METABOLISM

بسم الله الرحمن الرحيم

Final – Lecture 3

Lipid digestion, absorption and transport (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Written by:

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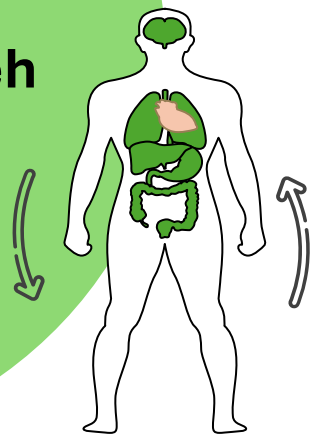
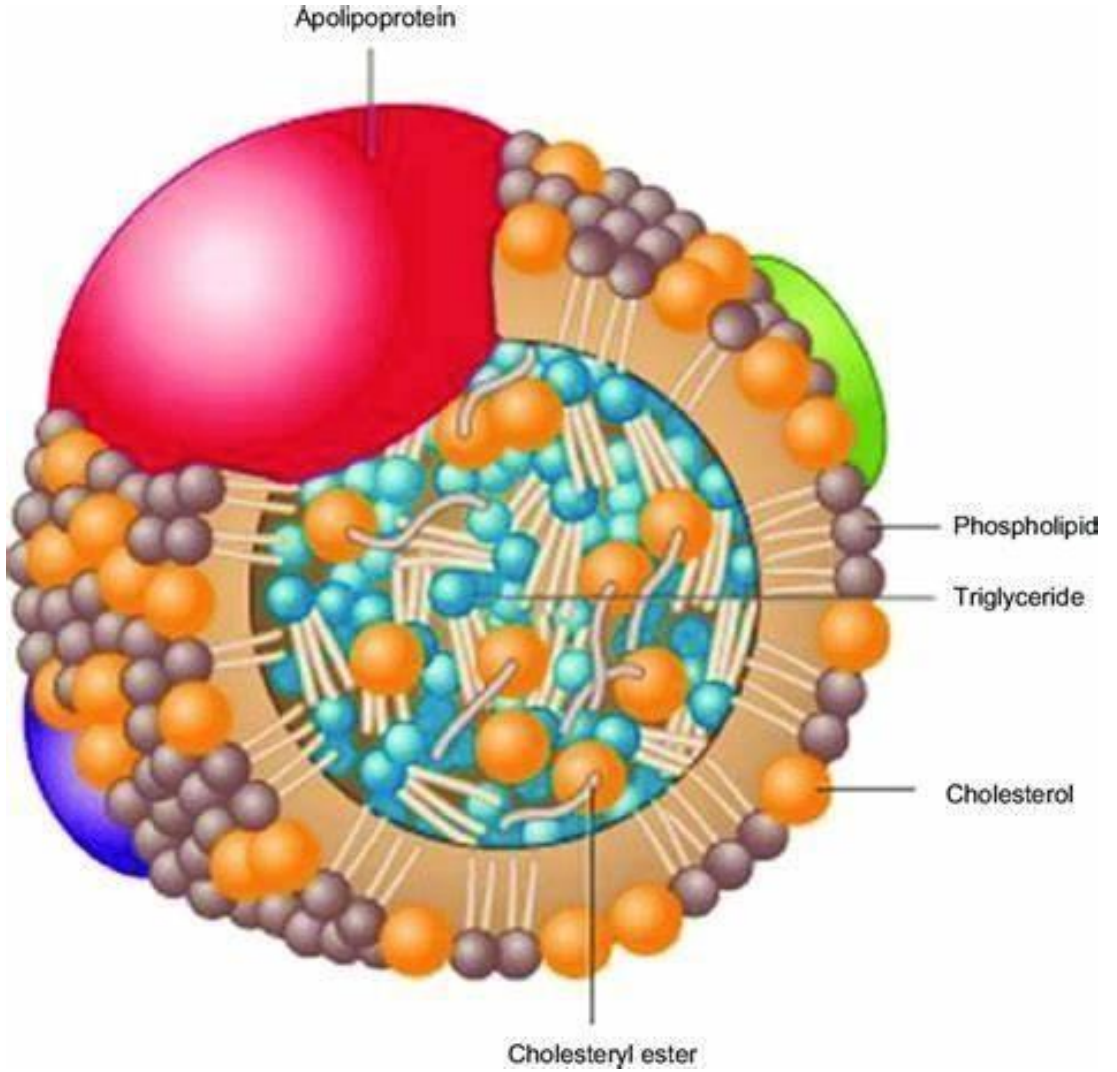


Metabolism of lipids:

