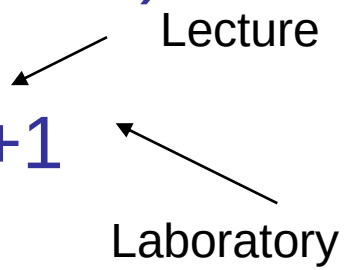
CDL Advances Chemical Studies (ACS)



Metabolic Biochemistry 7 CFU = 6+1

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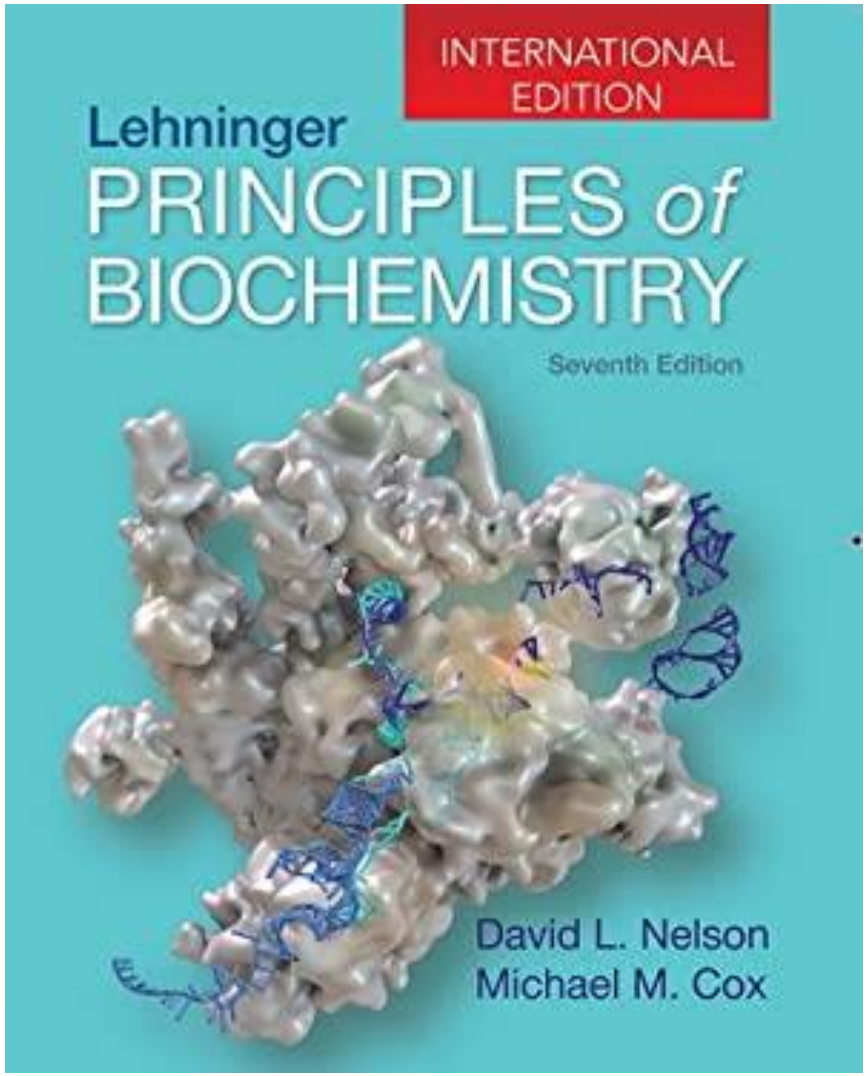
Course Contents

We will review the structures of the simplest compounds and then continue with more complex compounds

Complex compounds

- Carbohydrates: glycosaminoglycans and proteoglycans; protein glycosylation (N-, O- glycosylation and GPI-linked proteins);
- Lipids: polyunsaturated fatty acids; arachidonic acid cascade; eicosanoids; phospholipases.


INTERNATIONAL EDITION
Lehninger
PRINCIPLES of BIOCHEMISTRY
Seventh Edition
David L. Nelson
Michael M. Cox

LIPIDS

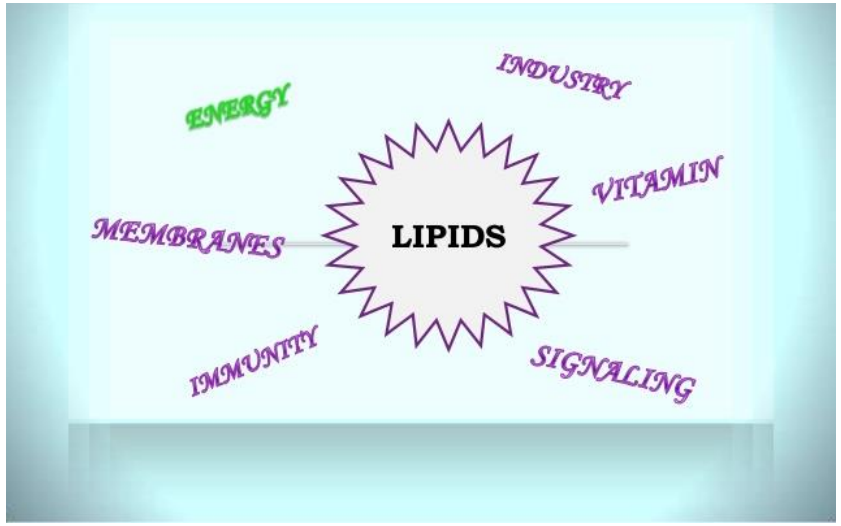
Lipids are a class of macromolecules that are nonpolar and hydrophobic in nature.

Lipids are organic molecules insoluble in water, soluble in non-polar solvents such as ether, chloroform, etc…

Functions of Lipids

Energy Storage
Large amount of energy is released from their oxidation.
(Triacylglycerols),

Surface coating and protection, thermal insulation (waxes).



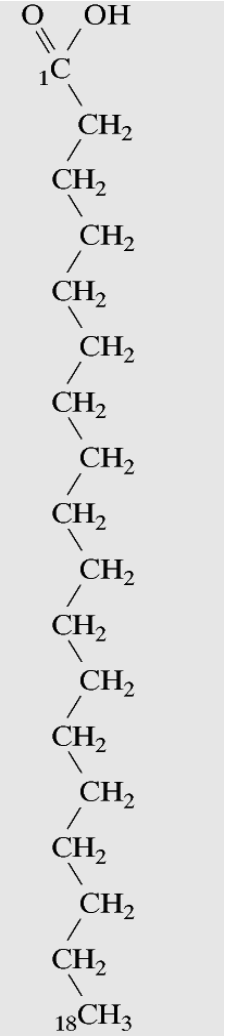
Structural: Fats also make cell membranes and coatings (i.e. fruit coats)(glycerophospholipids Sphingolipids)

Metabolic regulators , hormonal type, cell recognition

The basic structure is formed by FATTY ACID

A fatty acid molecule has two distinct regions:

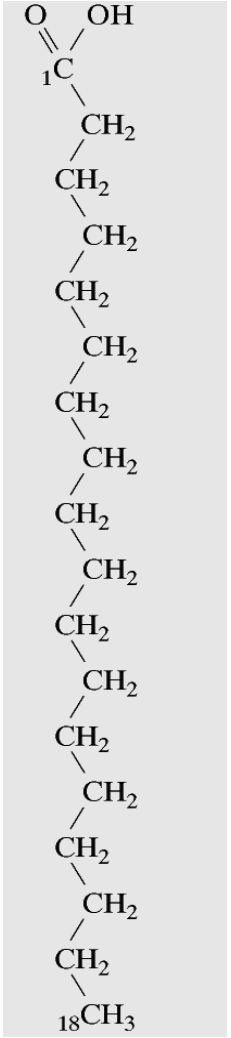
- a long, hydrophobic hydrocarbon chain,
- a carboxylic acid group, (hydrophilic portion)



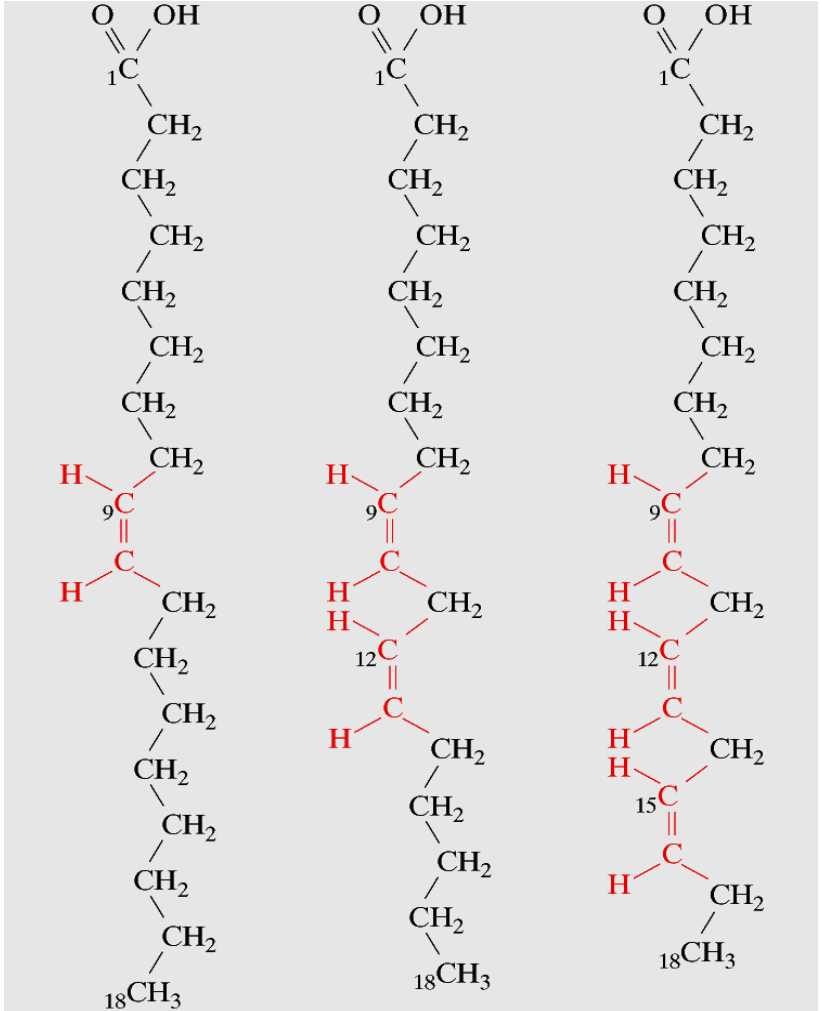
Consequentially, fatty acids are amphipathic because contain two distinct regions (hydrophobic and hydrophilic).

Fatty acids can be distinguished in

- Saturated Fatty Acids



- Unsaturated Fatty Acids (mono-unsaturated and poly-unsaturated)



Fatty acid: The basic structure of fats is a hydrocarbon backbone with a carboxyl group attached (-COOH in C 1)

They usually contain an even number of carbon atoms (typically 12–20).

They can be distinguished

Saturated,

Unsaturated : mono-unsaturated

poly-unsaturated

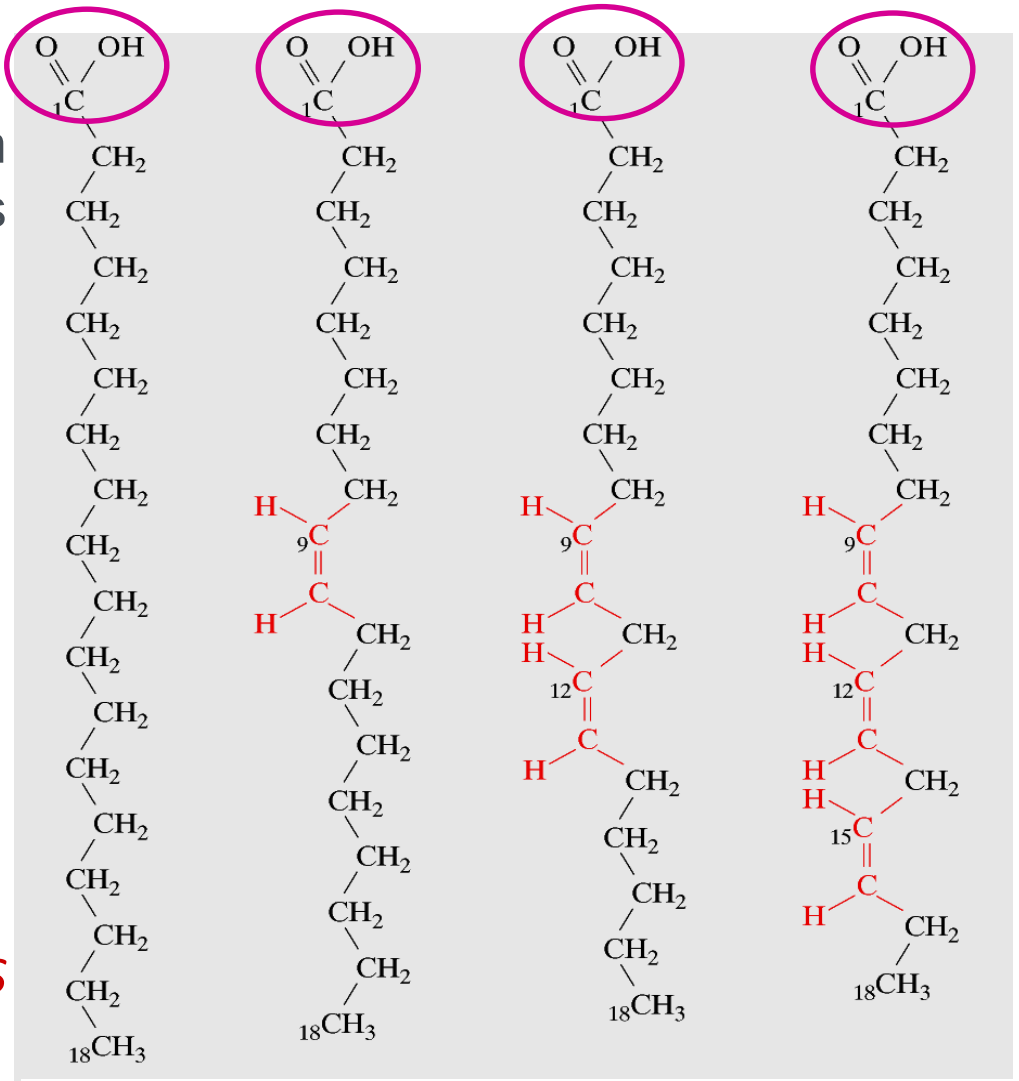
double bond:

- 9-10 position ,
- 12-13 position,
- 15-16 position

Commonly, double bond is in *CIS* conformation

Indicate with Δ^n

n = double bond position



Stearic acid. Oleic acid Linoleic acid linolenic acid

Octadecanoic

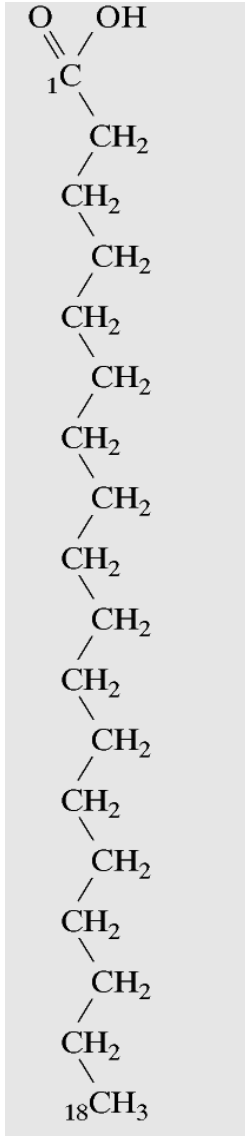
cis-Δ^9-octadecanoic

cis-$\Delta^{9,12}$-octadecanoic

cis-$\Delta^{9,12,15}$-octadecanoic

Saturated Fatty Acids

Hydrocarbon tail

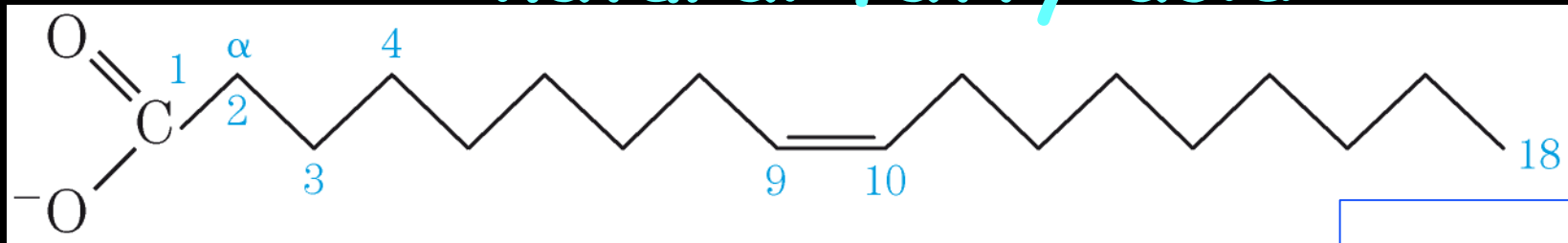


Abbreviation: 18:0

Common name: Stearic acid

IUPAC: n-Octadecanoic acid

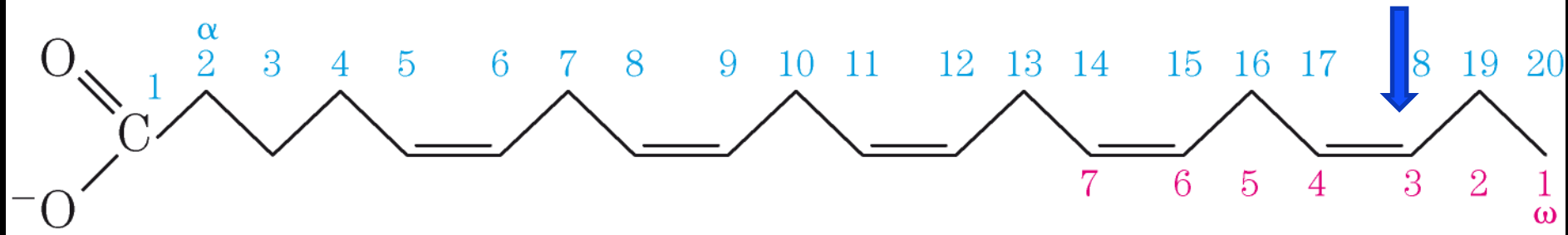
Two conventional nomenclature of natural fatty acid



(a) 18:1(Δ^9) Cis-Δ^9-Octadecanoic acid

(Oleic acid)

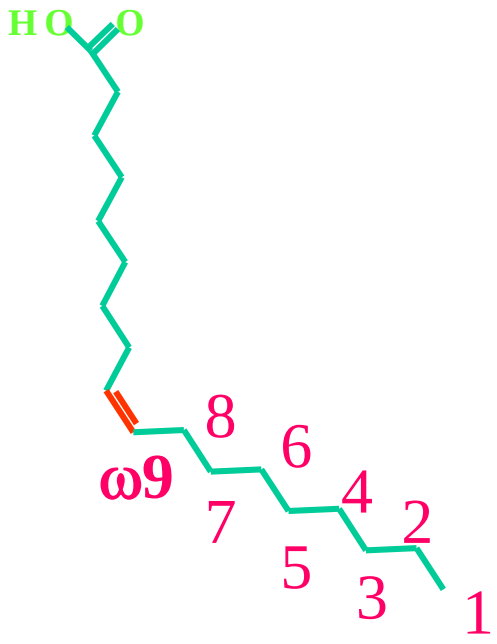
The numbering of the chain starts on the opposite side with respect to -COOH



(b) 20:5($\Delta^{5,8,11,14,17}$) Eicosapentanoic acid (EPA), ω-3

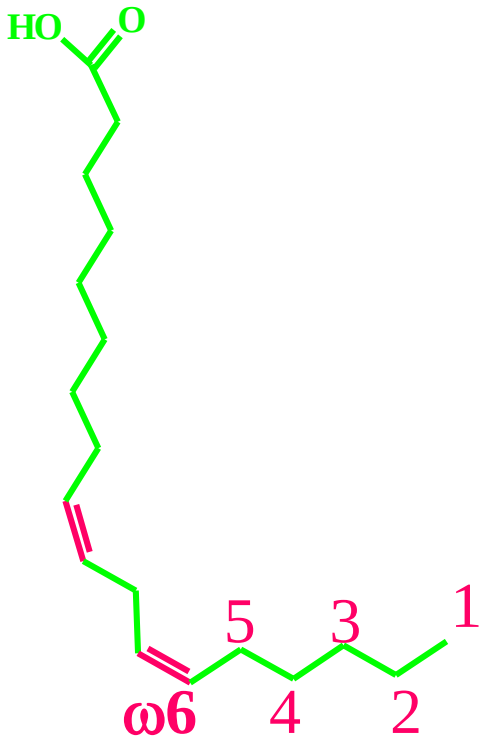
ω

Unsaturated Fatty Acids



Oleic acid
(18:1 Δ^{9})

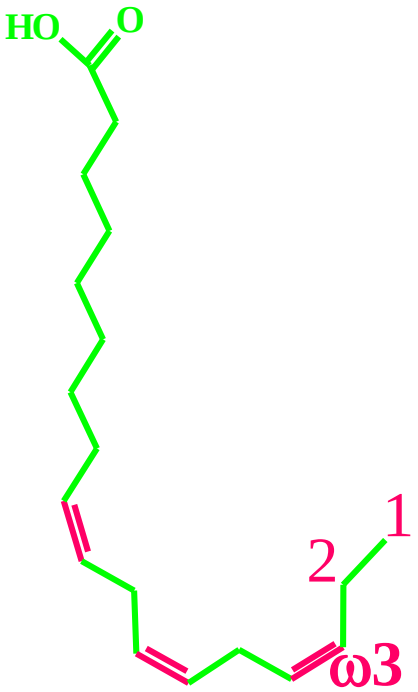
ω-9



Linoleic acid
(18:2 $\Delta^{9,12}$)

ω-6

vegetable oils



α-Linolenic acid
(18:3 $\Delta^{9,12,15}$)

