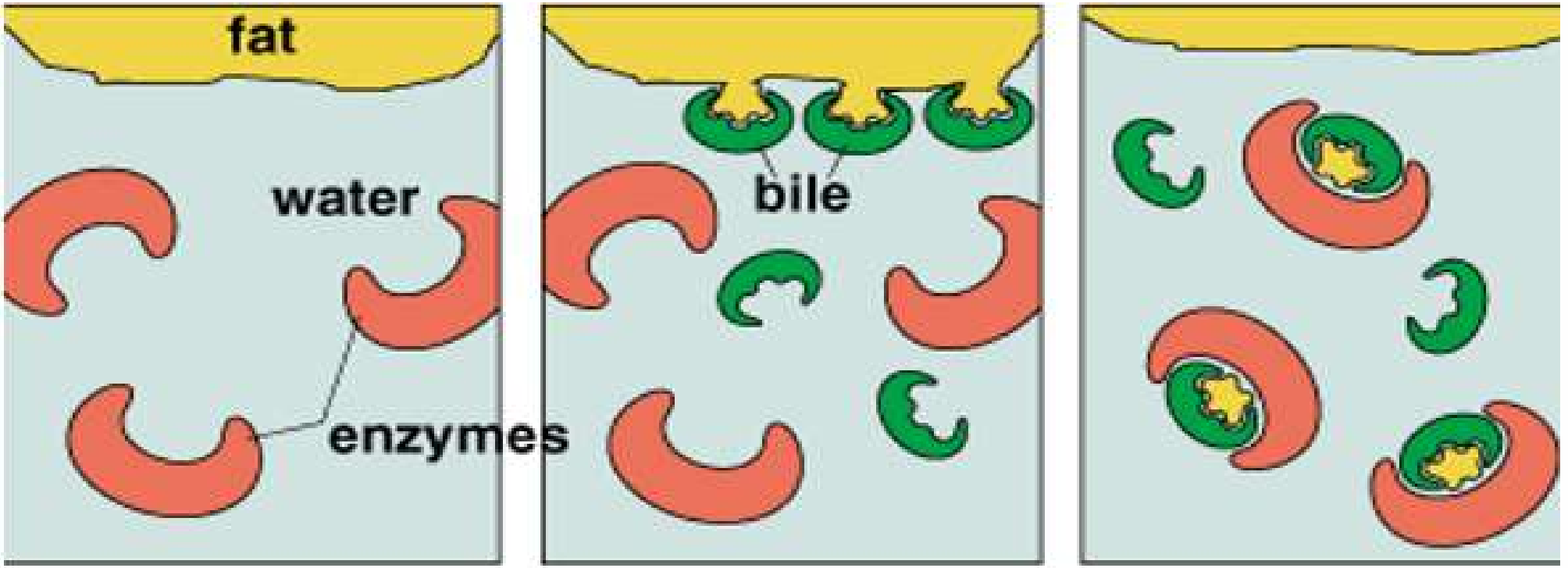
Emulsification increases the surface area of lipid droplets, therefore the digestive enzymes can effectively act.

Mechanisms:

1. Mechanical mixing by peristalsis
2. Detergent effect of bile salts:



Bile salts interact with lipid particles and aqueous duodenal contents, stabilizing the particles as they become smaller, and preventing them from coalescing



Fat and water tend to separate. Enzymes are in the water and can't get at the fat.

Bile (an emulsifier) arrives. Bile has an affinity for both fat and water and can therefore bring the fat into the water.

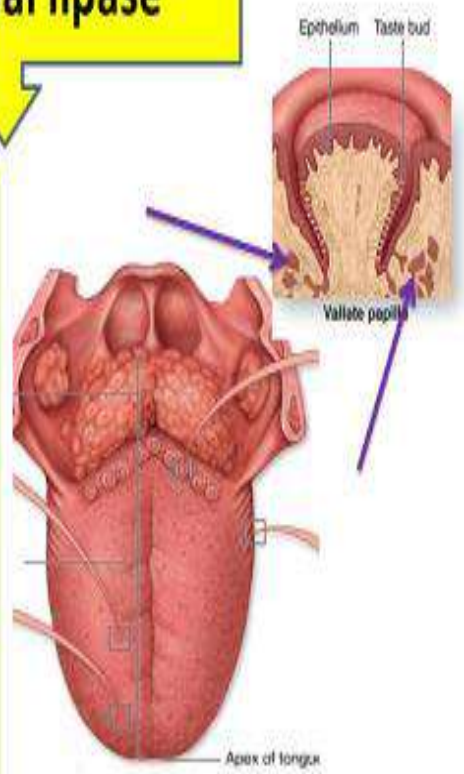
After emulsification, the fat is mixed in the water solution, so fat-digesting enzymes have access to it.

Digestion of lipids

Digestion in the mouth

1- Lingual lipase

- secreted by the dorsal surface of the tongue (Von-Ebner's glands)
- Is not of much significance in humans compared to rat or mouse



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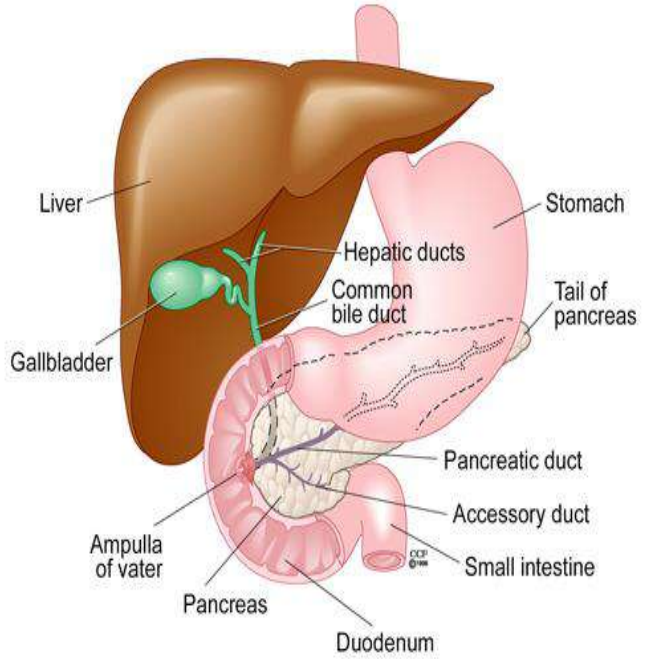
Digestion of lipids

- In mouth the Lingual Lipase is responsible about a weak digestion of lipids:
  - Secreted by Ebner's glands on the dorsal surface of the tongue.
  - A weak digestion of lipids because:
    1. Lack of Emulsification
    2. Short duration

Digestion of lipids

Digestion in the stomach



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Digestion of lipids

- The effects of gastric lipases (in the stomach) on TAG is little significance in adults:

1. No significant amount of lipase is present in the secretion of stomach
2. Lack of Emulsification
3. Unfavourable Stomach pH (The acid pH of gastric secretion)

Digestion of lipids

- Gastric lipase plays a vital role in digesting milk fat in neonates and infants.
  - Earlier Action by breaking Down the Membrane (phospholipids and cholesterol in the milk fat globule membrane).
  - By partially digesting milk fat, gastric lipase helps compensate for the lower activity of pancreatic lipase in neonates and infants.

Digestion of lipids

Digestion in the Small Intestine

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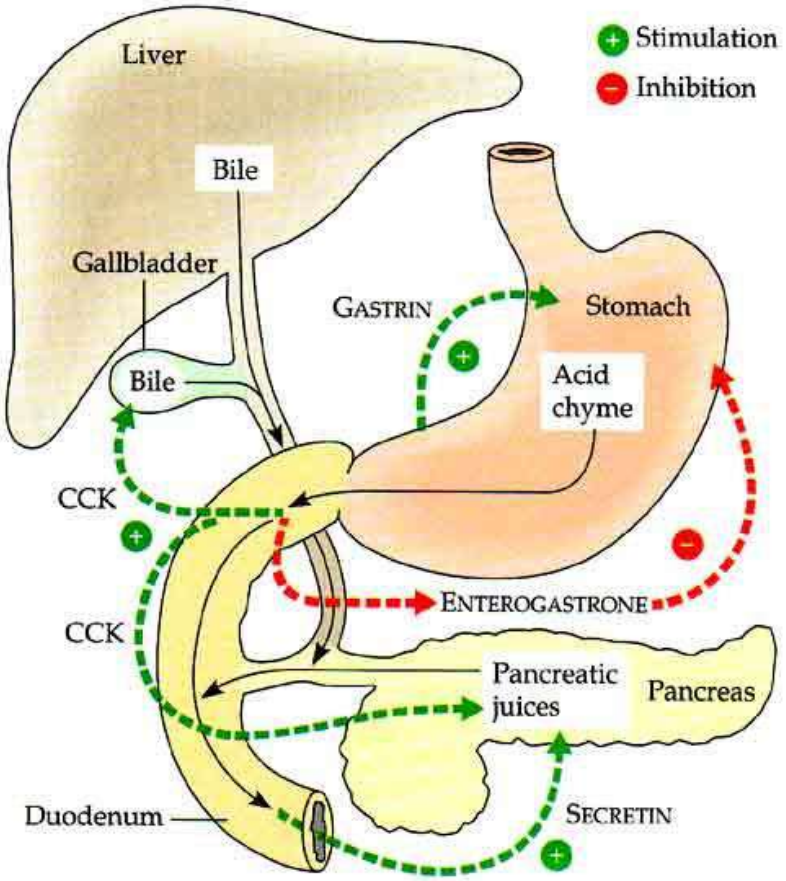
Chyme enters the small intestine

- Chyme is a mixture of partially digested food and stomach acid that leaves the stomach and enters the small intestine.
- Chyme contains: Partially broken down proteins, carbohydrates, and fats as well as stomach acid

