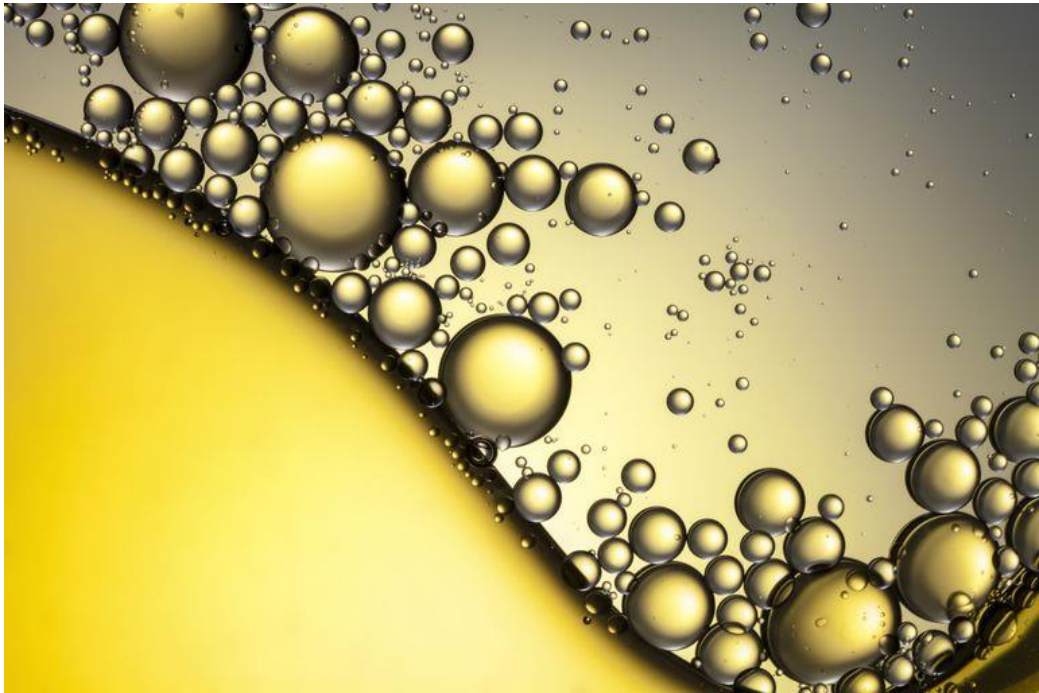
Lipids
of physiological significance

Lipids I

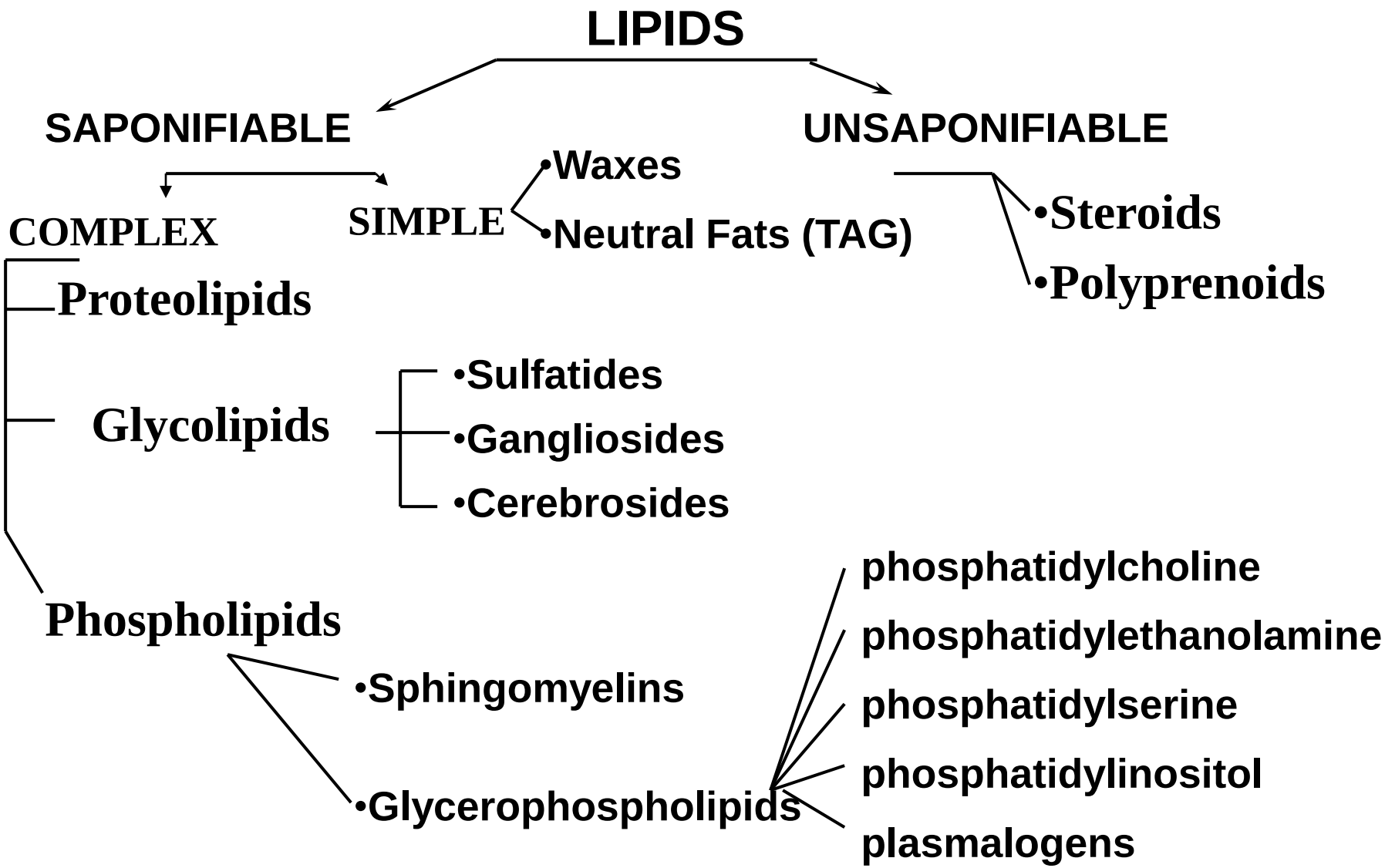
Lipids

heterogeneous group of compounds, that are

- **insoluble in water**
- **soluble in nonpolar solvents**

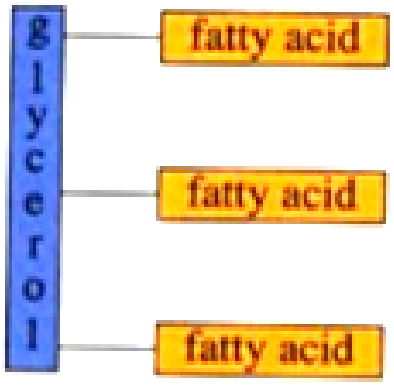


Classification of lipids

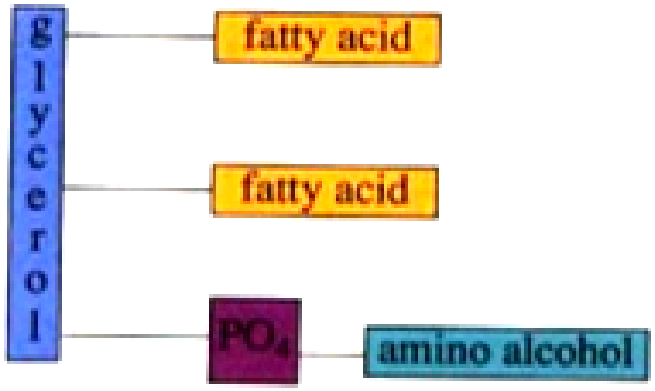


LIPIDS

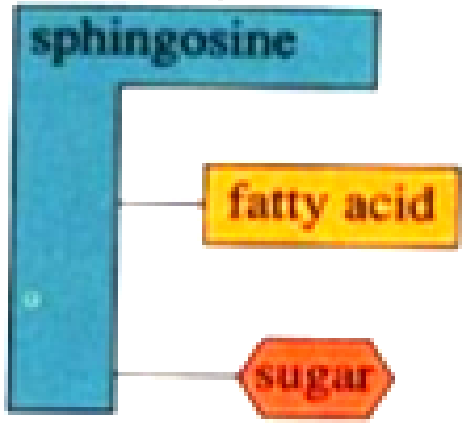
TAG



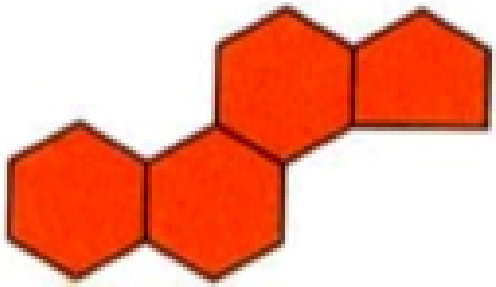
Phospholipid



Glycolipid



Steroid



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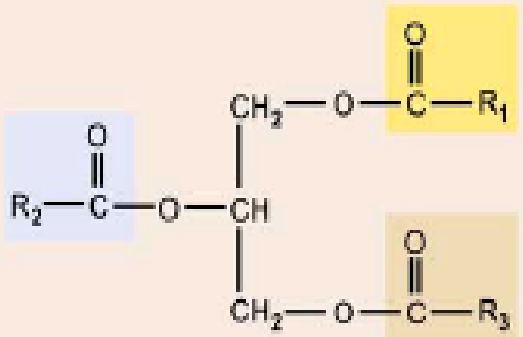
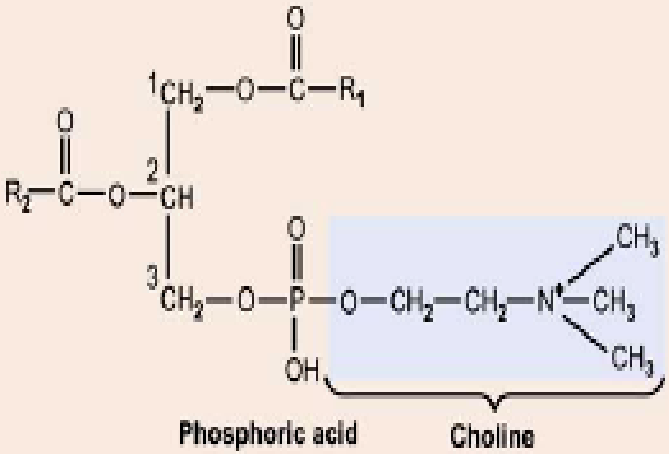
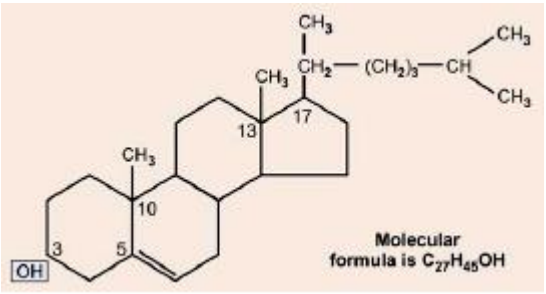
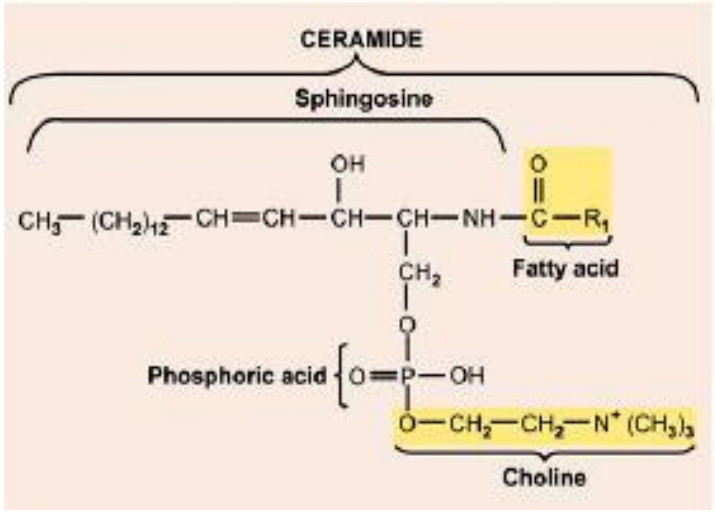