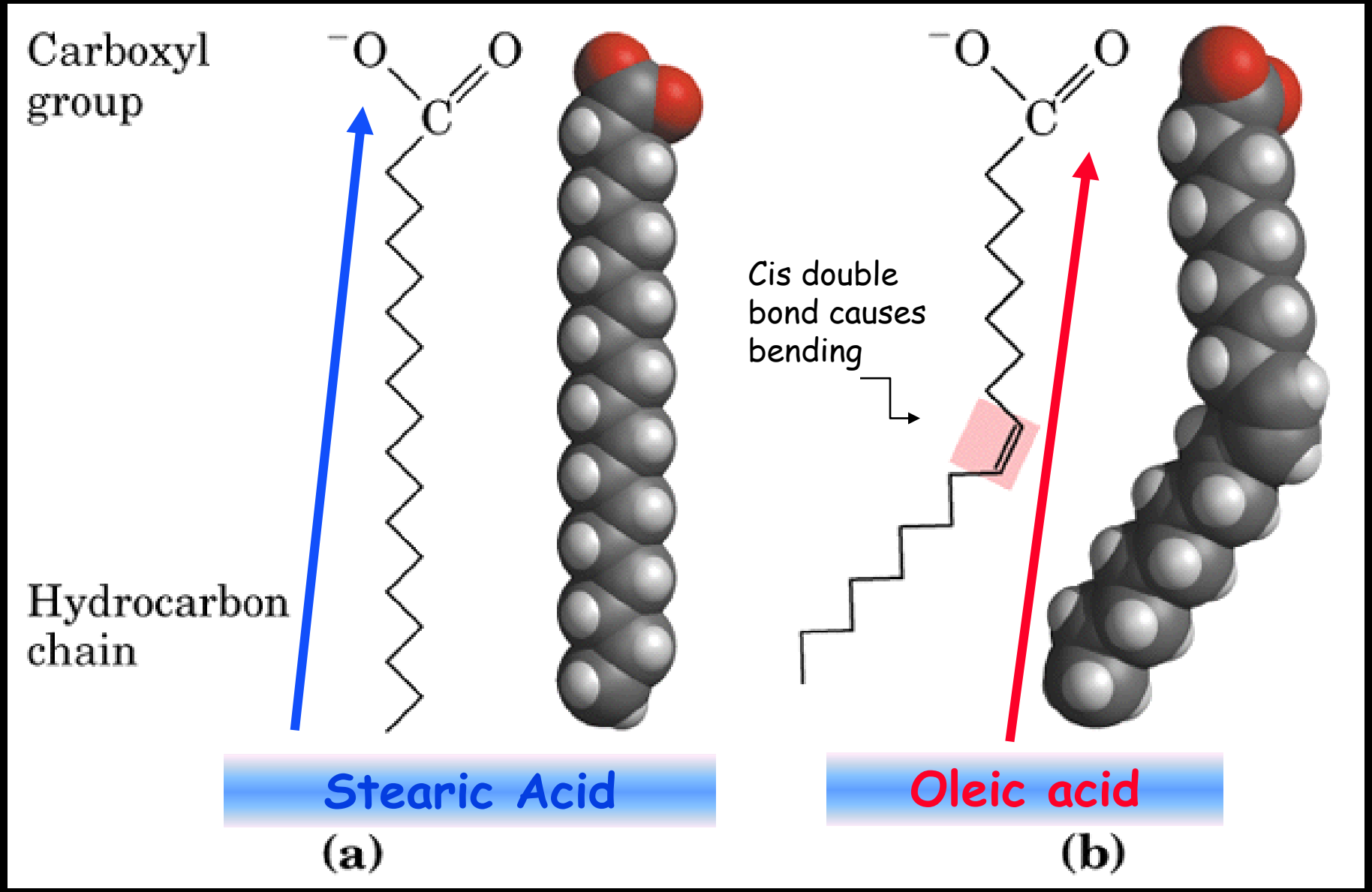
ω-3

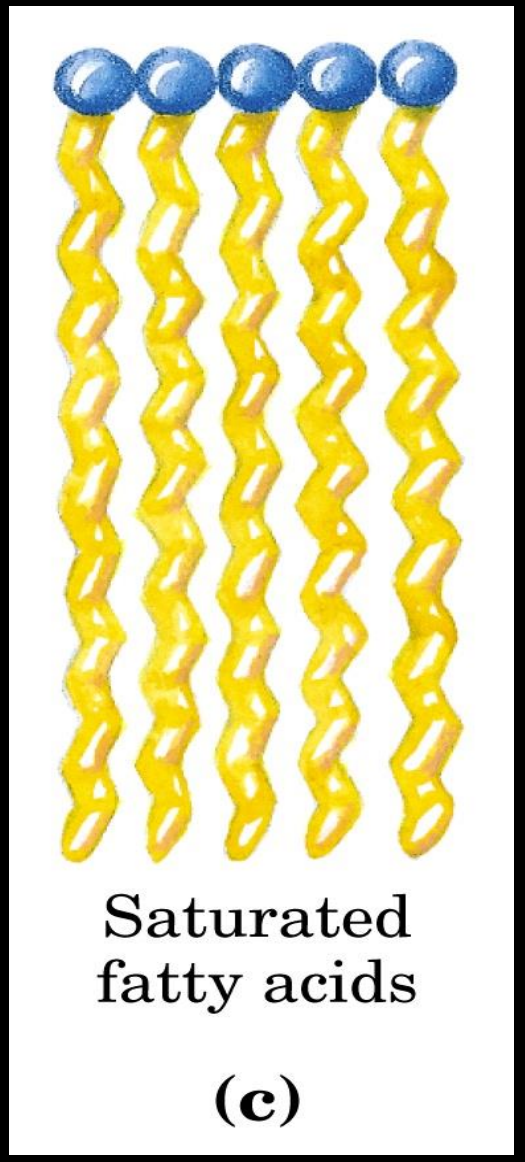
Fishes's fat

Essential fatty acids

Carbon skeleton	Structure*	Systematic name†	Common name (derivation)	Melting point (°C)	Solubility at 30 °C (mg/g solvent)	
					Water	Benzene
12:0	$CH_3(CH_2)_{10}COOH$	*n*-Dodecanoic acid	Lauric acid (Latin *laurus*, "laurel plant")	44.2	0.063	2,600
14:0	$CH_3(CH_2)_{12}COOH$	*n*-Tetradecanoic acid	Myristic acid (Latin *Myristica*, nutmeg genus)	53.9	0.024	874
16:0	$CH_3(CH_2)_{14}COOH$	*n*-Hexadecanoic acid	Palmitic acid (Latin *palma*, "palm tree")	63.1	0.0083	348
18:0	$CH_3(CH_2)_{16}COOH$	*n*-Octadecanoic acid	Stearic acid (Greek *stear*, "hard fat")	69.6	0.0034	124
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		

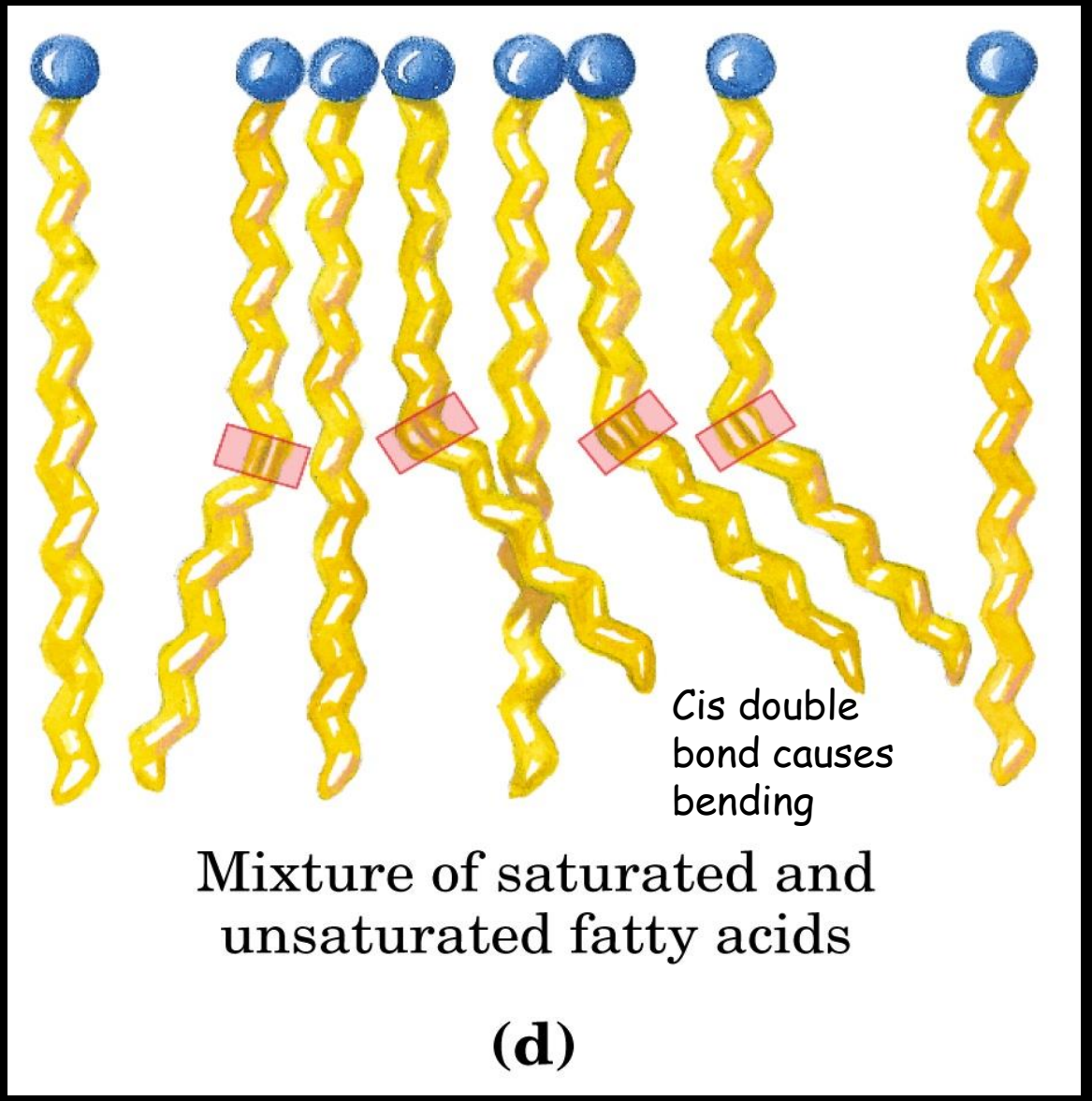
Conformations





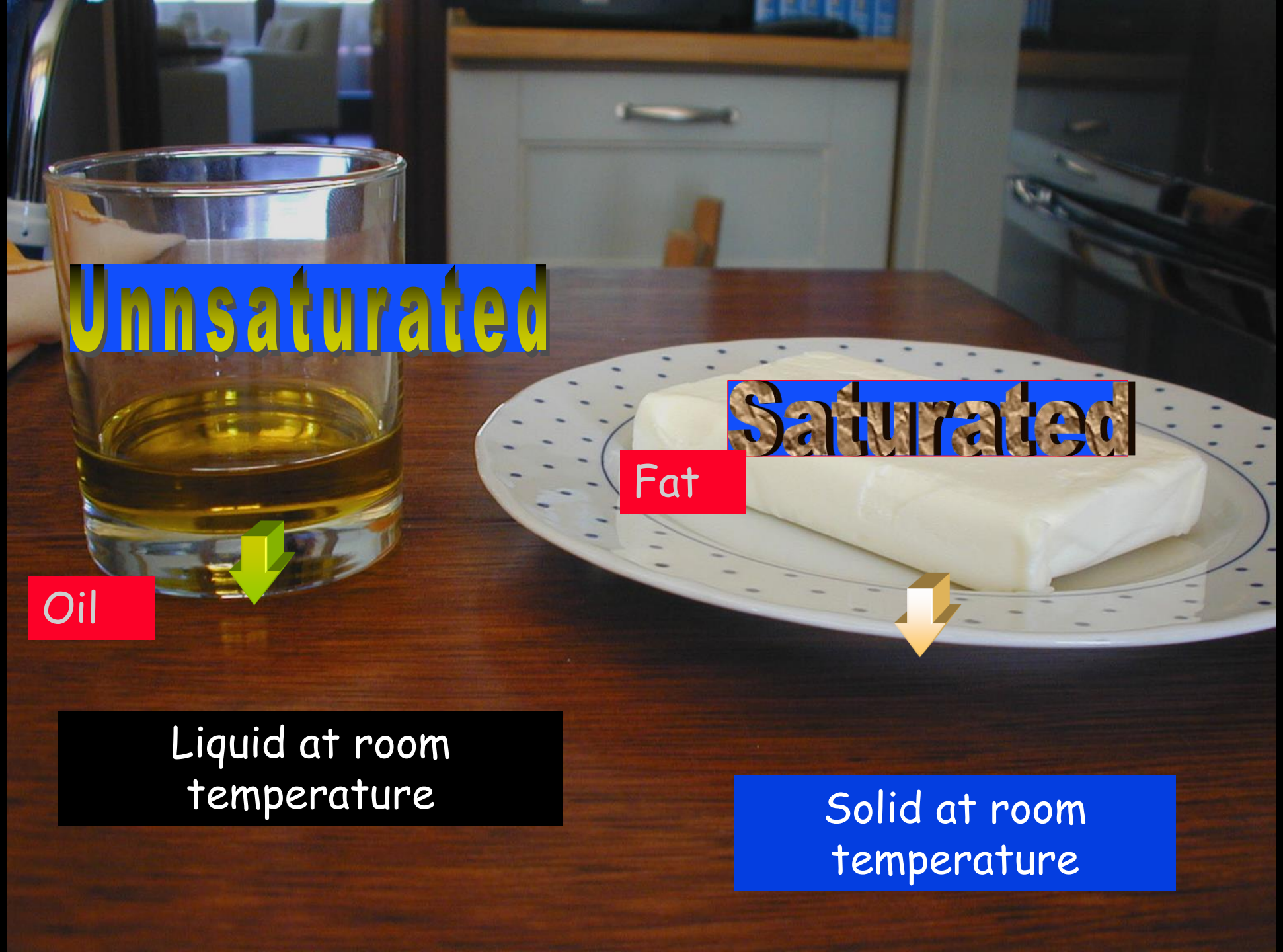
Saturated fatty acids

(c)



Mixture of saturated and unsaturated fatty acids

(d)


Unnsaturated
Oil
Liquid at room temperature
Saturated
Fat
Solid at room temperature

Natural fatty acids

SATURATED

Carbon skeleton	Structure*	Systematic name†	Common name (derivation)	Melting point (°C)	Solubility at 30 °C (mg/g solvent) Water	Benzene
12:0	$CH_3(CH_2)_{10}COOH$	*n*-Dodecanoic acid	Lauric acid (Latin *laurus*, "laurel plant")	44.2	0.063	2,600
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16:1(Δ^9)	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	*cis*-9-Hexadecenoic acid	Palmitoleic acid	−0.5		
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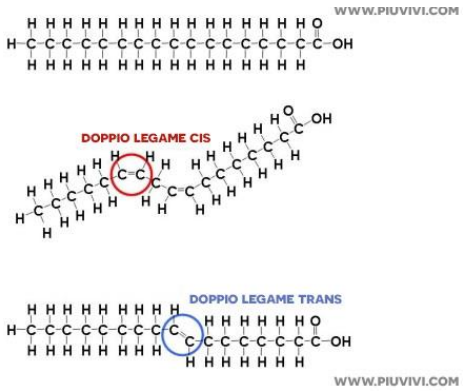
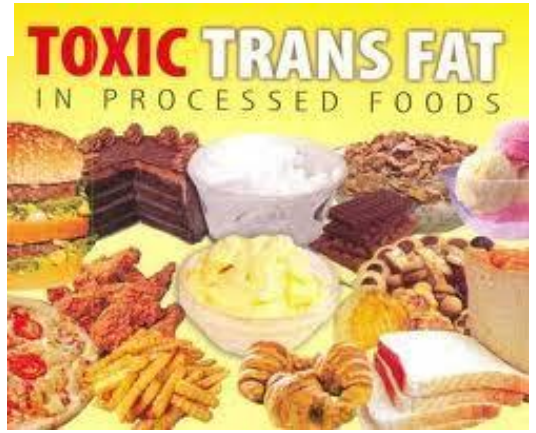
18:3($\Delta^{9,12,15}$)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis*-,*cis*-,*cis*-9,12,15-Octadecatrienoic acid	α-Linolenic acid	−11		
20:4($\Delta^{5,8,11,14}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	*cis*-,*cis*-,*cis*-,*cis*-5,8,11,14-Icosatetraenoic acid	Arachidonic acid	−49.5		

UNSATURATED

Unsaturated fatty acids in contact with oxygen, convert double bond in aldehyde and carboxyl groups .
Short aldehydes and carboxylates are generated that provide a rancid smell to food





To make fats solid, you can hydrogenate them.
In this process the double bonds react with molecular hydrogen on catalysts (nickel or platinum), which transform them into single C-C bonds.
It is a typical reaction of alkenes to alkanes.

This reaction produces trans fatty acid

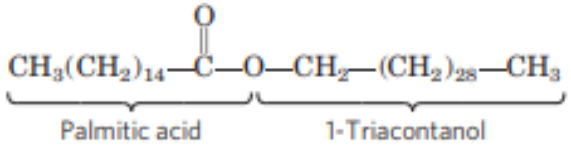
Trans fats contribute to heart disease, cancer, bone problems, hormonal imbalances and skin diseases, infertility, pregnancy difficulties, breastfeeding problems, low weight babies, growth problems and learning difficulties in children.

Waxes Serve as Energy Stores and Water Repellents

The term "wax" originates in the Old English weax, meaning "the material of the honeycomb

Esters of long-chain (C14 to C36) saturated fatty acids

Esters unsaturated of long-chain (C16 to C30) fatty acids



(a)

Triacontanoylpalmitate, the major component of beeswax, is an ester of palmitic acid with the alcohol triacontanol.

honeycomb

FUNCTIONS: related to their water-repellent properties and their firm consistency

Birds, particularly waterfowl, secrete waxes to keep their feathers water-repellent.

The shiny leaves of holly and many tropical plants are coated with a thick layer of waxes, which prevents excessive evaporation of water and protects against parasites.

Biological waxes: applications in the pharmaceutical, cosmetic, and other industries.

- Lanolin (from lamb's wool),
- Beeswax
- Carnauba wax (from a Brazilian palm tree)
- Wax extracted from spermaceti oil (from whales)

widely used in the manufacture of lotions, ointments, and polishes.

Lipids Function

1) Storage Lipids and COATING

triacylglycerols (triglycerides):fats, oils and waxes

2) Membrane Lipids

glycerophospholipids

sphingolipids

3) Steroids

Cholesterol and their derivatives:

- cholesterols esters
- vitamin D
- hormones
- bile acid

1) STORAGE LIPIDS : TRIGLYCERIDES

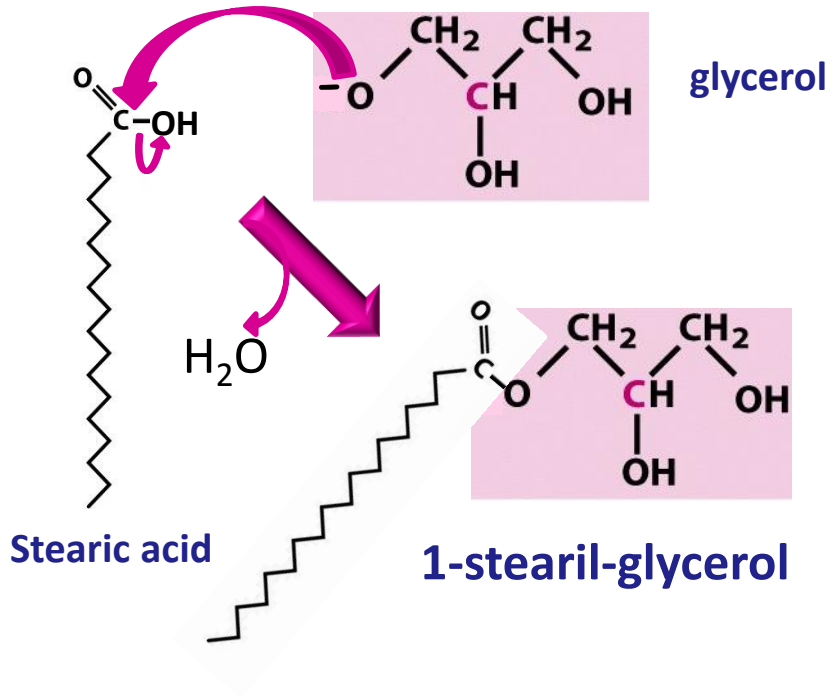
Energy is released from their oxidation.

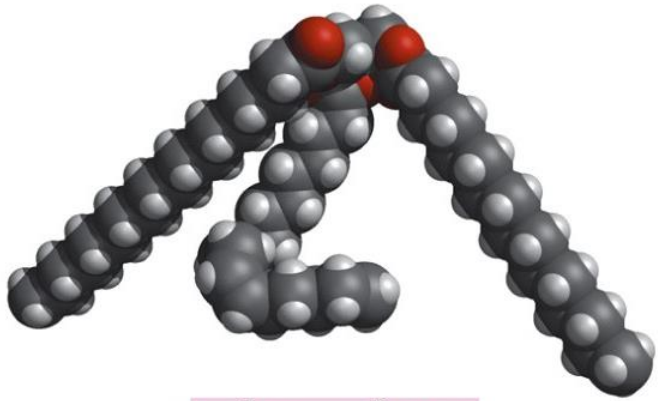
→ **Neutral lipids, apolar**

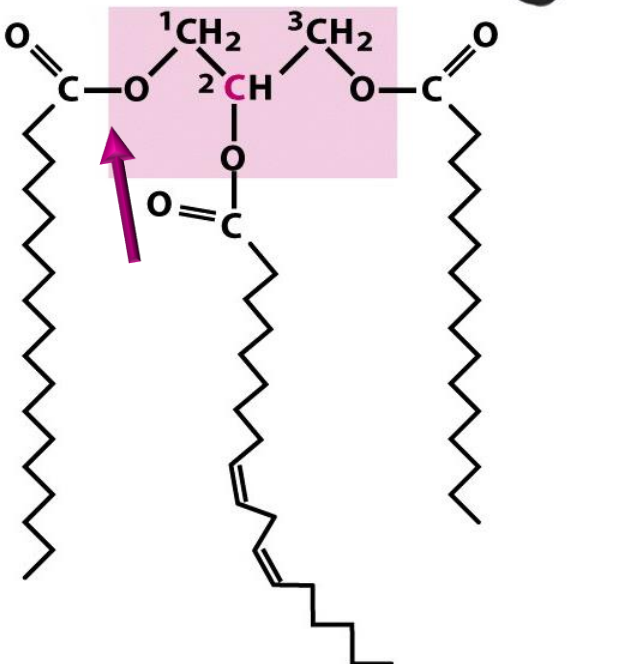
Stored in anhydrous form in fat cells in membrane-limited vacuoles,

Mobilized to produce energy under fasting conditions (for example during sleep).

Glycerol + fatty acid
(ester bond)







1-stearil,2-linoleil,3-palmitoil glycerol

Figure 10-3
Lehninger Principles of Biochemistry, Fifth Edition

Triacylglicerol, Diacylglicerol, and Monoacylglicerol.

