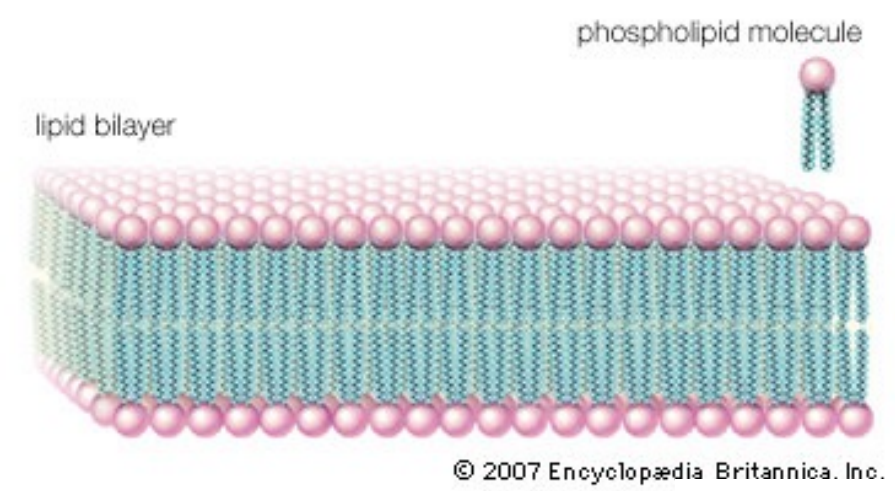
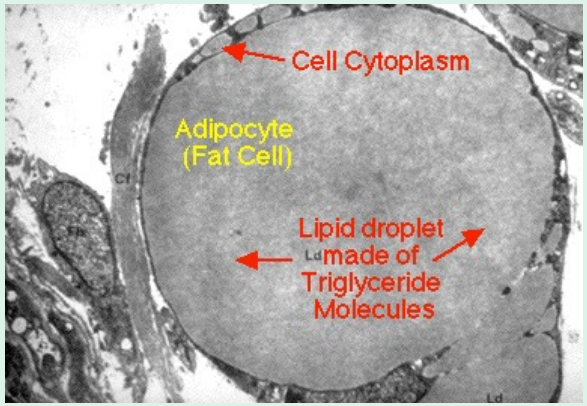
Biomolecules: lipids

Lipids: functions.

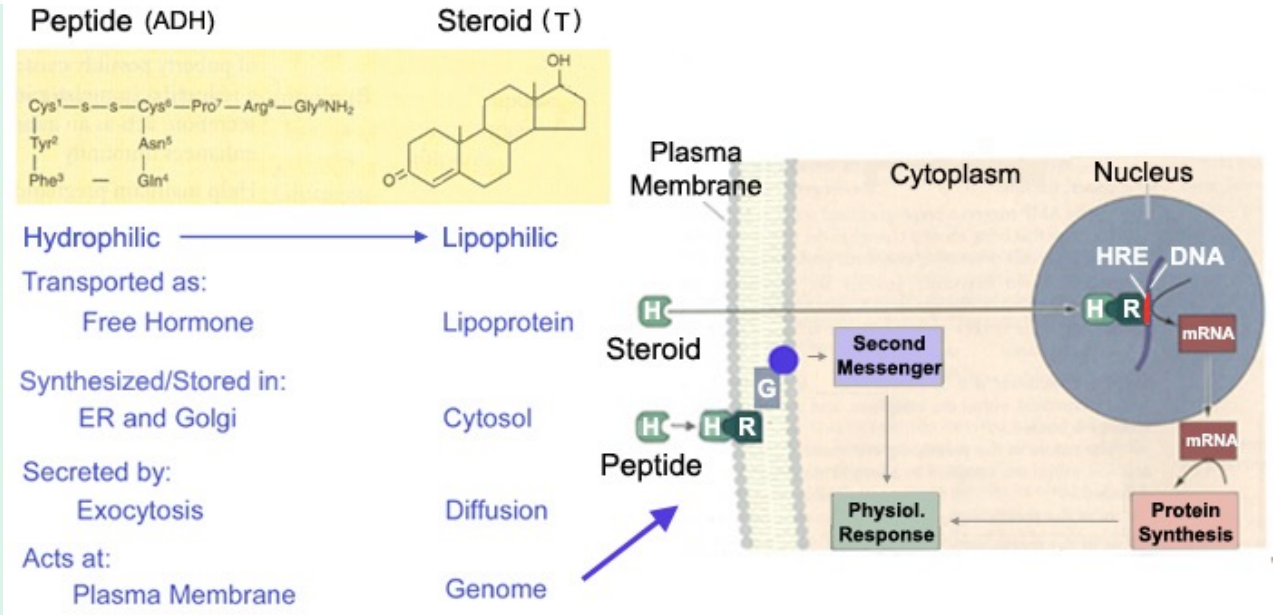
Structure





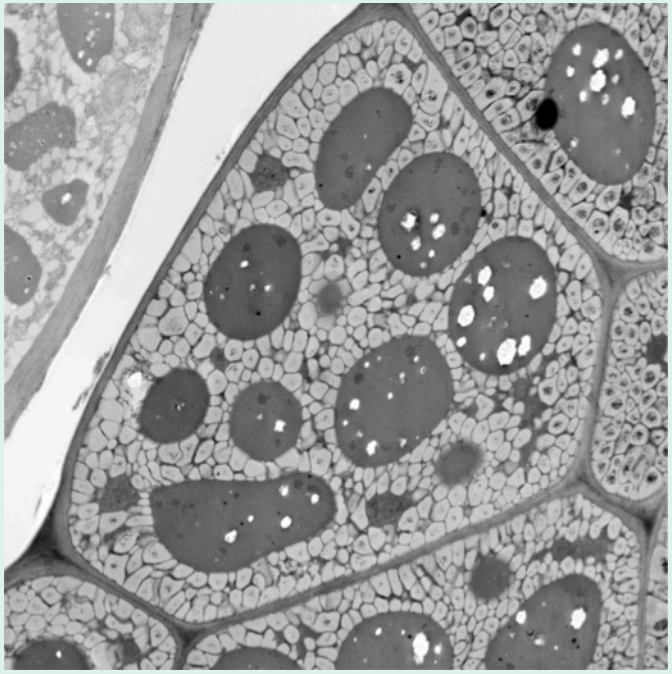
Energy storage

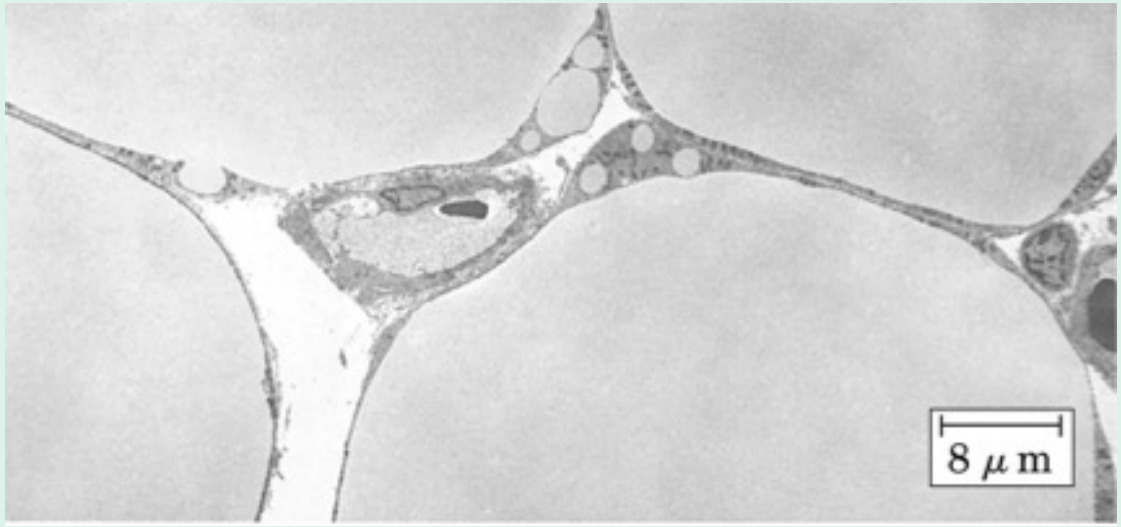
Signalling.



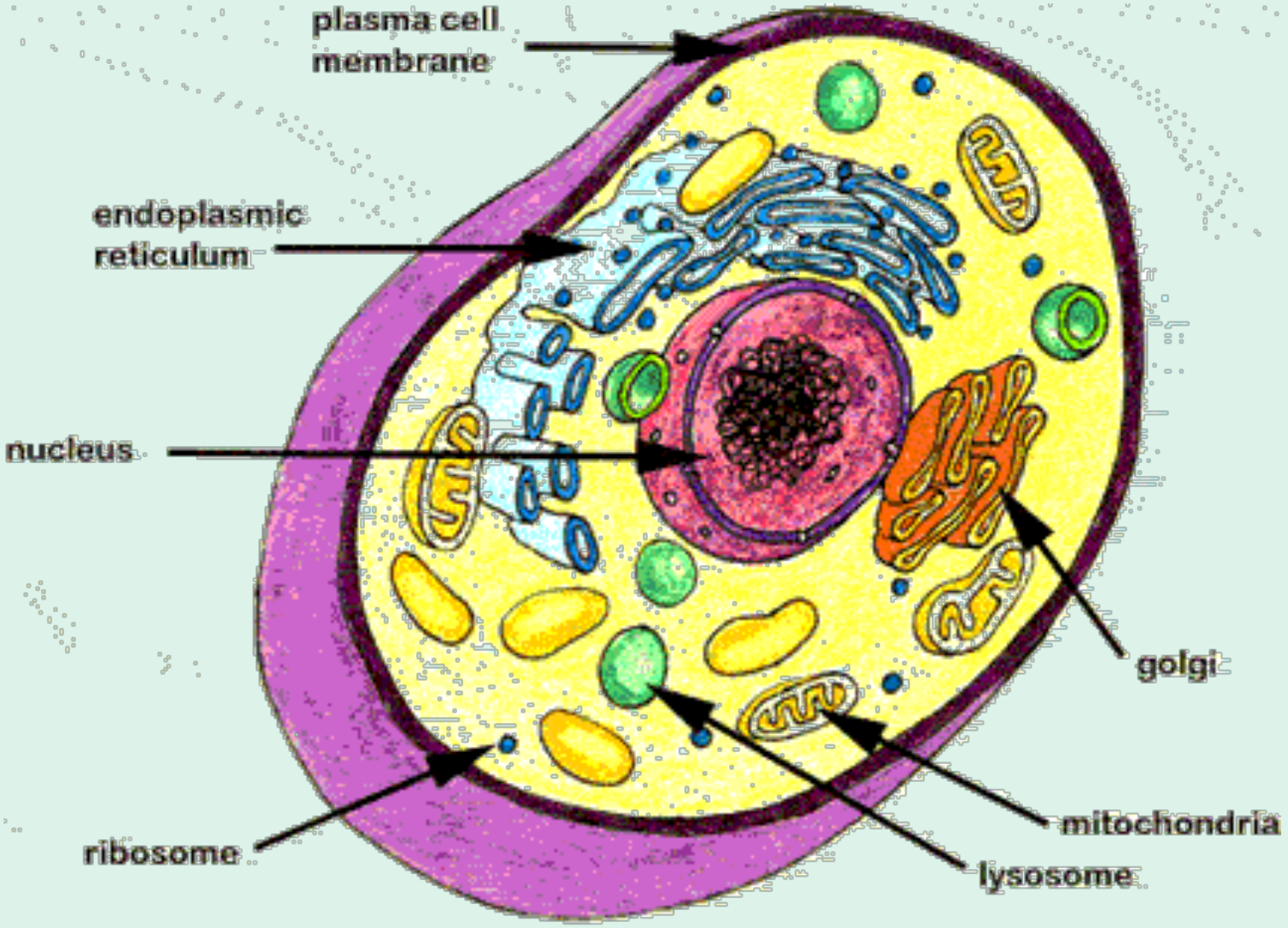
Organic biomolecules: lipids

- Organic amphiphilic compounds insoluble in water
- Easily extracted from animal and vegetal cells using apolar solvents
- Fundamental to build cell's shape and organelles
- They form a heterogeneous class, difficult to classify in a simple manner





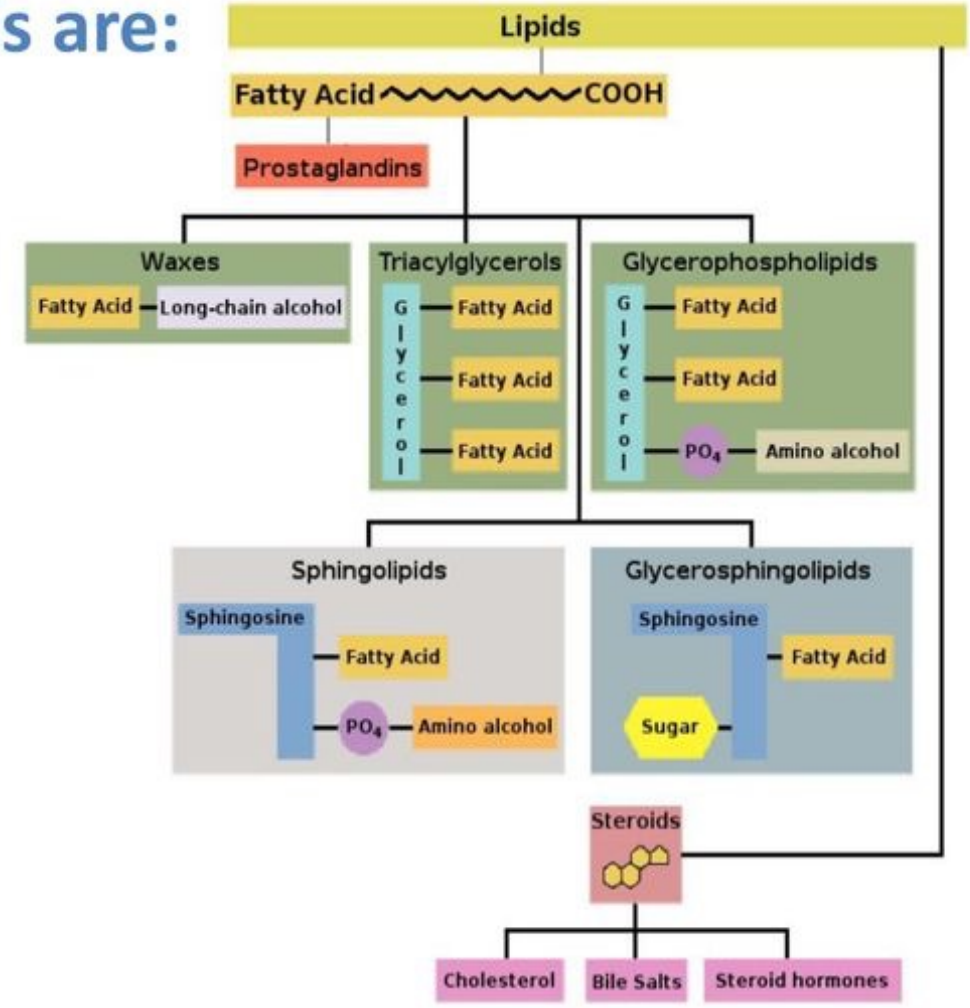
Compartmentalization is essential for a living cell



Lipids Classification

- **The major classes of lipids are:**

1. Fatty acids.
2. Triglycerols.
3. Glycerphospholipids.
4. Sphingolipids.
5. Steroids.



A short list of lipid classes

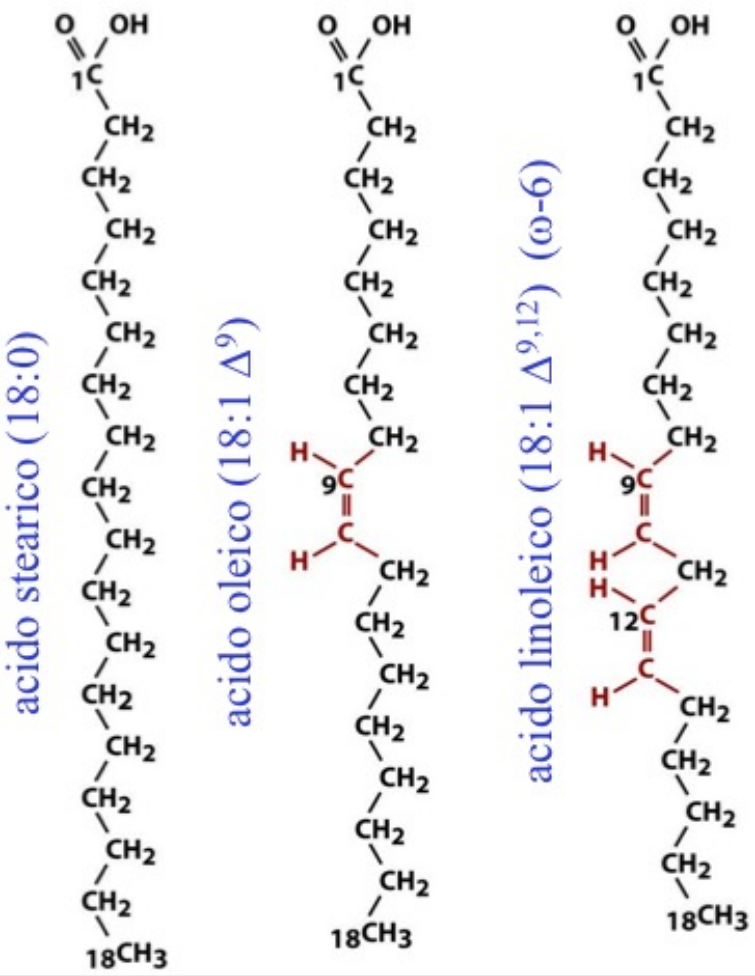
- **Fatty acids (FA)**: organic carboxylic acids with long carbon chains (C >7), saturated, unsaturated, subjected to esterification
- **Glycerides**: mono-, di-, tri-esters of fatty acids and glycerol
- **Ceramides**: esters of sphingosine and fatty acids
- **Phospholipids**: di-esters of glycerol-3-Phosphate or esters of sphingosine-phosphate
- **Cerebrosides (glycolipids)**: esters of sphingosine with 1 FA and 1 sugar with 6-C (hexose)
- **Gangliosides**: glycolipids in which the sugar moiety is complex and branched
- **Steroids:** derivatives of cholesterol **(**cicle-pentane-peri-hydro-phenanthrene**)**
- **Terpenoids**: compounds made by repetitions of isoprenes units (2-methyl-butadiene)

Heat (energy) production

Compound	Kcal/g
Methane	13.3
Octane	11.5
Stearic Acid (lipids)	9.5
Alanine (protein)	4.4
Glucose (sugars)	3.7

Lipids allow efficient energy storage, also due to the fact that they are stored in an anhydrous manner.

The most common FAs in biological membranes



In the membrane there are always FA with an even number of C.

In case there are, double bonds are always in cis configuration.

The old notation ω-3, ω-6 and ω-9 refers to the position of the first double bond, counting how many carbon atoms are left before the end

Some naturally occurring Fatty Acids

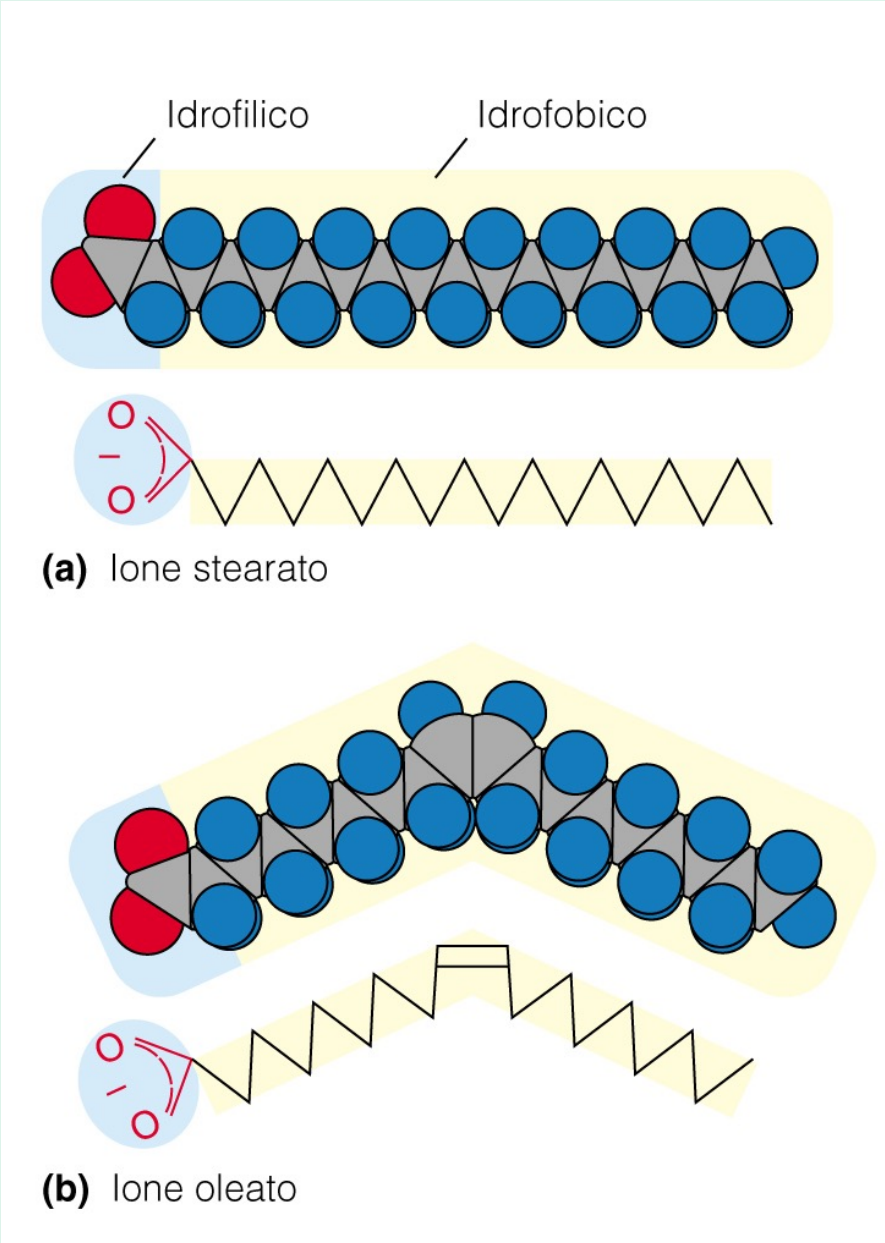
Carbon skeleton	Structure*	Systematic name†	Common name (derivation)	Melting point (°C)
12:0	$CH_3(CH_2)_{10}COOH$	*n*-Dodecanoic acid	Lauric acid (Latin *laurus*, "laurel plant")	44.2
14:0	$CH_3(CH_2)_{12}COOH$	*n*-Tetradecanoic acid	Myristic acid (Latin *Myristica*, nutmeg genus)	53.9
16:0	$CH_3(CH_2)_{14}COOH$	*n*-Hexadecanoic acid	Palmitic acid (Latin *palma*, "palm tree")	63.1
18:0	$CH_3(CH_2)_{16}COOH$	*n*-Octadecanoic acid	Stearic acid (Greek *stear*, "hard fat")	69.6
20:0	$CH_3(CH_2)_{18}COOH$	*n*-Eicosanoic acid	Arachidic acid (Latin *Arachis*, legume genus)	76.5
24:0	$CH_3(CH_2)_{22}COOH$	*n*-Tetracosanoic acid	Lignoceric acid (Latin *lignum*, "wood" + *cera*, "wax")	86.0
16:1(Δ^9)	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	*cis*-9-Hexadecenoic acid	Palmitoleic acid	−0.5
18:1(Δ^9)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	*cis*-9-Octadecenoic acid	Oleic acid (Latin *oleum*, "oil")	13.4
18:2($\Delta^{9,12}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis*-,*cis*-9,12-Octadecadienoic acid	Linoleic acid (Greek *linon*, "flax")	−5
18:3($\Delta^{9,12,15}$)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis*-,*cis*-,*cis*-9,12,15-Octadecatrienoic acid	α-Linolenic acid	−11
20:4($\Delta^{5,8,11,14}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	*cis*-,*cis*-,*cis*-,*cis*-5,8,11,14-Icosatetraenoic acid	Arachidonic acid	−49.5

INSATURATED FATTY ACIDS always have the *cis* form of the double bonds.