Absorption and transport

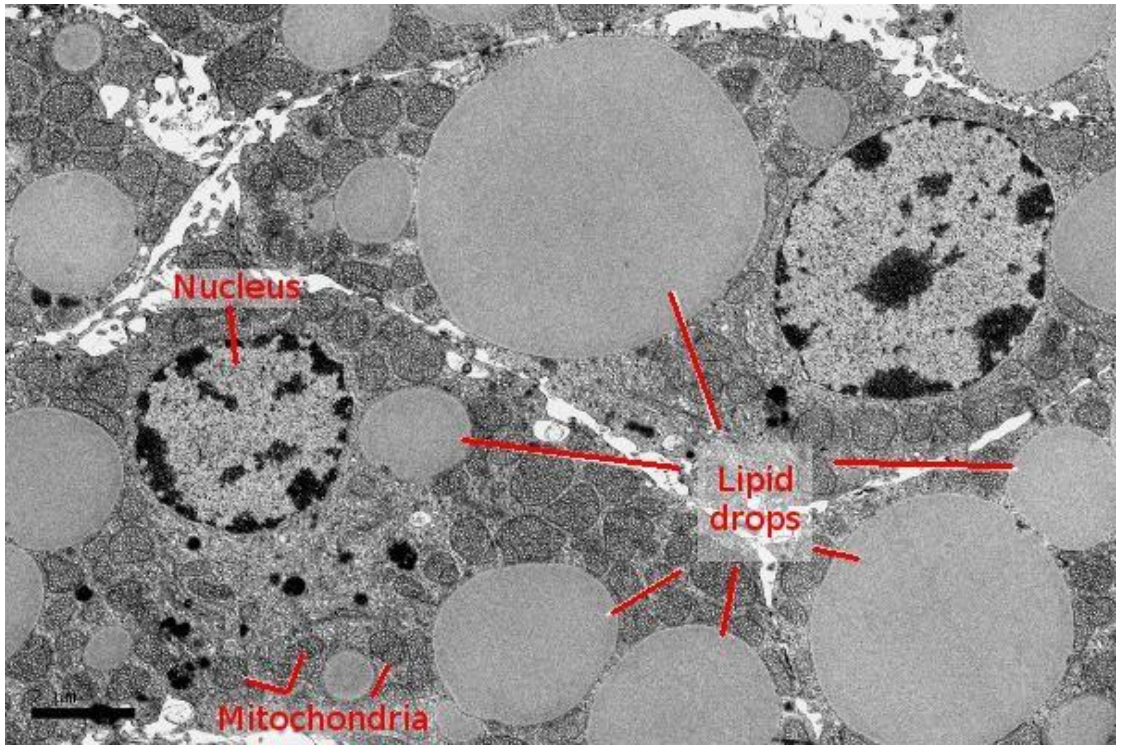
Dr. Diala Abu-Hassan

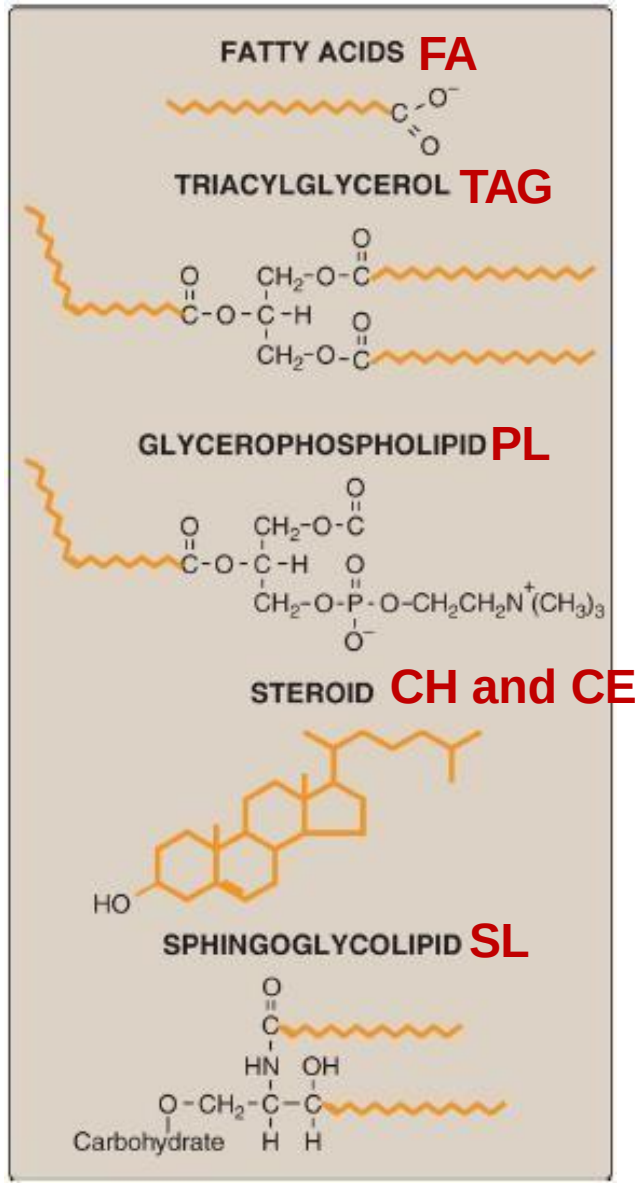


Lippincott's Biochemistry, Ch. 15

Lipids-review

- Lipids are heterogeneous, hydrophobic, compartmentalized in membranes, as droplets of triacylglycerol (TAG), or in lipoprotein (LP) particles, or protein-bound.
- Functions: Energy, structures, molecular precursors (e.g., vitamins, signaling)
- The major dietary lipids are triacylglycerol, cholesterol, and phospholipids.



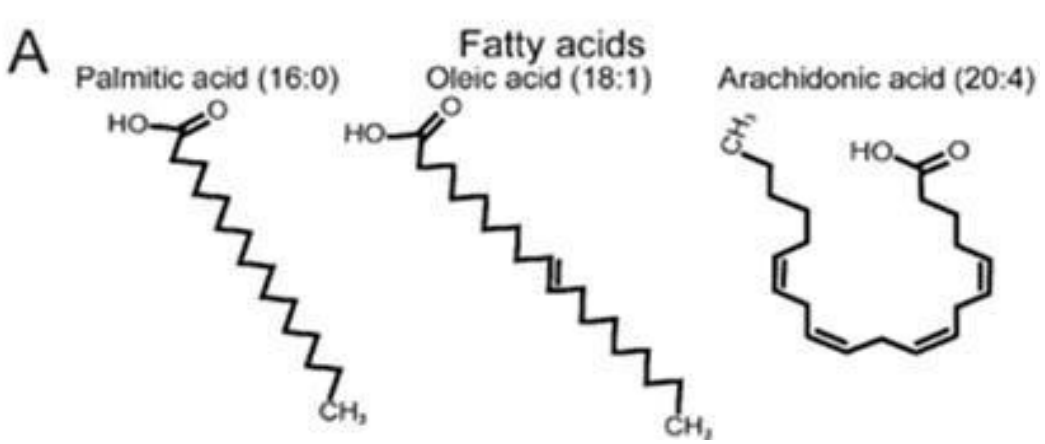


Lipids-review – further explanation

- Lipids are heterogenous group of molecules, they don't have a strict functional group that characterize them, they have different structures, what is common between these lipids is that they are all considered hydrophobic.
- As these lipids are hydrophobic, they don't like to face watery compartments, that's why they tend to cluster forming droplets with their polar groups facing the hydrophilic environment, remember that this clustering is mediated by hydrophobic interactions.
- Lipids have multiple functions, they store energy, they form structural units for membranes, they serve as a precursor for many anabolic pathways that synthesize sex hormones, vitamins, bile acids, they are also involved in signaling pathways. (remember PIP2, DAG)
- Lipids are obtained from our diet, most of them are in the form of TAGs (found in fat and oil), cholesterol is found in animal-based food. Lipids are also used as emulsifiers (e.g., lecithin; another name for phosphatidylcholine) in food industries.