Membrane Lipids: glycerophospholipids sphingolipids, cholesterol

Lipids and proteins are the two major components of all membranes ;

Lipids are major components of Membranes

Proteins

From about 20% in the myelin sheath to over 70% in the inner membrane of mitochondria

Their concentrations vary greatly between different membranes:

Contain:

- One Polar head
- Two Hydrophobic tails

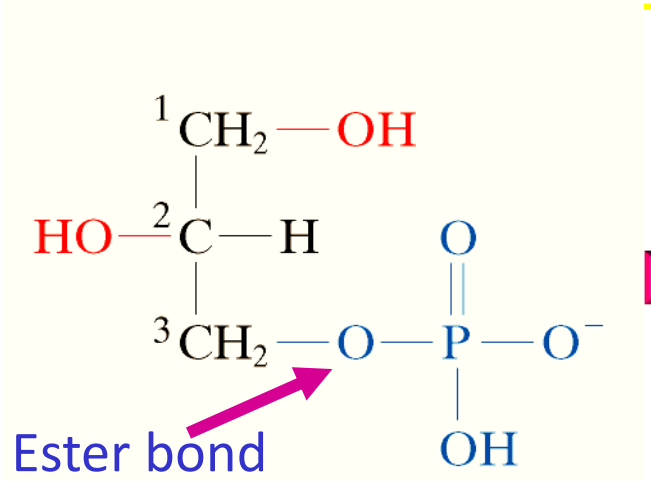
Three major lipids components of eucariotic mambranes:

Membrane Lipids: glycerophospholipids
sphingolipids,
cholesterol

- **Glycerophospholipids (phosphoglycerides)**

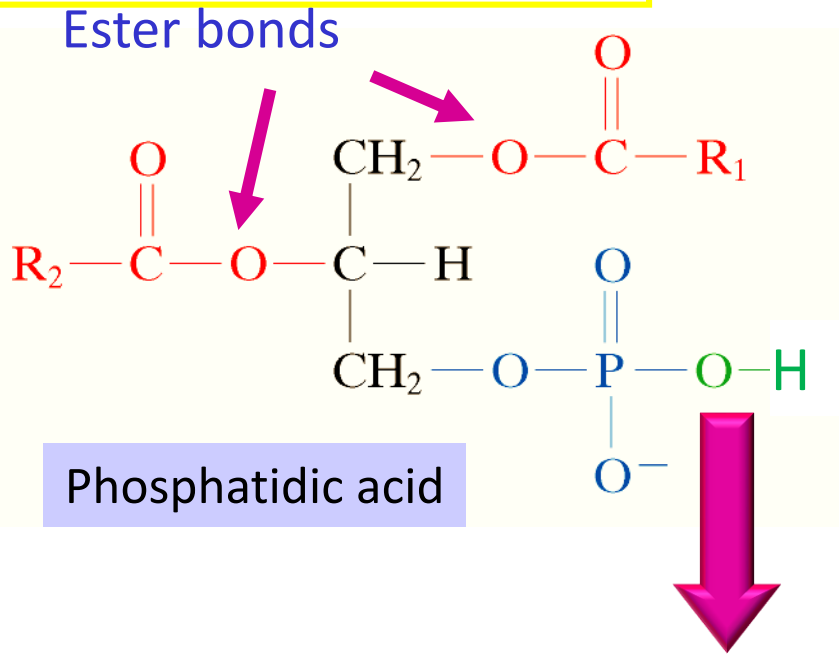
They have a glycerol molecule with a phosphates esterified at carbon atom (C3)

and two long chains of fatty acid esterified to the remaining carbon atoms



glycerol 3-phosphates

+ 2 R-COO$^-$

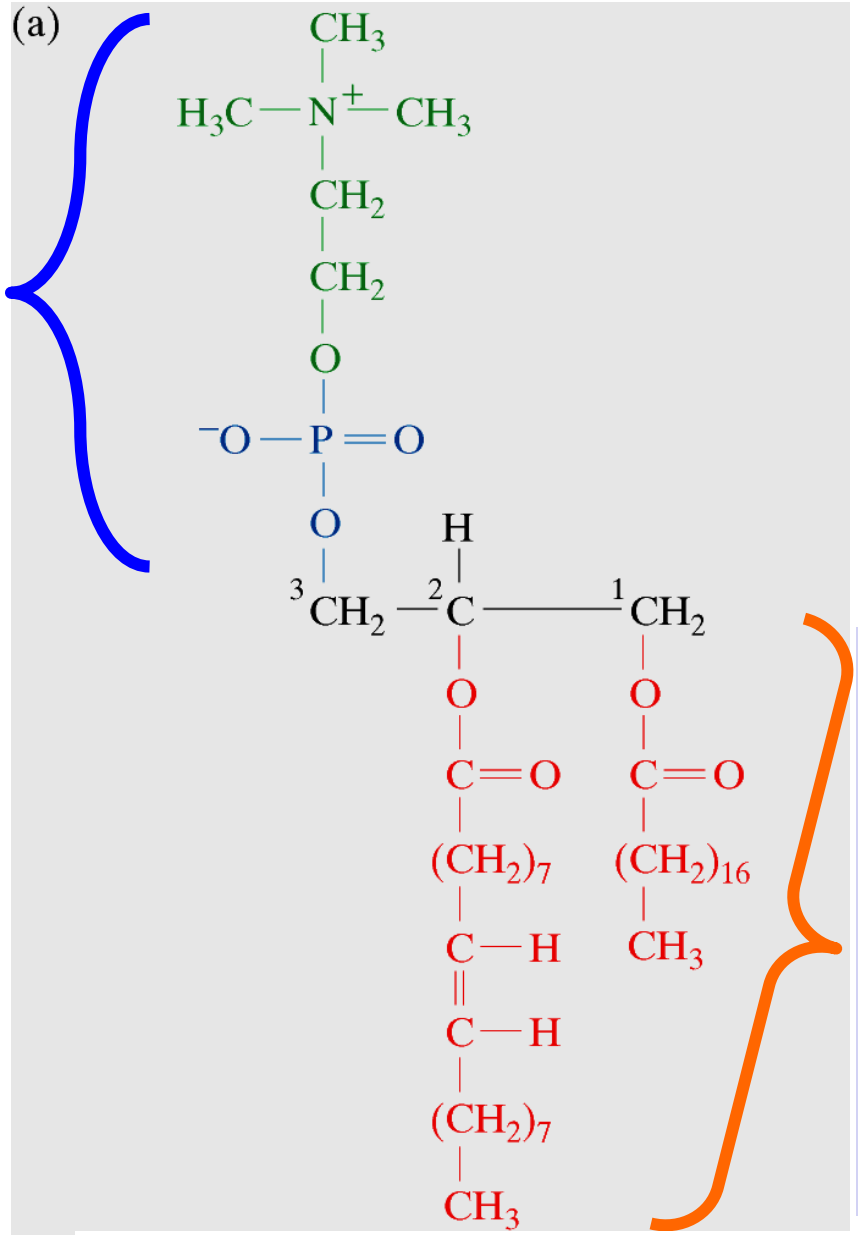


Phosphatidic acid

The phosphate usually forms a second bond with an alcoholic group of another molecules to form "polar head" of glycerophospholipids.

GLYCEROPHOSPHOLIPIDS ARE Amphipatic MOLECULES

Polar Head. hydrofilic: phosphates + Choline



Glycerophospholipids differ for head polar and the type of fatty acid.

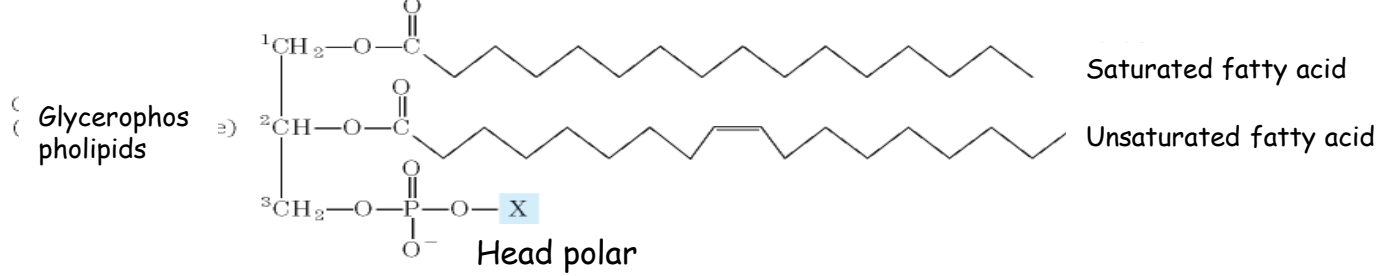
Fatty acid differ for the number of carbon atoms and unsaturated

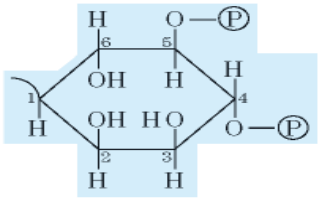
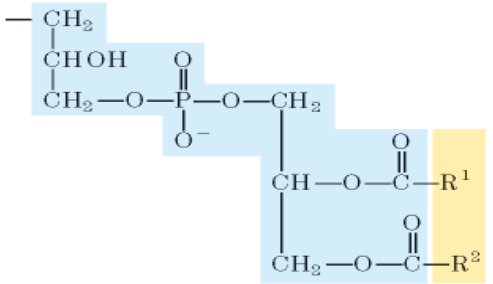
Hydrophobic tail: glycerol + hydrocarburic chain (stearic in C1 e oleic in C2)

-on C1 usually saturated acilic chain

-on C2 usually unsaturated chain

GLYCEROPHOSPHOLIPIDS



name	Name X-O	X	Charge at pH 7
Phosphatidic acid	—	—H	−1
Phosphatidylethanolamine	Ethanolamine	—CH_2—CH_2—$\overset{+}{N}H_3$	0
Phosphatidylcholine	Choline	—CH_2—CH_2—$\overset{+}{N}(CH_3)_3$	0
Phosphatidylserine	Serine	—CH_2—$CH(COO^-)$—$\overset{+}{N}H_3$	−1
Phosphatidylglycerol	Glycerol	—CH_2—$CH(OH)$—CH_2—OH	−1
Phosphatidylinositol 4-5 bisphosphates	Inositol 4-5 bisphosphates		−4
Dihosphatidylglycerol (cardiolipin)	Phosphatidylglycerol		−2

Sphingolipids

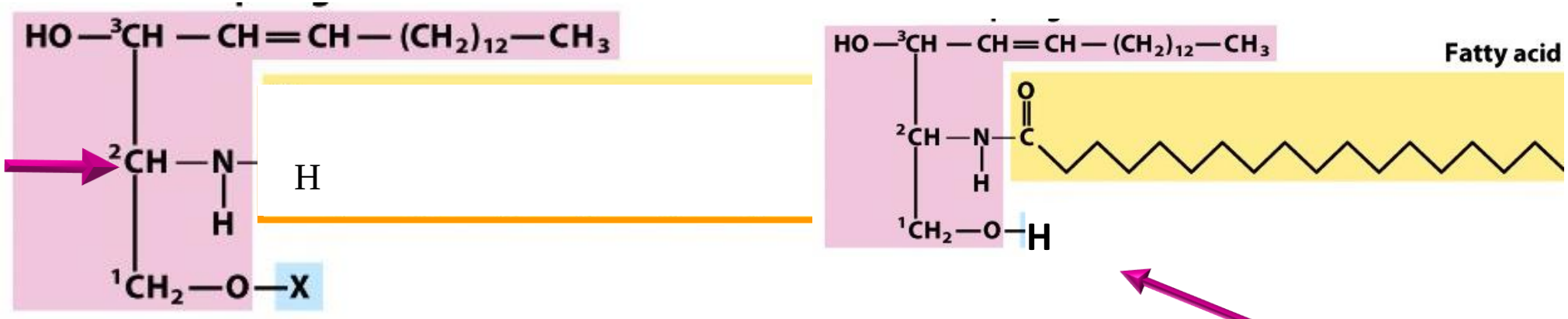
Sphingolipids contain a molecule of sphingosine instead of glycerol

Sphingosine (ammino alcohol of 18 carbon atoms)

- a monounsatur hydrocarburic long chain in C-3,
- two OH- groups in C-3 and C-1
- one aminic group in C-2.

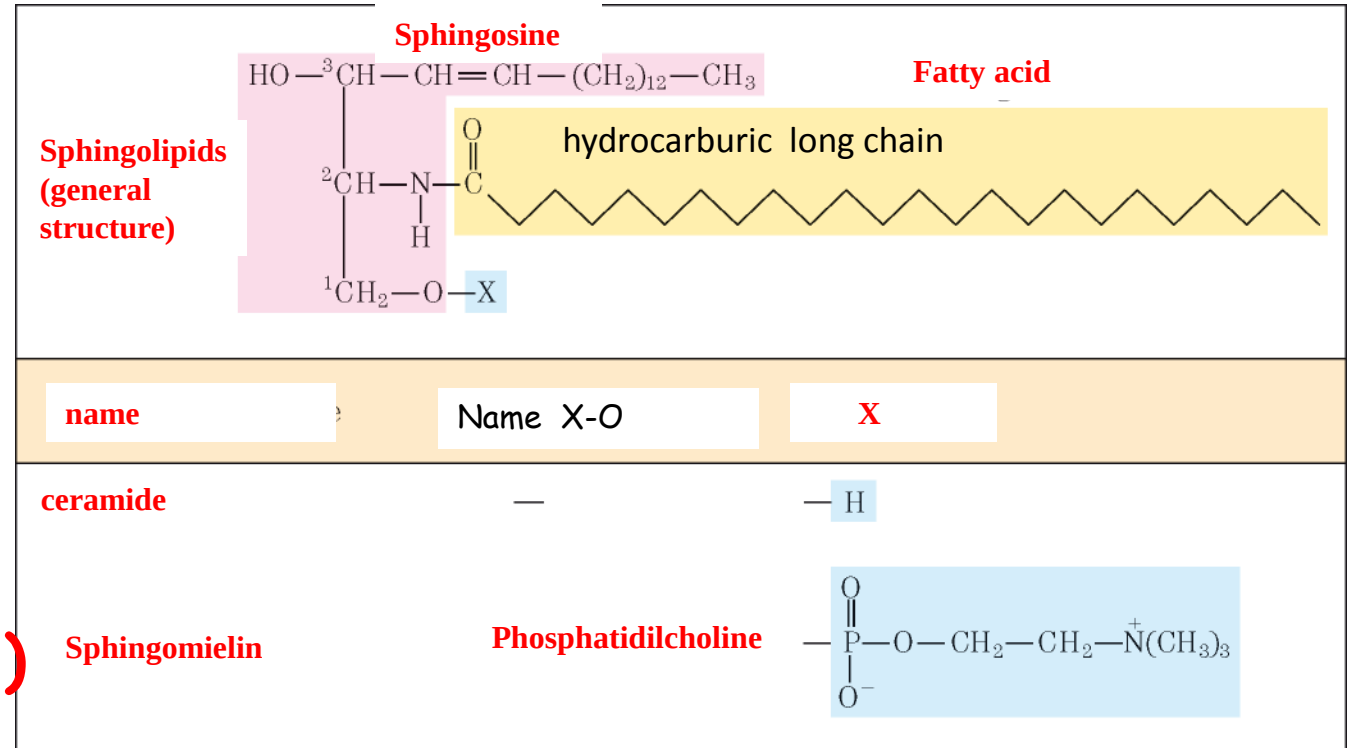
Sphingosine: fatty acid in C2 and H atom in C1 (CERAMIDE).

CERAMIDE is the basic structural of sphingolipids: fatty acid is linked to amminic group by CARBAMIDIC bond.



Ceramide
polar head in C1

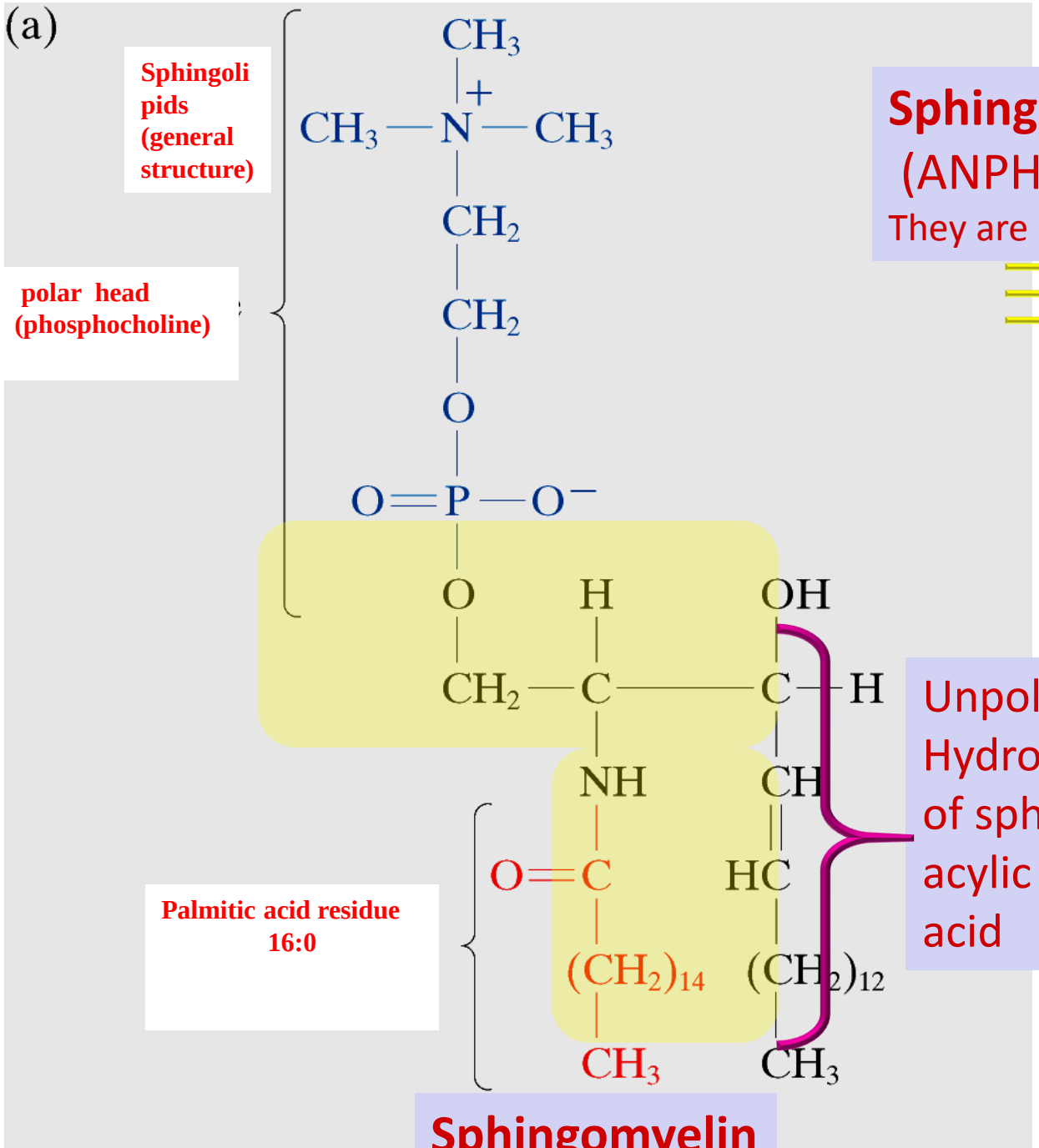
sphingolipids



1)

Sphingosine (18 carbon atoms)

- 2 OH- groups in C-3 and C-1
- 1 aminic group in C-2.

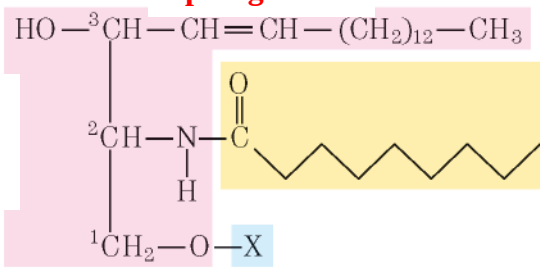


Sphingomyelins:
(ANPHIPATIC)
They are Phospholipids

Unpolar tails: Hydrocarburic chain of sphingosine and acylic chain of fatty acid

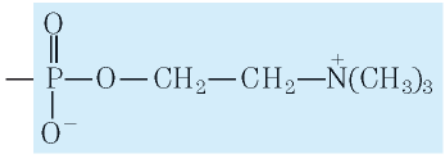
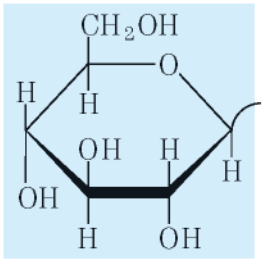
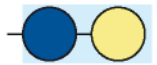
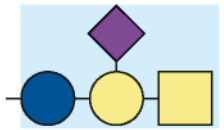
Sphingolipids

Sphingosine



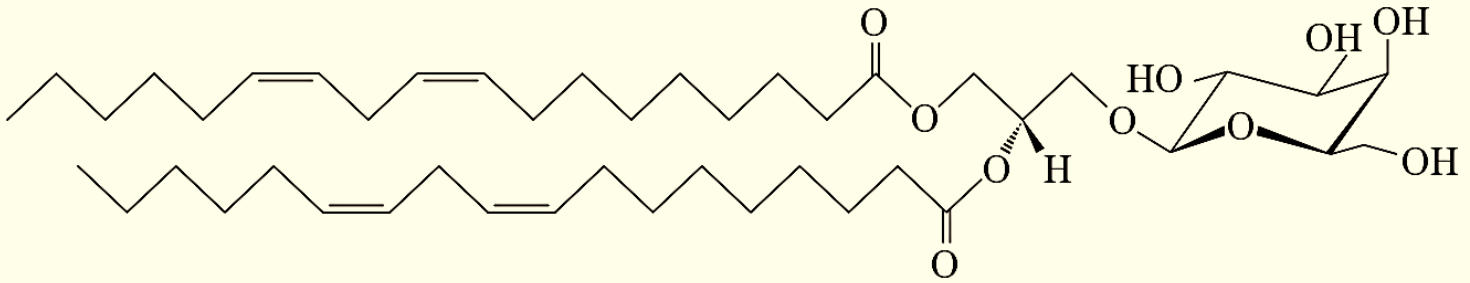
Fatty acid

Sphingolipids (general structure)

	name	Name X-O	X
	ceramide	—	— H
1)	Sphingomielin	Phosphatydilcholine	
2)	Neutral glycolipids (Glycosilcerebroside)	Glucose	
3)	Lactosilceramide (globoside)	Di-tri or tetrasaccharides	
4)	Ganglioside GM2	complex oligosaccharides	

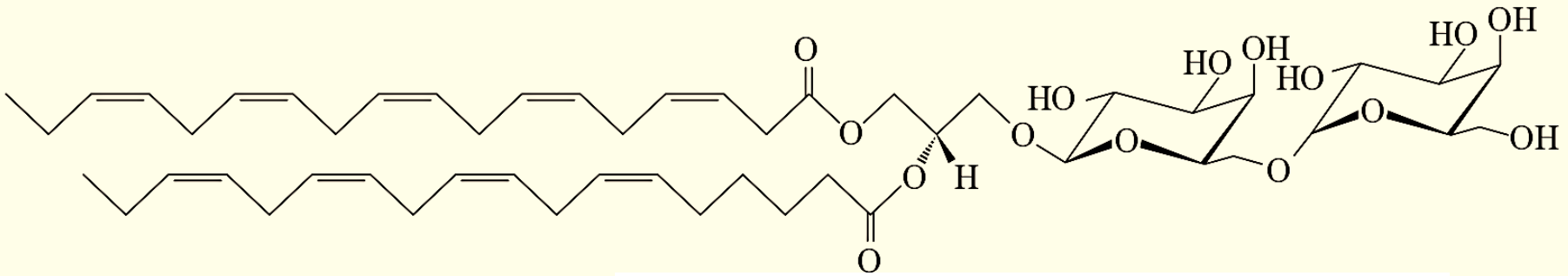
GLYCOLIPIDS: glycerol and polar head with monosaccharides or disaccharides.