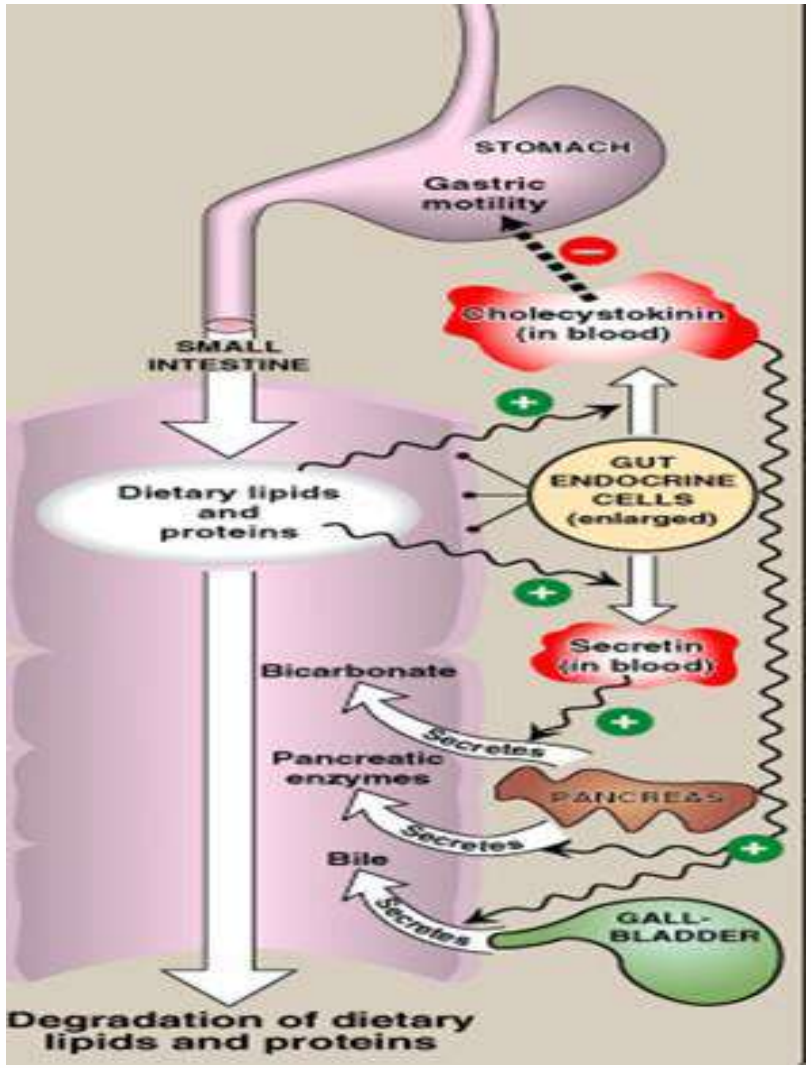


Hormonal response

- The presence of chyme in the small intestine stimulates the release of hormones from the small intestine lining cells.
- These hormones include:
  - Secretin
  - Cholecystokinin (CCK)

Hormonal response: Cholecystokinin (CCK):

- Acts on the gallbladder, causing it to contract and release bile into the small intestine
- Acts on the exocrine cells of the pancreas, causing them to release digestive enzymes containing lipase
- Decrease gastric motility, resulting in a slower release of the gastric contents into the small intestine



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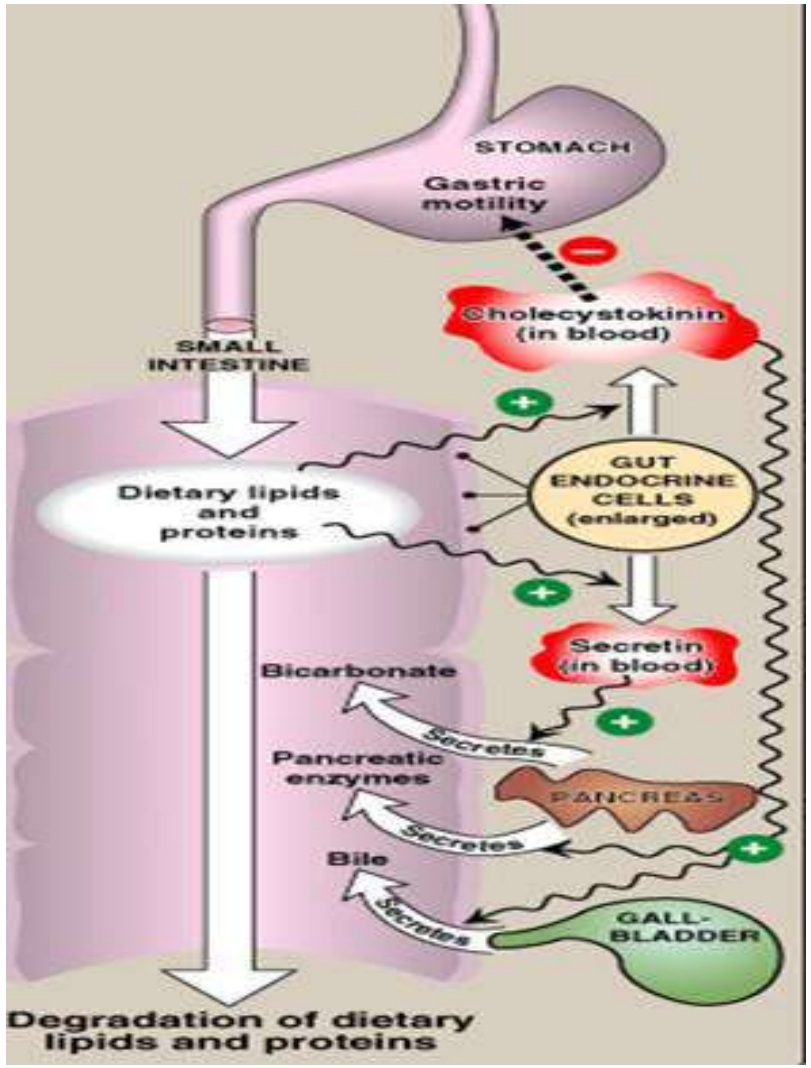
Hormonal response: Secretin:

- Causes the pancreas to release a solution enriched in bicarbonate that helps neutralize the pH of the acidic chyme and changes the pH to the alkaline side, which is necessary for the activity of pancreatic and intestinal enzymes.



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Lipid digestive enzymes

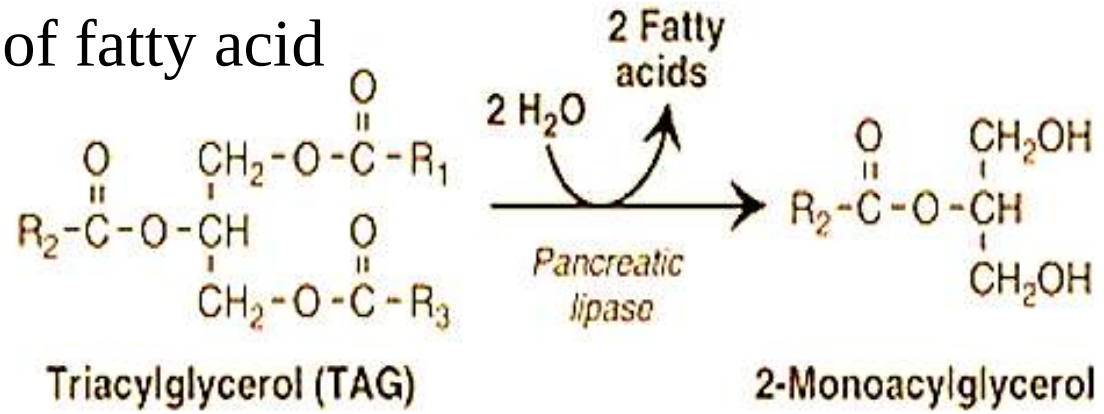
- Three lipid digestive enzymes secreted by pancreas are:

1. **Pancreatic lipase → (TAGs)**
2. **Cholesterol esterase → (CE)**
3. **Phospholipase → (PL)**

Action of pancreatic enzymes on dietary lipids in the small intestine

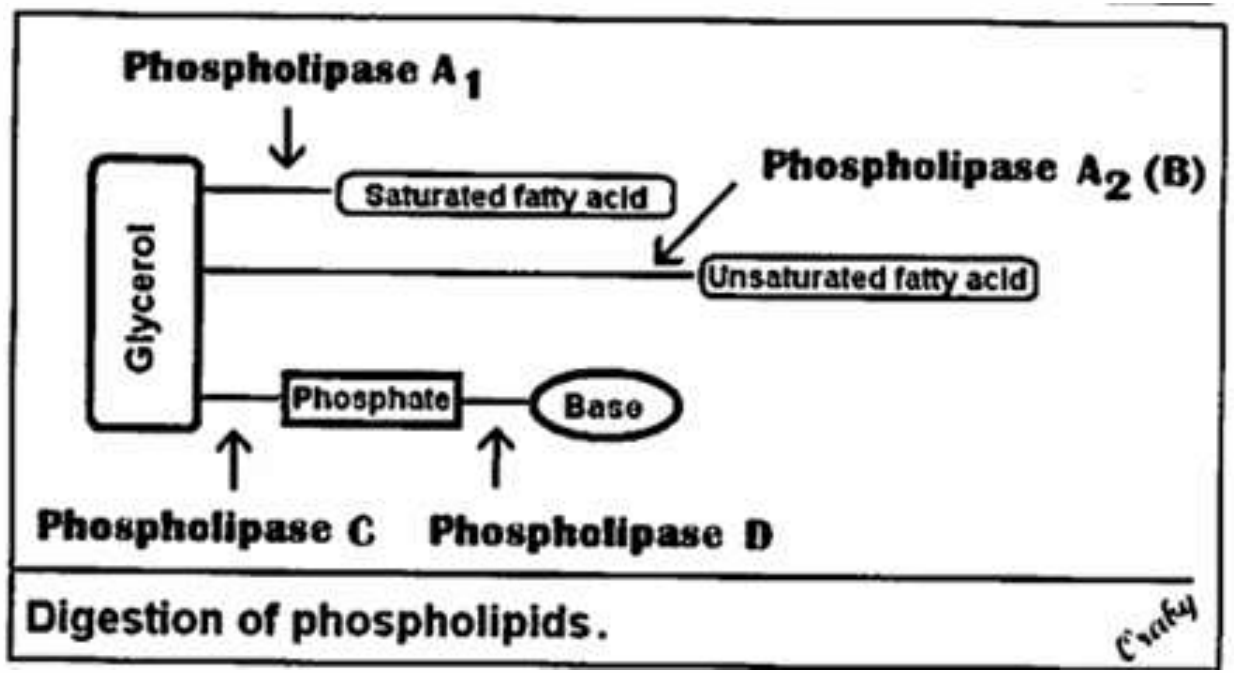
Emulsified TAGs are readily attacked by pancreatic lipase in the small intestine

- Lipase hydrolyses F.A. in the 1 and 3 positions of the TAGs, producing 2 monoacylglycerols (MAG) and two molecules of F.A.
- Slow subsequent isomerization of the 2 MAG to 1 or 3 MAG, then hydrolyzed to glycerol and a third molecule of fatty acid



Hydrolysis of dietary phospholipids (PL) by pancreatic phospholipases

- Phospholipids may be absorbed as such or digested by phospholipase enzymes (A1, A2 (B), C, and D)
- They act phospholipids on hydrolyzing them into fatty acids, glycerol, phosphate and nitrogenous bases.