Angle of about 30.

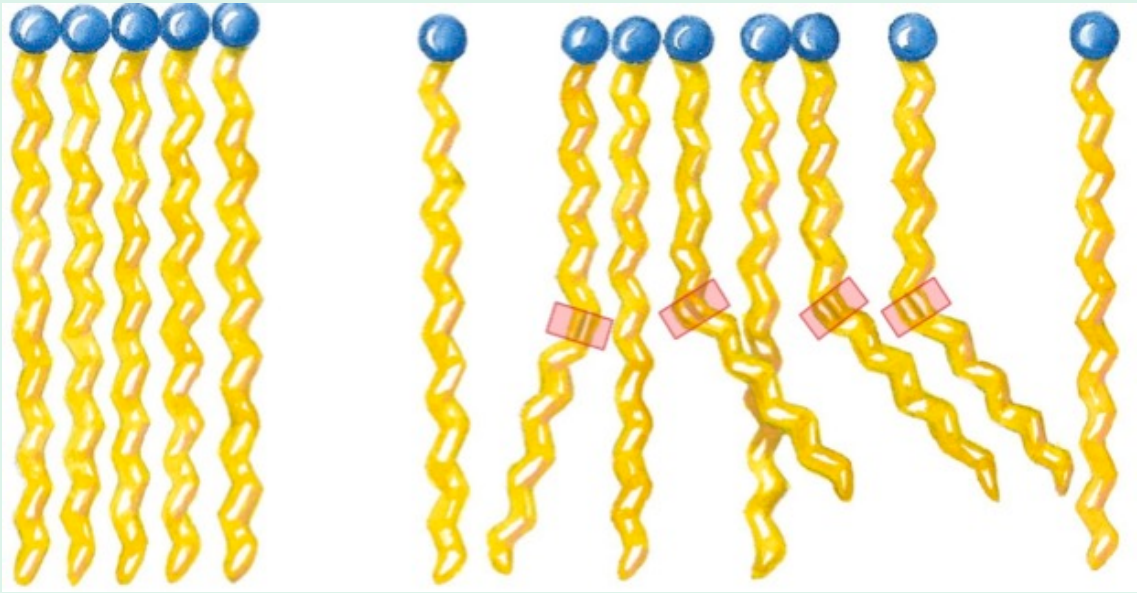
The larger the number of cis bonds,
the lower the possibility to form
Vdw interactions (lower melting points).

Free fatty acids are normally absent in the cell.



FAs packing

- 3D packing or assembly of FAs depends on the degree of unsaturation (no. of double bonds)
- The main consequence of this packing is the melting temperature: saturated FAs are solid at RT, unsaturated FAs have lower Tm)
- FAs spontaneously assemble in aqueous solutions in order to decrease the hydrophobic effect of water



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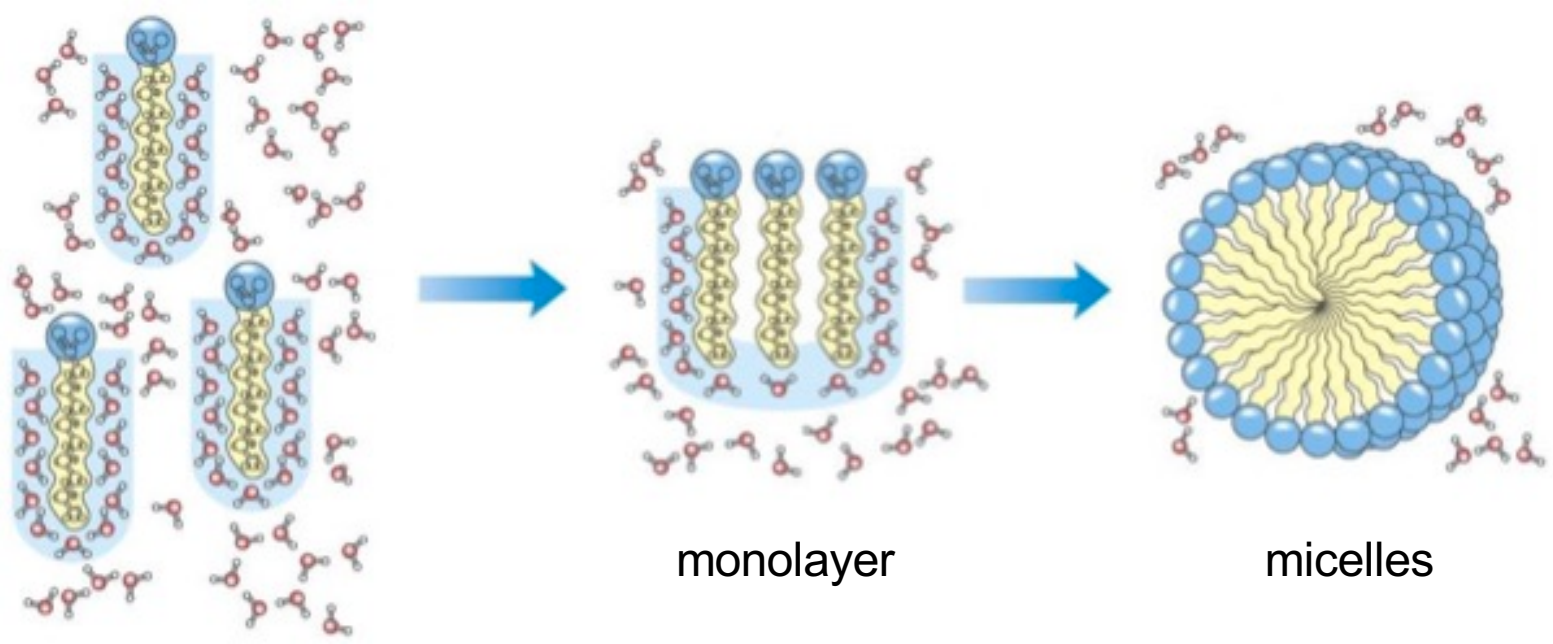
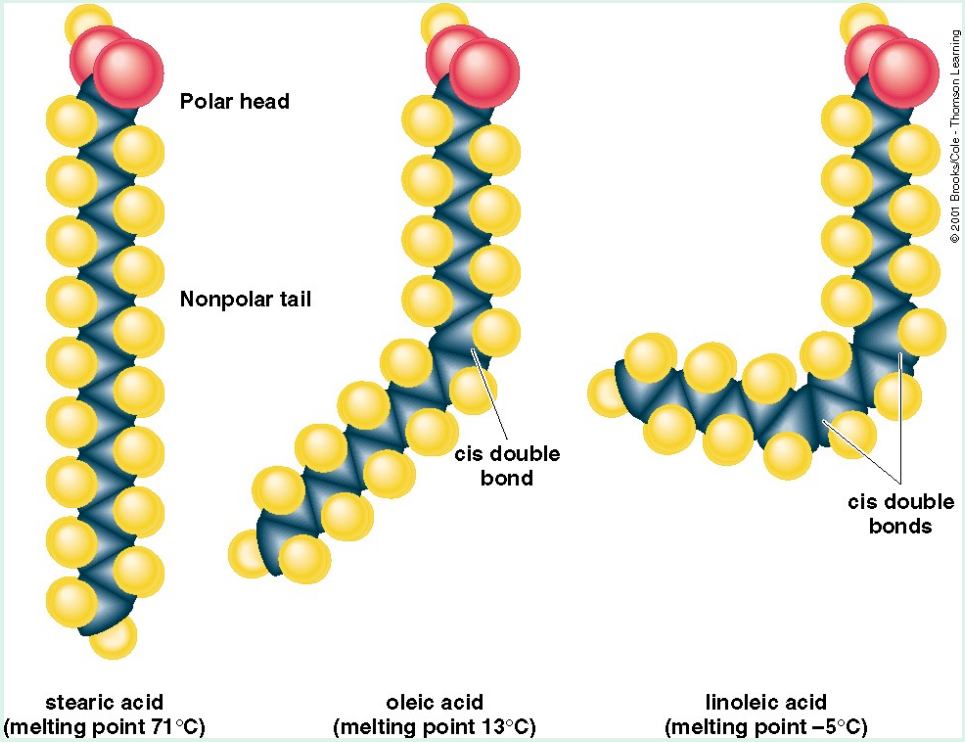


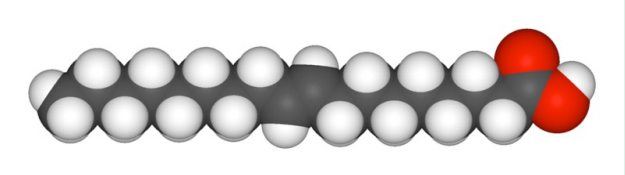
Melting point increases with molecular mass and decreases with the degree of insaturation.



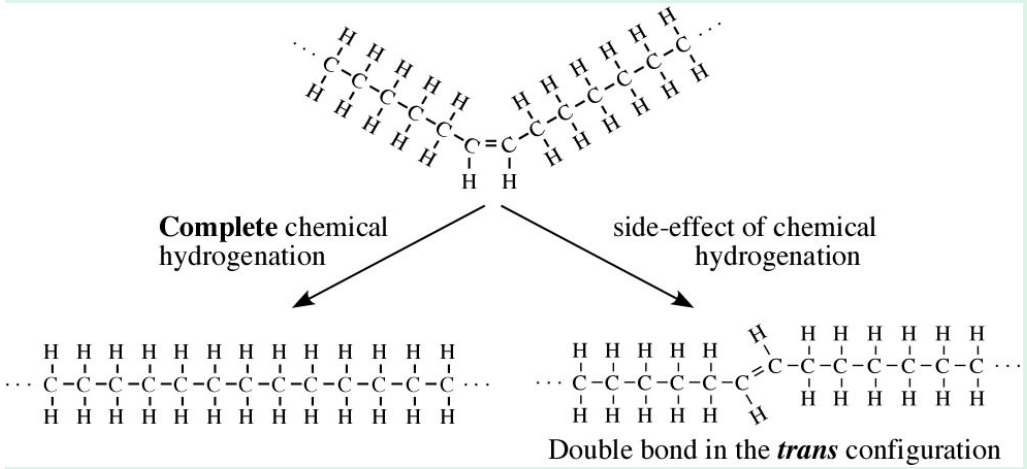
Fatty acids from plants tend to have a higher degree of insaturation and are liquid at room temperature,

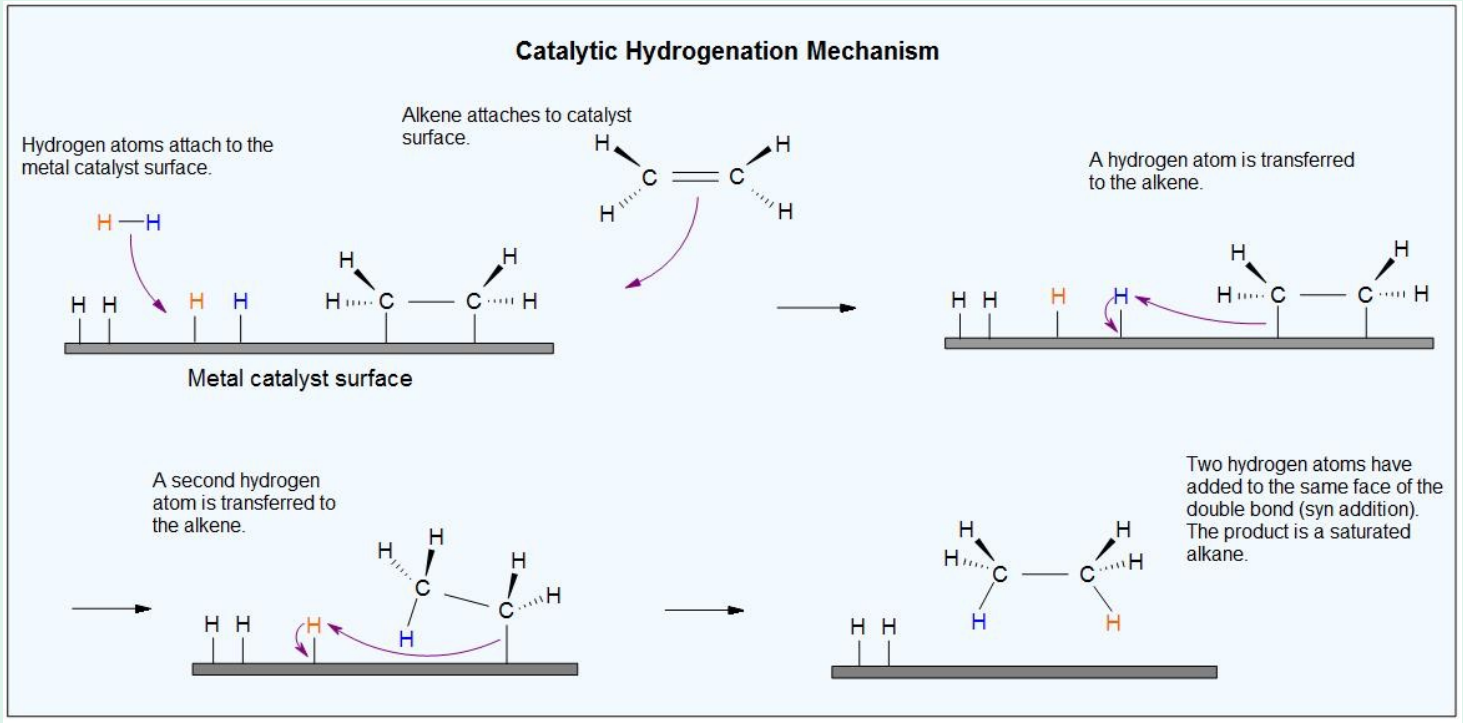
By industrial hydrogenation, oils from plants becaome solid at r.t. (higher melting point).
Trans double bonds are introduced.

Acido elaidico (trans)



Lipid hydrogenation



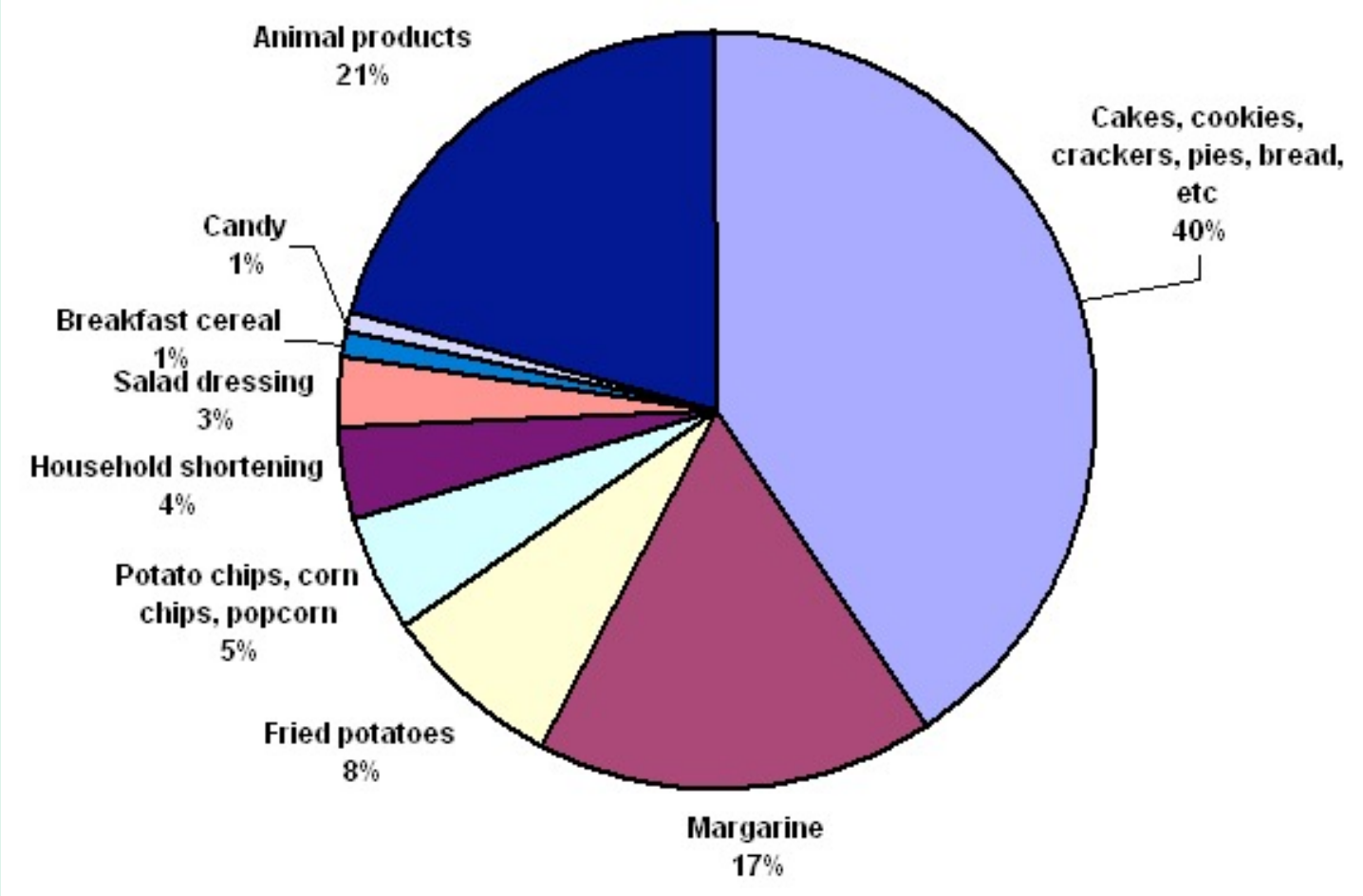


The partial hydrogenation of fats with industrial methods leads to the formation of unsaturated lipids in trans configuration.

Reaction with numerous applications, especially in the treatment of oils and fats in the food industry; through a partial hydrogenation the vegetable oils, normally liquid, are converted into solid or semi-solid fats (such as margarine).

Typically, the reagent used is gaseous hydrogen, H_2, in the presence of metal catalysts such as Ni, Pd or Pt. The reaction is generally carried out under rather drastic conditions, at high temperatures and pressures.

Main dietary sources of trans fats for the adult American population. Average intake of trans fat equal to 5.8 g (2.6% of total calories).



As early as 1988 there were suggestions in the scientific literature that trans fats could be a cause of the large increase in coronary artery disease. In 1994, it was estimated that trans fats caused 20,000 deaths annually in the US from heart disease.

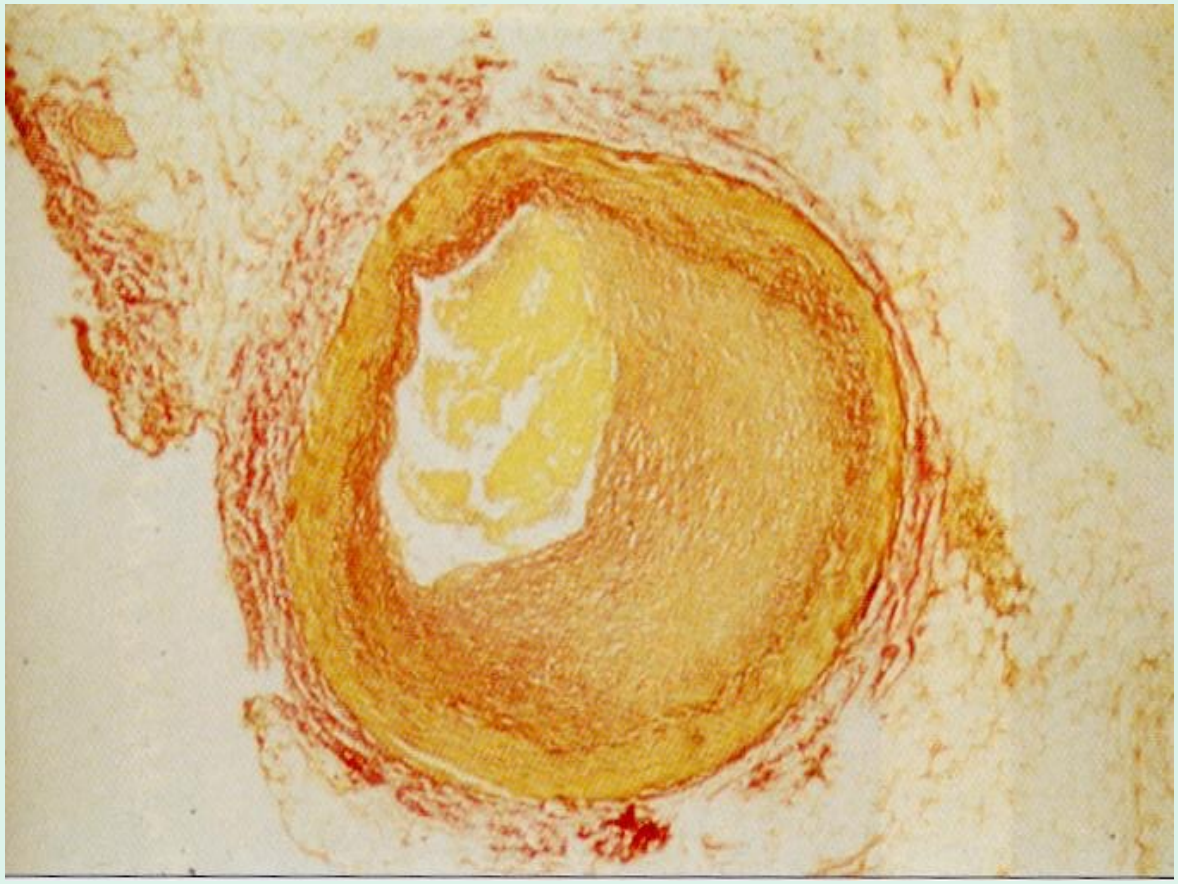
1. Food and nutrition board, institute of medicine of the national academies (2005). *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. National Academies Press. p. 423.

