DOCTOR 2020 | JU

METABOLISM

WRITER : Ahmad **ZAIDAN**

CORRECTOR : Ali **ALMAHROOK**

DOCTOR: Mamoun **AHRAM**

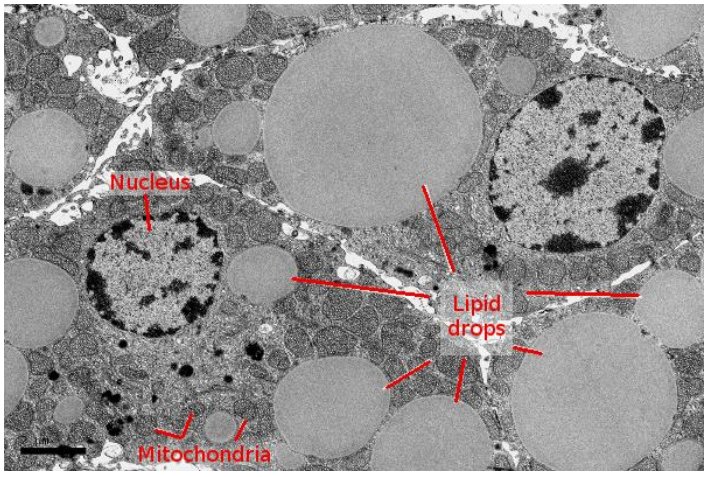
Metabolism of Lipids

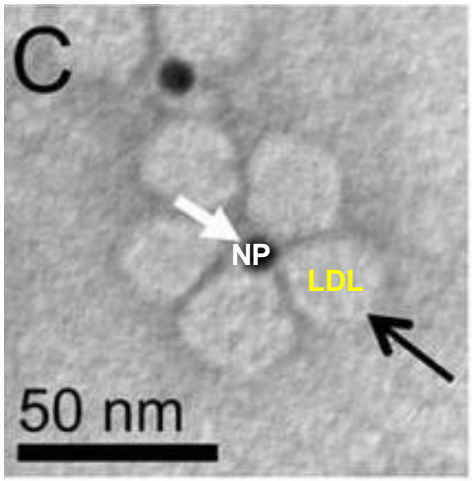
They are 4 types of macromolecules in our body:

1. Carbohydrates 2. Nucleic acids 3. Proteins 4. Lipids

The first three types are polymers (composed of repeating subunits). However, lipids aren't

Lipids are organic macromolecules, heterogeneous, hydrophobic, compartmentalized (because of their insolubility) in 1. Membranes 2. as droplets of triacylglycerol (TAG) 3. Transported in the blood in association of protein like lipoprotein (LP) particles or albumin