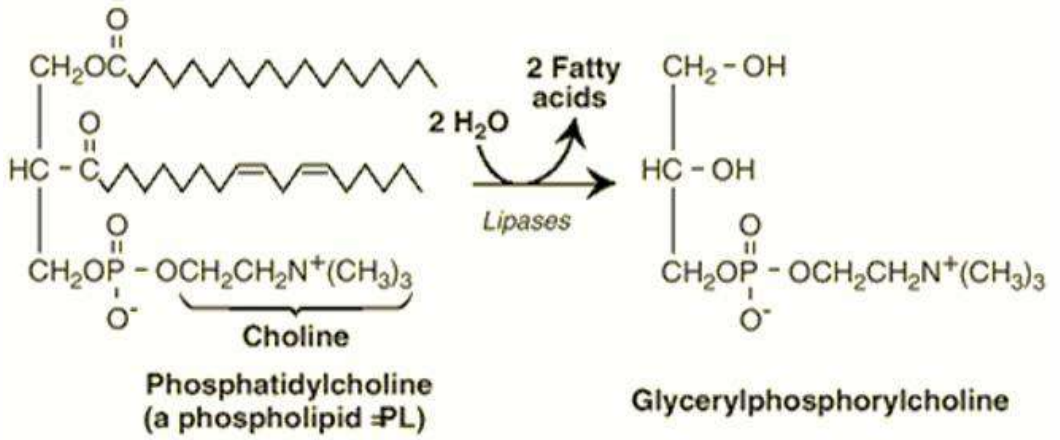


Digestion of phospholipids.

Hydrolysis of dietary phospholipids (PL) by pancreatic phospholipase-A2

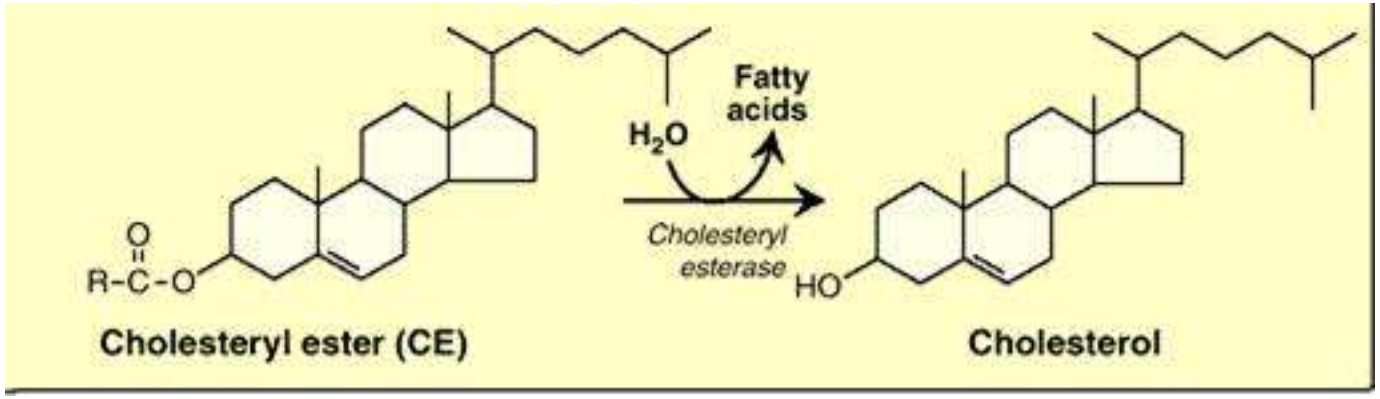
- This enzyme catalyzes the hydrolysis of F.A. at the 2-position of the glycerophospholipids, leaving lysophospholipids which being **detergent, aid emulsification and digestion of lipids**

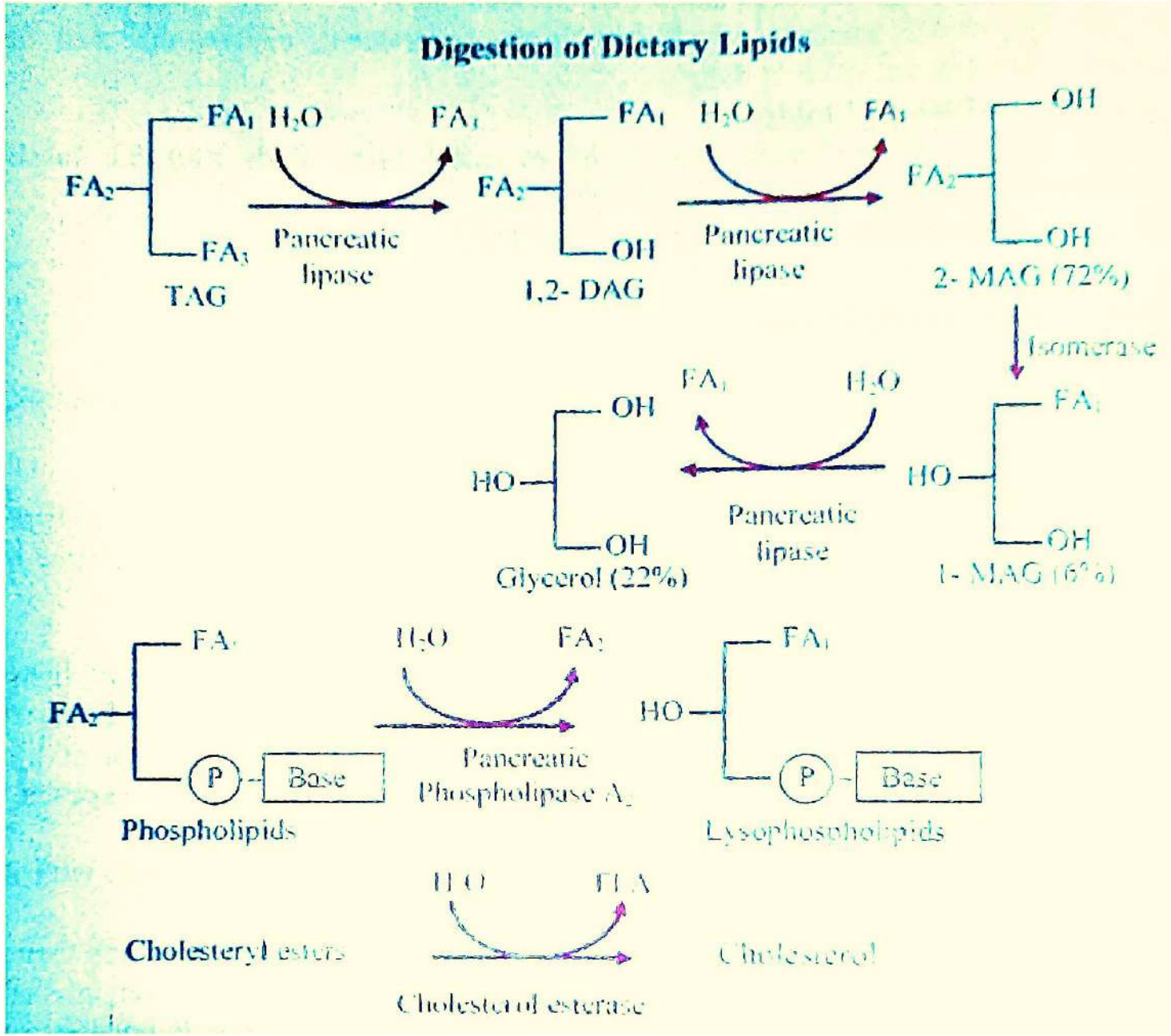
- Phospholipase A2 requires Ca^{2+} for its function.



Hydrolysis of cholesterol ester CE

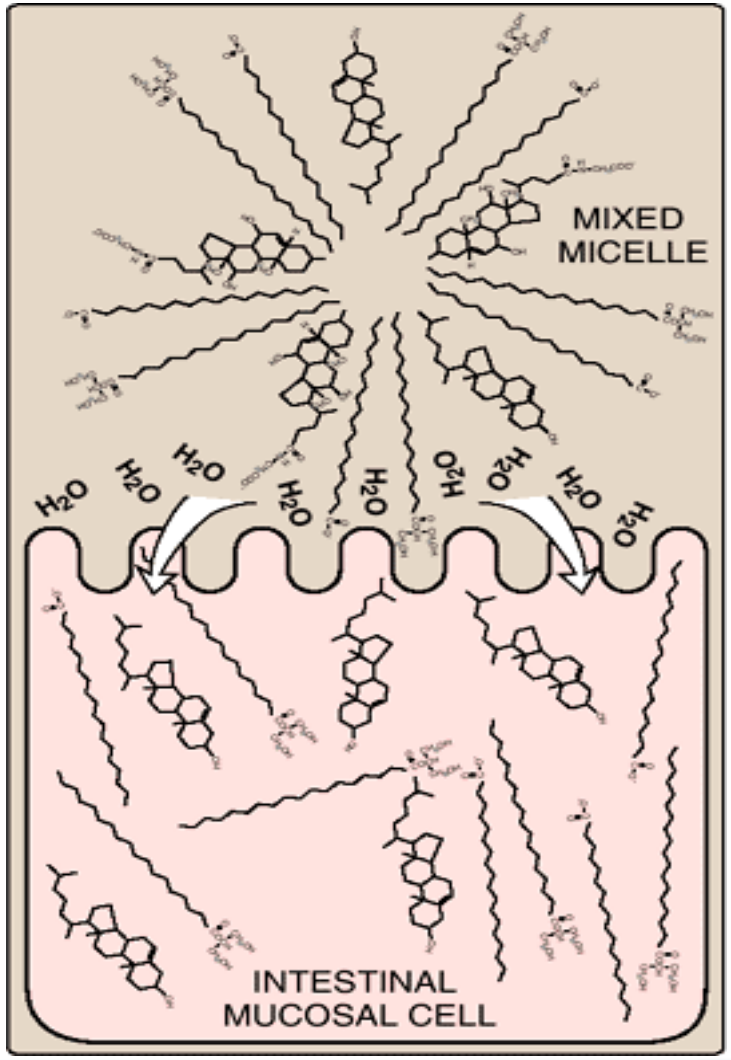
- Cholesterol esters are hydrolyzed by pancreatic **cholesterol esterase, which produce cholesterol plus free fatty acid**




