PASSION ACADEMIC TEAM

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Sheet# 2

YU - MEDICINE

GASTROINTESTINAL SYSTEM

Lec. Title : Enzymes of GIT . Written By : Abdullah Ananzeh

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Lecture 1 part 2

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Table 27.5. Properties of the GLUT 1-GLUT 5 Isoforms of the Glucose Transport Proteins

Transporter	Tissue Distribution	Comments
GLUT 1	Human erythrocyte Blood-brain barrier Blood-retinal barrier Blood-placental barrier Blood-testis barrier	Expressed in cell types with barrier functions; a high-affinity glucose transport system
GLUT 2	Liver Kidney Pancreatic β-cell Serosal surface of Intestinal mucosa cells	A high capacity, low affinity transporter. May be used as the glucose sensor in the pancreas.
GLUT 3	Brain (neurons)	Major transporter in the central nervous system. A high-affinity system.
GLUT 4	Adipose tissue Skeletal muscle Heart muscle	Insulin-sensitive transporter. In the presence of insulin the number of GLUT 4 transporters increases on the cell surface. A high-affinity system
GLUT 5	Intestinal epithelium Spermatozoa	This is actually a fructose transporter.

Genetic techniques have identified additional GLUT transporters (GLUT 7-12), but the role of these transporters has not yet been fully described.

We have different types of transporters for the digested molecules

We have more than 14 types of GLUT for specifity for glucose transportation which is the abundant molecule

>specifity is according to the needs of tissues >for ex GLUT5 is abundant in intestinal cells as well as spermatoal cells (lactose to be transported thers)

Insulin Stimulation

>for these molecules to be expressed on cells they are synthesized then stored in vacuoles to be expressed according to certain signalling mechanisms (insulin is an example)

>there is signalling pathway that stimulates the expression of GLUTs (not the synthesis//they are already synthesized but not yet expressed)