2. Food and nutrition board, institute of medicine of the national academies (2005). *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. National Academies Press. p. 504.

3. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC (April 13, 2006). "Trans Fatty Acids and Cardiovascular Disease". New England Journal of Medicine 354 (15): 1601–1613.

Trans unsaturated fats increase the risk of chronic cardiovascular disease by inducing an increase in LDL cholesterol and a decrease in HDL cholesterol.

Atherosclerotic deposit



The biochemical mechanism that leads to the increased risk of chronic cardiovascular disease related to the intake of trans fats is not clear. It is hypothesized that since they are not recognized by lipases, they remain in circulation for longer, increasing the formation of atherosclerotic plaques.

Pancreatic Lipase

"On a per-calorie basis, trans fats appear to increase the risk of CHD more than any other macronutrient, conferring a substantially increased risk at low levels of consumption (1 to 3% of total energy intake)". The study (3) estimates that between 30,000 and 100,000 cardiac deaths per year in the United States are attributable to the consumption of trans fats.

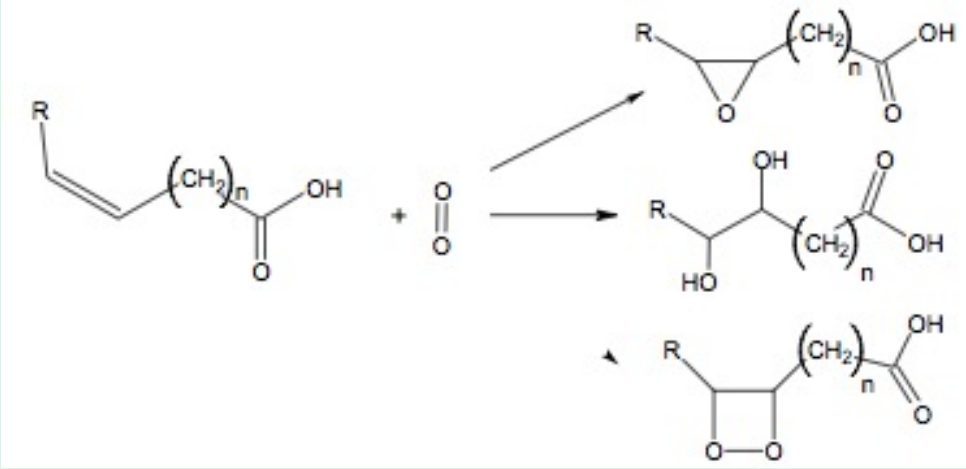
- Denmark (since 2003) has regulated the trans fat content, it cannot exceed 2% in the single ingredient. A 50% reduction in chronic cardiovascular diseases is expected.
- Switzerland adopted the same limits in 2008.
- New York City and California imposed a declaration of hydrogenated fats contents in restaurants.

FATTY ACIDS REACTIONS

- They are weak acids with Ka 10^{-5} – 10^{-6}, decreasing with increasing chain length
- They can form:
  - esters after reacting with alcohols
  - amides after reacting with amines
  - salts after reacting with a strong base (NaOH / KOH)
- They can be oxidised by enzymes to release energy (beta-oxidations)

Which reactions do FAs undergo?

- Unsaturated FAs can also be oxidised by oxygen radicals, giving rise to epoxides, di-oles, peroxides
- These byproducts are degraded into aldehydes and short chain FA, and are responsible for the bad smell/taste of out-of-date fat

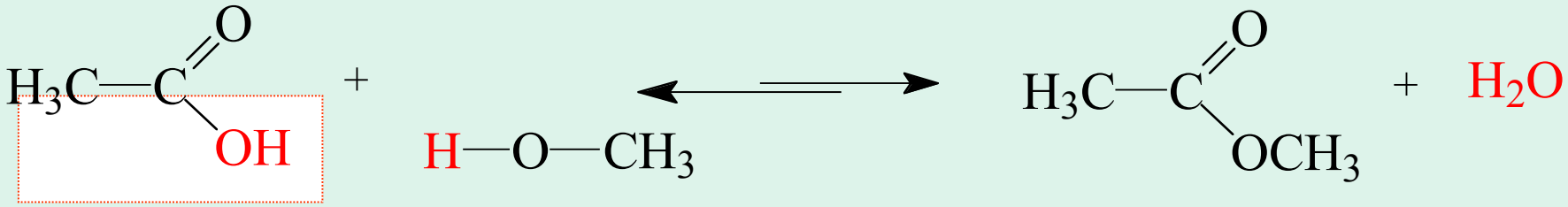


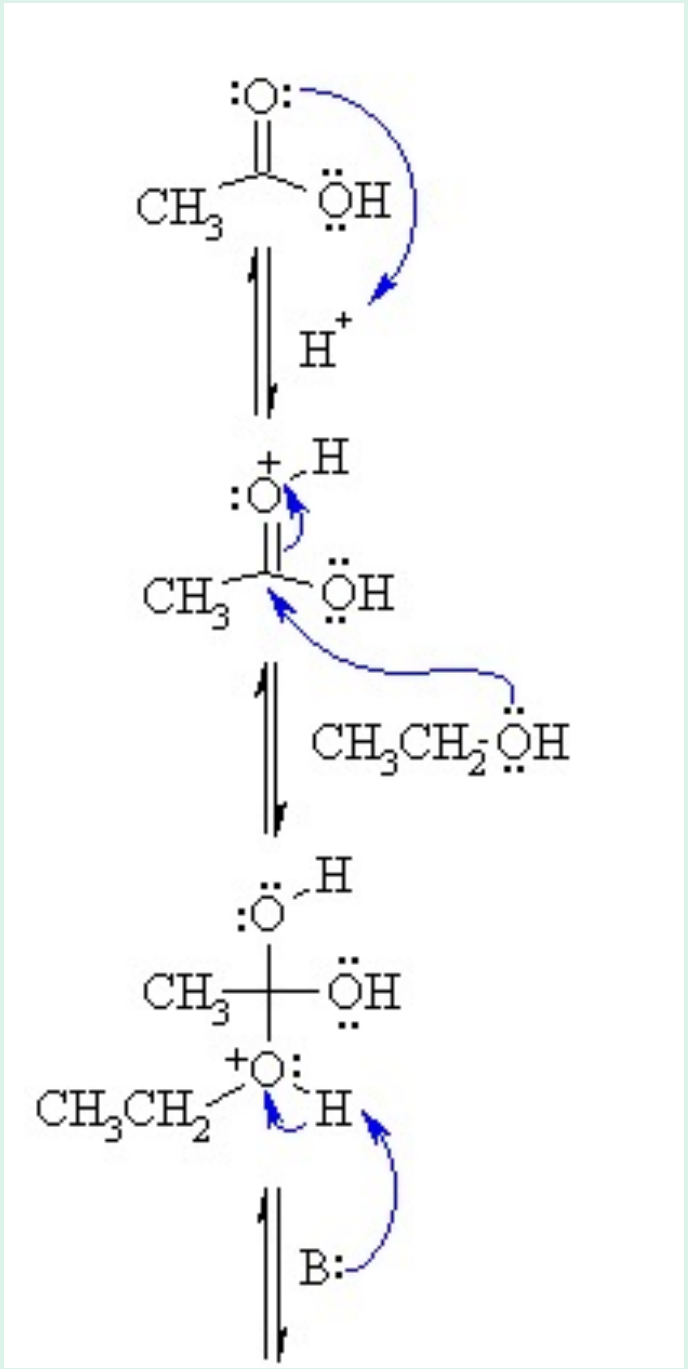
epoxide

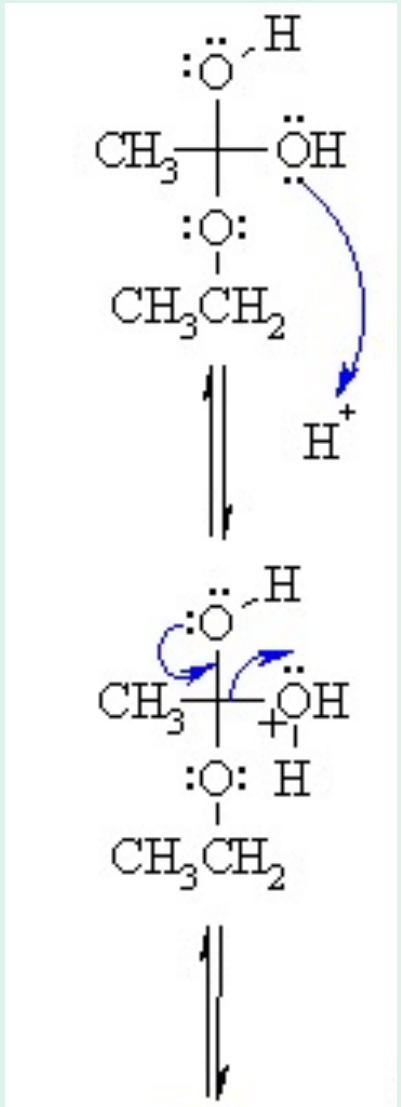
di-ole

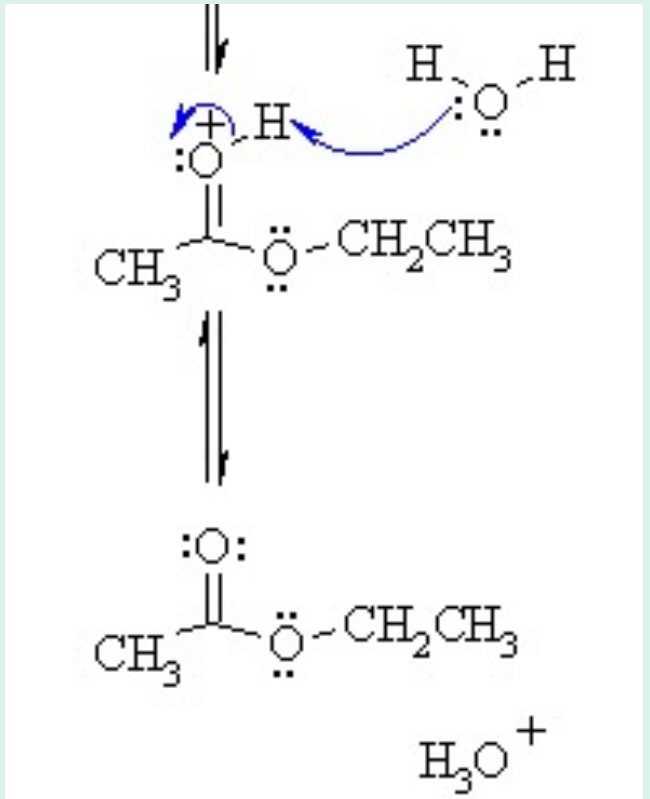
peroxide

Carboxylic acid + alcohol= esther



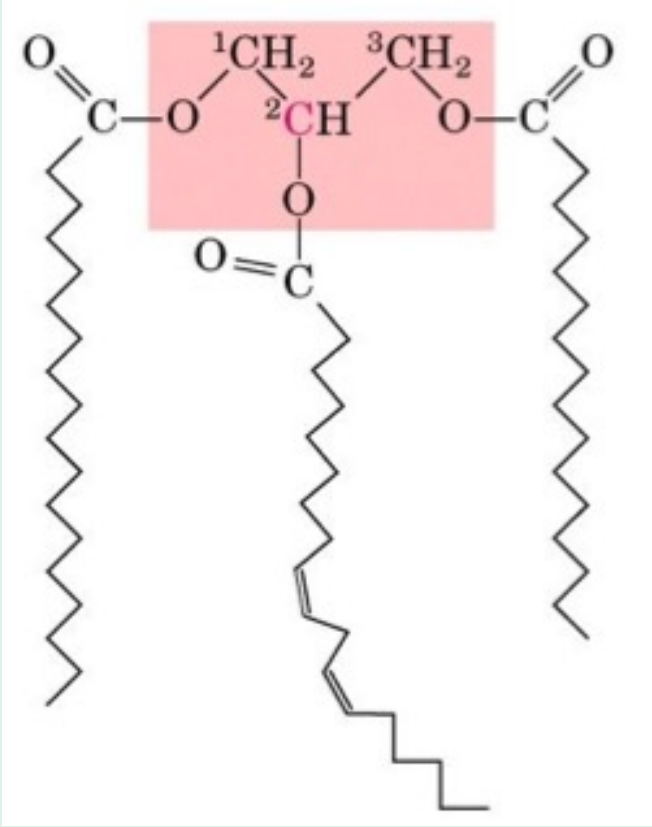

CH3
OH
H+
CH3CH2
OH
B:

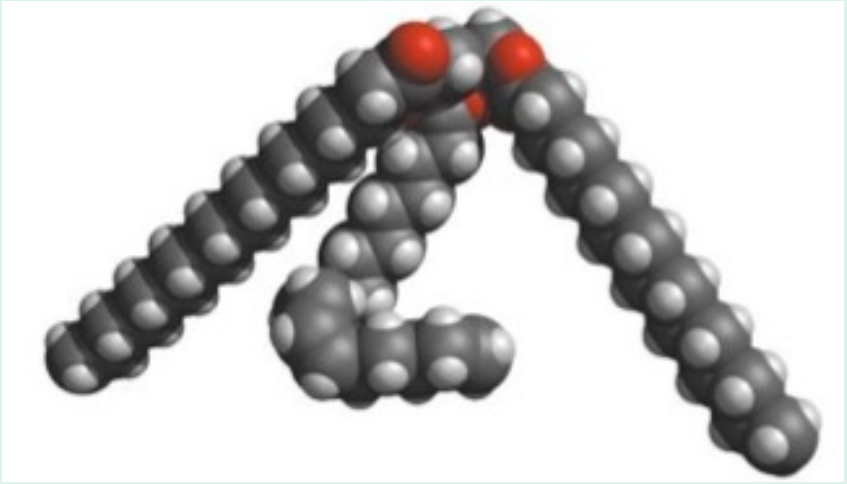

H
CH3
OH
CH3CH2
H+
CH3
OH
H
CH3CH2


H
H
H
CH3
CH2CH3
CH3
CH2CH3
H3O+

Mono-, di- and tri-glycerides

- Esters of FA(s) with glycerol (1,2,3-propan-tri-ole)
- Triglycerides are neutral lipids used for storage, they are confined in specialised vacuoles of special cells (adipose cells)

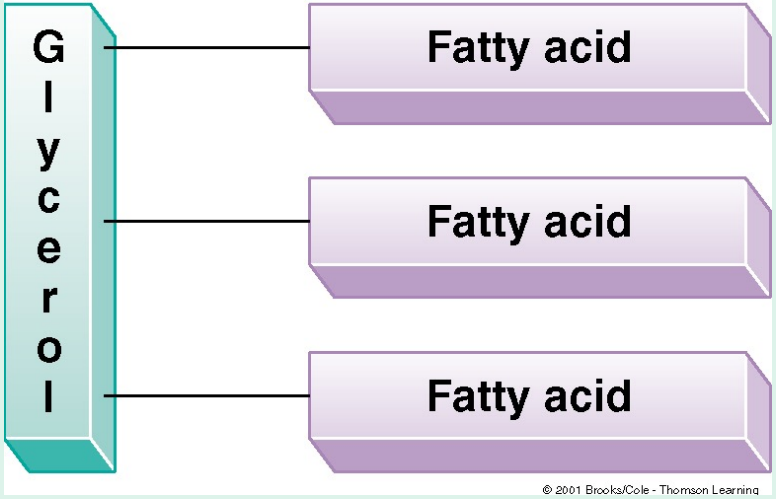


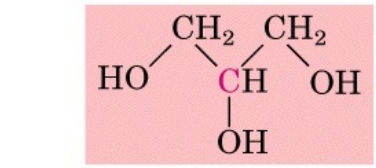


1-stearoyl-2-linoleyl-3-palmitoyl-glycerol

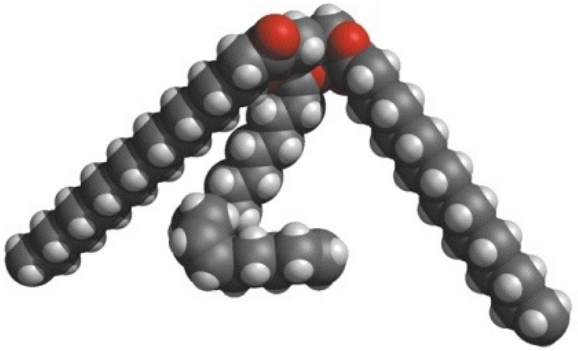
Triglycerides are energy storage molecules in the adipocytes.

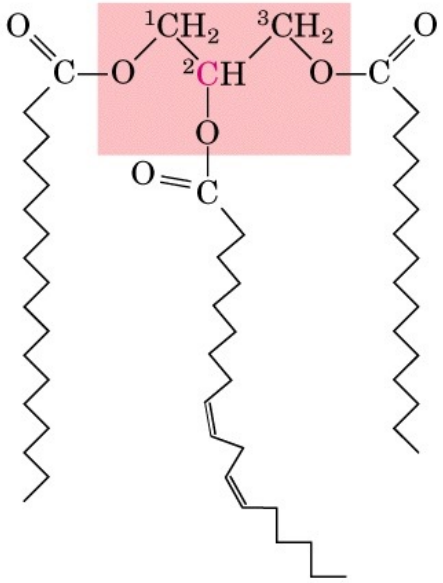
The following diagram may help you remember the components of a triglyceride.





Glycerol



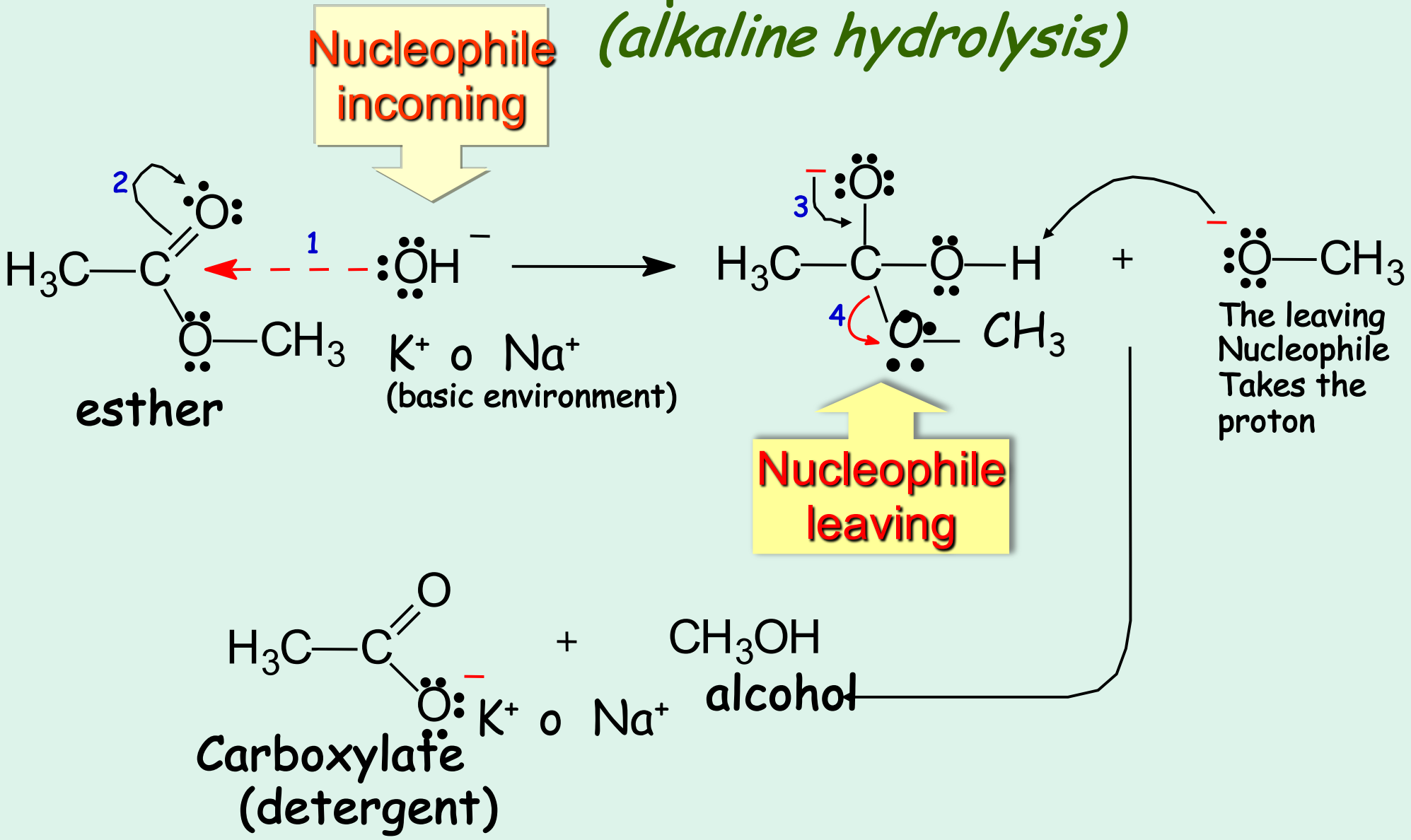


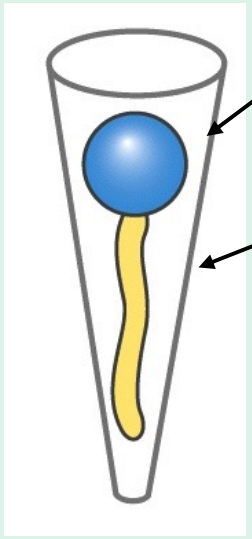
1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol

Soap production

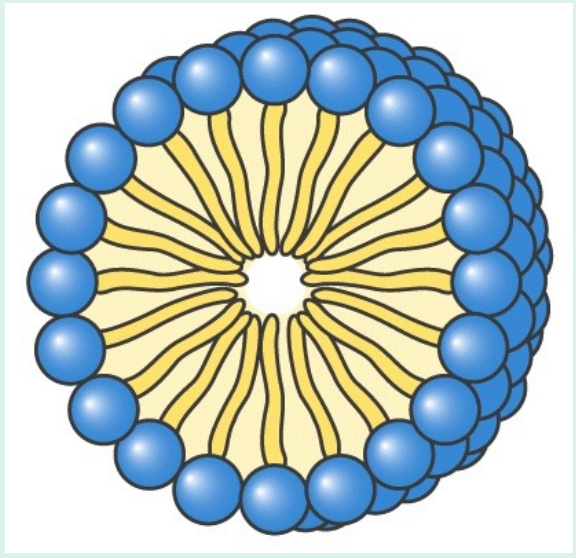
- Soap is the sodium / potassium salt of long chain FAs
- It is produced from either animal or vegetal fat
- The reaction is an alkaline hydrolysis performed at high temperature
- This reaction produces 1 mol of glycerol and 3 mol of salt per 1 mol of triglyceride
- The % of unsaturated FA and presence of additives give solid or liquid soap at room temperature

