Lipids

Summer 2023

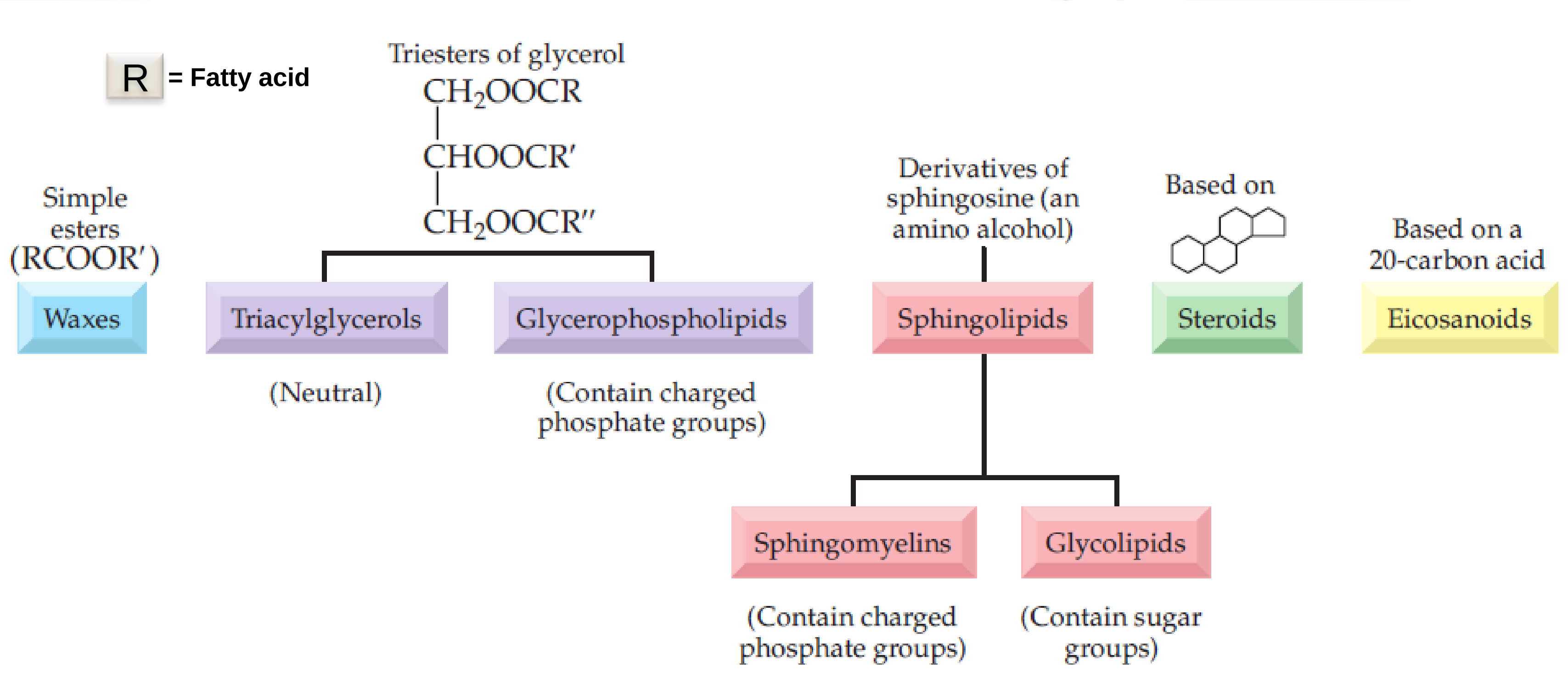
Lipids

- Lipids are a heterogeneous class of naturally occurring organic compounds that share some properties based on structural similarities, mainly a dominance of nonpolar groups.

- They are Amphipathic in nature.
- They are insoluble in water, but soluble in fat or organic solvents (ether, chloroform, benzene, acetone).
- They are widely distributed in plants & animals.

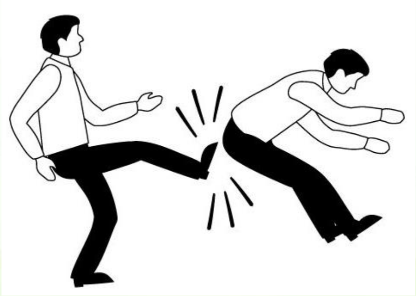
Classes

- Simple lipids (fats, oils, and waxes)
- Complex lipids (glycerides , glycerophospholipids, sphingolipids, glycolipids, lipoproteins)
- Derived lipids (fatty acids, alcohols, eicosanoids)
- Cyclic lipids (steroids)



Lipid Functions

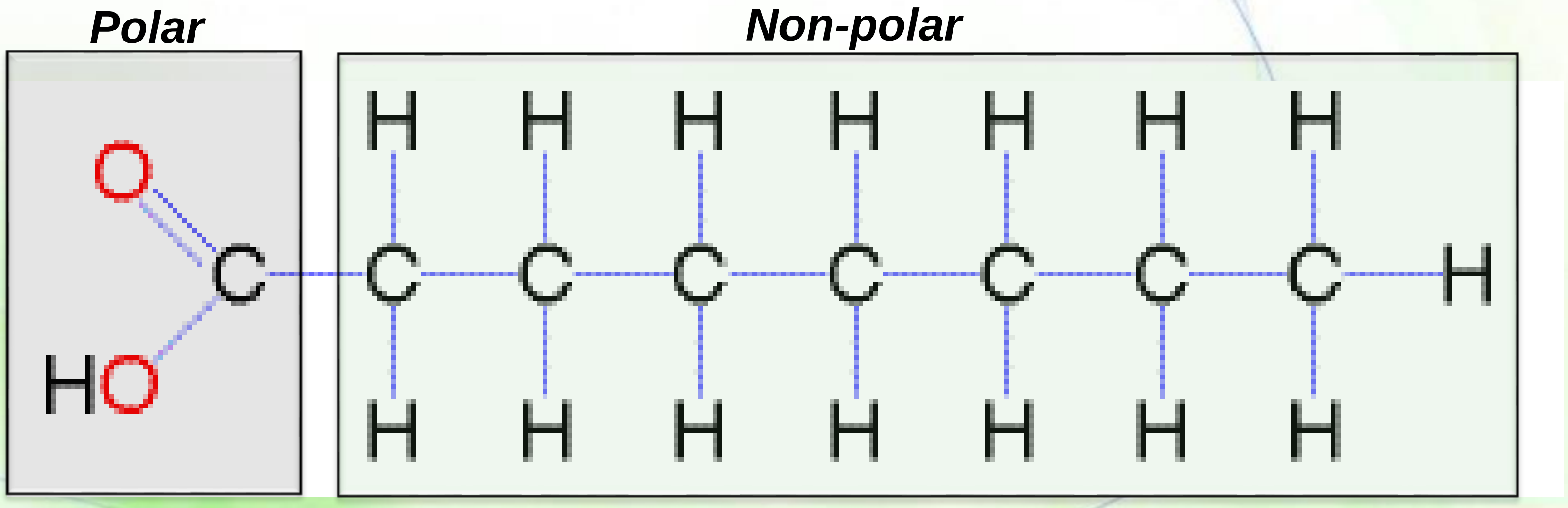
- Lipids include:
  - Storage lipids
  - Structural lipids in membranes
  - Lipids as signals, cofactors & pigments
- A major source of energy
  - They are storable to unlimited amounts (vs. carbohydrates)
  - They provide a considerable amount of energy to the body (25% of body needs) & provide a high-energy value (more energy per gram vs. carbohydrates & proteins)
- Structural components (cell membranes)
- Precursors of hormones and vitamins
- Shock absorbers and thermal insulators



Fatty acids

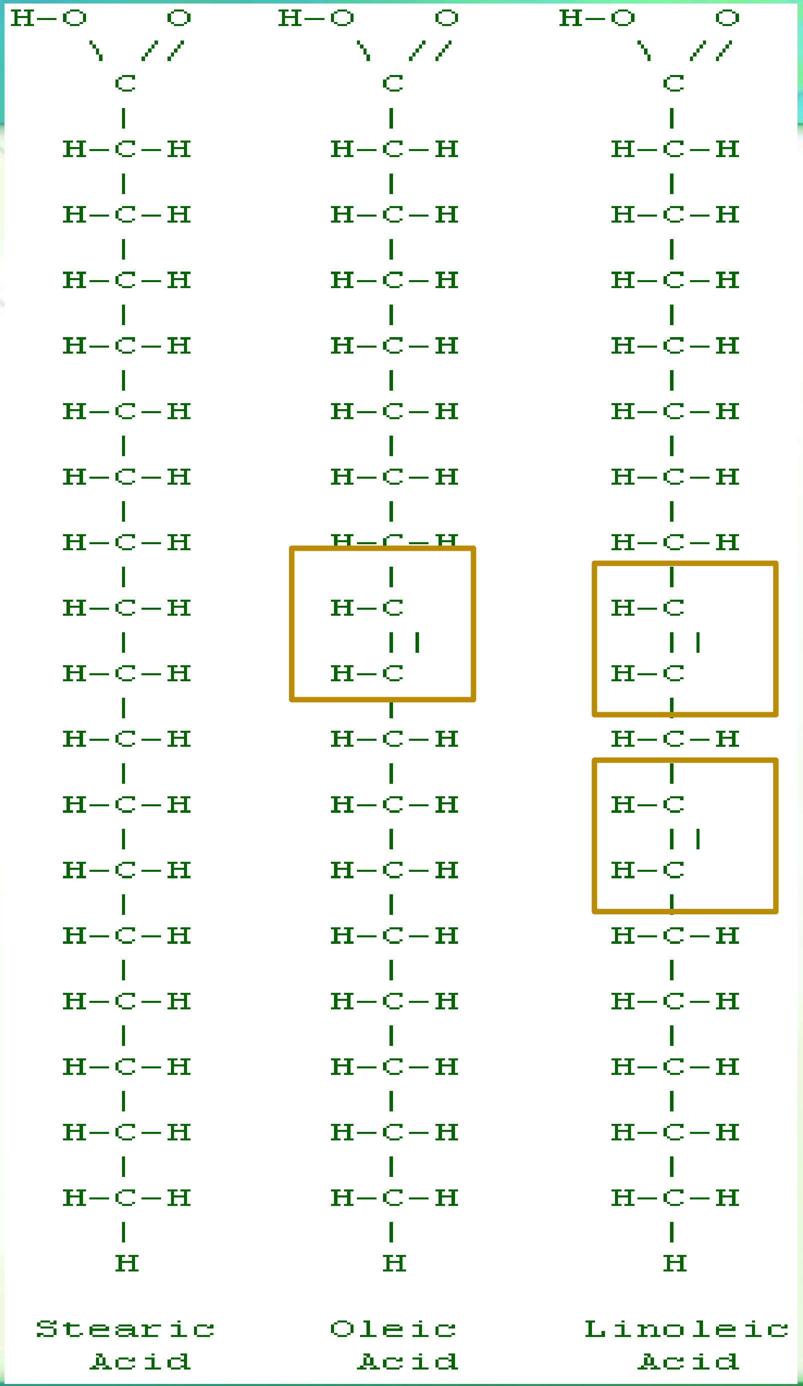
- Aliphatic mono-carboxylic acids
- Formula: R-(CH_2)n-COOH
- Lengths
  - Physiological (12-24)
  - Abundant (16 and 18)
- Degree of unsaturation
- Amphipathic molecules

Functions:
- **Building blocks of other lipids**
- **Modification of many proteins (lipoproteins)**
- **Important fuel molecules**
- **Derivatives of important cellular molecules**

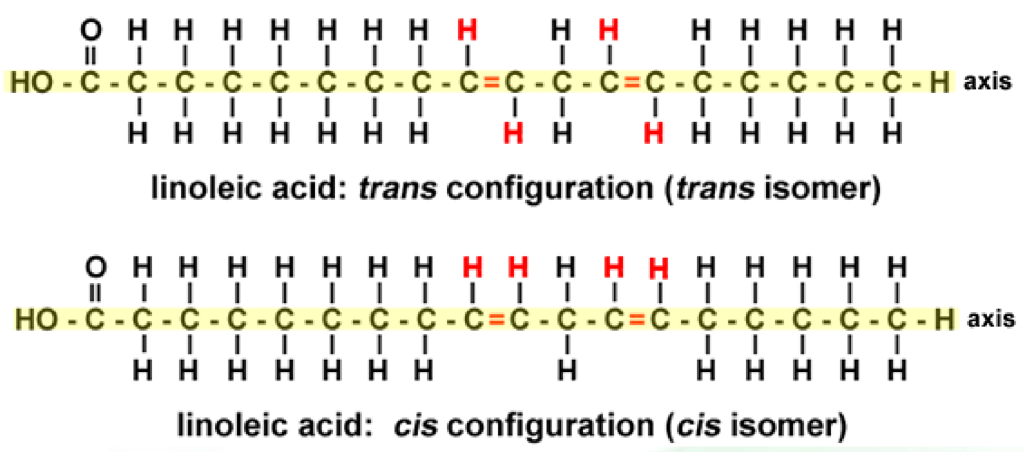


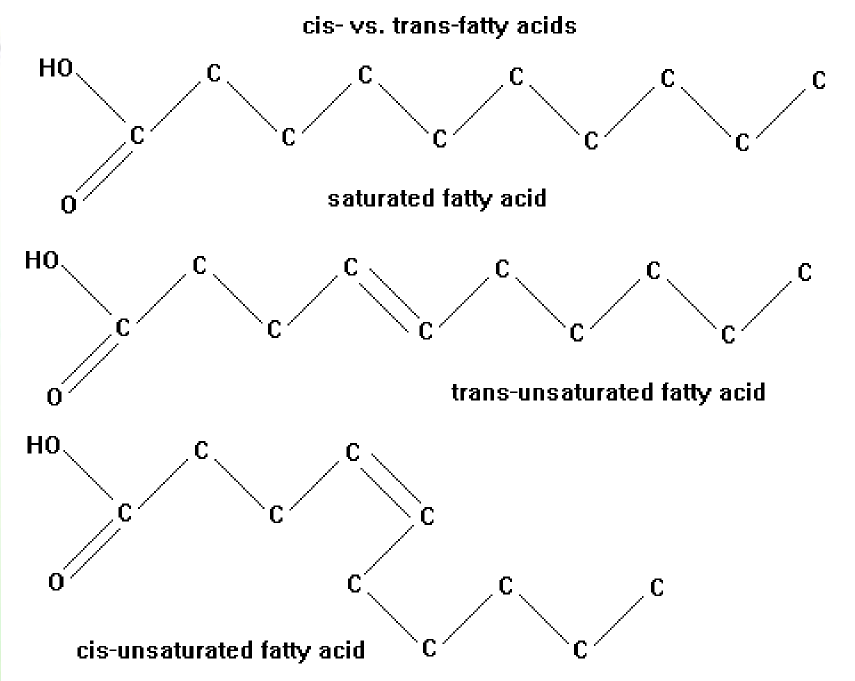
Types of fatty acids

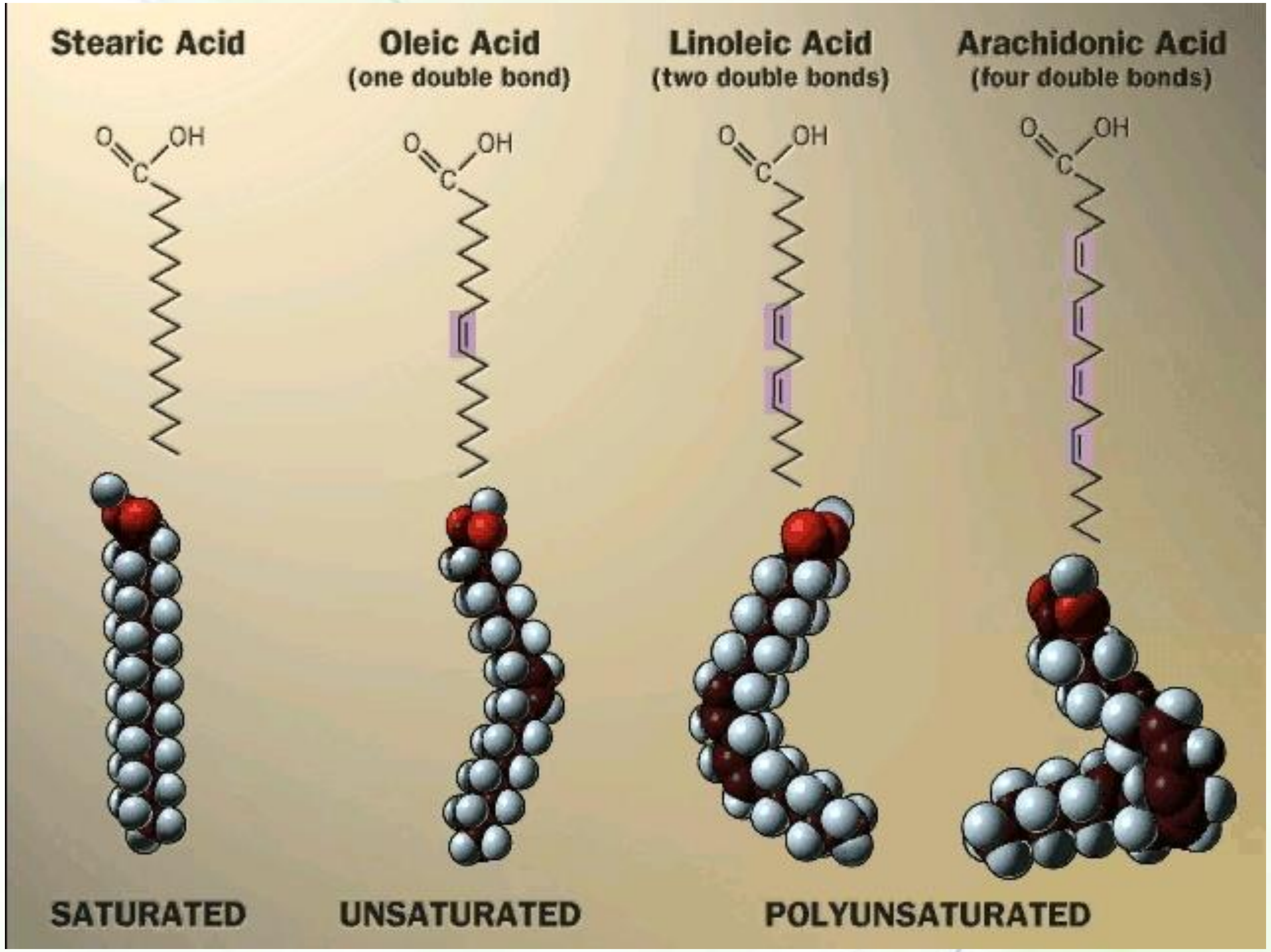
- Saturated fatty acids are those with all of the C-C bonds being single.
- Unsaturated fatty acids are those with one or more double bonds between carbons:
  - Monounsaturated fatty acid: a fatty acid containing one double bond.
  - Polyunsaturated fatty acids contain two or more double bonds.