Phospholipid

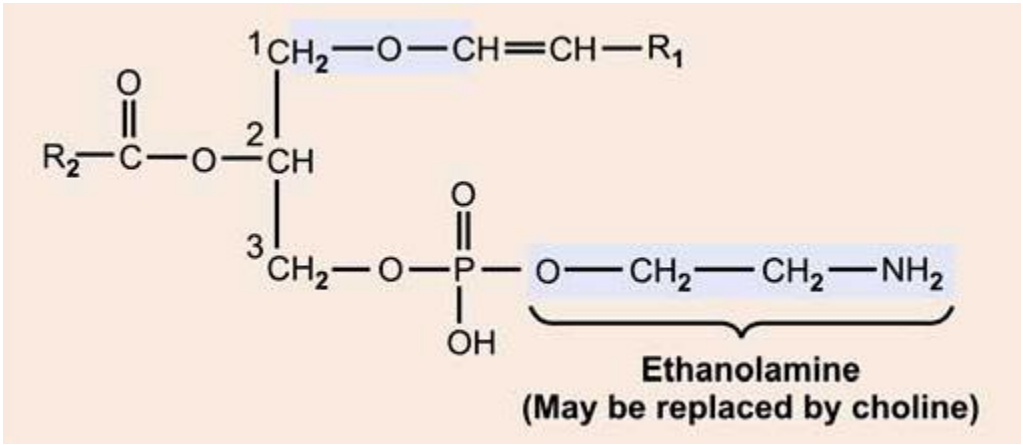




Cholesterol

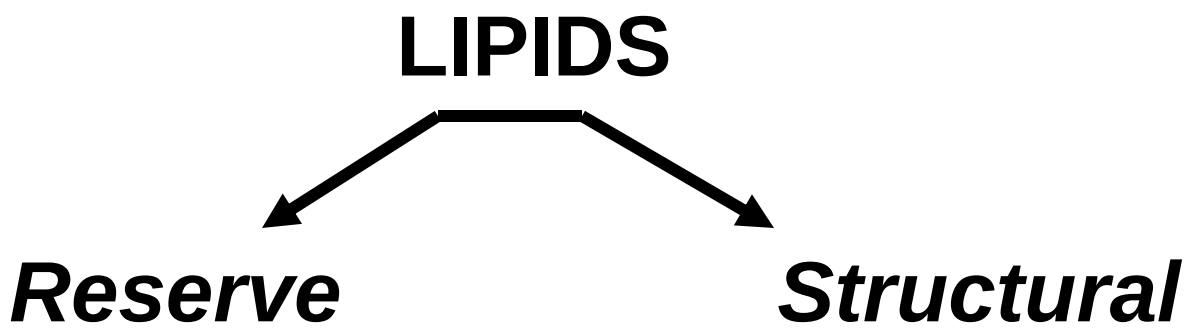


Sphingomyelin



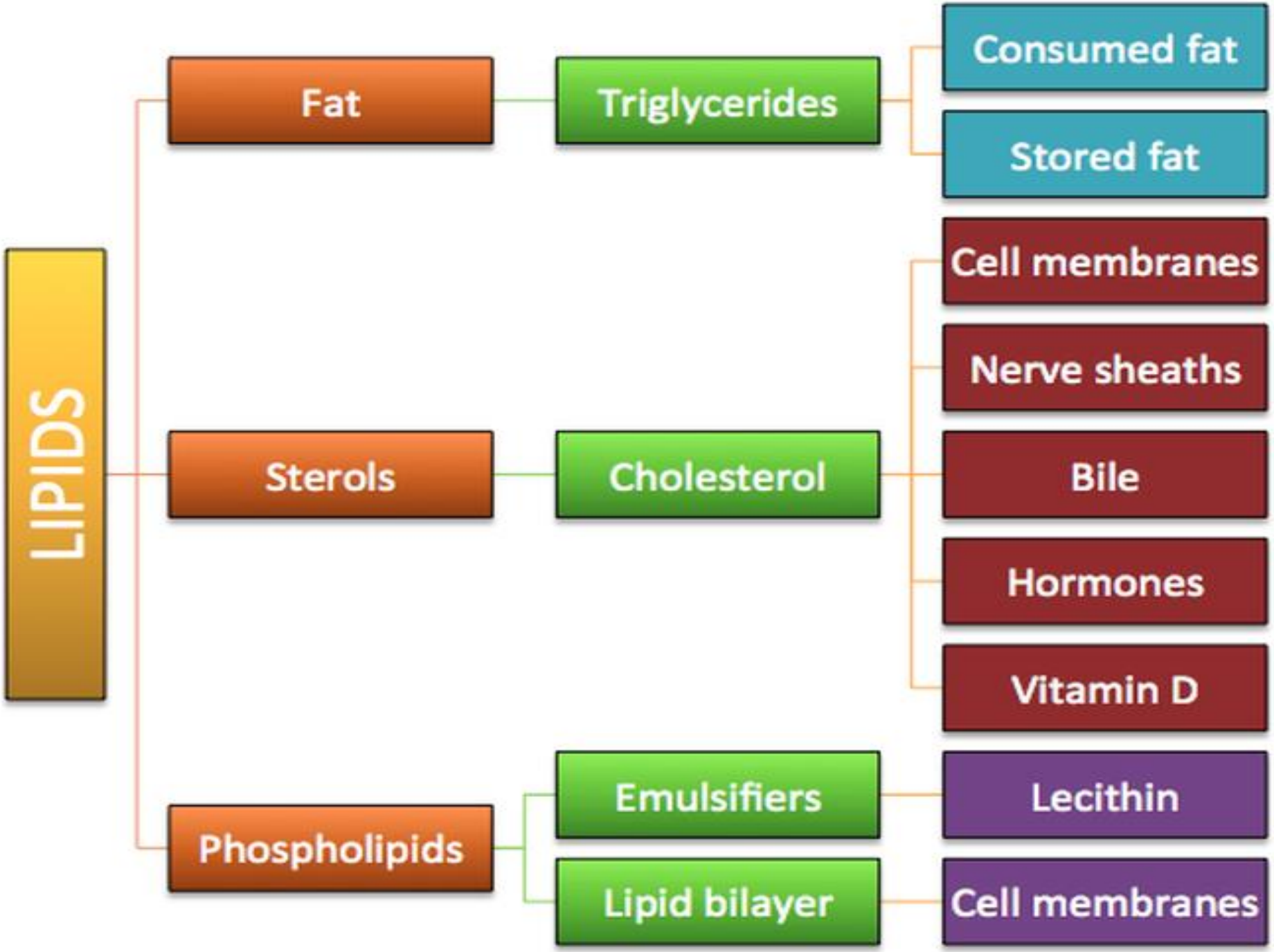
Plasmalogens

Classification of lipids
(according to physiological value)



FUNCTIONS OF LIPIDS

- Energetic
- Structural
- Transport
- Thermal insulator
- Electrical insulator
- Hormonal
- Protection of organs and tissues from mechanical damage
- Dietary lipids – source of fat-soluble vitamins and essential fatty acids
- Source of water


LIPIDS
Fat
Triglycerides
Consumed fat
Stored fat
Sterols
Cholesterol
Cell membranes
Nerve sheaths
Bile
Hormones
Vitamin D
Phospholipids
Emulsifiers
Lecithin
Lipid bilayer
Cell membranes

Lipids of human tissues

10-12 % of body weight

(2-3 kg structural lipids, other – reserve)

- **Adipose tissue: 75 % of dry weight**
- **Nervous tissue: 50 % of dry weight**

  (30% sphingomyelins,

  10% cholesterol,

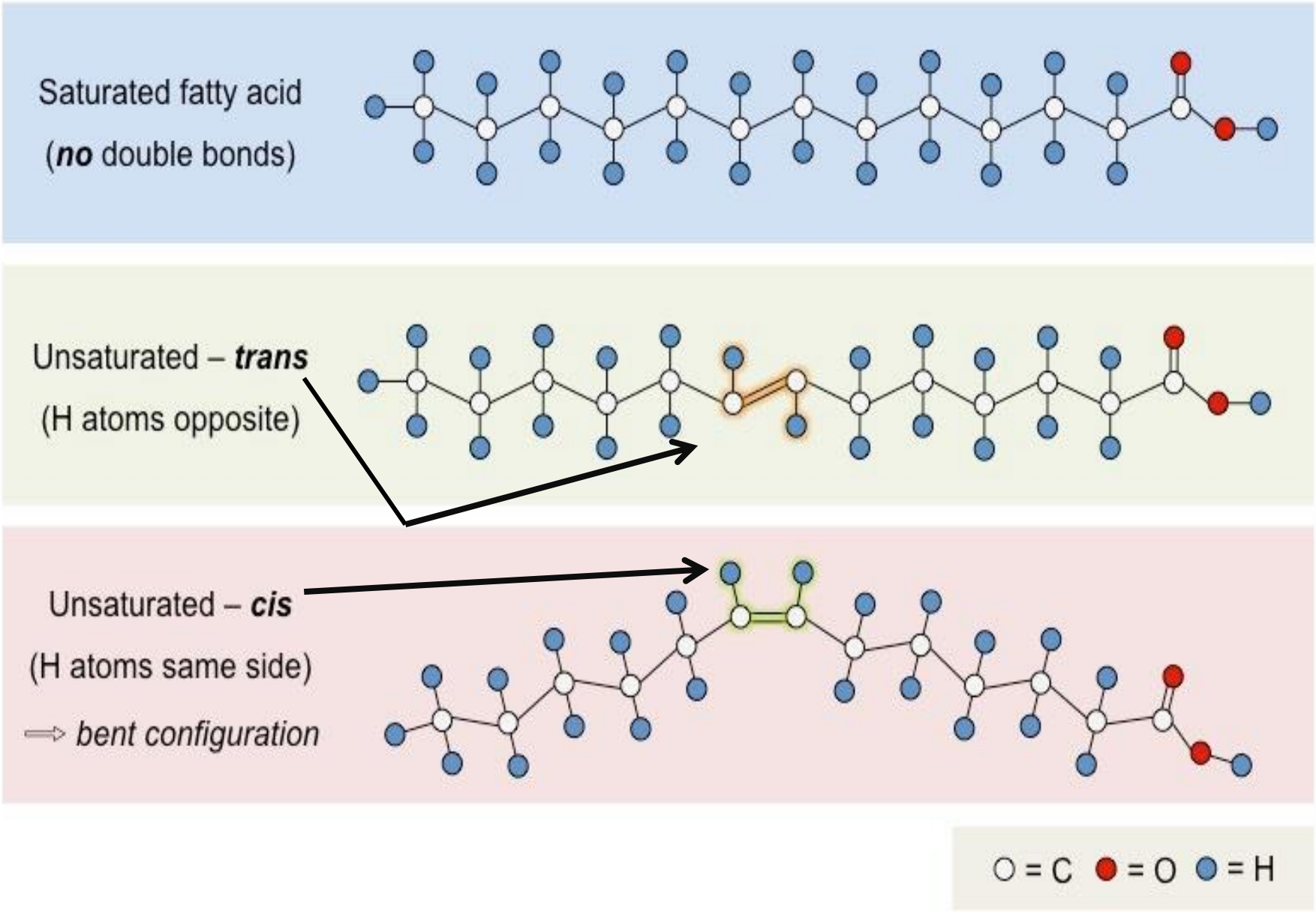
  7% gangliosides and cerebrosides)
- **Liver: 10-14%**

Fatty acids of human tissues: classification, representatives

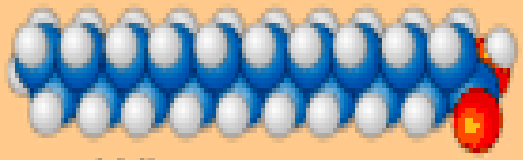
- **Saturated (palmitic, stearic)**
- **Monounsaturated (palmitoleic, oleic)**
- **Polyunsaturated (linoleic, linolinic, arachidonic)**

Saturated	None	
Monounsaturated	One	
Polyunsaturated	Multiple (>1)	

Types of Fatty Acids

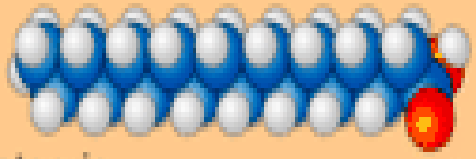


Saturated fatty acid



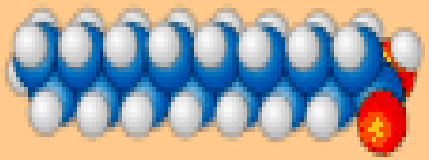
arachidic

$C_{20}H_{40}O_2$



stearic

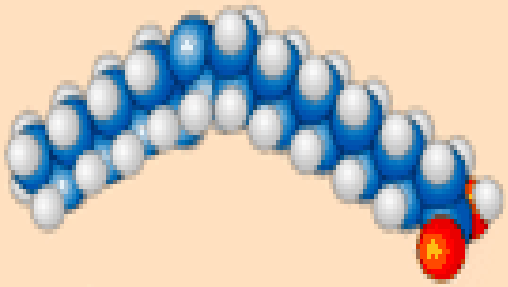
$C_{18}H_{36}O_2$



palmitic

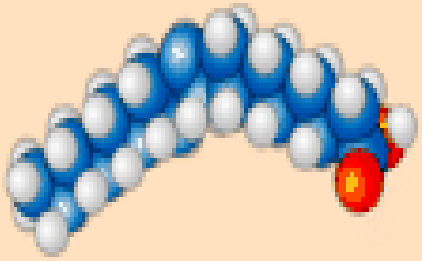
$C_{16}H_{32}O_2$

Monounsaturated fatty acid



erucic

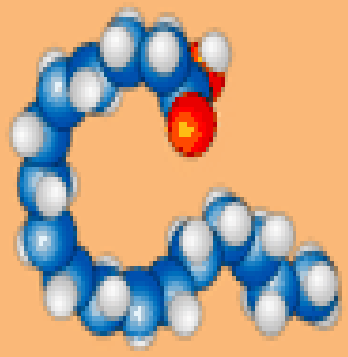
$C_{22}H_{42}O_2$



oleic

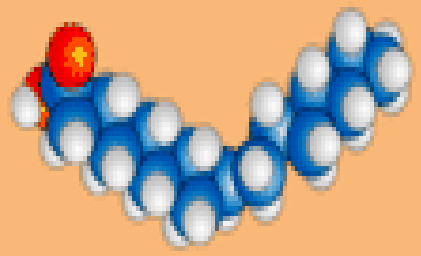
$C_{18}H_{34}O_2$

Polyunsaturated fatty acid



arachidonic

$C_{20}H_{32}O_2$



linoleic

$C_{18}H_{32}O_2$

Functions of Fatty Acids

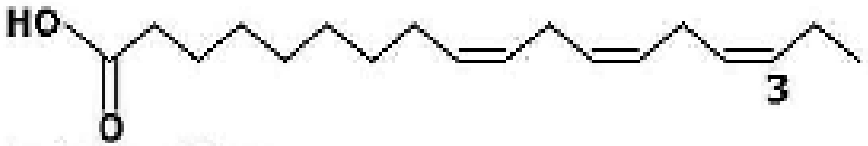
1) Fatty acids are **building blocks of phospholipids and glycolipids.**

2) Many proteins are modified by the **covalent attachment of fatty acids, which target them to membrane locations**

3) Fatty acids are **fuel molecules**. They are stored as triacylglycerols. Fatty acids mobilized from triacylglycerols are oxidized to meet the energy needs of a cell or organism.