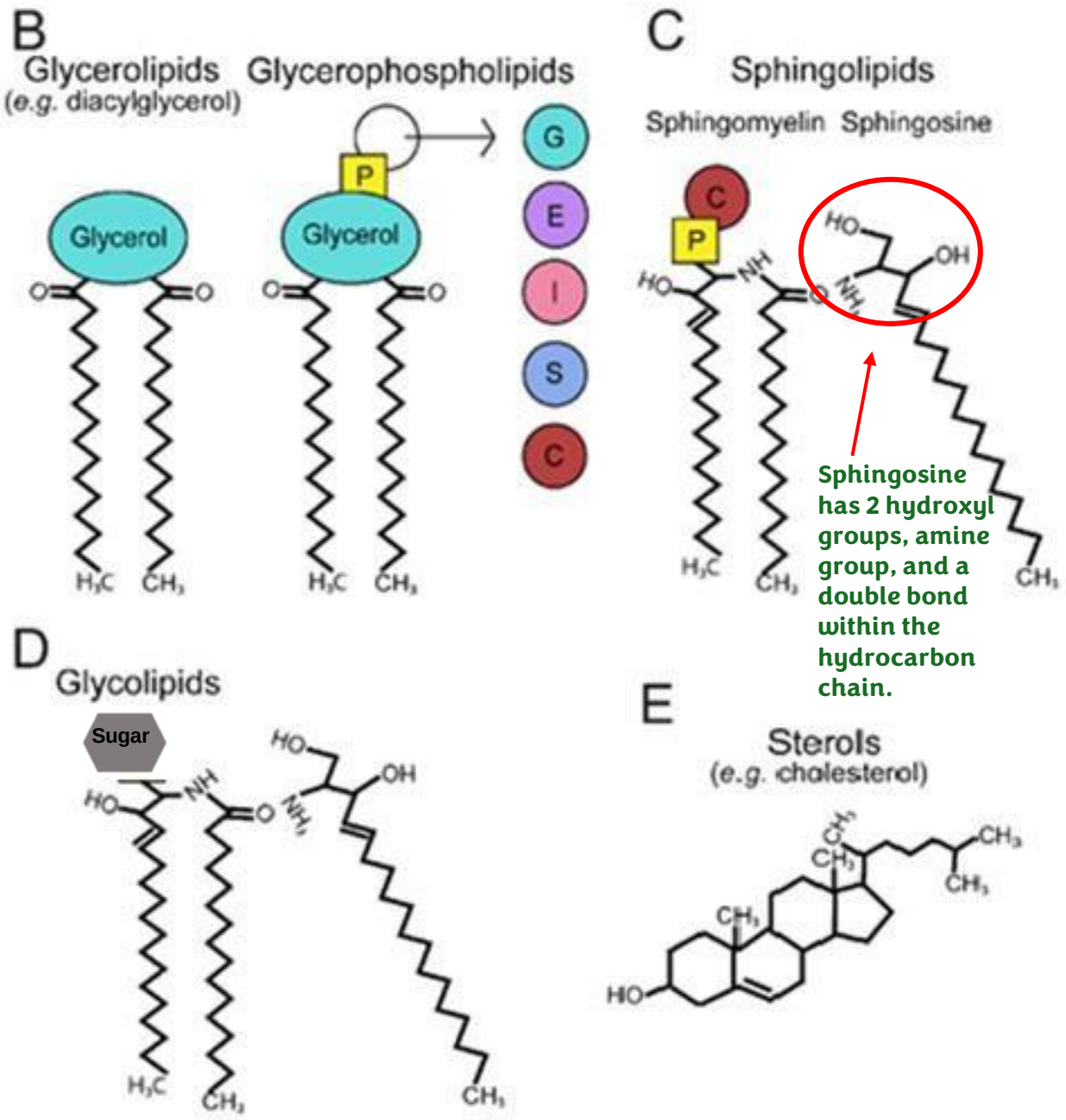
TAGs: Triacyl Glycerols

Structure and classification of lipids



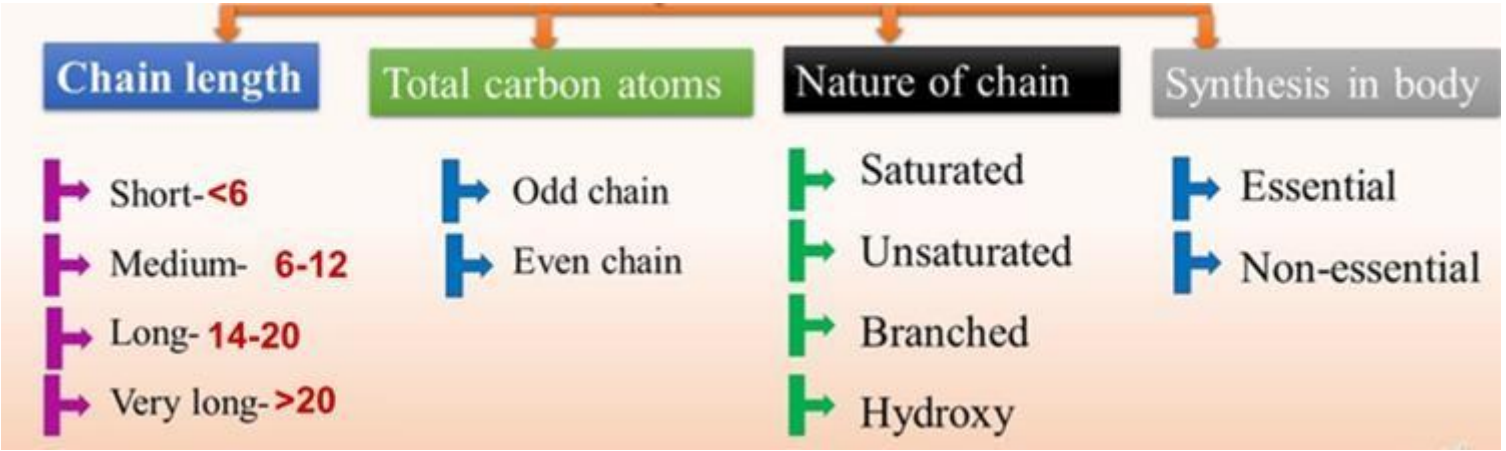
A Lipid could be structured of:

- **Fatty acid**: carboxylic acid with long hydrocarbon chain, could be saturated, monounsaturated, polyunsaturated.
- **Glycerophospholipid**: two fatty acids joined to a glycerol molecule, with a phosphate group attached to glycerol, different groups bound to the phosphate gives us different types of glycerophospholipids.
- **Sphingolipid**: a sphingosine molecule (has a long hydrocarbon chain within its structure) attached to a fatty acid and a phosphocholine giving sphingomyelin, substituting the phosphocholine with sugars gives us a glycolipid.
- **Sterol:** a steroid nucleus (three six-membered rings and one five-membered ring fused to each other) with side chains attached to these rings, cholesterol (which is a sterol), could be used to synthesize vitamins and bile acids.