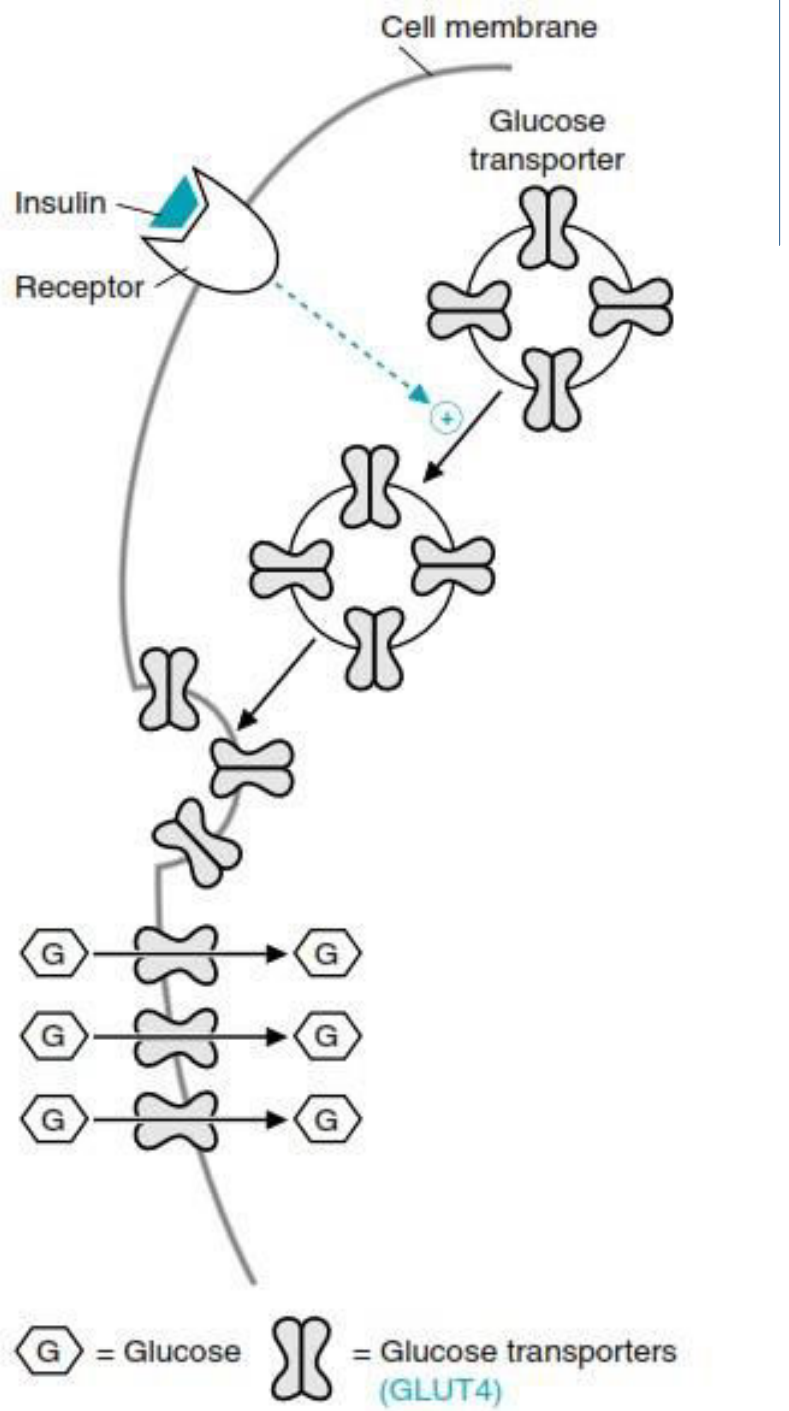


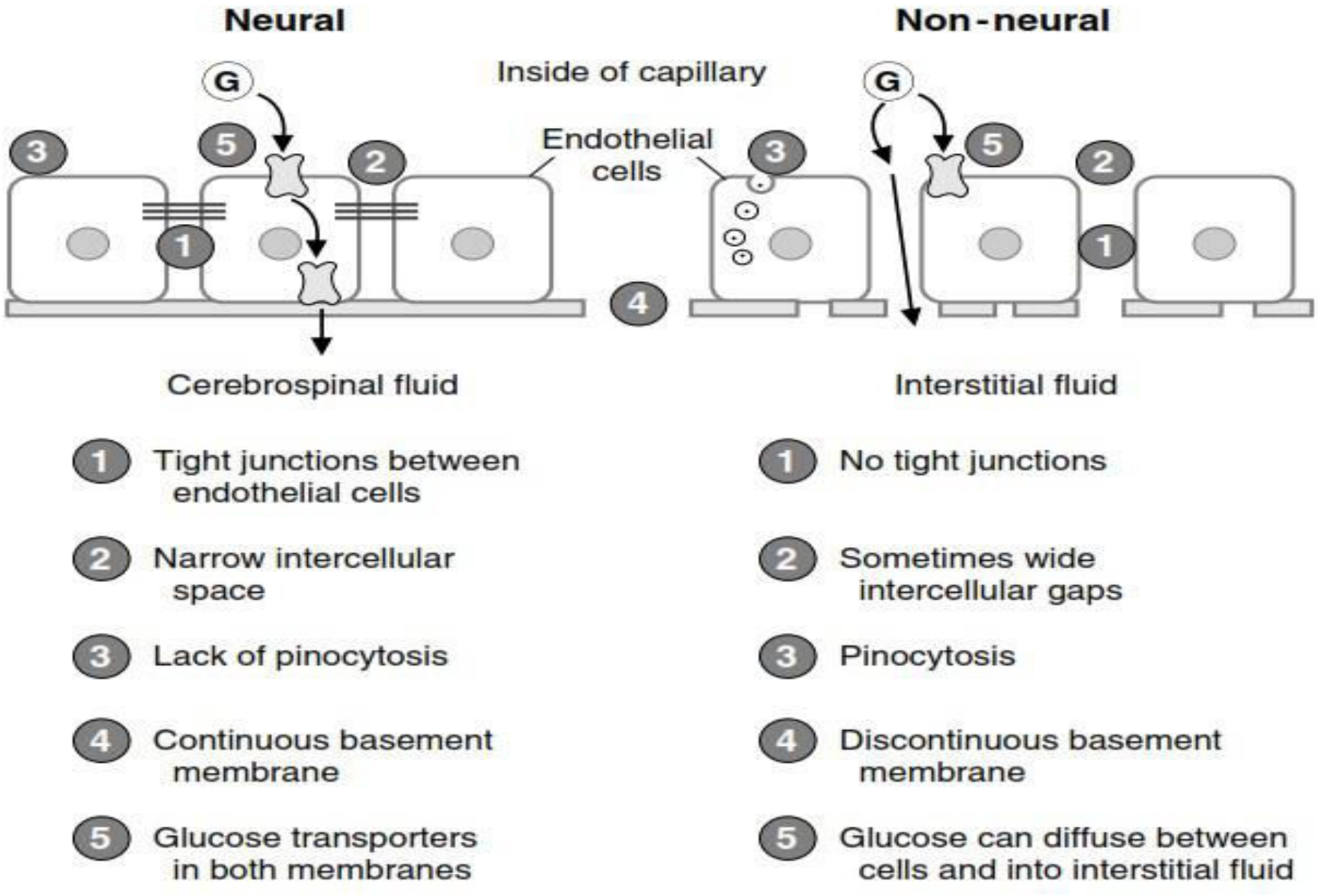
Fig. 27.13. Stimulation by insulin of glucose transport into muscle and adipose cells. Binding of insulin to its cell membrane receptor causes vesicles containing glucose transport proteins to move from inside the cell to the cell membrane.

GLUCOSE TRANSPORT THROUGH THE BLOOD-BRAIN BARRIER AND INTO NEURONS

Just to compare two different types of tissues in our body and the need to express certain types of GLUT or not

>neural vs non-neural cells
1)neural cells have no gaps(tight junctions) while non-N have spaces for glucose and other solutes
2)neural cells contains BBB that inhibits transportation of many solutes to neural tissue in order to avoid the toxicity >there is special transportation system

3)continuous basement membrane=no spacial gaps



Digestion and Transport of Dietary Lipids

Gall bladder stores and concetrates bile while liver synthesizes it

DIGESTION OF TRIACYLGLYCEROLS

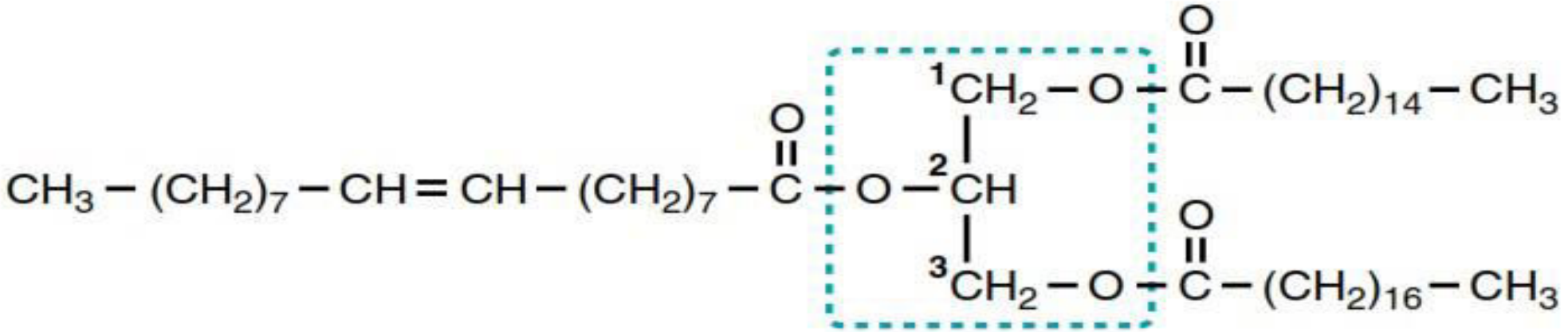
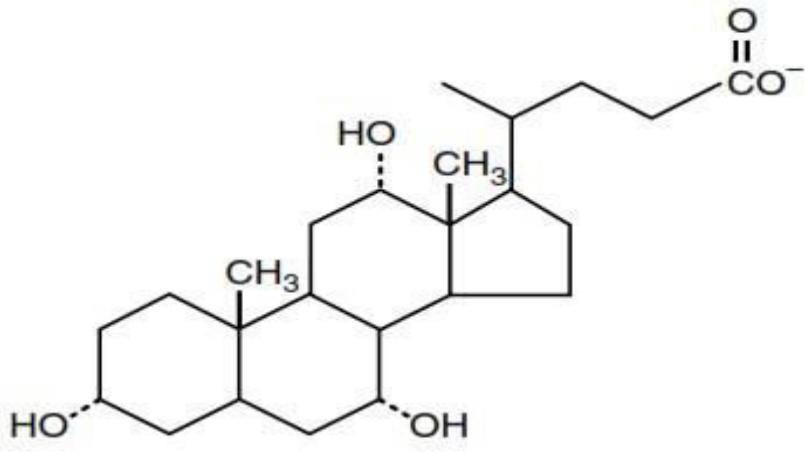


Fig. 32.1. Structure of a triacylglycerol. The glycerol moiety is highlighted, and its carbons are numbered.