Cis vs. trans bonds





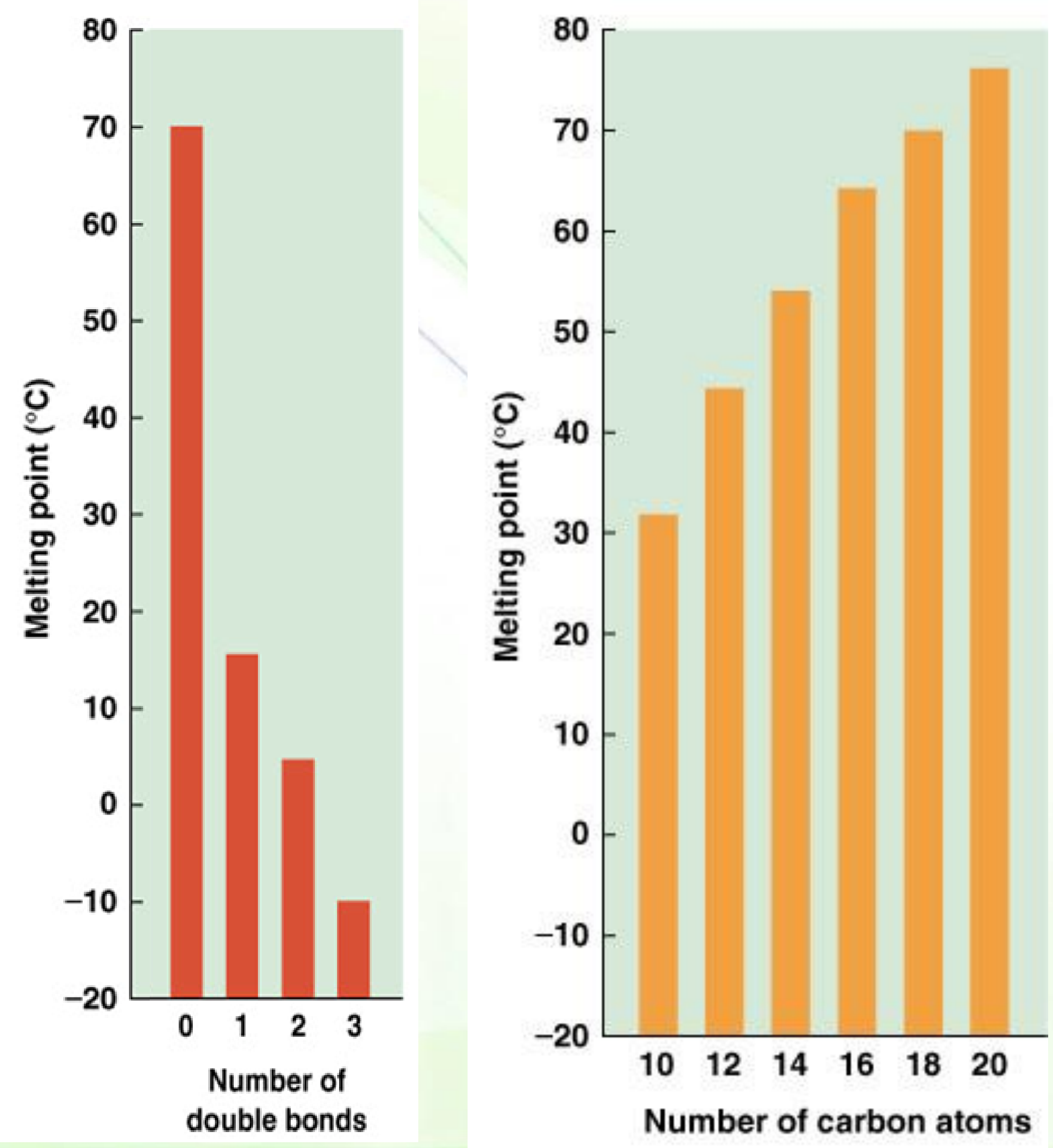


Physiologically:

- **cis isomer predominates**
- **trans is rare**

Properties of fatty acids

- The properties of fatty acids (melting point) are dependent on chain length and degree of saturation.



Properties of saturated fatty acids

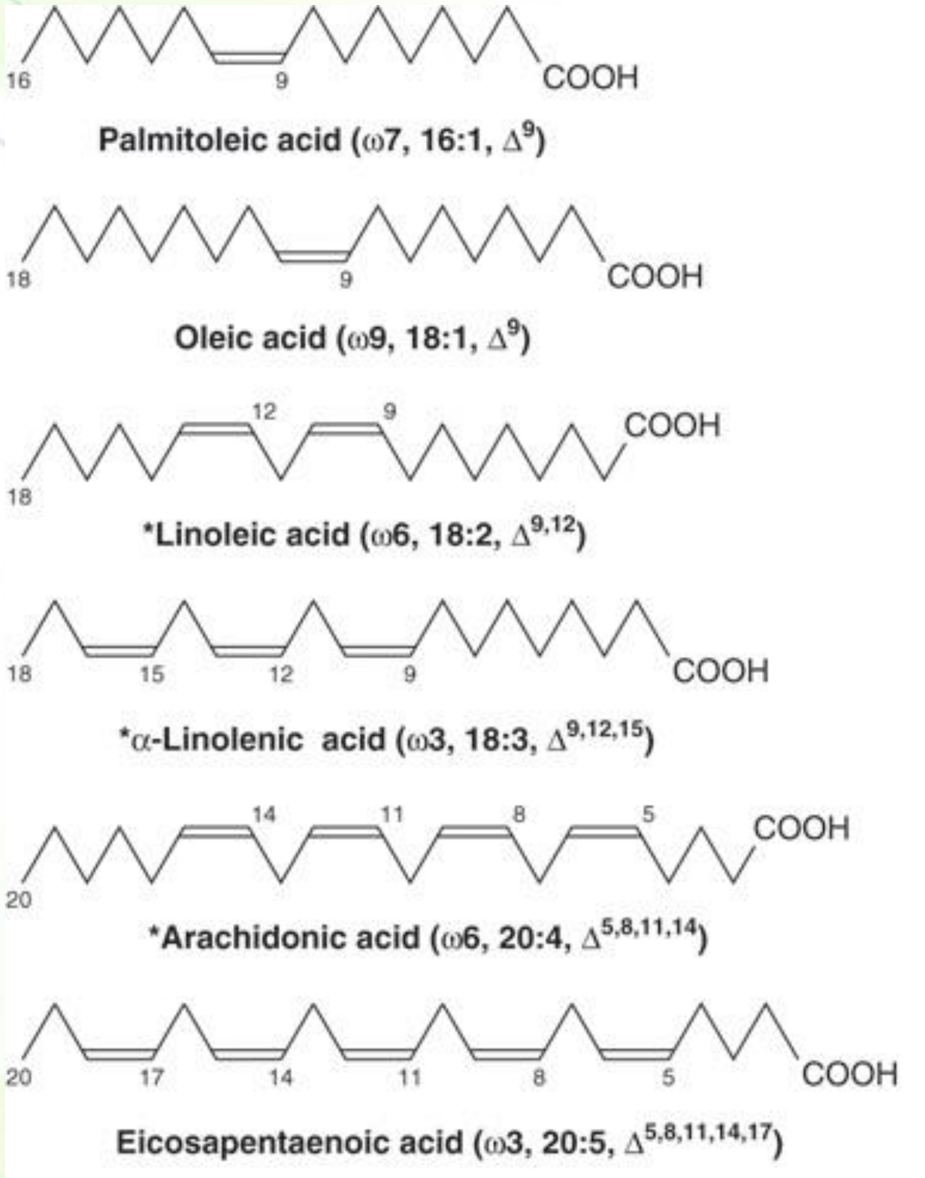
Short chain F.A. (2-4)	Medium-chain F.A. (6-10)	Long chain F.A. (12-20)
They are liquid in nature	Solids at room temperature	Solids at room temperature
Water-soluble	Water-soluble	Water-insoluble
Volatile at RT	Non-volatile at RT	Non-volatile
Acetic, butyric, caproic FA	Caprylic & capric F.A.	Palmitic and stearic F.A

Greek number prefix

Number	prefix	Number	prefix	Number	prefix
1	Mono-	5	Penta-	9	Nona-
2	Di-	6	Hexa-	10	Deca-
3	Tri-	7	Hepta-	20	Eico-
4	Tetra-	8	Octa-		

Naming of a fatty acid

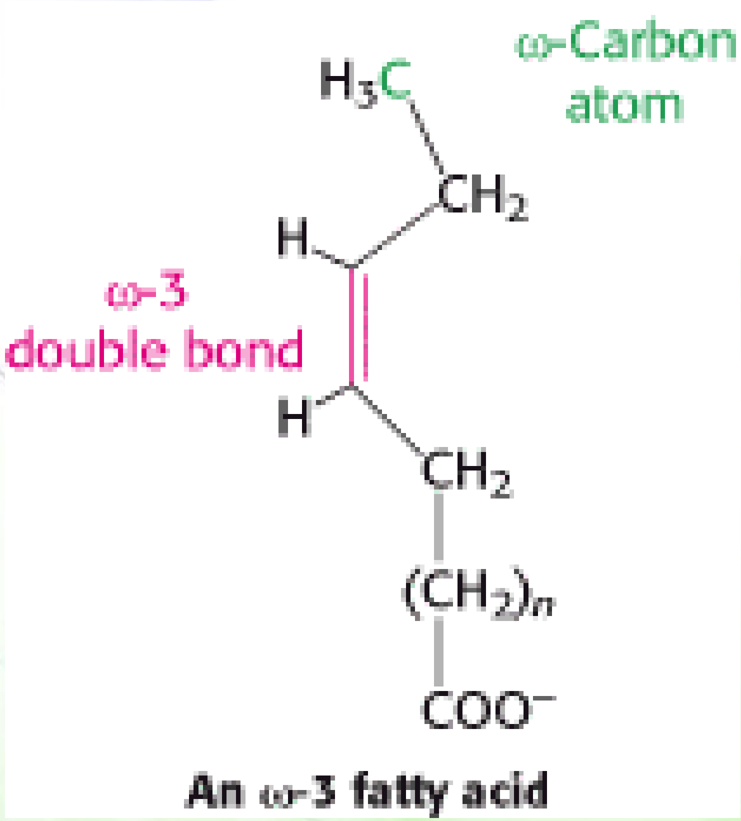
- Alkane to oic
  - Octadecane (octa and deca) is octadecanoic acid
    - One double bond = octadecenoic acid
    - Two double bonds = octadecadienoic acid
    - Three double bonds = octadecatrienoic acid
- Designation of carbons and bonds
  - 18:0 = a C18 fatty acid with no double bonds
    - stearic acid (18:0); palmitic acid (16:0)
  - 18:2 = two double bonds (linoleic acid)
- Designation of the location of bonds
  - Δn: The position of a double bond
    - cis-Δ9: a cis double bond between C 9 and 10
    - trans-Δ2: a trans double bond between C 2 and 3



Number of carbons	Number of double bonds	Common name	Systematic name	Formula
14	0	Myristate	n-Tetradecanoate	$CH_3(CH_2)_{12}COO^-$
16	0	Palmitate	n-Hexadecanoate	$CH_3\,(CH_2)\,_{14}COO$-
18	0	Stearate	n-Octadecanoate	$CH_3(CH2)\,_{16}COO$-
18	1	Oleate	cis-Δ^9-Octadecenoate	$CH_3(CH_2)\,_7CH{=}CH(CH_2)\,_7COO$-
18	2	Linoleate	cis,cis-Δ^9,Δ^{12}-Octadecadienoate	$CH_3(CH_2)_4CH{=}CHCH_2CH(CH_2)_7COO$-
18	3	Linolenate	all-cis-Δ^9,Δ^{12},Δ^{15}-Octadecatrienoate	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO$-
20	4	Arachidonate	all-cis-Δ^5,Δ^8,Δ^{11},Δ^{14}-Eicosatetraenoate	$CH_3(CH_2)_4\,(CH{=}CHCH_2)_4(CH_2)_2\,COO$-

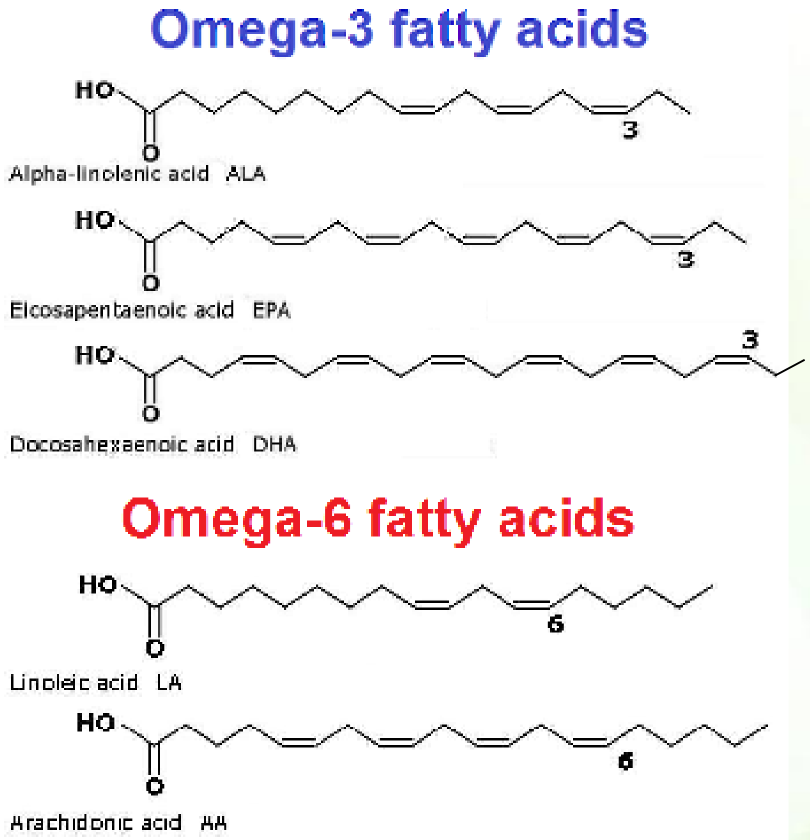
Another way of naming

- (ω)-C: distal methyl C as #1

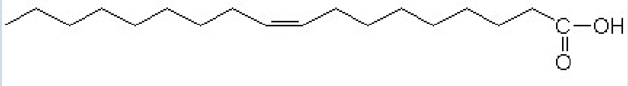
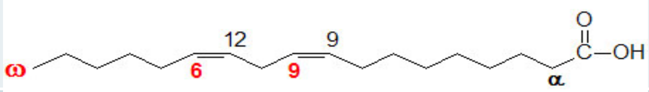
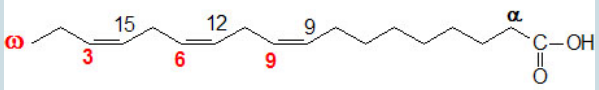
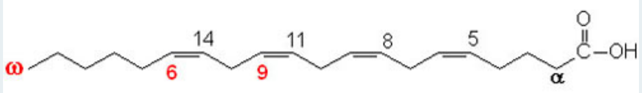
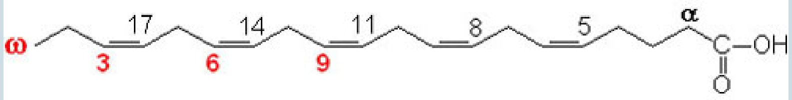
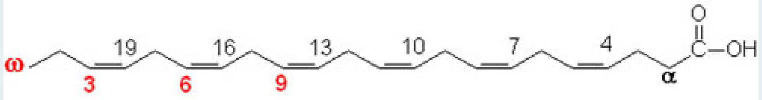


An ω-3 fatty acid

Per softgel		
Organic Flaxseed Oil (Linseed Oil)		400mg
Pure Fish Oil		400mg
Starflower Oil (Borage Oil)		400mg
typically providing:		
Alpha Linolenic Acid (ALA)	Omega-3	200mg
Docosahexaenoic Acid (DHA)	Omega-3	48mg
Eicosapentaenoic Acid (EPA)	Omega-3	72mg
Gamma Linolenic Acid (GLA)	Omega-6	88mg
Linoleic Acid (LA)	Omega-6	204mg
Oleic Acid	Omega-9	168mg



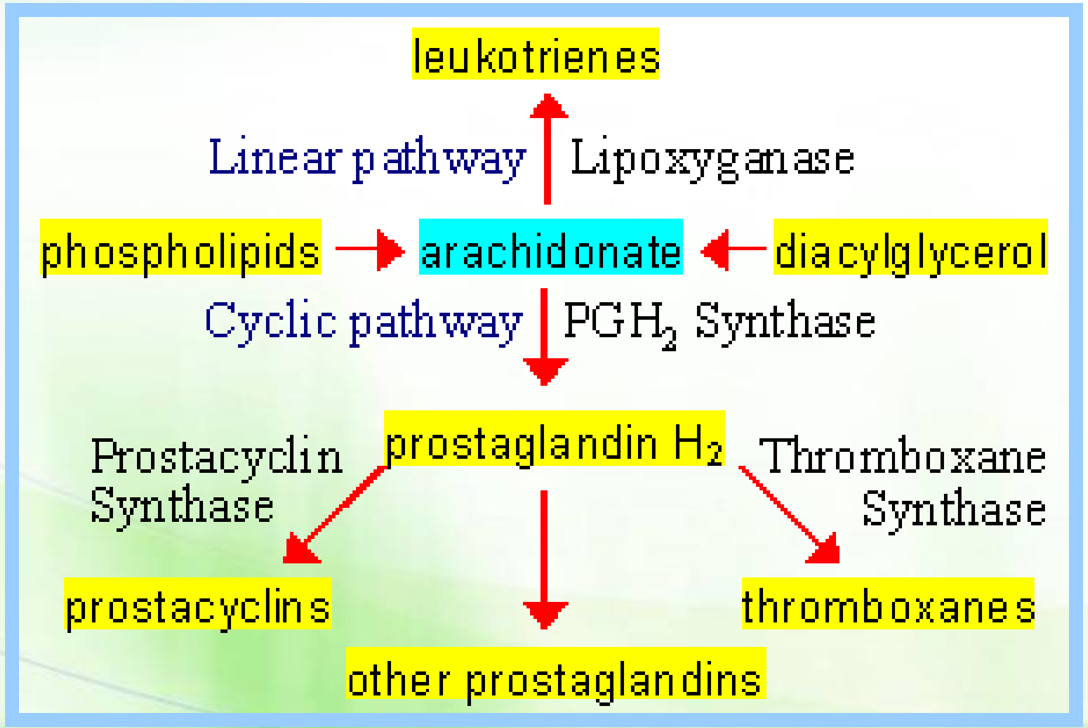
- **Linoleic acid: precursor of arachidonates**
- **Linolenic acid: precursor of EPA and DHA**