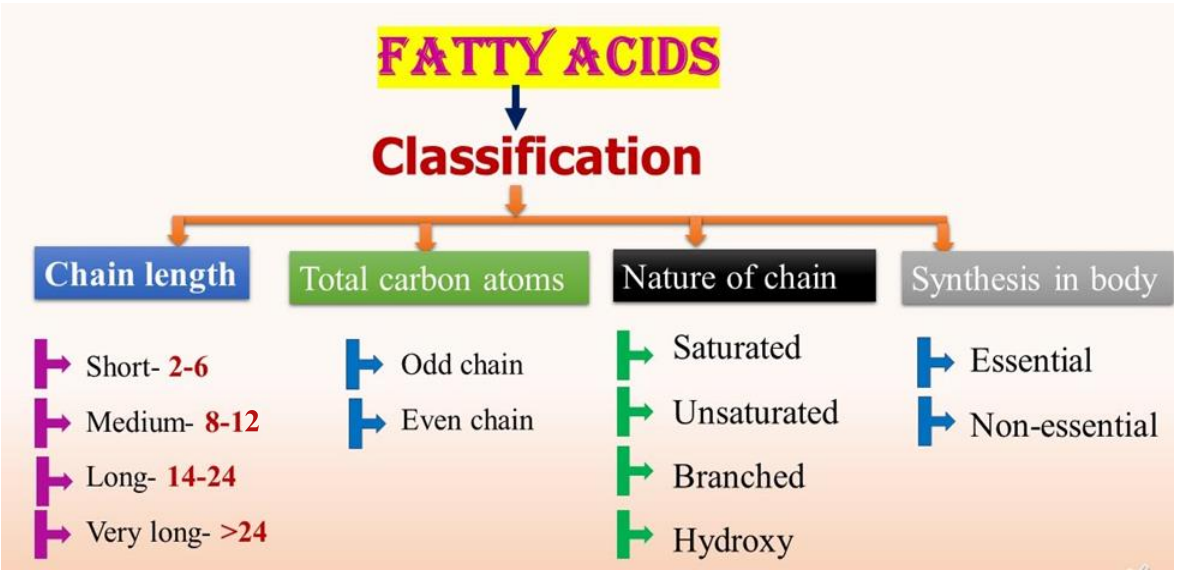


Heterogenous: they are not polymers + similarities among lipids are few (the main one they are hydrophobic)

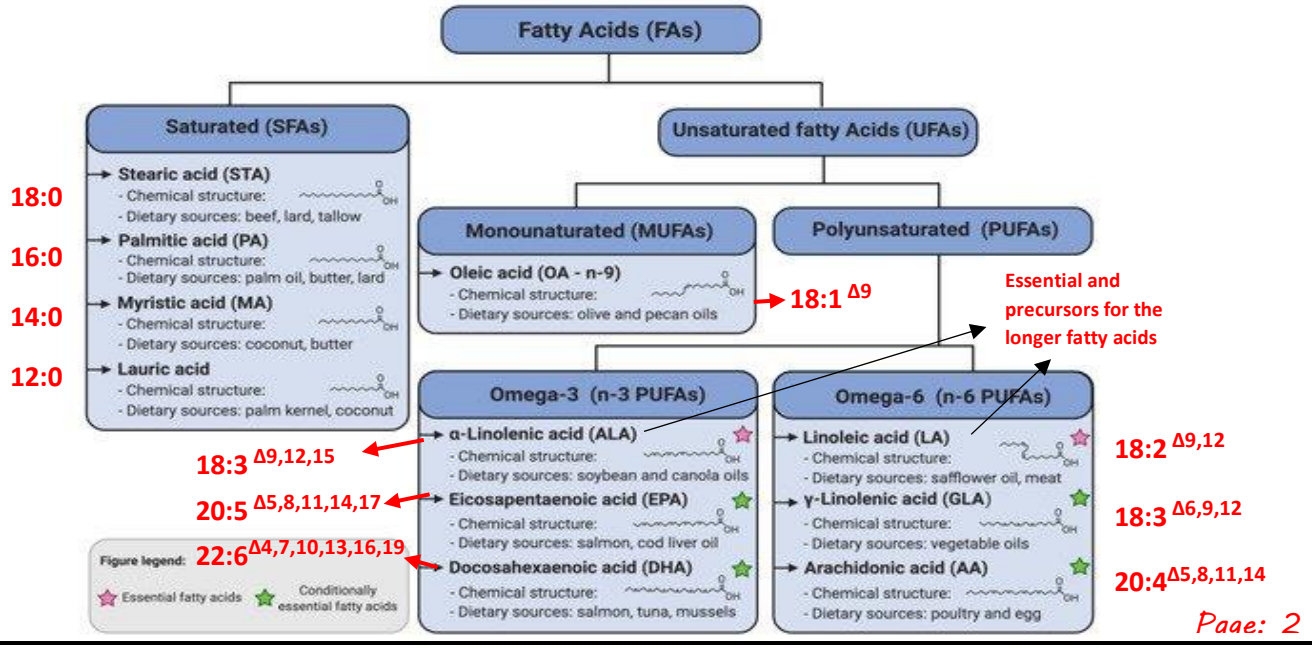
Functions: Energy, structures (membranes that permits partitioning of the aqueous contents and subcellular structures), molecular precursors (ex. fat-soluble vitamins, signaling molecule (inositol), steroid hormones, eicosanoids)