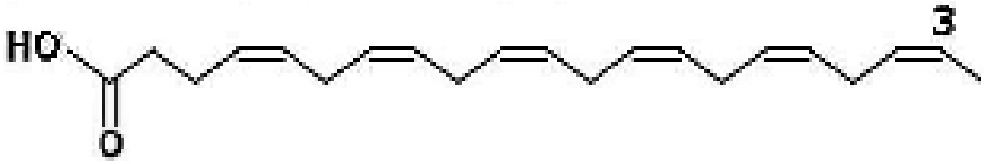
4) Fatty acid **derivatives serve as hormones and intracellular messengers**

Omega-3 fatty acids



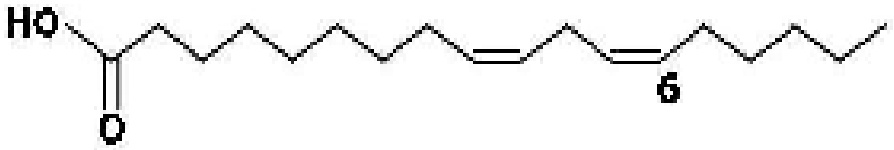
Alpha-linolenic acid ALA

Eicosapentaenoic acid EPA

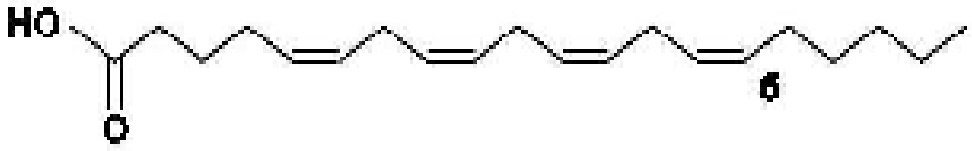


Docosahexaenoic acid DHA

Omega-6 fatty acids

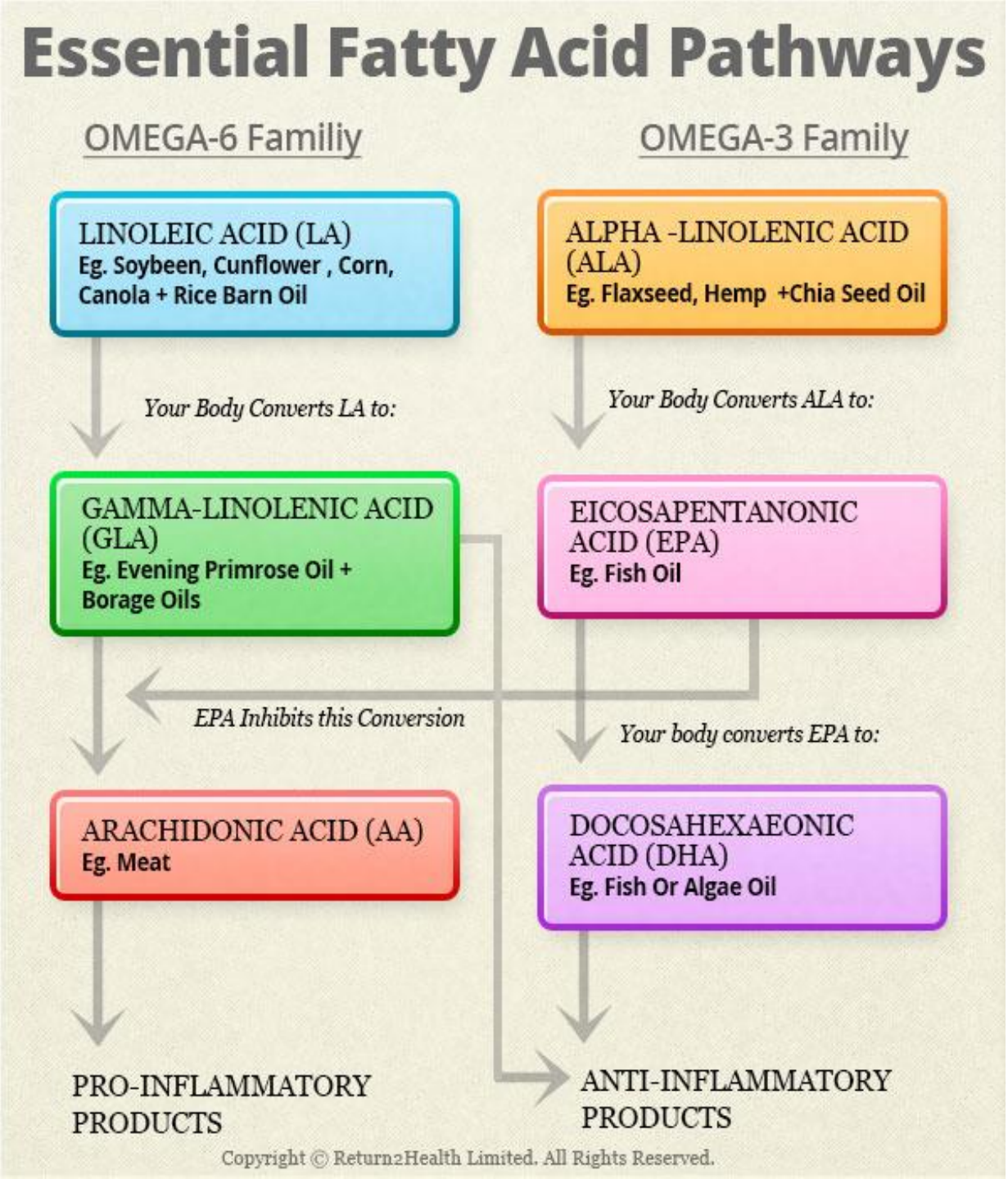


Linoleic acid LA



Arachidonic acid AA

Essential Fatty Acid Pathways



ESSENTIAL FATTY ACIDS SOURCES AND THEIR PROPERTIES

Seed oils, avocado

OMEGA 6
Linoleic acid

OMEGA 3
Linolenic acid

Nuts, flax, chia, hemp Oily fish

Evening primrose oil, borage oil, black currant oil

Gamma Linolenic acid (GLA)

Eicosapenta-enoic acid (EPA)

Oily fish, fish oils and krill oil

Prostanoids series 1 with properties: vasodilator, anticoagulant, antiinflammatory

Arachidonic acid (AA)

Docosahexaenoic Acid (DHA)

vasodilatory properties, Anti-coagulant, minor proinflammatory (mediators of inflammation)

2 series prostanoids, effect:vasoconstrictor, platelet aggregator, strong pro-inflammatory

Oily fish and fish oils, krill

Essential for vision, for the nervous system and pregnancy.

* Alcohol,tobacco, trans fat and certain drugs prevents steps marked with *, so the use of these substances restrains the benefits of omega 3 and omega 6 (inhibit enzymes that transform them).Moreover, an excess of omega-6 (fried, animal fat, a lot of oil, pastries, margarine, etc.) produces an excess of AA and decreases inflammatory omega-3.

Dietary lipids

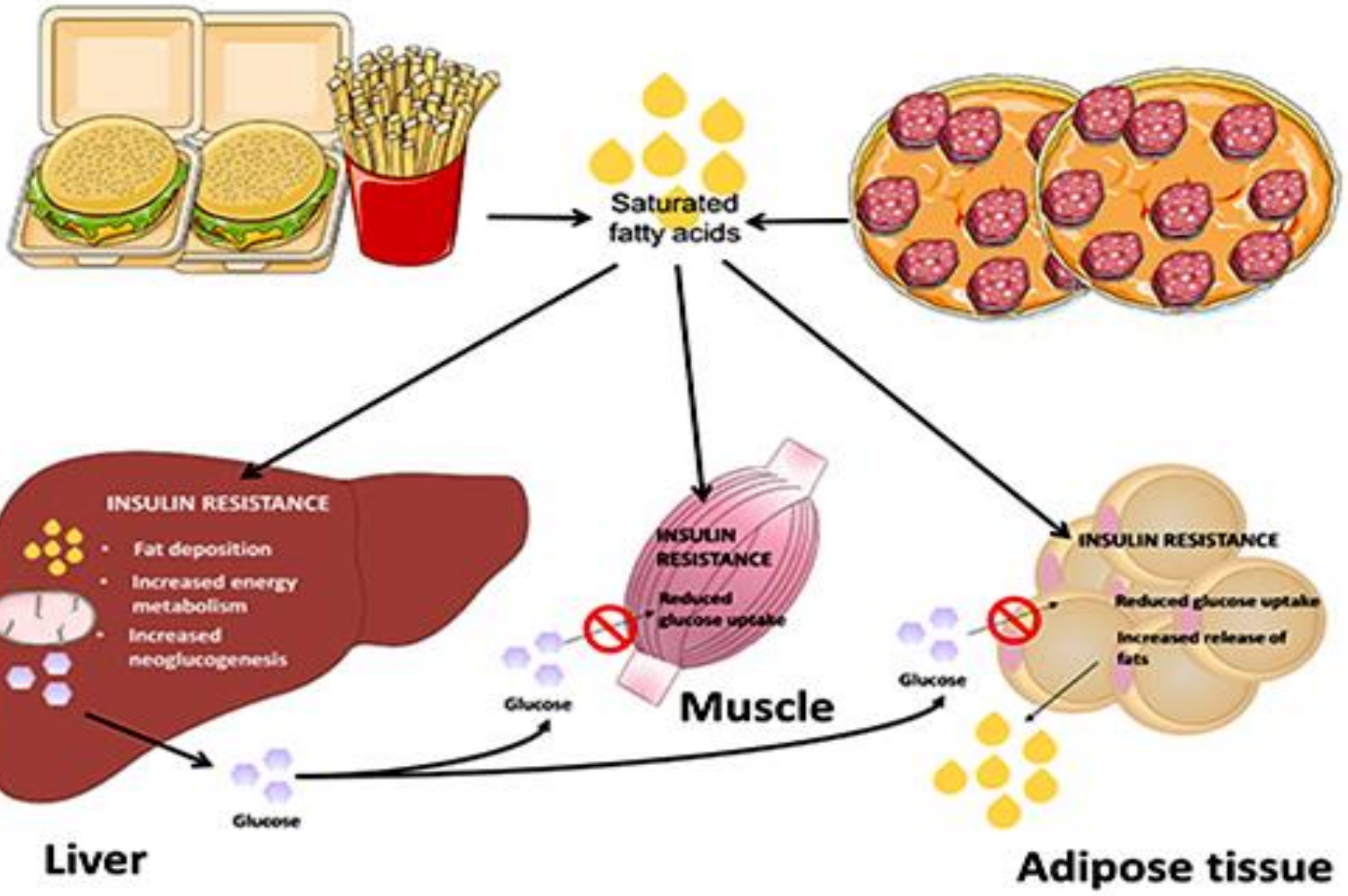
70-140 g per day

(depend on age, sex, physical work and climate)

10 % oils

With a balanced diet fats should provide no more than 30% of total calories

Impact of a meal rich in saturated fatty acids

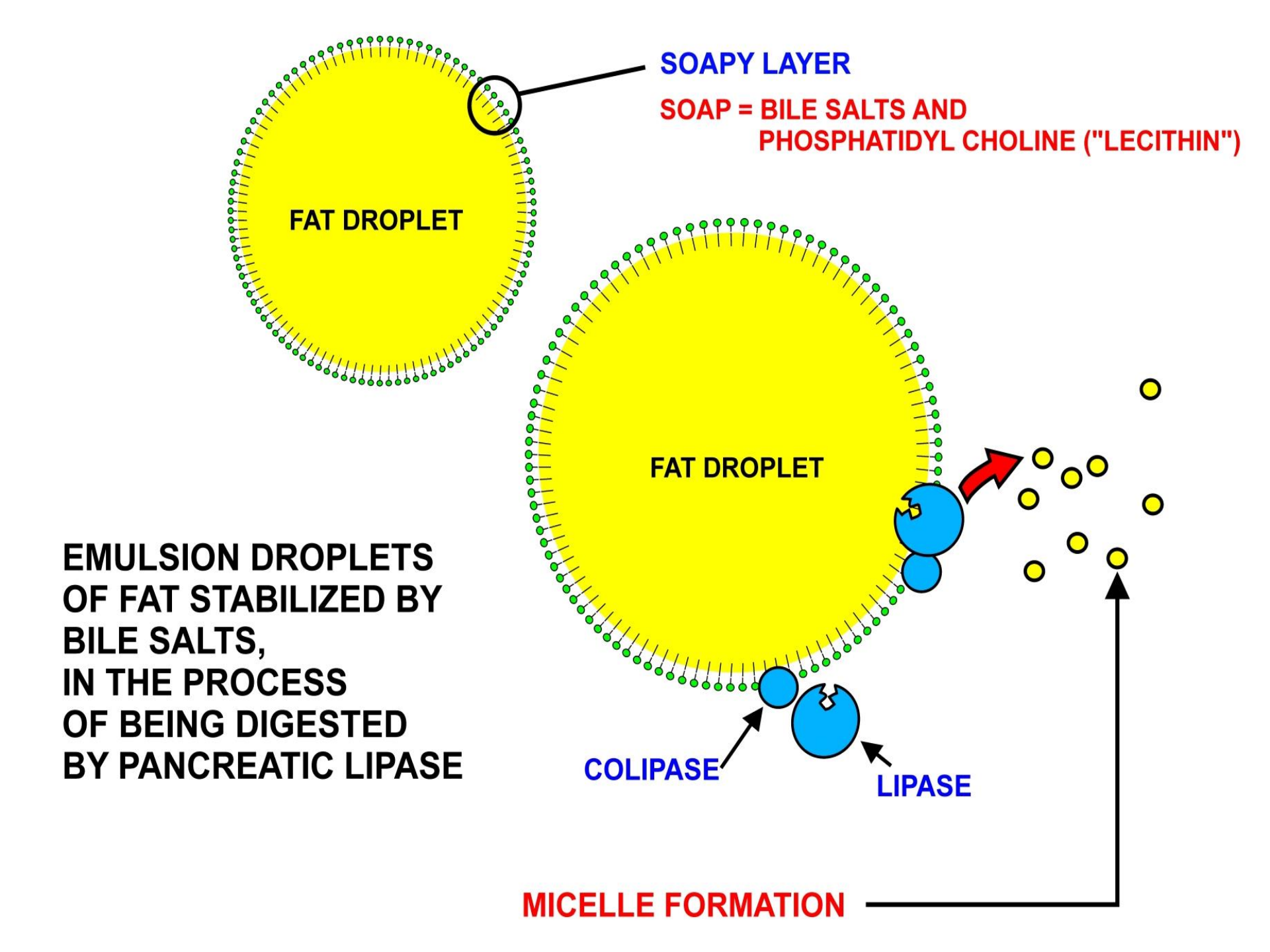


Digestion of lipids

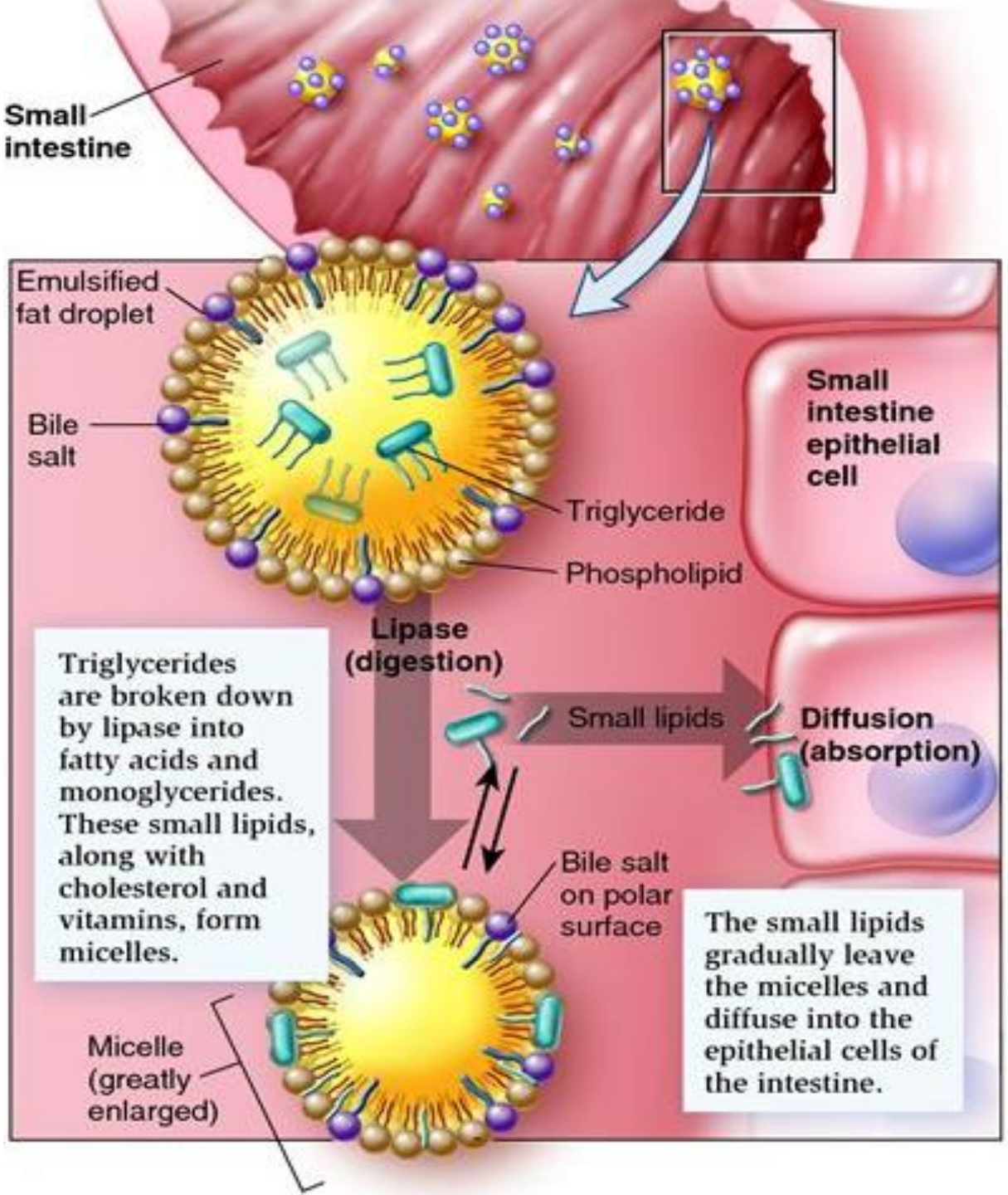
The main cleavage site of lipids is the **small intestine**.