Numerical Symbol	Common Name and Structure	Comments
$18:1^{\Delta 9}$	Oleic acid 	Omega-9 monounsaturated
$18:2^{\Delta 9,12}$	Linoleic acid 	Omega-6 polyunsaturated
$18:3^{\Delta 9,12,15}$	α-Linolenic acid (ALA) 	Omega-3 polyunsaturated
$20:4^{\Delta 5,8,11,14}$	Arachidonic acid 	Omega-6 polyunsaturated
$20:5^{\Delta 5,8,11,14,17}$	Eicosapentaenoic acid (EPA) 	Omega-3 polyunsaturated (fish oils)
$22:6^{\Delta 4,7,10,13,16,19}$	Docosahexaenoic acid (DHA) 	Omega-3 polyunsaturated (fish oils)

Derived fatty acids:
Eicosanoids

Arachidonate

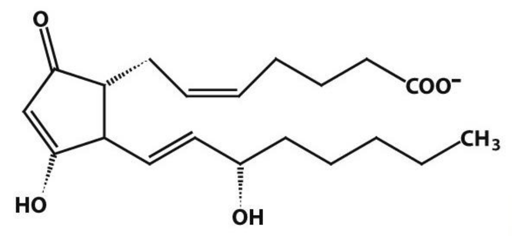
all *cis*-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-eicosatetraenoate, $CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2COO^-$



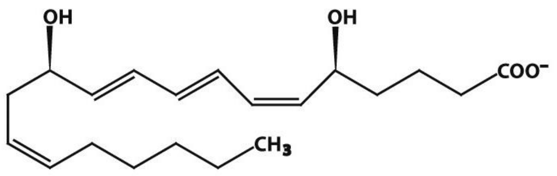
Eicosanoids and their functions

They control cellular function in response to injury

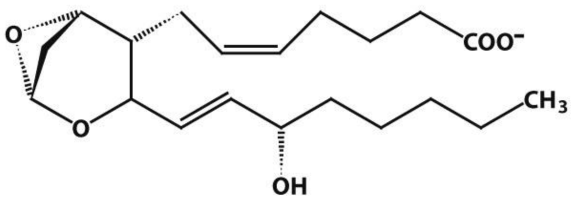
- Prostaglandins
  - Induction of inflammation
  - Inhibition of platelet aggregation
    - Inhibition of blood clotting
- Leukotrienes
  - Constriction of smooth muscles
    - Asthma
- Thromboxanes
  - Constriction of smooth muscles
  - Induction of platelet aggregation
- Prostacyclins
  - An inhibitor of platelet aggregation
  - Induction of vasodilation



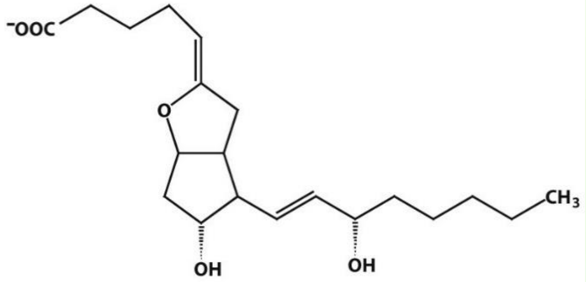
Prostaglandin E_2



Leukotriene B_4

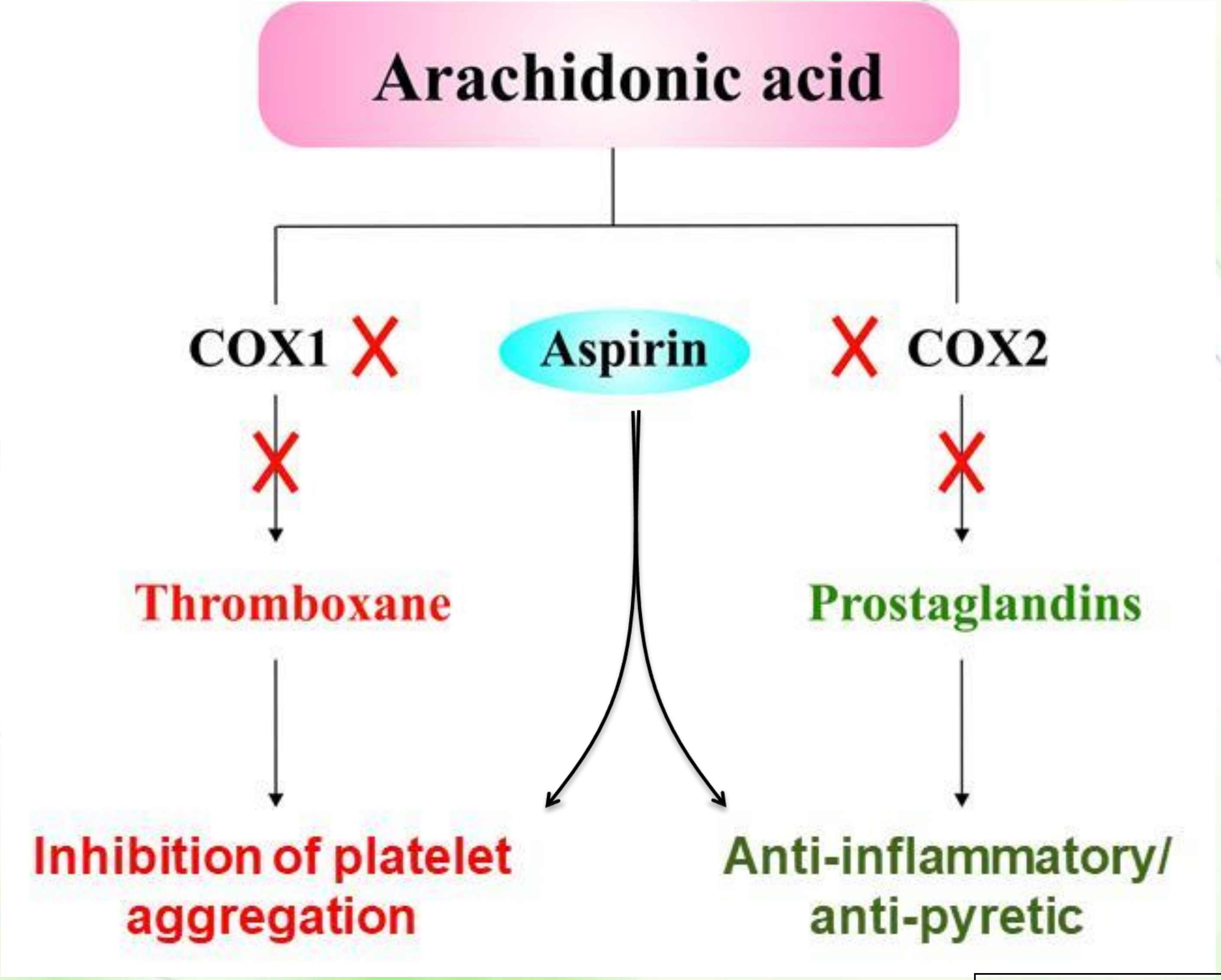


Thromboxane A_2 (TXA_2)



Prostacyclin (PGI_2)

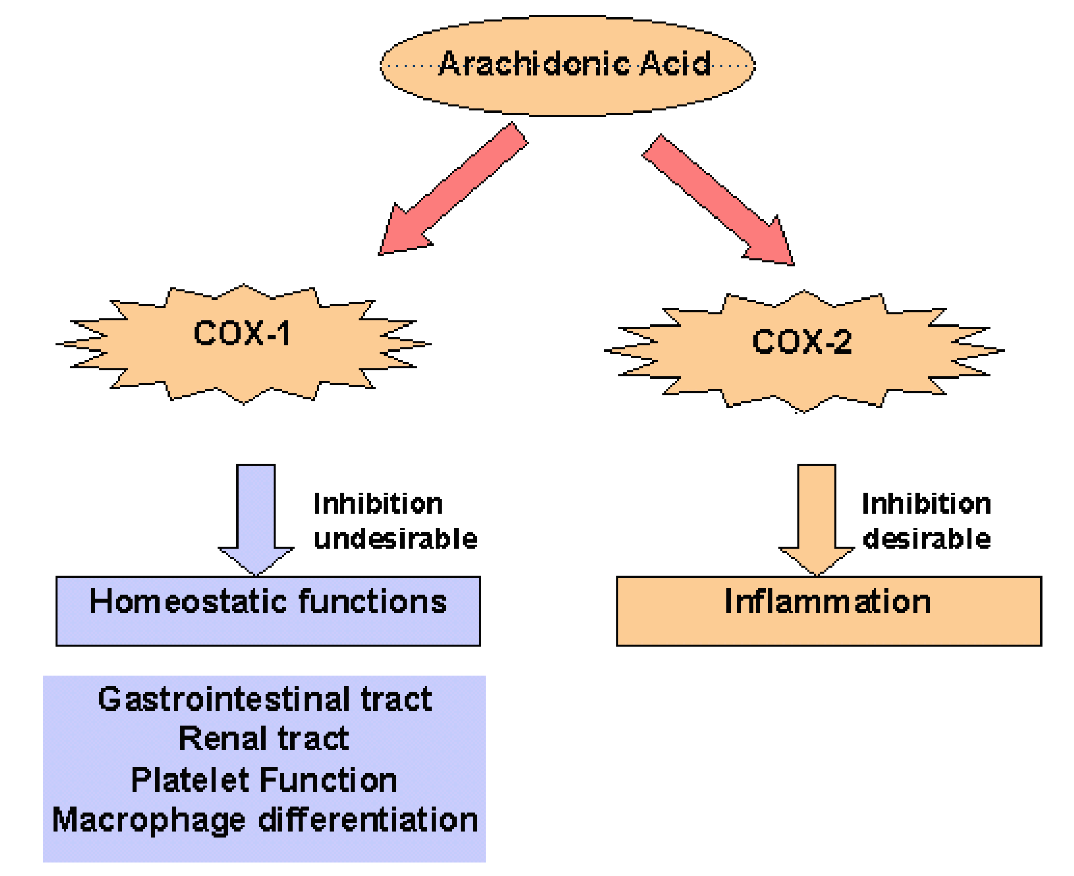
Aspirin is good



COX: Cyclooxygenase

Targets of Aspirin

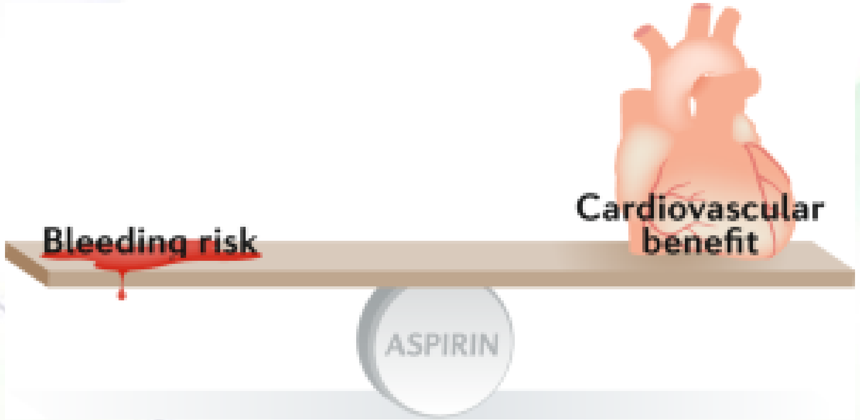
- Cyclooxygenase is present in three forms in cells, COX-1, COX-2, and COX-3.
- Aspirin targets both, but COX-2 should only be the target.

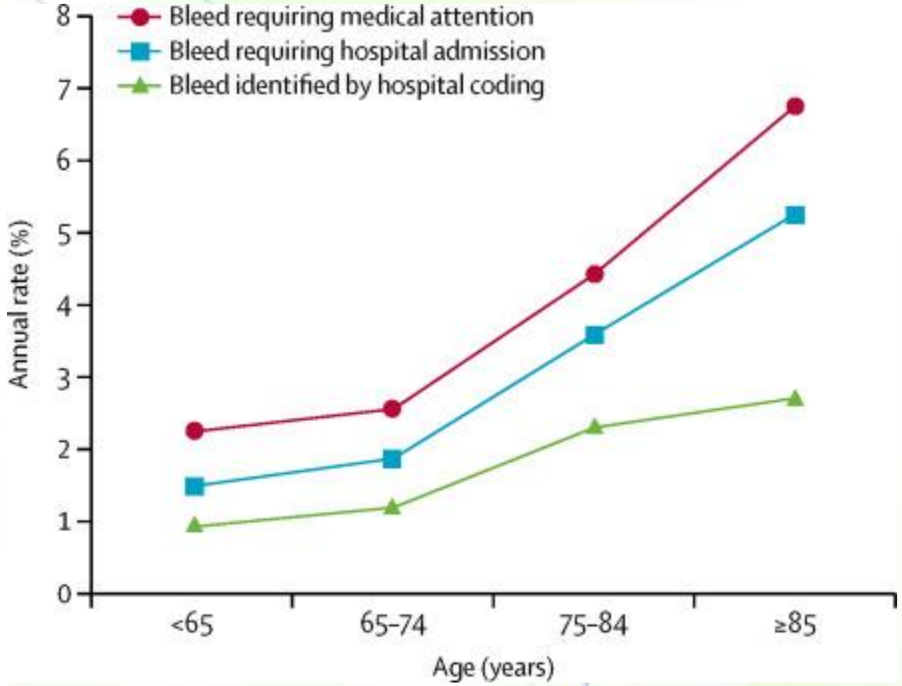


Aspirin is bad

Cardiovascular disease vs. bleeding

- Aspirin also causes excessive bleeding among the elderly.





Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study

Linxin Li, Olivia C Geraghty*, Ziyah Mehta, Peter M Rothwell, on behalf of the Oxford Vascular Study*

Interpretation In patients receiving aspirin-based antiplatelet treatment without routine PPI use, the long-term risk of major bleeding is higher and more sustained in older patients in practice than in the younger patients in previous trials, with a substantial risk of disabling or fatal upper gastrointestinal bleeding. Given that half of the major bleeds in patients aged 75 years or older were upper gastrointestinal, the estimated NNT for routine PPI use to prevent such bleeds is low, and co-prescription should be encouraged.

Celebrex

- A new generation drug, Celebrex, targets COX2, but is prescribed with a strong warning of side effects on the label.

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).
- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Omega fatty acids

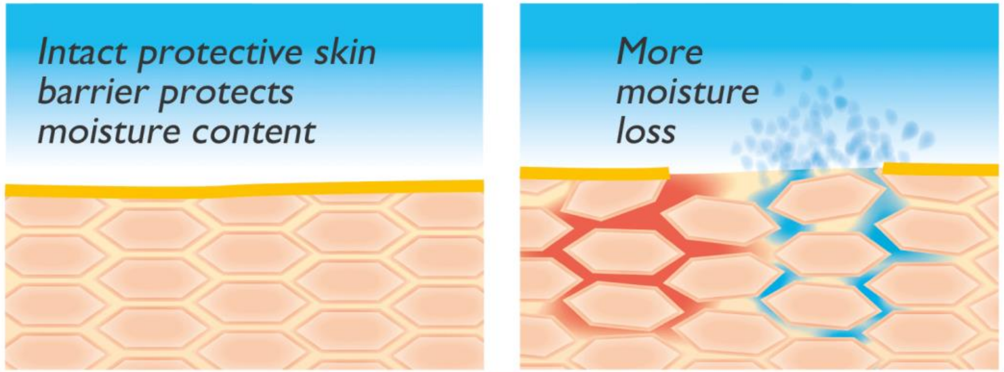
- Omega-3 fatty acids
  - α-linolenic acid → eicosapentaenoic acid (EPA) → docosahexaenoic acid (DHA)
    - They reduce inflammatory reactions by:
      - Reducing conversion of arachidonic acid into eicosanoids
      - Promoting the synthesis of anti-inflammatory molecules
- Omega-6 fatty acids:
  - Arachidonic acid
    - stimulates platelet and leukocyte activation,
    - signals pain,
    - Induces bronchoconstriction,
    - regulates gastric secretion
- Omega-9 fatty acids
  - Oleic acid
    - Reduces cholesterol in the circulation

Why is linoleic acid essential?

1. It serves as a precursor of arachidonic acid.
2. It covalently binds another fatty acid attached to cerebrosides (to be discussed) in the skin, forming an unusual lipid (acylglucosylceramide) that helps to make the skin impermeable to water.

    This function of linoleic acid may help to explain the red, scaly dermatitis and other skin problems associated with a dietary deficiency of essential fatty acids.

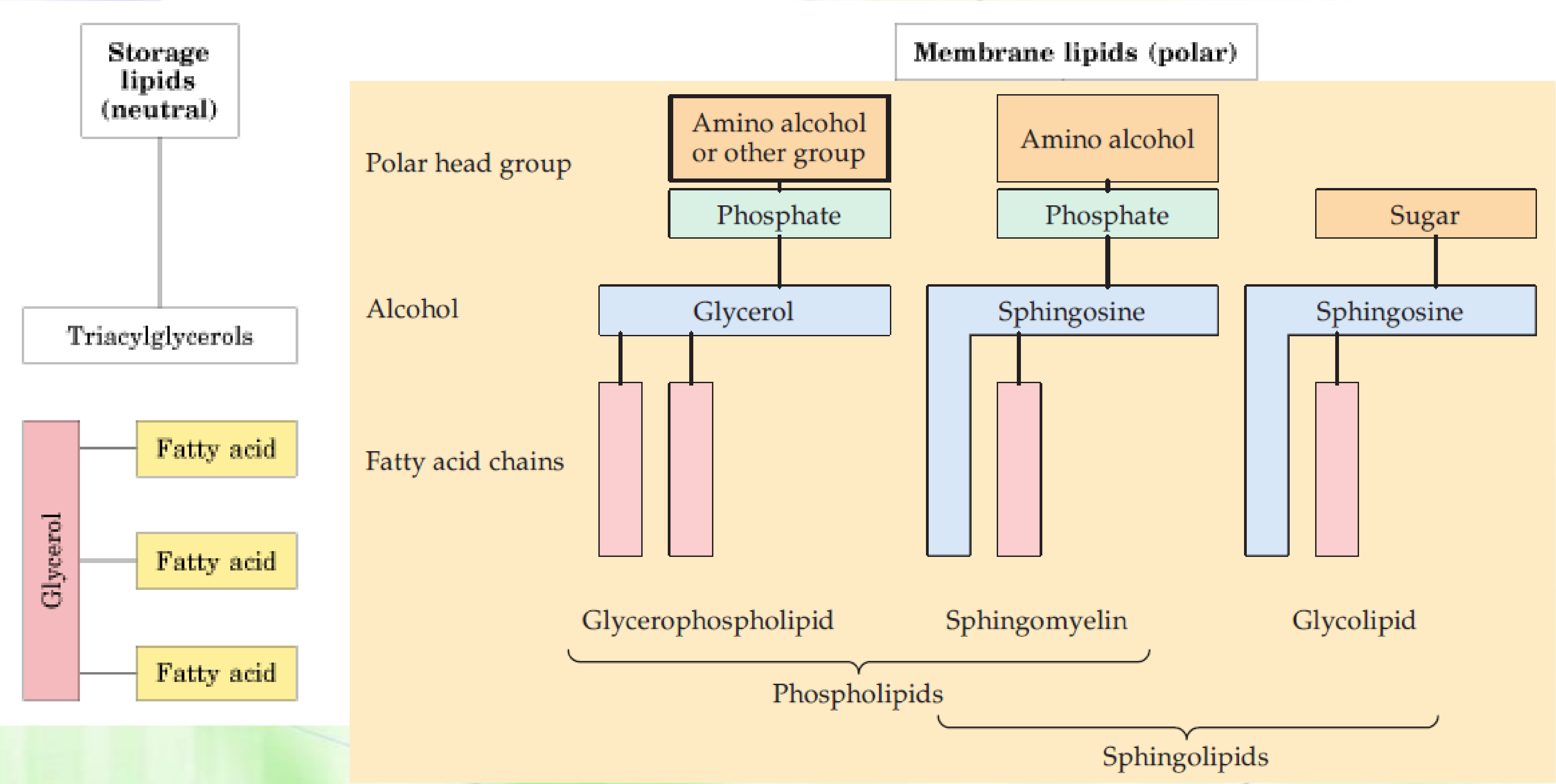
3. It is the precursor of important neuronal fatty acids.