GENERAL VIEW:

There are many forms of lipids. They can be found as fatty acids (FA) which can be saturated or monounsaturated (cis vs trans) or polyunsaturated. Also, they can be found as glycerolipids (ex. diglyceride & triglyceride (also known as triacylglycerol TAG)), glycerophospolipids (PL) (glycerol with 2 fatty acids and phosphate group with small hydrophilic group (ex. Choline, serine, inositol, ethanolamine), sphingolipids (SL) which has sphingosine backbone which is attached to a fatty acid and another group (phosphorylcholine in sphingomyelin, monosaccharide in cerebrosides, cluster of sugars in ganglioside). Also, they can be found as steroids such as cholesterol (CH) and cholesterol ester (CE).



- **Fatty acids can be classified based on multiple criteria**
- **Most abundant fatty acids 16-18 carbon**
- **Even chains are dominant (more common than odd ones)**
- **Saturated means there is no double bonds while unsaturated means they have double bonds and unsaturated could be mono or poly**
- **Unsaturated could be cis which will result in a kink or trans (no kinks)**
- **Branched and hydroxy are not important in this course**
- **Essential means we must get them from diet while non-essential means we can synthesize them in our bodies**
- **Double bonds in FA are always spaced at three-carbon intervals.**
  Ex. Arachidonic acid $20:4^{\Delta 5,8,11,14}$
  (20 carbon with 4 double bonds, Δ: the locations of double bonds)
- **The addition of double bonds decreases the melting temperature (Tm) of a fatty acid. However, increasing the chain length increases the Tm.**
- **Membrane lipids typically contain unsaturated long chain fatty acid (LCFA) to maintain fluidity with cis orientation which will result in a kink (more space between FAs)**



Omega 3 means the distance between omega carbon (the furthest carbon from carboxylic group) and the double bond is 3 carbons. The same rule is applied on omega 6

Omega system doesn't into consideration the additional double bonds

Forms of fatty acids

Free fatty acids (FFA): occur in all tissues and plasma (particularly during fasting)

Indeed, they are not free, they are bound to albumin or lipoproteins

>90% of the plasma fatty acids are in the form of fatty acid esters (primarily TAG, cholesteryl esters, and phospholipids) contained in circulating lipoprotein particles.

Plasma FFA are transported on albumin from adipose tissue to most tissues.

FFA can be oxidized by many tissues:

- **Liver and muscle, to provide energy**
- **Liver to synthesize ketone body**

Structural FA (main form): membrane lipids as phospholipids and glycolipids

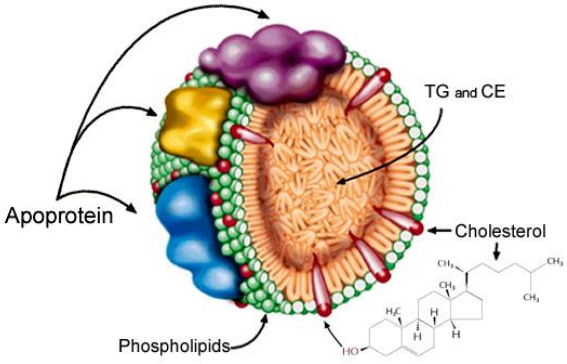
Protein-associated FA facilitate membrane attachment.

FAs are precursors of the hormone-like prostaglandins

Esterified FAs: in the form of TAG stored in white adipose tissues as the major energy reserve of the body.