To increase the contact surface with hydrophilic enzymes fats should be **emulsified** (break into small drops).

Emulsification takes place under the action of bile salts. Peristalsis and bubbling CO_2 also promote emulsification.

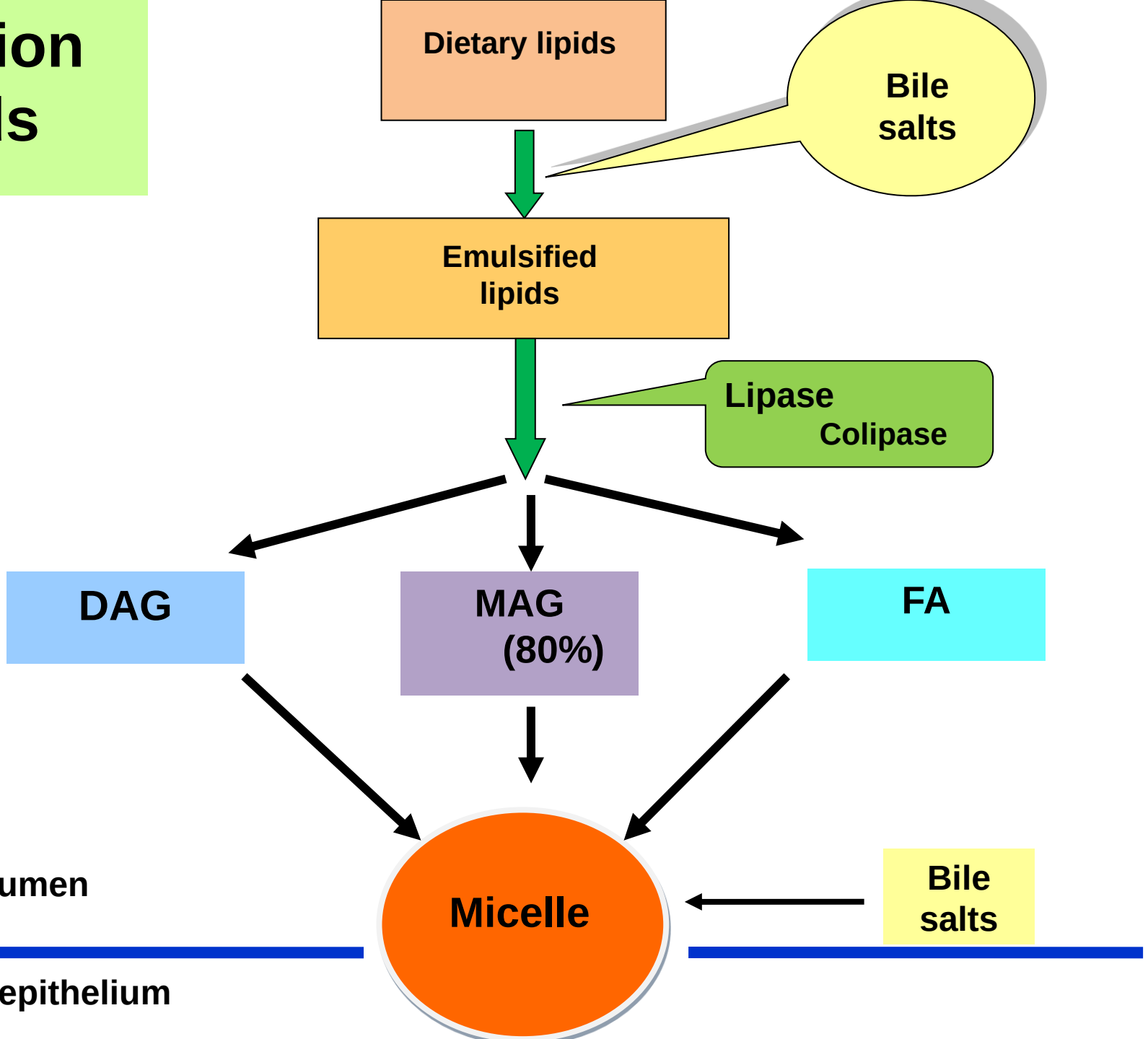

SOAPY LAYER
SOAP = BILE SALTS AND
PHOSPHATIDYL CHOLINE ("LECITHIN")
FAT DROPLET
FAT DROPLET
EMULSION DROPLETS
OF FAT STABILIZED BY
BILE SALTS,
IN THE PROCESS
OF BEING DIGESTED
BY PANCREATIC LIPASE
COLIPASE
LIPASE
MICELLE FORMATION

Digestion of emulsified fats



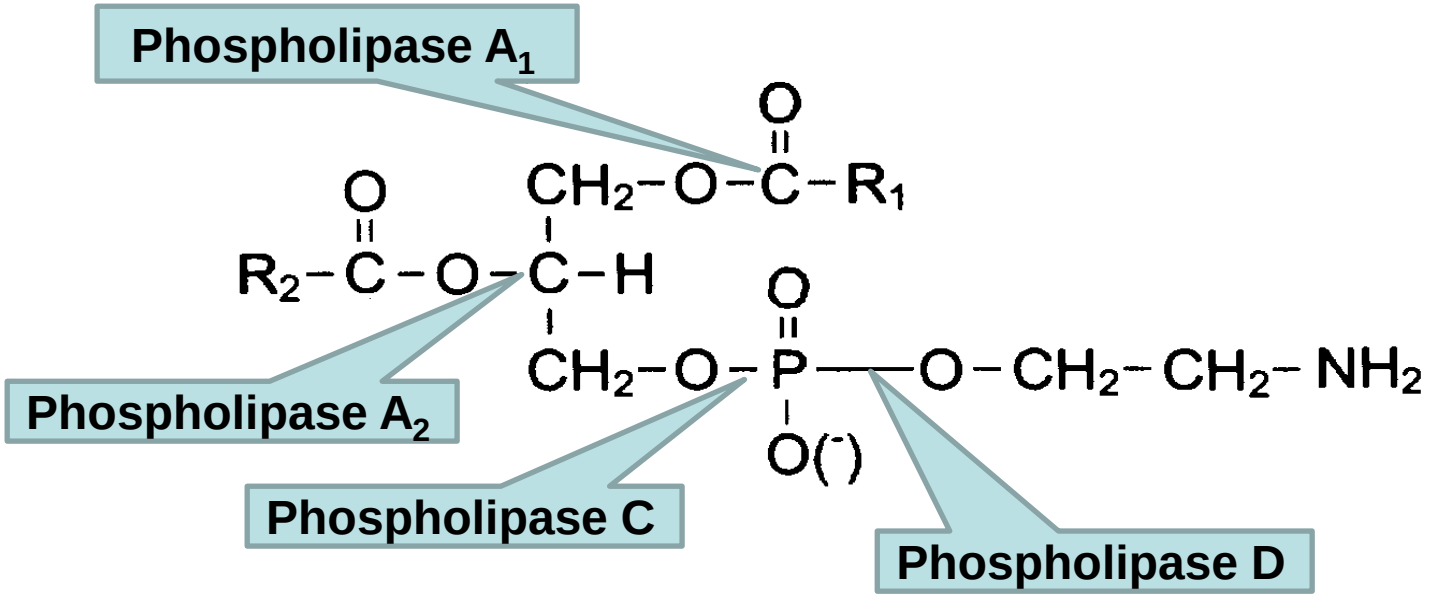
Absorption of lipids

Digestion of lipids



Digestion of lipids

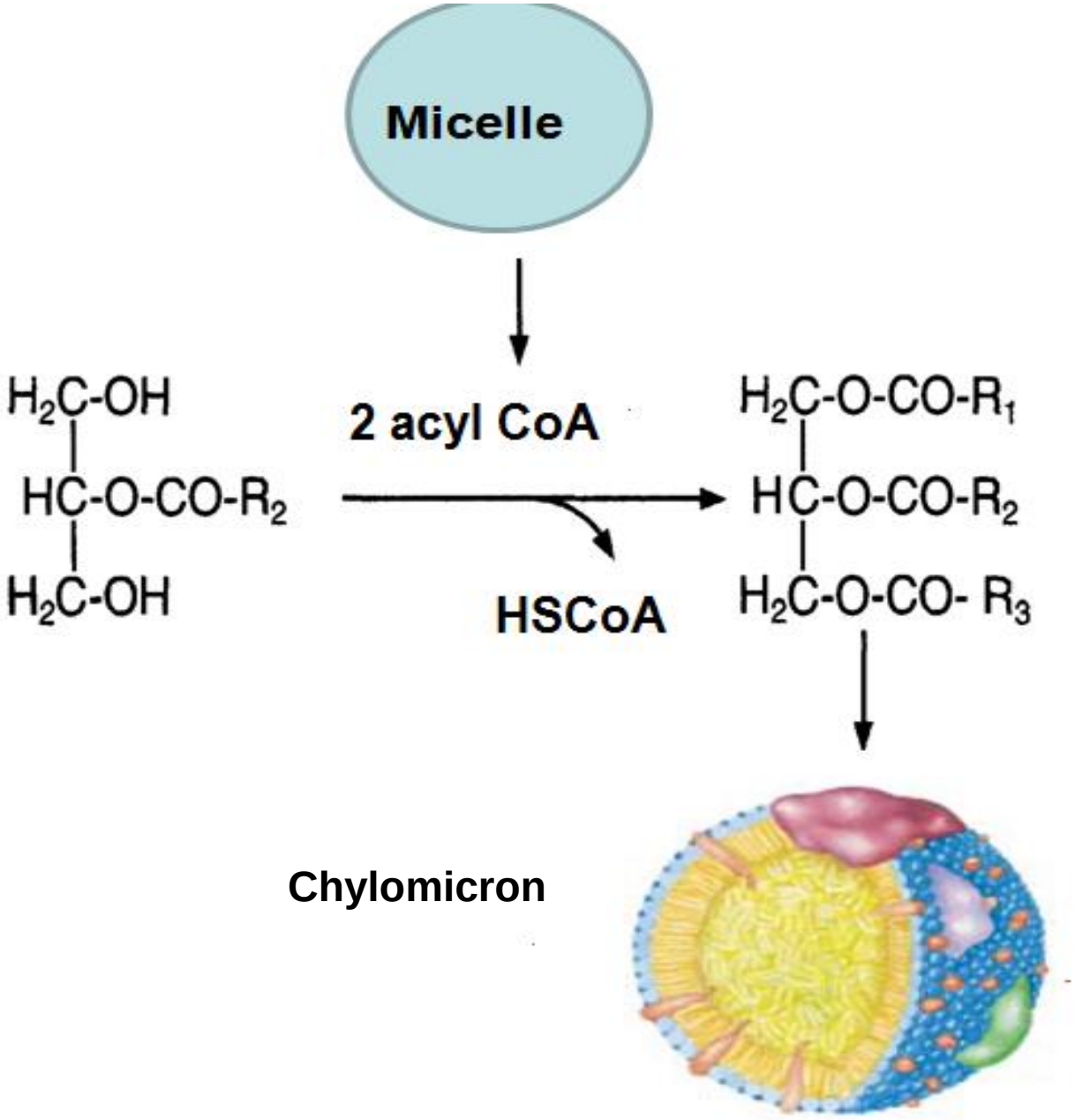
- **Phospholipids are hydrolyzed by pancreatic phospholipase A_1, A_2, C, and D.**