Saponification Reaction
(alkaline hydrolysis)

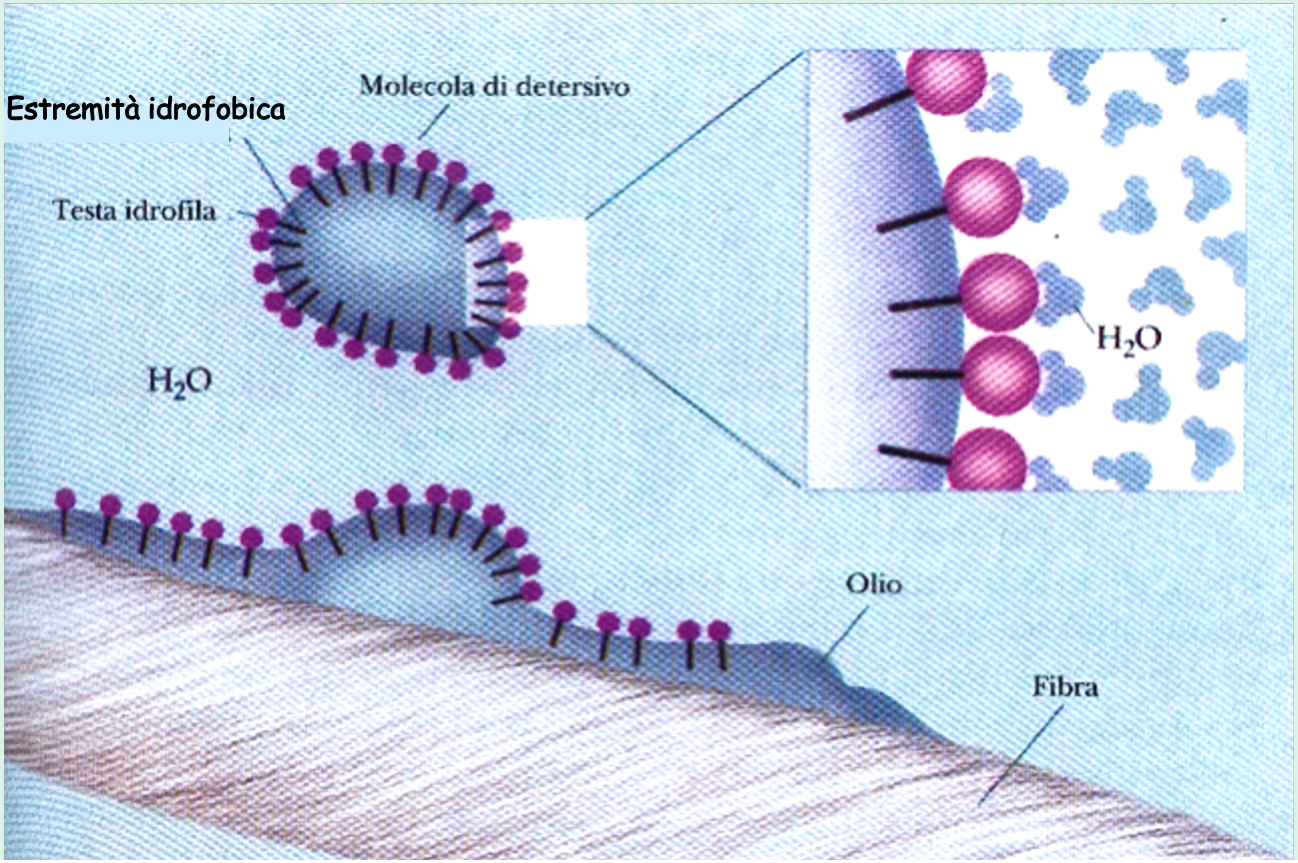




Detergent activity (soap)
(soap=fatty acid salt)



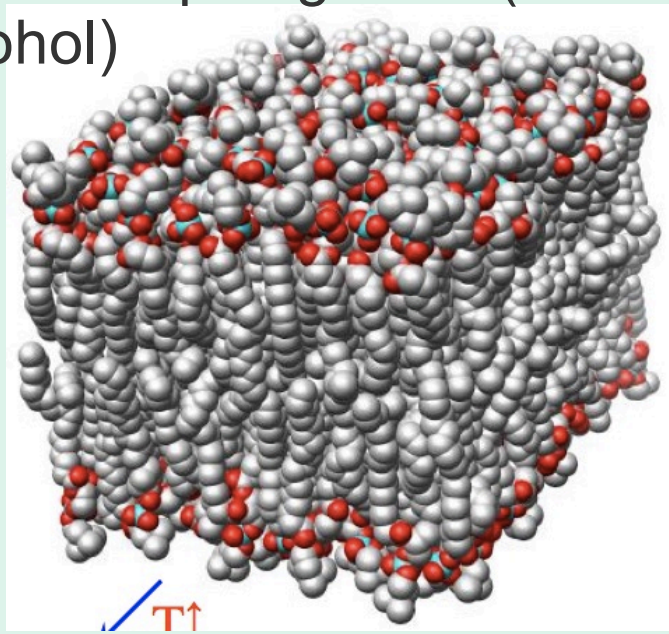
micella



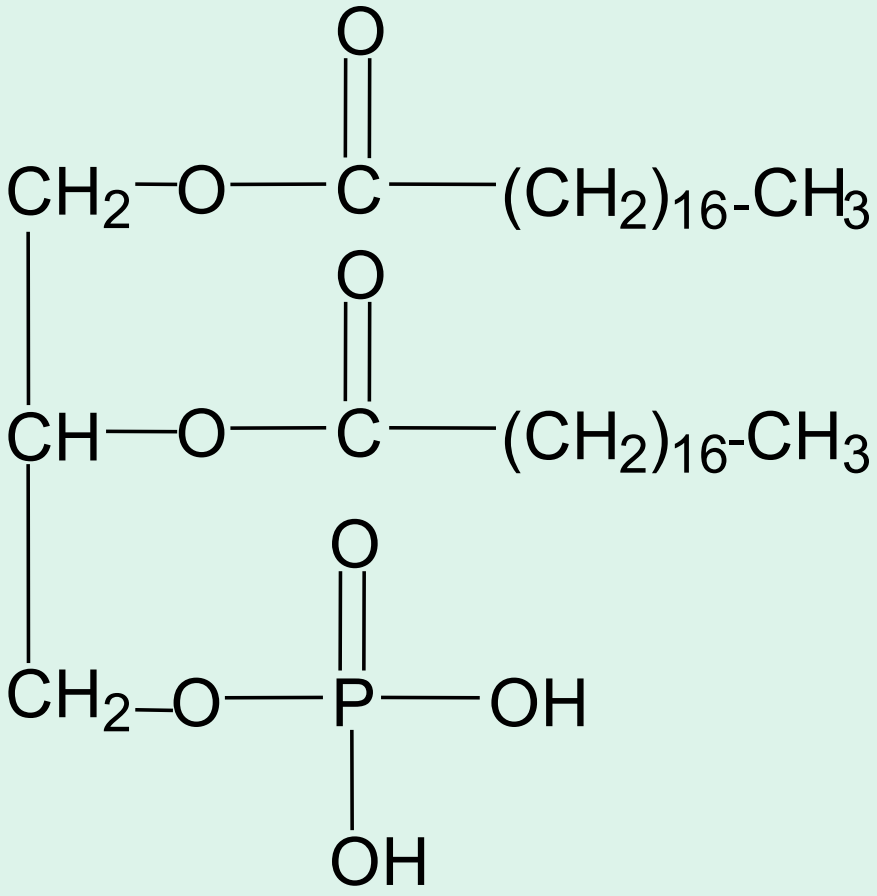
Phospholipids

- These molecules are the scaffold of the membrane lipid bilayer and contain a polar head

- The term phospholipids include two types of polar lipids present in biological membranes:
  - **Glycerol-phospholipids**, synthesized starting from glycerol-3-phosphate (G3P, an intermediate of glucose metabolism)
  - **Sphingolipids**, synthesized from sphingosine (a complex aliphatic amino-alcohol)

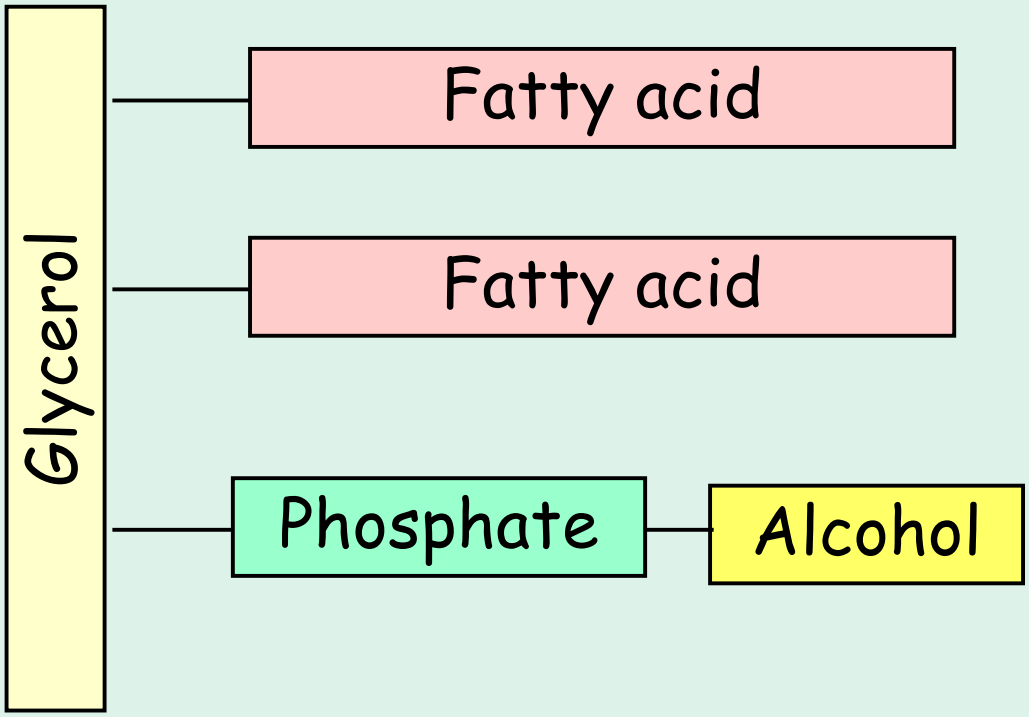


Phosphatidic acid: esther of glycerol with phosphoric acid and two fatty acids



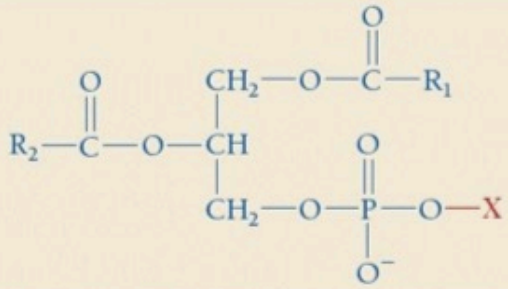
Phosphoglycerides

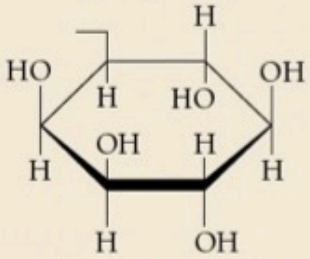
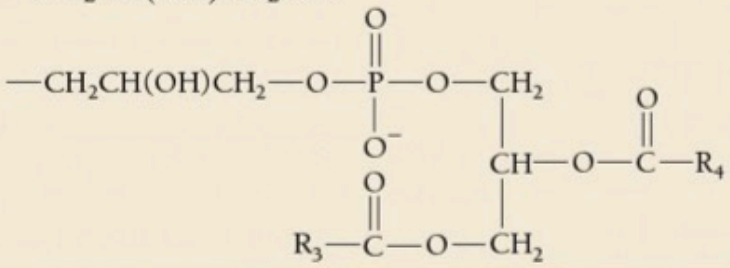
Glycerol + 2 fatty acids+ phosphate + alcohol



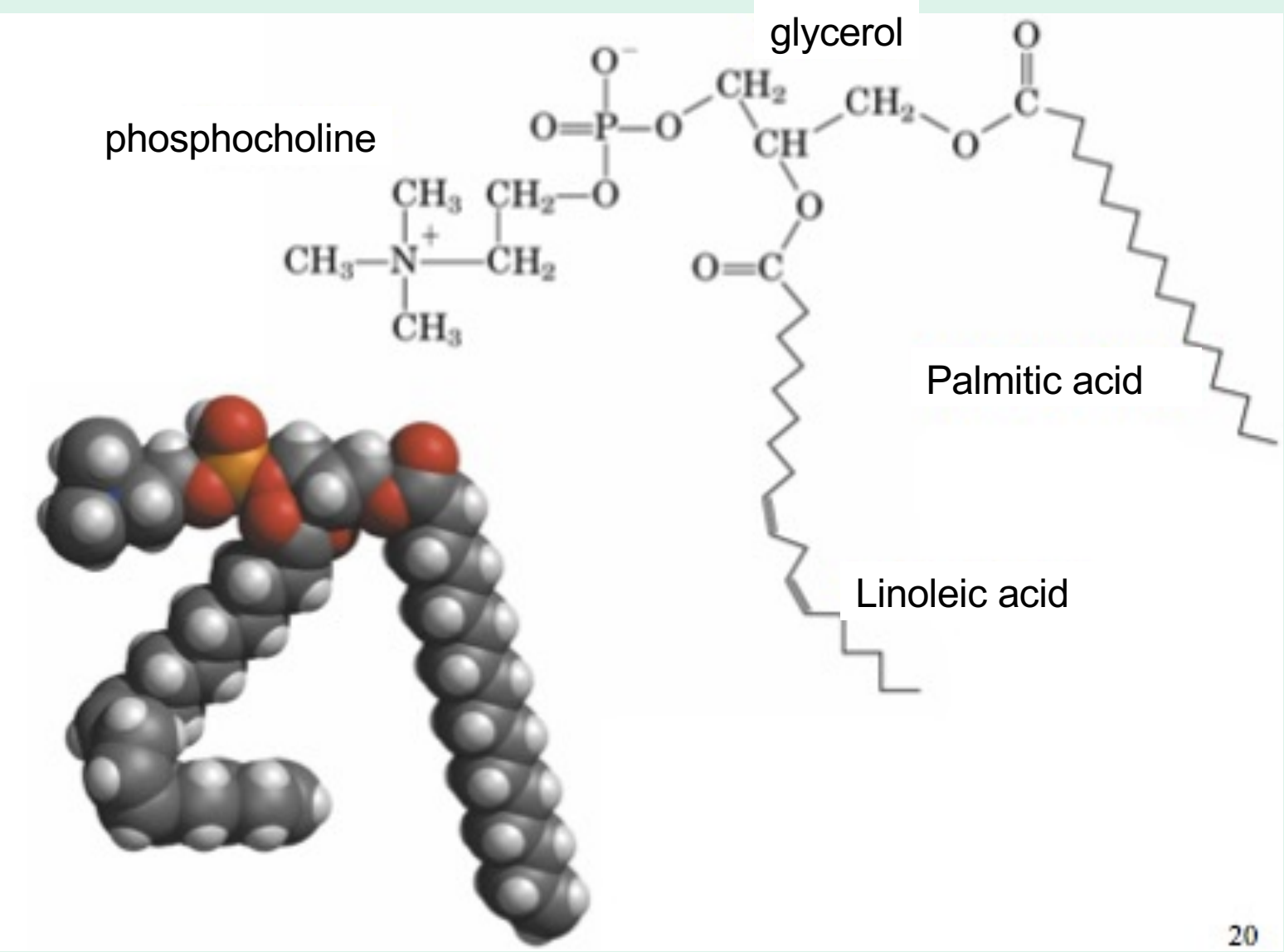
In phosphglycerides a fourth (polar/charged) component is bound to the phosphate..

Common classes of glycerophospholipids

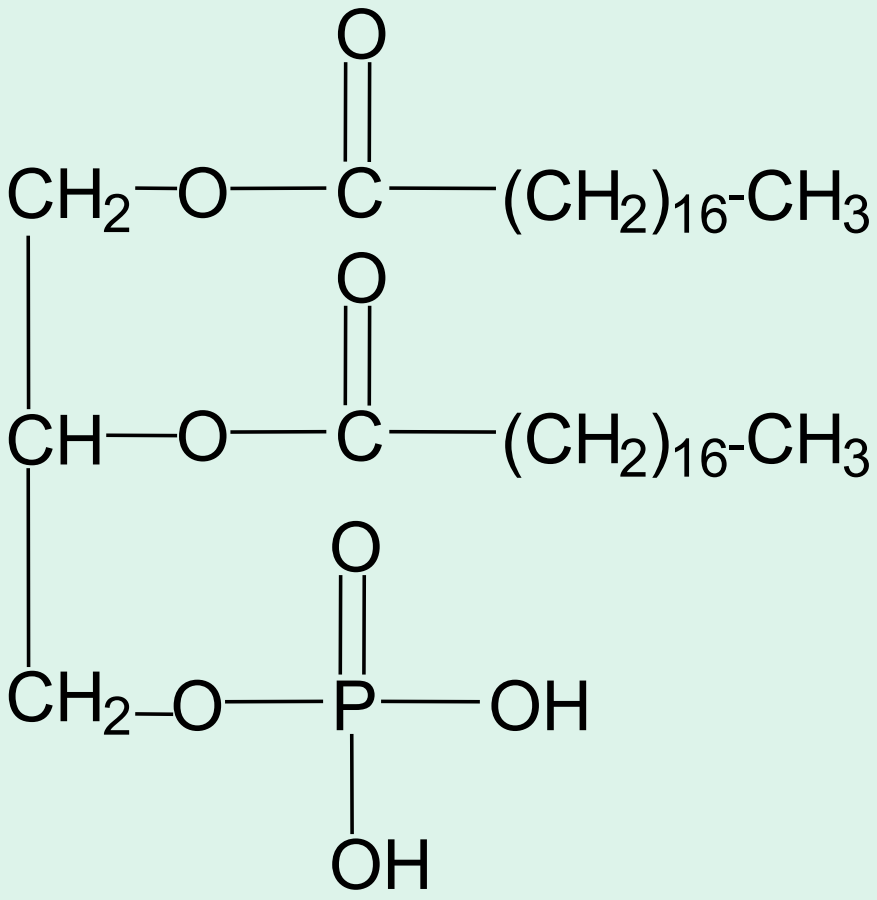


Name of X—OH	Formula of −X	Name of Phospholipid
Water	—H	Phosphatidic acid
Ethanolamine	$-CH_2CH_2NH_3^+$	Phosphatidylethanolamine
Choline	$-CH_2CH_2N(CH_3)_3^+$	Phosphatidylcholine (lecithin)
Serine	$-CH_2CH(NH_3^+)COO^-$	Phosphatidylserine
myo-Inositol		Phosphatidylinositol
Glycerol	$-CH_2CH(OH)CH_2OH$	Phosphatidylglycerol
Phosphatidylglycerol		Diphosphatidylglycerol (cardiolipin)

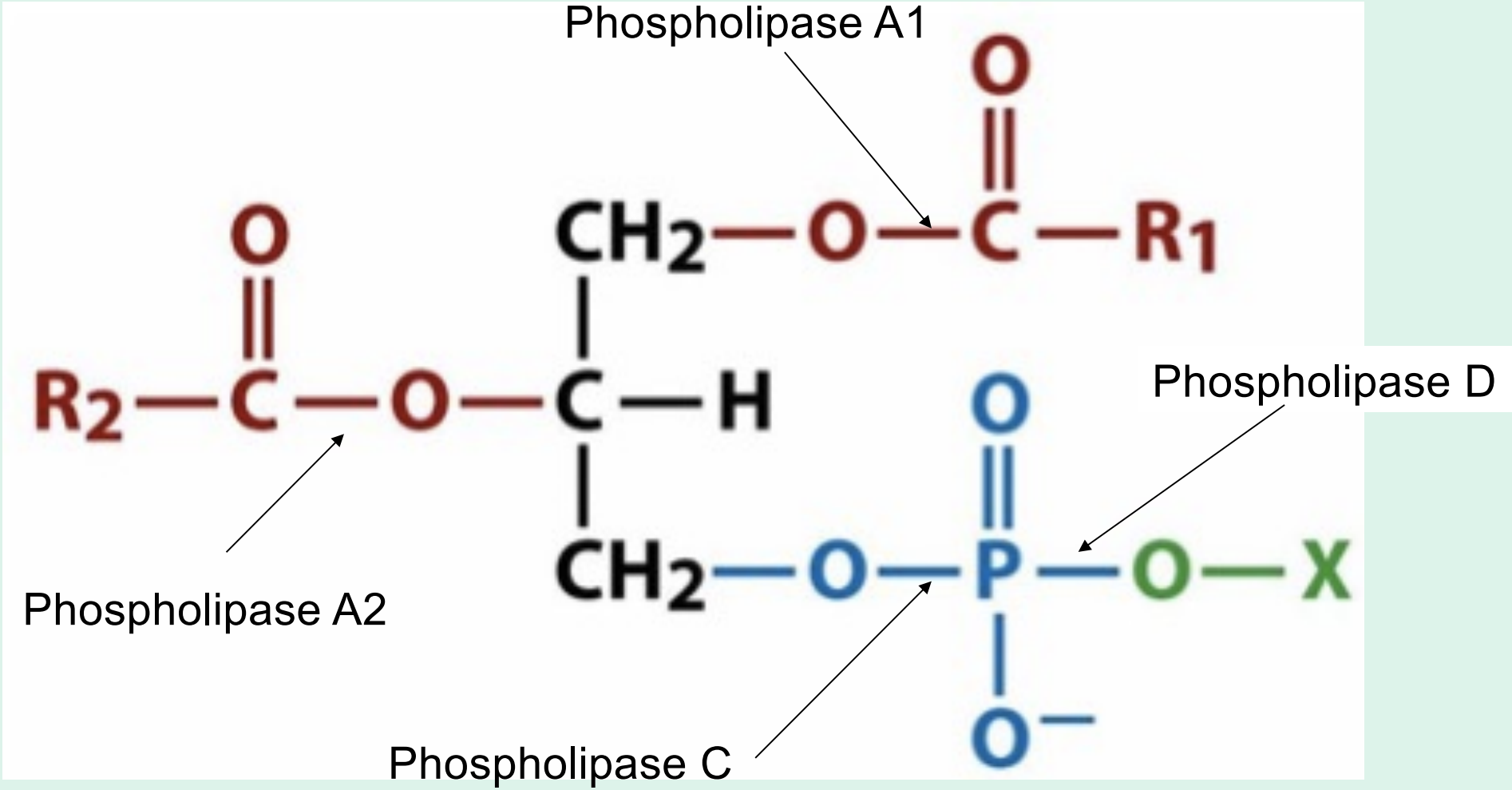
A typical mammalian phospholipid: phosphatidyl-choline (PC)



Phosphatidic acid is the simplest phospholipid.