Lipoproteins

- **Micelles like structures with external hydrophilic environment and internal hydrophobic core.**
- **They are also associated with other protein that are responsible to function and identity of lipoproteins.**
- **Function: transport of lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) in blood plasma.**



- **There are many kinds of lipoprotein that differ in terms of density: protein ratio to lipids content (the more the lipid content is, the less density & the more the protein content is, it will become heavier and denser) and size**

Note that Y axis represents density, and it is increasing by going downward

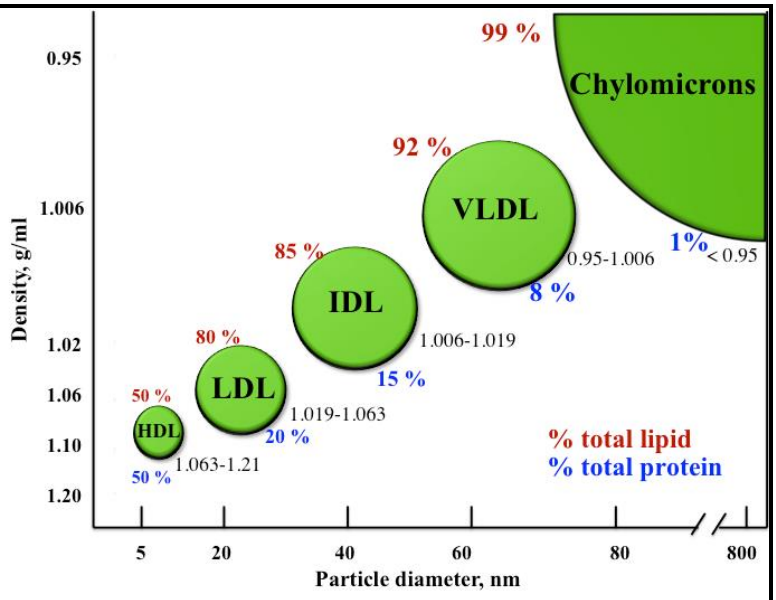
X axis represents diameter (size)

Chylomicrons are the largest with least dense

VLDL: very low-density proteins

IDL: intermediate density protein (not very important)