Triacylglycerols are the major fat in the human diet because /most abundant molecule as a lipid or fat

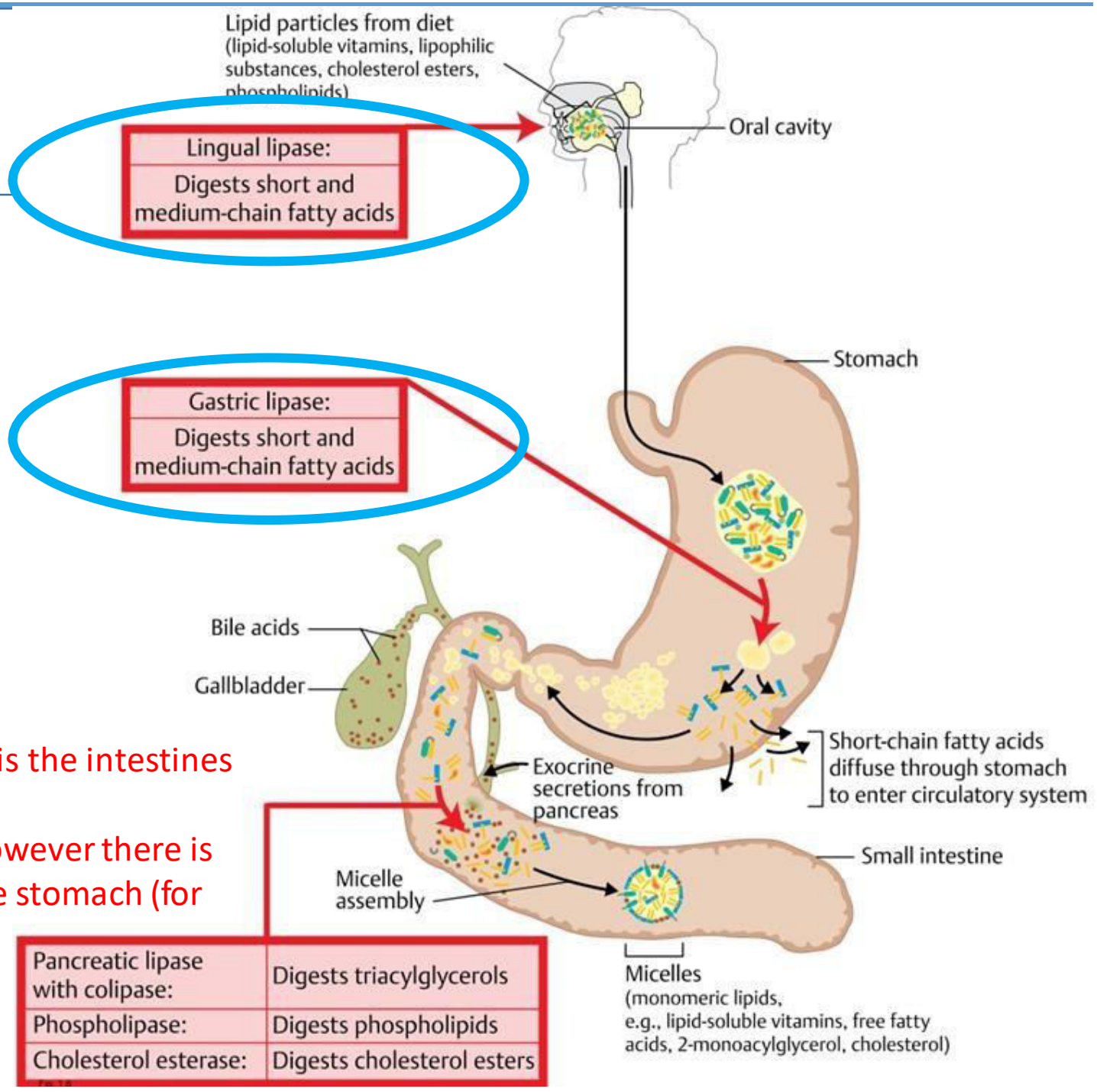
Glycerol is alcohol as we know ,connected to three fatty acids by ester(COO) bonds as you see

Major fat component found in the human diet ,it's the simplest fat to be digested



Cholate

Fig. 32.2. Structure of a bile salt. The bile salts are derived from cholesterol and retain the cholesterol ring structure. They differ from cholesterol in that the rings in bile salts contain more hydroxyl groups and a polar side chain and lack a 5-6 double bond.



Pancreatic lipase with colipase:	Digests triacylglycerols
Phospholipase:	Digests phospholipids
Cholesterol esterase:	Digests cholesterol esters

Here we will focus on the sites of lipid digestion

Previously we had known that the site of lipid digestion is the intestines (its not totally!)

The most of lipid digestion occurs in SI by the lipases ,however there is digestion process that occurs in the mouth as well as the stomach (for certain extent only)

We don't rely on oral and gastric lipases but they are present ,*gastric lipase is also called acid resistant lipase