Phospholipases are enzymes specialised in the hydrolysis of single ester bonds



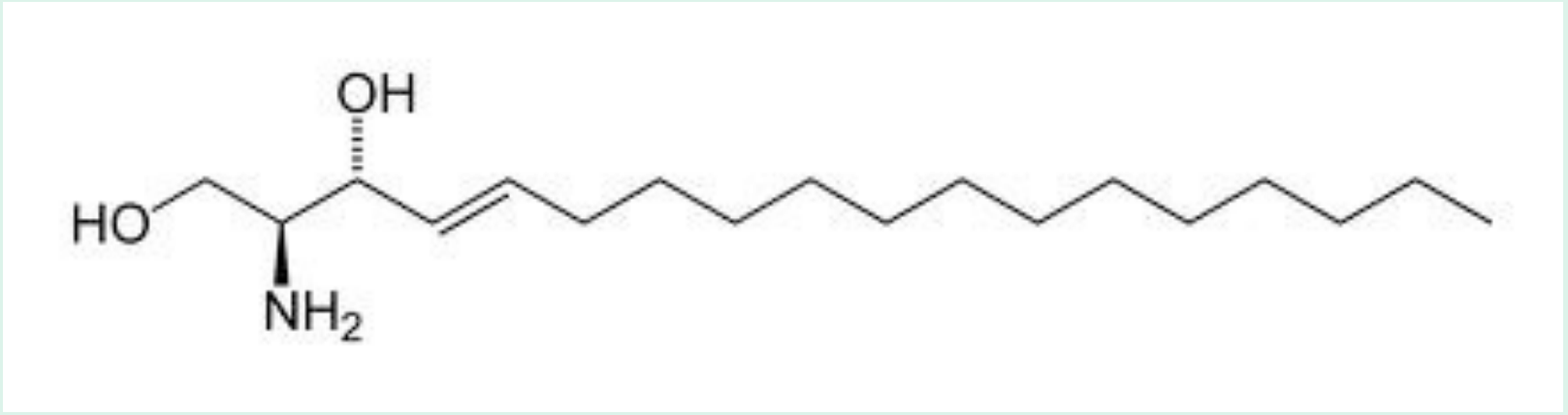
Sphingolipids

- These lipids account for 20-30% of plasma membrane, especially in cells of the central nervous system

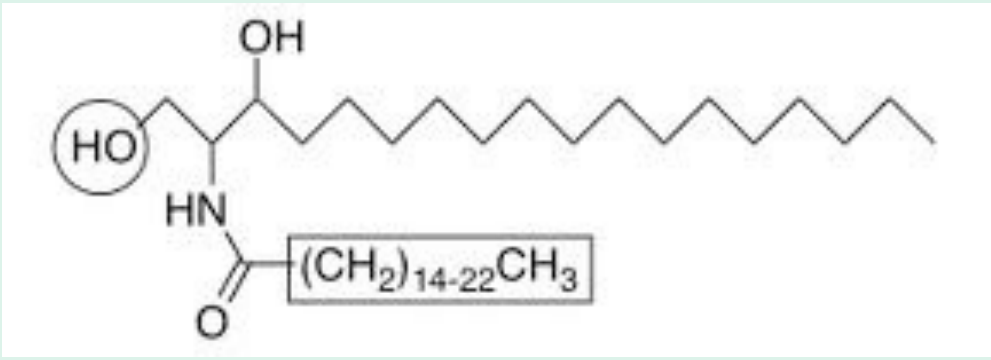
- In this case the scaffold is the trans unsaturated 18-C amino alcohol called **sphingosine**

Sphingosine and its derivatives

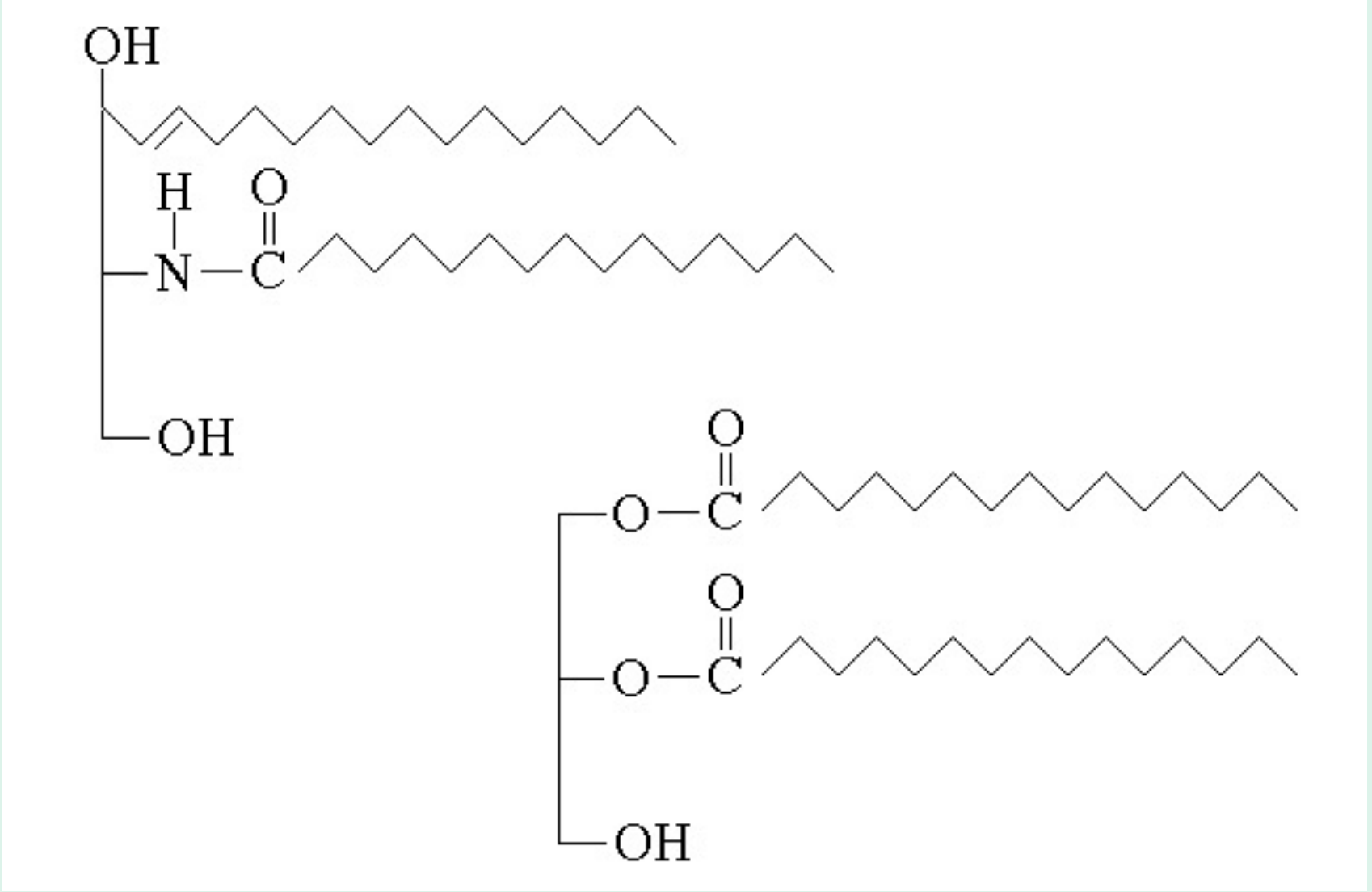
18 Carbon atons amino-alcohol



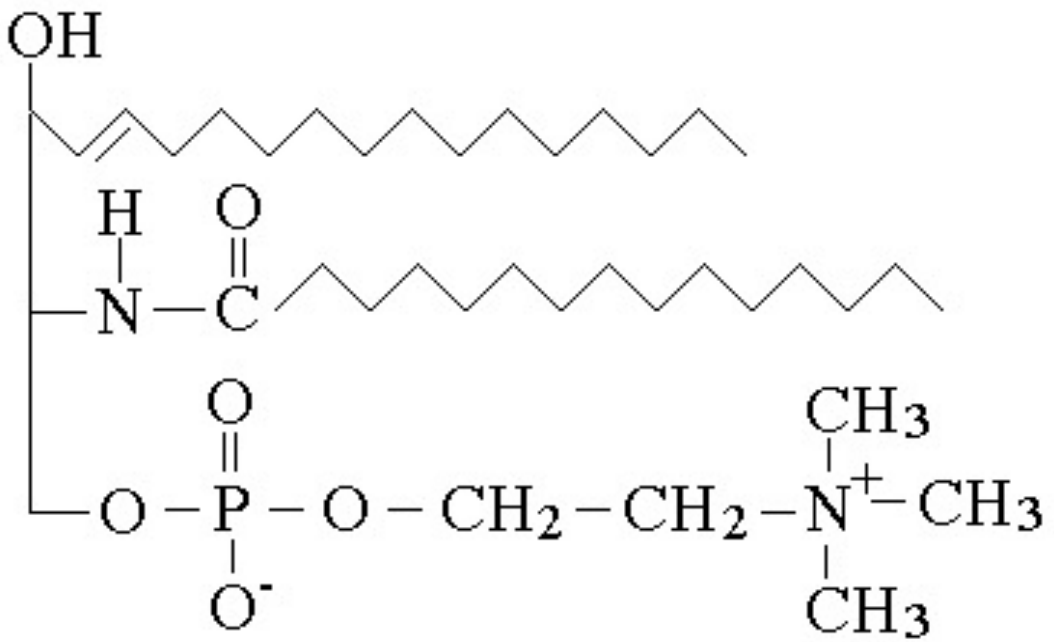
Sphingosine + fatty acid = ceramide



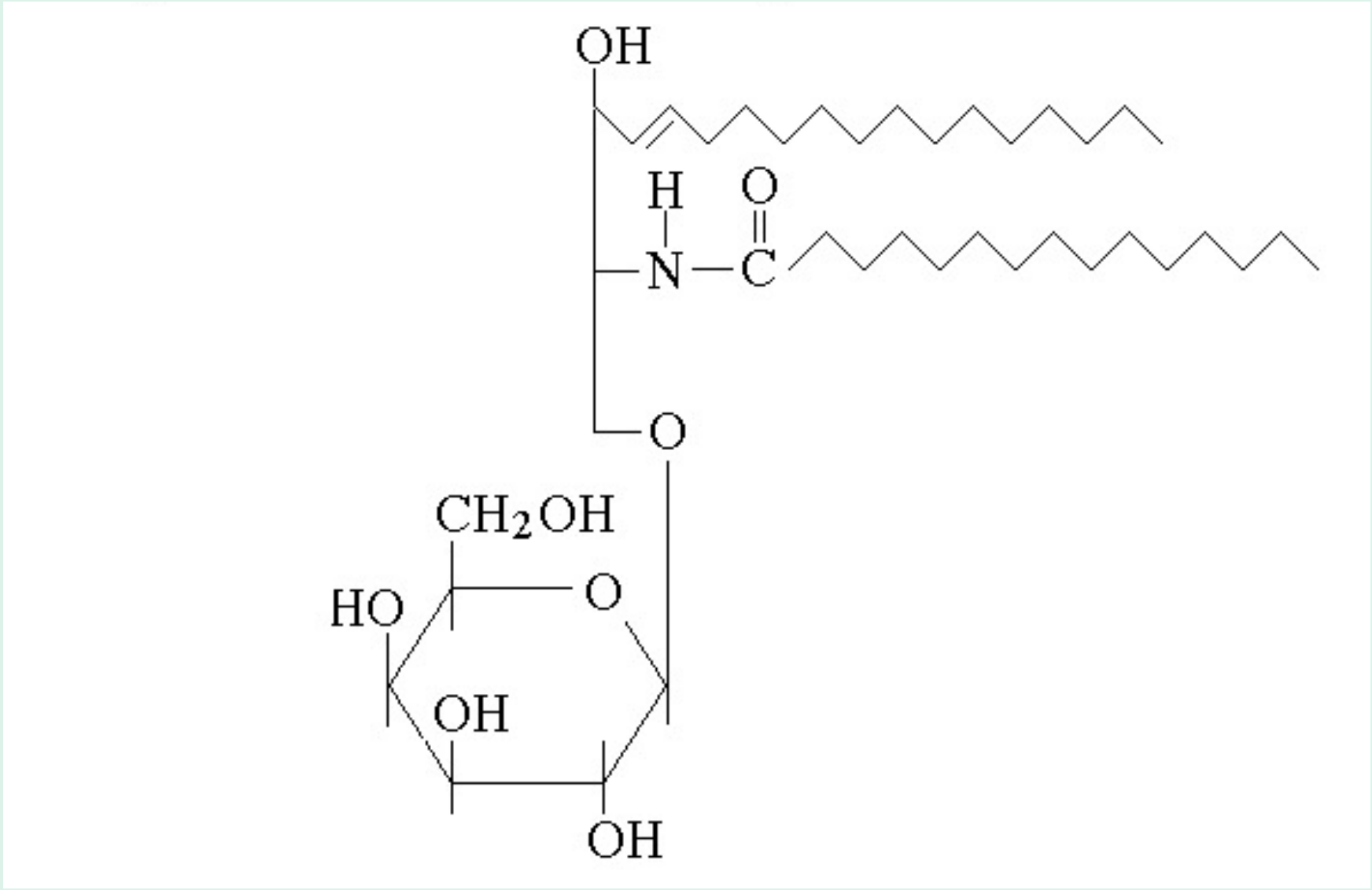
A ceramide looks like a diglyceride



Sphingomyelin looks like a phospholipid
and it is abundant in neurons

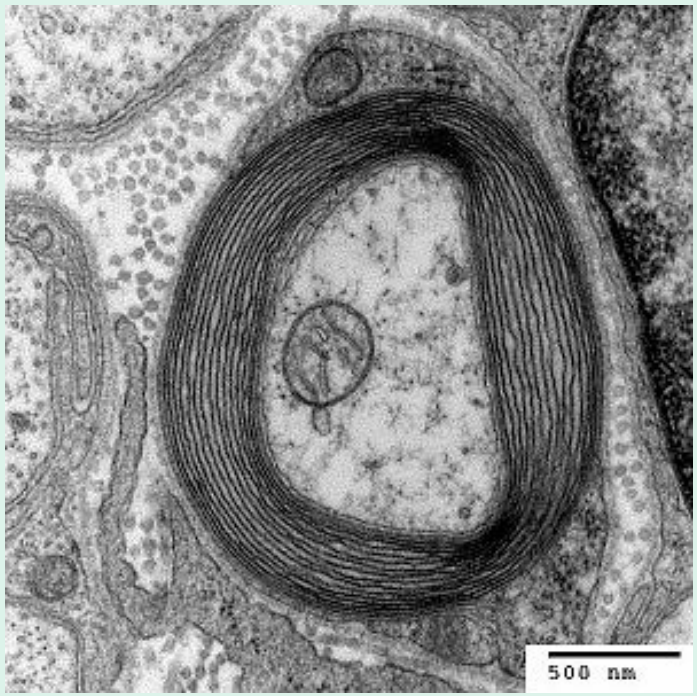


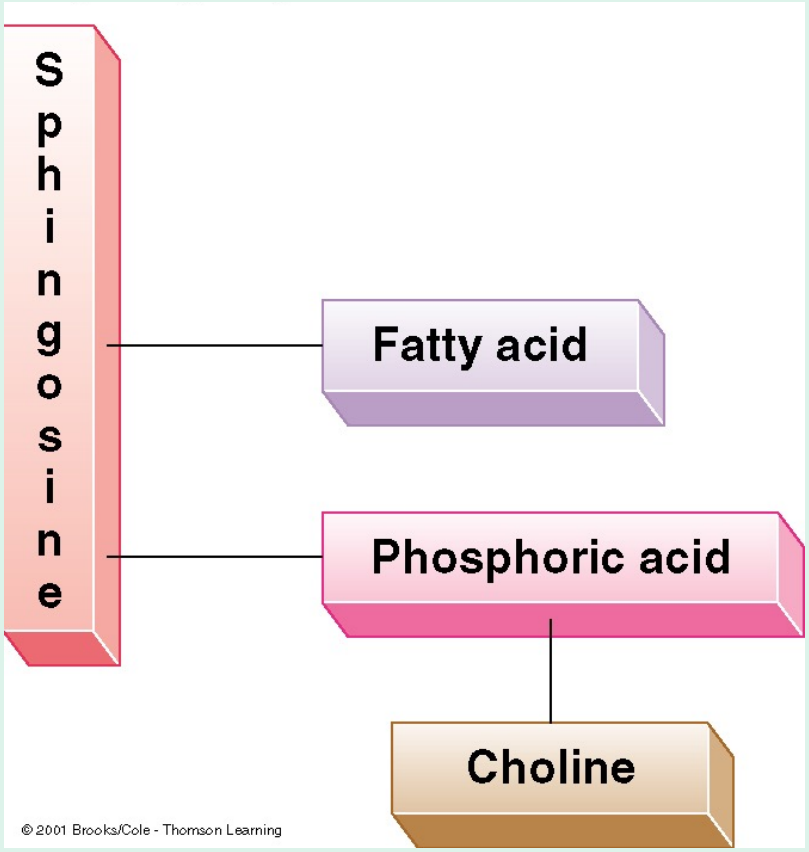
Glycosphingolipids are abundant in the SNC.



Sphingolipids

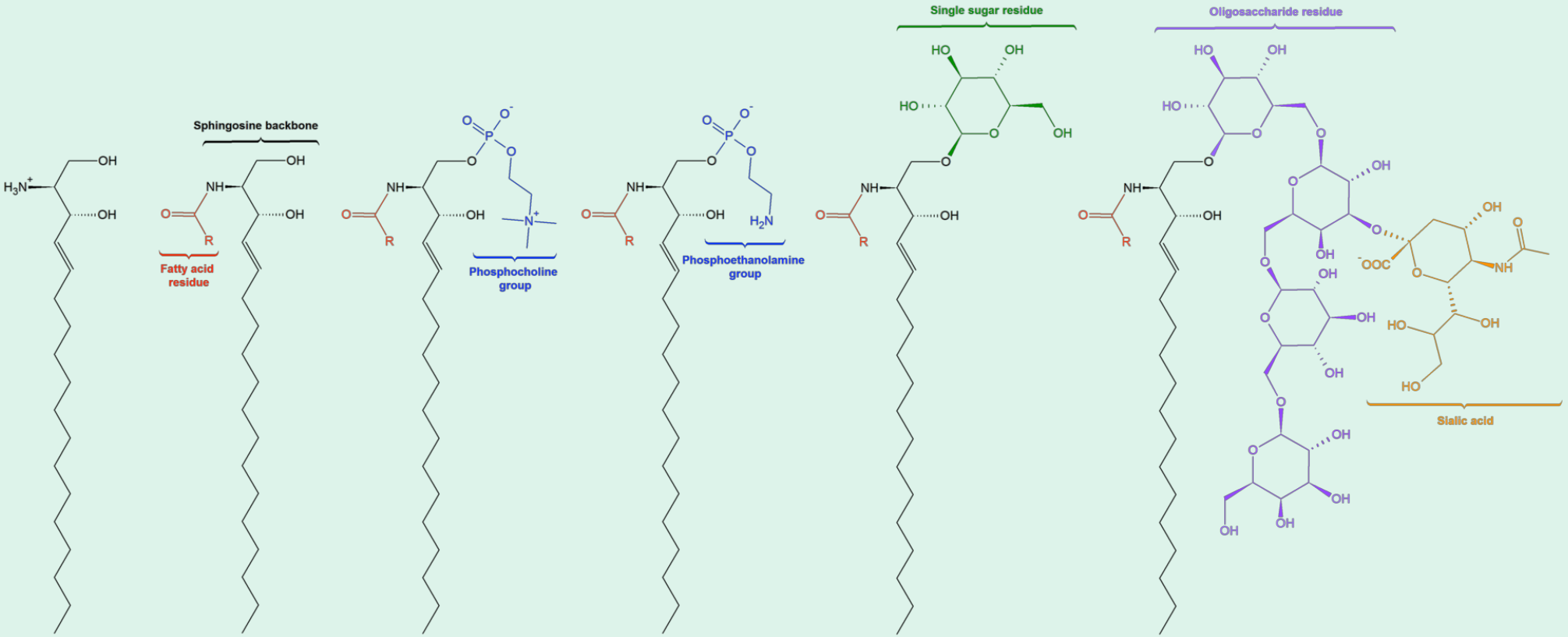
Are important components of the myeline sheath. In humans they make up to 25% of lipids.