They are not phosphorilated



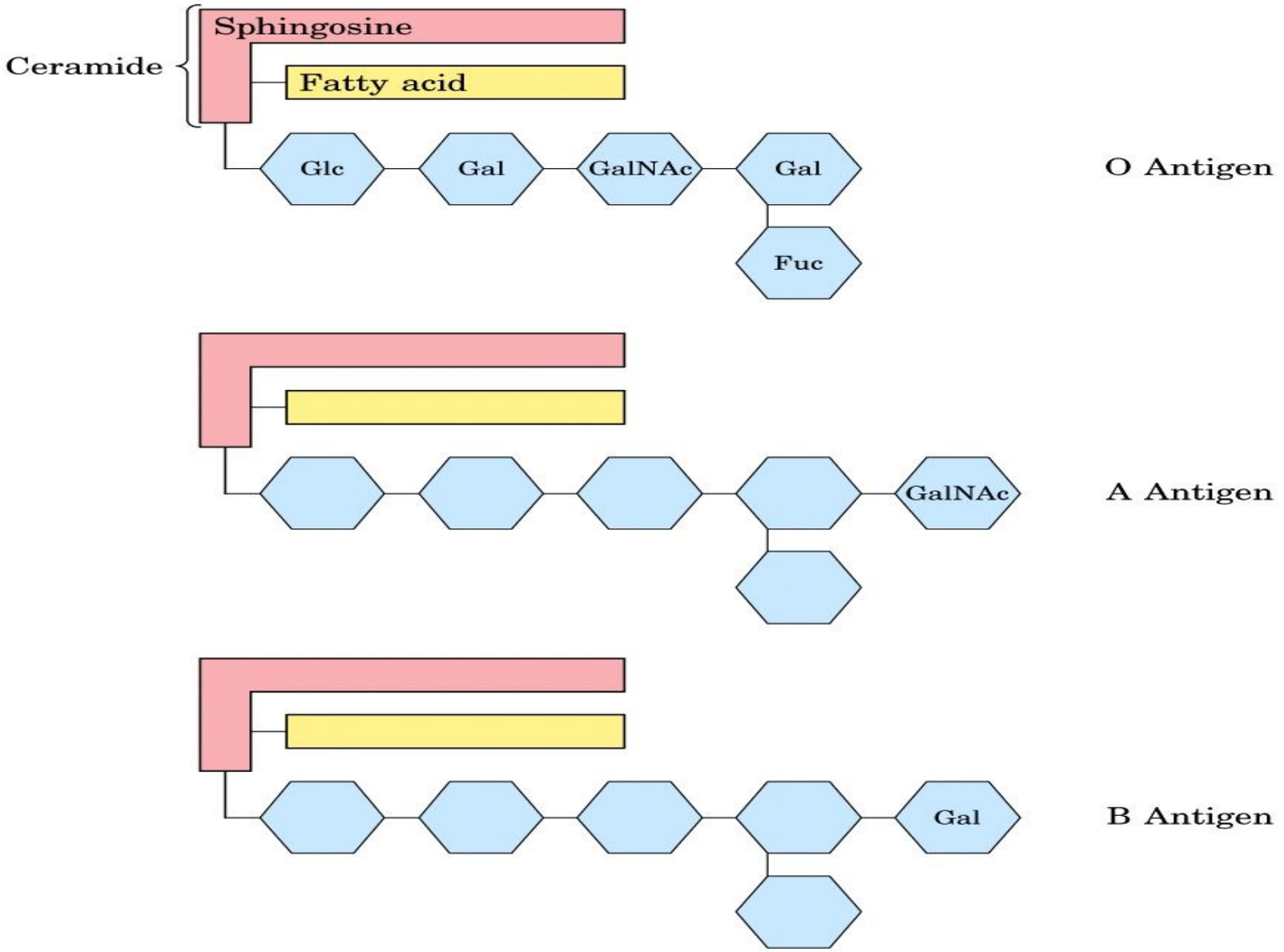
GALACTOLIPIDS

Monogalactosildiacylglycerol (MGDG)



Digalactosildiacylglycerol (DGDG)

Glycophingolipids in Blood groups



GLYCOSPHINGOLIPIDS

Not contain phosphorus but contain carbohydrates in glycosidic linkage to the primary alcohol of a ceramide

1)Cerebrosides

2) Globosides

} NEUTRAL GLYGOLIPIDS

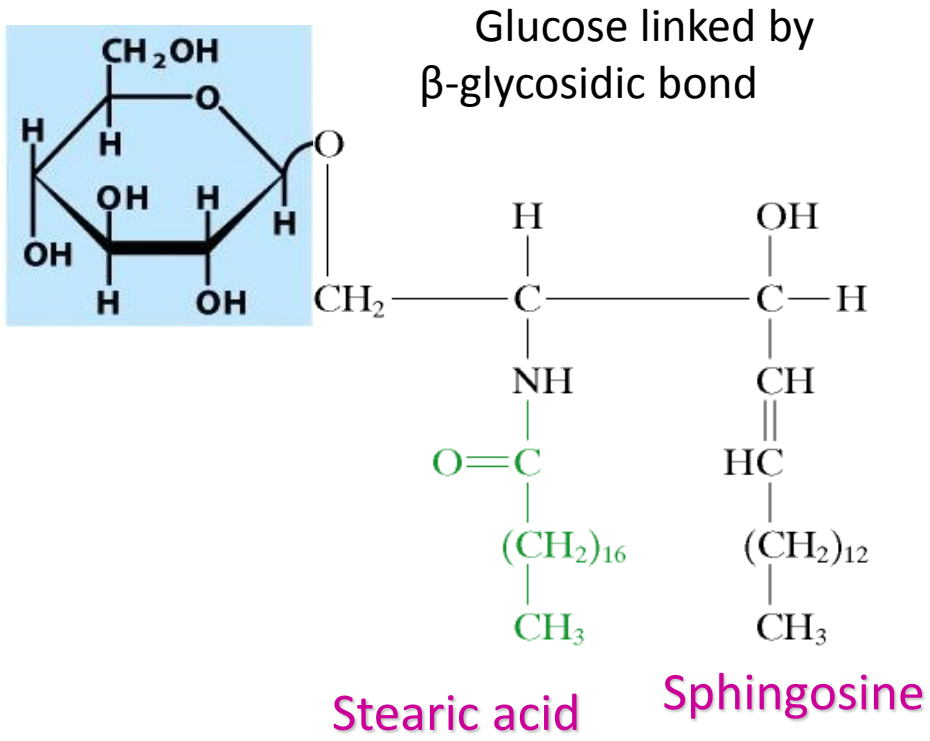
3)Gangliosides — POLAR GLYGOLIPIDS

GLYCOSPHINGOLIPIDS

1)Cerebrosides

a single Glucose or galactose linked to a ceramide by glycosidic bond

GLUCOSYLCERAMIDE



GLYCOSPHINGOLIPIDS

1)Cerebrosides
2) Globosides
3)Gangliosides

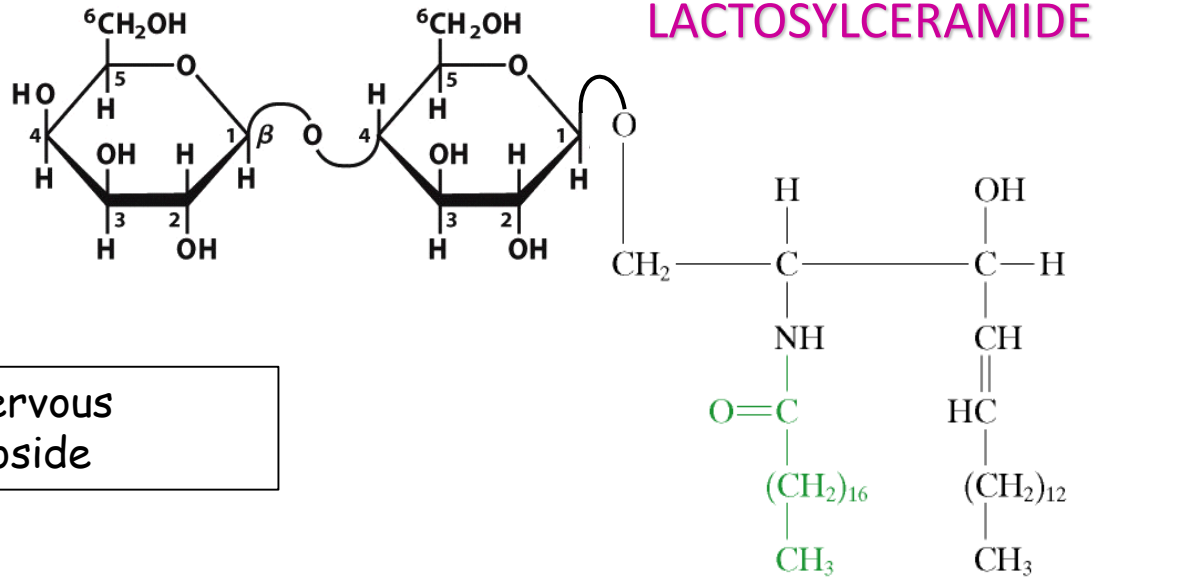
2) Globosides: are ceramide oligosaccharides

two or more neutral monosaccharides (usually galactose or glucose, or N-acetylgalactosamine) linked to a ceramide by glycosidic bond

The oligosaccharides are uncharged

Globosidi:
LACTOSYLCERAMIDE

Lactosylceramide is present in the erythrocyte membrane



Another globoside of the nervous system is ceramide-tri-hexoside

Stearic acid

Sphingosine

Ceramide-hexoside accumulates in kidney of patients with Fabry's disease,
A deficiency of lysosomial alpha-galactosidase A.

GLYCOSPHINGOLIPIDS

1)Cerebrosides
2) Globosides
3)Gangliosides

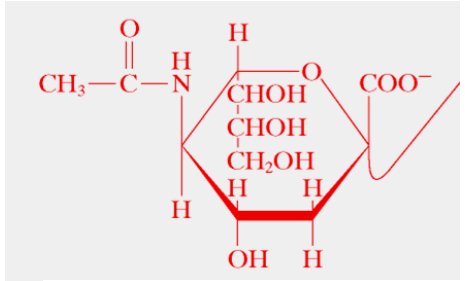
3)Gangliosides: First identification in high concentrations in the central nervous system ganglia cells

Sialic acid is highly contained in ganglia cells of the central nervous system

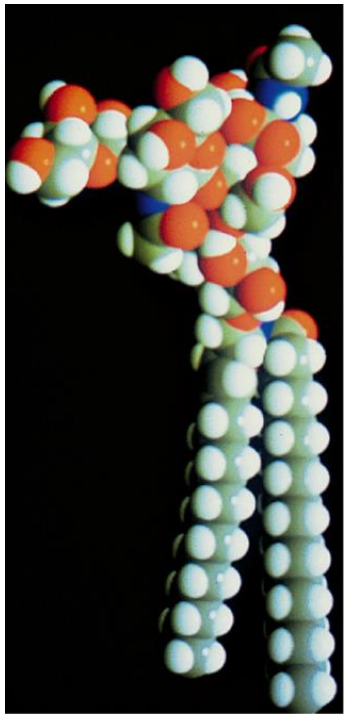
- CNS (50% of total sialic acid is represented)
- Non-nerveous cells (10% of the total sialic acid)

(plasma membrane of cells or other tissue)

- Main components of cell-surface membranes
- Constitute 6% of brain lipids.



N-Acetylneuraminic (sialic acid) (NANA)



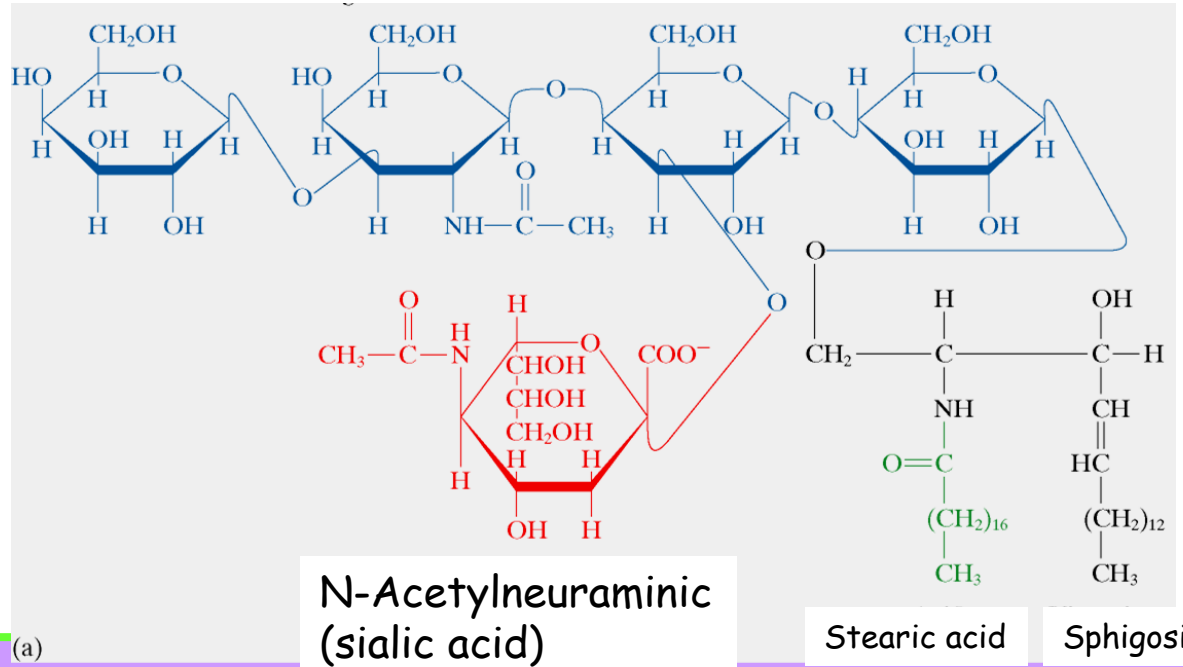
- Gangliosides have considerable physiological and medical significance.
- Receptors for bacterial protein toxins.

GLYCOSPHINGOLIPIDS

3)Gangliosides

- a oligosaccharide containing one or more sialic acid

- Have a polar head with negative charge at pH 7



N-Acetylneuraminic (sialic acid) (NANA)

Stearic acid

Sphigosine

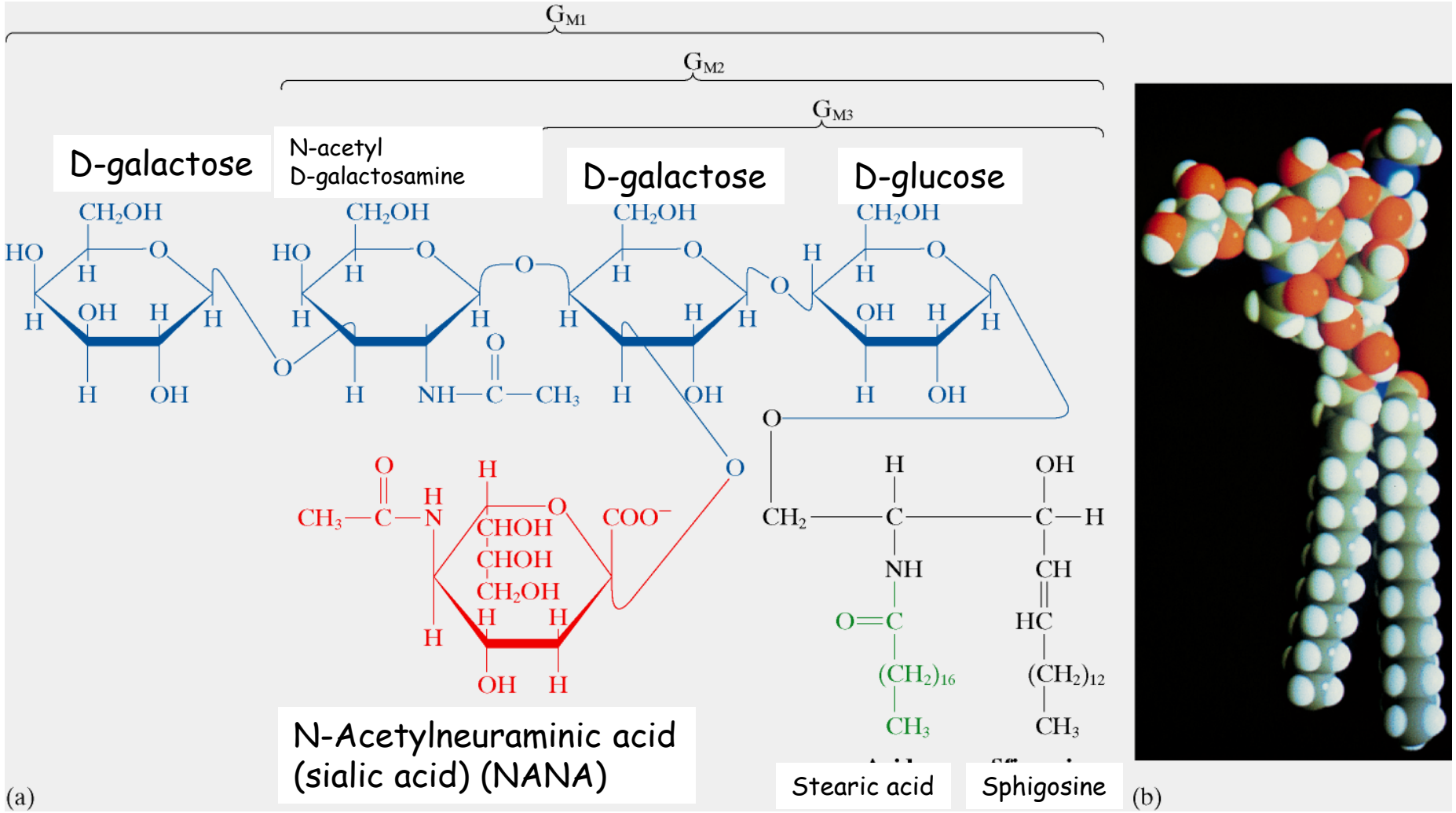
GANGLIOSIDES

Nomenclature

Depends on the number of sialic acids

GM: one sialic acid residue
GD: two sialic acid residues
GT: three sialic acid residues
GQ: four sialic acid residues

GANGLIOSIDES

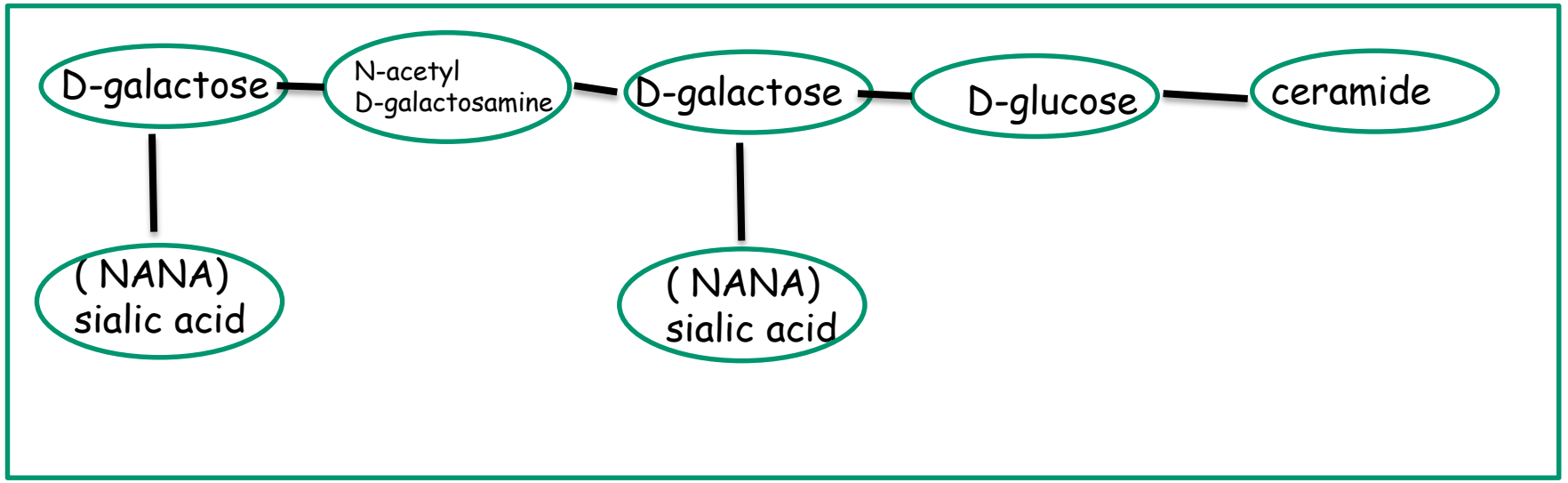


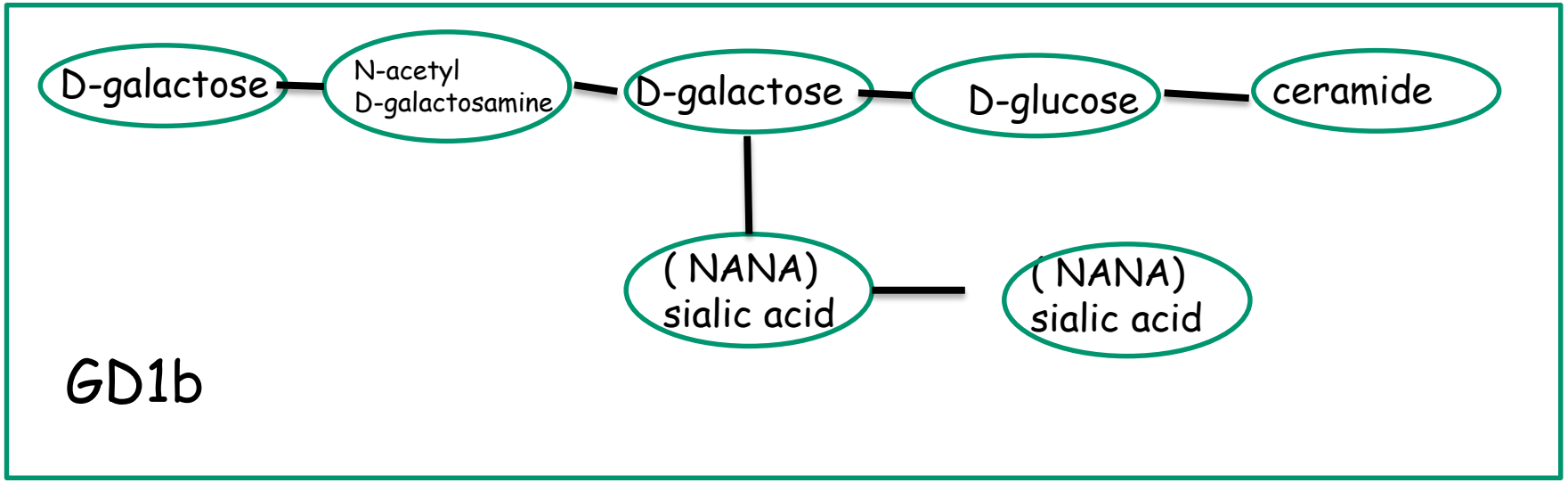
Gangliosides GM2 e GM3 differ from GM1 only by the sequential absences of-
the terminal D-galactose and N-acetyl D-galactosamine residues.