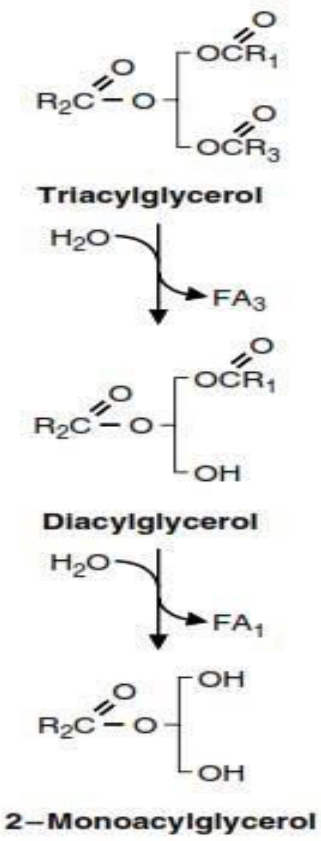
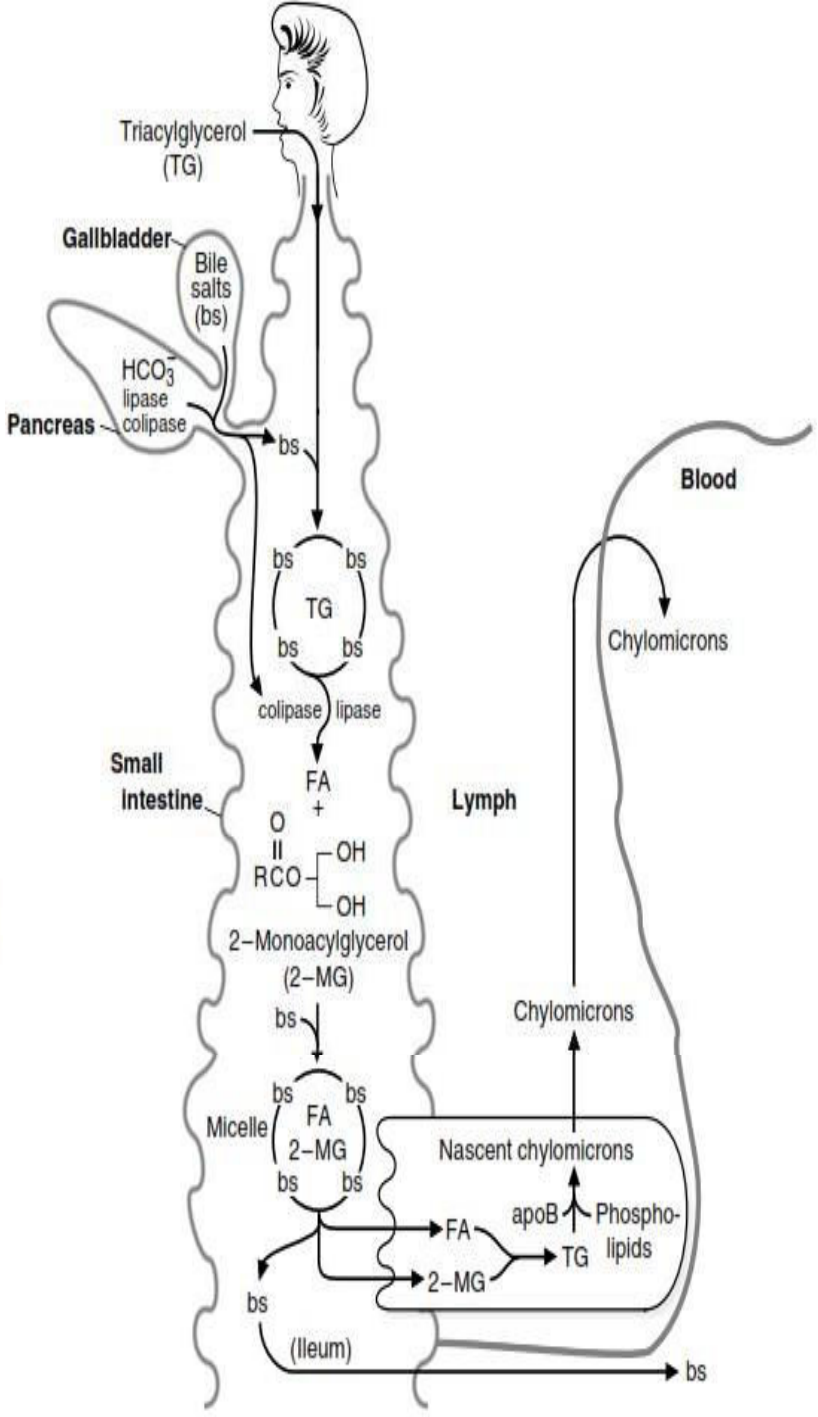


Fig. 32.4. Action of pancreatic lipase. Fatty acids (FA) are cleaved from positions 1 and 3 of the triacylglycerol, and a monoacylglycerol with a fatty acid at position 2 is produced.

We break C1 or C3 to form monoacylglycerol
>>>lipases have no access to reach the C2



Gastric and lingual lipases are necessary in breast feeding age ,to digest fats in mothers milk also the acidity in infants is lower than in adults which requires the help of these enzymes alot

The colipase binds to the dietary fat and to the lipase, thereby increasing lipase activity.

Short- and medium-chain fatty acids (C4 to C12) do not require bile salts for their absorption.
Digeste lipids are absorbed by lacteals of LN

Compared to proteins,carbs,nucleic acids Lipids differ in their solubility (hydrophobic)
Water soluble molecules are easily digested by enzymes(water soluble)
Lipids hydrophicity acts as obsticle/barrier for enzyme function>this is why we need bile salts/acid
Bile salts :bile conjugated to Na for ex as aprecipetate
In case bile is a solute its in acidic form

From page 33 :cholate or cholic acids are responsible for emulsification of lipids in order to to facilitate the digestion process by the formation of micelles (not only circular >they have globular structure ,it can have irregular structure means soluble in water In the end)

From page 34:reformation of large lipid molecules called nascent chylomicrons ,CM :rejoin what we digested from fats(reformation of TG),there is conjugation of lipoproteins which serves to increase the solubilty

Bec chylomicrons are large they are transported by exoicytosis rather than diffusion

pancreatic esterases and phospholipase A2.

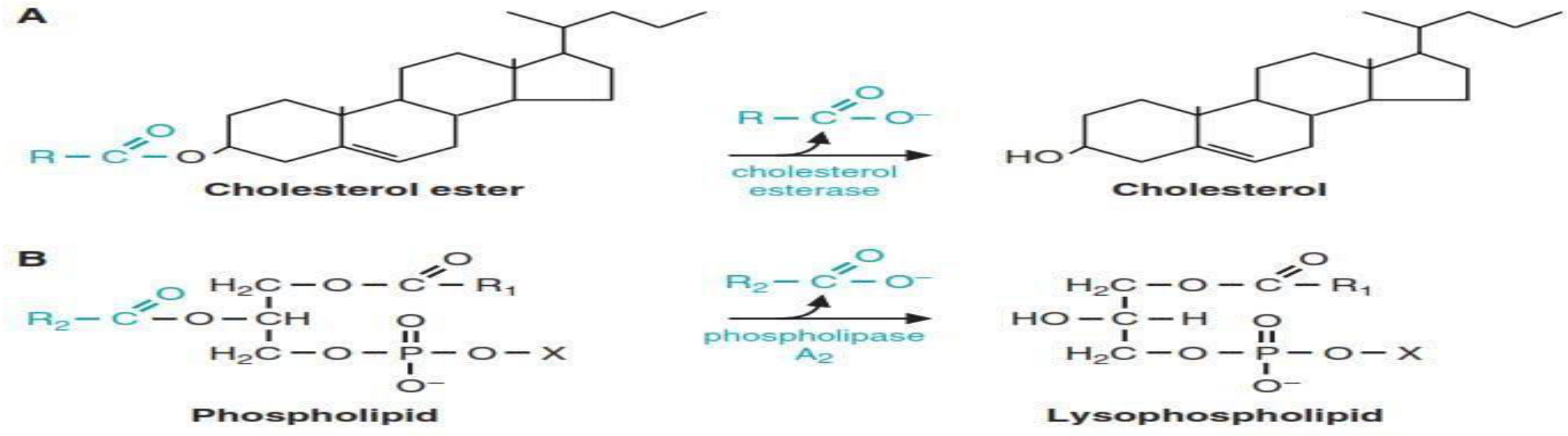


Fig. 32.5. Action of pancreatic esterases (A) and phospholipase A2 (B).