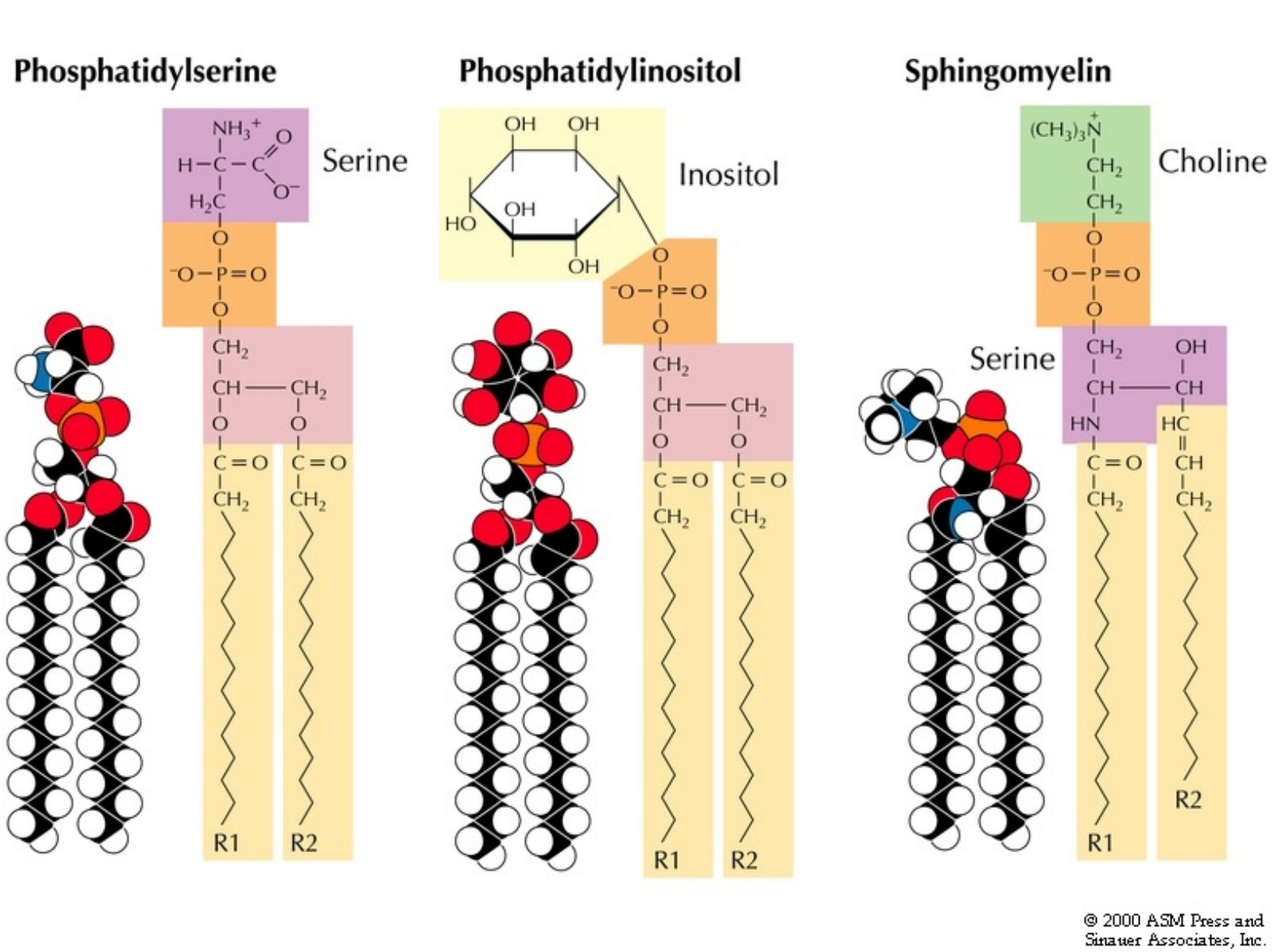


sphingomyelin

Sphingolipids

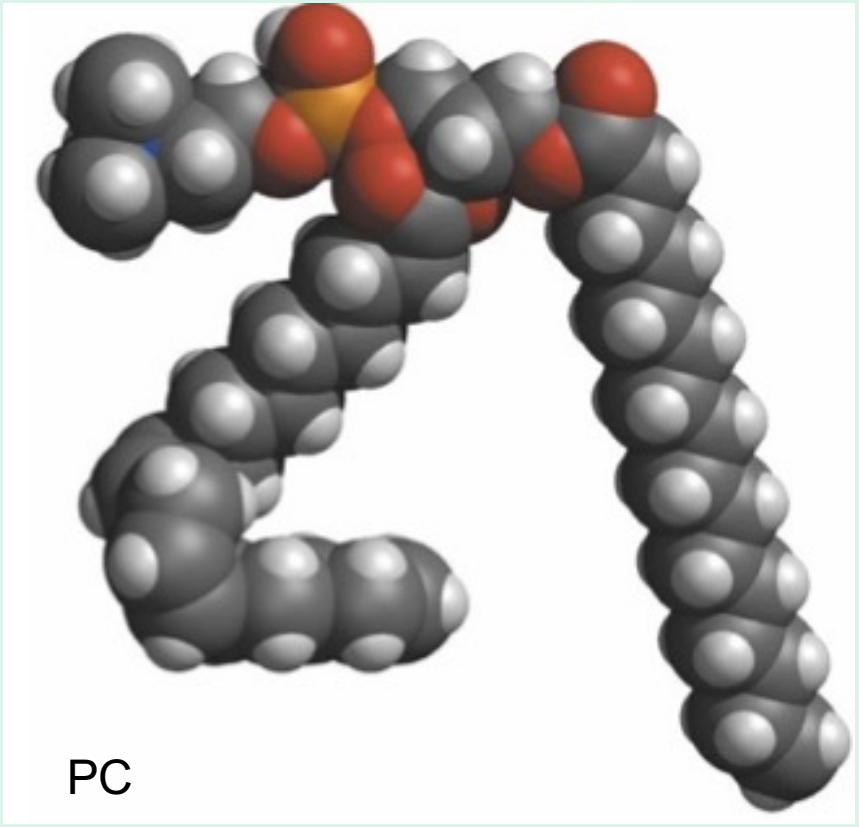


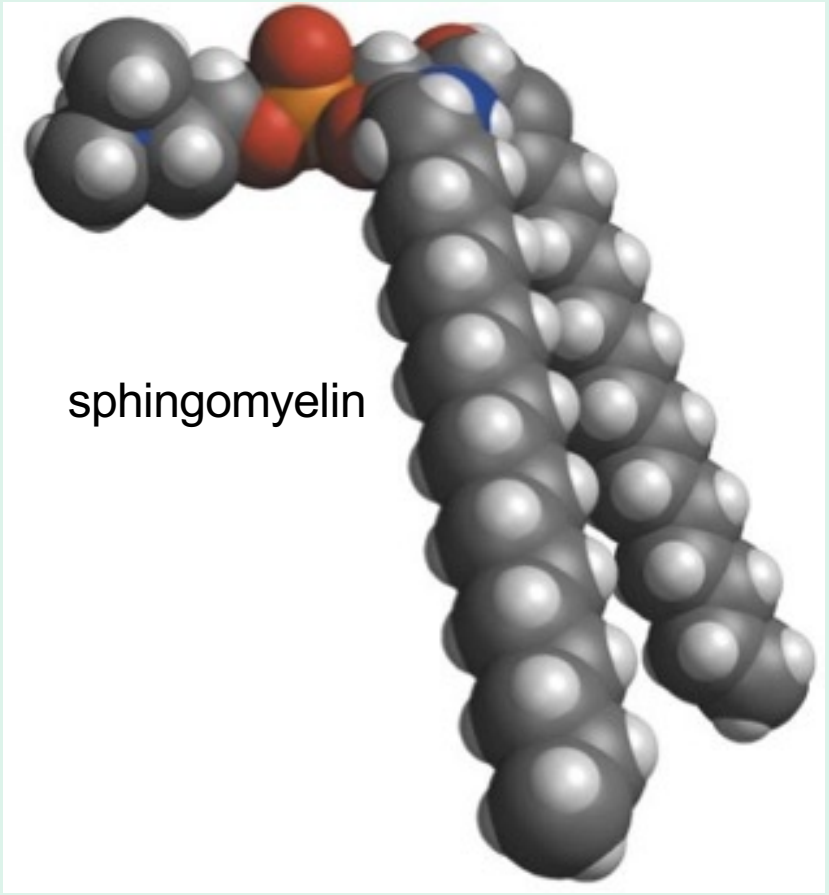
Membrane lipids are amphipathic (amphiphilic)



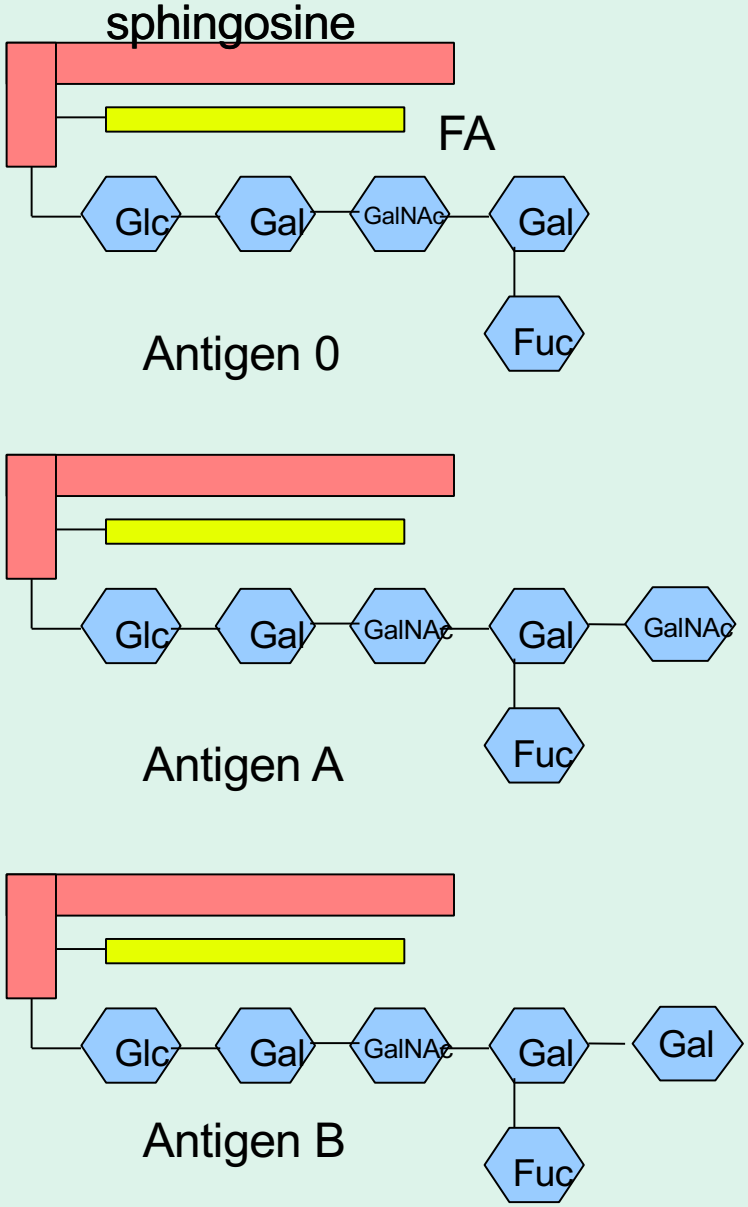
Glycerol-phospholipids vs sphingolipids

- Despite the different chemical origin, the two molecules have a similar 3D spatial arrangement and a similar charge (polar) distribution



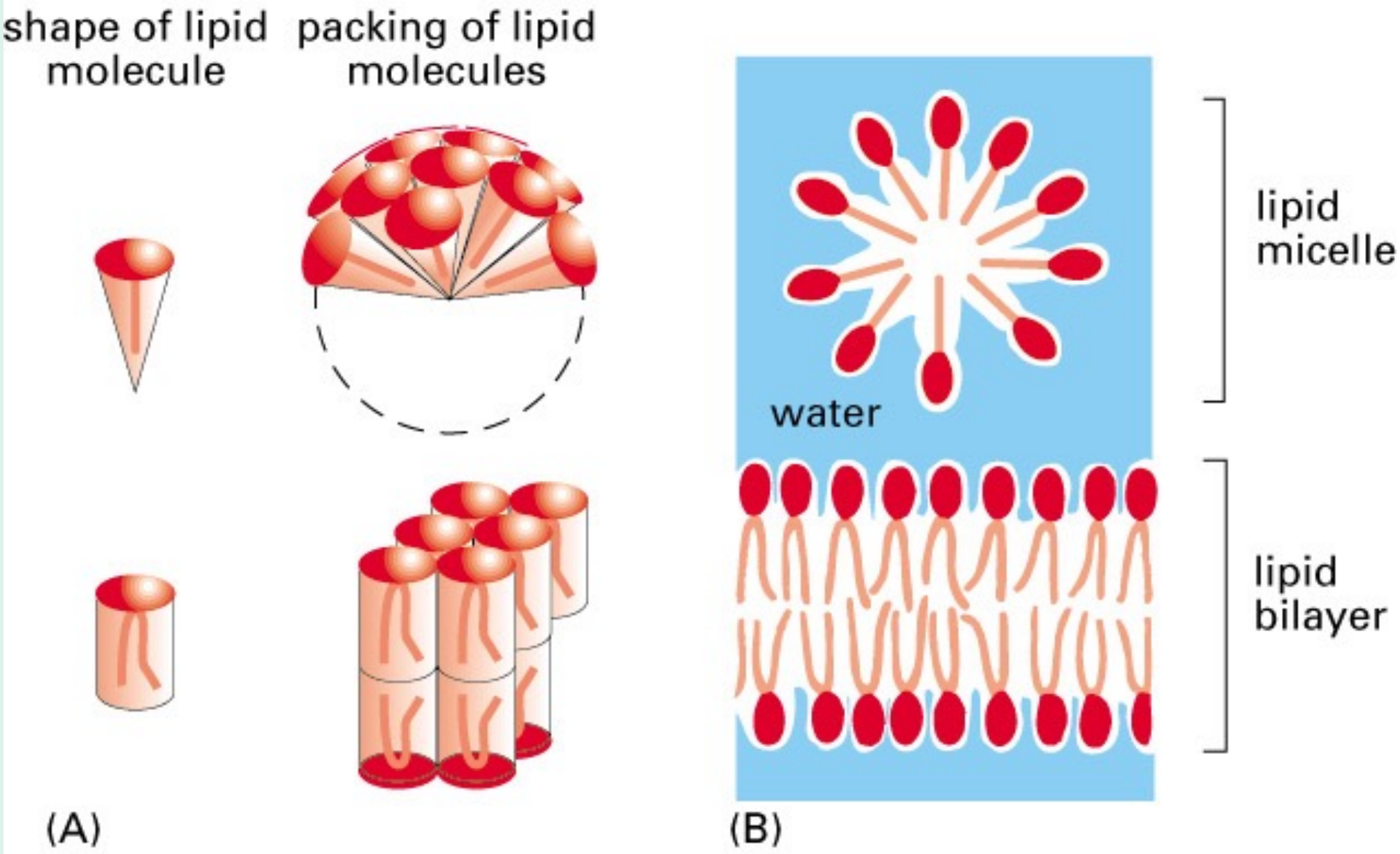


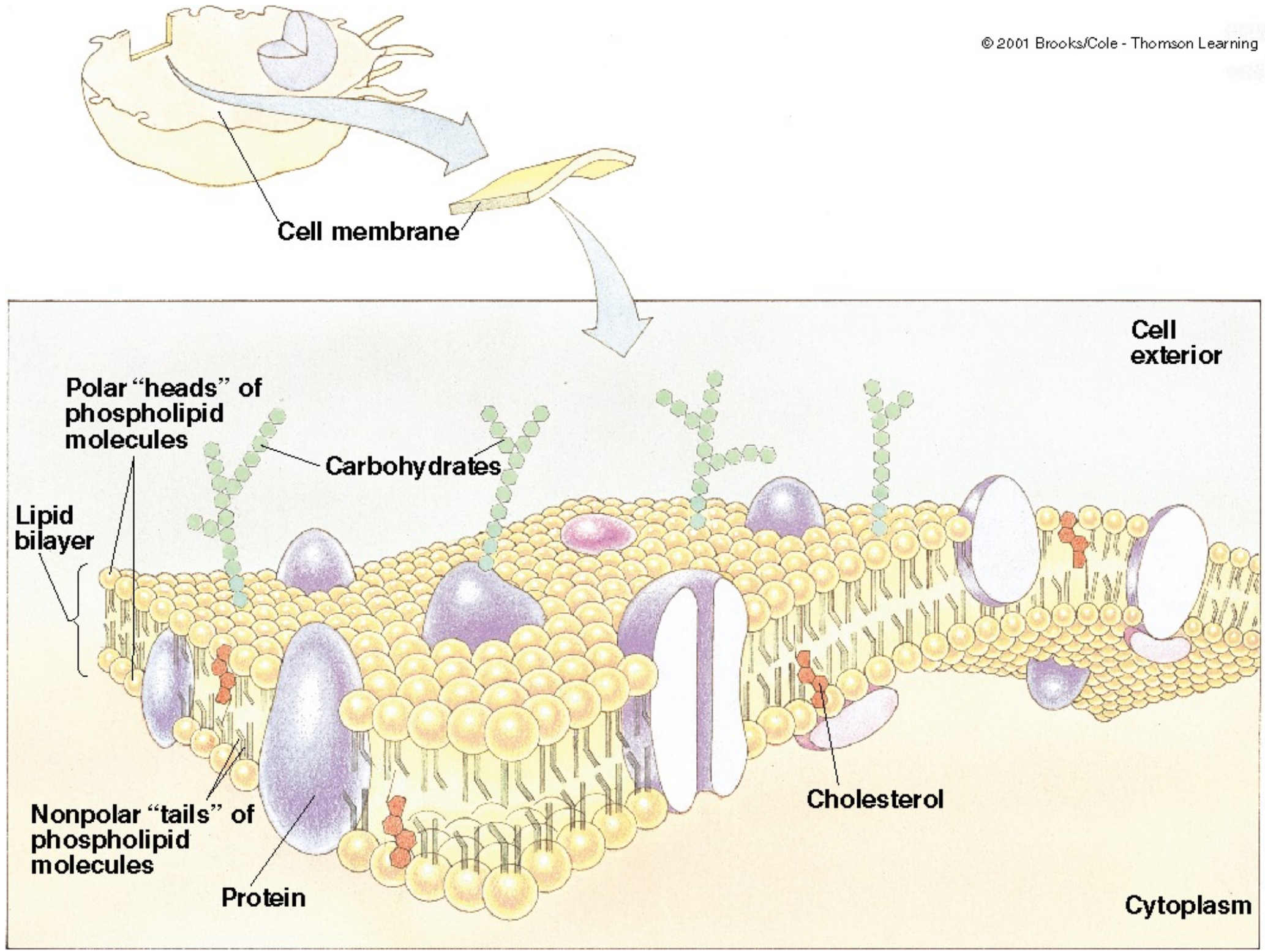
Gangliosides

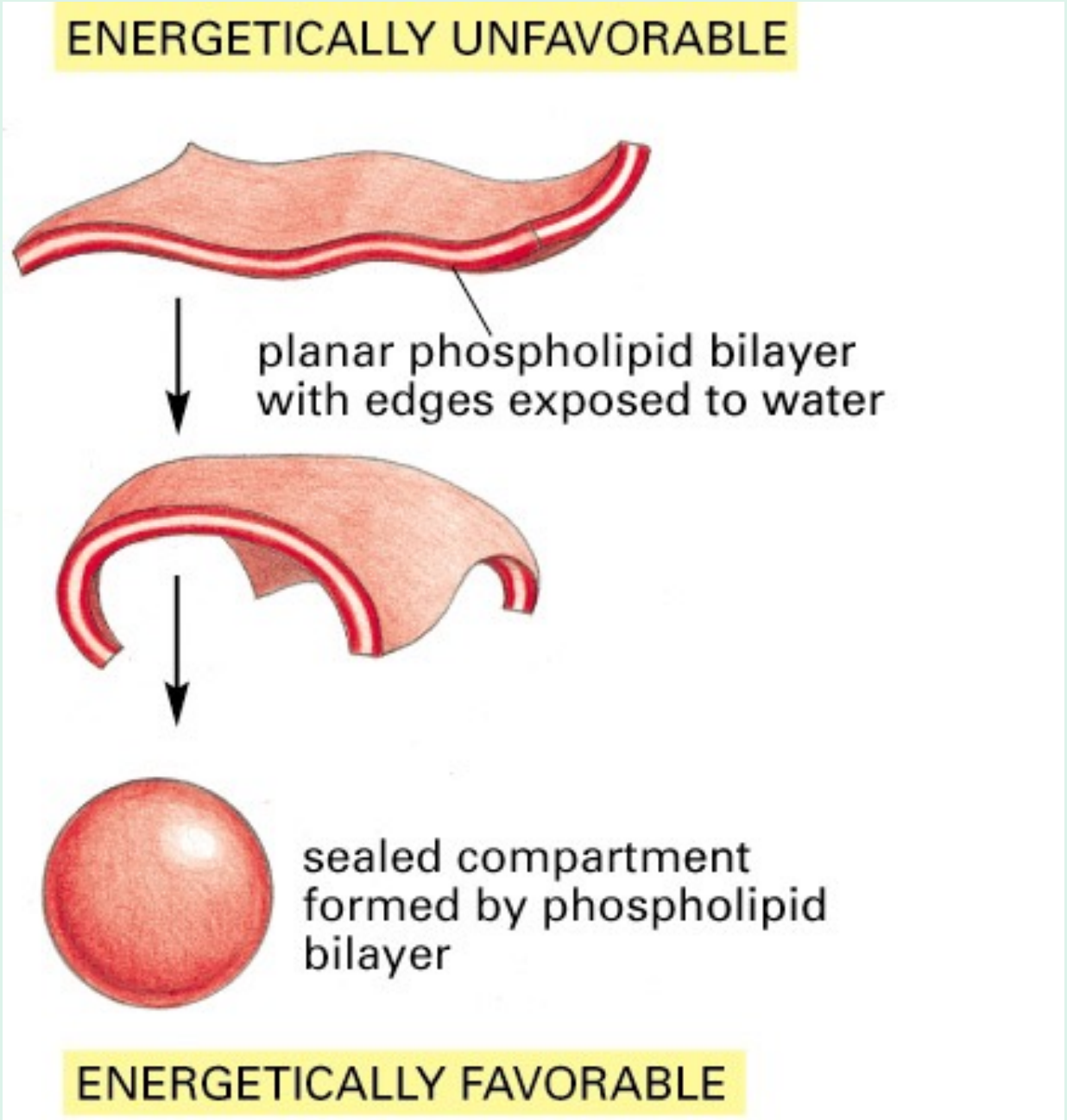


- Both Gangliosides and Cerebrosides contain sugars → they are always present only on the external leaflet of the membrane bilayer
- Gangliosides are responsible for the blood groups

Formation of lipid bilayer: an energy minimization process






ENERGETICALLY UNFAVORABLE
planar phospholipid bilayer
with edges exposed to water
sealed compartment
formed by phospholipid
bilayer
ENERGETICALLY FAVORABLE