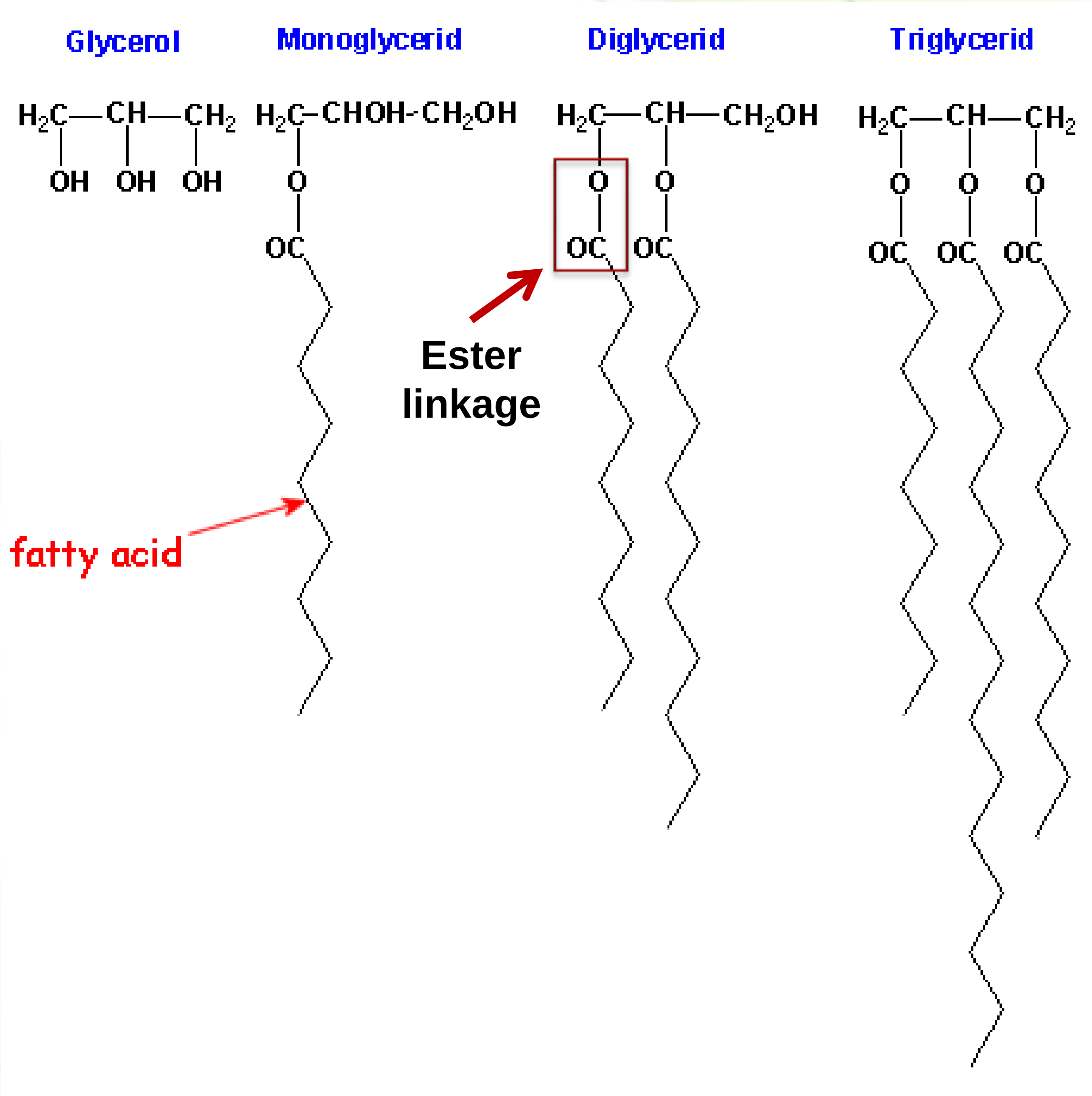
Intact protective skin barrier with linoleic acid rich lipids

Loss of lipids results in break-down in skin barrier function. The skin loses a large amount of water and dries out.

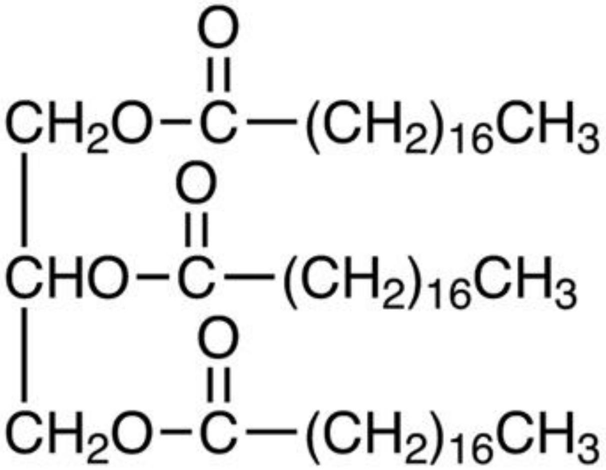
Complex lipids


Storage lipids (neutral)
Triacylglycerols
Glycerol
Fatty acid
Fatty acid
Fatty acid
Membrane lipids (polar)
Polar head group
Alcohol
Fatty acid chains
Amino alcohol or other group
Phosphate
Glycerol
Amino alcohol
Phosphate
Sphingosine
Sugar
Sphingosine
Glycerophospholipid
Sphingomyelin
Glycolipid
Phospholipids
Sphingolipids

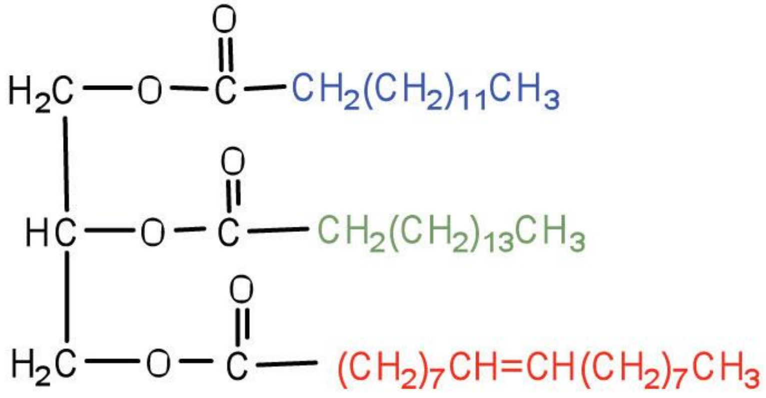
Triglycerides



Types of glycerides



Tristearin
a simple triglyceride

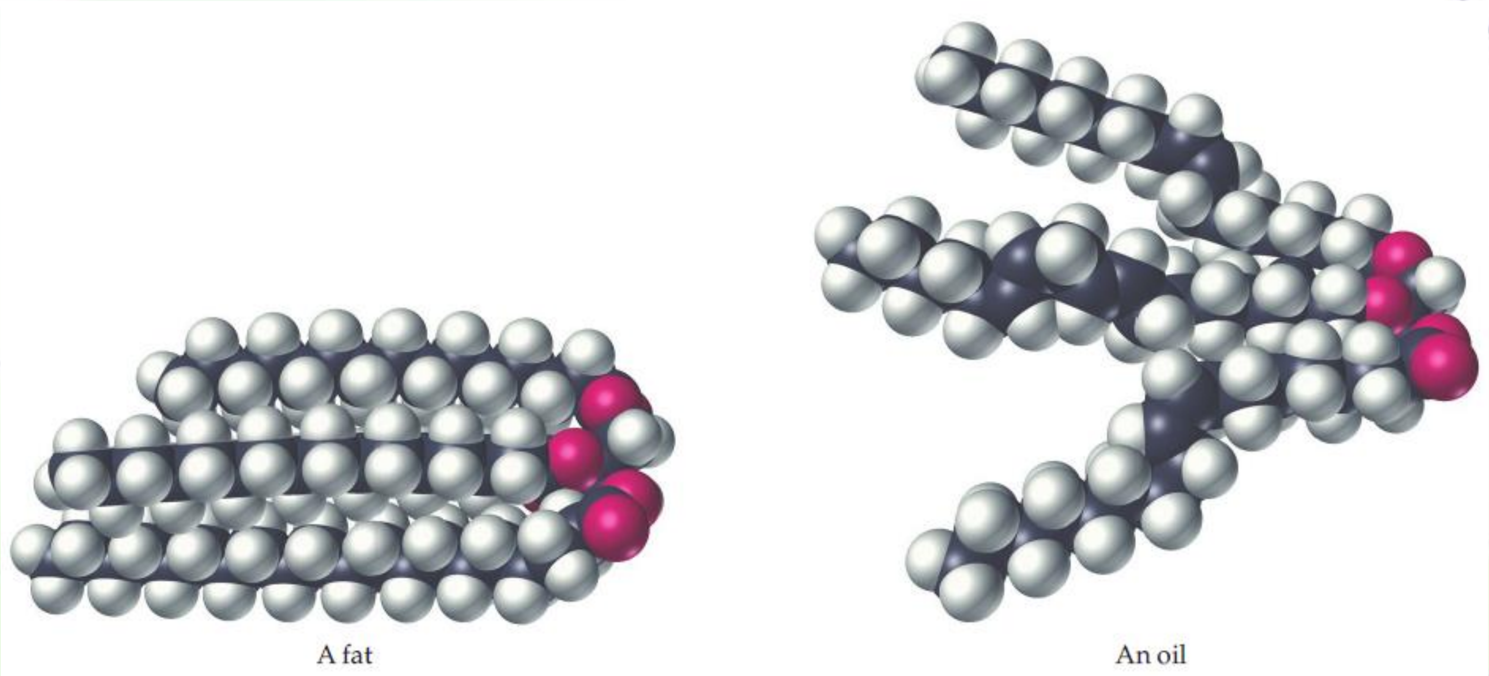


a mixed triglyceride

How soluble will a triglyceride be if fatty acids are unsaturated?

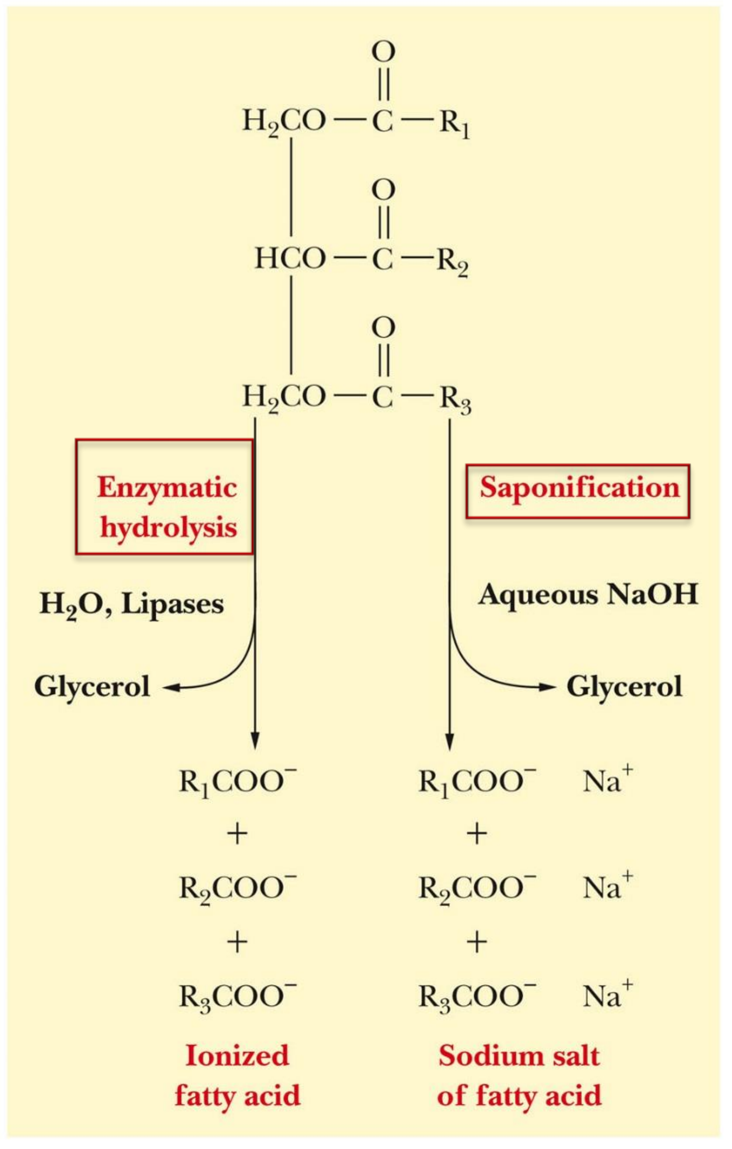
Solid vs. liquid fats

- Vegetable oils consist almost entirely of unsaturated fatty acids, whereas animal fats contain a much larger percentage of saturated fatty acids.
  - This is the primary reason for the different melting points of fats and oils.



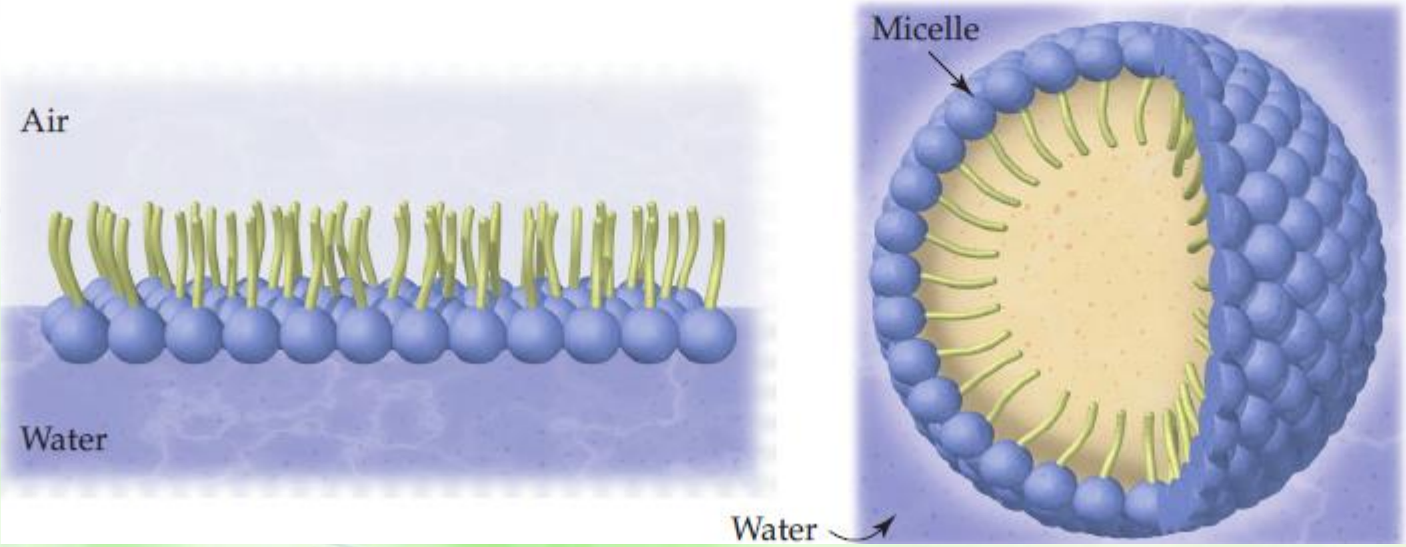
Saponification

- Hydrolysis: steam, acid, enzyme (e.g., lipase of pancreas)
- Saponification: Alkaline hydrolysis produces salts of fatty acids (soaps). Soaps cause emulsification of oily material.



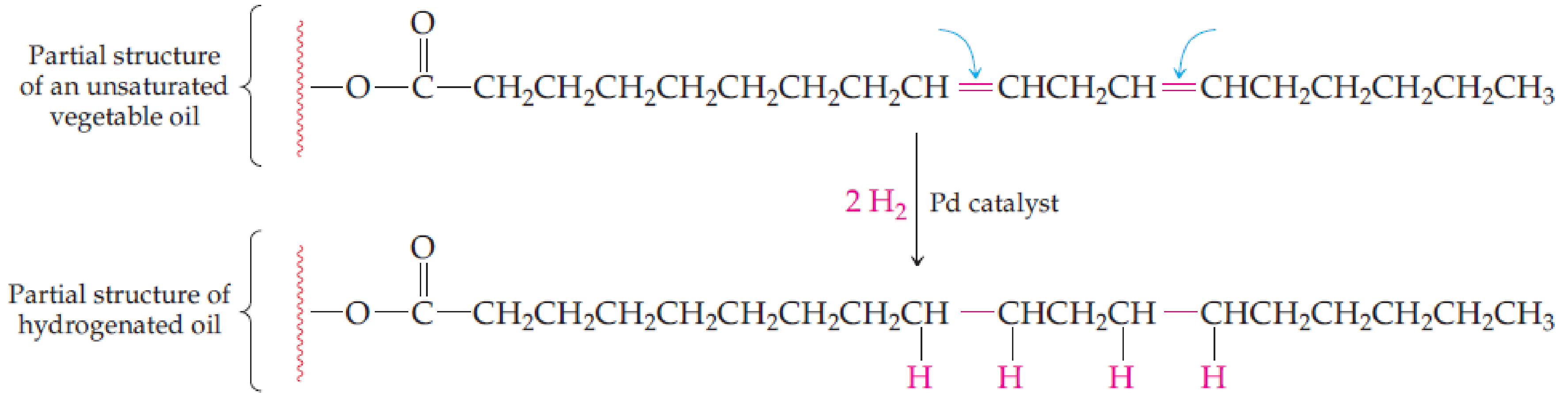
How does soap work?

- When mixed with water, the hydrophobic hydrocarbon tails cluster together to create a nonpolar microenvironment and the hydrophilic ionic heads interact with water.
- The resulting spherical clusters are called micelles.
- Grease and dirt are trapped inside micelles and the complex can be rinsed away.