Digestion of Dietary Lipids
FA1
H2O
FA1
FA2
FA3
TAG
Pancreatic lipase
FA1
H2O
FA1
FA2
OH
1,2- DAG
Pancreatic lipase
OH
FA2
OH
2- MAG (72%)
Isomerase
FA1
H2O
OH
HO
OH
Glycerol (22%)
Pancreatic lipase
FA1
HO
OH
1- MAG (6%)
FA1
H2O
FA2
FA2
P
Base
Phospholipids
Pancreatic Phospholipase A2
FA1
HO
P
Base
Lysophospholipids
H2O
FA
Cholesteryl esters
Cholesterol esterase
Cholesterol

Products of lipid digestion

1. **Micelles** are free fatty acids, free cholesterol, 2-monoacylglycerol, small amount of 1-monoacylglycerol, lysophospholipid, and Fat soluble vitamins A, D, E and K these together with bile salts.
2. **Glycerol, SCFA, and MCFA**



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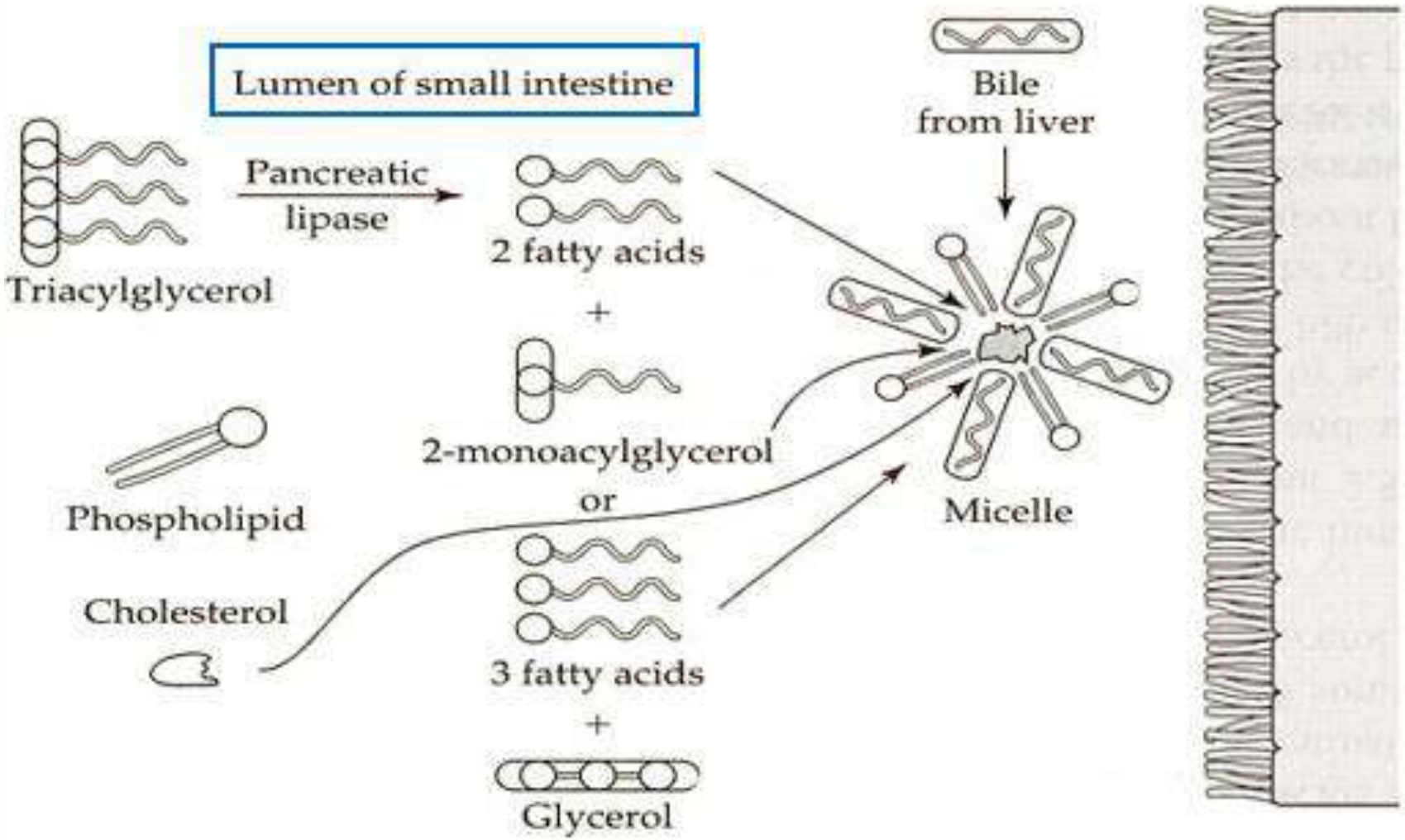
Products of lipid digestion



Absorption of lipids by intestinal mucosal cells

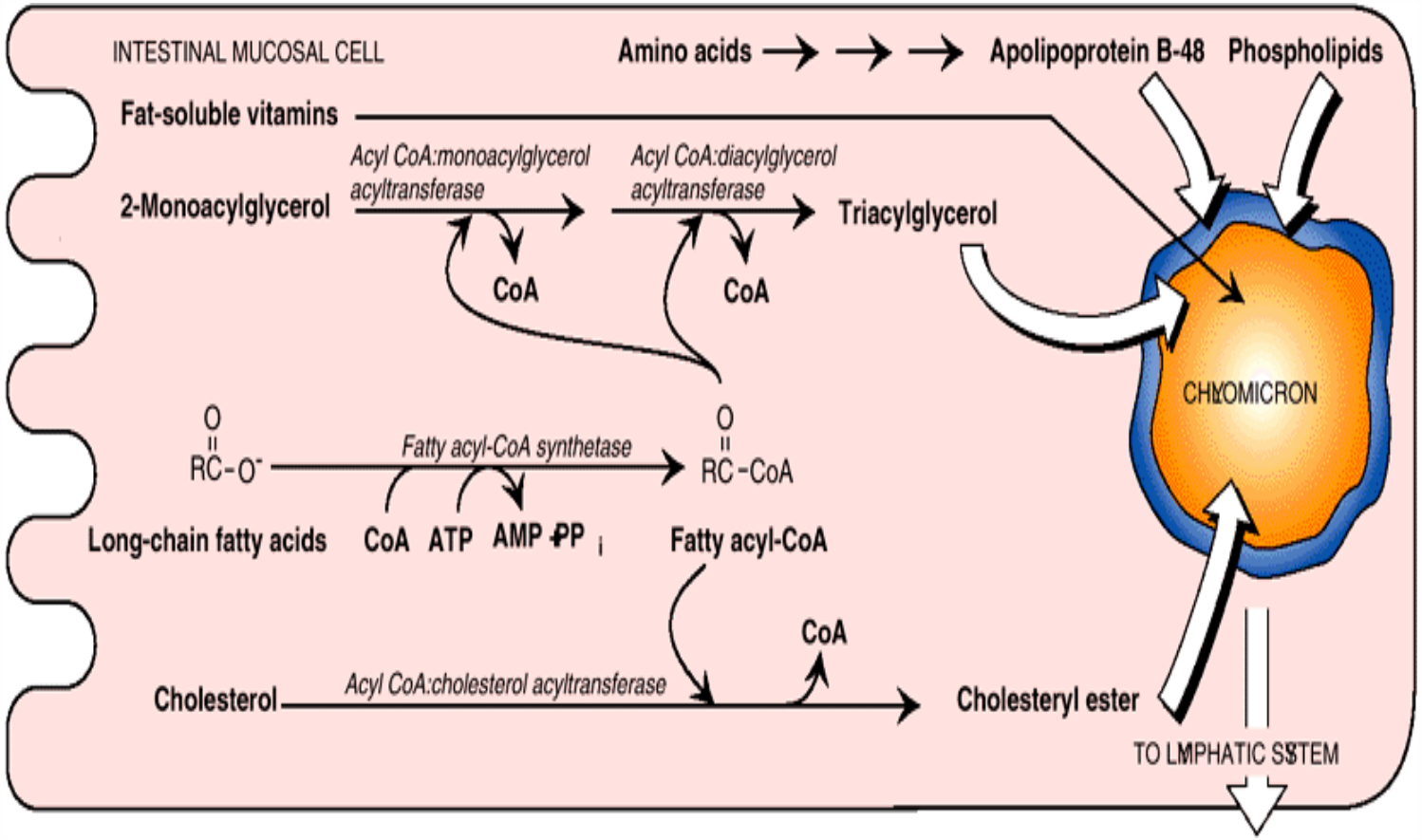
Absorption of lipids by intestinal mucosal cells

- Short and medium chain fatty acids do not require bile salts for their absorption.
  - They are absorbed directly into intestinal epithelial cell.
  - Because they do not need to be packaged into chylomicrons, they enter the portal blood rather than lymph and are transported to the liver bound to serum albumin.