GANGLIOSIDES

Gangliosides GD1a differ from GD1b on the basis of the sialic acid position

GD1a

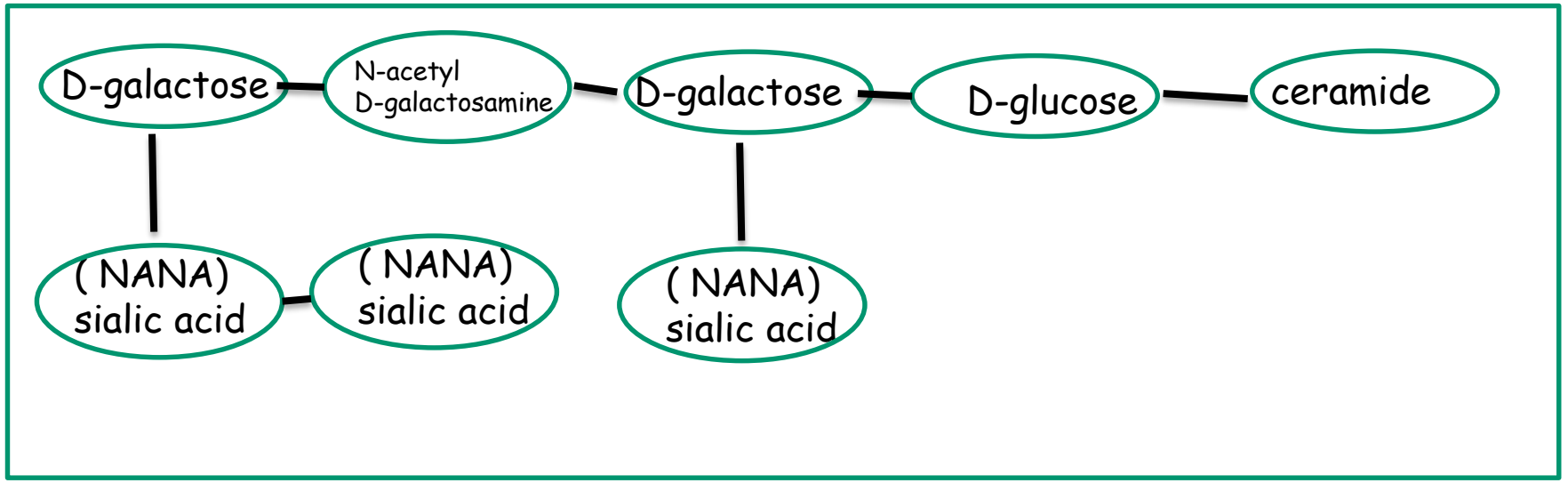


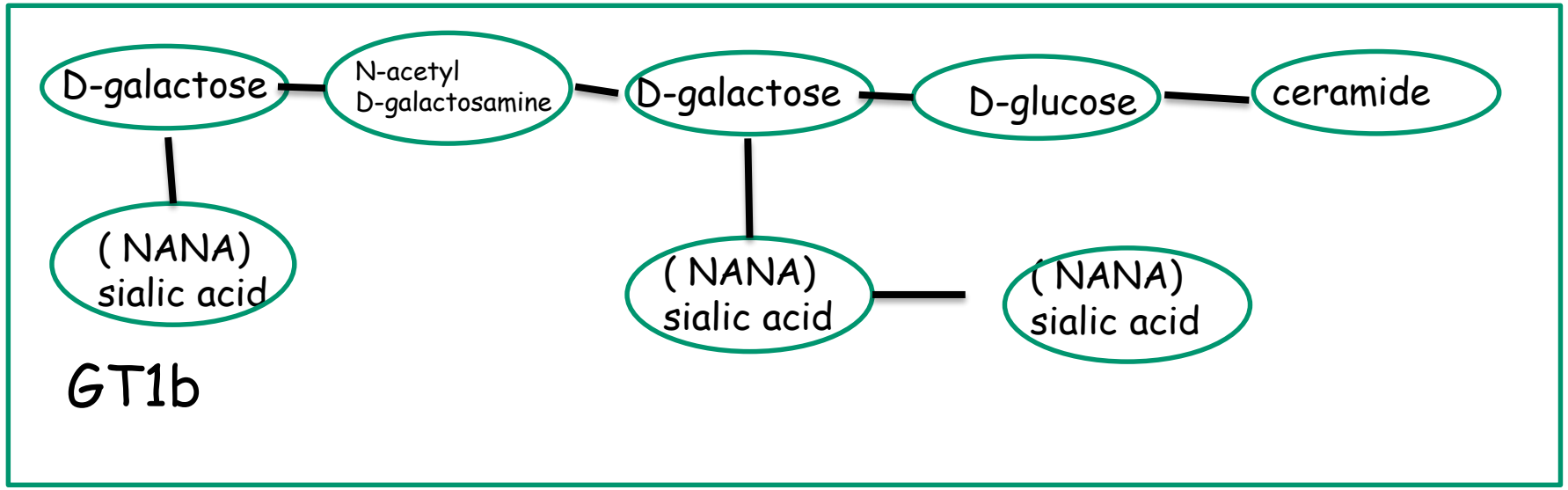


GANGLIOSIDES

Gangliosides GT1a differ from GT1b on the basis of the sialic acid position

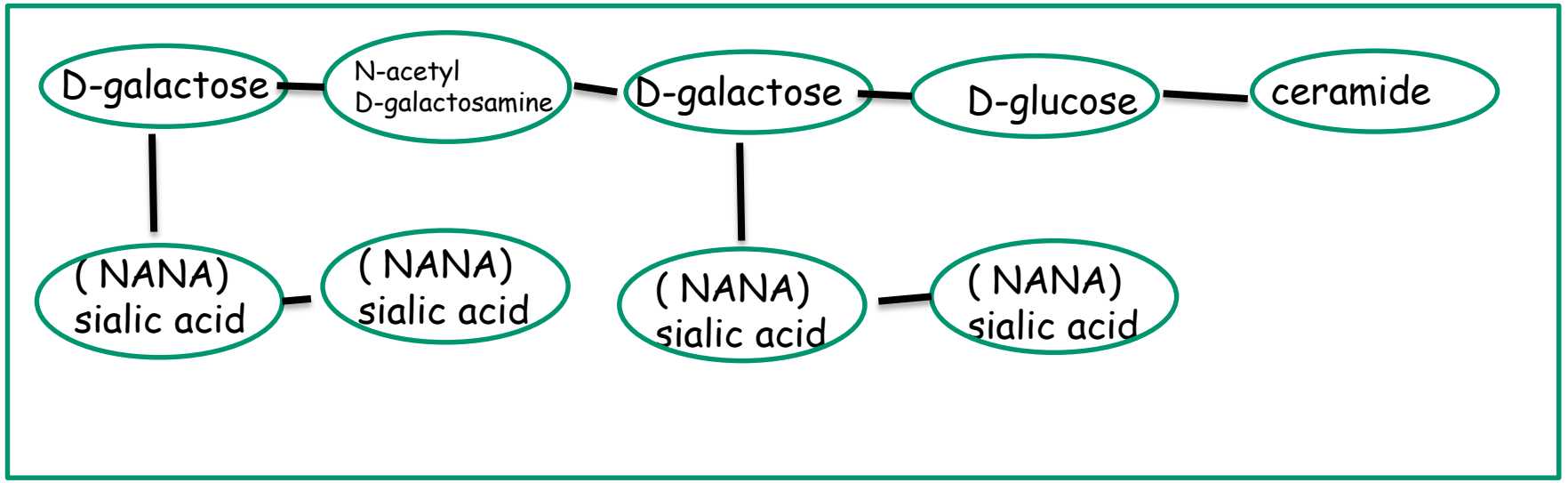
GT1a





GANGLIOSIDES

GQ1b



GQ: four sialic acid residues

GANGLIOSIDES

Gangliosides on intestinal mucosal cells bind cholera toxin , an 84-kDa protein secreted by pathogen *Vibrio cholerae*

The toxin stimulates secretion of chloride ions into the gut lumen, resulting in the copious diarrhea of cholera.

Gangliosides may also bind other toxins, such as tetanus toxin, and certain viruses, such as flu virus.

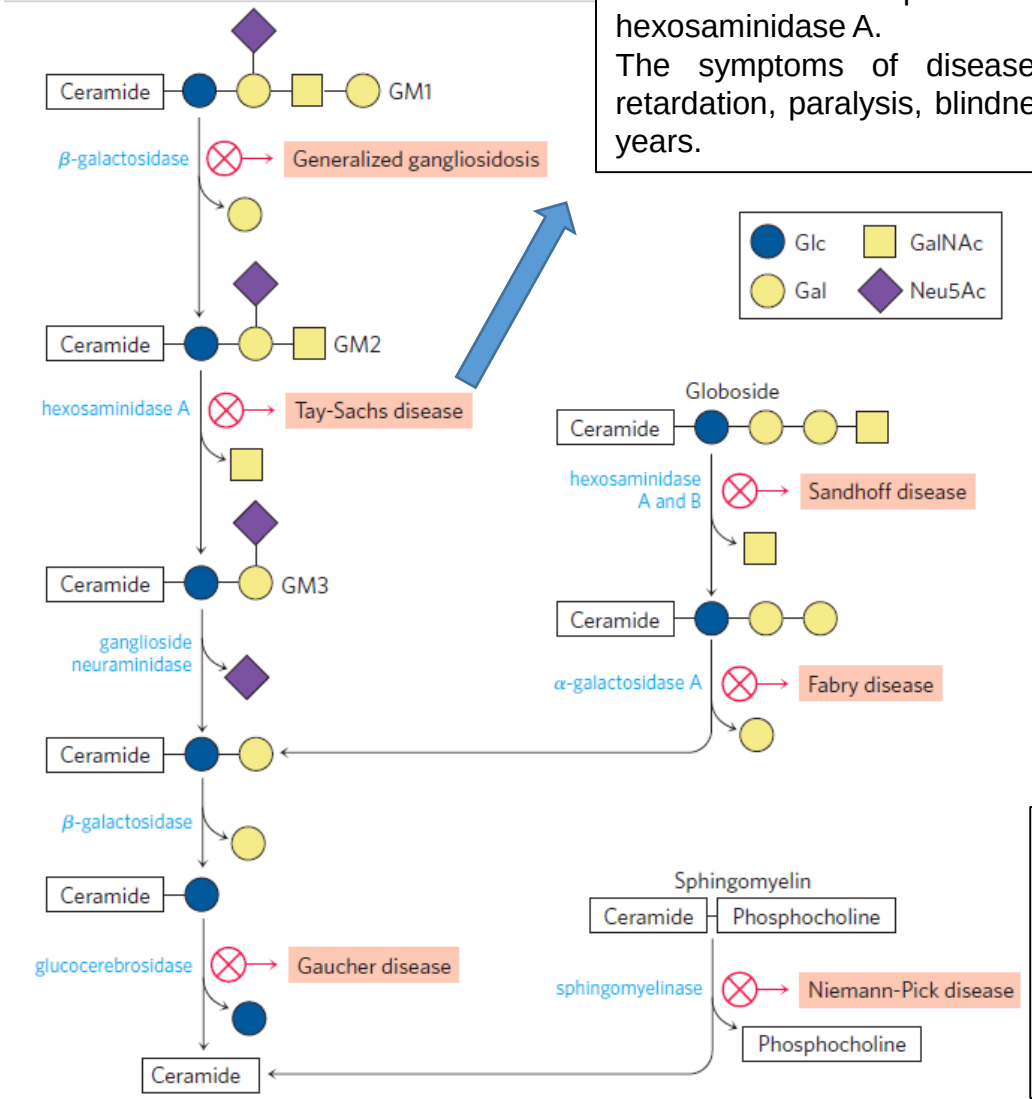
Disease:

- **GM1 Gangliosidosis (autosomal recessive metabolic disease) characterized by:**

- **Impaired psychomotor function**
- **Mental retardation**
- **Hepatosplenomelaly**
- **Death within the first few years of life**

- **Accumulation of GM1 is due to a marked deficiency of B-galactosidase**
-
- **Tay-Sachs disease (accumulation of GM2 in brain)**

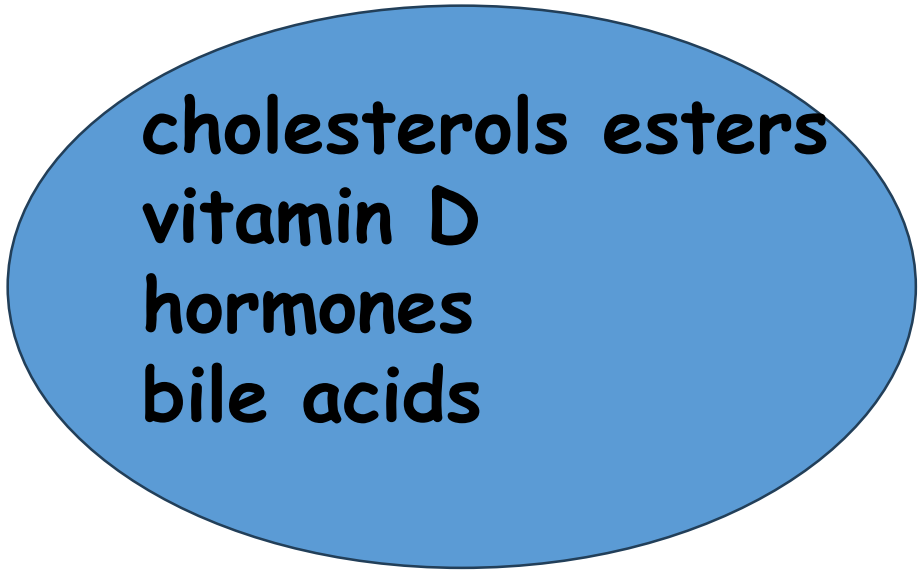
Tay-Sachs disease, in which ganglioside GM2 accumulates in the brain and spleen owing to lack of the enzyme hexosaminidase A.
The symptoms of disease are progressive developmental retardation, paralysis, blindness, and death by the age of 3 or 4 years.



is caused by a rare genetic defect in the enzyme sphingomyelinase,which cleaves phosphocholine from sphingomyelin. Sphingomyelin accumulates in the brain, spleen, and liver. The disease becomes evident in infants and causes mental retardation and early death

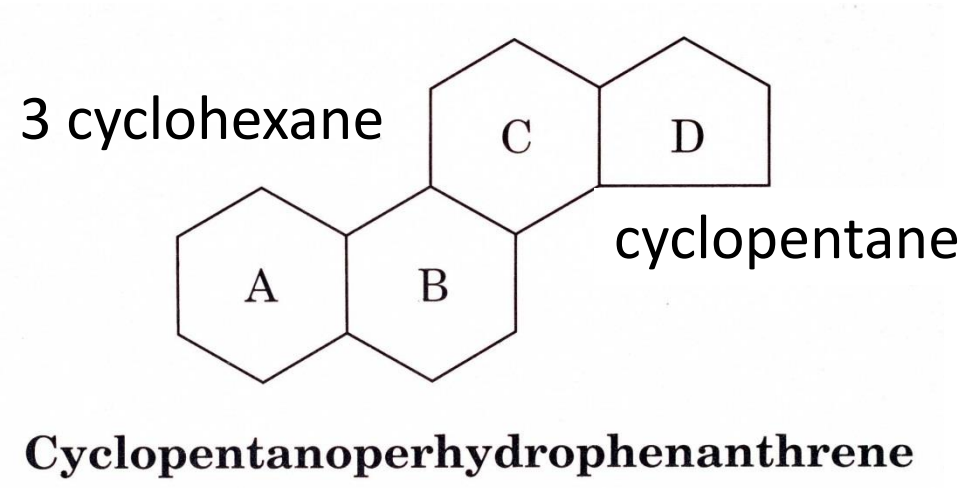
Steroids

Cholesterol and their derivatives:



Cholesterol

Component of cell membranes
Starting molecule for the synthesis of other steroid

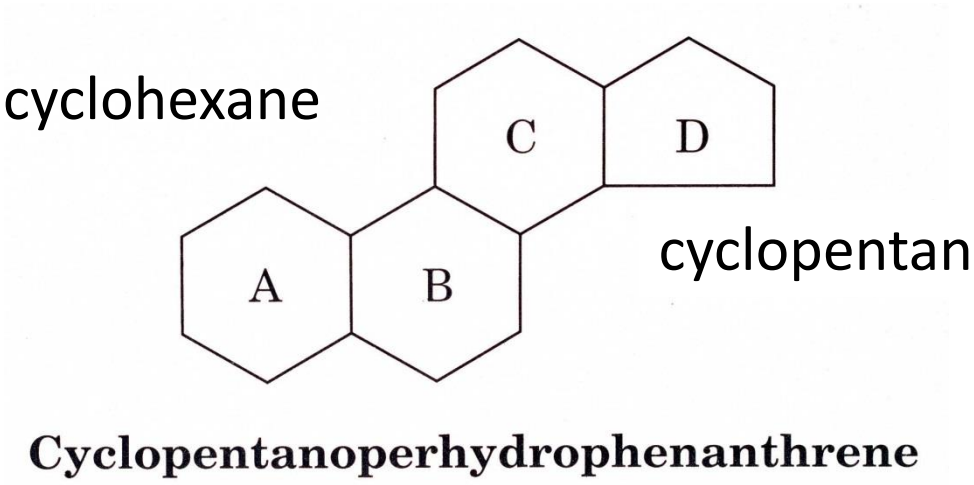


- Structural lipids of membrane
- Precursors of bile acids
- Metabolic precursors of steroid hormones and vitamins
- Cofactors in more reactions

Steroids

Steroids are derivatives of cyclopentanoperhydrophenanthrene

3 cyclohexane



cyclopentane

Cyclopentanoperhydrophenanthrene

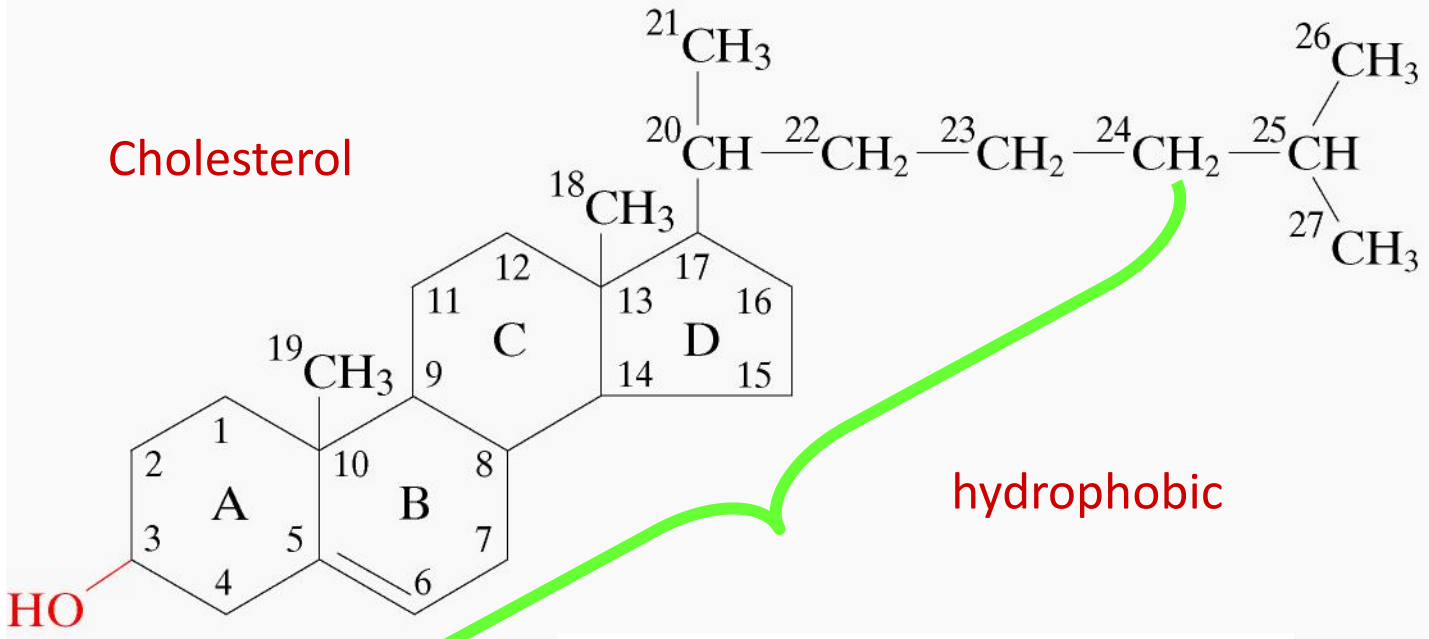
Steroids

Derivatives of Cyclopentaneperhydrophenanthrene

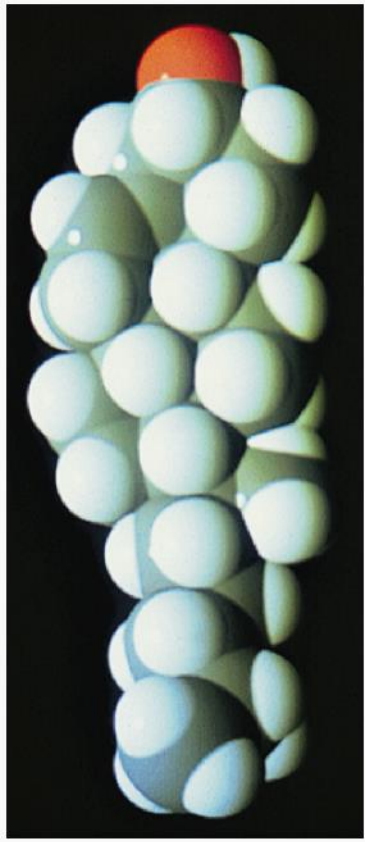
Steroid nucleus is rather rigid , Planar structure

Structural lipids of cellular membranes

(a)



(b)

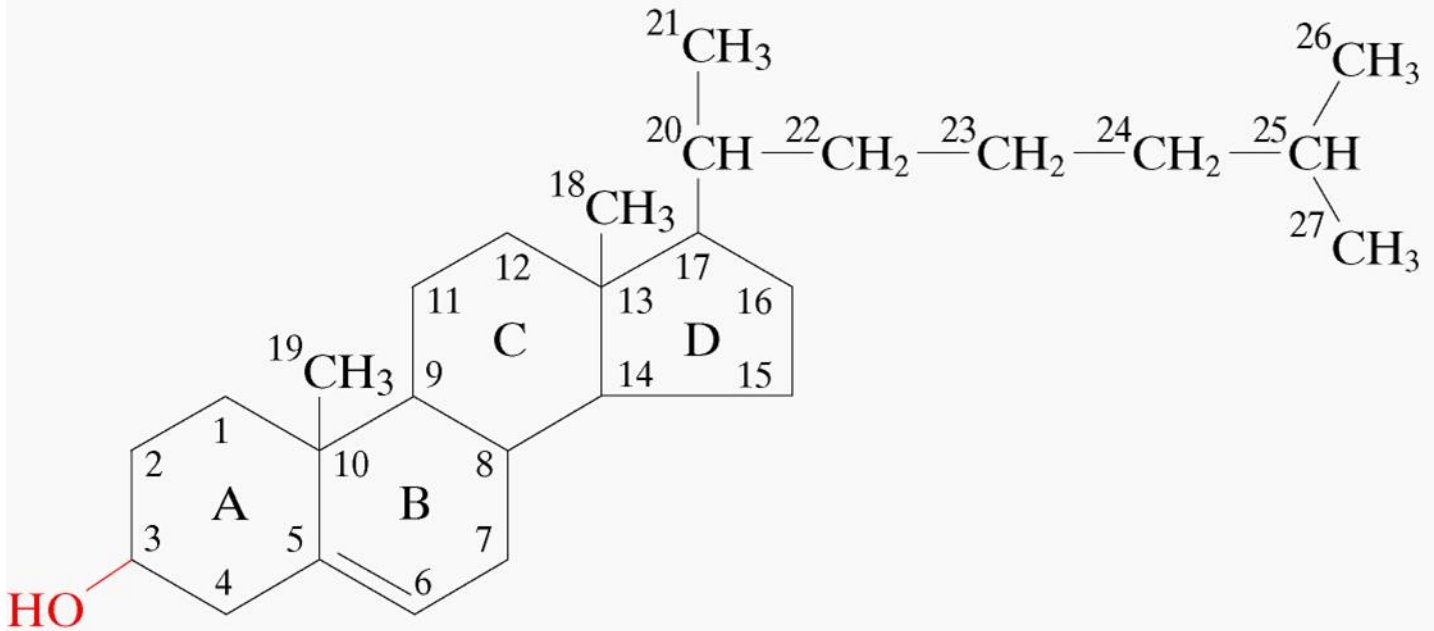


Polar head
Free cholesterol is esterified
by fatty acid

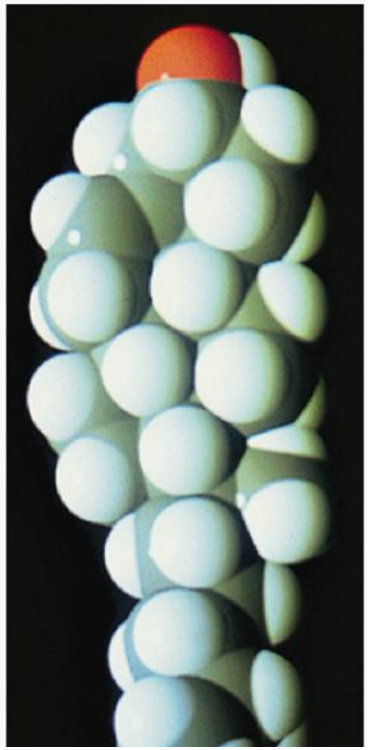
Sterol abundant in animals cells membranes
Anphipatic