Hydrogenation

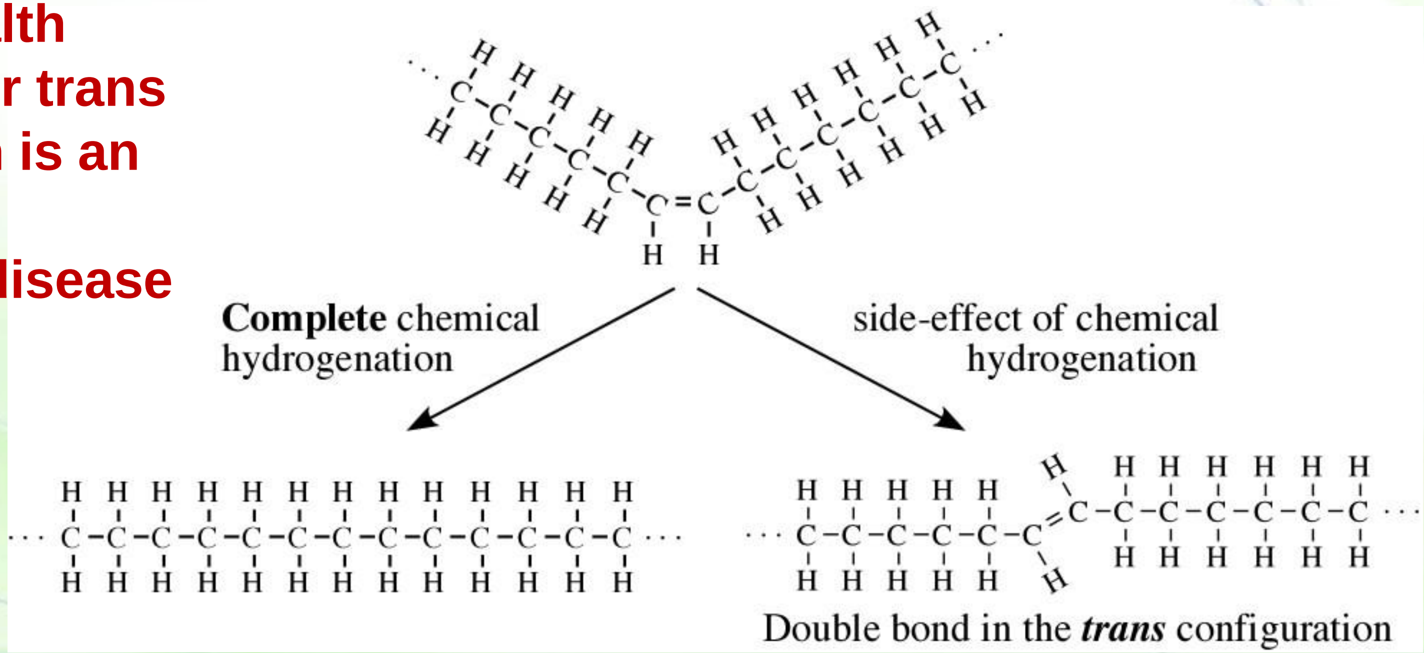
- The carbon-carbon double bonds in vegetable oils can be hydrogenated to yield saturated fats in the same way that any alkene can react with hydrogen to yield an alkane.



Trans fat

- Although the animal fat is unhealthy, it has better cooking properties and better taste.
- Therefore, chemists invented a method of converting unsaturated oil into solid form by partially hydrogenating it.
- Partial hydrogenation converts some, but not all, double bonds into single bonds generating (trans fats).

The primary health risk identified for trans fat consumption is an elevated risk of coronary heart disease (CHD).



Example: margarine

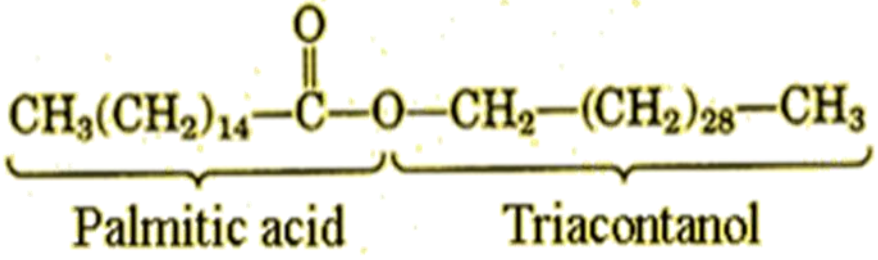
- In margarine, only about two-thirds of the double bonds present in the starting vegetable oil are hydrogenated, so that the margarine remains soft in the refrigerator and melts on warm toast.

Nutrition Facts

Serving Size 1 Tbsp (14g)
Servings Per Container 32

Amount Per Serving	
Calories 100	Calories from Fat 100
	% Daily Value*
Total Fat 11g	17%
Saturated Fat 2g	10%
Trans Fat 3g	
Cholesterol 0mg	0%

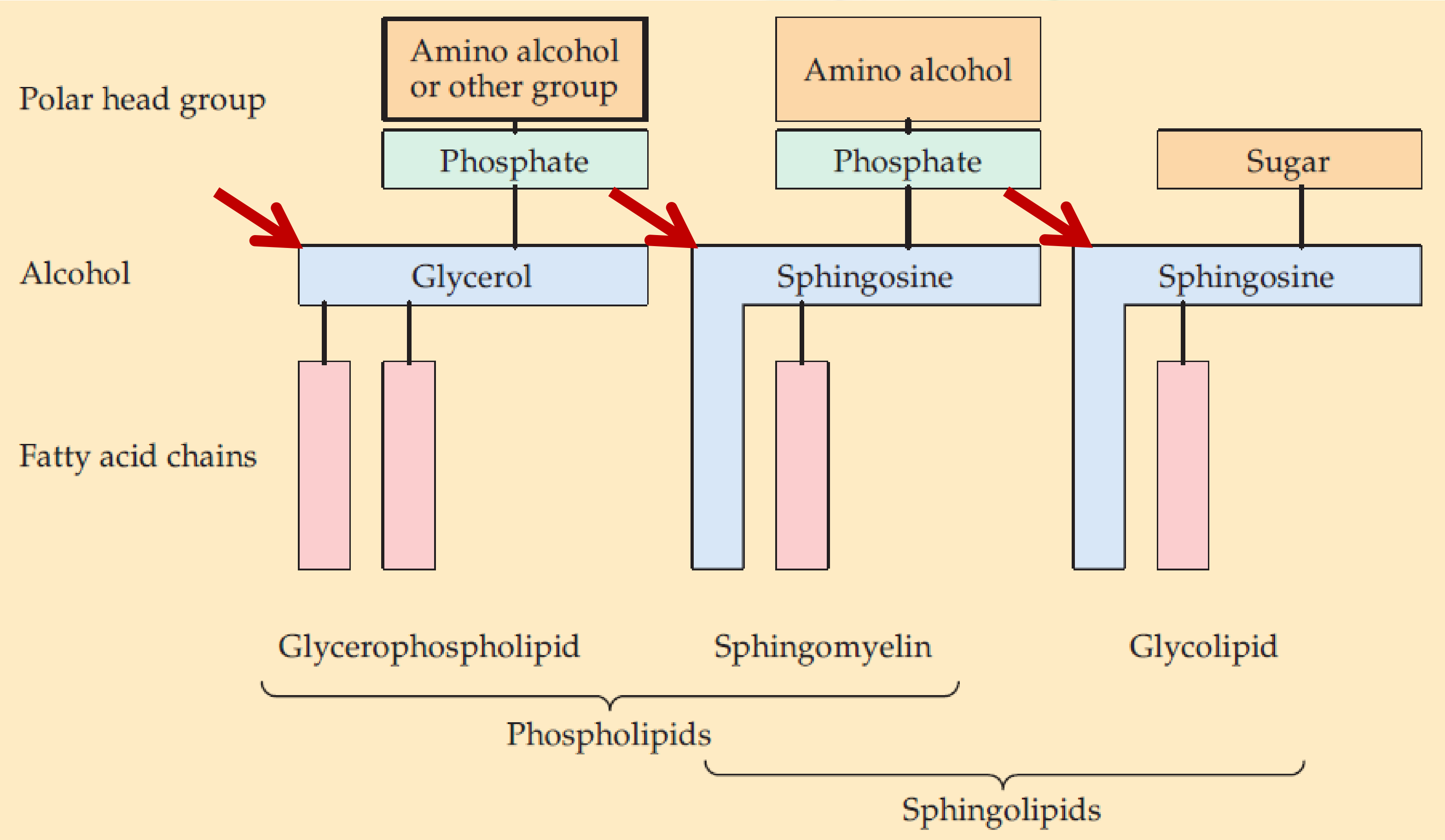
Waxes



- Solid simple lipids containing a monohydric alcohol (C16 ~ C30, higher molecular weight than glycerol) esterified to long-chain fatty acids (C14 ~ C36). Examples: palmitoyl alcohol
- Insoluble in water
- Are not easily hydrolyzed (fats) & are indigestible by lipases
- Are very resistant to rancidity
- Are of no nutritional value
- Coatings that prevent loss of water by leaves of plants

Type	Structural Formula	Source	Uses
Beeswax	$CH_3(CH_2)_{14}-\overset{O}{\overset{\|}{C}}-O-(CH_2)_{29}CH_3$	Honeycomb	Candles, shoe polish, wax paper
Carnauba wax	$CH_3(CH_2)_{24}-\overset{O}{\overset{\|}{C}}-O-(CH_2)_{29}CH_3$	Brazilian palm tree	Waxes for furniture, cars, floors, shoes
Jojoba wax	$CH_3(CH_2)_{18}-\overset{O}{\overset{\|}{C}}-O-(CH_2)_{19}CH_3$	Jojoba	Candles, soaps, cosmetics

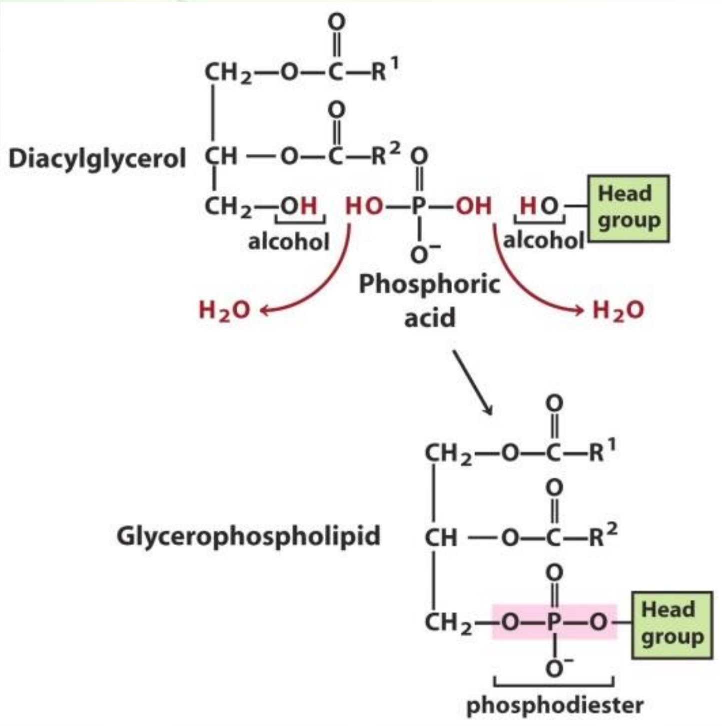
Membrane lipids



The most prevalent class of lipids in membranes is the <u>glycerophospholipids</u>

Phospholipids (phosphoacylglycerols)

- Phosphatidic acids
- Phosphatidylcholine (lecithin)
  - Most abundant membrane lipid
- Cephalins
  - Phosphatidylethanolamine
  - Phosphatidylserine
    - abundant in brain
- Phosphatidylinositol
  - sends messages across cell membranes
- Cardiolipin
- Plasmalogens



Phosphatidic acid	—	$-H$
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	$-CH_2-CH(COO^-)-\overset{+}{N}H_3$

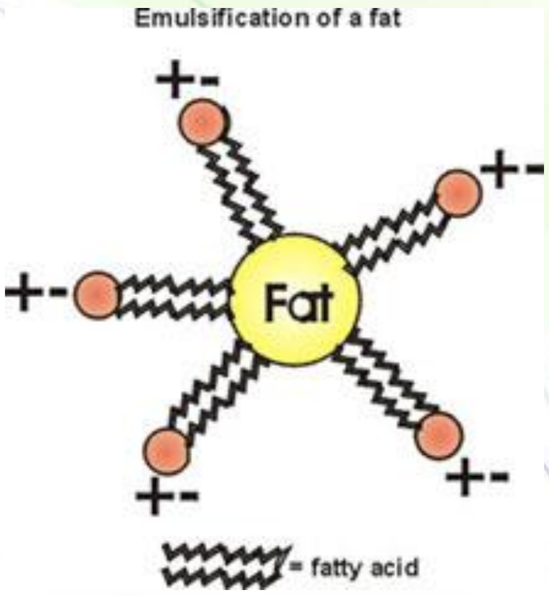
Glycerophospholipids - Lecithins

- Snake venom contain lecithinase, which hydrolyzes polyunsaturated fatty acids and converting lecithin into lysolecithin
  - hemolysis of RBCs

Phosphatidylcholine **Choline** $-CH_2-CH_2-\overset{+}{N}(CH_3)_3$

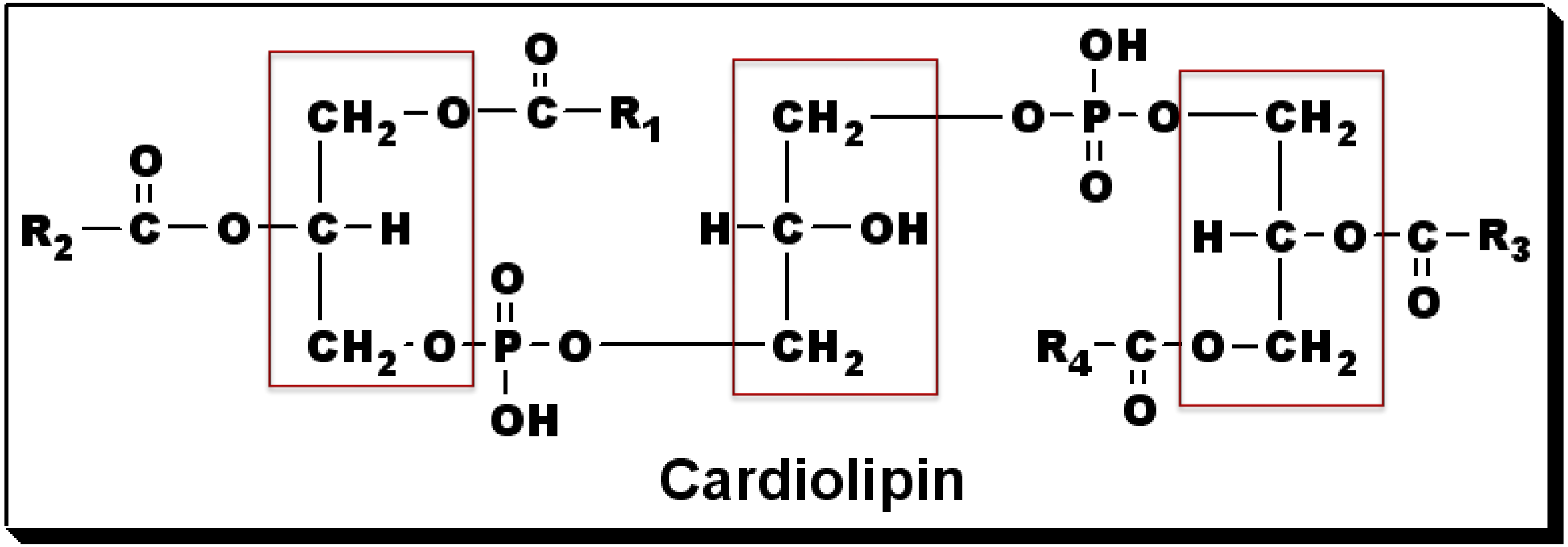
Emulsification

- Because of their amphipathic nature, they act as emulsifying agents, that is substances that can surround nonpolar molecules and keep them in suspension in water.



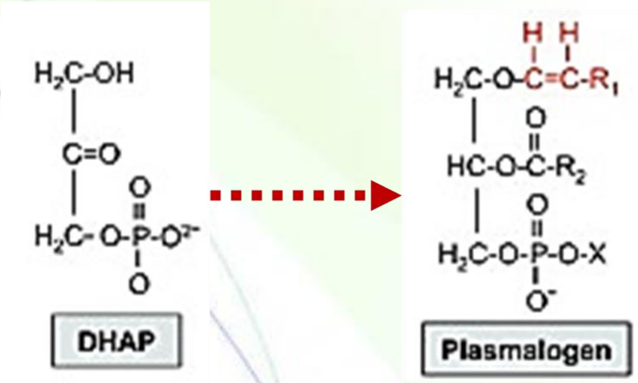
Glycerophospholipids - Cardiolipins

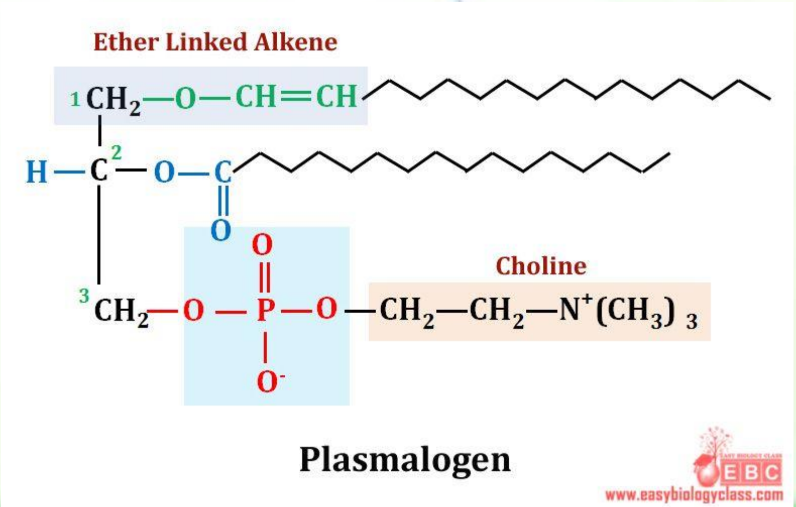
- Diphosphatidyl-glycerol
- Found in the inner membrane of mitochondria
- Initially isolated from heart muscle (cardio)
- Structure: 3 molecules of glycerol, 4 fatty acids & 2 phosphate groups