Absorption of lipids by intestinal mucosal cells

- The mixed micelles approach the brush border membrane of the intestinal mucosal cells
- The lipid components of mixed micelles pass through and are absorbed into mucosal cells of the jejunum and ileum by diffusion

Absorption of lipids by intestinal mucosal cells



Absorption of lipids by intestinal mucosal cells

- The utilization of fatty acids for resynthesis of triacyglycerols first requires their conversion to active form acyl-CoA by the action of acyl-CoA synthetase (thiokinase)
- The absorbed lysophospholipids and cholesterol are also reacylated with acyl-CoA to regenerate PL and CE

Absorption of lipids by intestinal mucosal cells

- The free glycerol released in the intestinal lumen is not reutilized but passes directly to the portal vein. However, the glycerol-3-phosphate, formed within the intestinal cells by the glucose, can be reutilized for triacylglycerol synthesis.

Transport

- Triacylglycerol, phospholipid, cholesterol esters synthesized in the intestinal mucosa and fat soluble vitamins are transported from the mucosal cells into the lymph in the form of lipoprotein known as **chylomicrons** because they are insoluble in water.

Transport

- The chylomicrons pass from lymph into the blood through the thoracic duct.
- After a fatty meal, the plasma is milky in appearance due to the presence of these particles

Errors of lipids digestion and absorption

Lipid malabsorption

- Lipid malabsorption results in a loss of lipid in the faeces or urine.

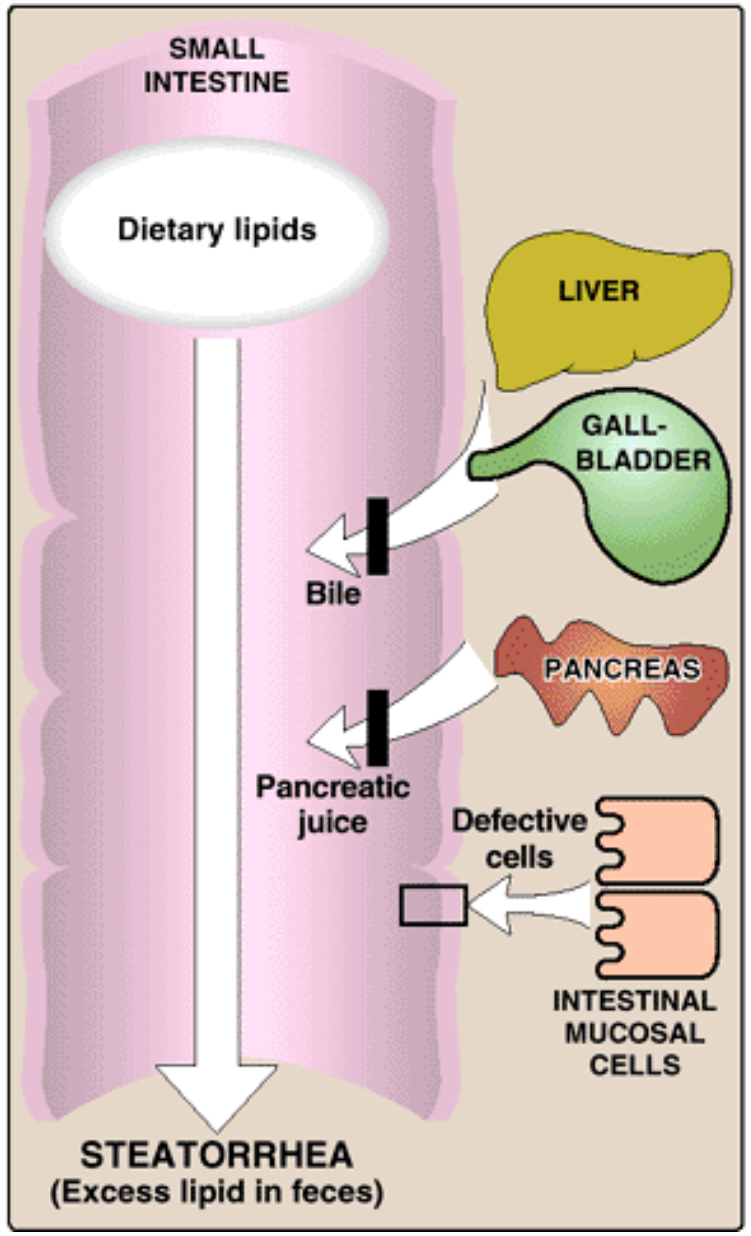
1. **Steatorrhea is** Conditions in which the faeces contain large amounts of fat as much as 30g/day in the faeces. Normally 5g/day.

2. **Chyluria (milky urine)** is the presence of fat (chylomicrons) in urine after fatty meal.

Steatorrhea

The most common causes are:

- Pancreatic enzyme deficiency
- Bile salt deficiency occurs in liver disease or due to obstruction in the bile duct
- Defective in the intestinal mucosal cells



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Chyluria

- It is an uncommon medical condition resulting from an abnormal communication between the abdominal lymphatic system and the urinary tract, which results in the presence of chyle in the urine, making it appear milky white.

Thanks

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Medical Biochemistry

Protein digestion

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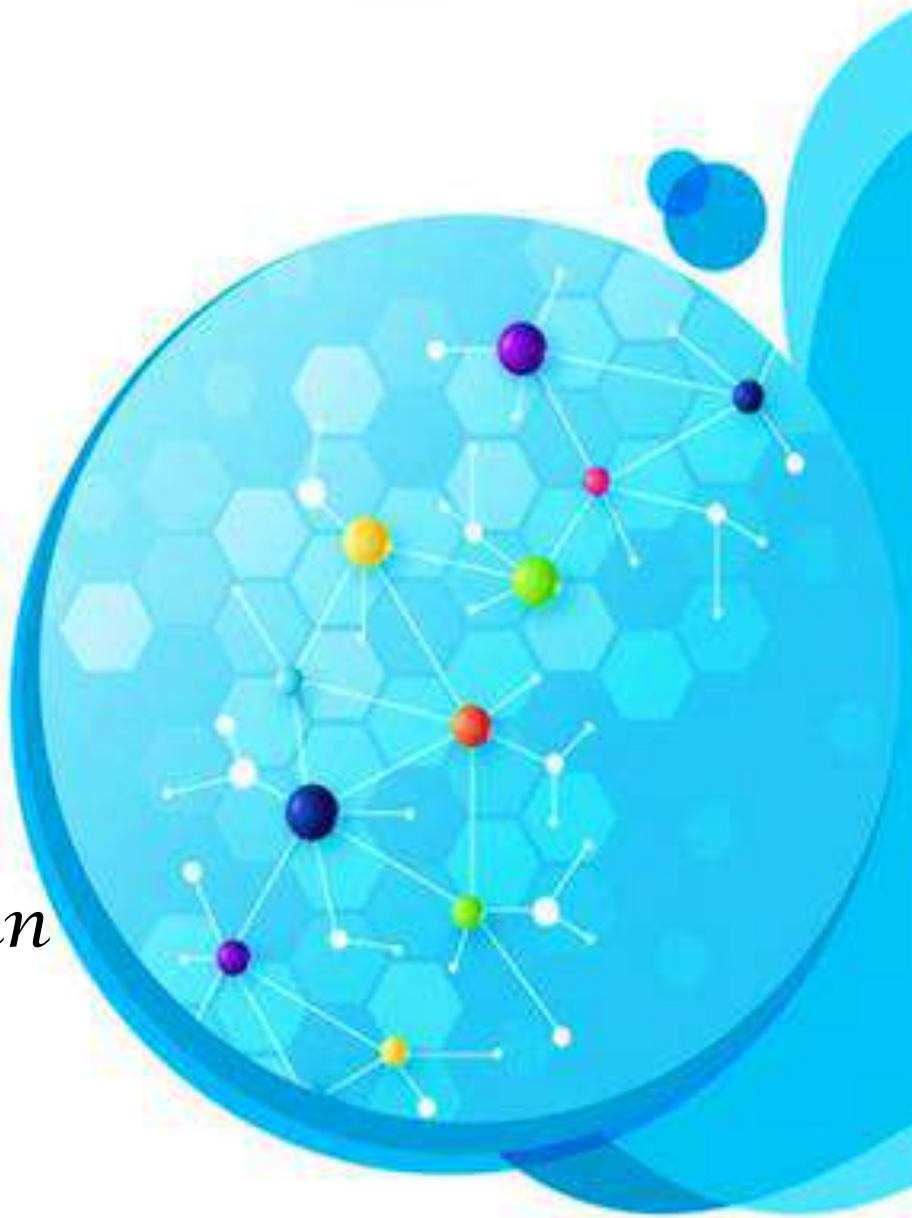
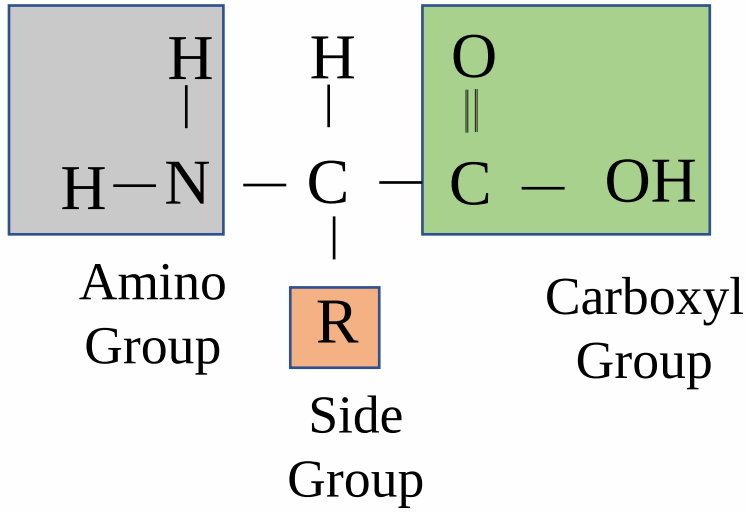