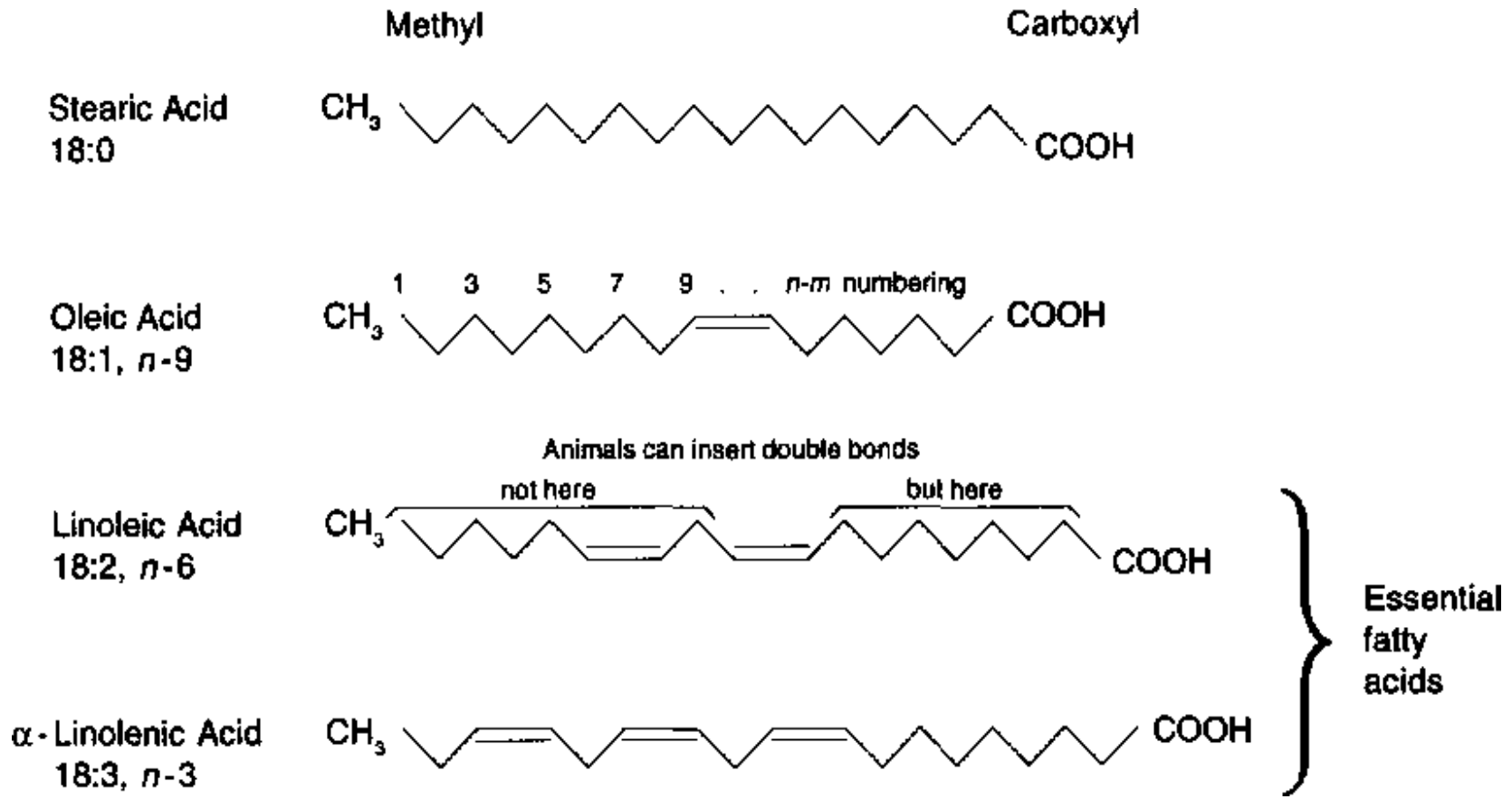
Fatty Acids

- Double bonds in FA are always spaced at three-carbon intervals.
- The addition of double bonds decreases the melting temperature (Tm) of a fatty acid.
- Increasing the chain's length increases the Tm.
- Membrane lipids typically contain unsaturated long-chain fatty acids (LCFA) to maintain fluidity.
- Fatty acids with double bonds beyond the 10th carbon are essential.



Notice the different classifications of FAs, the predominant FAs in our bodies is even with 16 and 18 carbons chain.

FA: Fatty Acid



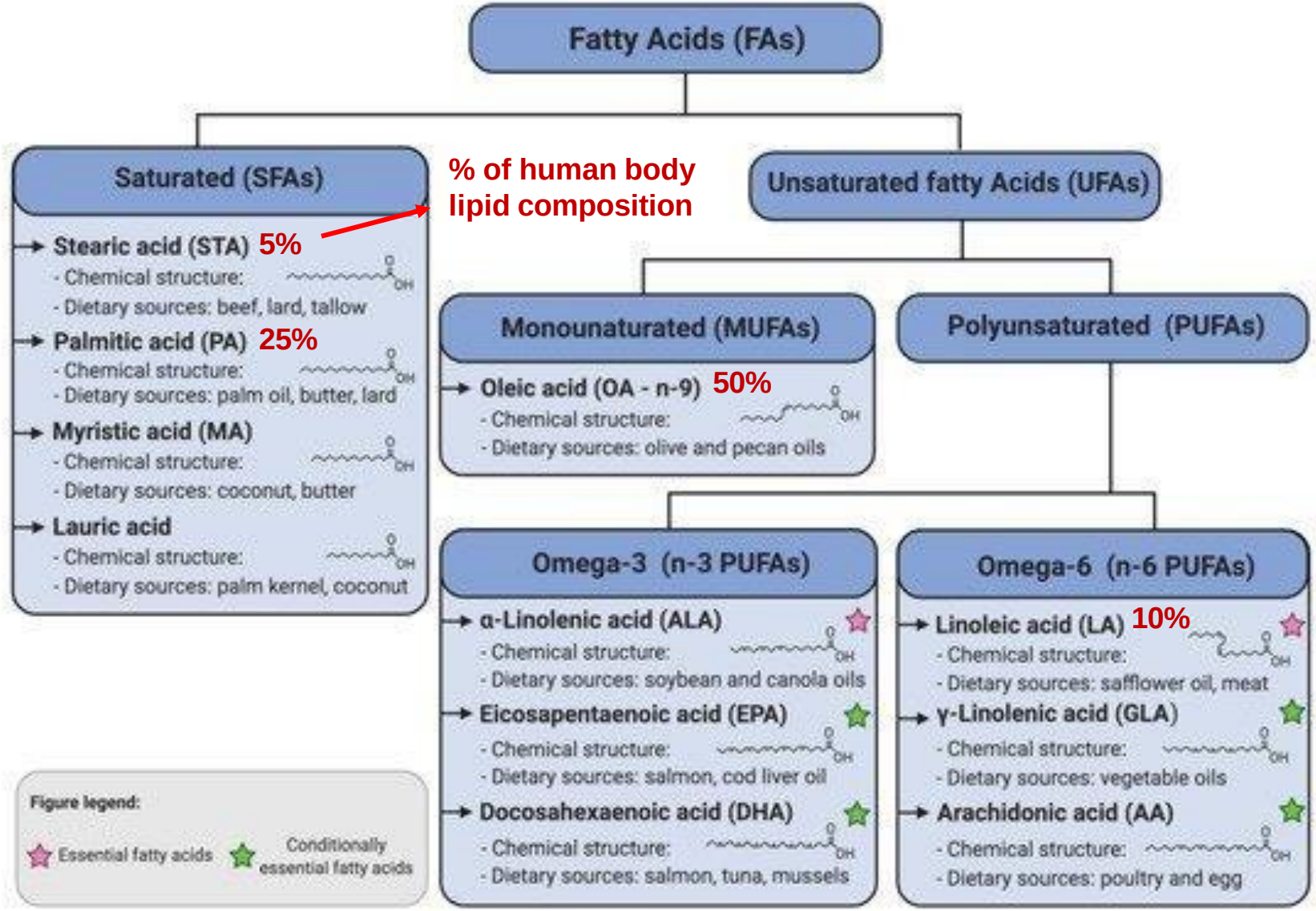
- ***One of the classifications of FAs is:***
  - Essential FAs: linoleic acid and linolenic acid, we get them from our diet as our bodies they can't synthesize FAs that have a very long chain with double bonds farther than carbon number 10 or 12; as we don't have the enzyme that can introduce these double bonds.