We have different kinds of phospholipases like PLA2,PLC,PLD (A2,C,D)
The result of PLA2 is lysophospholipid and free faty acid

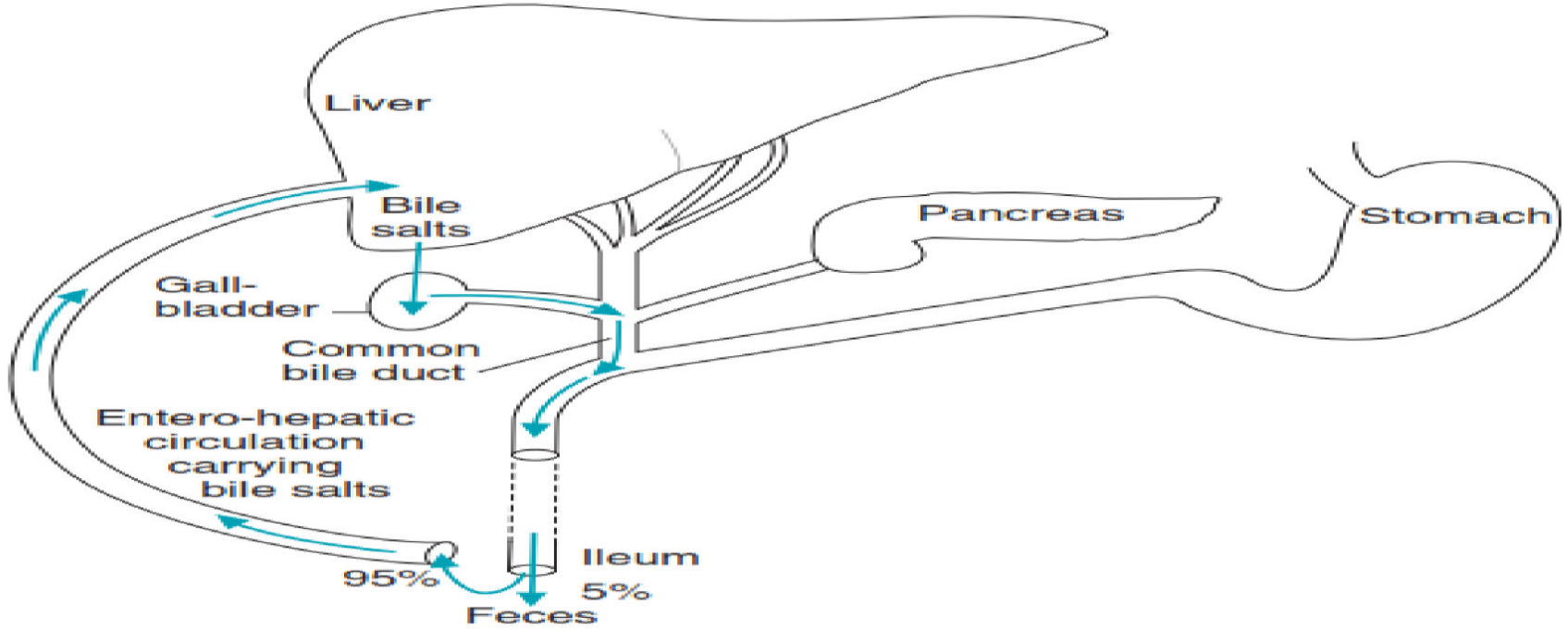


Fig. 32.6. Recycling of bile salts. Bile salts are synthesized in the liver, stored in the gall-bladder, secreted into the small intestine, resorbed in the ileum, and returned to the liver via the enterohepatic circulation. Five percent or less of luminal bile acids are excreted in the stool under normal circumstances.

Bile salt can be reabsorbed from the intestines >we have 95% as secondary bile salt
The one that is secreted by the liver or gall bladder is called primary
Bile salt is inhibitor for the lipase (how eventhough it emulsifies lipids to be more soluble ?)ذائبية هو صح بزيد
الدهون بس ما بسهل وصول الانزيم لايبيز لالها فبالتالي انا محتاج لاشي يسهل وصوله وهاي وظيفة الCOLIPASE

Protein Digestion and Amino Acid Absorption

The digestion of proteins begins in the stomach and is completed in the intestine

Proenzymes (zymogens) → **Active enzymes**

Pepsinogen —(H^+)→ Pepsin

Trypsinogen —(enteropeptidase)→ Trypsin

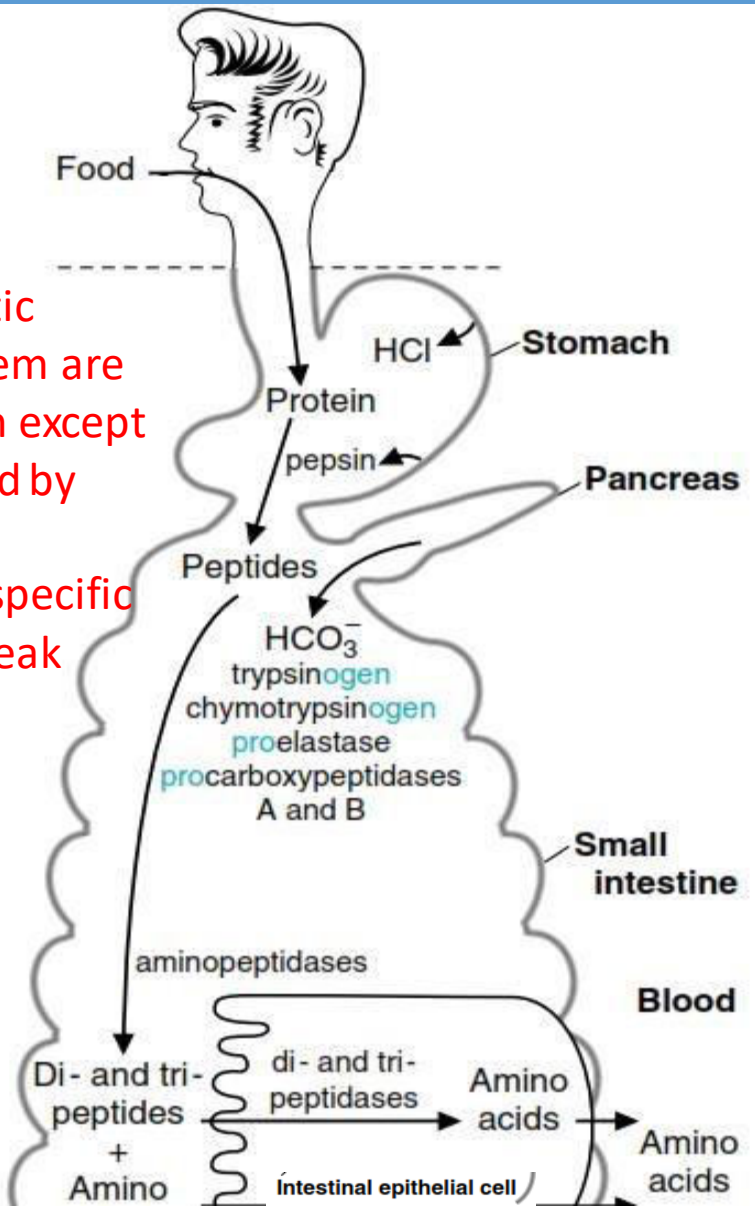
Chymotrypsinogen —(trypsin)→ Chymotrypsin