Detergents

Figure of a Detergent Monomer

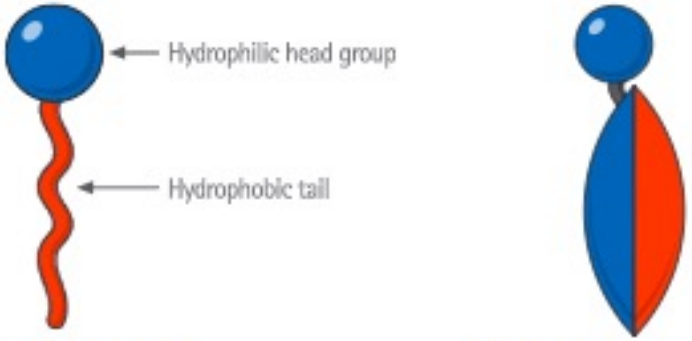


Figure 1A

Figure 1B

Molecular Shapes of Detergents and Lipids

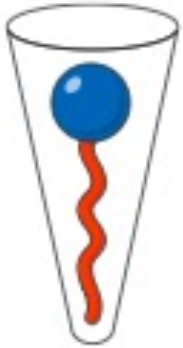


Figure 2A

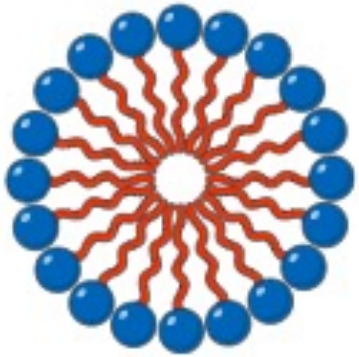


Figure 2B

Figure 2C

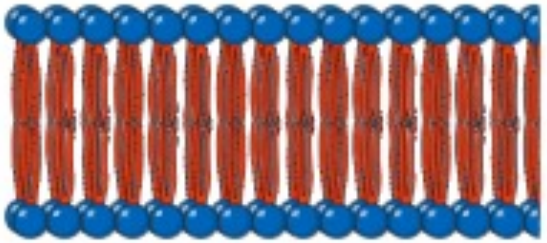
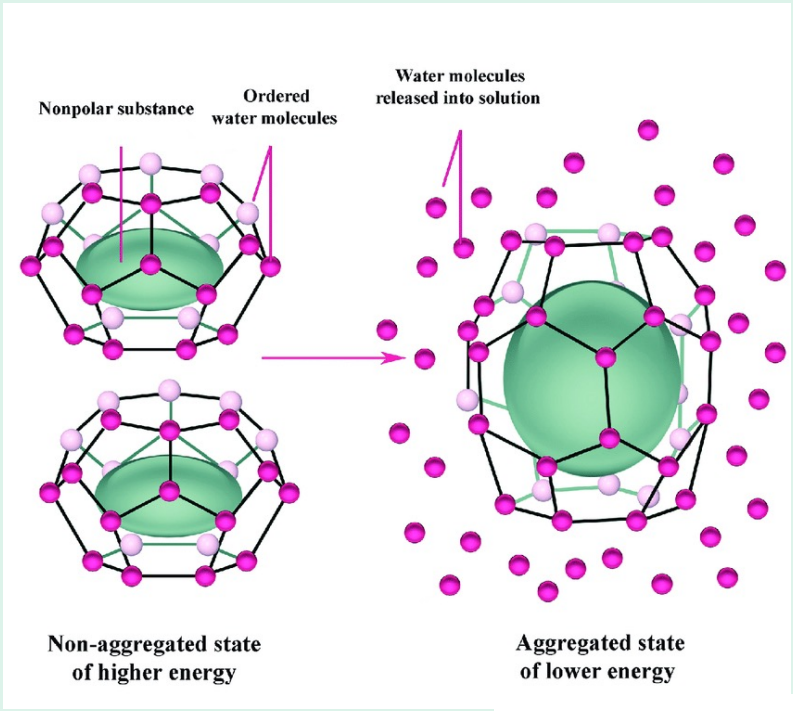
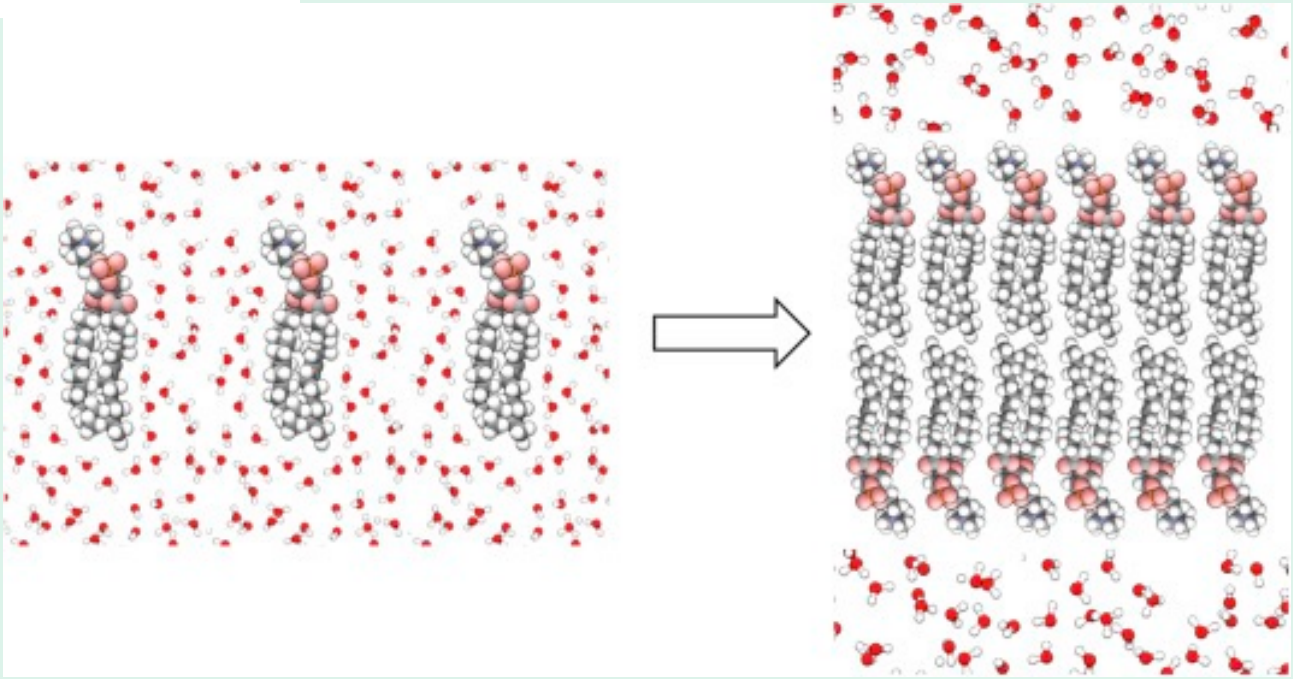
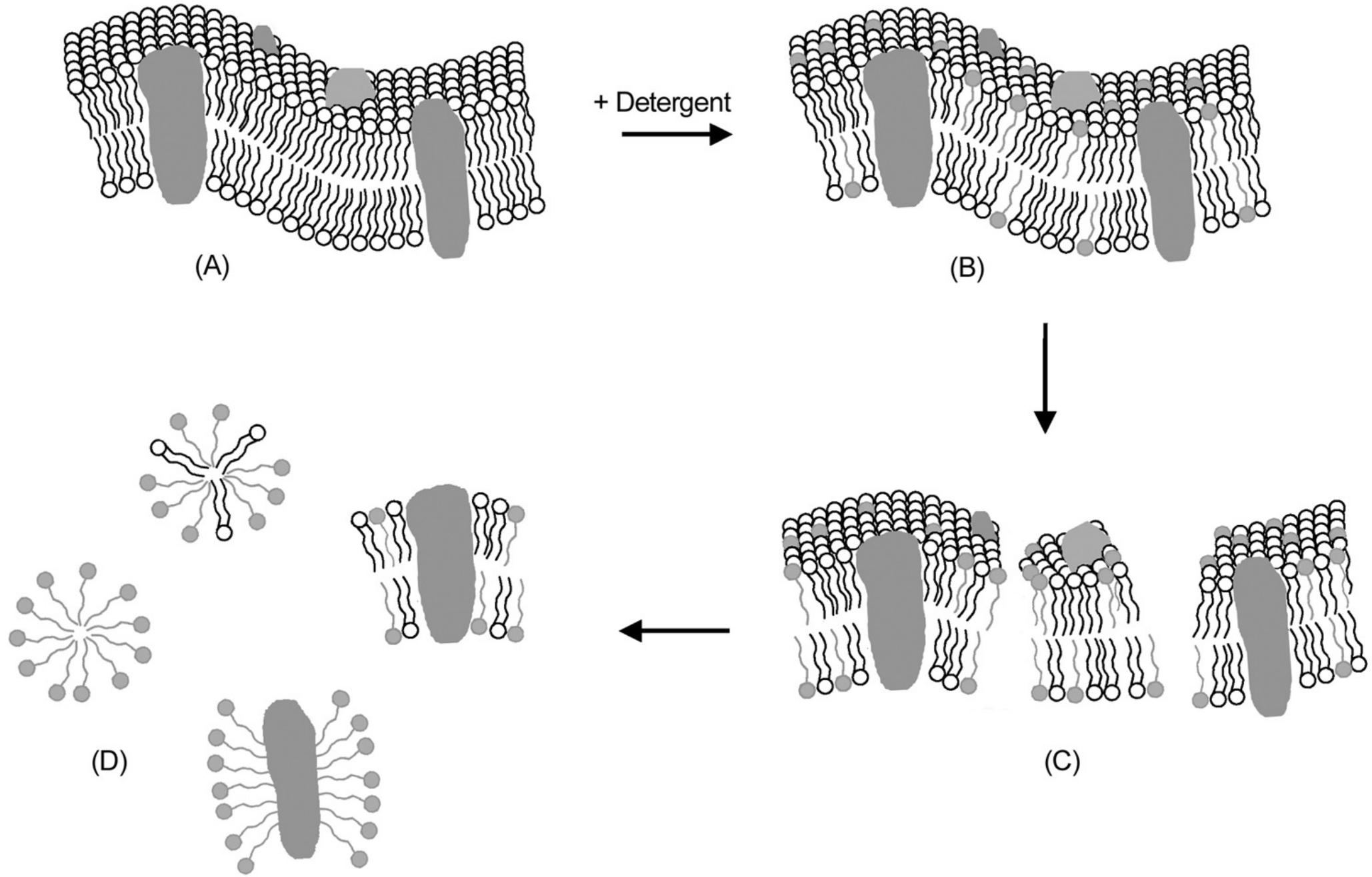


Figure 2D

Hydrophobic effect: lipid sequestration from water increases entropy

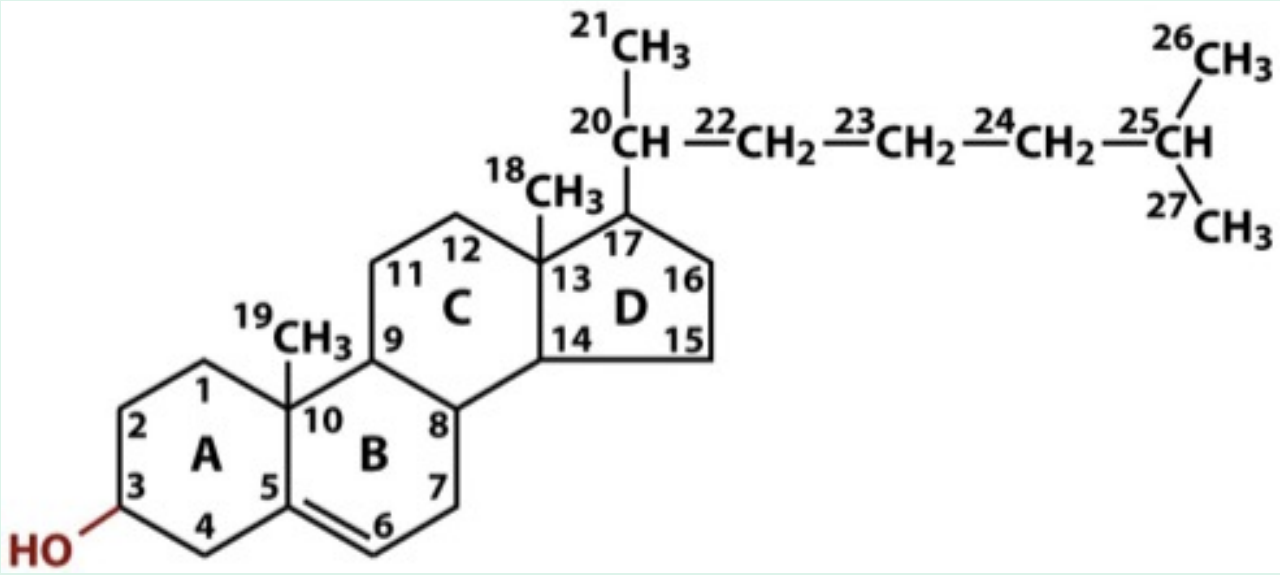





+ Detergent
(A)
(B)
(C)
(D)

Sterols

- This class is found almost exclusively in eukaryotes
- They have a common cyclic non-aromatic scaffold derived from cicle-pentane-peri-hydro-phenanthrene
- They have both structural and hormonal/signalling function
- The presence of 4 fused rings rigidifies the molecule → once inserted into the membranes it affects fluidity
- In mammals the precursor form all steroid hormones is cholesterol, whose OH group in C3 makes it slightly polar



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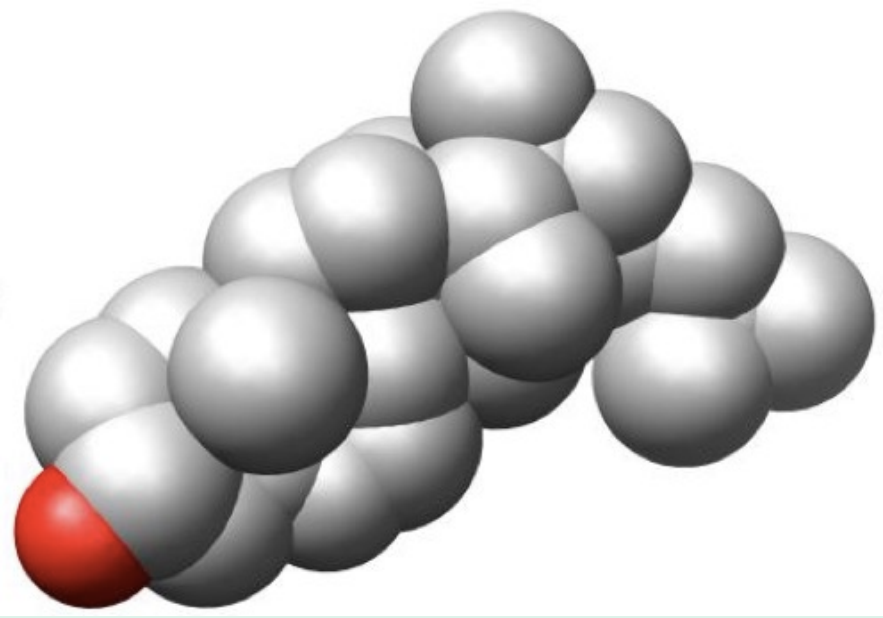
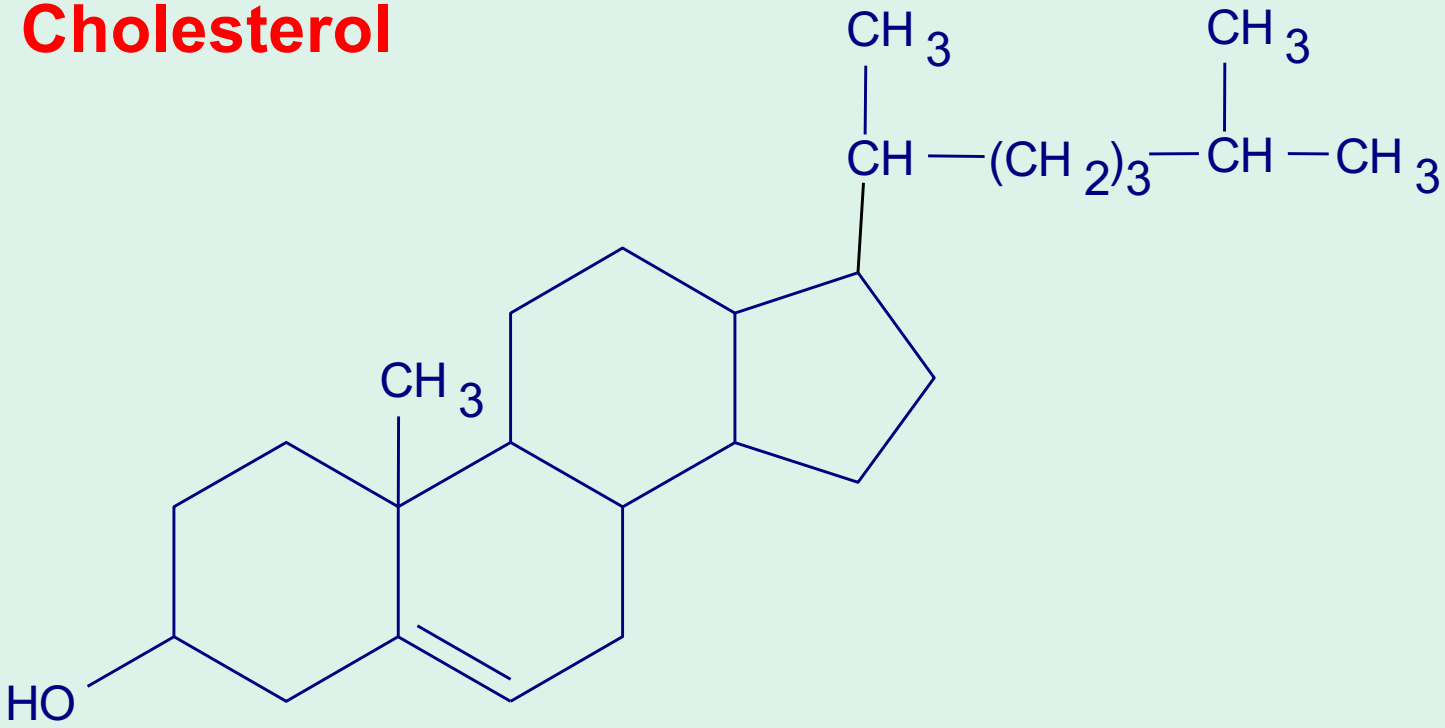


Steroid hormones

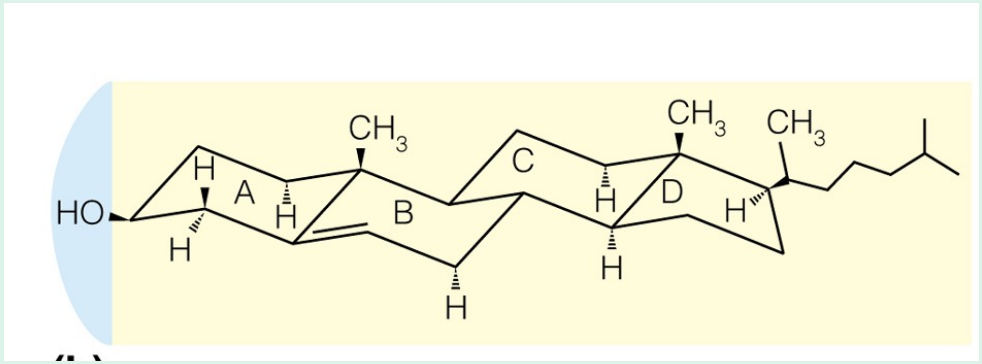
- **Glucocorticoids** (ex. Cortisol): hormones synthesised by the surrenal cortex glands, affecting the metabolism of carbohydrates, proteins and lipids. They also affect inflammatory and stress responses.
- **Mineral-corticoids** (ex. Aldosterone): hormones synthesised by the surrenal cortex glands, affecting water and salt excretion from kidneys.
- **Androgens** (ex. Testosterone) and **estrogens** (ex. beta-estradiol): crucial hormones for a correct sexual development and functionality, they are synthesised by either testes (male) or ovaries (female)
- They are all slightly more soluble than cholesterol

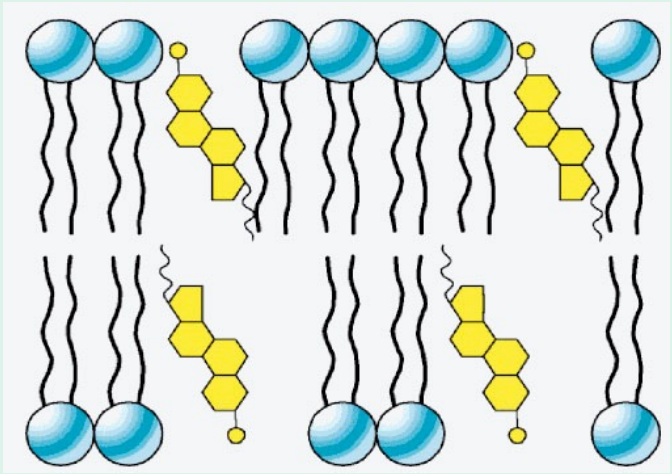
Cholesterol

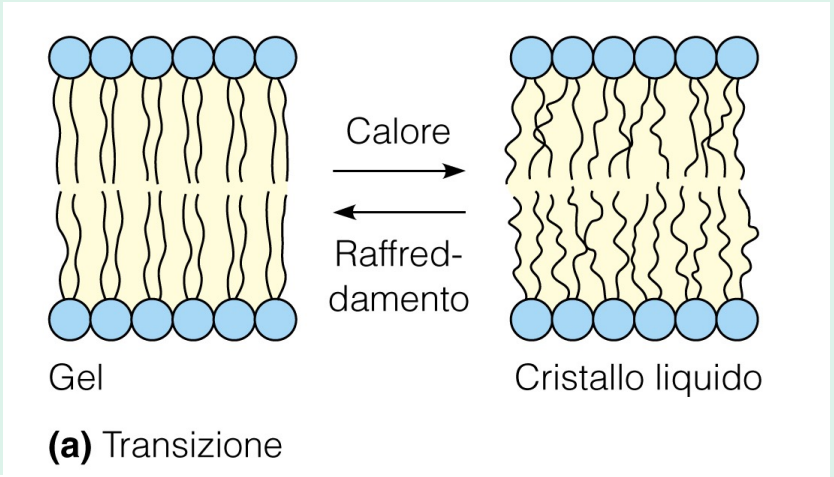


- From the diet and hepatic synthesis.
- insoluble, found in membanes.
- Steroid hormons synthesis.
- Bile salts synthesis.
- High blood levels-> cardiovascolar diseases.