Plants= stigmasterol
mushrooms= ergosterol

(a)



(b)



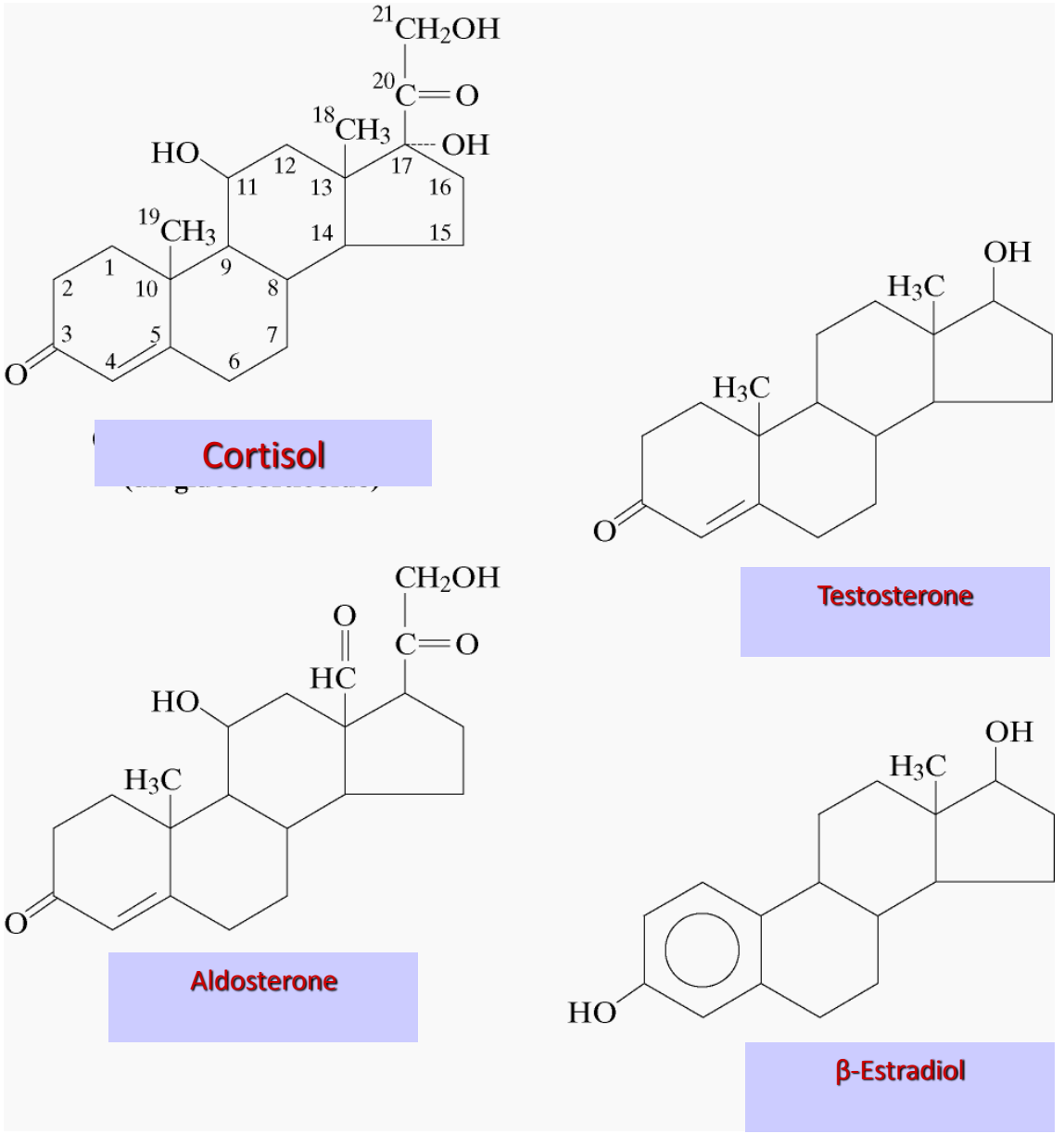
Constituent of cell membranes

It is clearly essential to life, yet its deposition in arteries has been associated with cardiovascular disease and stroke, two leading causes of death in humans

Steroids are precursors of Steroid hormones

Check the funcionality of different organs.

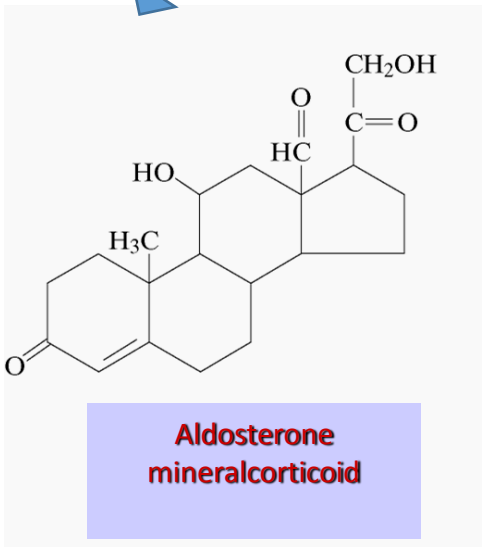
Regulate gene espression, metabolism and reproduction.



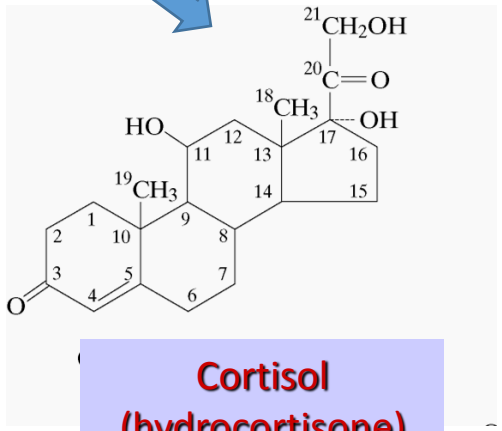
Steroid hormones

Adrenal cortex produce at least 50 different adrenocortical steroid

In the adrenal cortex



Aldosterone
mineralcorticoid



Cortisol
(hydrocortisone)
glucocorticoid

Classified according to the physiological responses they evoke:

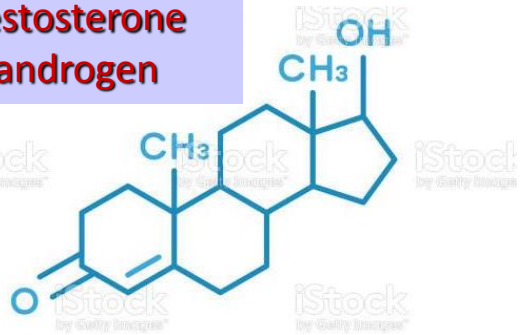
- Glucocorticoids
- Mineralcorticoids
- Androgens and estrogens

- Mineralcorticoids (to regulate the excretion of salt and water by the kidney)

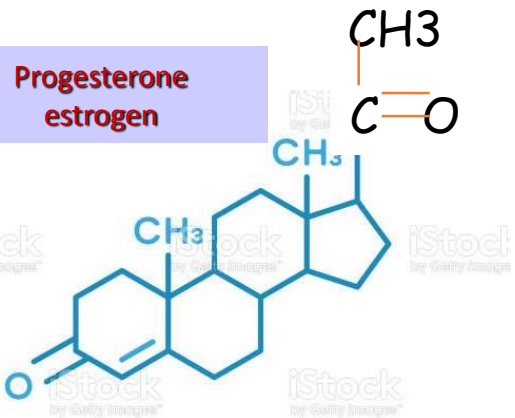
- Glucocorticoids (affect carbohydrates, protein and lipid metabolism and influence a wide variety of other vital functions including inflammatory reaction and the capacity to cope with stress

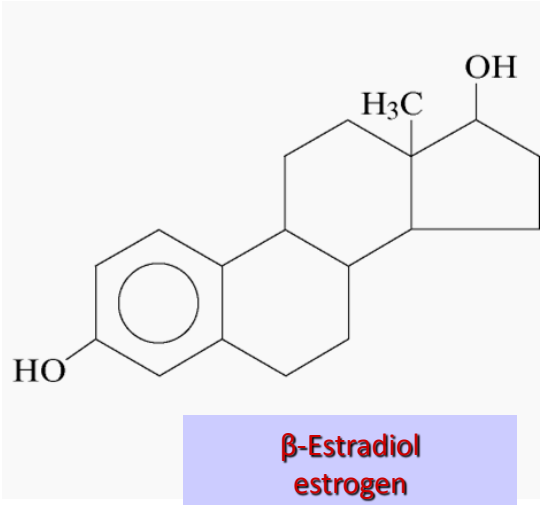
- Androgens and estrogens
  (producted by testes and ovaries)
  - (affect sexual development and function.)

testosterone
androgen



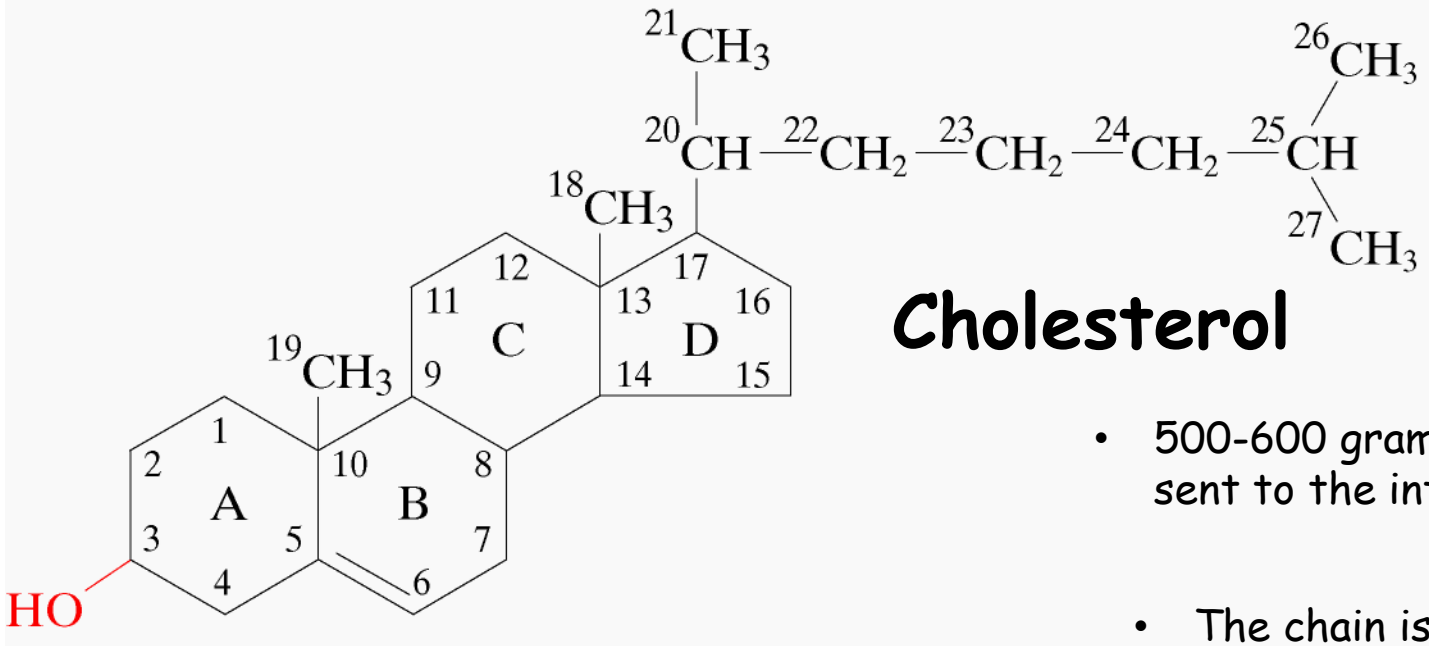
Progesterone
estrogen





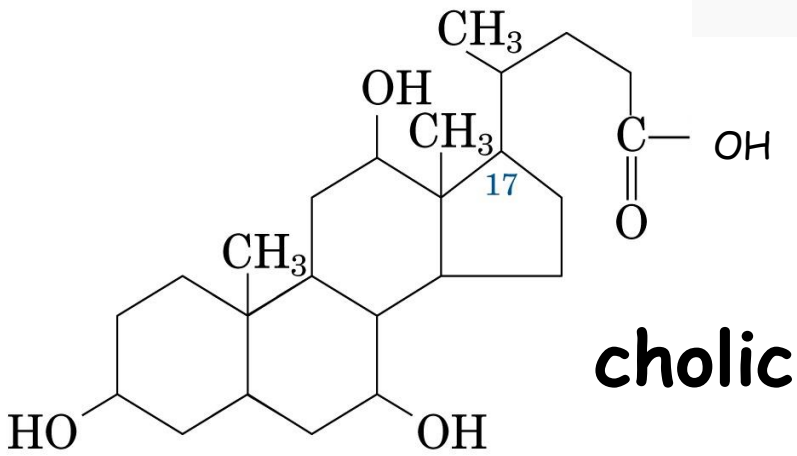
β-Estradiol
estrogen

Bile salts: derived from cholesterol



Cholesterol

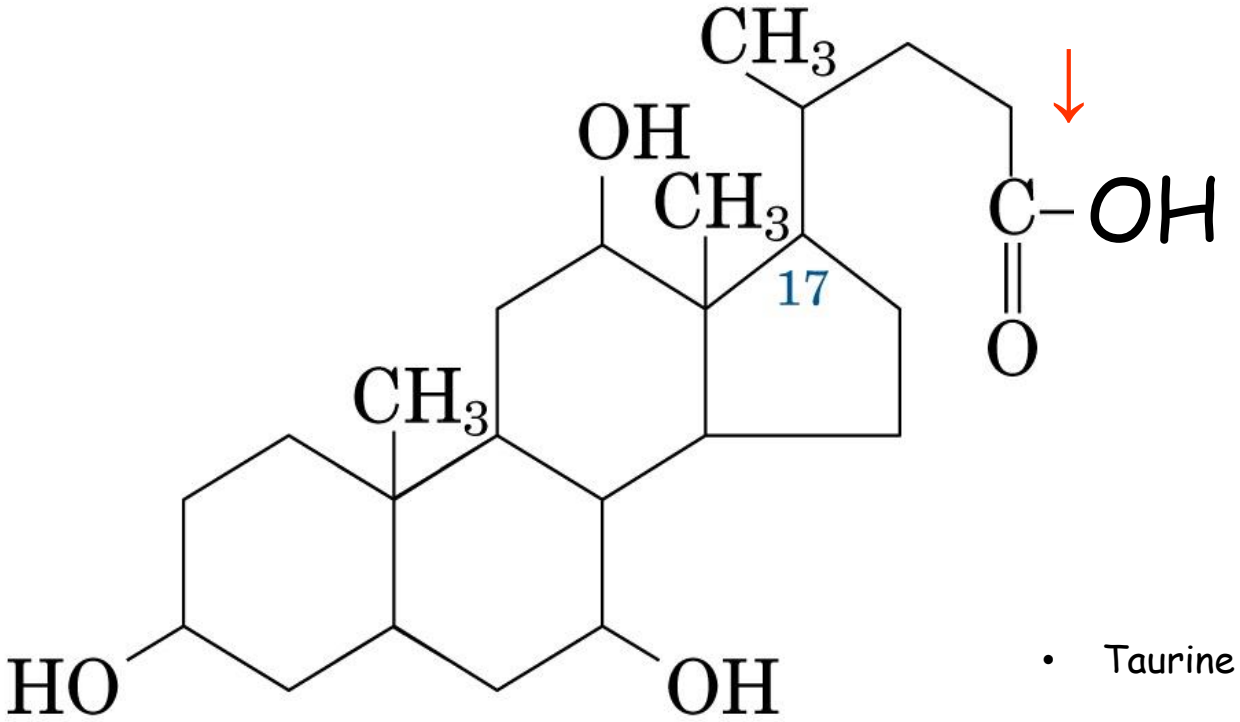
- 500-600 grams of cholesterol per day is sent to the intestin by bile
- The chain is shortened and carboxylated



cholic acid

- A glycine or taurine molecule is bound to the COOH

Bile salts: cholic acid + taurine or glycine



- Taurine is an amine with a sulfonic group

Taurocholic acid: R—COOH + $NH_2—CH_2—CH_2—SO_3^-$

taurine

Glycocholic acid R—COOH + $NH_2—CH_2—COO^-$

glycine

Bile salts: cholic acid + taurine or glycine

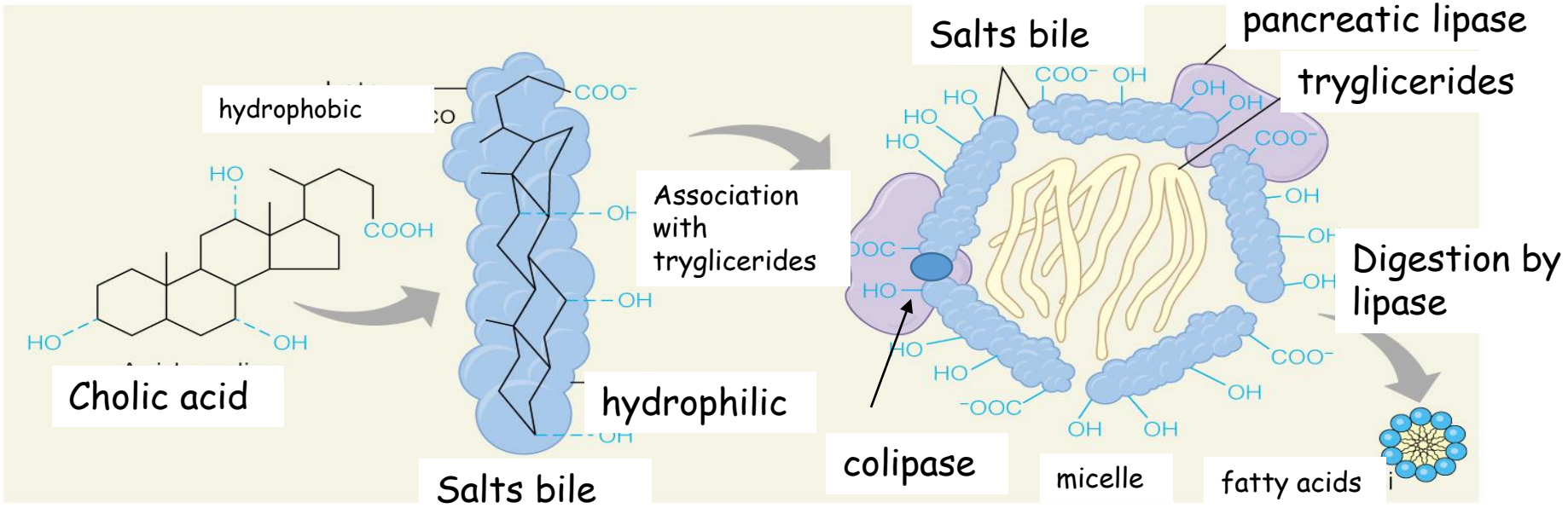
Taurocholic acid

Glycocholic acid

Function:

- Release during digestion into the duodenum.
- Solubilize ingested fat and fat-soluble vitamins, facilitating their digestion and absorption.

Emulsifying capacity of bile salts



- Polar groups are located in the same face as the steroid nucleus

  - Polar face interacts with the solvent
  - Apolar face makes contact with food lipids (tryglicerides and esters of cholesterol)

- Action:

Salts bile Fragment the large lipid drops, increasing the surface accessible to the pancreatic lipase.
Lipase converts triglycerides into free fatty acids

Colipase is needed to anchor the lipase to the droplet surface

Essential fatty acids or PUFA

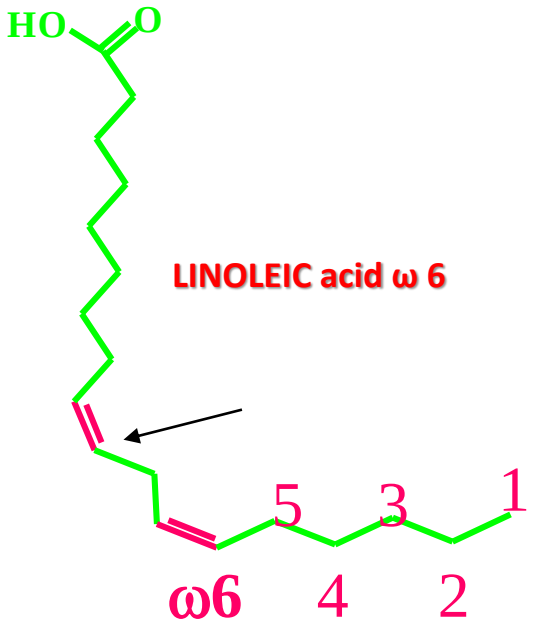
Not synthetized in the body and should be supplied through diet

Not synthetized in human body due to lack of the desaturase enzyme which introduces double bonds beyond 9th and 10th carbon atom

Poly-unsaturated

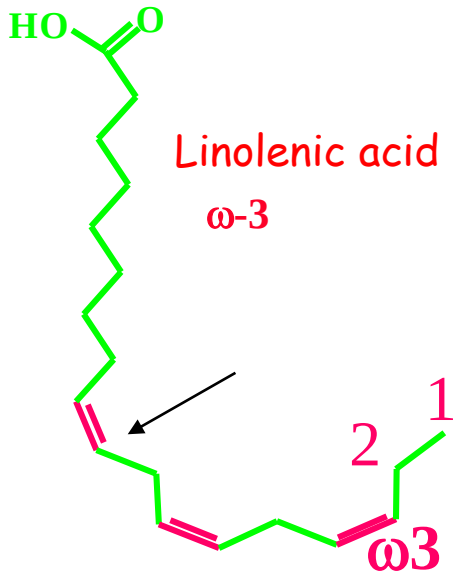
Contain more than one double bond

Essentially fatty acids :
Linoleic acid, linolenic acid and arachidonic acid.