Proelastase —(trypsin)→ Elastase

Procarboxypeptidases —(trypsin)→ Carboxypeptidases

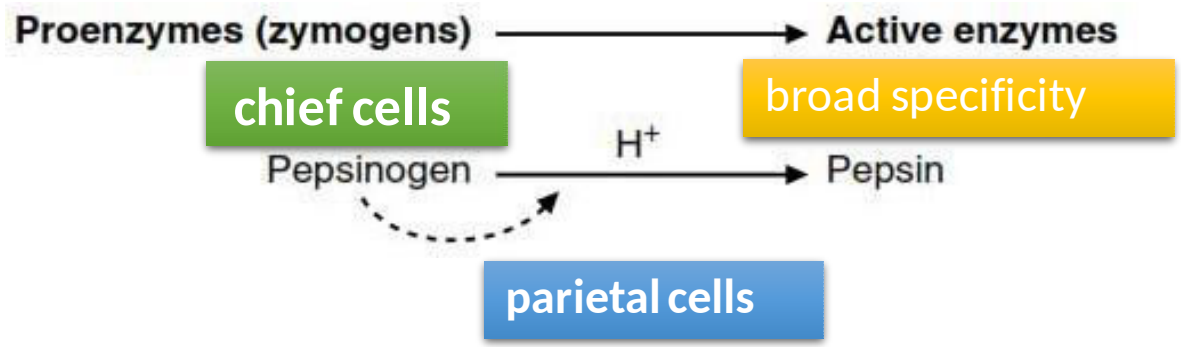
Fig. 37.2. Activation of the gastric and pancreatic zymogens. Pepsinogen catalyzes its own cleavage as the pH of the stomach drops. Trypsinogen is cleaved by enteropeptidase in the intestine to form the active protease trypsin. Trypsin then plays a key role by catalyzing the cleavage and activation of the other pancreatic zymogens.

Those are pancreatic proteases ,all of them are activated by trypsin except trypsin ,its activated by enteropeptidase
Each protease has specific peptide bond to break



Digestion of Proteins in the Stomach

There is inactive form of pepsin (zymogen/pepsinogen) that are activated by HCL to form pepsin
Also there is self activation for pepsin for itself
Pepsin has a broad specifity rather than specific site



In carbs we have a polyglucose molecules ,the bond between them is very similar alpha1-4 glycosidic bonds so we need one enzyme type unless we have branches
In proteins we have different amino acids so we multiple enzymes in order to match the bond
For ex a bond between alanin and alanin differs from that between alanin and glutamic acid
In the end we have aminopeptidases,dipeptidases,tripeptidases inorder to absorb single amino acids in the end (we only absorb monomers not dimers(dimers and larger molecules are antigenic they cause sensitivity))

Digestion of Proteins by Enzymes from the Pancreas

Trypsinogen —enteropeptidase→ Trypsin

Chymotrypsinogen —trypsin→ Chymotrypsin

Click to add text

Proelastase —trypsin→ Elastase

Procarboxypeptidases —trypsin→ Carboxypeptidases

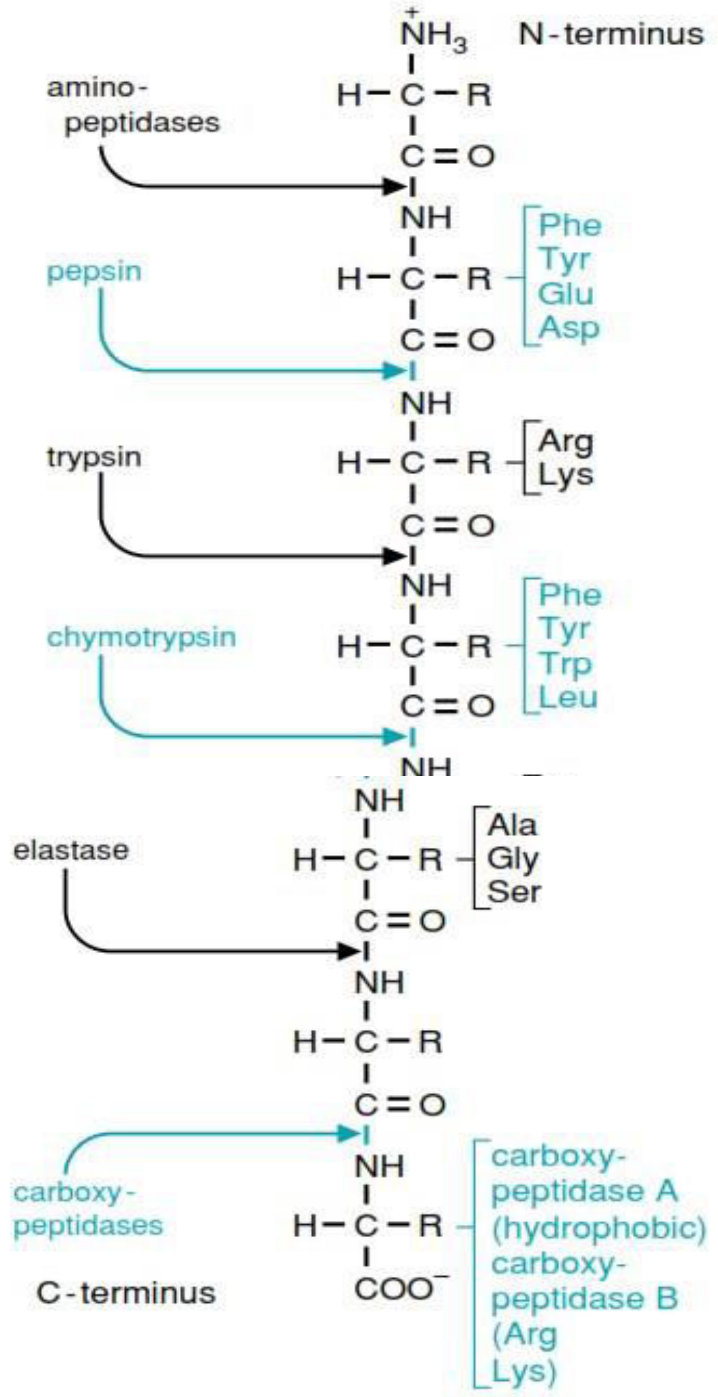


Fig. 37.2. Activation of the gastric and pancreatic zymogens. Pepsinogen catalyzes its own cleavage as the pH of the stomach drops. Trypsinogen is cleaved by enteropeptidase in the intestine to form the active protease trypsin. Trypsin then plays a key role by catalyzing the cleavage and activation of the other pancreatic zymogens.