Plasmalogens

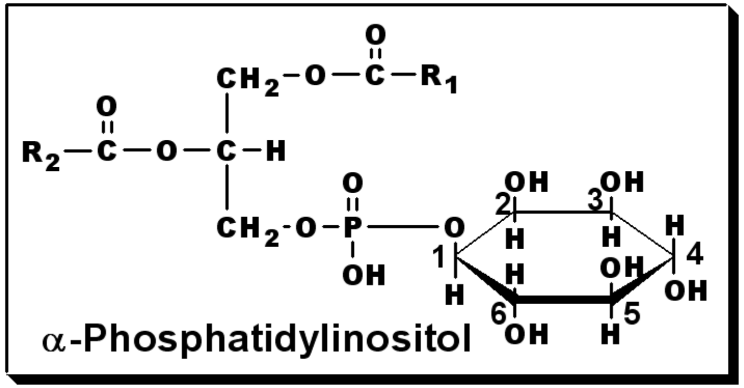
- They are found in the cell membrane phospholipids fraction of brain & muscle, liver, and semen.
- They have a protective role against reactive oxygen species
- Structure:
  - Precursor: Dihydroxyacetone phosphate
  - Unsaturated fatty alcohol at C1 connected by ether bond
  - In mammals: at C3; phosphate + ethanolamine or choline
- Major classes of plasmalogens
  - Ethanolamine plasmalogen (myelin-nervous tissues)
  - Choline plasmalogen (cardiac tissue)
    - Platelet activating factor
  - Serine plasmalogens





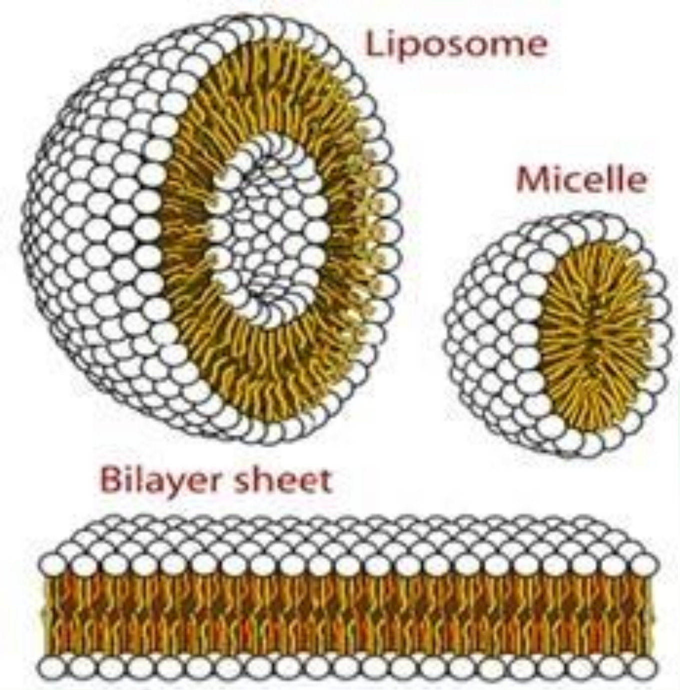
Glycerophospholipids - Inositides

- Phosphatidyl inositol
- Nitrogenous base: cyclic sugar alcohol (inositol)
- Structure: glycerol, saturated FA, unsaturated FA, phosphoric acid, & inositol
- Source: Brain tissues

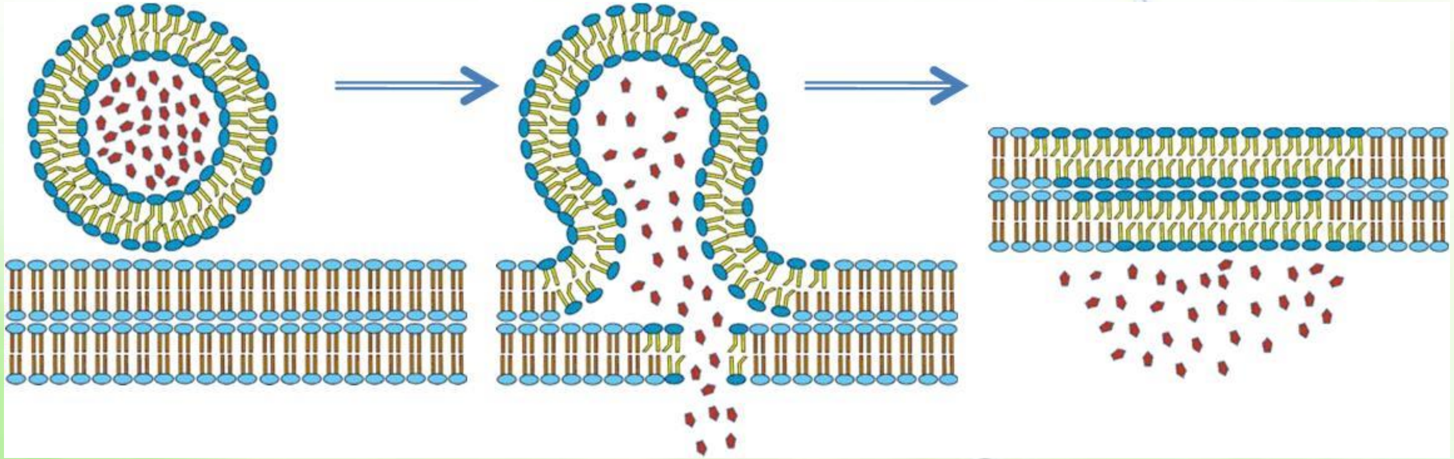


- Functions:
  - Major component of cell membrane
  - Second messenger during signal transduction
  - On hydrolysis by phospholipase C, phosphatidyl-inositol-4,5-diphosphate produces diacyl-glycerol (DAG) & inositol-triphosphate (IP3); which liberates calcium

The different structures of phospholipids

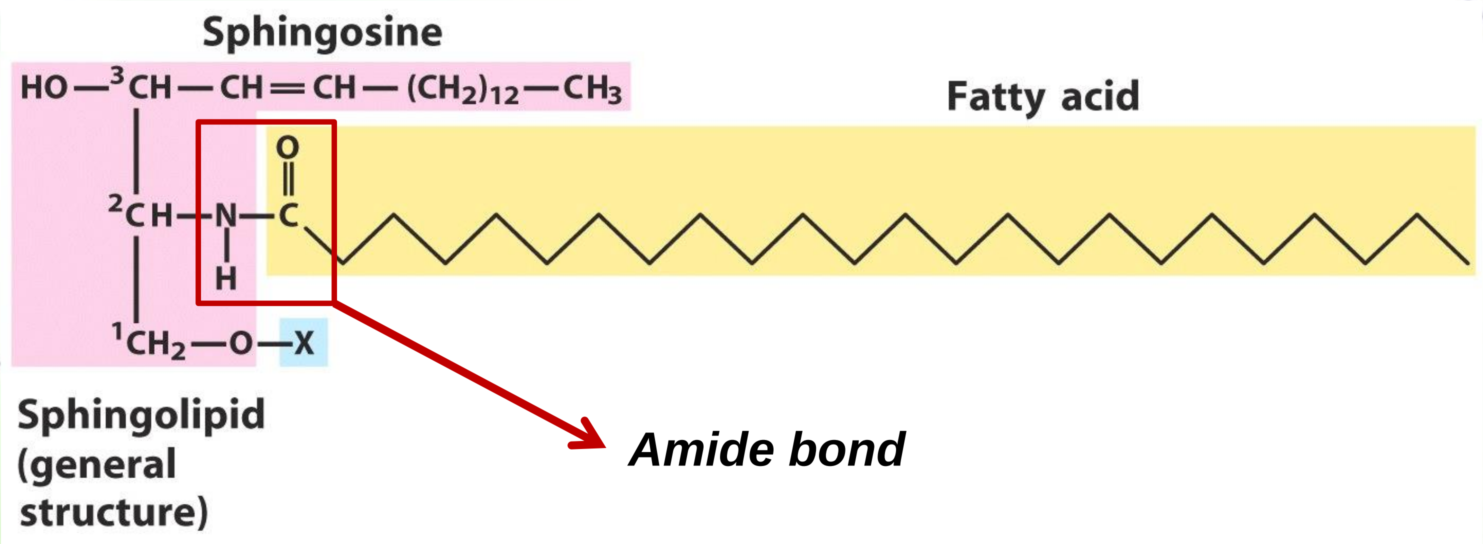


Uses of liposomes: delivery



Sphingolipids

- Sphingolipids are found in the plasma membranes of all eukaryotic cells and is highest in the cells of the central nervous system
- The core of sphingolipids is the long-chain amino alcohol, sphingosine

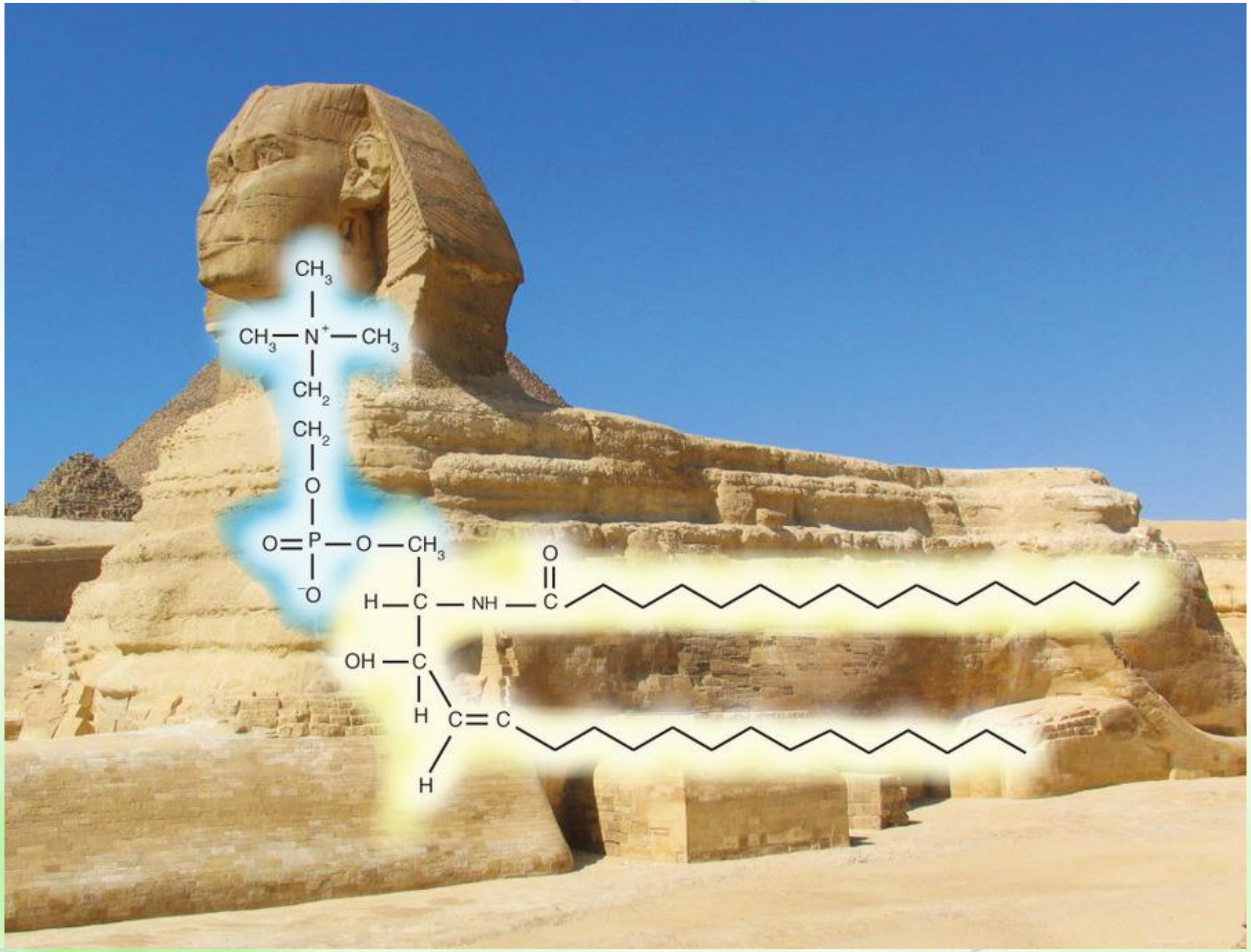


Mysterious lipids

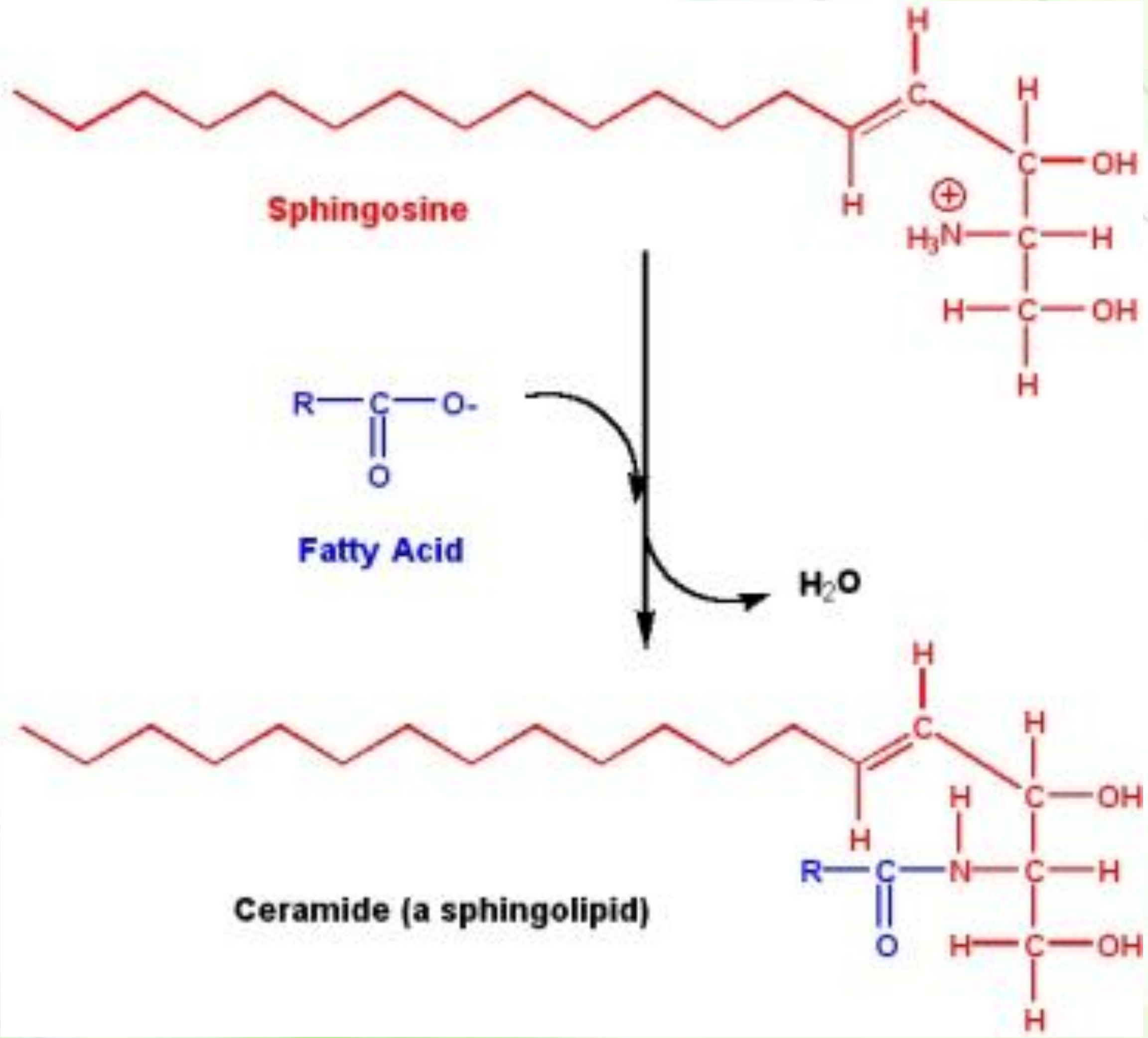
Sphynx → sphingolipids

<u>Trivia</u>

Named for the Sphinx of Thebes, who killed passersby that could not solve her riddles