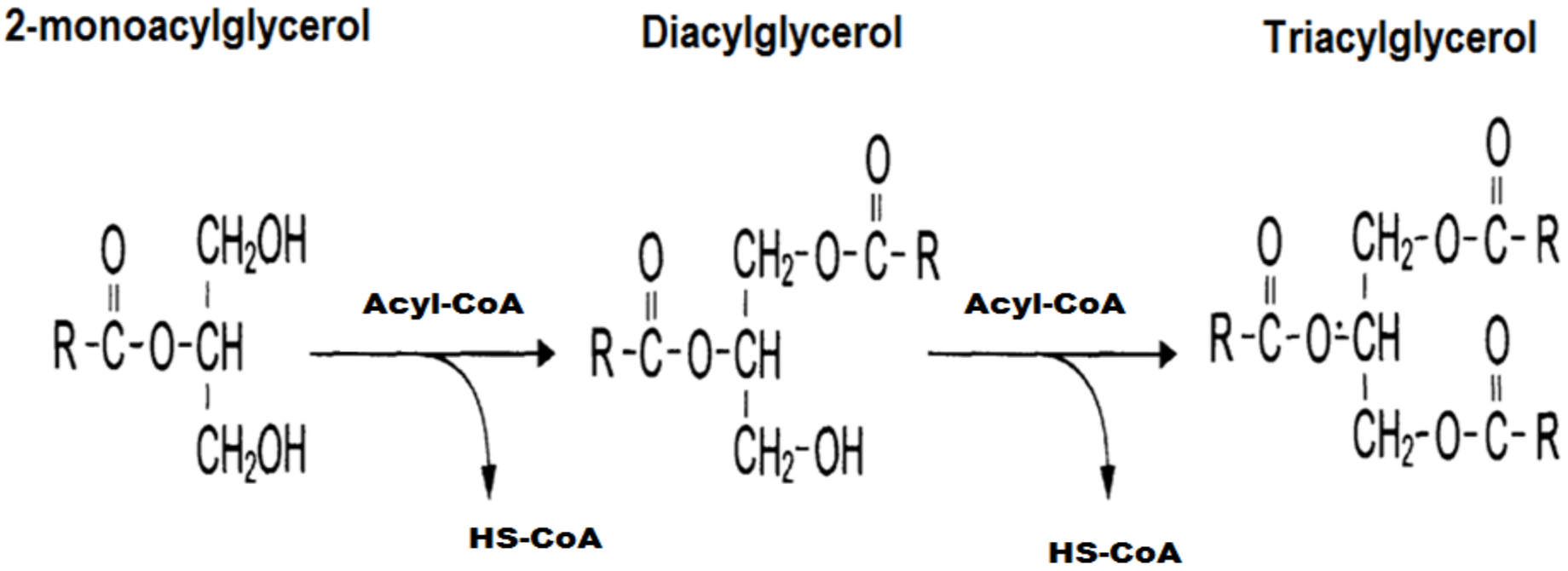
- **Esters of Cholesterol are digested by pancreatic cholesterol esterase**

Absorption of lipids in the gastrointestinal tract

Intestinal epithelium

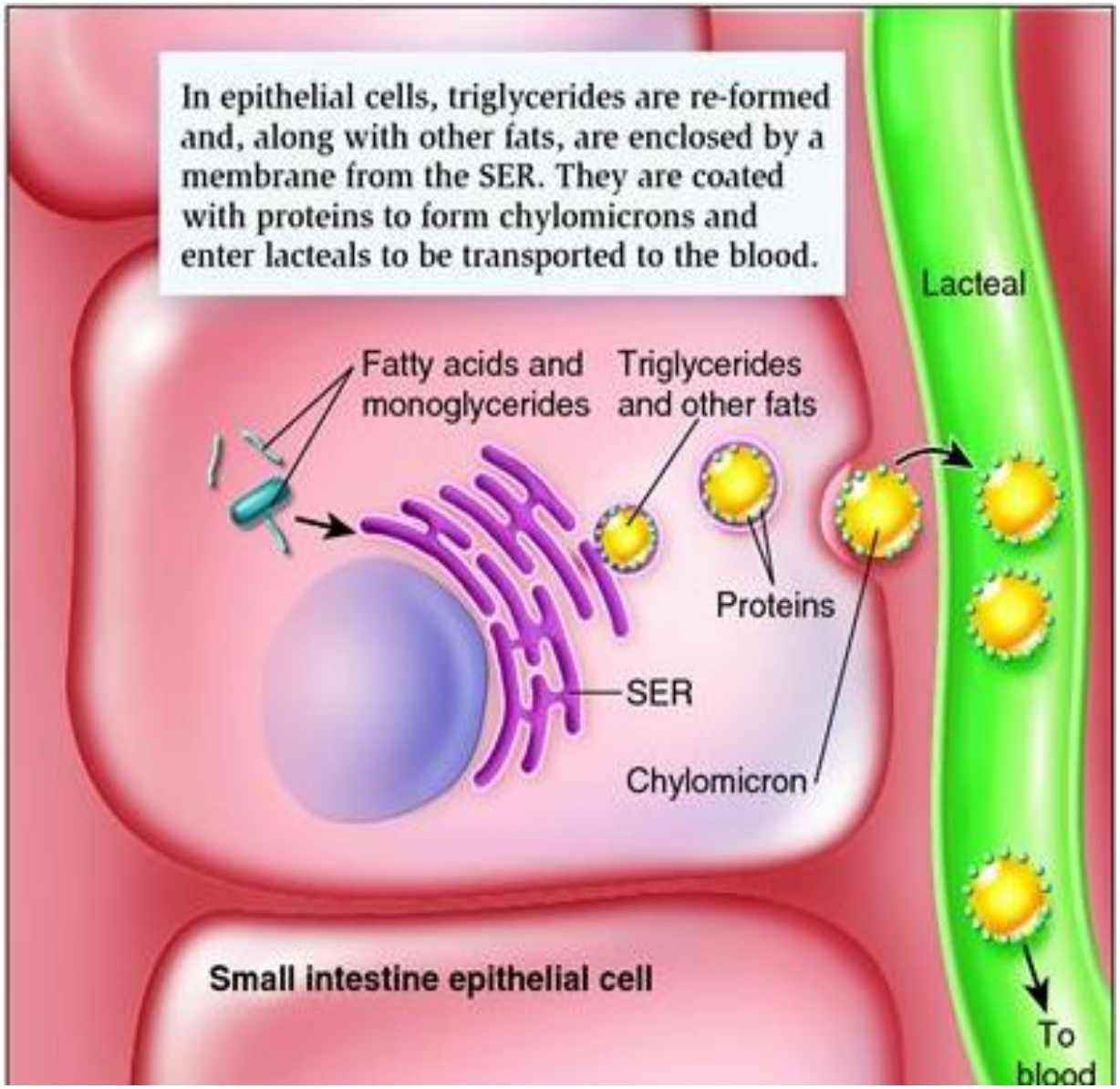


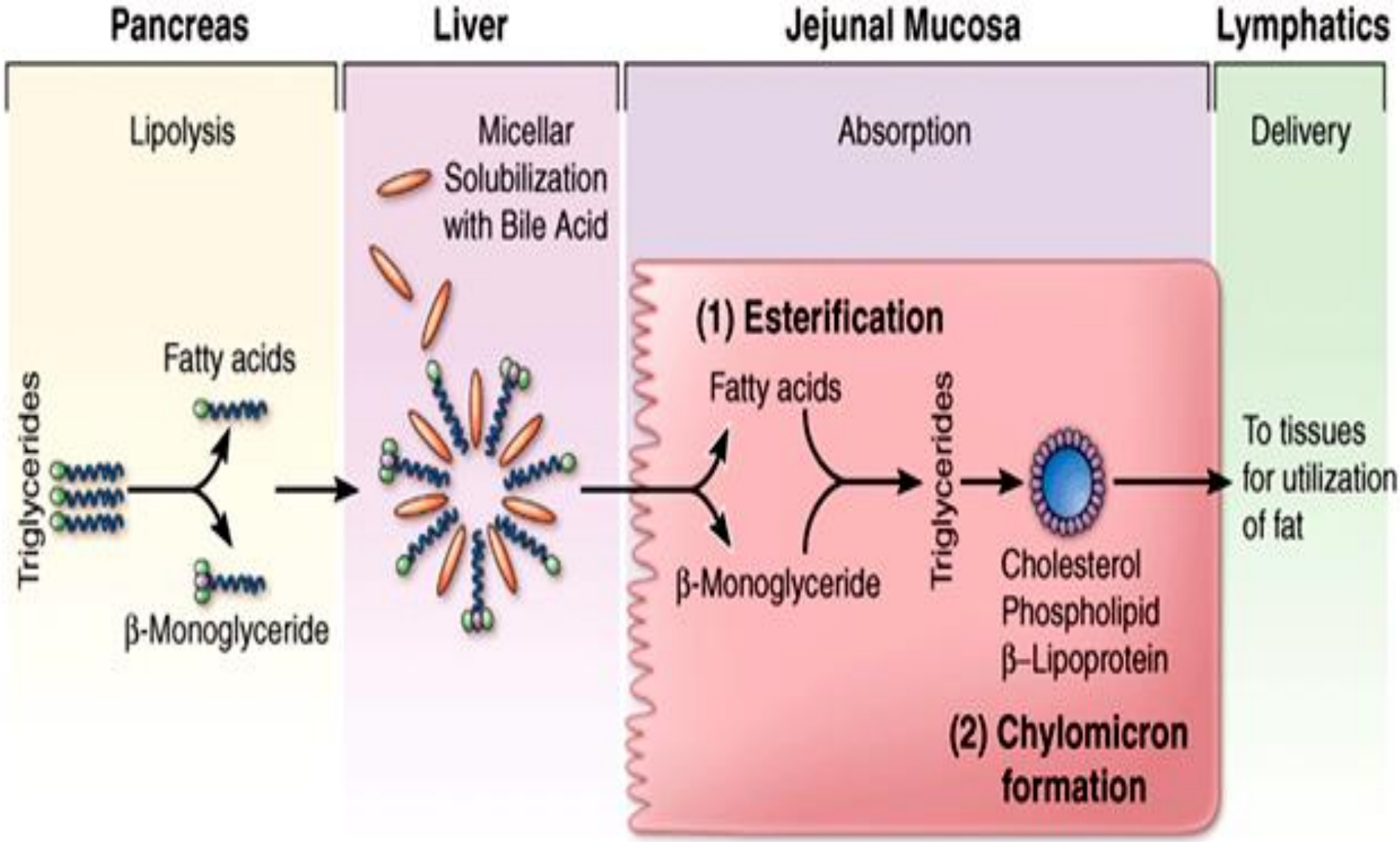
Re-esterification inside mucosal cell to form triacylglycerol (resynthesis of triacylglycerol).



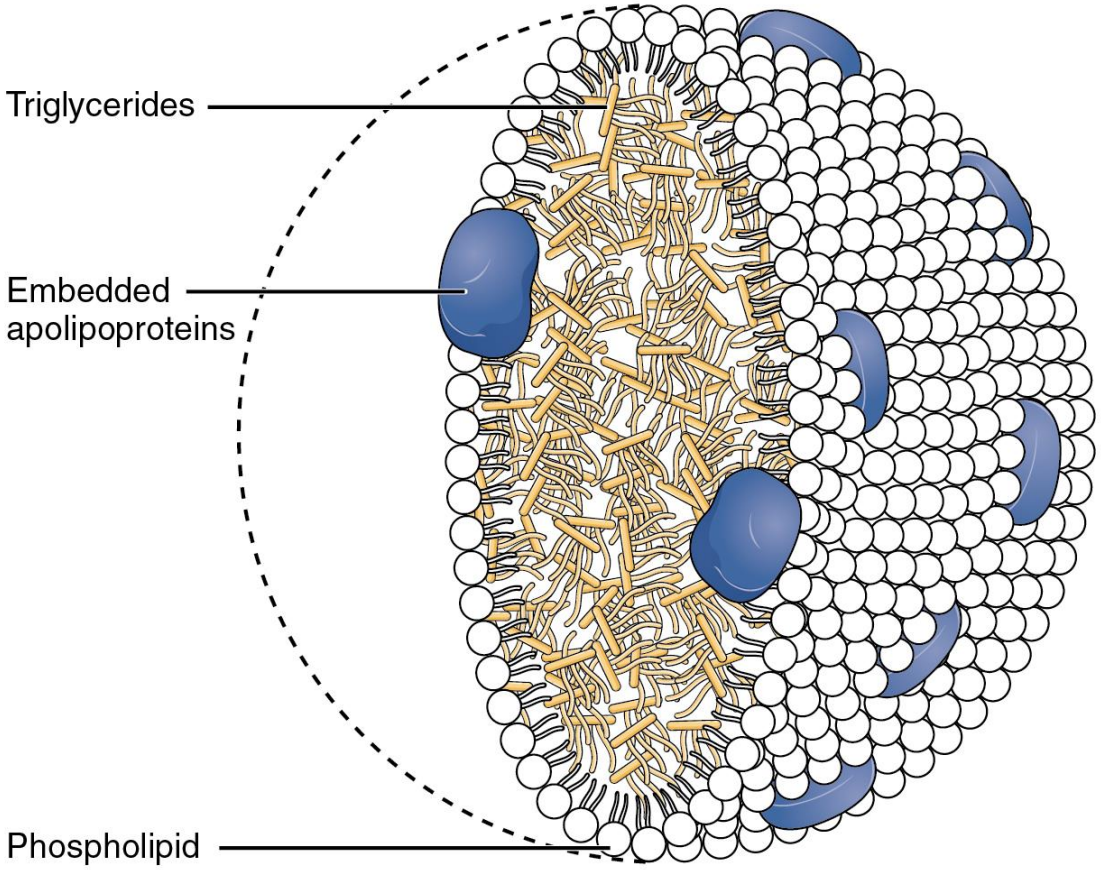
Resynthesis of triacylglycerols

Formation and release of chylomicrons

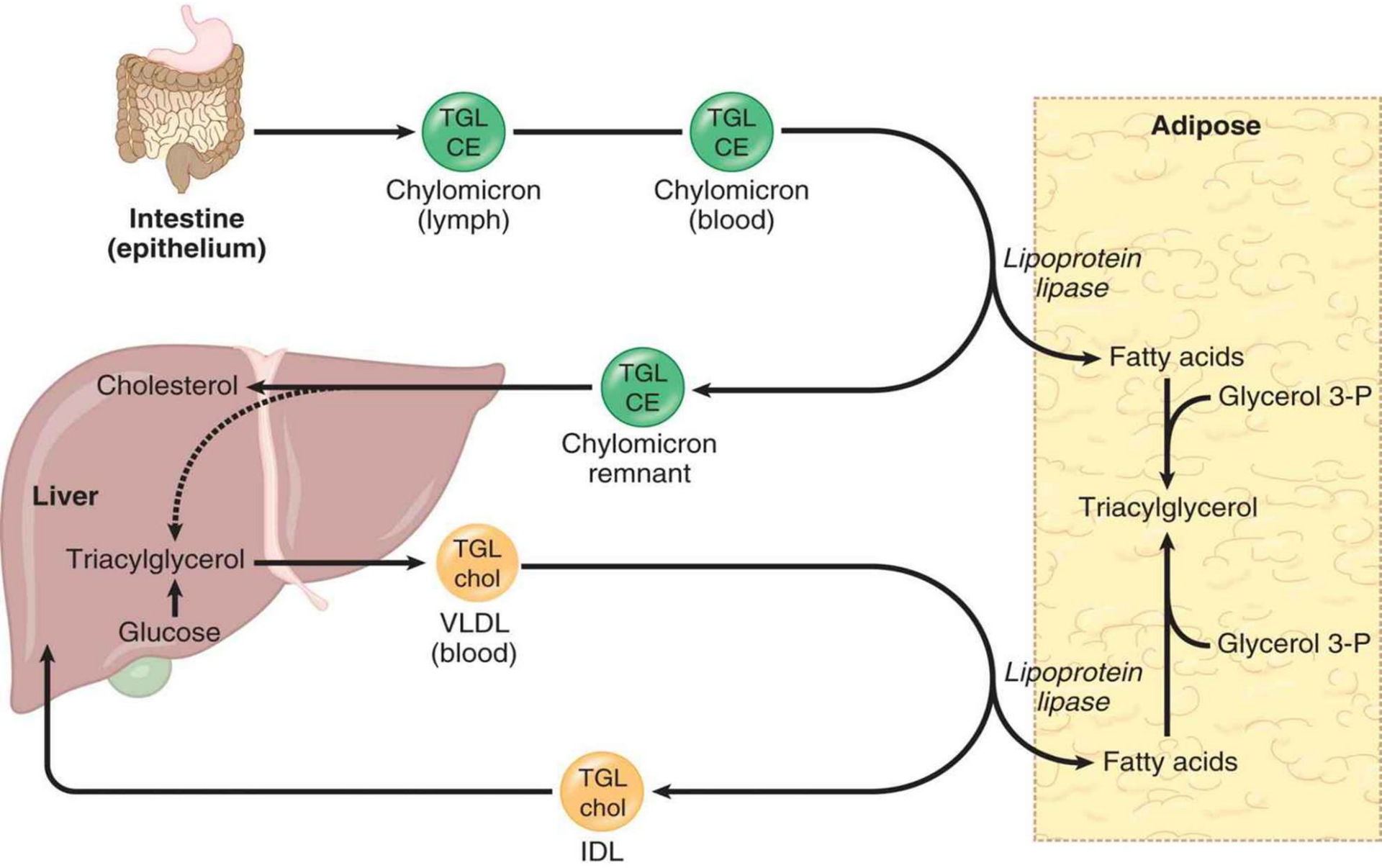



Pancreas
Liver
Jejunal Mucosa
Lymphatics
Lipolysis
Micellar Solubilization with Bile Acid
Absorption
Delivery
Triglycerides
Fatty acids
β-Monoglyceride
(1) Esterification
Fatty acids
β-Monoglyceride
Triglycerides
Cholesterol
Phospholipid
β-Lipoprotein
(2) Chylomicron formation
To tissues for utilization of fat