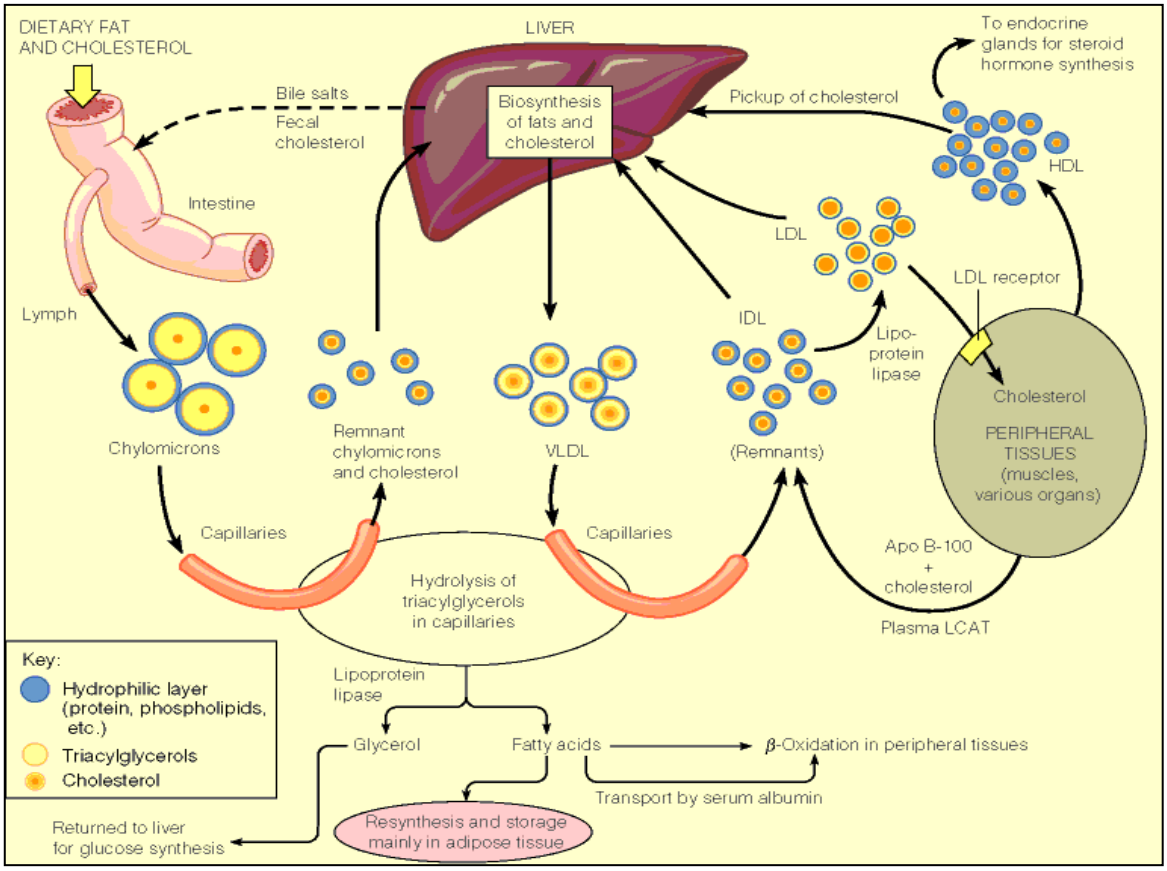
LDL & HDL: Low & High density proteins



	Chylomicrons	VLDL	LDL	HDL
Density (g/ml)	< 0.94	0.94-1.006	1.006-1.063	1.063-1.210
Diameter (Å)	2000-6000	600	250	70-120
Site of synthesis	Intestine	Liver	Liver	Liver, intestine
Total lipid (wt%)	99	92	85	50
Triacylglycerols	85	55 Liver	10	6
Cholesterol esters	3	18	50 (bad)	40 (good)
Apolipoproteins	A, C, E, B48	C, B100, E	B100	A, C, E
Function	Transport of dietary TG	Transport of liver TG	Transport of cholesterol to peripheral tissues	Transport of cholesterol from peripheral tissues (cholesterol scavengers)

Notice that both LDL & HDL carry high amount of cholesterol esters, so why one is good while the other is bad ?

LDL carry cholesterol esters to the peripheral tissues and it can accumulate in the blood forming clots causing myocardial infraction & artherosclerosis while HDL carry cholesterol esters from peripheral tissues back to liver to get rid of them.



Dietary lipids are carried with chylomicrons which carries more TAG than cholesterol from intestine to liver. As they travel, lipases that exist on the surface of endothelial cells extract TAG from chylomicrons to the peripheral tissues forming what we call remnant chylomicrons which are smaller and have more cholesterol in relative to TAG

VLDLs which are synthesized in the liver carry lipids from liver which will be converted to IDL by endothelial lipases, then IDL will be converted to LDL by the same process

LDL will carry cholesterol to the peripheral tissues

There are 2 pathways: external pathway that transport dietary lipids to liver and internal pathway that transport cellular lipids to the liver by HDL

Digestion in stomach

Lipid digestion in stomach is limited

There are 3 types of digestive lipases: (2 of them are considered as the responsible one for stomach digestion)

1.lingual lipase (minimal digestion) which is secreted in saliva (not efficient because it doesn't spend that much time in contact with lipids)

2.gastric lipase (10-30% of TAG digestion) which is secreted in gastric mucosa

both enzymes are acid stable. However, they are not that efficient, they hydrolyze TAG with short or medium FA

Significance: Important for infants (milk fat) and patients of pancreatic lipase-deficiency or pancreatic insufficiency (e.g., cystic fibrosis).

Short- and medium-chain fatty are absorbed in stomach by the action of these 2 enzymes.