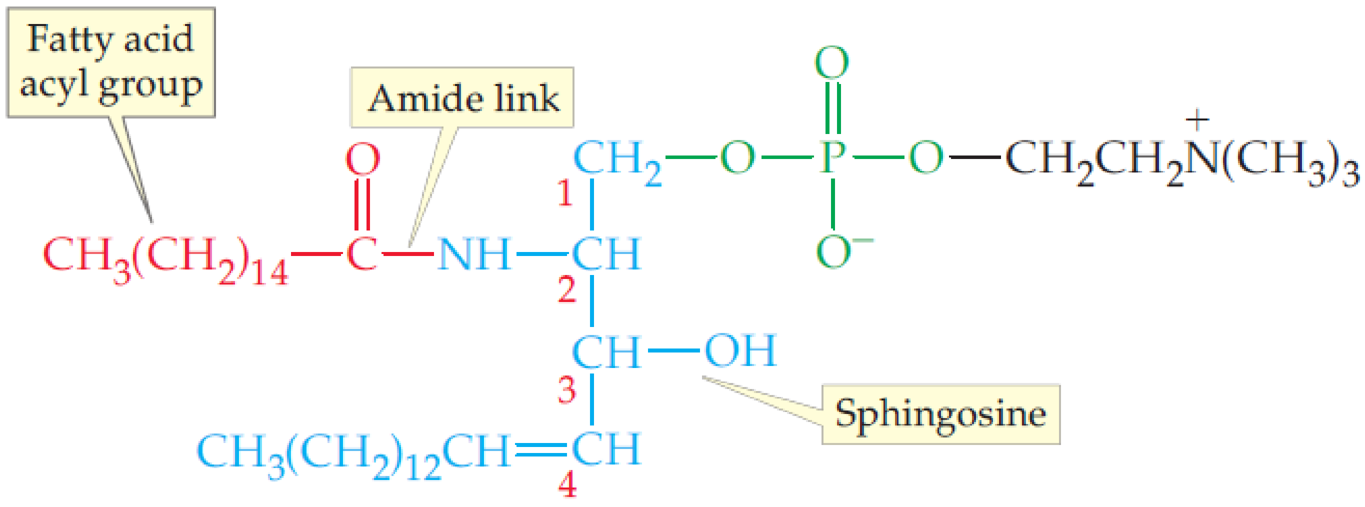


Ceramide



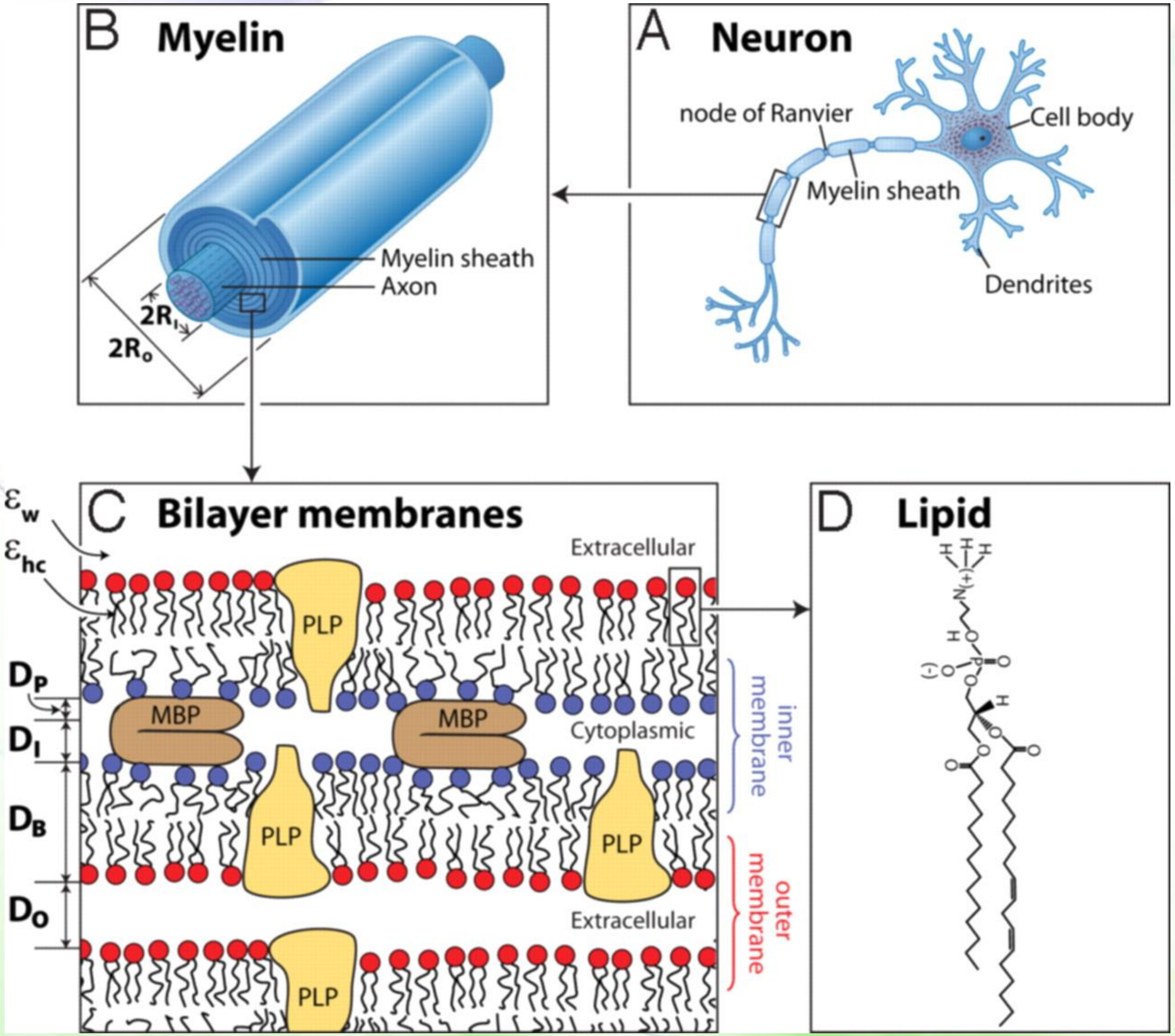
Types of sphingolipids

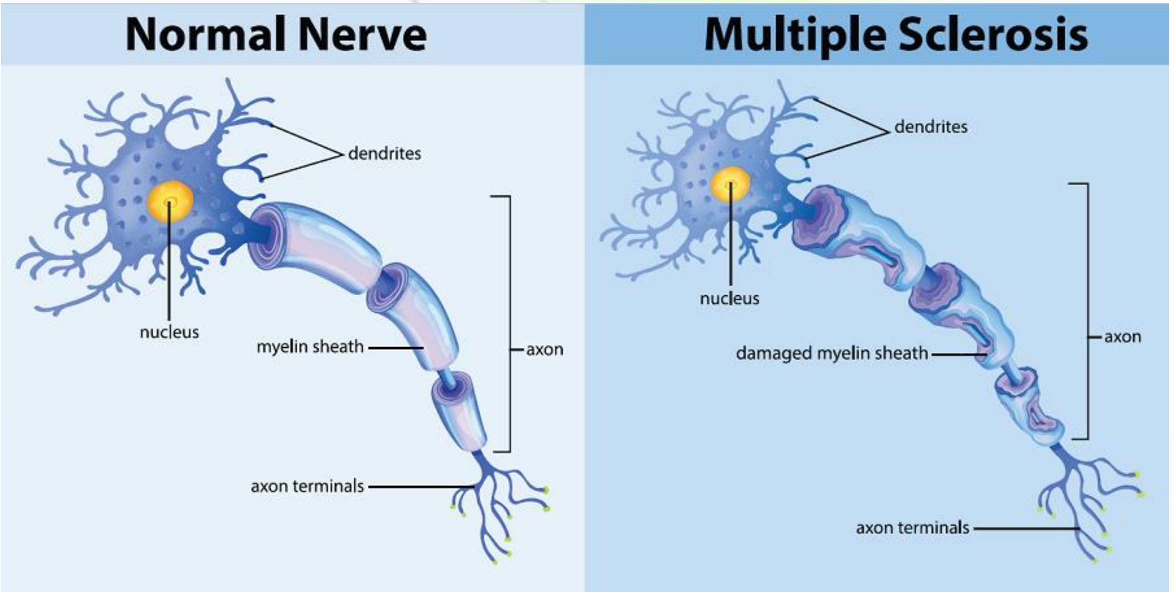
- The sphingolipids are divided into two subcategories:
  - Sphingomyelin
    - It is a sphingolipid that is a major component of the coating around nerve fibers.
    - The group attached to C1 is a phosphocholine
  - Glycosphingolipid (or glycolipids)



A sphingomyelin (a sphingolipid)

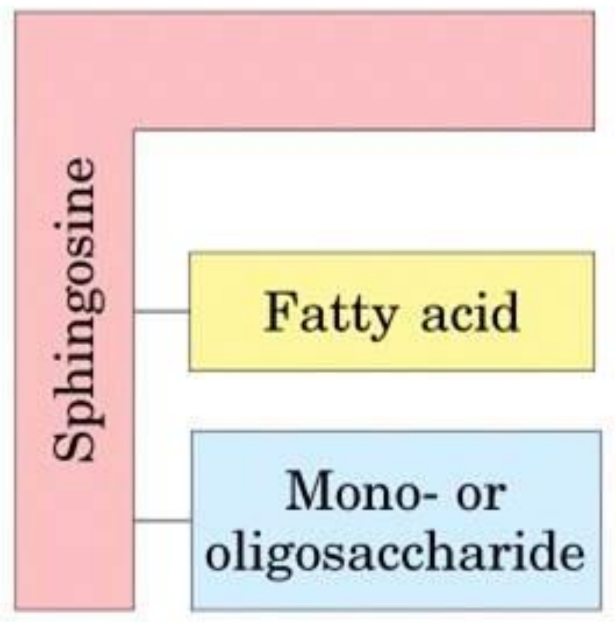
Zooming into the myelin





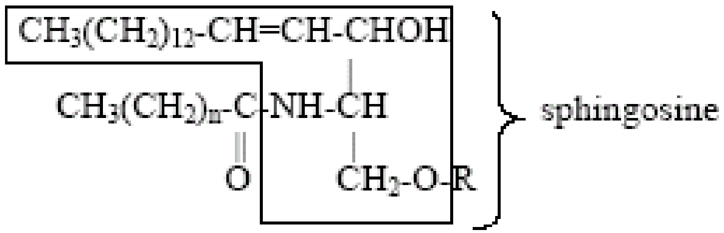
Glycolipids

- Sphingolipids can also contain carbohydrates attached at C-1 and these are known as glycolipids
- Glycolipids are present on cell membranes and act as cell surface receptors that can function in cell recognition (e.g., pathogens) and chemical messengers
- There are three types of glycolipids
  - Cerebrosides
  - Globosides
  - Gangliosides



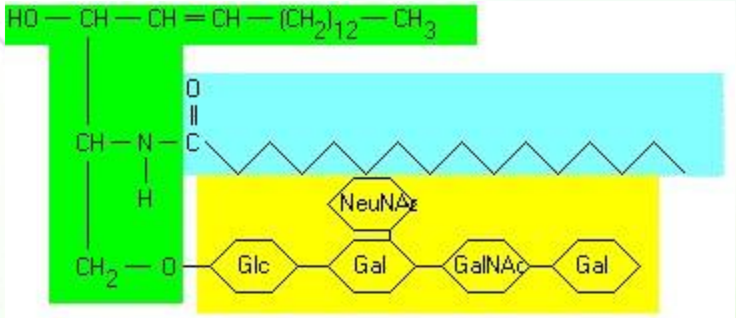
Glycolipids

- Cerebrosides: the simplest glycolipids, contain a single hexose (galactose or glucose).
- Globosides and gangliosides are more complex glycolipids.
- Both contain glucose, galactose, and N-acetylgalactosamine, but gangliosides must also contain sialic acid.

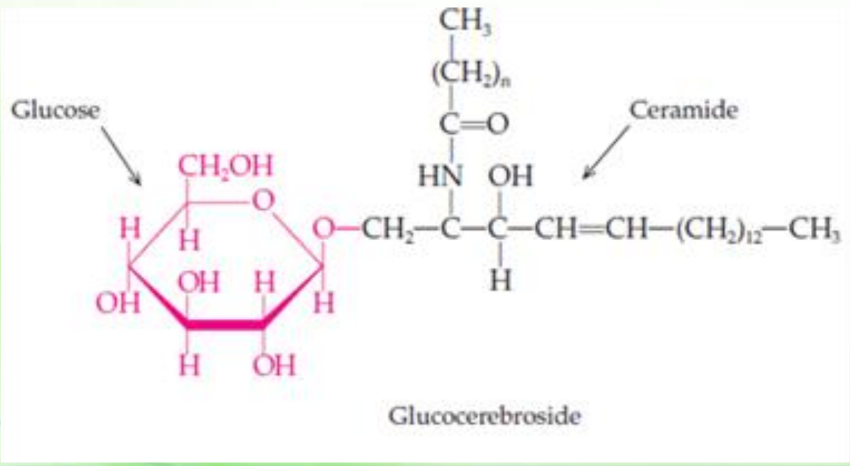


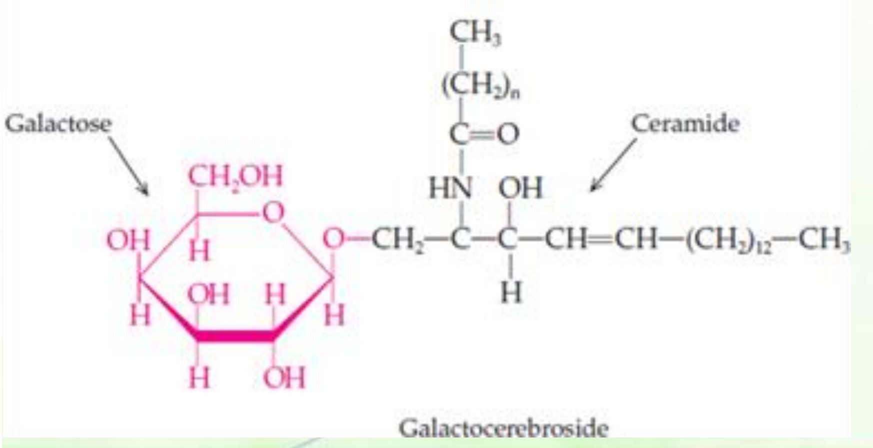
glycolipids: Cerebroside, Globoside, Ganglioside

Sphingolipid type	R group
Ceramide	H
Sphingomyelin	phosphocholine
Cerebroside	monosaccharide (galactose or glucose)
Globoside	two or more sugars (galactose, glucose, N-acetylglucosamine
Ganglioside	three or more sugars including at least one sialic acid



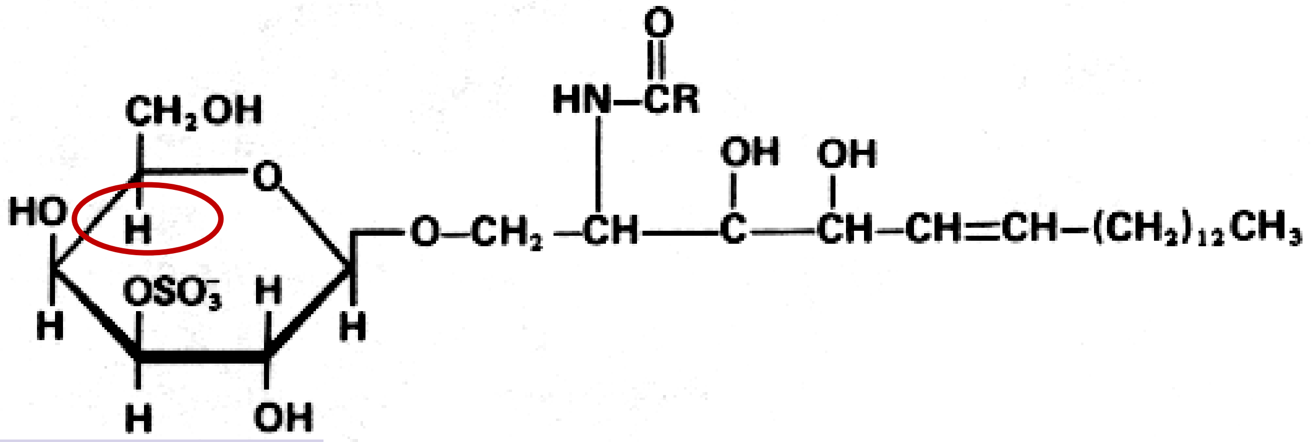
Gangliosides are bound by cholera toxin in the human intestine facilitating its endocytosis into the cells.

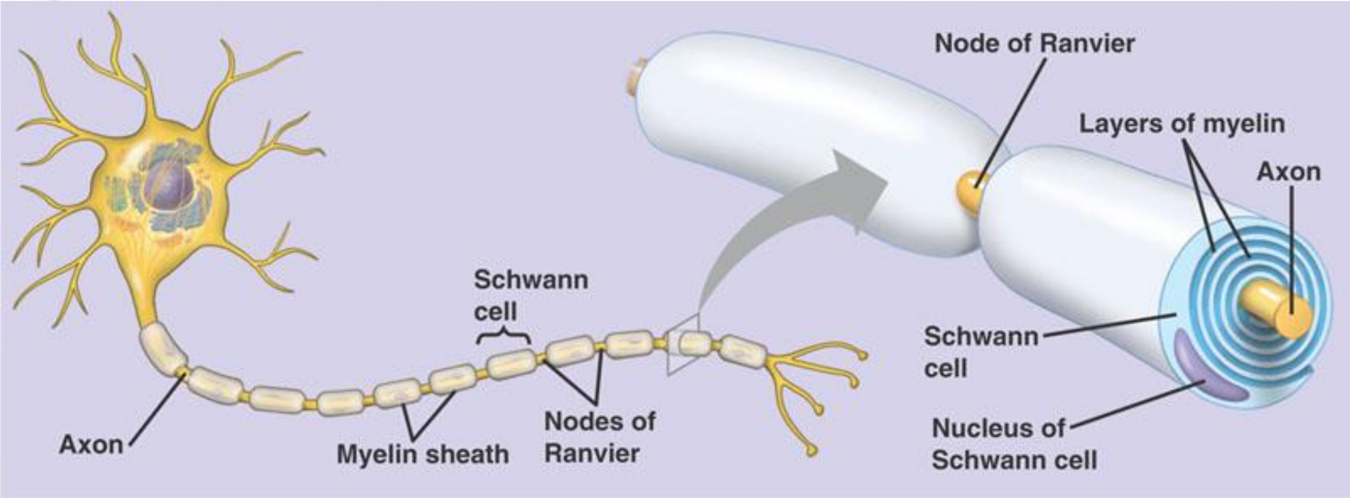




Sulfatides

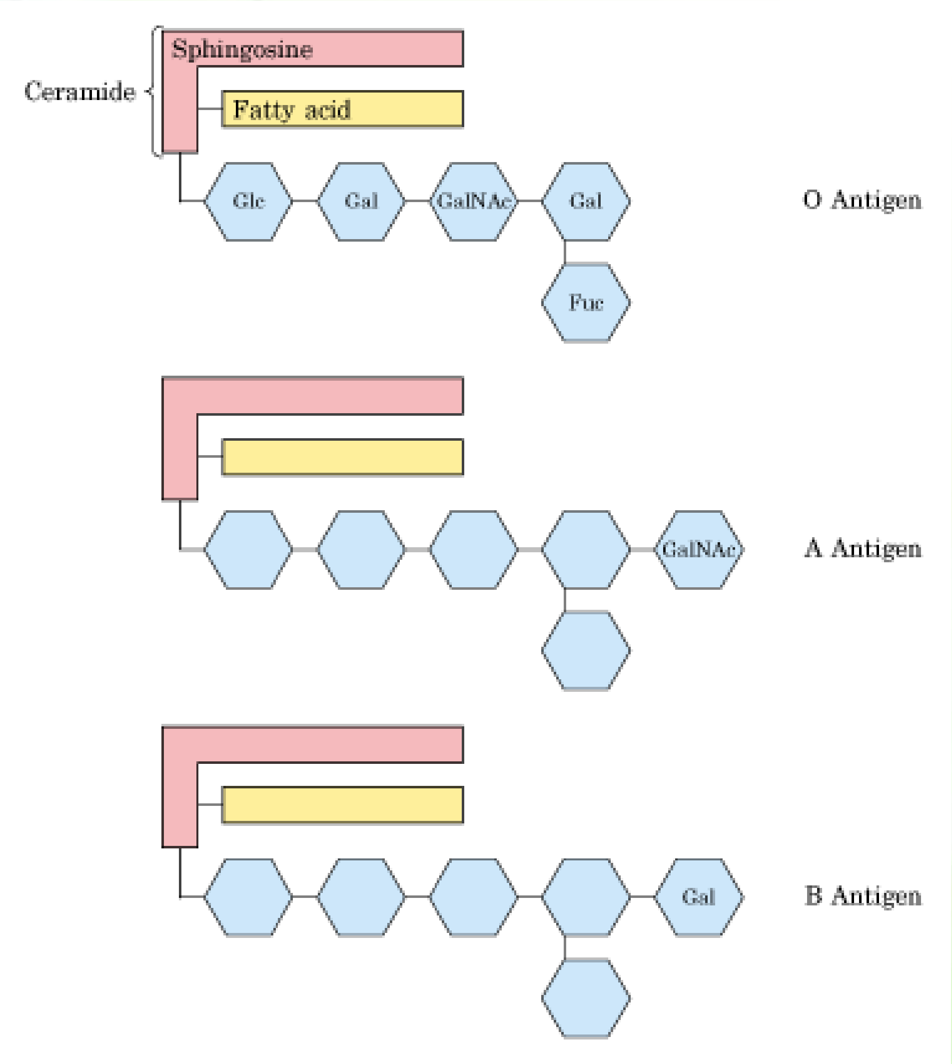
- Synthesized from galactocerebroside
- Abundant in brain myelin