  - Non-essential FAs: can be synthesized in our bodies.

Not all the long unsaturated FAs are essential, only linoleic and linolenic acids are essential; as they are used in the synthesis of arachidonic acid.

Fatty Acids

- Stearic (18C) and Palmitic (16C) acids (Saturated FAs) constitute 30% of total body FAs.
- Palmitic acid is present more as it is used more in the **synthesis** of other FAs and as **lipid anchor** for proteins by binding to them covalently, in a process named palmitoylation; myristylation also happens using myristic acid.
- Oleic acid, which is a monounsaturated FA, constitutes around 50% of FAs.



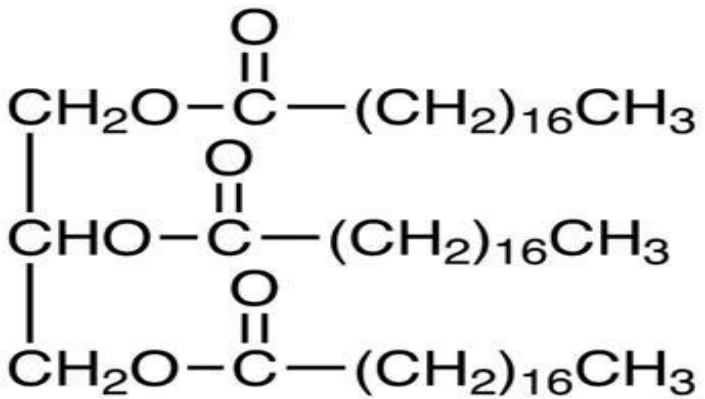
Forms of fatty acids

- **Free fatty acids** (FFA): occur in all tissues and in plasma (particularly during fasting).
  - >90% of the plasma fatty acids are in the form of fatty acid esters (primarily TAG, cholesteryl esters, and phospholipids) carried by circulating lipoprotein particles.
  - ➢ FFA is found under fasting conditions, glucagon gets released and the binding of it to lipocytes will increase the hydrolysis of the ester bonds in TAG.
  - Plasma FFA are transported on albumin from adipose tissue (where they are stored) to most tissues (where they are needed to provide energy).
  - ➢ As long chain FAs have big hydrophobic parts, they can't move by their own through the blood, binding to albumin will mediate their transport, short and medium chain FAs move by their own.
- **FFA can be oxidized** (broken up into acetyl CoA) in many tissues:
  - Liver and muscle, to provide energy
  - ➢ Under fasting conditions, the liver extracts energy by introducing the acetyl-CoA molecules, that are provided from the catabolism of FAs, into the Krebs cycle, remember that under fasting condition, the liver will also start the pathway of gluconeogenesis to provide glucose for other tissues, both processes of gluconeogenesis and Krebs cycle consumes oxaloacetate, so the liver will balance these pathways and use the excess acetyl-CoA in ketogenesis.
  - Liver to synthesize ketone body

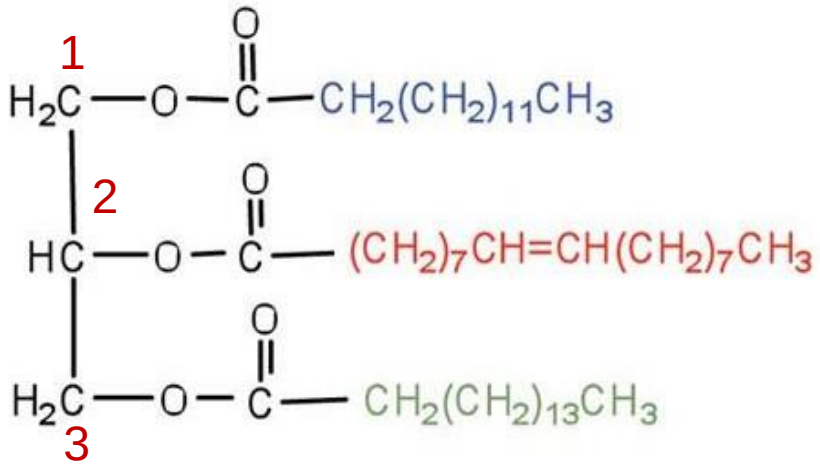
Forms of fatty acids-pt.2

- **Structural FA**: membrane lipids as phospholipids and glycolipids.
- **Protein-associated FAs** facilitate membrane attachment.
  - Such in the FAs that are used in palmitoylation and myristylation.
- **FAs are precursors** of the hormone-like prostaglandins.
  - Synthesis of arachidonic acid from fatty acid precursors (specifically linoleic acid), arachidonic acid is used for the synthesis of prostaglandins, thromboxanes, leukotrienes.
- **Esterified FAs**: in the form of TAG stored in white adipose tissues as the major energy reserve of the body.
  - FAs are esterified to cholesterol (in FAs associated to lipoproteins) or esterified to TAG (the storage form of lipids in lipocytes).