Pepsin and aminopeptidases
>pepsin has broad specifity
from the figure you have to know that there is specific locations in the peptide

aminopeptidase breaks any peptide bond followed by phenylalanine,tyrosine,glutamic or aspartic acid at the n terminal end (right to it) (it digests the peptide bond when these amino acids on the right side of it /downwards)

pepsin digest peptidebond when Asp,tyr,phe,trp on the left side of it

carboxypeptide :it digest the c terminal end

there sth related to c terminus and some to N terminus
صح مختصه بس مش مختصه بنوع واحد من الاحماض الامينية يعني ممكن لاربعة مع بعض المطلوب تعرف انه could occur to group of AA with similar properties وهكذا

Digestion of Proteins by Enzymes from Intestinal Cells

1. **Aminopeptidases**, located on the brush border, cleave one amino acid at a time from the amino end of peptides.

   Also carboxy peptidases

2. **Intracellular peptidases** act on small peptides that are absorbed by the cells.

Clinical correlations

Individuals with genetic deficiencies of the sucrase-isomaltase complex show symptoms of sucrose intolerance but are able to digest normal amounts of starch in a meal, without problems. The maltase activity in the glucoamylase complex, and residual activity in the sucrase-isomaltase complex (which is normally present in excess of need) is apparently sufficient to digest normal amounts of dietary starch.

They will have indigestion of sucrise only but other sugars are perfectly digested
Causes are genetic mutations in these enzymes

The epithelial cells of the kidney, which reabsorb glucose into the blood, have Na^+-dependent glucose transporters similar to those of intestinal epithelial cells. They are thus also able to transport glucose against its concentration gradient. Other types of cells use mainly facilitative glucose transporters that carry glucose down its concentration gradient.

The erythrocyte (red blood cell) is an example of a tissue in which glucose transport is not rate-limiting. Although the glucose transporter (GLUT 1) has a K_m of 1 to 7 mM, it is present in extremely high concentrations, constituting approximately 5% of all membrane proteins. Consequently, as the blood glucose levels fall from a postprandial level of 140 mg/dL (7.5 mM) to the normal fasting level of 80 mg/dL (4.5 mM), or even the hypoglycemic level of 40 mg/dL (2.2 mM), the supply of glucose is still adequate for the rates at which glycolysis and the pentose phosphate pathway operate.

Numbers are not required

The most abundant glucose transporter in the RBCs is GLUT 1 and its insulin independent
It has very strange Km (1-7) which means there is a broad range of Km(strange as its normally a constant value)
This leads to special ability to take glucose even if the blood glucose is low

Al Martini has continued to abuse alcohol and to eat poorly. After a particularly heavy intake of vodka, a steady severe pain began in his upper mid-abdomen. This pain spread to the left upper quadrant and eventually radiated to his mid-back. He began vomiting nonbloody material and was brought to the hospital emergency room with fever, a rapid heart beat, and a mild reduction in blood pressure. On physical examination, he was dehydrated and tender to pressure over the upper abdomen. His vomitus and stool were both negative for occult blood.

Blood samples were sent to the laboratory for a variety of hematologic and chemical tests, including a measurement of serum amylase and lipase, digestive enzymes normally secreted from the exocrine pancreas through the pancreatic ducts into the lumen of the small intestine.

Alcoholic patient,eat poorly,he has vomiting,diarrhea and some sort of pain
Read It to take an idea of his history

Al Martini's serum levels of pancreatic amylase (which digests dietary starch) and pancreatic lipase were elevated, a finding consistent with a diagnosis of acute and possibly chronic pancreatitis. The elevated levels of these enzymes in the blood are the result of their escape from the inflamed exocrine cells of the pancreas into the surrounding pancreatic veins. The cause of this inflammatory pancreatic process in this case was related to the toxic effect of acute and chronic excessive alcohol ingestion.

At the end due to elevation in pancreatic amylase he has pancreatitis (inflammation of pancreatic tissue)

Q: When he was finally able to tolerate a full diet, **Al Martini's** stools became bulky, glistening, yellow-brown, and foul smelling. They floated on the surface of the toilet water. What caused this problem?

ANS:He have steatorrhea(fatty stools) due to inability to digest lipids as he has enzymatic problems bec of pancreatitis

For your knowledge the cause for enzymatic problems could be other than pancreatitis

Al Martini's stool changes are characteristic of steatorrhea (fat-laden stools caused by malabsorption of dietary fats), in this case caused by a lack of pancreatic secretions, particularly pancreatic lipase, which normally digests dietary fat.

Steatorrhea also may be caused by insufficient production or secretion of bile salts. Therefore, **Michael Sichel** might also develop this condition.

التهاب البنكرياس فكرته انه :للفهم
البنكرياس بزيد افرازه للانزيمات بشكل مفرط بالدم بدل افرازه على الاكل في الاثني عشر فبصير عندي نغيرات بالبراز تدل على عدم قدرة هضم سليمة

We mentioned this before

Bile salts inhibit pancreatic lipase activity by coating the substrate and not allowing the enzyme access to the substrate. The colipase relieves the bile salt inhibition, and allows the triglyceride to enter the active site of the lipase.

The exocrine pancreas secretes phospholipase A2 in an inactive zymogen form, prophospholipase A2. The enzyme is activated in the intestinal lumen by proteolytic cleavage by trypsin. Pancreatic lipase, however, is secreted in its active form, and only needs to bind colipase and substrate to be active.

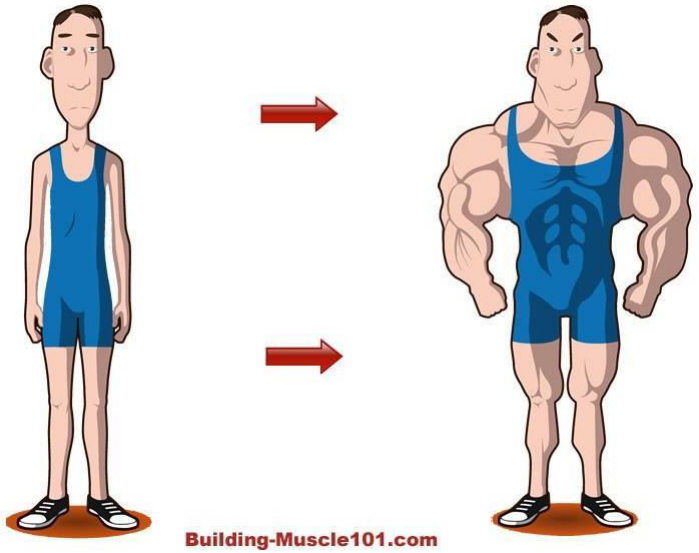
Trypsin activates also phospholipase A2 which is phospholipid digestion enzyme

Elastase is also found in neutrophils, white blood cells that have the job of engulfing and destroying invading bacteria. Neutrophils frequently act in the lung, and elastase is sometimes released into the lung as the neutrophils work. In normal individuals, the released elastase is blocked from destroying lung cells by the action of circulating α-1-antitrypsin, a protease inhibitor synthesized and secreted by the liver. Certain individuals have a genetic mutation that leads to the production of an inactive α-1-antitrypsin protein (α-1-antitrypsin deficiency). The lack of this enzyme activity leads to the development of emphysema caused by proteolytic destruction of lung cells, which results in a reduction in the expansion/contraction capability of the lungs.