Linoleic acid
(18:2 $\Delta^{9,12}$)

vegetable oils



α-Linolenic acid
(18:3 $\Delta^{9,12,15}$)

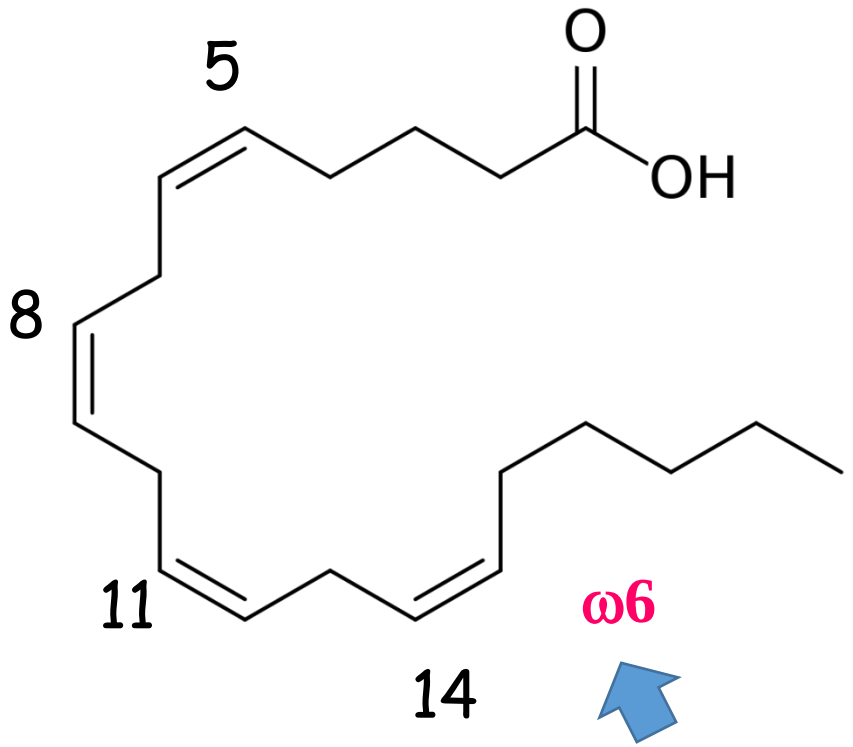
Fishes's fat

Essential fatty acids or PUFA

Arachidonic acid (Contains 20 Carbon atoms)

(ARA, 20:4$\Delta^{5,8,11,14}$)

Cis-,cis-,cis-,cis-5,8,11,14 Icosatetraenoic acid



number the chain on the opposite side with respect to the carboxyl group

Eicosanoids

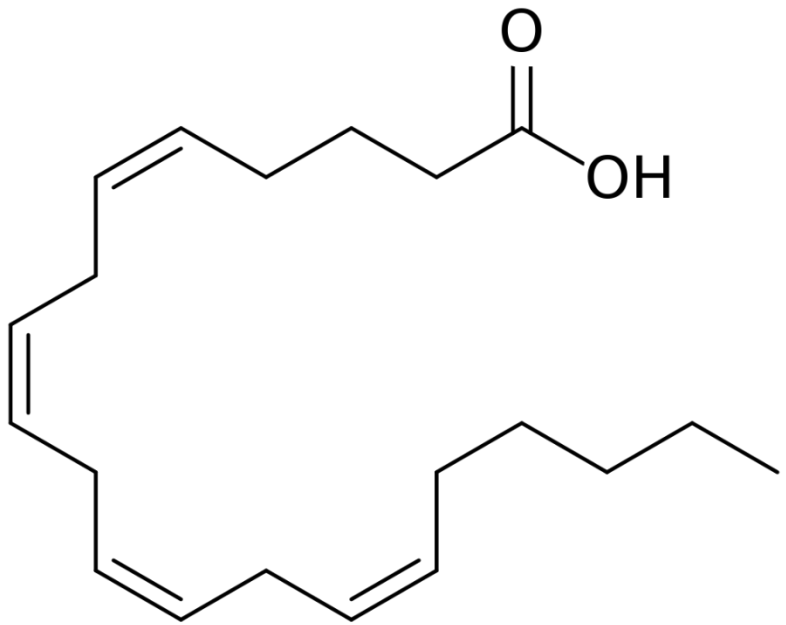
Greek eikosi, “twenty”
(Contains 20 Carbon atoms)

substances that act only on cells near the point of hormone synthesis instead of being transported in the blood to act on cells in other tissues or organs.

- Eicosanoids derive from arachidonic acid (essential fatty acid)
- Arachidonic acid should be supplied through diet.
- Our cells can not synthesis .

- We can produce it, starting by linoleic acid (essential fatty acid it too)

They control numerous important homeostatic and inflammatory processes and they are locally acting signaling molecules.



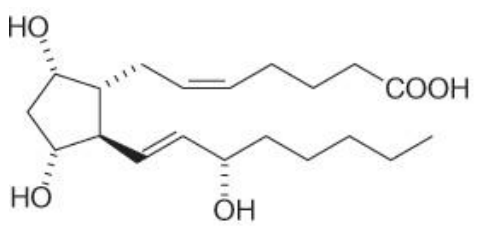
Arachidonic acid

(ARA, 20:4$\Delta^{5,8,11,14}$)

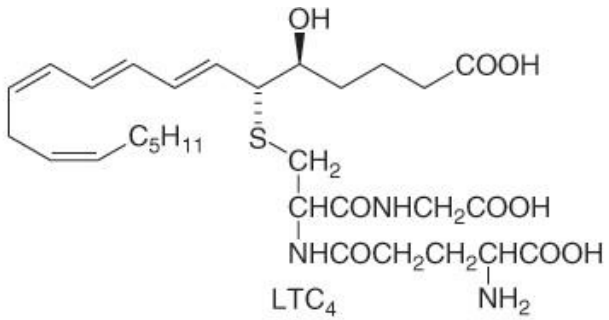
Arachidonic acid is the precursor of all eicosanoid.

Eicosanoids can be divided into several important classes:

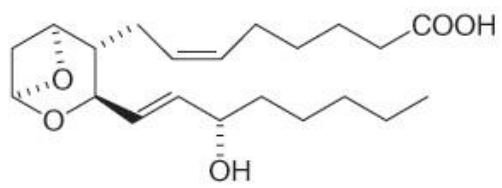
- prostaglandins,
- leukotrienes
- tromboxane
- prostacyclin
- and others.



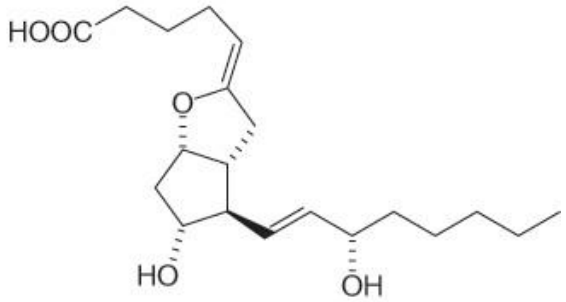
$PGF_{2\alpha}$
a prostaglandin



LTC_4
a leukotriene



TA_4
a thromboxane



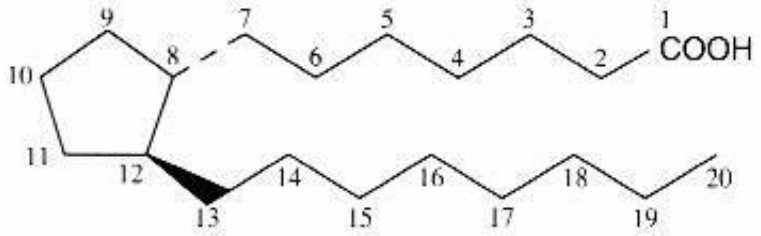
PGI_2
a prostacyclin

- **Prostaglandins** are important in communication between cells

by Bengt Samuelsson
and
Sune Bergström.

- Prostaglandins (PGs) called from prostate gland (first identified in human semen in 1930)

Contain a five-carbon ring originating from the chain of arachidonic acid.



Prostanoic Acid

Their name derives from the prostate gland, the tissue from which they were first isolated.

Two groups of prostaglandins were originally defined:
- PGE (*e*ther-soluble)
- PGF (*f*osfat (Swedish for phosphate) buffer–soluble).

Prostaglandins are all derivatives of prostanoic acid (C20) in which carbon atoms C8 to C12 comprise a cyclopentane ring

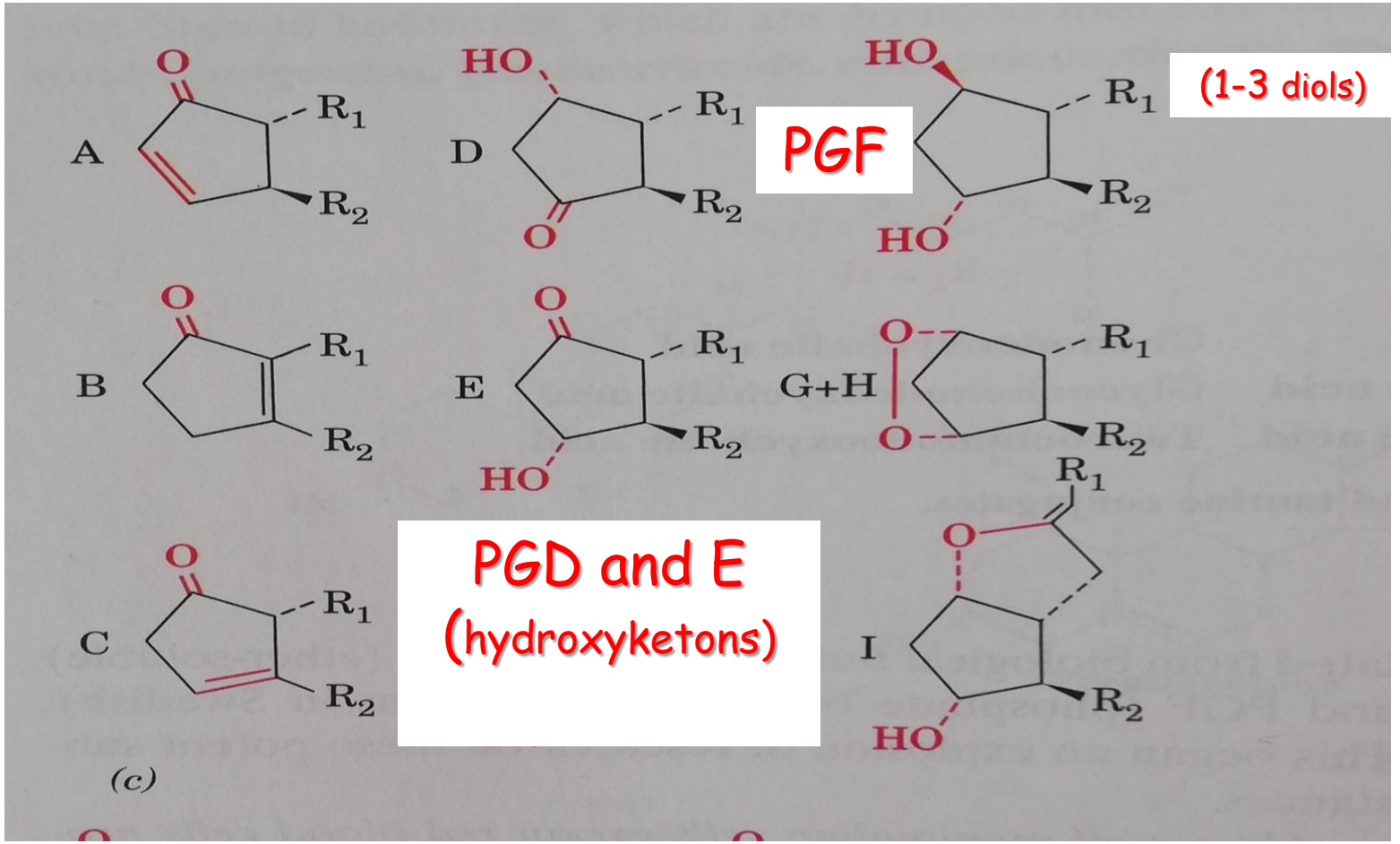
Five-carbon ring

- Prostaglandins A through I differ in the substituents on the cyclopentane ring

PGA
(Unsaturated ketons)

PGB
(Unsaturated ketons)

PGC
(Unsaturated ketons)



PGE (ether-soluble) and PGF (fosfat buffer–soluble).
Each group contains numerous subtypes, named PGE1, PGE2, PGF1,

Prostaglandins are produced in:

Uterine level

promote muscle contraction during menstruation and labor. (conception, luteolysis, menstruation, parturition)

Renal level

regulate perfusion and filtration processes

Prostaglandins have many functions:

Gastric level

protect the stomach wall from the action of hydrochloric acid.

Vascular level

in the processes of homeostasis and platelet aggregation.

- Leukotrienes **First identification in leucocytes**

They are powerful biological signals.

Synthetized by a variety of white blood cells, mast-cells, as well as lung , spleen, brain and heart.

Leukotrienes contribute to the asthmatic and allergic reactions (i.e caused by pollen)-

They act by supporting and amplifying inflammatory processes

They promote the contraction of the smooth muscle of the lung where they can cause asthma attacks, if produced in excessive quantities

Treatment of asthma used drugs such as prednisone
that inhibit the synthesis of leukotrienes or their receptors.

Arachidonic acid

LOX → Leukotrienes

Lipoxygenase enzyme (LOX)

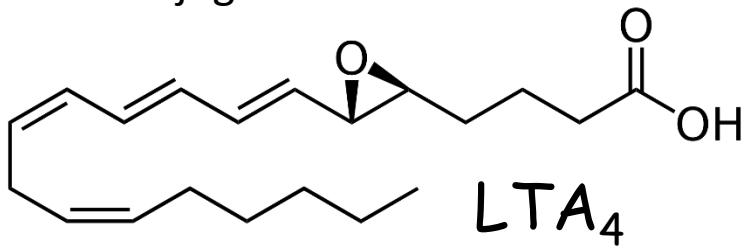
- Leukotrienes

Leukotrienes are indicated with letters LT.

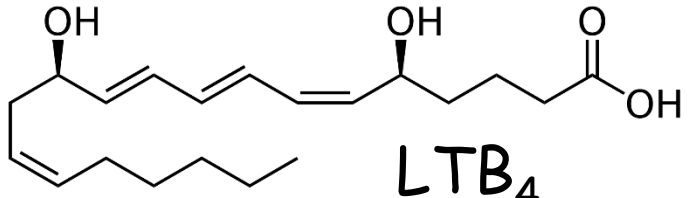
- A, B, C, D and E

Four double bonds, three of them conjugated.
Common property of A4, B4, C4, D4, and E4.

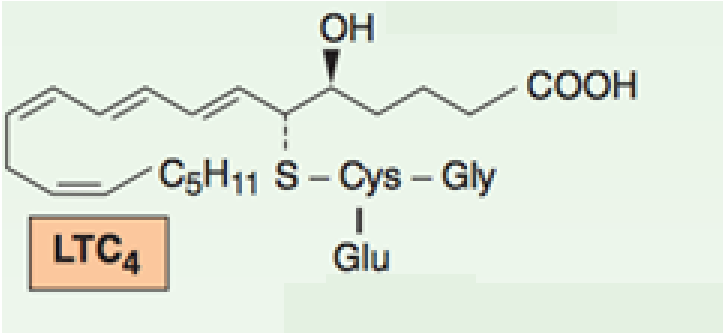
contain three conjugated double bonds.

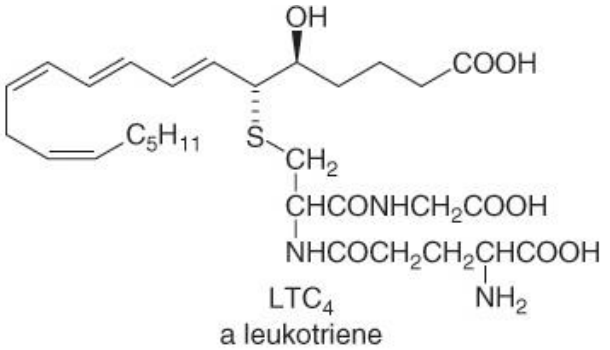


LTA_4

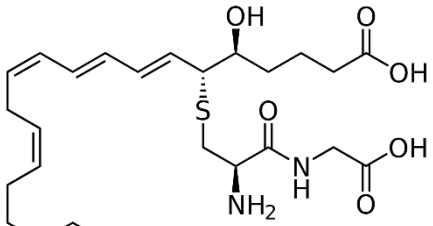


LTB_4

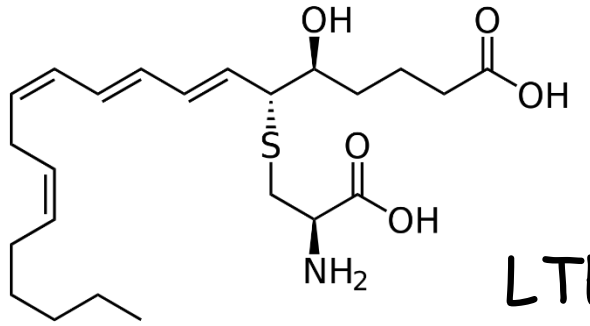




C6 (3 aminoacid bonded)



LTD_4



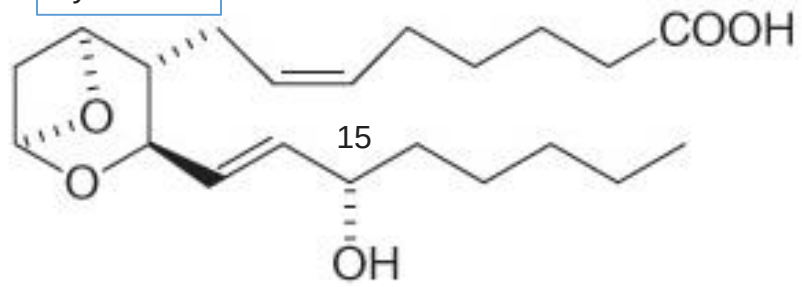
LTE_4

- **Tromboxane:** indicated with letters TX.

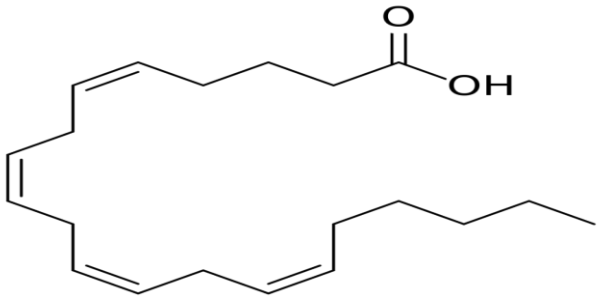
Structure:
an oxygen incorporated to form a six-membered ring

Pyran cyclic

Contain 20 carbon atoms

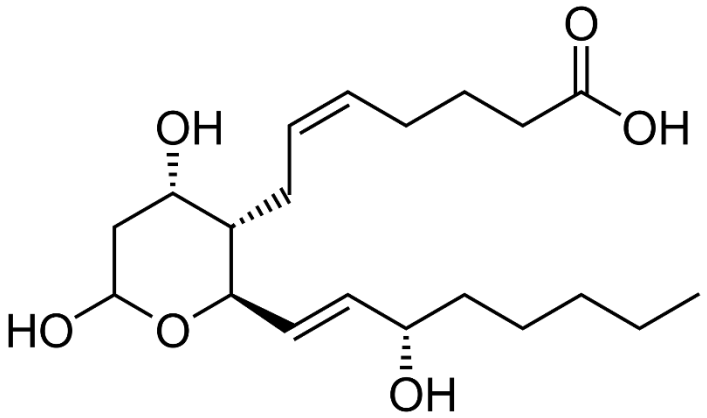


Thromboxane A synthase



Arachidonic acid

TA2.



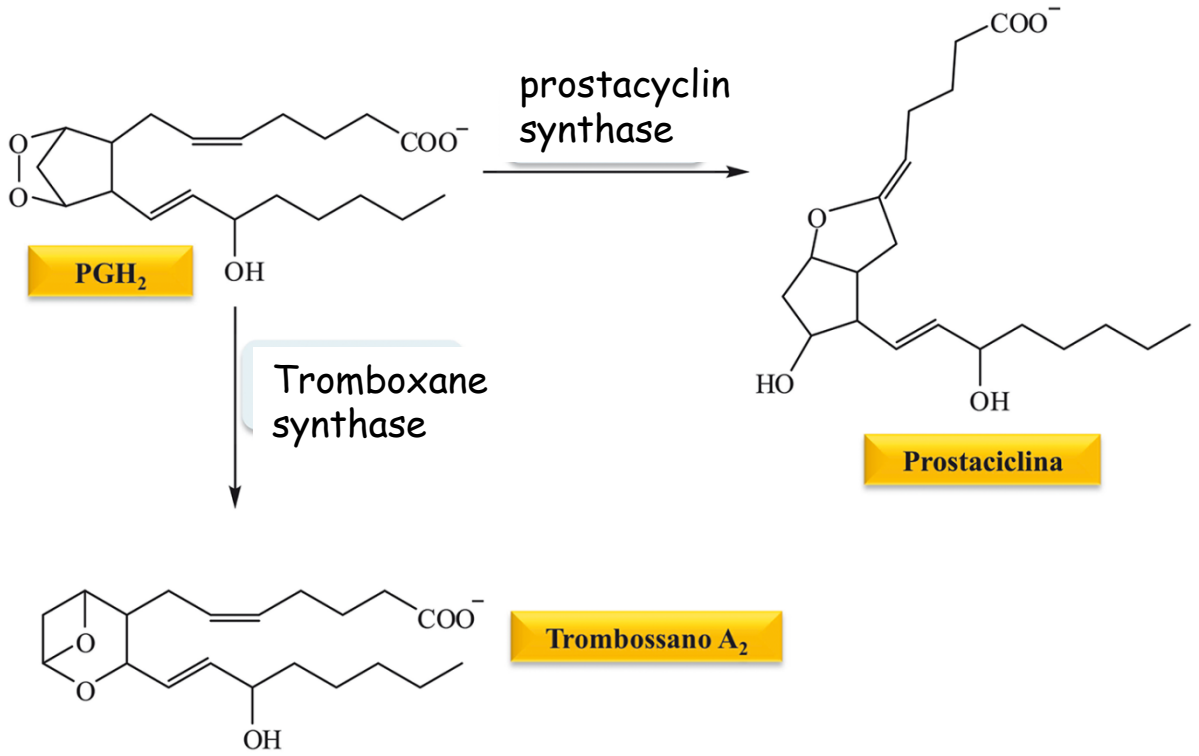
TB2.