Triacylglycerol



Tristearin
a simple triglyceride

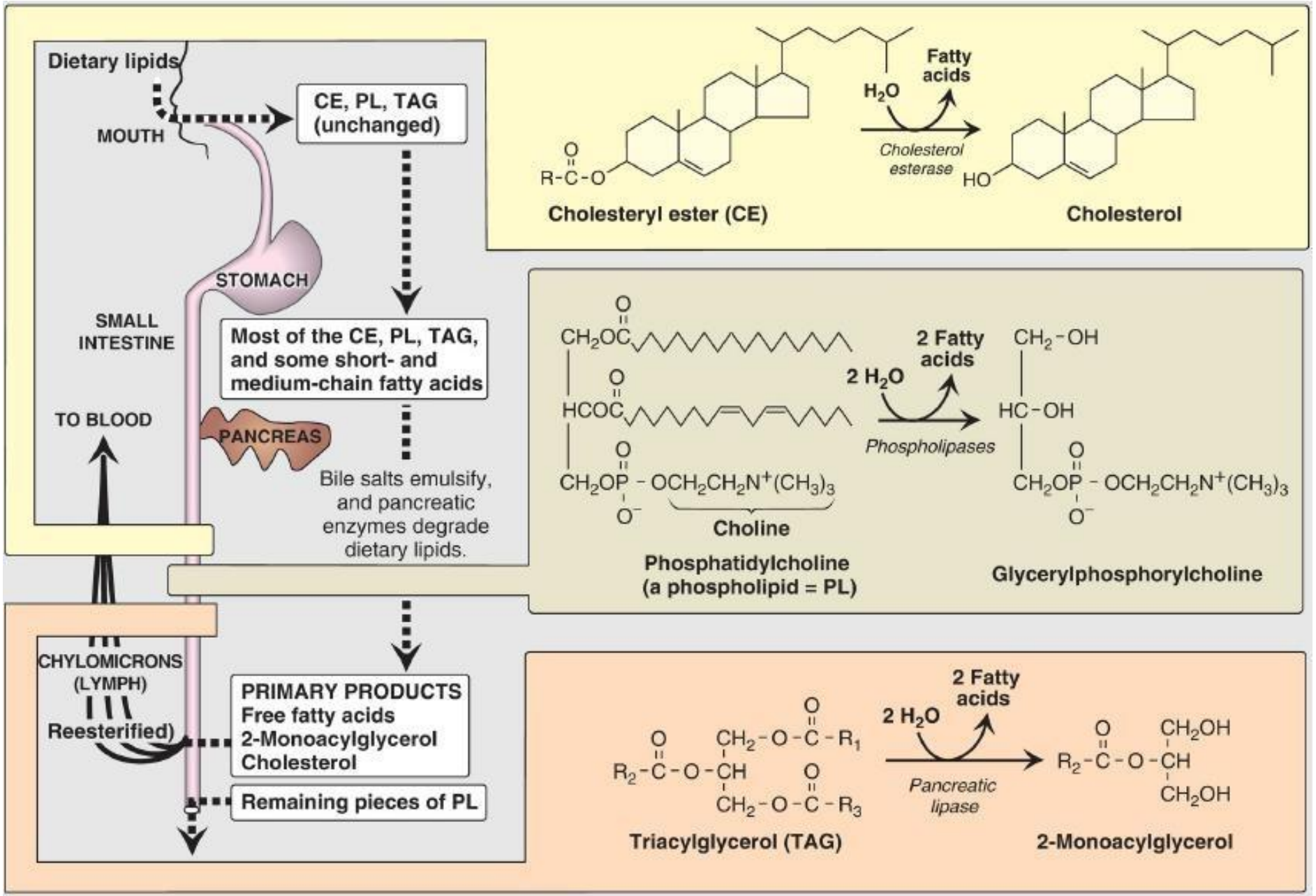


a mixed triglyceride

TAG is composed of a glycerol molecule attached to three FAs with ester bonds, the FAs could be all saturated, all unsaturated or mixed, usually the middle one is unsaturated.

Digestion of lipids

More complex than sugar digestion since there are many different types of lipids with different bonds to be digested



Steps of Lipid Digestion

1. Oral cavity (lingual lipase):
   - Secreted from the back of the tongue and is then mixed with the saliva.
   - Separates FAs from the backbone in TGAs.
   - A small % of FAs are produced as food stays in the mouth only for little time.
   - Only hydrolyzes Small- and Medium-chain FAs (SCFAs and MCFAs, respectively).
   - Acid stable; it can work in the stomach after it moves with the food (see next point).

2. Stomach (gastric lipase):
   - Secreted from the gastric mucosa.
   - Same function as lingual lipase (and only SCFAs and MCFAs as well).
   - Both gastric and lingual lipases function in the stomach (acid stable).

3. Intestines (specifically the duodenum):
   - Pancreatic lipase hydrolyzes long-chain FAs (LCFAs) from TAGs.
     - The presence of LCFAs in the diet inhibits lingual and gastric lipases.
     - Pancreatic lipase cleaves both FAs at C1 and C3 of the glycerol backbone of TAGs.
     - The result is a mixture of 2-monoacylglycerols and free FAs.
   - Phospholipase:
     - Cleaves both FAs of glycerophospholipids, leaving glycerylphosphorylcholine.
   - Cholesterol esterase:
     - Hydrolyses cholesterol esters, producing cholesterol and free FAs.

Digestion in the stomach

- Acid-stable lipases: lingual lipase and gastric lipase (responsible for 30% of lipid hydrolysis)
- They have an optimum pH of 2.5 – 5.
- They do not require bile acid or colipase for optimal enzymatic activity **(their substrate are polar [SCFA & MCFA])**.

Unlike pancreatic lipase which needs emulsifiers for LCFAs

- Gastric lipase will be stopped by long chain free fatty acids
- Main target: triacylglycerols with short- and medium-chain fatty acids (≤ 12 carbons)
- Significant in infants and patients with pancreatic lipase deficiency or pancreatic insufficiency (e.g., cystic fibrosis).
  - The action of lingual lipase is significant in newborn infants.
- Short- and medium-chain fatty are absorbed in the stomach.
- **Short- and medium chain FAs are the main FAs in breast milk.**

Fatty acids	*Human milk*[a] *%*
4:0	—
6:0	—
8:0	0.16
10:0	1.82
10:1 + 11:0	—
12:0	7.89
13:0	—
14:0	9.45
14:1 + 15:0 + 15:1	0.84
16:0	22.78
16:1 + 17:0 + 17:1	3.04
18:0	6.51
18:1 (*n*-9)	28.72
18:2 (*n*-6)	15.12
18:3 (*n*-6)	0.15
18:3 (*n*-3)	0.82
20:0	0.40
20:1	0.21
20:2	0.31
20:3 (*n*-6)	0.53
20:4 (*n*-6)	0.52
20:5 (*n*-3)	0.10
22:0	—
22:1	—
22:4 (*n*-6)	0.08
22:5 (*n*-6)	0.01
22:5 (*n*-3)	0.17
22:6 (*n*-3)	0.32
24:0	0.04

Wet nursing (الإرضاع)

- Breast milk was found to contain microvesicles that contain mRNA and the enzyme reverse transcriptase, which can form cDNA from mRNA and implement it into the infant's genome!
- Breast milk can also influence the DNA of the infant epigenetically by methylation (inactivating some genes).