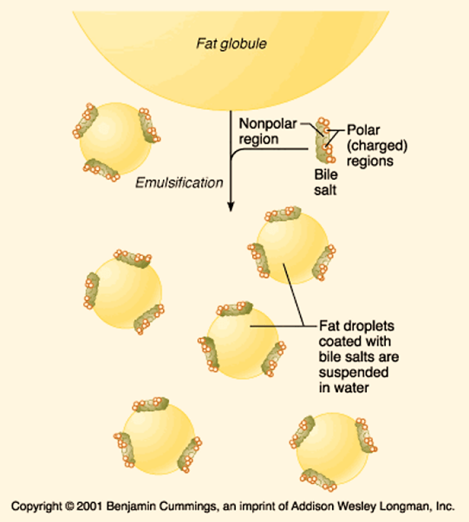
The doctor said there is variation in types of fatty acids in milk fat. However, the most common one that exist in milk fat is the long chain fatty acids, so these enzymes are not that significant to infants from the doctor's point of view, but the book has mentioned this information, so we must know it.

Emulsification in the small intestine

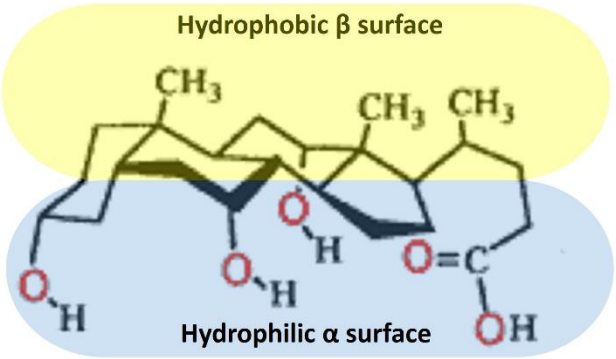
It is defined as process in which large lipid droplets are broken down into several smaller ones, consequently increasing the surface area of the hydrophobic droplets to enable enzymes to act on them more effectively.

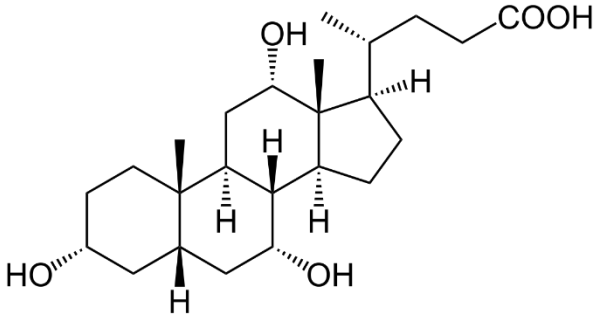
Two mechanisms of emulsification in <u>the duodenum</u>:

- **Peristalsis: mechanical mixing leading to smaller droplets**
- **Conjugated bile salts (cholesterol amphipathic derivatives) ex. Cholic acid**
  Amphipathic means it can be divided into two regions: hydrophobic and hydrophilic



We can discriminate between hydrophobic and hydrophilic regions only by looking to the 3D shape (left photo)