A shematic diagram of a chylomicron



Metabolism of Chylomicrons



Disorders in digestion and absorption of lipids in the gastrointestinal tract

In all these disorders the feces contain much unsplit fat or unabsorbed higher fatty acids

this state referred as

steatorrhea

Normally less than 5 % of ingested fat
is excreted in faeces.

steatorrhea

- **Pancreatogenic**

(deficient supply of pancreatic lipase to the intestine)

- **Hepatogenic**

(disordered delivery of bile to the intestine)

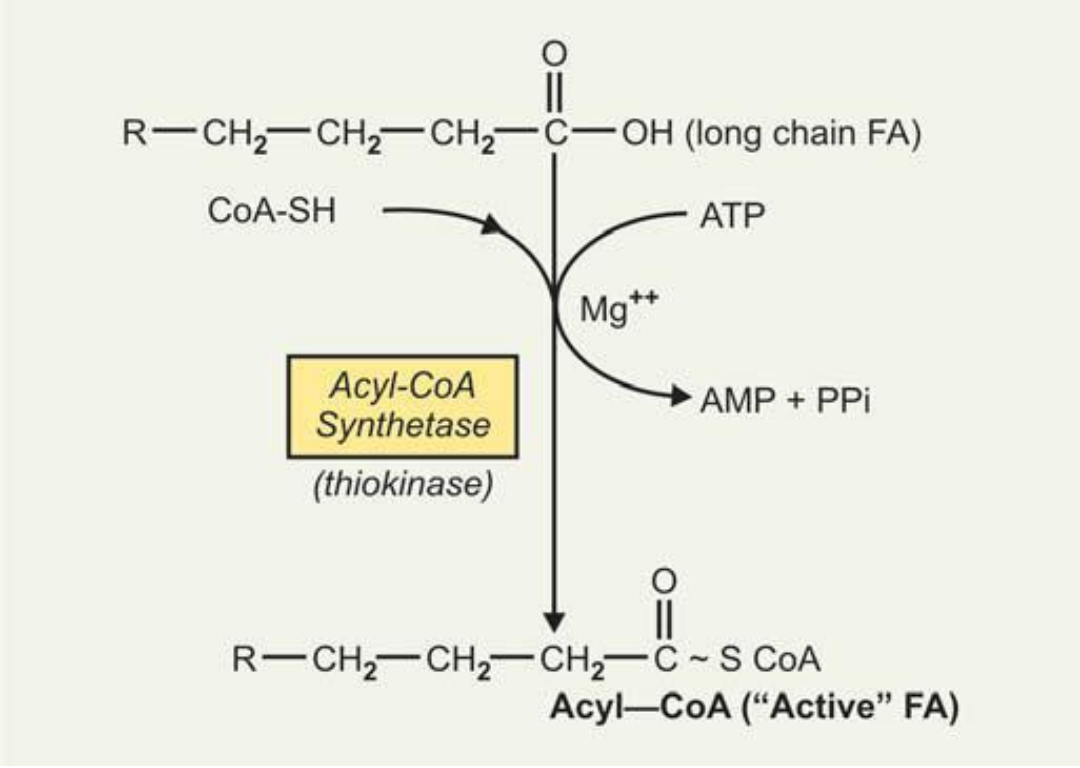
- **Enterogenic (deseased GI tract)**

Oxidation of fatty acids

- **Occurs in mitochondria**

- **The fatty acids are first converted to their acyl coenzyme A derivatives**

Activation of fatty acids



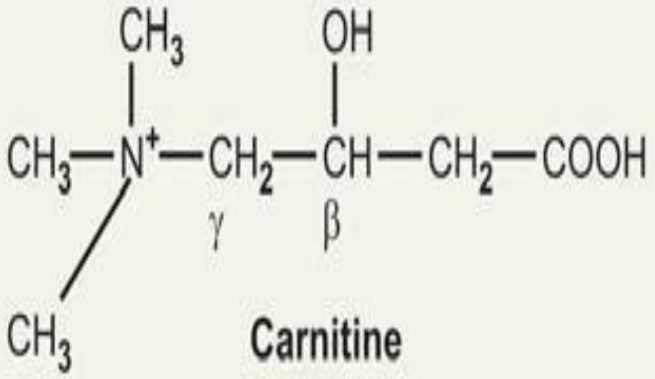
RCOOH + HSCoA + ATP

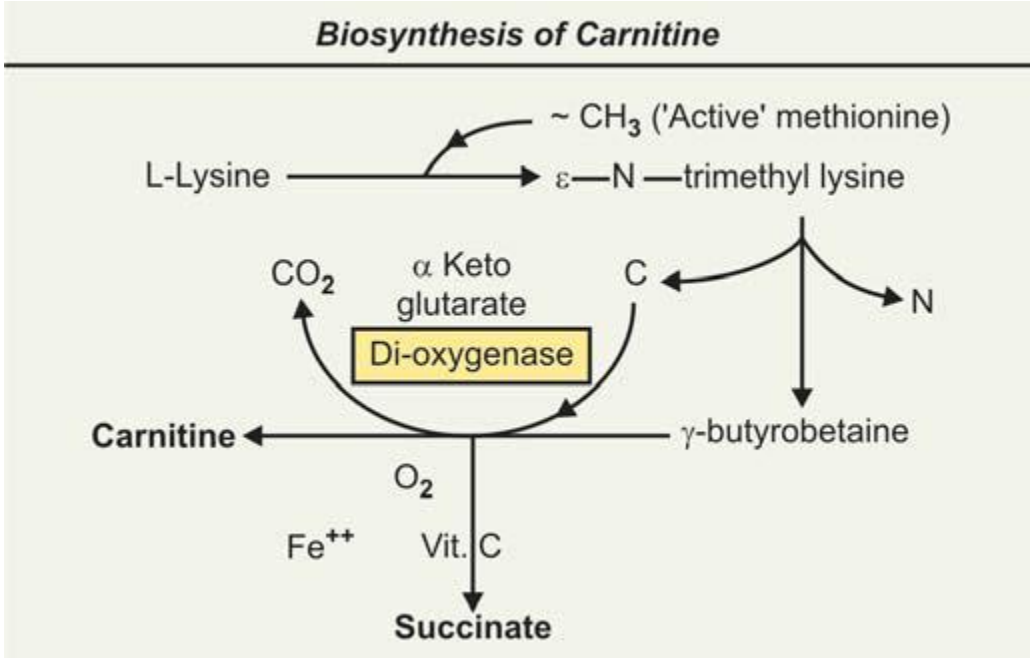
RCO~CoA + AMP + PP_i

enzyme: acyl-CoA-synthetase

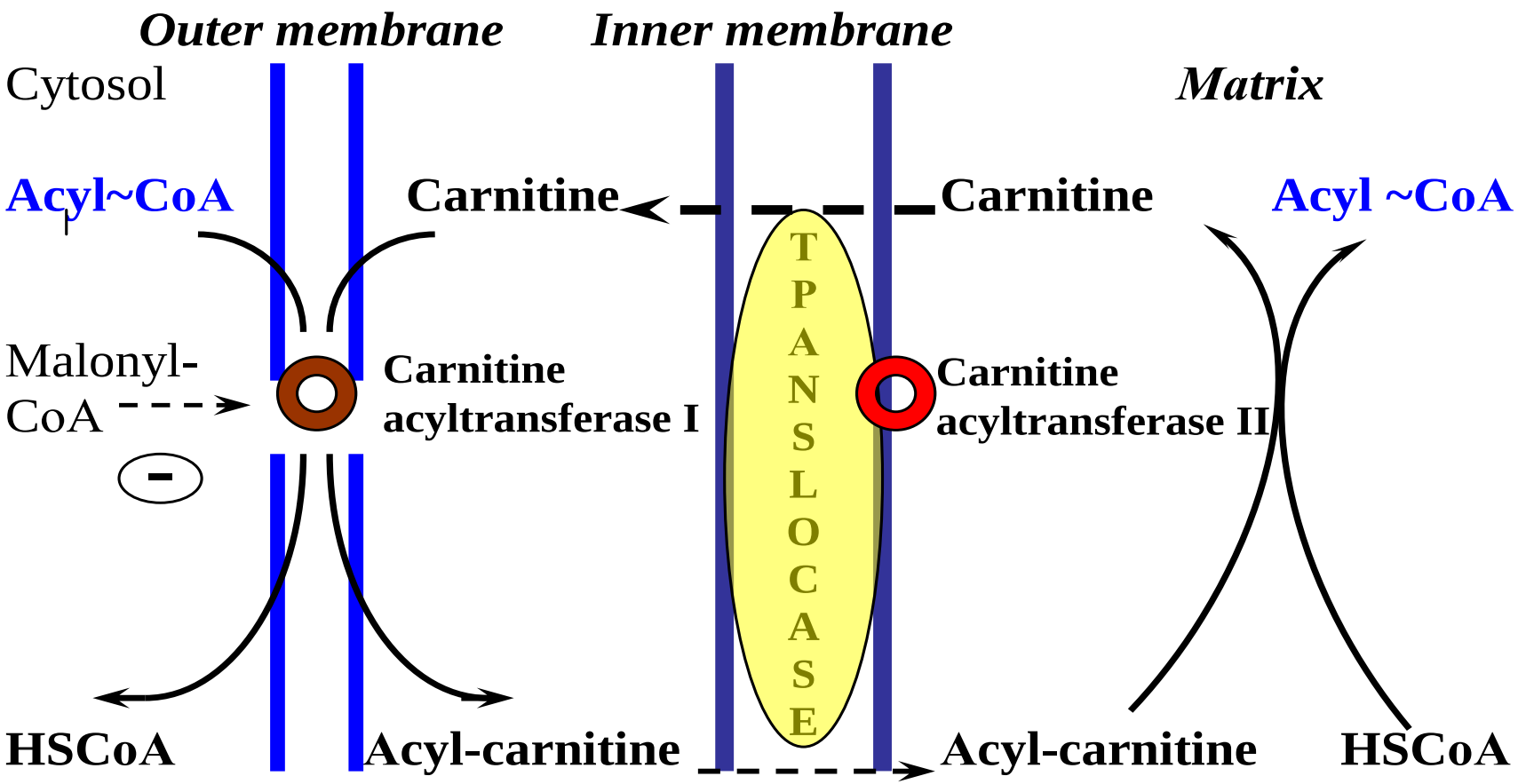
(found in the endoplasmic reticulum, peroxisomes, mitochondria)

CARNITINE


CH3
OH
CH3—N+—CH2—CH—CH2—COOH
γ
β
CH3
Carnitine


Biosynthesis of Carnitine
~ CH3 ('Active' methionine)
L-Lysine
ε—N—trimethyl lysine
CO2
α Keto glutarate
C
N
Di-oxygenase
Carnitine
γ-butyrobetaine
O2
Fe++
Vit. C
Succinate

Role of carnitine in the transport of long-chain FA



Carnitine deficiency

Deficiency of carnitine can occur:

(a) In newborns: specially premature infants, owing to inadequate synthesis or renal leakage.

(b) In adults:

losses can occur in hemodialysis

in patients with organic acidurias, carnitine is lost in urine being conjugated with organic acid.

Treatment: oral therapy with carnitine.