RESEARCH ARTICLE

Breastfeeding effects on DNA methylation in the offspring: A systematic literature review

Fernando Pires Hartwig[1,2]*, Christian Loret de Mola[1], Neil Martin Davies[2,3], Cesar Gomes Victora[1], Caroline L. Relton[2,3]

1 Postgraduate Programme in Epidemiology, Federal University of Pelotas, Pelotas, Brazil, **2** MRC Integrative Epidemiology Unit, School of Social & Community Medicine, University of Bristol, Bristol, United Kingdom, **3** School of Social and Community Medicine, University of Bristol, United Kingdom

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Ozkan *et al. Clinical Epigenetics* 2012, **4**:14
http://www.clinicalepigeneticsjournal.com/content/4/1/14

CLINICAL EPIGENETICS

HYPOTHESIS Open Access

Milk kinship hypothesis in light of epigenetic knowledge

Hasan Ozkan*, Funda Tuzun, Abdullah Kumral and Nuray Duman

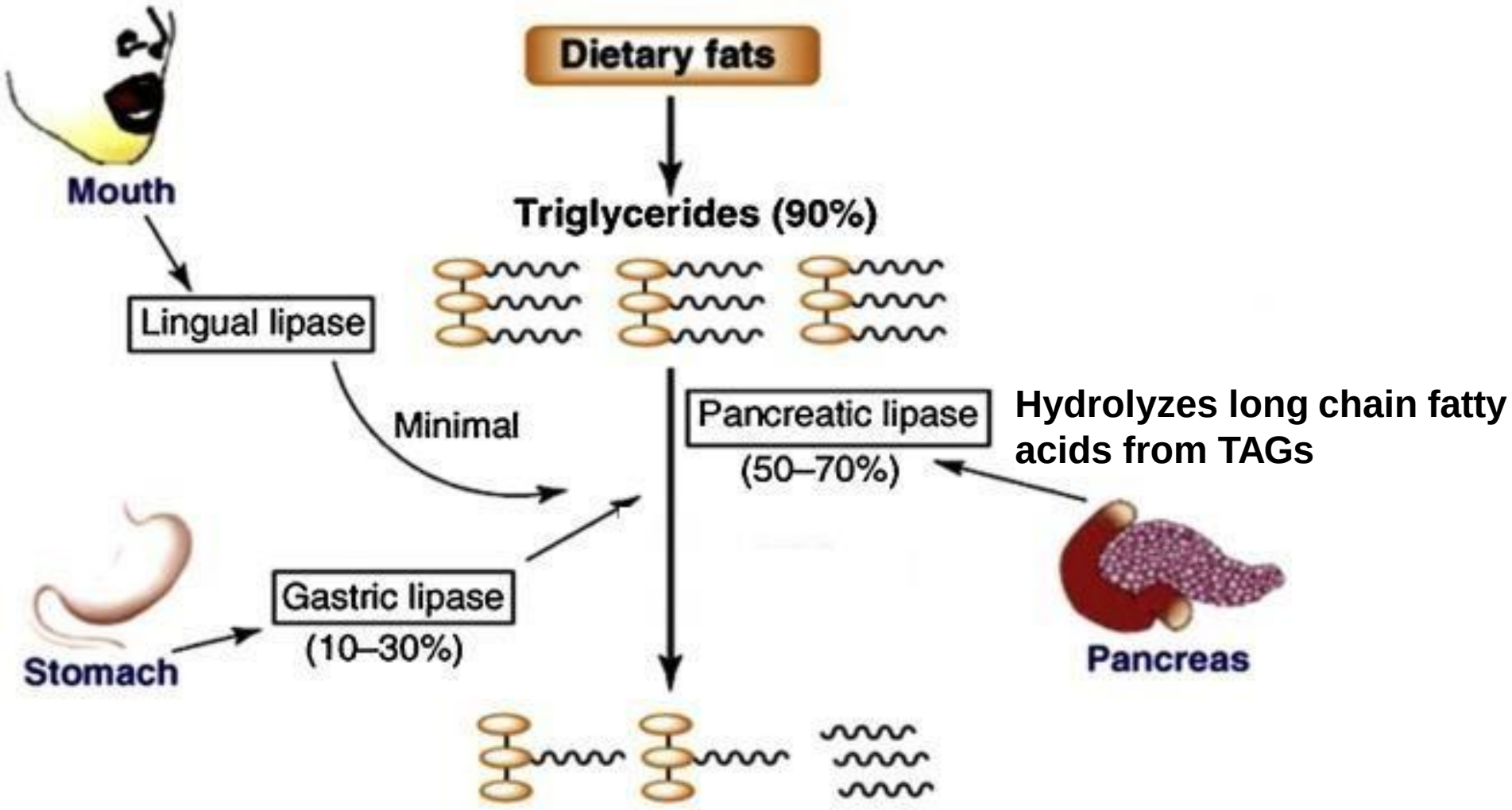
THEORETICAL BIOLOGY AND MEDICAL MODELLING

REVIEW Open Access

Integration of maternal genome into the neonate genome through breast milk mRNA transcripts and reverse transcriptase

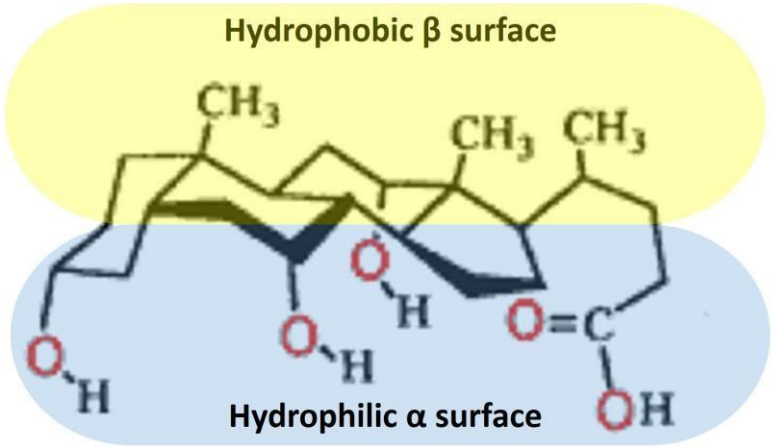
M Kemal Irmak[1*], Yesim Oztas[2] and Emin Oztas[3]