The pancreas synthesizes and stores the zymogens in secretory granules. The pancreas also synthesizes a secretory trypsin inhibitor. The need for the inhibitor is to block any trypsin activity that may occur from accidental trypsinogen activation. If the inhibitor were not present, trypsinogen activation would lead to the activation of all of the zymogens in the pancreas, which would lead to the digestion of intracellular pancreatic proteins. Such episodes can lead to pancreatitis.

intestinal epithelial pinocytosis,

Trace amounts of polypeptides pass into the blood. They may be transported through intestinal epithelial cells, probably by pinocytosis, or they may slip between the cells that line the gut wall. This process is particularly troublesome for premature infants, because it can lead to allergies caused by proteins in their food.



Excess proteins and muscle mass

Adults cannot increase the amount of muscle or other body proteins by eating an excess amount of protein. If dietary protein is consumed in excess of our needs, it is converted to glycogen and triacylglycerols, which are then stored.

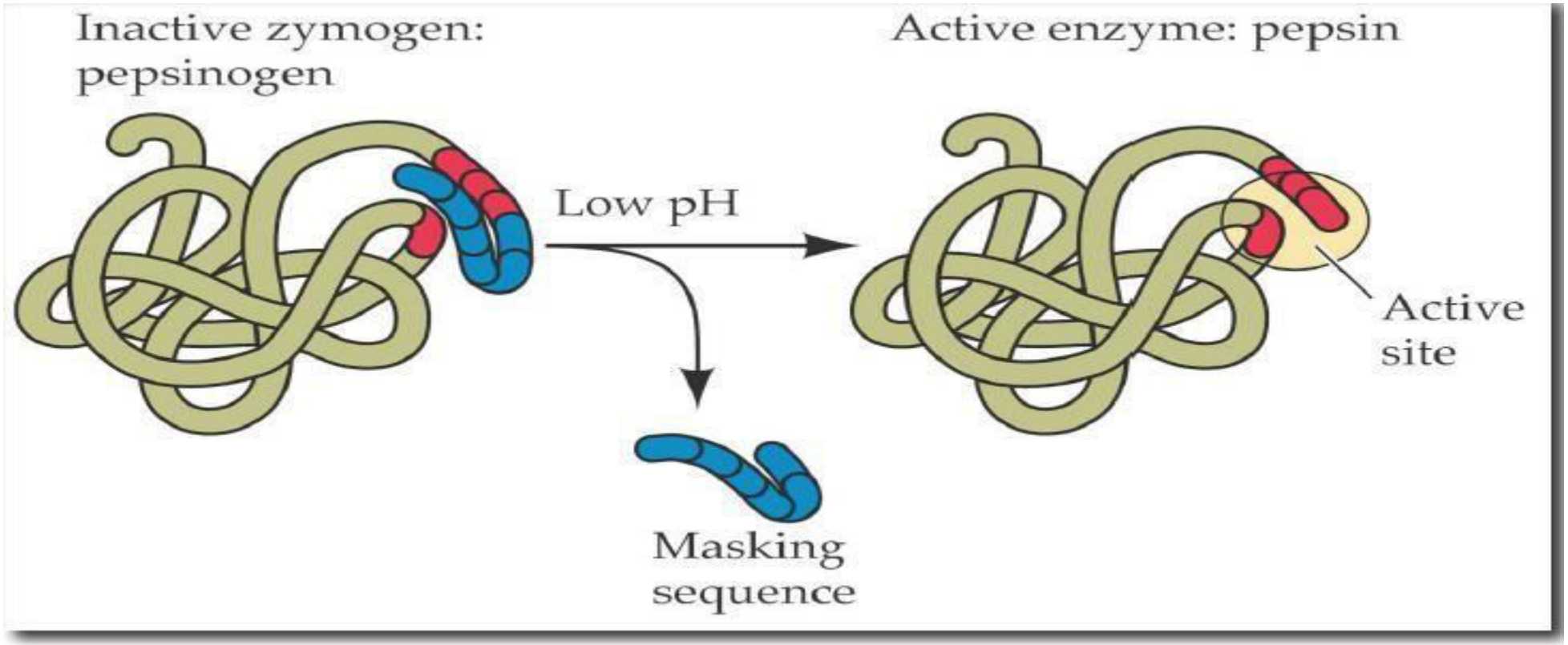
Can we increase our proteins by just amino acids ?
No ,in fact these amino acids are residues that can be converted to carbohydrate molcules that can be transformed to fats but they could make proteins if you are practicing excercises

H+

Pepsinogen ----------> Pepsin

(MW 40,000) (MW 33,000)

Autocatalysis



At the molecular level we activate zymogen to active enzyme by cleaving some part of the zymogen(asking sequence)

Neutral Amino Aciduria (Hartnup Disease)

Transport functions, like enzymatic functions, are subject to modification by mutations. An example of a genetic lesion in epithelial amino acid transport is Hartnup disease, named after the family in which the disease entity resulting from the defect was first recognized. The disease is characterized by the inability of renal and intestinal epithelial cells to absorb neutral amino acids from the lumen. In the kidney, in which plasma amino acids reach the lumen of the proximal tubule through the ultrafiltrate, the inability to reabsorb amino acids manifests itself as excretion of amino acids in the urine (amino aciduria). The intestinal defect results in malabsorption of free amino acids from the diet. Therefore the clinical symptoms of patients with this disease are mainly those due to essential amino acid and nicotinamide deficiencies. The pellagra-like features (see p. 1121) are explained by a deficiency of tryptophan, which serves as precursor for nicotinamide. Investigations of patients with Hartnup disease revealed the existence of intestinal transport systems for di- or tripeptides, which are different from the ones for free amino acids. The genetic lesion does not affect transport of peptides, which remains as a pathway for absorption of protein digestion products.

Silk, D. B. A. Disorders of nitrogen absorption. In: J. T. Harries (Ed.), *Clinics in Gastroenterology: Familial Inherited Abnormalities*, Vol. 11: London: Saunders, 1982, pp. 47–73.

Hartnup disease:named after tha family which have this disease ,they have neutral amino acid malabsorbtion so its called neutral amino aciduria (amino acids in the urine)

The transporters in kidney works for general classes not single AA (one transporter is for acidic AA another for neutral AA and so on).Due to the loss of these amino acids in urine(normally there is no AA,glucose,TriG in urine)

Babies may have glucose in their urine as the threshold of glucose is relatively low

This condition leads to pellagra:خمول عدم القدرة على العمل