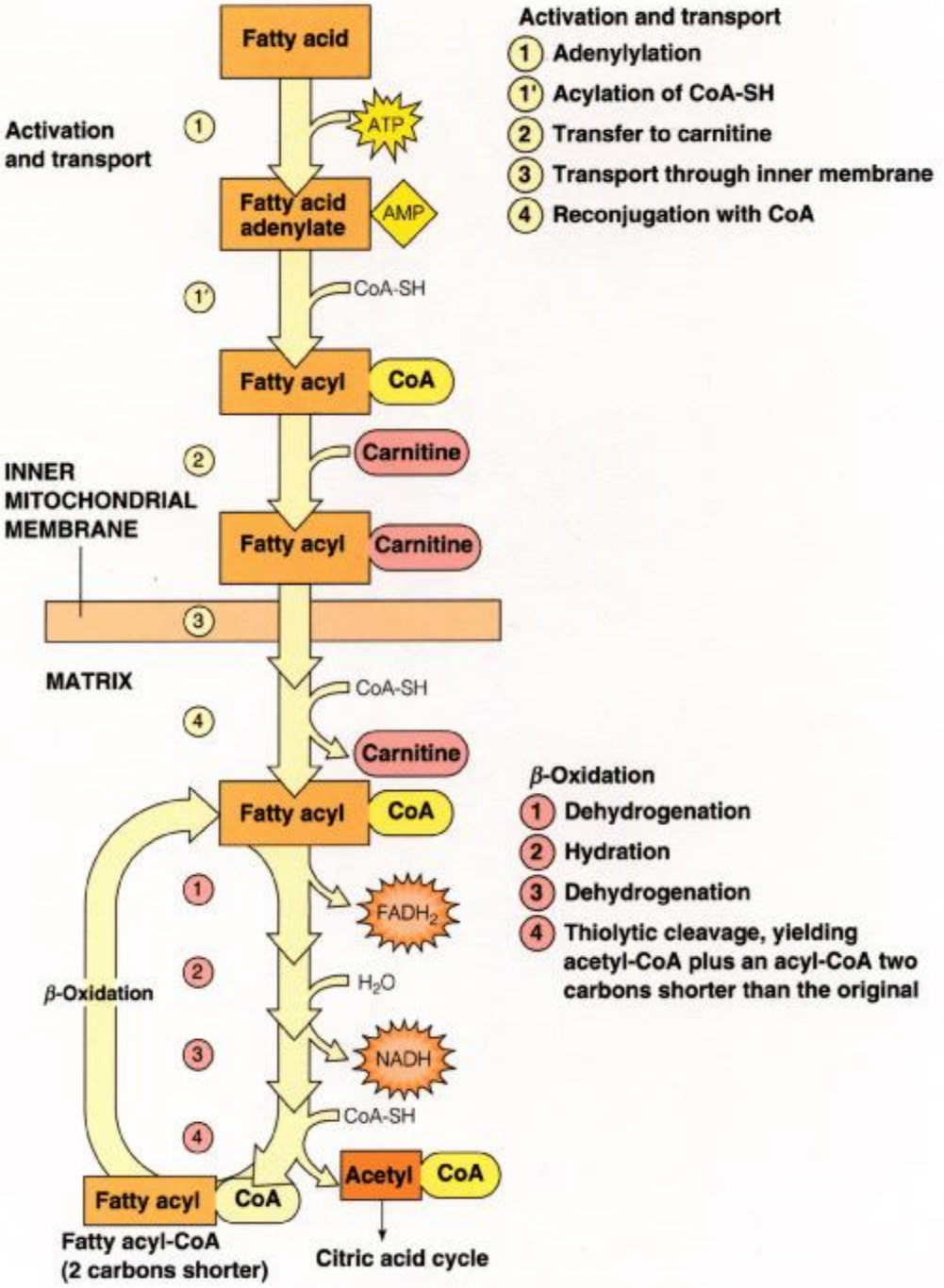
Oxidation of fatty acids

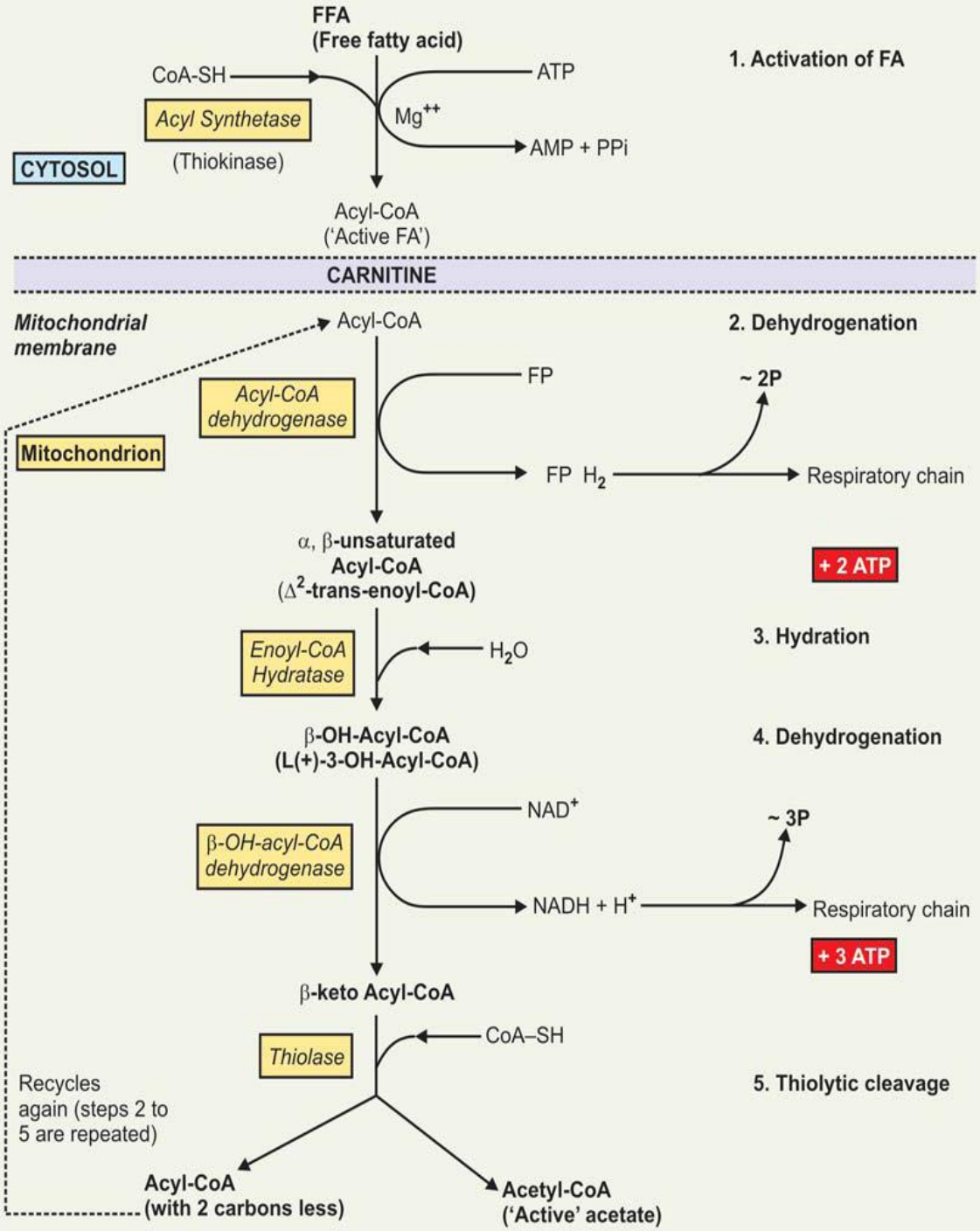
In β-oxidation two carbons are cleaved from acyl-CoA molecules, starting at the carboxyl end, forming acetyl-CoA

A new acyl-CoA is two carbons shorter than the original acyl-CoA

The pathway produces $FADH_2$ and NADH

(Harper's Illustrated Biochemistry)




FFA
(Free fatty acid)
1. Activation of FA
CoA-SH
ATP
Acyl Synthetase
Mg++
AMP + PPi
CYTOSOL
(Thiokinase)
Acyl-CoA
('Active FA')
CARNITINE
Mitochondrial membrane
Acyl-CoA
2. Dehydrogenation
Acyl-CoA dehydrogenase
FP
~ 2P
Mitochondrion
FP H2
Respiratory chain
α, β-unsaturated Acyl-CoA
(Δ2-trans-enoyl-CoA)
+ 2 ATP
Enoyl-CoA Hydratase
H2O
3. Hydration
β-OH-Acyl-CoA
(L(+)-3-OH-Acyl-CoA)
4. Dehydrogenation
β-OH-acyl-CoA dehydrogenase
NAD+
~ 3P
NADH + H+
Respiratory chain
+ 3 ATP
β-keto Acyl-CoA
Thiolase
CoA–SH
Recycles again (steps 2 to 5 are repeated)
5. Thiolytic cleavage
Acyl-CoA
(with 2 carbons less)
Acetyl-CoA
('Active' acetate)

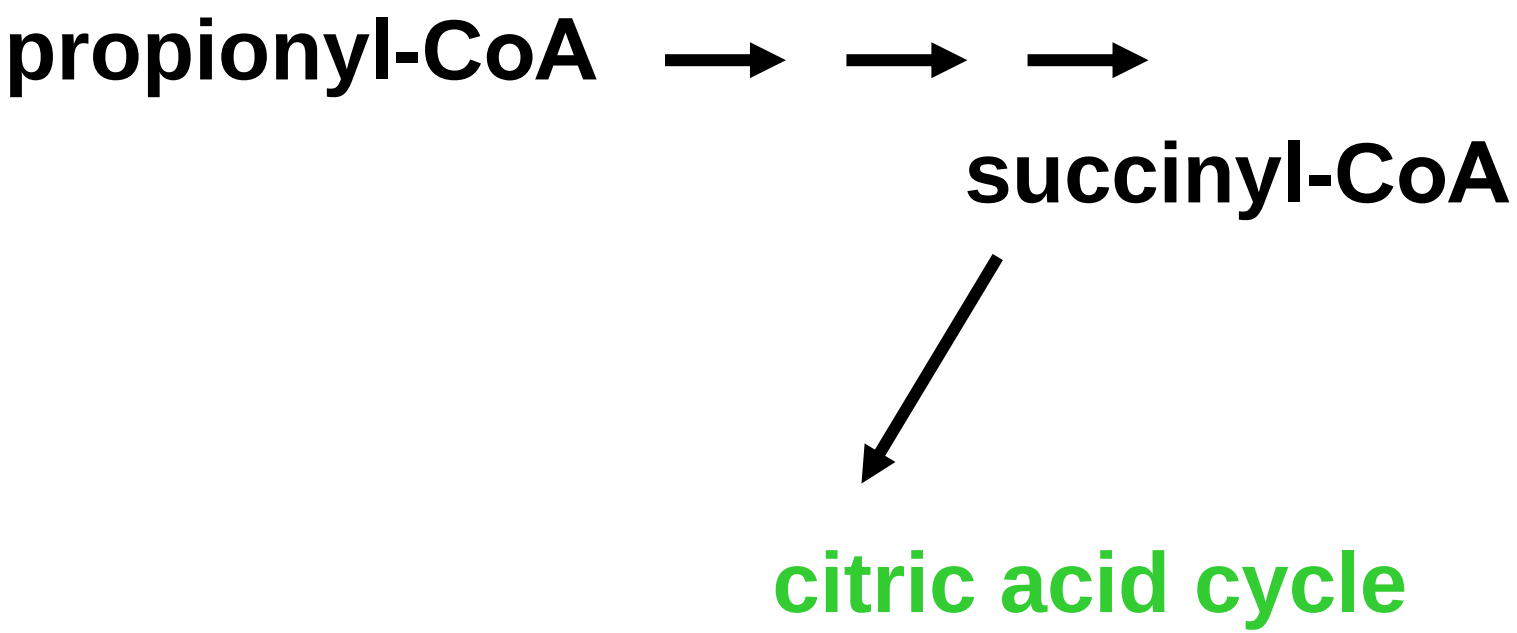
ATP Formation in the oxidation of palmitic acid

7 NADH	x 3 (2.5)	21 (17.5)
7 $FAДH_2$	x 2 (1.5)	14 (10.5)
8 Acetyl-CoA	x 12 (10)	96 (80)
TOTAL		131 (108)
		- 1(2)

Oxidation of fatty acids with odd number of carbon atoms

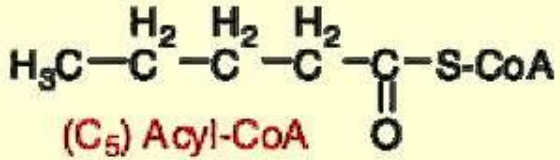
- **Fatty acids with an odd number of carbon atoms are oxidised by β-oxidation pathway to produce acetyl-CoA until a 3-carbon residue propionyl-CoA is left.**
- **Propionyl-CoA is metabolised to succinyl-CoA through methyl malonyl-CoA.**

Oxidation of fatty acids with odd number of carbon atoms

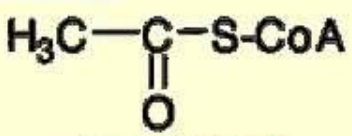


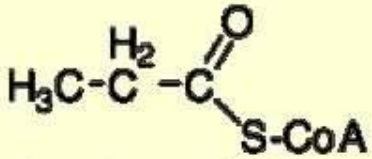
SLM, 3,11,12

Oxidation of Odd-Numbered Fatty Acids



b oxidation



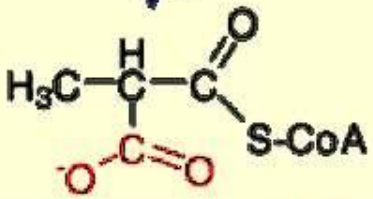


ATP

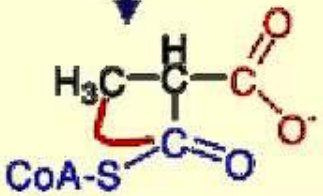
ADP + Pi

HCO3

biotin

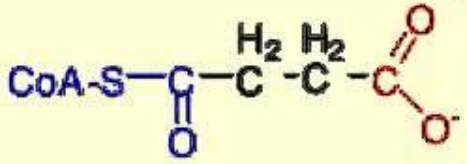


Epimerase



mutase

Coenzyme B12



Odd chained fatty acids can contribute to gluconeogenesis

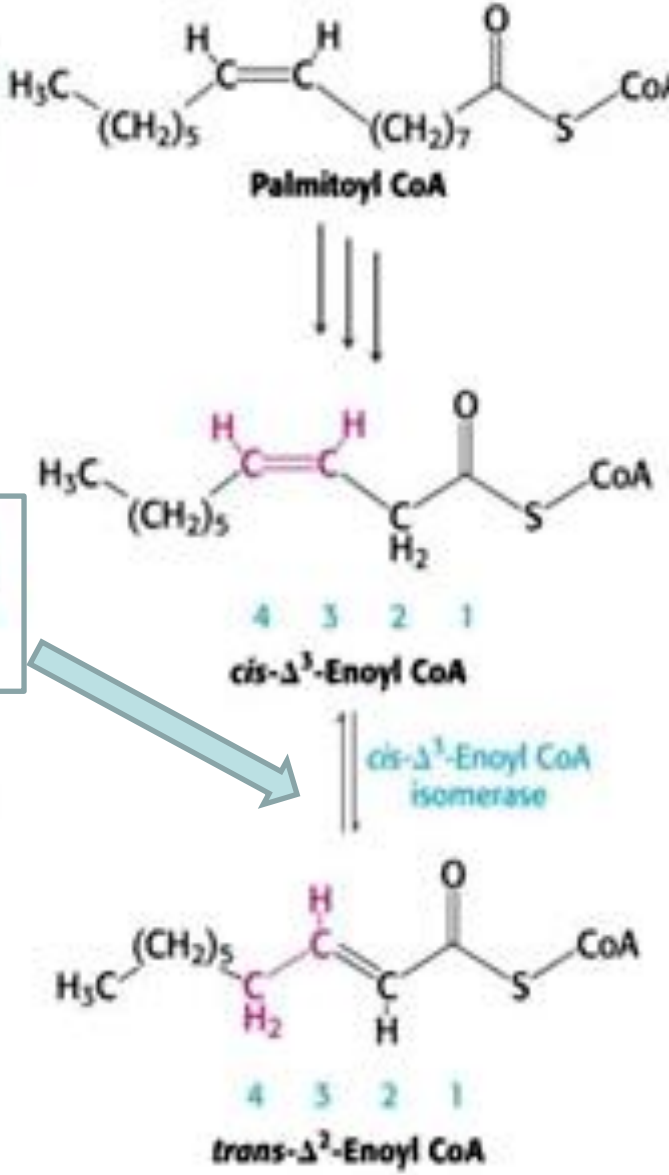
Gluconeogenesis

Oxaloacetate → TCA Cycle

Succinyl CoA is a TCA Cycle Intermediate

β-oxidation of unsaturated fatty acids

- β-oxidation occurs normally for 3 rounds until a cis-Δ^3-enoyl-CoA is formed.
- Acyl-CoA dehydrogenase can not add double bond between the α and β carbons.
- Enoyl-CoA isomerase converts this to trans- Δ^2 enoly-CoA
- Now the β-oxidation can continue on the hydration of the trans-Δ^2-enoyl-CoA
- Odd numbered double bonds handled by isomerase