Protein Digestion and Absorption

Amino Acids: Structure



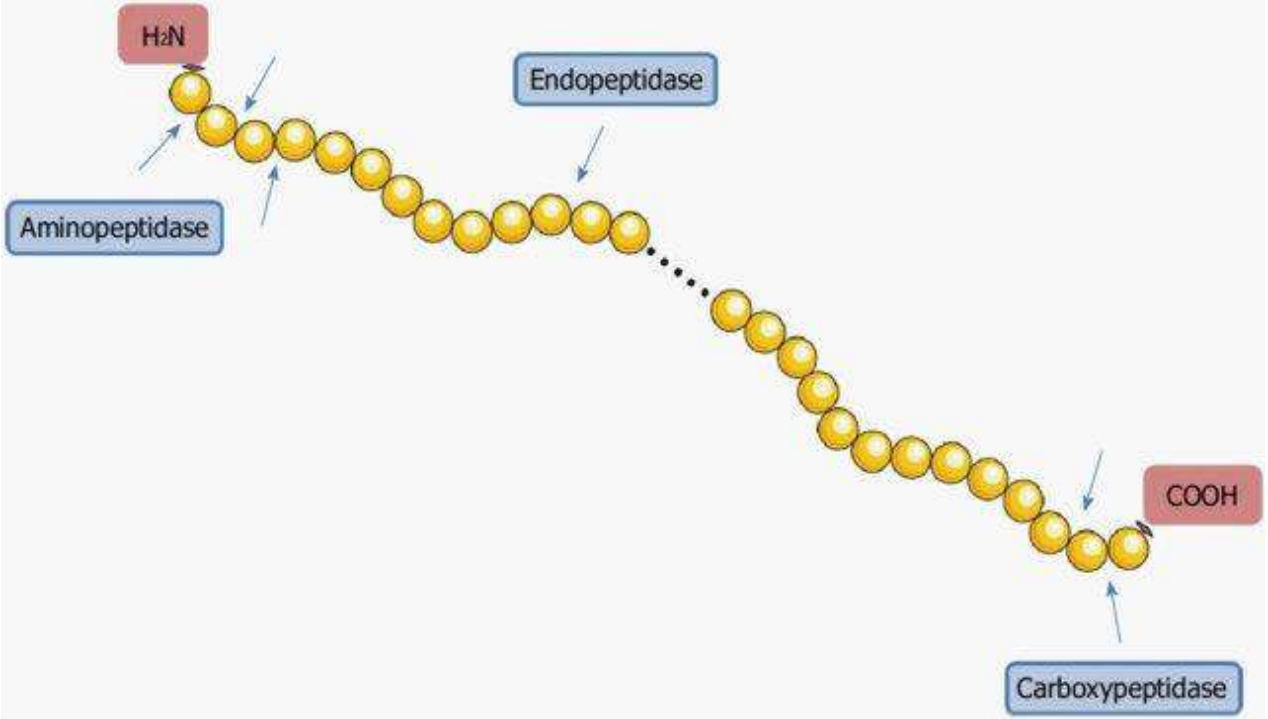
Peptidases are enzymes responsible for protein digestion

- **Most Peptidases are Produced as Zymogens:**
  - **Zymogens:** These are inactive forms of enzymes, specifically peptidases. They are produced by cells to prevent unwanted proteolytic activity within the cell itself.
  - **Activation:** Zymogens are typically activated by specific factors like cleavage of a peptide bond within the zymogen structure. This cleavage exposes the active site of the peptidase, allowing it to function.

Types of peptidases:

- **Endopeptidases:** They cleave internal peptide bonds e.g. pepsin, trypsin, chymotrypsin and elastases

- **Exopeptidases:** cleave one amino acid either from carboxy (COOH) terminal and so called Carboxypeptidases (A and B) or from amino terminal and so called Aminopeptidases.



Digestion in stomach

Pepsin & Renin (infants- casein)

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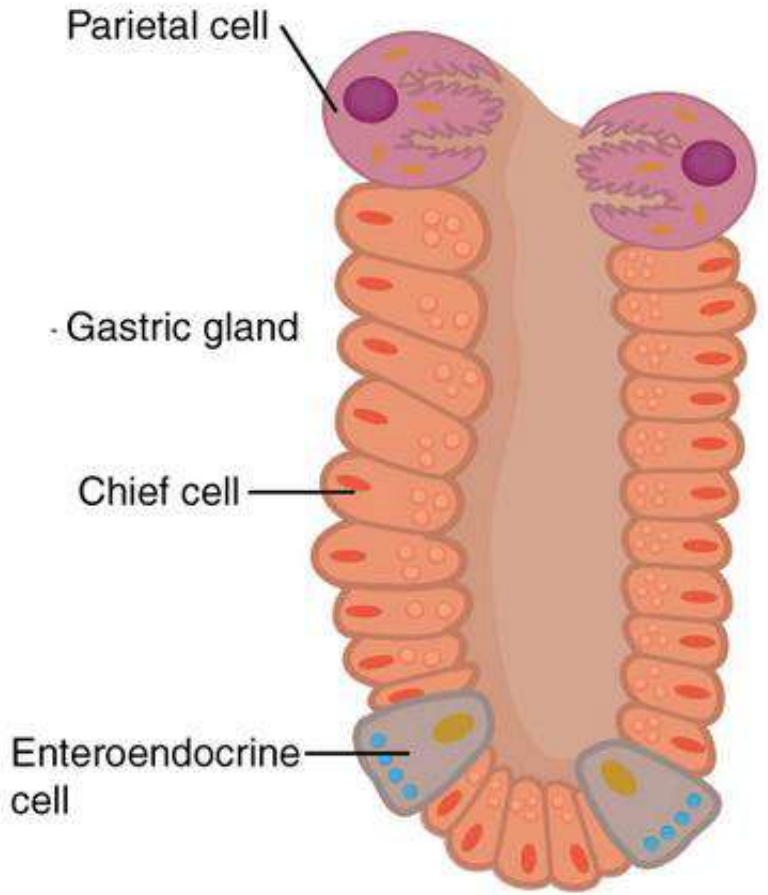
Protein digestion occur in stomach and intestine

- The digestion of proteins begins in the stomach, and upon food entering the stomach, the gastric mucosa is triggered to release a polypeptide hormone called **gastrin**. Gastrin has several key actions that contribute to protein digestion in the stomach: (Next slide)

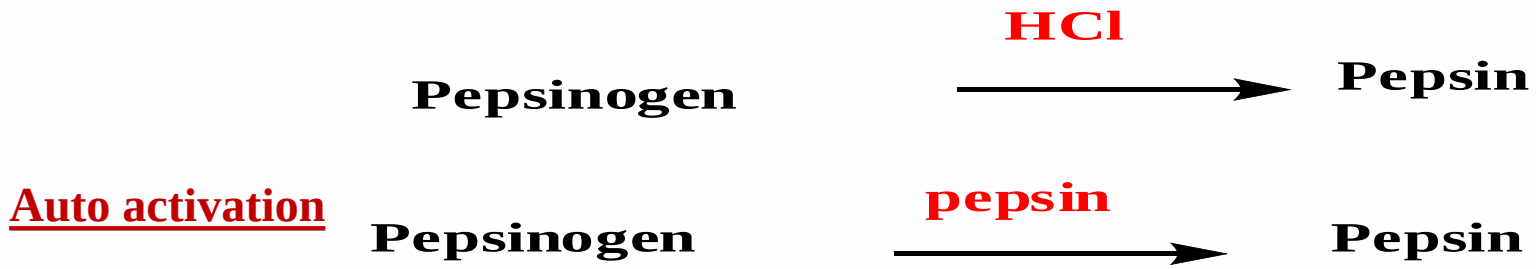
Gastrin has the following actions:

1. Gastrin binds to specific receptors on gastric parietal cells, promoting the release of hydrochloric acid (HCl).
2. stimulate the chief cells of gastric mucosa to secret the inactive zymogen "pepsinogen"



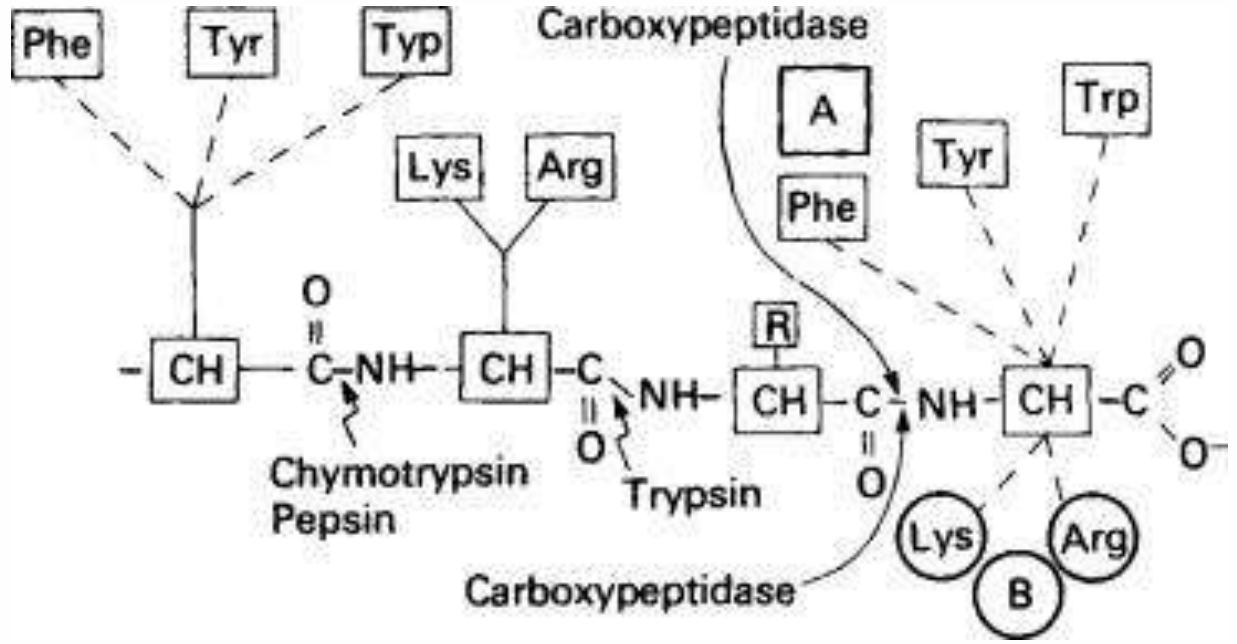
Hydrochloric acid (HCl) activates pepsinogen

- Pepsinogen is converted into its active form, pepsin, by the low pH created by HCl.
- Pepsin is an acid stable endopeptidase, partially hydrolyse the ingested proteins into large polypeptides and few amino acids.