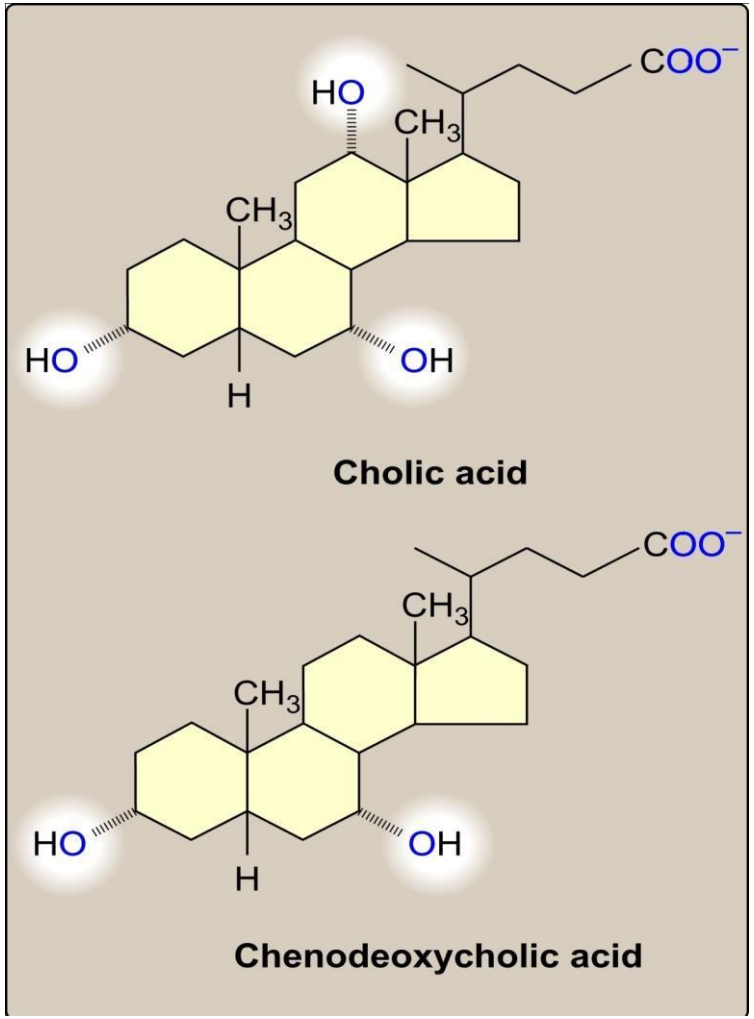
Degradation of triacylglycerol

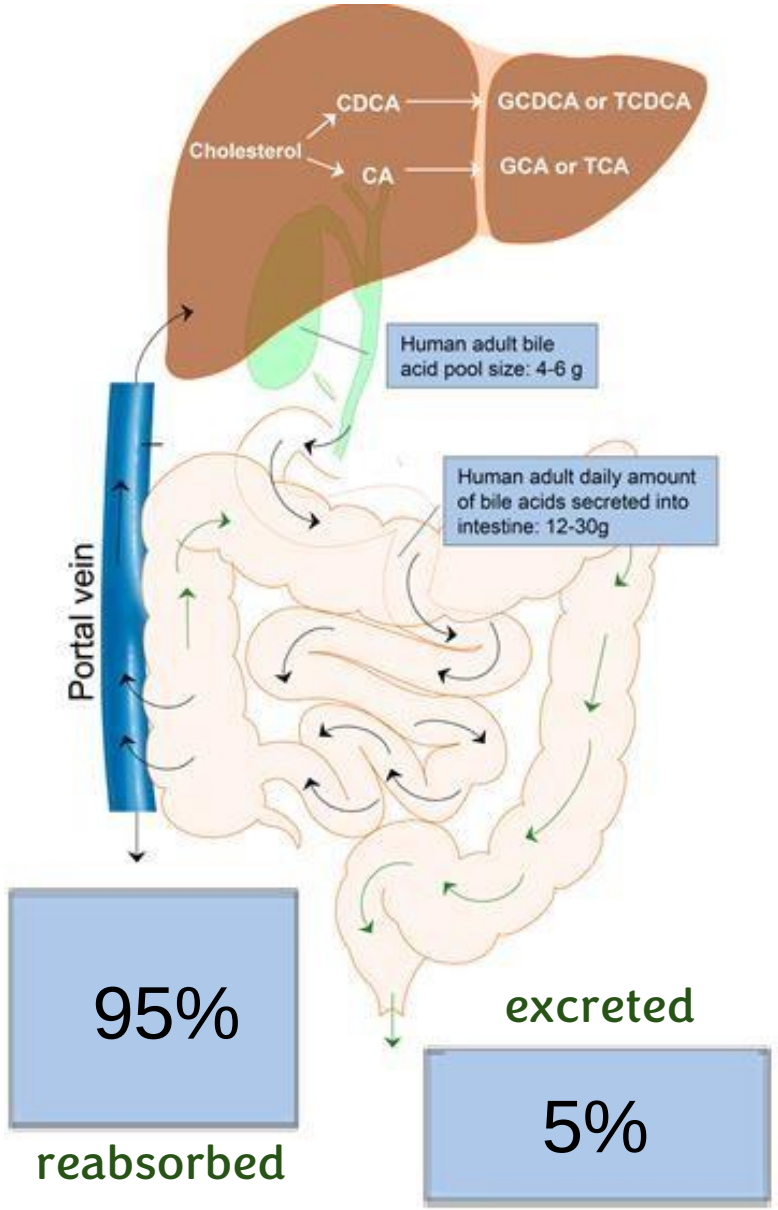


Emulsification: from drops to droplets

- Emulsification is defined as a process where one liquid is dispersed as small spherical droplets in a second immiscible (not homogeneous) liquid.
- Two mechanisms of emulsification in the duodenum:
  - Peristalsis: mechanical mixing leading to smaller droplets
  - Conjugated bile salts







Emulsifiers

Liver synthesizes and gallbladder stores.
After cholecystectomy, the patient cannot handle high-lipid meals as there is no stored bile acids.

- Cholesterol-derivative bile acids (from gallbladder → duodenum).
- Cholesterol is modified by adding more polar groups to it, making it have 2 surfaces, a polar one with all the polar groups, and a nonpolar one with the 4 hydrocarbon rings.
- See the previous slide *bottom left* for illustration.
- The polar surface binds the pancreatic lipase, while the nonpolar surface binds the nonpolar substrate (TAGs with LCFAs); this allows the close interaction that is needed for the catalytic activity to be done.
- Some cholesterol-lowering drugs increase the excretion of bile acids, forcing the liver to use cholesterol to synthesize new bile acids for emulsification since the reabsorbed amount is less.

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Lippincott Illustrated Reviews, 8th ed.
   Unit III, Chapter 15, Page 191

اللهم عليك باليهود
اللهم عليك بمن عادى أولياءك
اللهم عليك بمن ظلم عبادك
اللهم عليك بمن أمن العقاب

إنك على كل شيء قدير