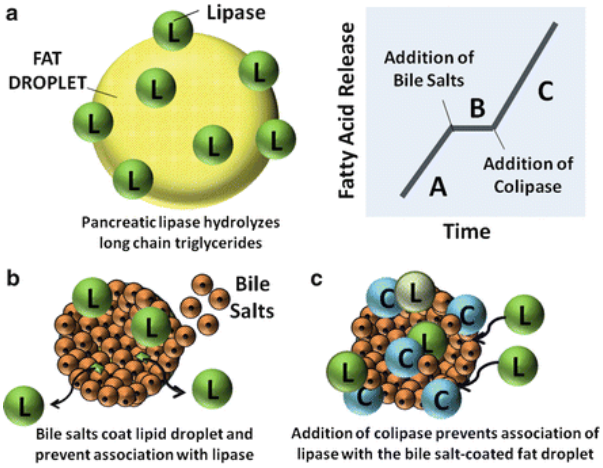


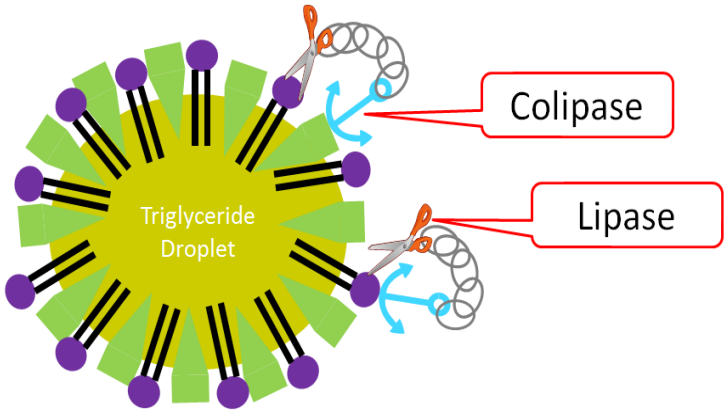
The third type of lipase is the pancreatic lipase which is responsible for 50-70% of TAG degradation

It works in association with colipase proteins (which will anchor lipase into the micelle interface at a ratio of 1:1)

Colipase is secreted as a zymogen from the pancreas (need proteolytic cleavage to be activated by trypsin)

Restores activity of lipase against inhibitors like bile salts

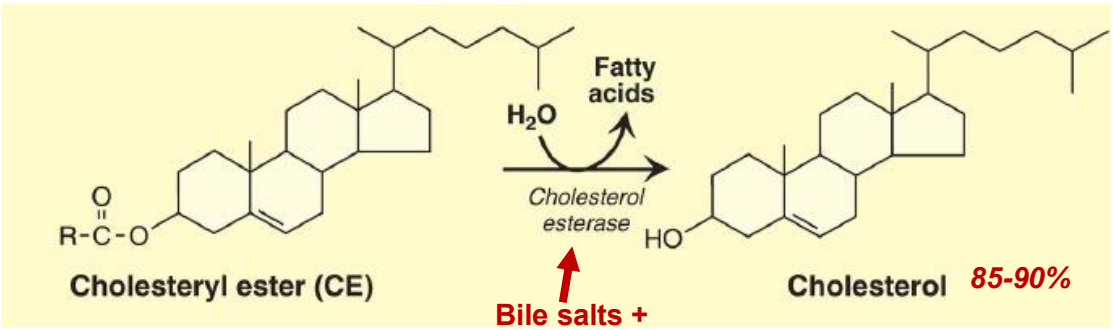




Combined pancreatic lipase-colipase deficiency is an orphan disease (rare disease)

There are a lot of digestive pancreatic enzymes (pancreatic lipase is one of them) whose secretion is hormonally controlled such as

Cholesterol esterase which hydrolyzes cholesterol ester resulting in cholesterol and fatty acid and it is activated by bile salts, so most of the cholesterol in the intestinal lumen is present as free cholesterol form