Pepsin is an Endopeptidase

- It primarily cleaves peptide bonds on the **carboxyl side (C-terminus)** of aromatic amino acids (phenylalanine, tyrosine, tryptophan) and hydrophobic amino acids (like leucine)



Digestion in small intestine

Pancreatic & Intestinal peptidases

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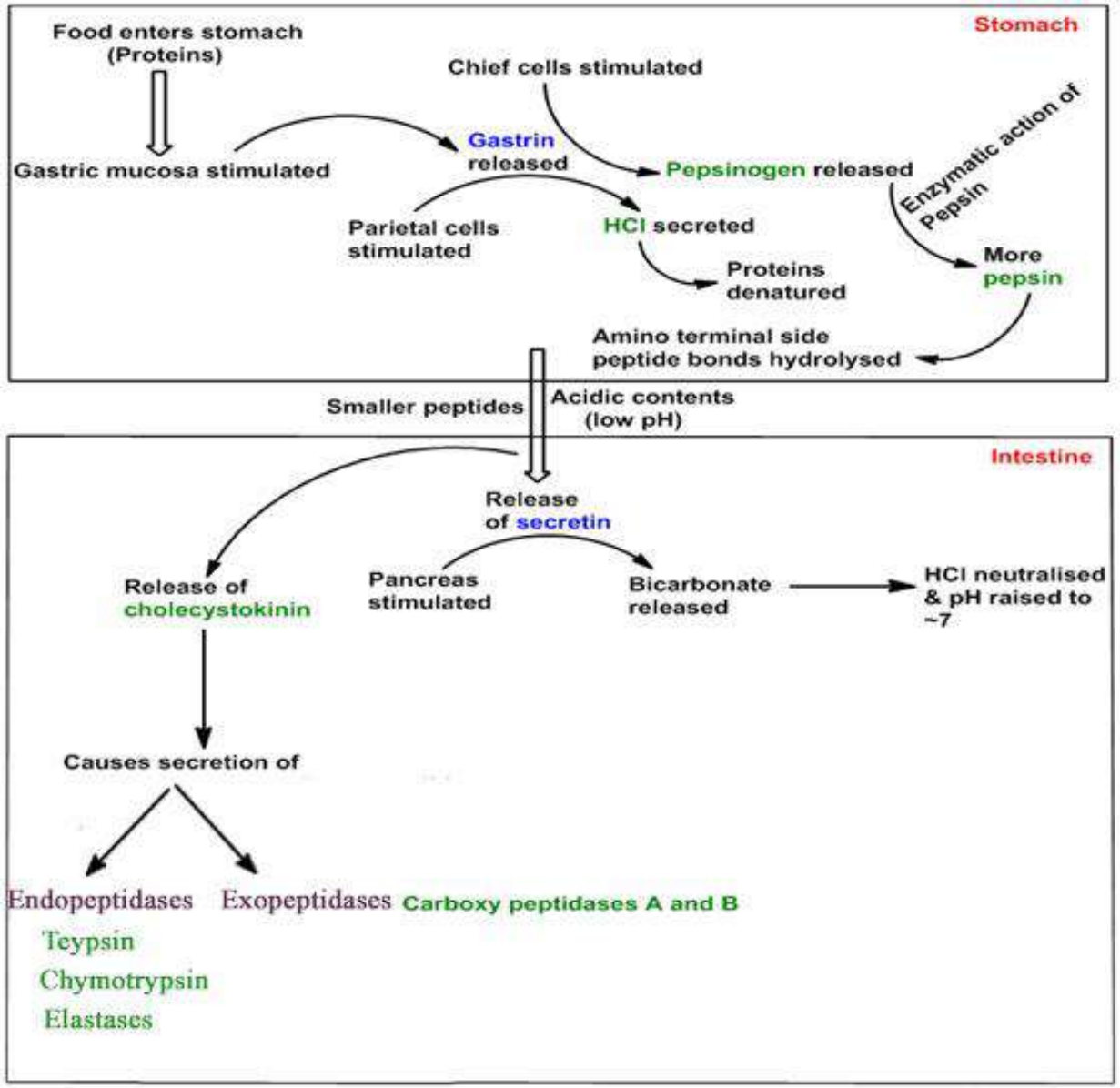
Hormonal response

- The presence of chyme in the small intestine stimulates the release of hormones from the small intestine lining cells.
- These hormones include:
  - Secretin
  - Cholecystokinin (CCK)

Hormonal response

- Pancreas secret several proenzymes into duodenum. The release and activation of pancreatic zymogens is mediated by the secretion of cholecystokinine and secretin (GIT hormones).

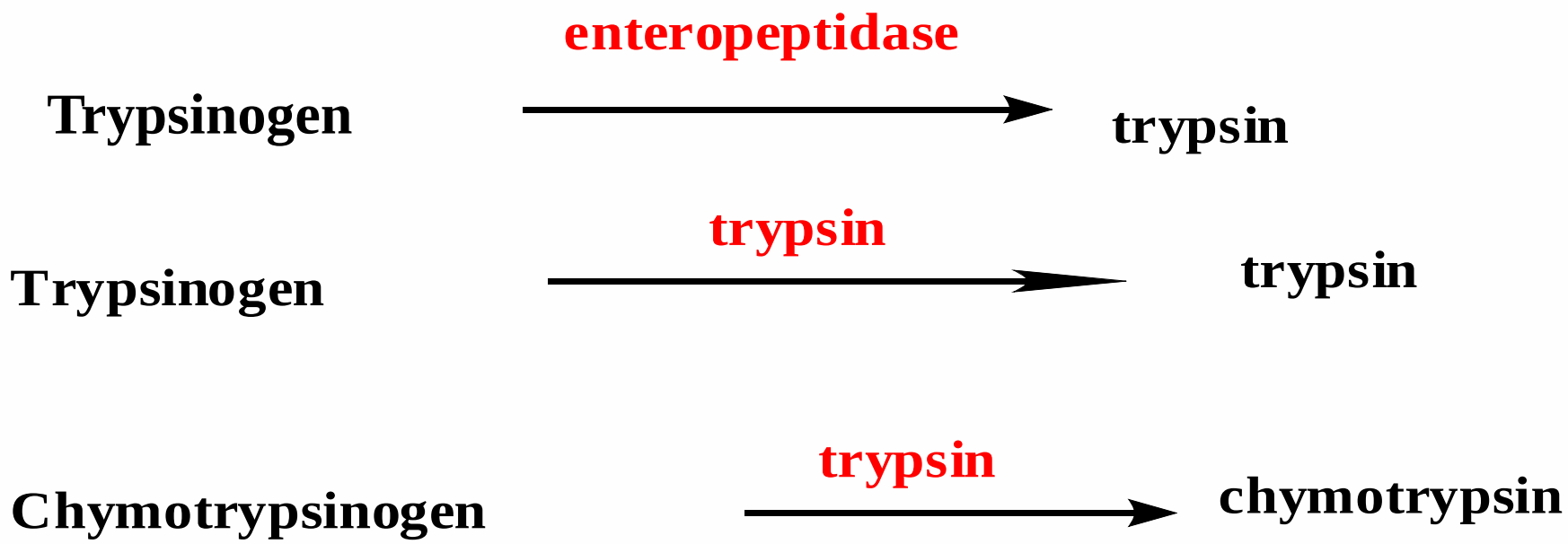


Activation of pancreatic zymogens:

The pancreatic zymogens are: **trypsinogen, chymotrypsinogen** and **pro-carboxypeptidases** (A and B).

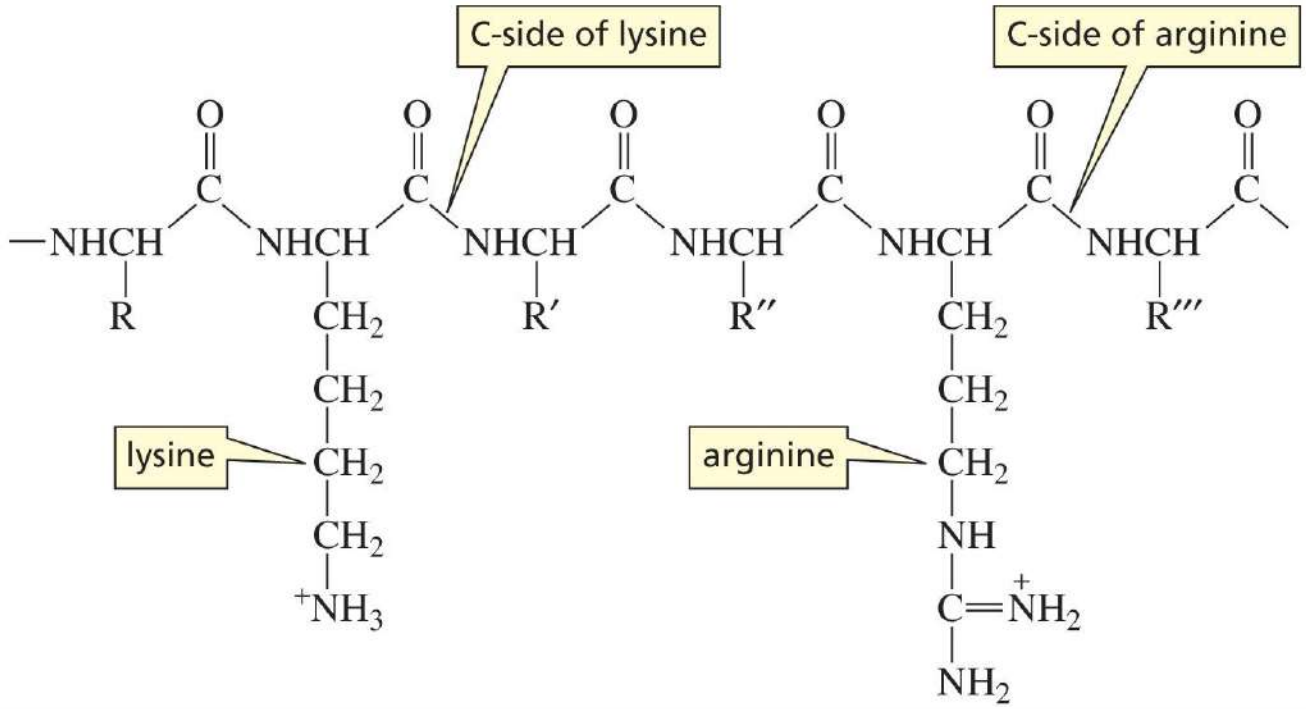
- **Enteropeptidase** (formerly called enterokinase, synthesized from intestinal mucosa) converts trypsinogen into active **trypsin**
- Trypsin activates more trypsinogen into trypsin

❑ Trypsin plays a significant role in activating many pancreatic zymogens: i.e activates chymotrypsinogen into **chymotrypsin** and pro-carboxypeptidase into **carboxypeptidase and** Proelastase into **elastase**.