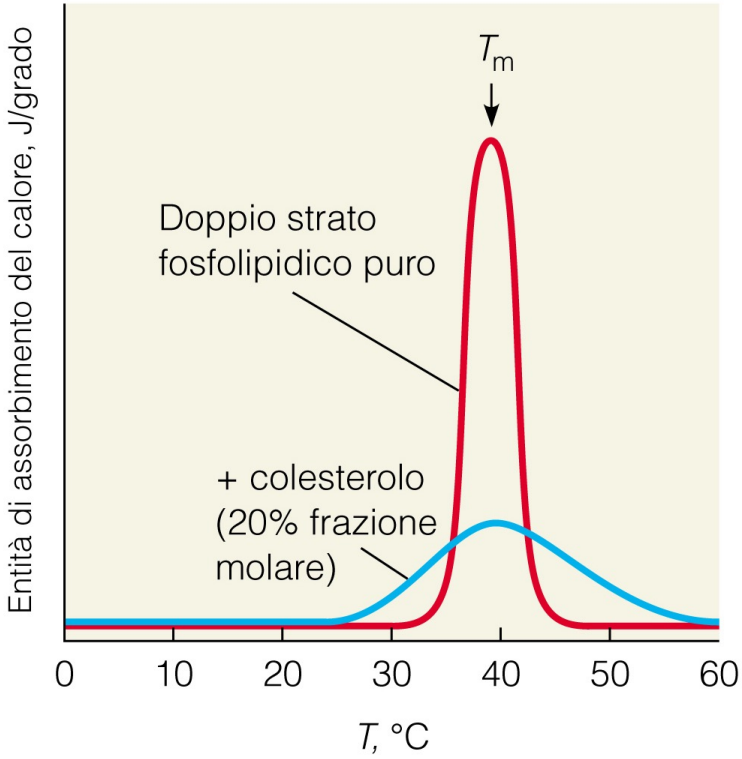
Membranes fluidity



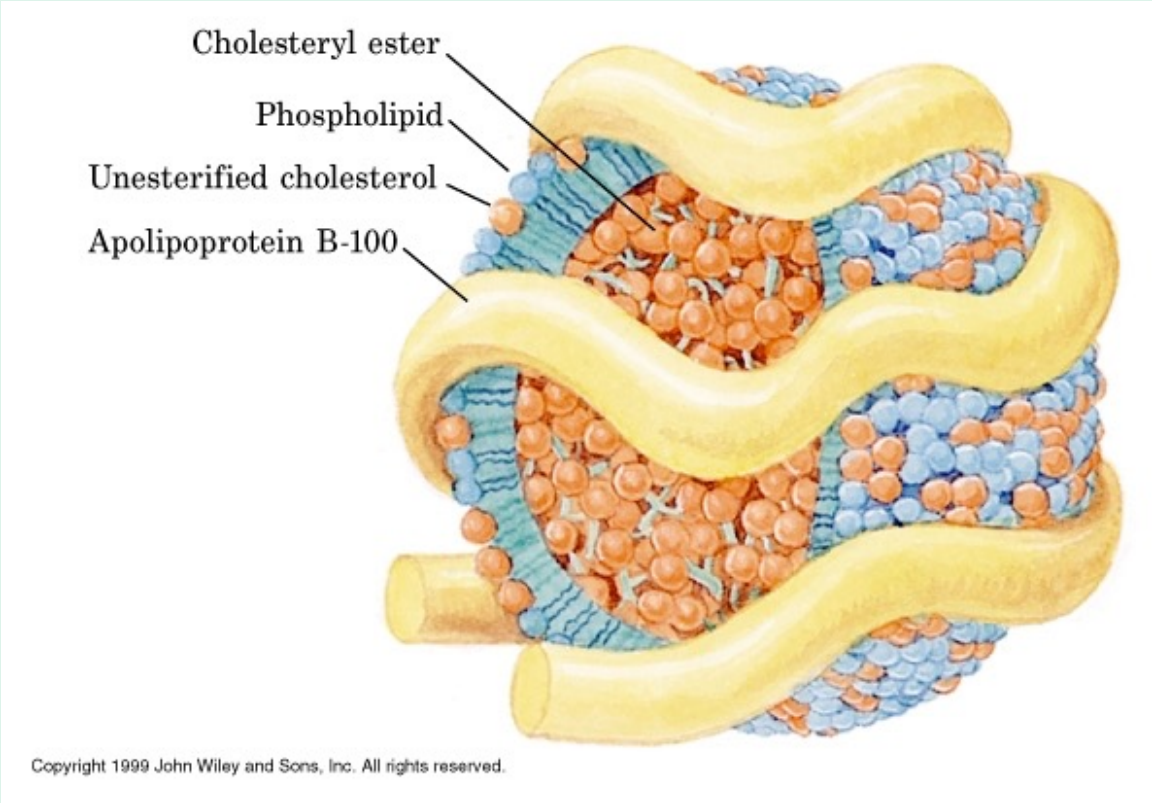




(a) Transizione



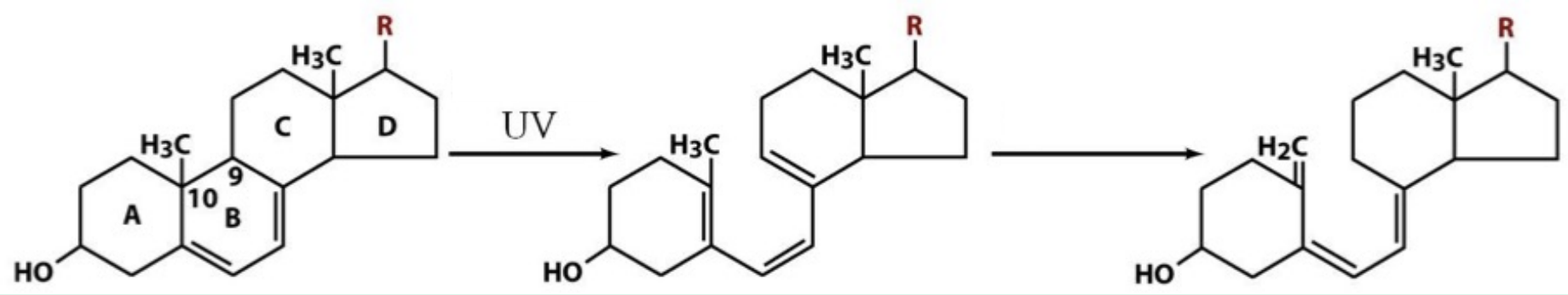
(b) Transizione con e senza colesterolo

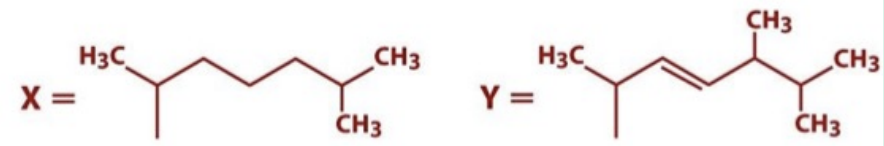


Cholesterol transportation in lipoproteic complexed (LDL)

Vitamin D

- Vitamin D is a regulator of Ca^{2+} homeostasis
- It is formed after photolysis of C9-C10 bond by UV light, followed by a spontaneous isomerization to vitamin D2 or D3
- Both these forms must be hydroxylated in the kidney (position C1) and in the liver (position C25) to give the active compound: 1-alpha-25-di-hydroxy-colecalciferol.

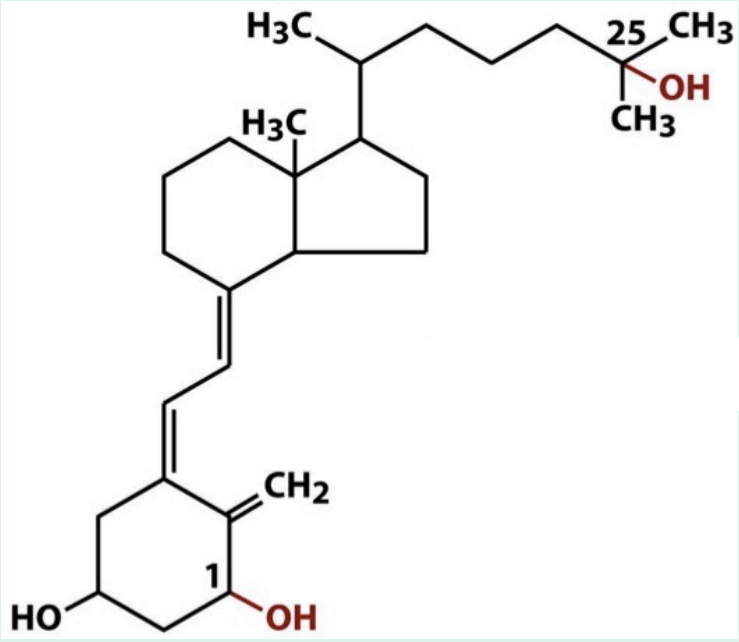




R = X vitamin D3
R = Y vitamin D2

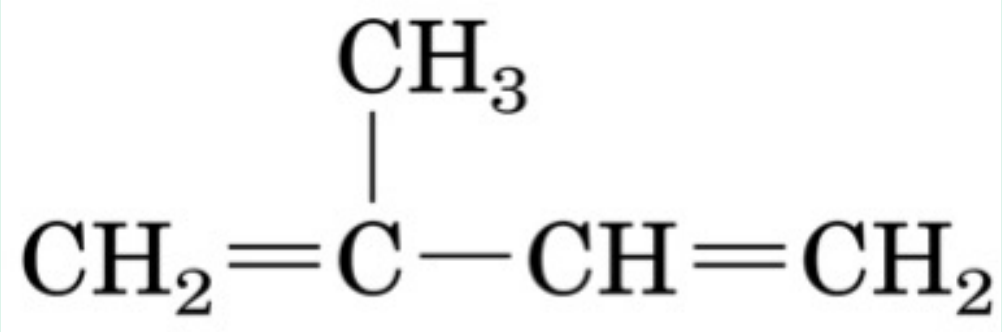
Vitamin D

- The active form of vitamin D (1,25-dihydroxyvitamin D) induces an increase in the plasma concentration of Ca^{2+}, thus favouring its uptake by intestinal cells.
- Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction with its receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%
- In this way these ions are deposited into bones and teeth.



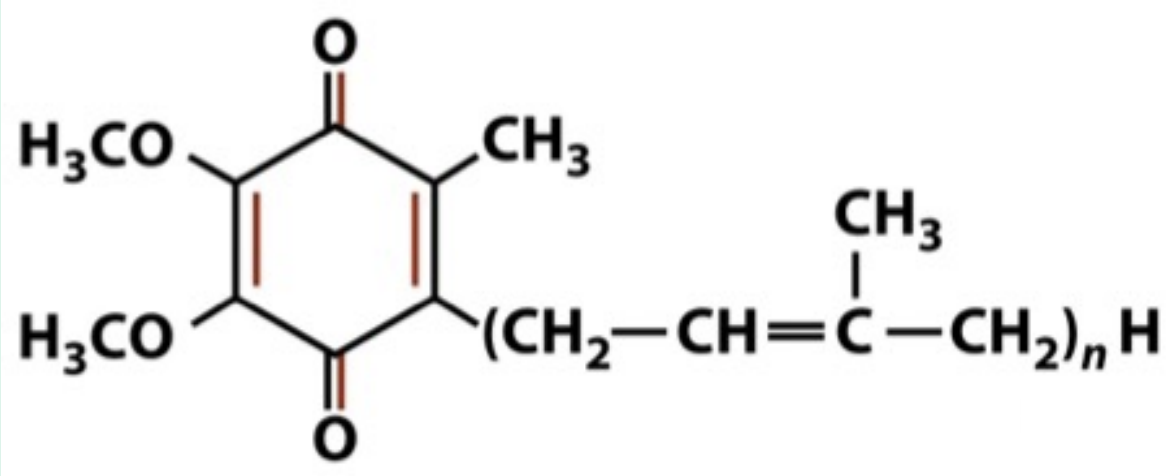
Terpenes and terpenoids

- Heterogenous class of hormones, co-enzymes, vitamins sharing only a part of the scaffold: a repeat of isoprene units



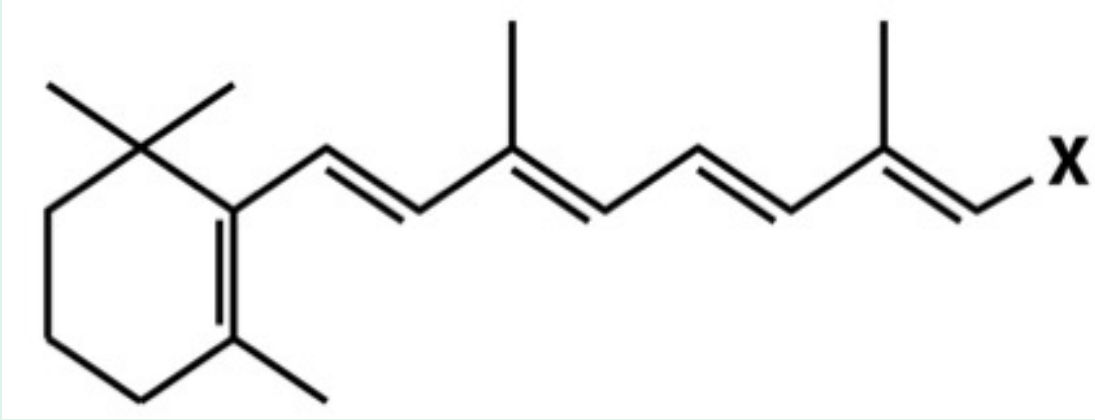
Coenzyme Q (ubiquinone)

- Shuttle of electrons in the respiratory chain in mitochondria, chloroplasts and in prokaryotes
- It is stably inserted in the membranes



Vitamin A (retinol)

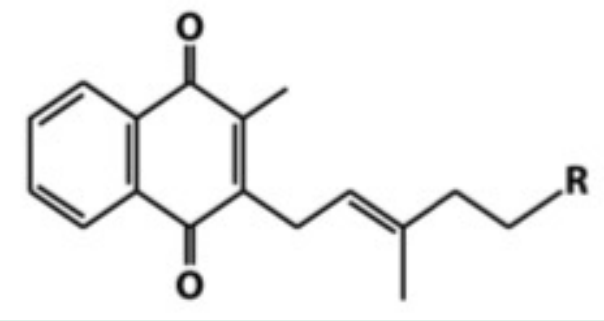
- Vitamin A is a derivative of beta-carotene, once oxidised into the aldehyde form (retinal) it is incorporated into the proteins of vision, where it helps transducing the light impulse into images
- Low levels supplied by the diet induce a reduced by-night vision
- Extremely low levels induce blindness (poverty-related blindness)

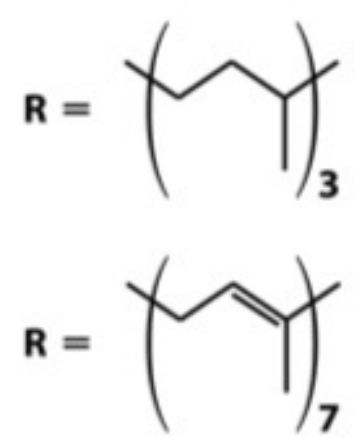


X = CH_2OH retinol
X = CHO retinal

Vitamin K

- This vitamin is only produced by plants and bacteria
- In humans it is produced by the intestinal commensals
- It is crucial for a proper blood coagulation



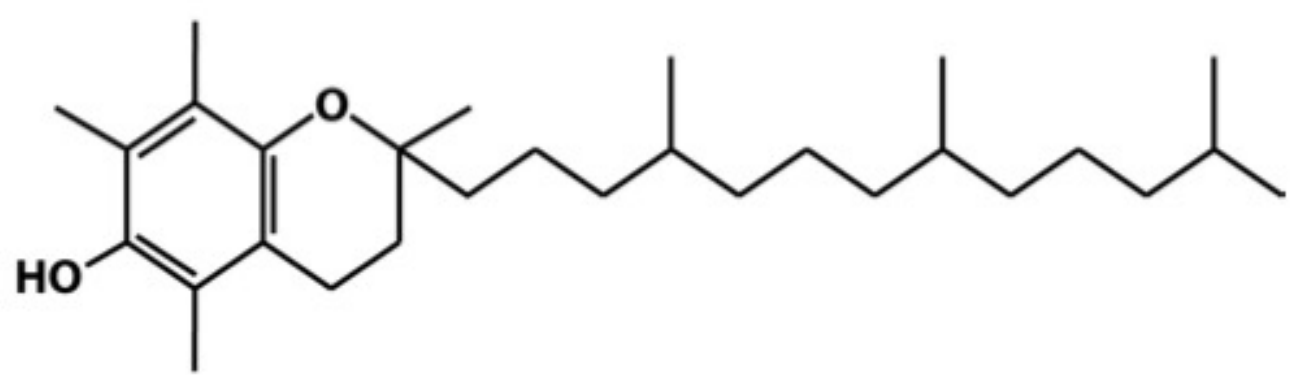


Vitamin K1 (plants)

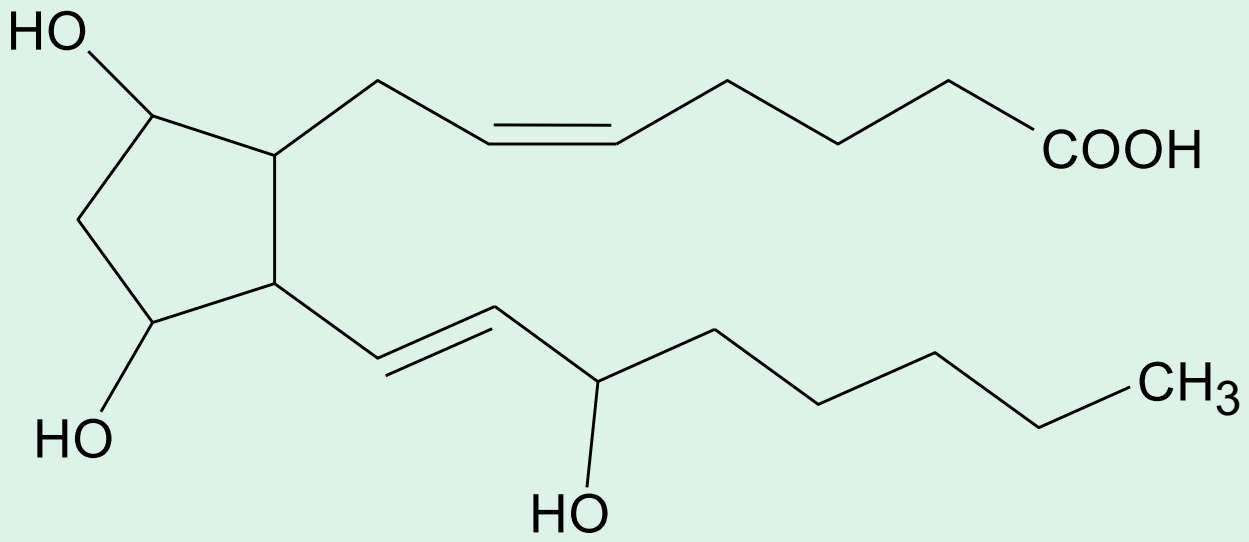
Vitamin K2 (bacteria)

Vitamin E

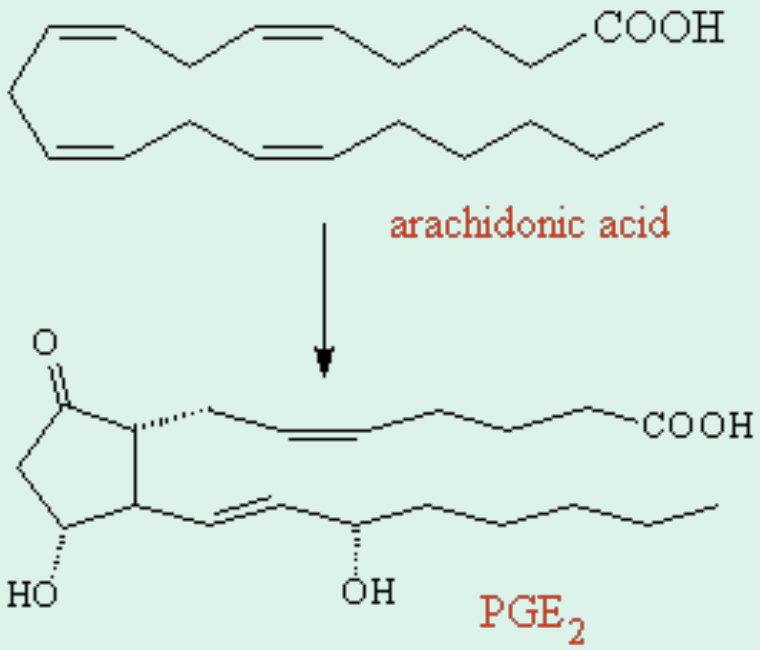
- Also known as alpha-tocopherol is an anti-oxidant, able to scavenge reactive oxygen species (ROS)
- It prevents oxidation of membranes and proteins



Prostaglandins are synthesized from arachidonic acid.



Hormone-like effect:
Fever, contraction, inflammation, asthma…
Their synthesis is inhibited by anti-inflammatory drugs such as aspirin.


COOH
arachidonic acid
O
COOH
HO
OH
PGE2

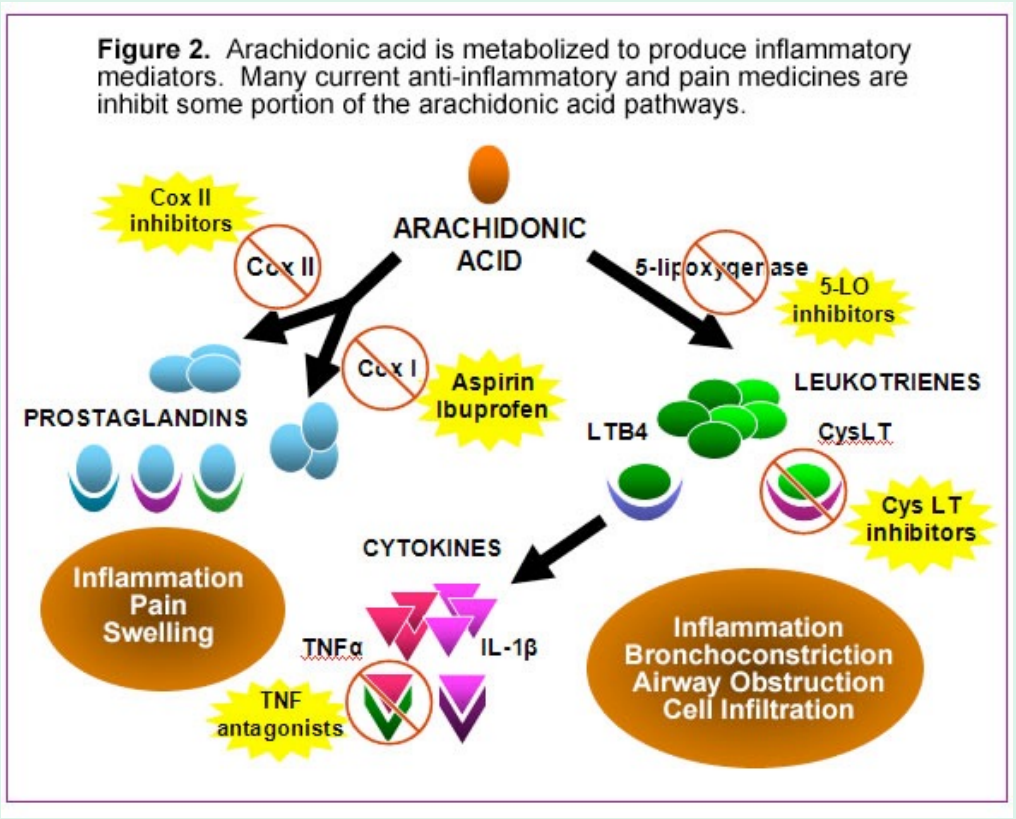


Figure 2. Arachidonic acid is metabolized to produce inflammatory mediators. Many current anti-inflammatory and pain medicines are inhibit some portion of the arachidonic acid pathways.
Cox II inhibitors
Cox II
ARACHIDONIC ACID
5-lipoxygerase
5-LO inhibitors
Cox I
Aspirin Ibuprofen
PROSTAGLANDINS
LEUKOTRIENES
LTB4
CysLT
Cys LT inhibitors
CYTOKINES
Inflammation Pain Swelling
TNFα
IL-1β
TNF antagonists
Inflammation Bronchoconstriction Airway Obstruction Cell Infiltration