Oxidation of unsaturated fatty acids

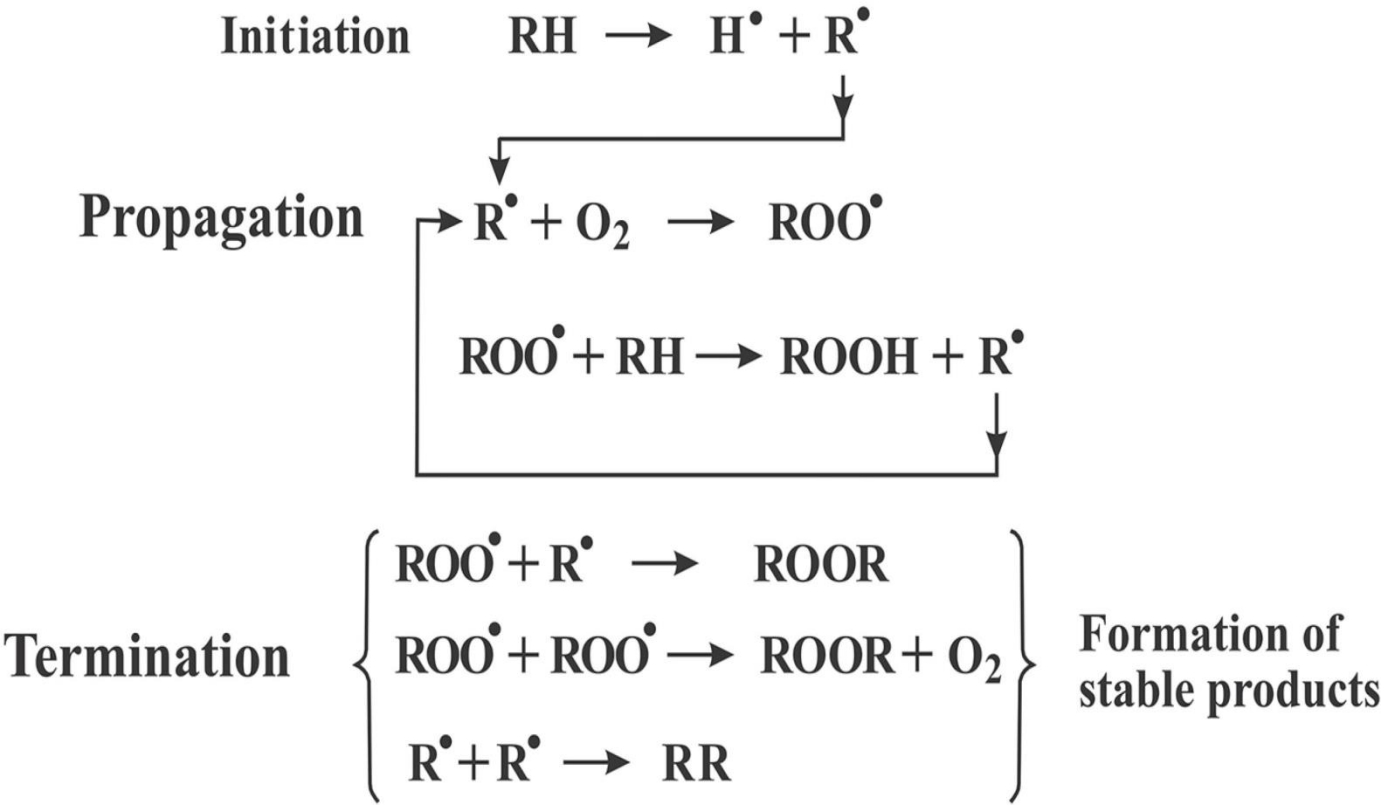
Δ^3*cis*$\rightarrow$ Δ^2-*trans*-enoyl-CoA isomerase

Lipid peroxidation

Lipid peroxidation is the result of damaging effect of reactive oxygen species (ROS) on polyunsaturated fatty acids which are constituents of membrane phospholipids

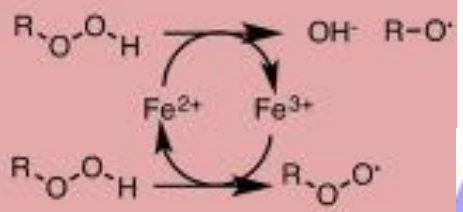
Lipid peroxidation

Lipid peroxidation is a chain reaction providing a continuous supply of ROS that initiate further peroxidation and thus has potentially devastating effects. The whole process can be depicted as follows:



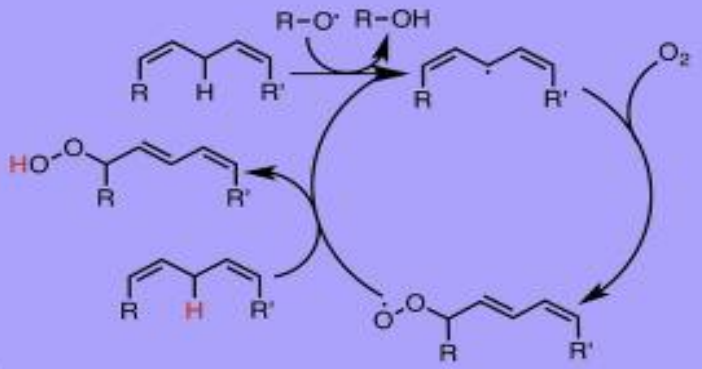
Lipid peroxidation

Initiation (Fenton Chemistry)

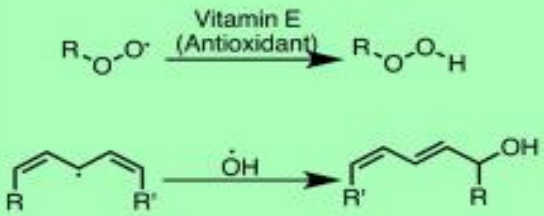


R= H or Alkyl PUFA

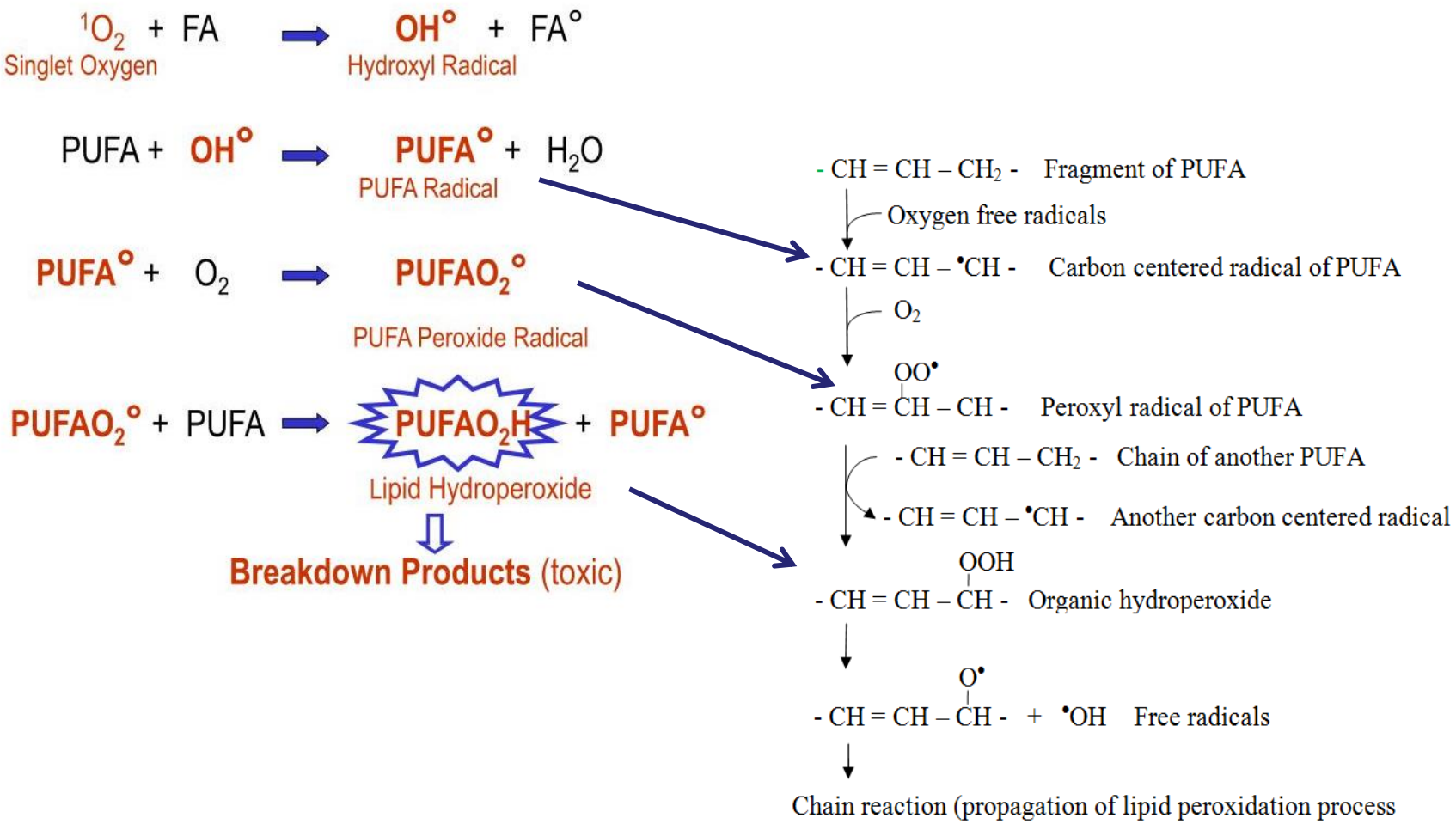
Propagation



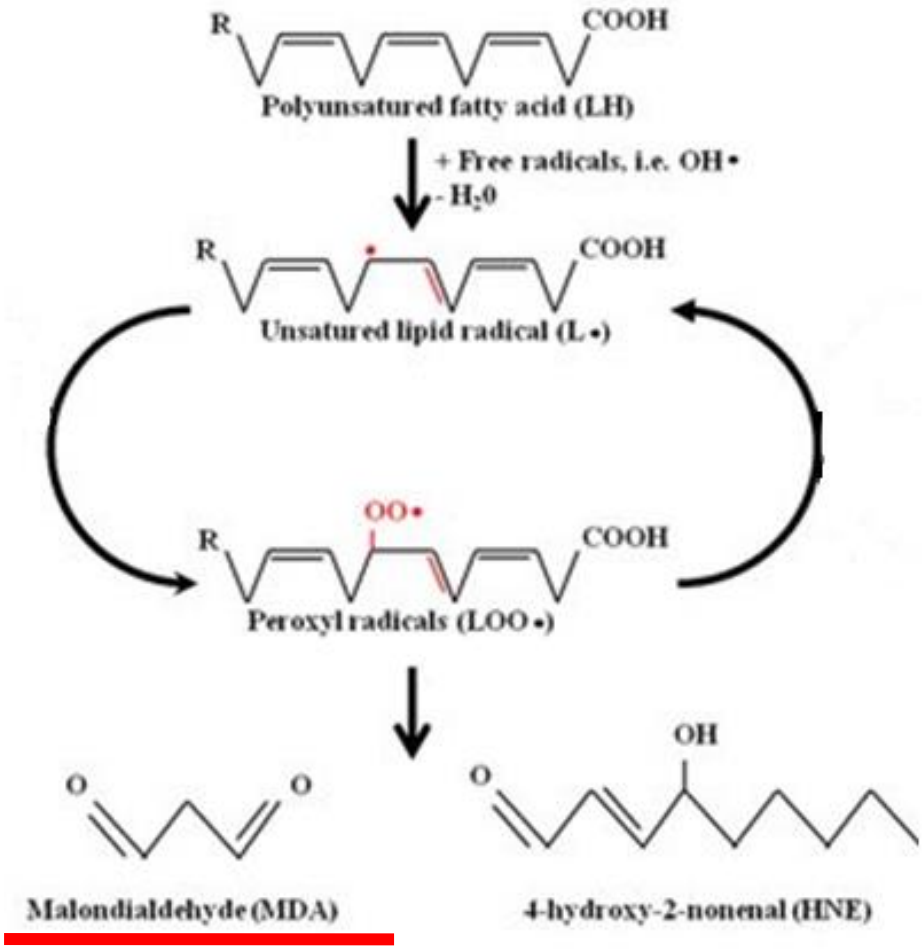
Termination



Lipid peroxidation



Lipid peroxidation



The reaction is initiated by an existing free radical (X•, R•), by light, or by metal ions.

Malondialdehyde is only formed by fatty acids with three or more double bonds and is used as **a measure of lipid peroxidation** together with ethane from the terminal two carbons of ω3 fatty acids and pentane from the terminal five carbons of ω6 fatty acids.

Lipid peroxidation

Peroxidation of lipids exposed to oxygen is responsible not only for deterioration of foods (rancidity), but also for damage to tissues *in vivo*, where it may be a cause of

cancer, inflammatory diseases, atherosclerosis, and aging

The deleterious effects are considered to be caused by free radicals, molecules that have unpaired valence electrons, making them highly reactive

Lipid peroxidation

To control and reduce lipid peroxidation, both humans in their activities and nature invoke the use of antioxidants.

Propylgallate, butylated hydroxyanisole, and butylated hydroxytoluene are antioxidants used as food additives. Naturallyoccurring antioxidants include vitamin E, which is lipid soluble, and urate and vitamin C, which are water soluble. Beta-carotene is an antioxidant at low PO_2.

Antioxidants fall into two classes:

(1) preventive antioxidants, which reduce the rate of chain initiation

(2) chain-breaking antioxidants, which interfere with chain propagation.