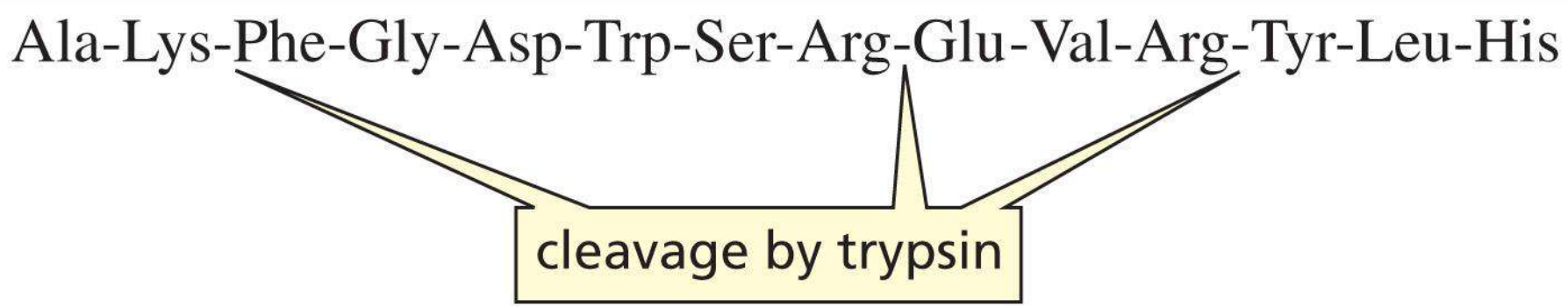


Trypsin

- Trypsin is an Endopeptidase Cleaves on carbonyl side (right) of Lysine (Lys) & Arginine ((Arg).

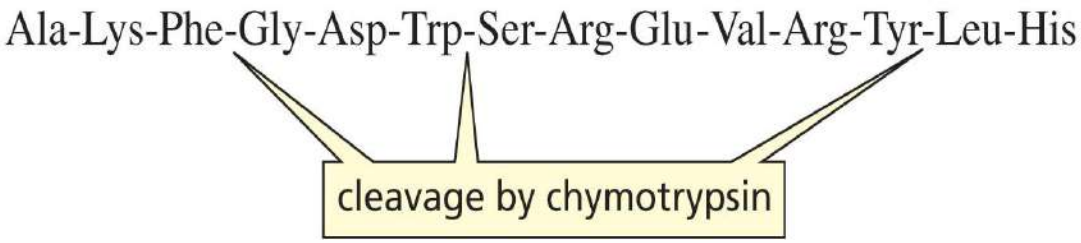


Cleavage by Trypsin



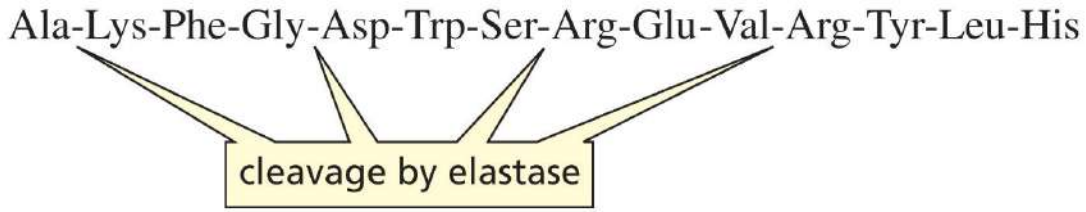
Chymotrypsin is an Endopeptidase

- Chymotrypsin cleaves on the right of amino acids that contain amino acids with aromatic six-membered rings (Phe, Tyr, and Trp).



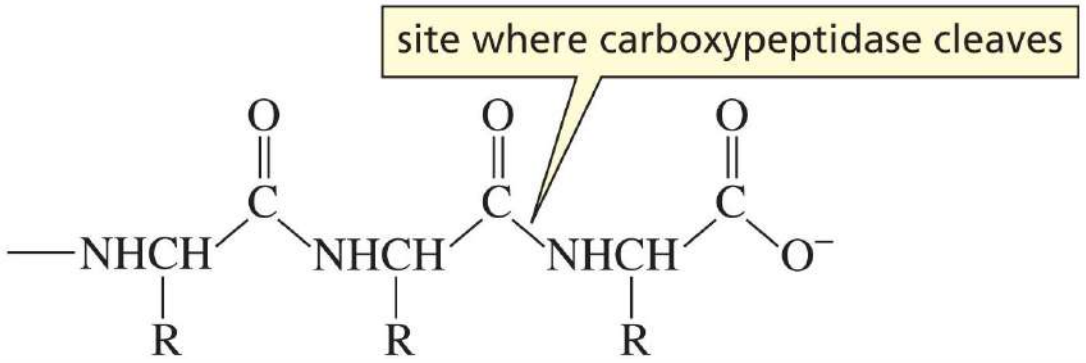
Elastase is an Endopeptidase

- Elastase cleaves on the right of small amino acids (Gly and Ala).

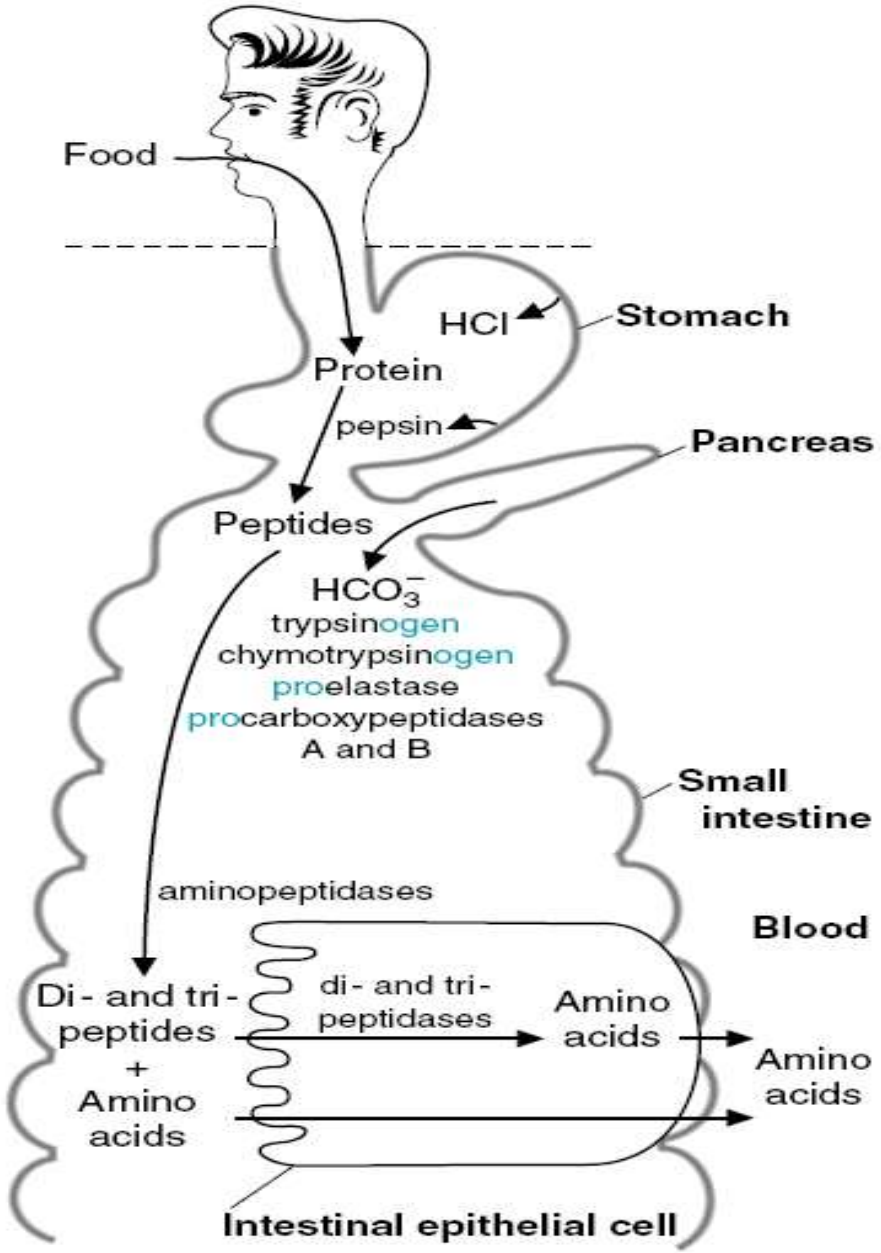


Carboxypeptidase catalyzes the hydrolysis of the C-terminal peptide bond.

- Carboxypeptidase is an exopeptidase.
- Carboxypeptidase A cleaves off the C-terminal amino acid (Phe, Tyr)as long as it is not Arg or Lys.
- Carboxypeptidase B cleaves off the C-terminal amino acid only if it is Arg or Lys.



Enzyme	Type	Cleavage Site	Specificity
Trypsin	Endopeptidase	Carboxyl side	Lysine (Lys), Arginine (Arg)
Chymotrypsin	Endopeptidase	Carboxyl side	Aromatic (Phe, Tyr, Trp), Large hydrophobic (Leu, Met)
Carboxypeptidase A	Exopeptidase	C-terminus	Aromatic (Phe, Tyr), Bulky aliphatic (Ile, Leu, Val)
Carboxypeptidase B	Exopeptidase	C- terminus	Basic (Lys, Arg)


Food
HCl
Stomach
Protein
pepsin
Pancreas
Peptides
HCO_3^-
trypsinogen
chymotrypsinogen
proelastase
procarboxypeptidases
A and B
Small intestine
aminopeptidases
Blood
Di- and tri-peptides
+
Amino acids
di- and tri-peptidases
Amino acids
Amino acids
Intestinal epithelial cell

Thanks
Lecture 3: Part 1