Tromboxane
vasosoconstrictor
potent hypertensive agent

they are produced by platelets and are involved in the formation of the clot

- Prostacyclin (PGI2)

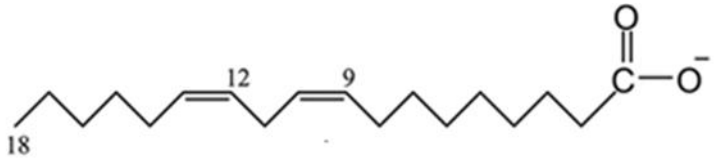
They are mainly found in the vessel wall, (inhibits platelet aggregation and acting as a vasodilator)



- They are found mainly in platelets(promotes platelet aggregation and vasoconstriction)

Arachidonic acid Synthesis

ARA is sinthetized from linoleic acid by desaturation with a Δ6 desaturase to yield γ -linolenic acid (GLA) followed by elongation and a second desaturation (by Δ 5 desaturase)

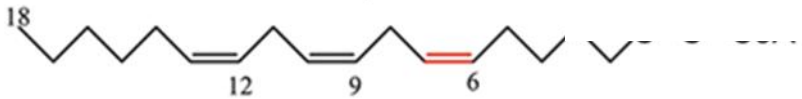


linoleic acid (18:2; $\Delta^{9,12}$)

Mammalian desaturases can introduce double bonds

-2H

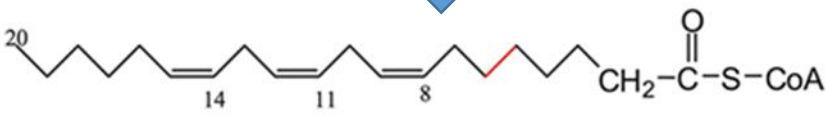
Δ^6 desaturase



γ-linolenic acid (GLA) (18:3; $\Delta^{6, 9, 12}$)

+2C

elongase

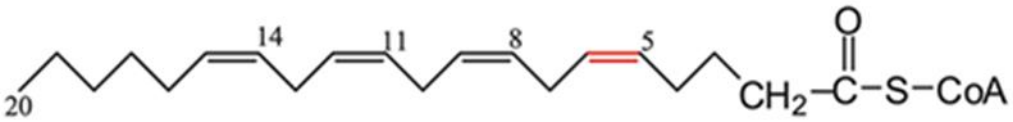


Dihomo γ-linolenic acid (DGLA)

(20:3; $\Delta^{8, 11, 14}$)

-2H

Δ^5 desaturase

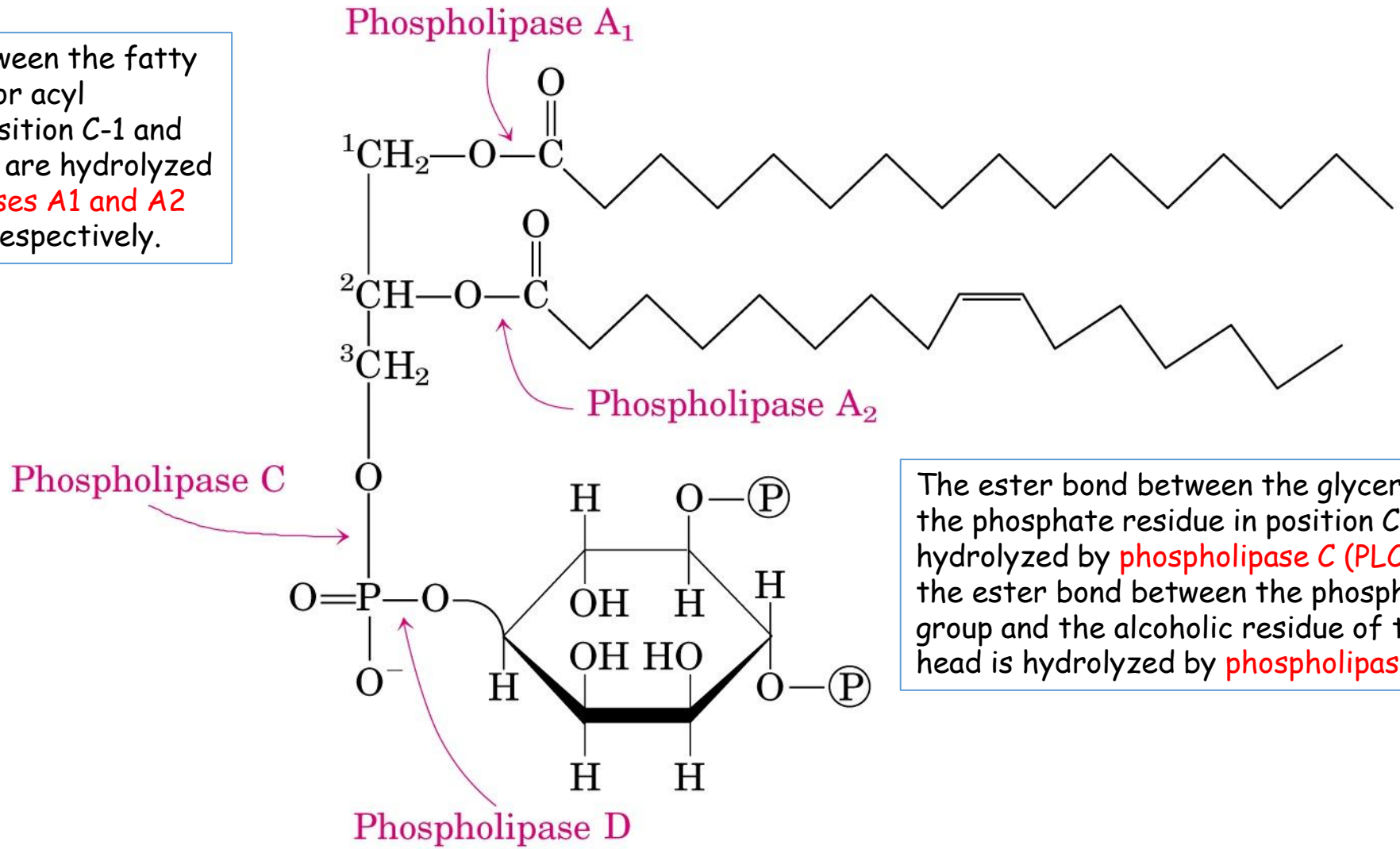


Acid arachidonic (20:4$\Delta^{5,8,11,14}$)

Phospholipids and Sphingolipids Are Degraded in Lysosomes by

Phospholipases

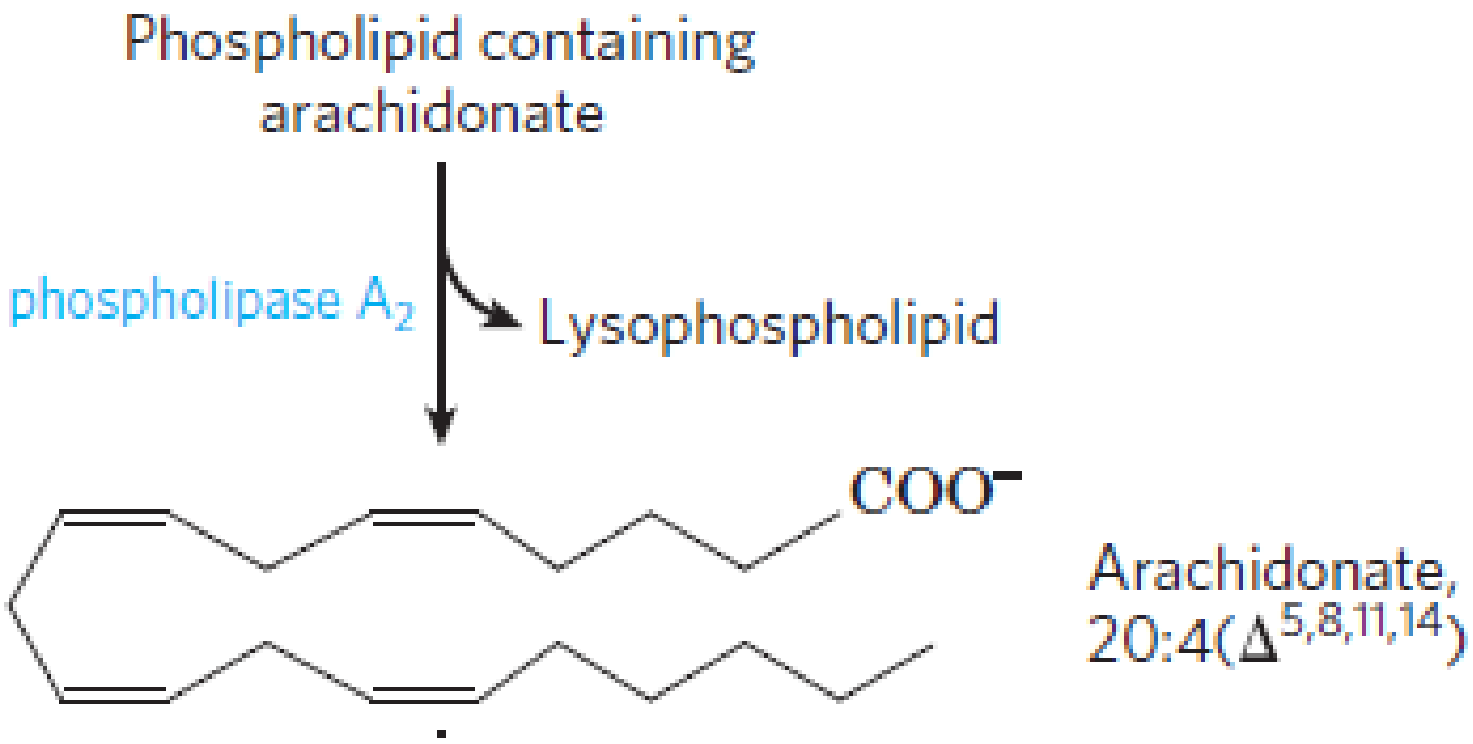
The bonds between the fatty acid residues (or acyl residues) at position C-1 and C-2 of glycerol are hydrolyzed by phospholipases A1 and A2 (PLA1, PLA2), respectively.



The ester bond between the glycerol and the phosphate residue in position C-3 is hydrolyzed by phospholipase C (PLC), while the ester bond between the phosphate group and the alcoholic residue of the polar head is hydrolyzed by phospholipase D.

C and D are considered **phosphodiesterases.**

Arachidonate is released from phospholipids by the action of phospholipase A2,



Arachidonic acid is released from the phospholipid membranes by phospholipase

Arachidonic acid

Arachidonic acid becomes the precursor of some metabolites, by 2 ways:

1) CYCLOXYGENASE pathway
(mainly activated in endothelial cells and platelets)

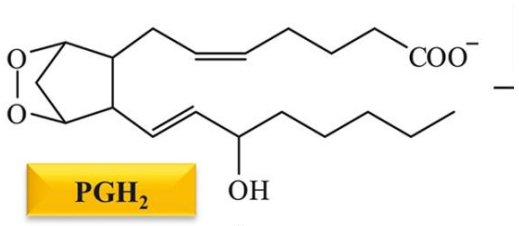
LOX (lipoxygenase)

LOX

→ Leukotrienes

2) LIPOXYGENASE pathway
(mainly activated in leukocytes)

COX
(ciclooxygenase)
Prostaglandin H2 synthase

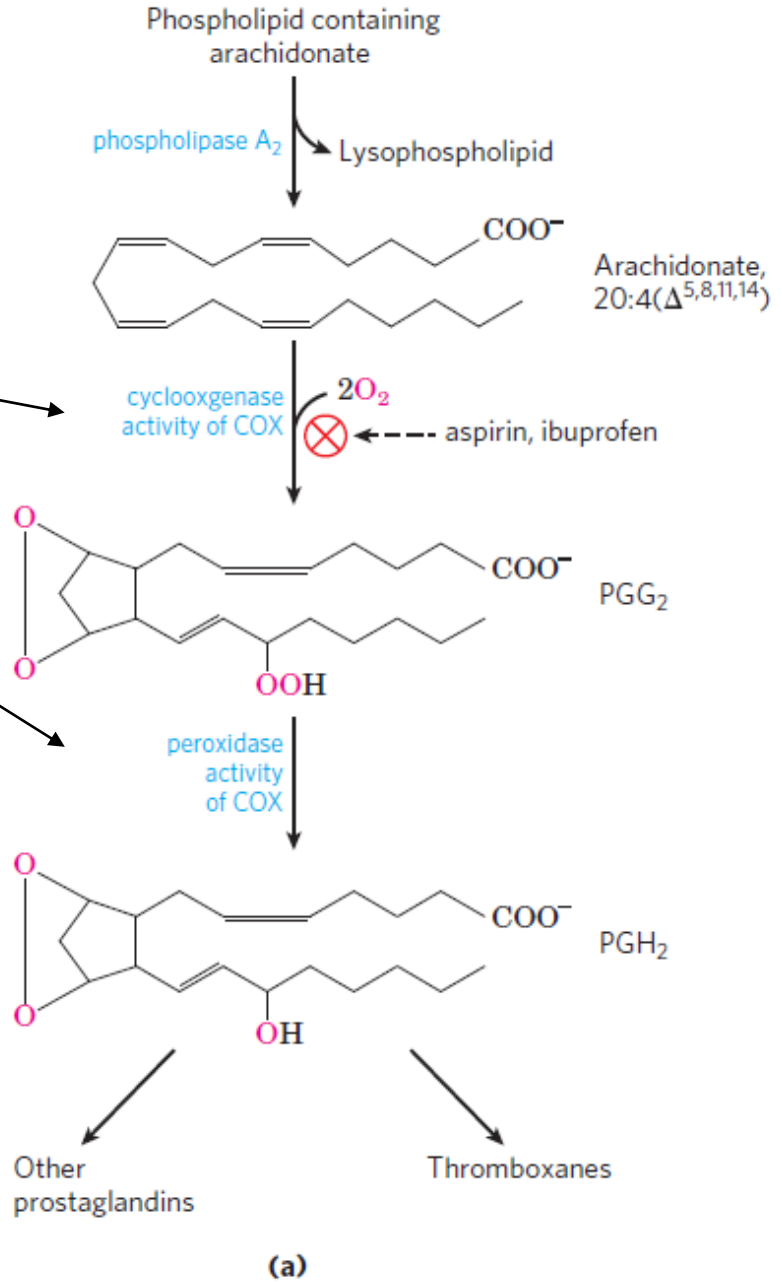


PGH_2

intermediate product
(prostaglandin H2)

CYCLOXYGENASE

(prostaglandin H2 synthase)



(a)

COX

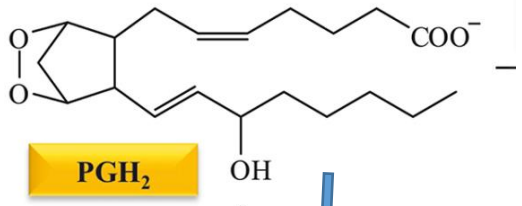
Two isoforms

COX 1
constitutive
(ubiquitous)

COX 2
inducible
(induced expression in inflammatory cells)

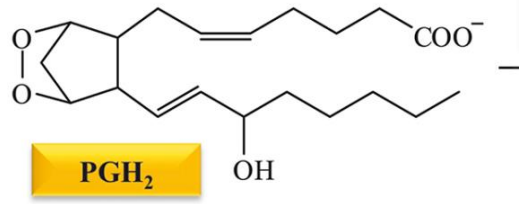
Arachidonic acid

COX 1



- Prostaglandins
  that protect the gastric mucosa

COX 2



- Prostaglandins

that mediate inflammation

)

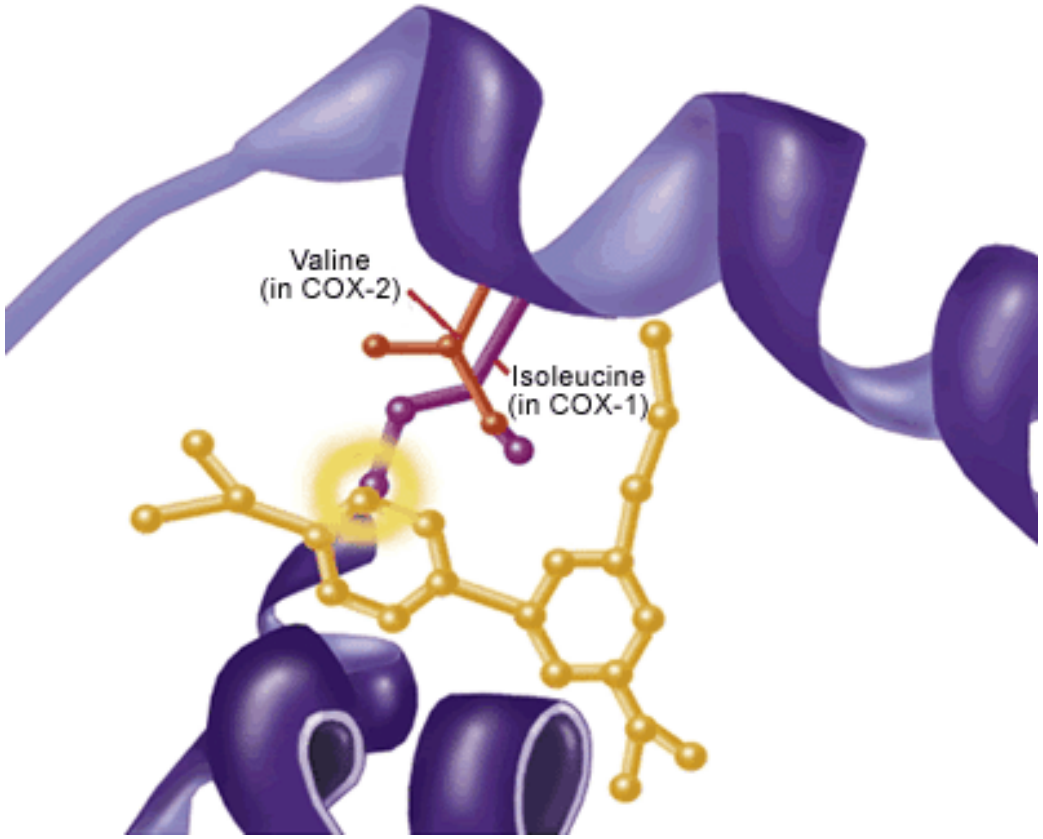
COX-1 and COX-2

They differ from aminoacid substitution
Ile to Val on 523 position

They are homodimers anchored to the inner membrane of the cells

COX contains a prosthetic group, a heme group with ferrous atoms which interacting with oxygen from Fe2 + becomes Fe 3+

Arachidonic acid (ARA) is bound in this pocket formed by 4 α helices with hydrophobic amino acids W F L V.



Arachidonic acid interacts with the catalytic site of COX (Tyr 385)

NSAIDs (non-steroidal anti-inflammatory drugs-)

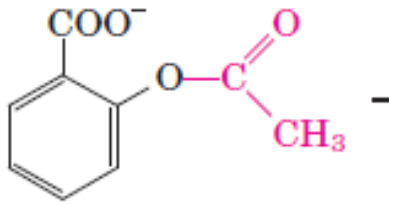
Block the activity of cycloxygenase

Inhibit the production of prostaglandins, thromboxanes and prostacyclins

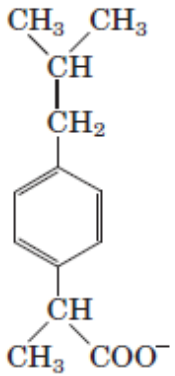
Acetylsalicylic acid
Ibuprofen (Brufen)
Nimesulide (Aulin)

} COX inhibitor

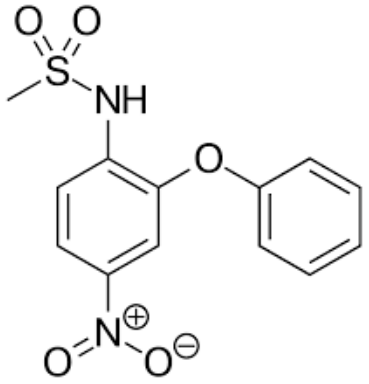
- Acetylsalicylic acid (Acetylation COX) (selective for COX 1)



Aspirin
(acetylsalicylate)

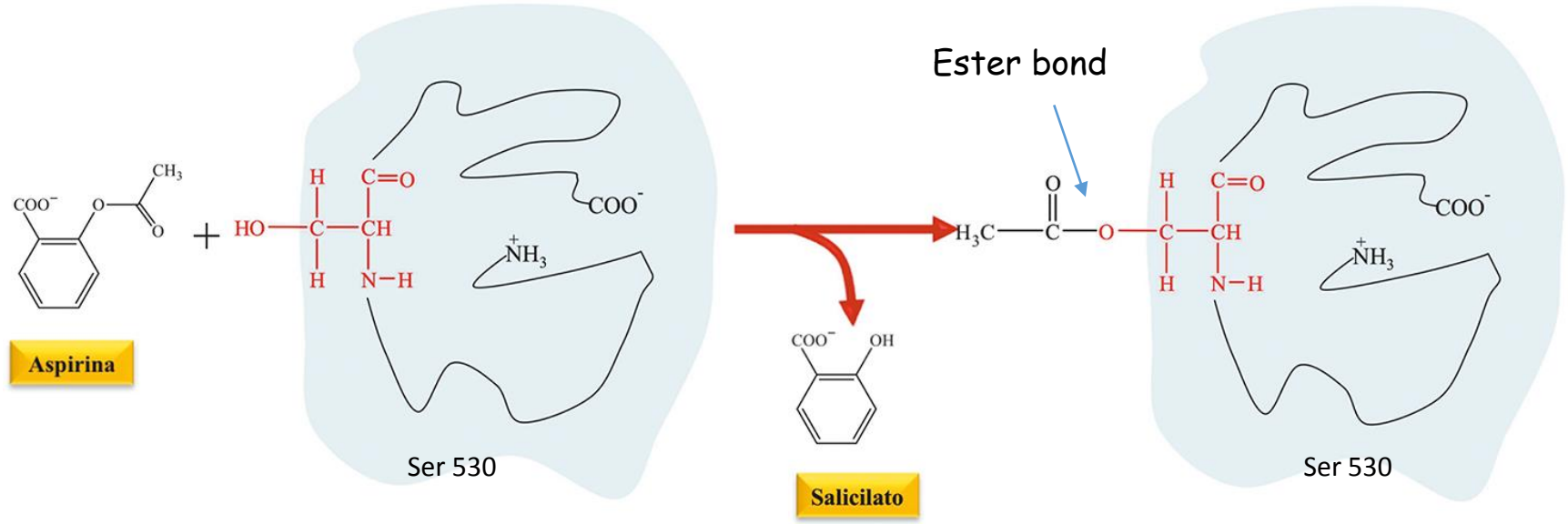


Ibuprofen



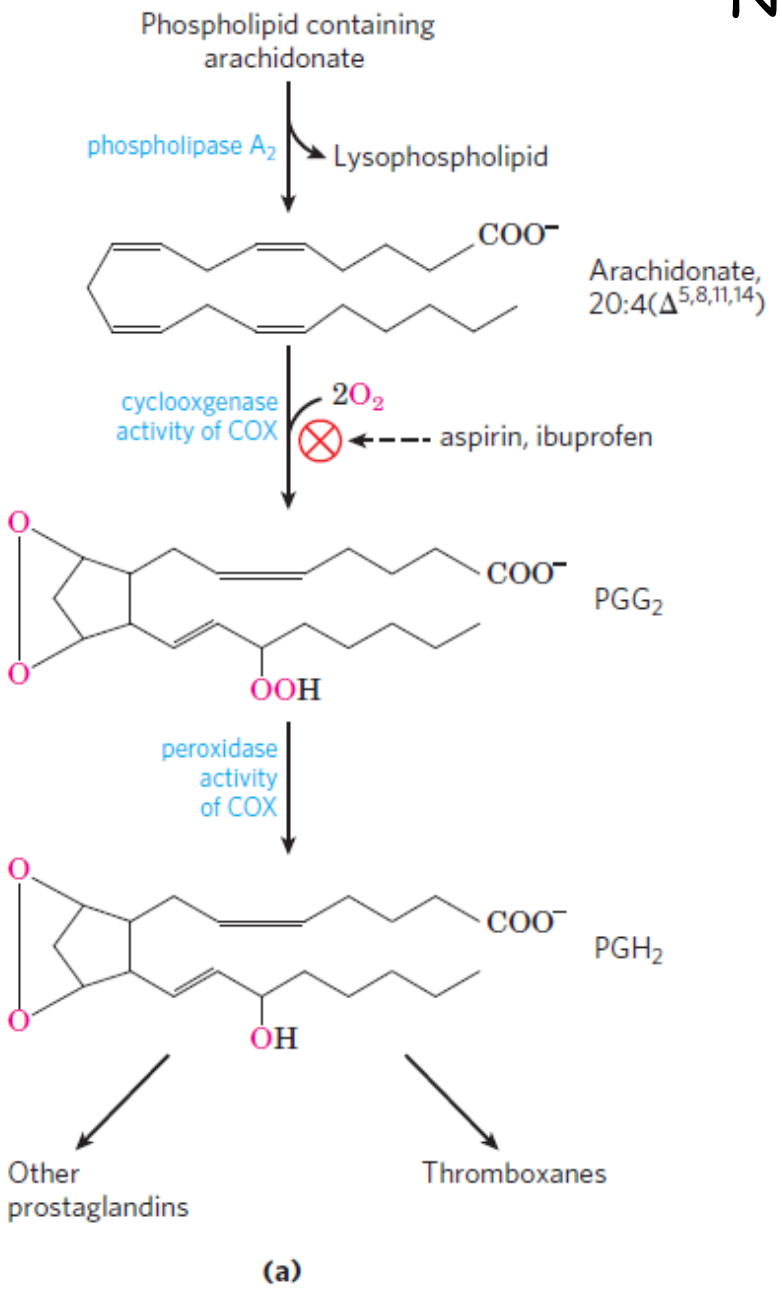
Nimesulide

- Acetylsalicylic acid (Acetylation COX) (selective for COX 1)



Aspirin inhibits COX 1 by acetylating an essential Ser residue on the enzyme.

NSAIDs (non-steroidal anti-inflammatory drugs-)



Aspirin inhibits COX 1 by acetylating an essential Ser residue on the enzyme.

Ibuprofen inhibit the same step, probably by miming the structure of the substrate or an intermediate in the reaction.

Steroidal anti-inflammatory: (cortisone)

Prednisone (Deltacortene), metil prednisolone, desametasone, betametasone (Bentelan)

Phospholipids

Phospholipase A_2 ← (Inhibit from Steroidal anti-inflammatory)

Arachidonic acid

Cycloxygenase ← (Inhibit from NSAIDs)

(non-steroidal anti-inflammatory drugs)

Prostaglandins

Acetylsalicylic acid
Ibuprofen
Nimesulide