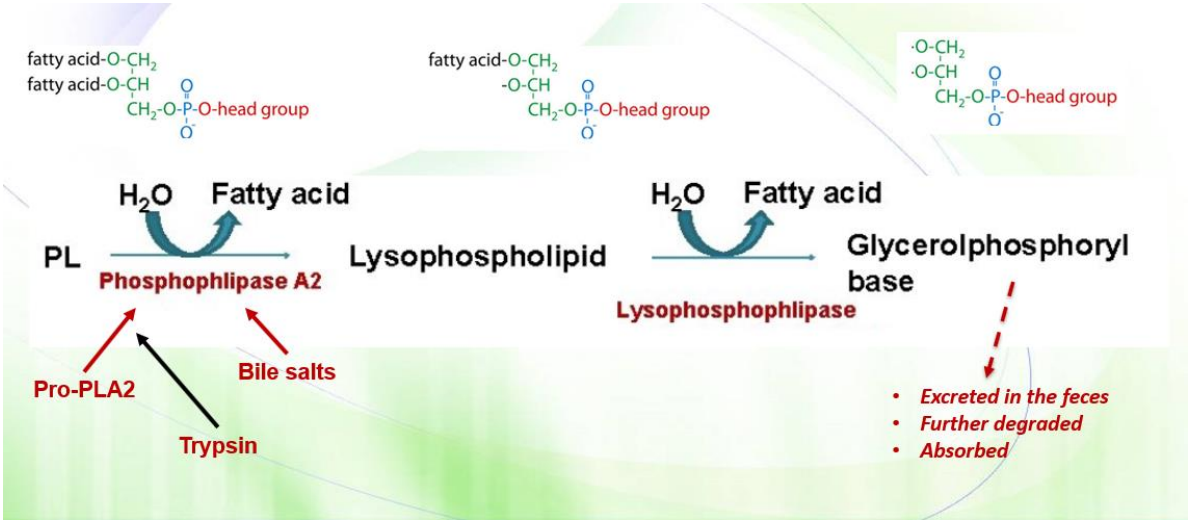


Phospholipase A2 which hydrolyzes phospholipids by removing the second fatty acid chain (internal fatty acid) resulting in lysophosphlipid molecule

It is secreted as proenzyme which needs trypsin to be activated (like colipase) and activated by bile salts (like cholesterol esterase)

Phospholipid – fatty acid number 2 = lysophosphlipid

Then lysophosphlipid is degraded by lysophosphlipase enzyme which will remove the remaining fatty acid forming glycerophosphoryl base which can be excreted in feces or further degraded or absorbed

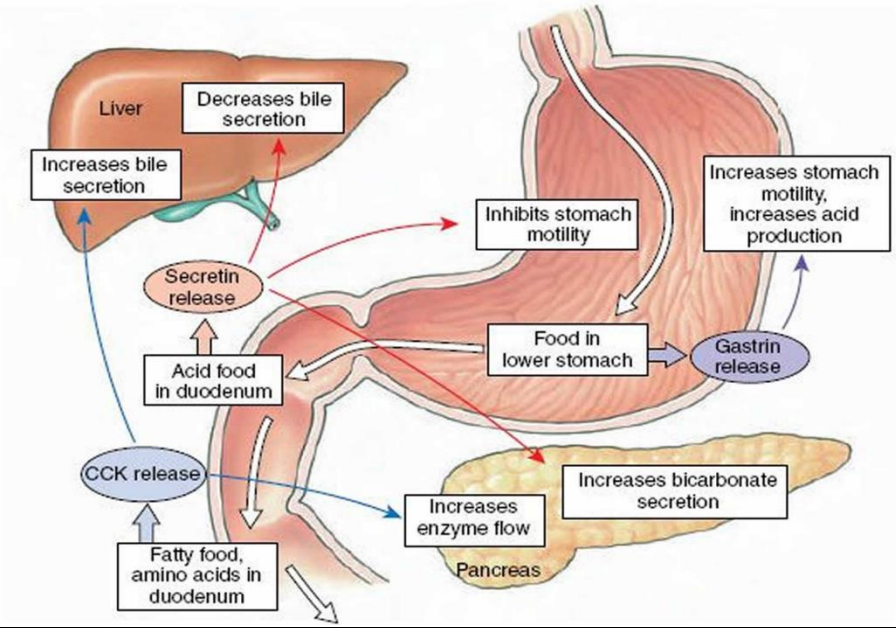


We said that pancreatic enzymes are hormonally controlled. The major ones are

1. **Peptide hormone cholecystokinin (CCK): activated by food (proteins and fats) that reaches duodenum and jejunum and has multiple functions:**
   A. **Induces contraction of the gallbladder to release bile (bile salts, phospholipids, and free cholesterol).**
   B. **Acts on the exocrine pancreatic cells to release digestive enzymes.**
   C. **Decreases gastric motility to slow down the release of gastric contents.**

2. **Secretin (peptide hormone) released in response to the low pH of the chyme entering intestine from the stomach. it acts pancreas to release a bicarbonate-rich solution to neutralize the pH and make it optimal for the digestive pancreatic enzymes and inhibits gastric motility.**

3. **Gastrin released in response to presence of food in the stomach, it increases stomach mortality and acid production.**



The End