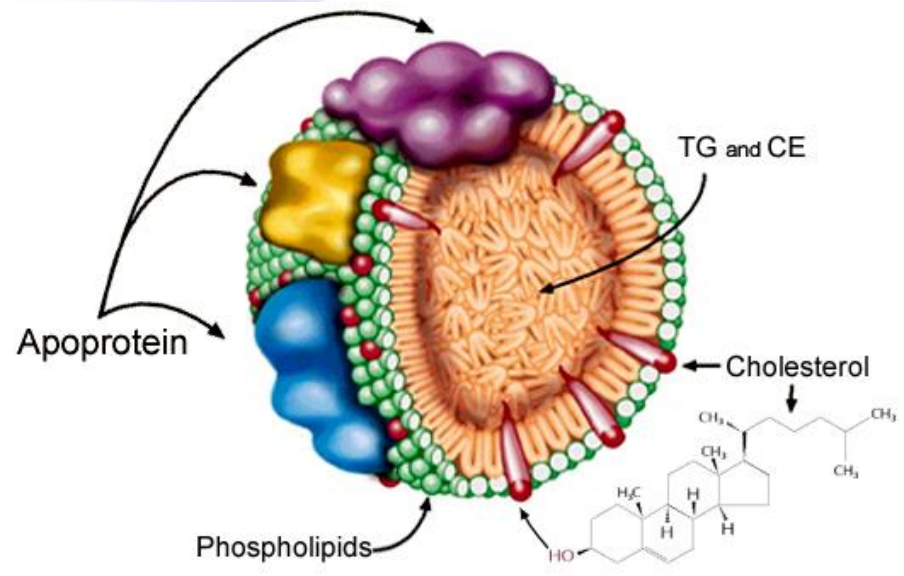


Sphingolipids and blood groups

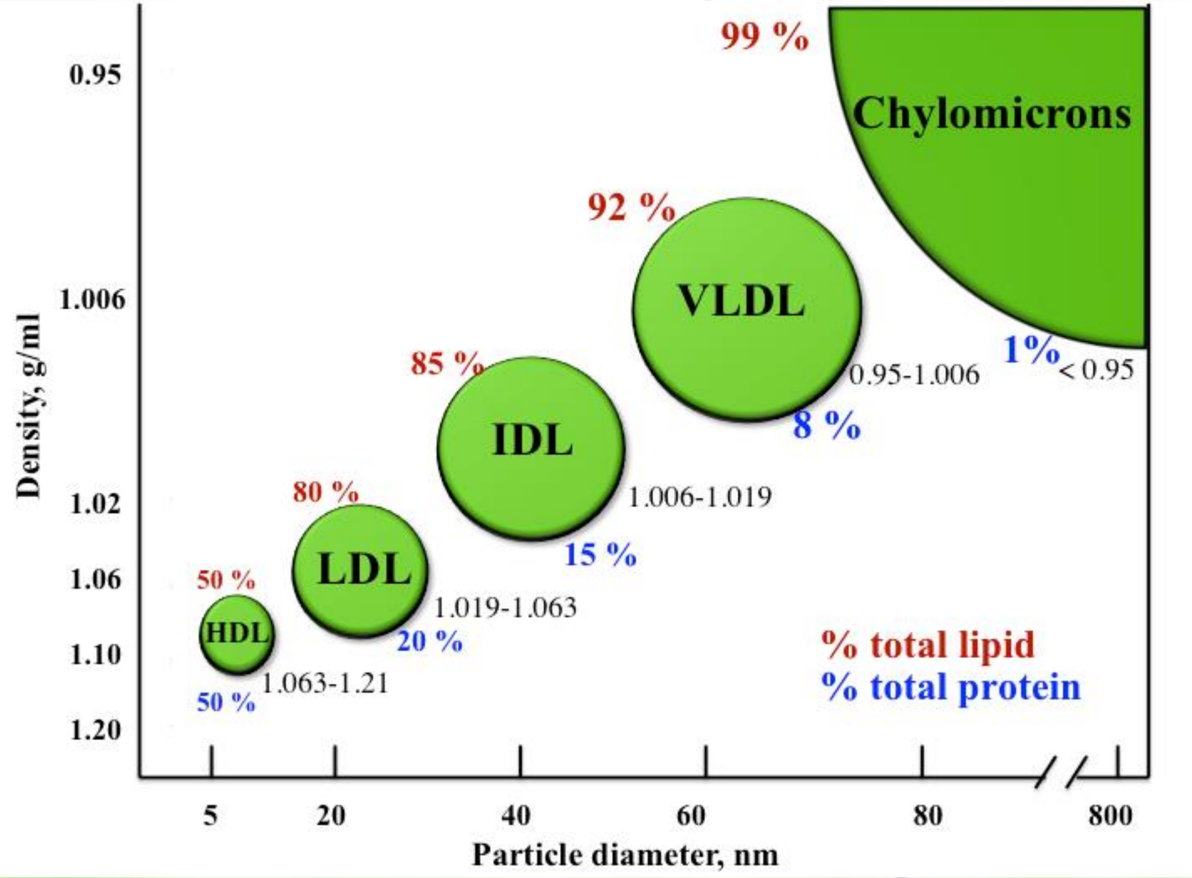
- Sphingolipids serve in intercellular communication and as the antigenic determinants of the ABO blood groups.
- Some are used as receptors by viruses and bacterial toxins.



Lipoproteins



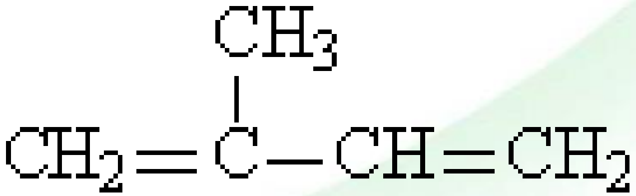
Function: transport of different types of lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) in blood plasma.



As lipid content increases, the density decreases

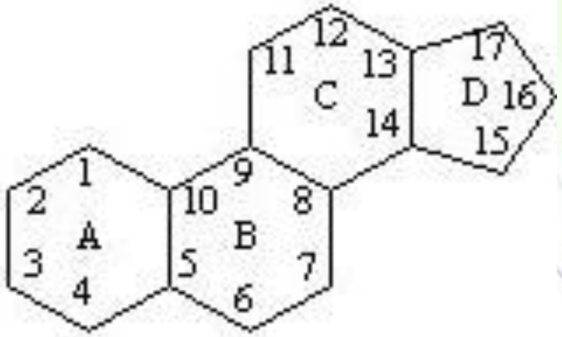
Steroids

The precursor



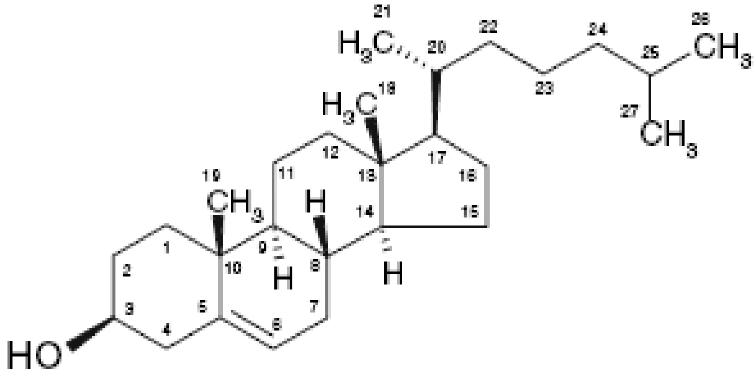
Isoprene

The nucleus



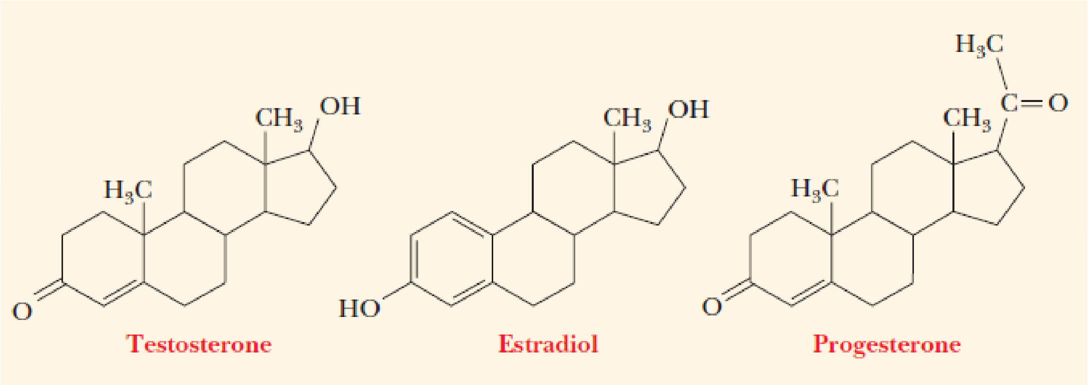
Steroid nucleus

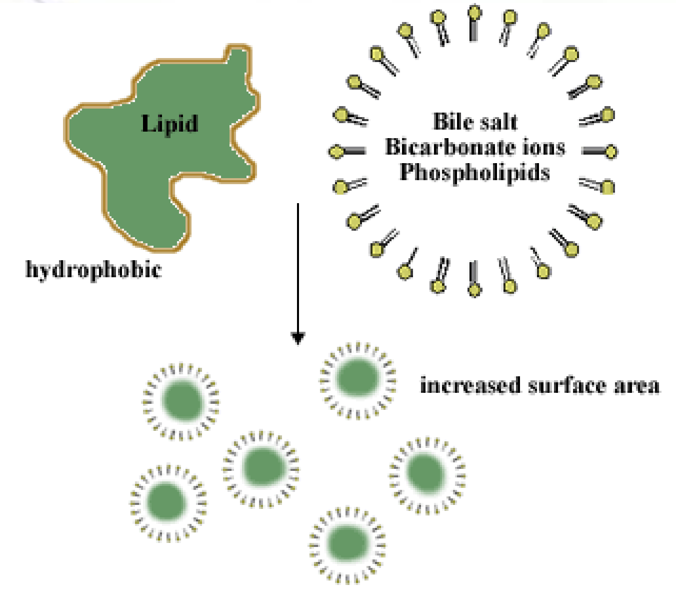
The most common steroid

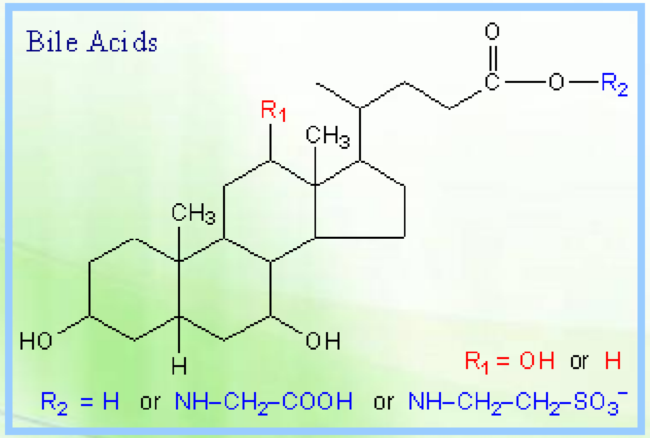


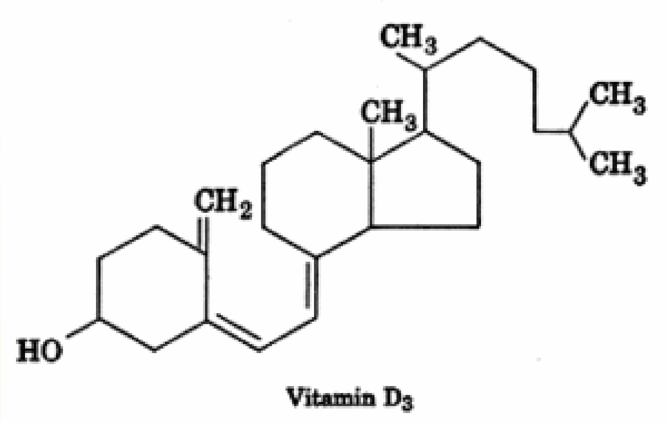
Products of cholesterol

- Hormones
  - Sex hormones (androgens,. estrogens, progestins)
- Vitamin D
- Bile acids (intestinal absorption of fat)



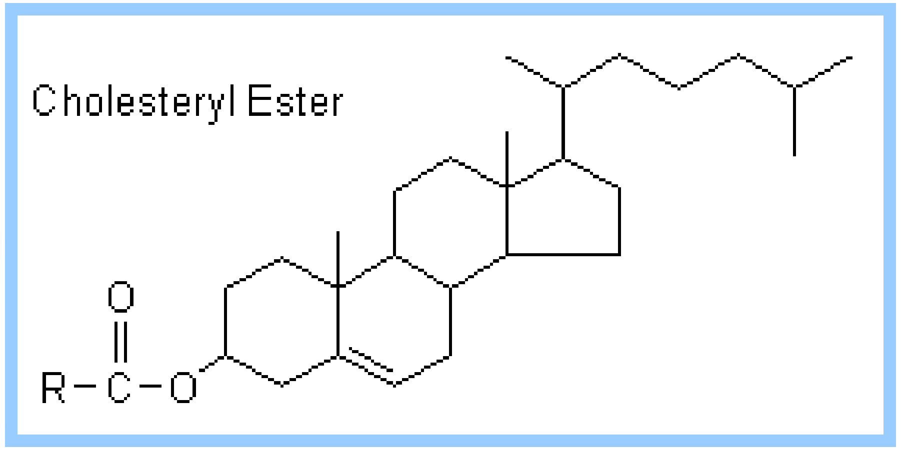


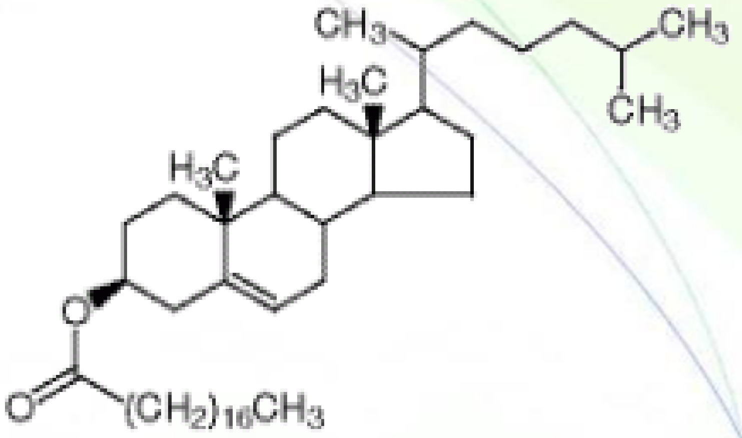




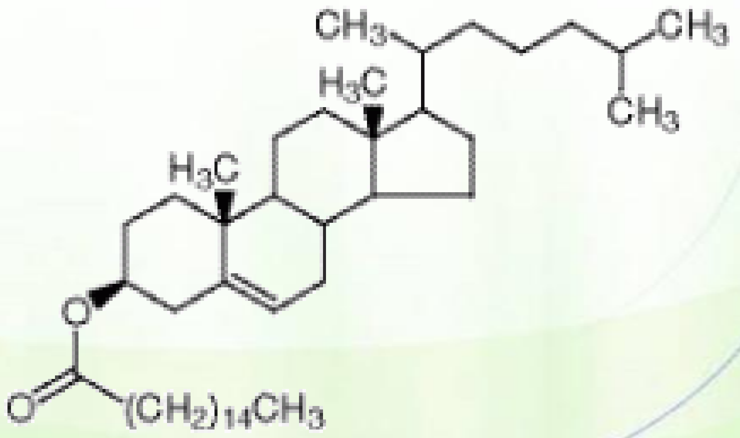
Cholesterol esters

- A cholesterol with a fatty acid attached at (-OH) of C3

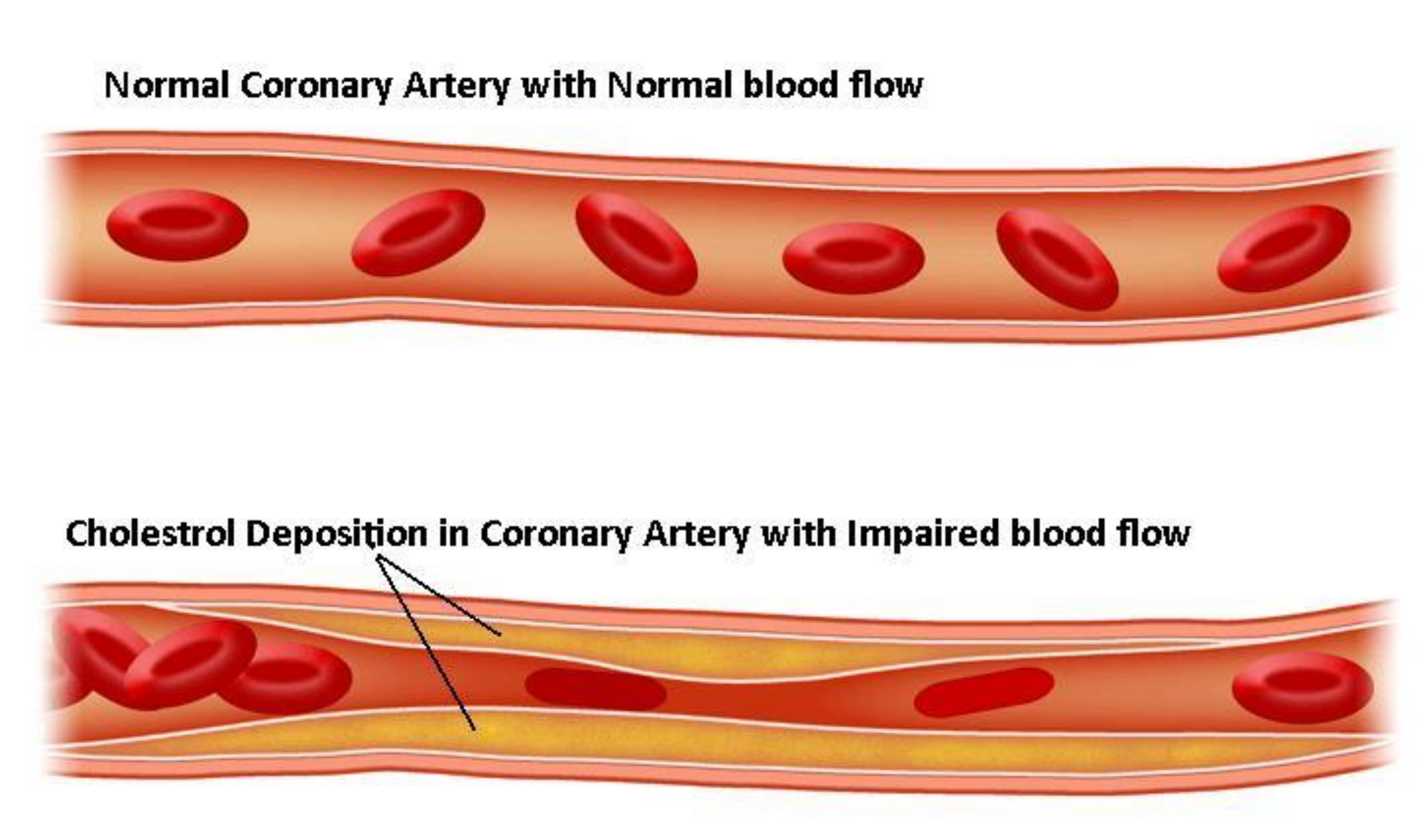




Name the molecules?

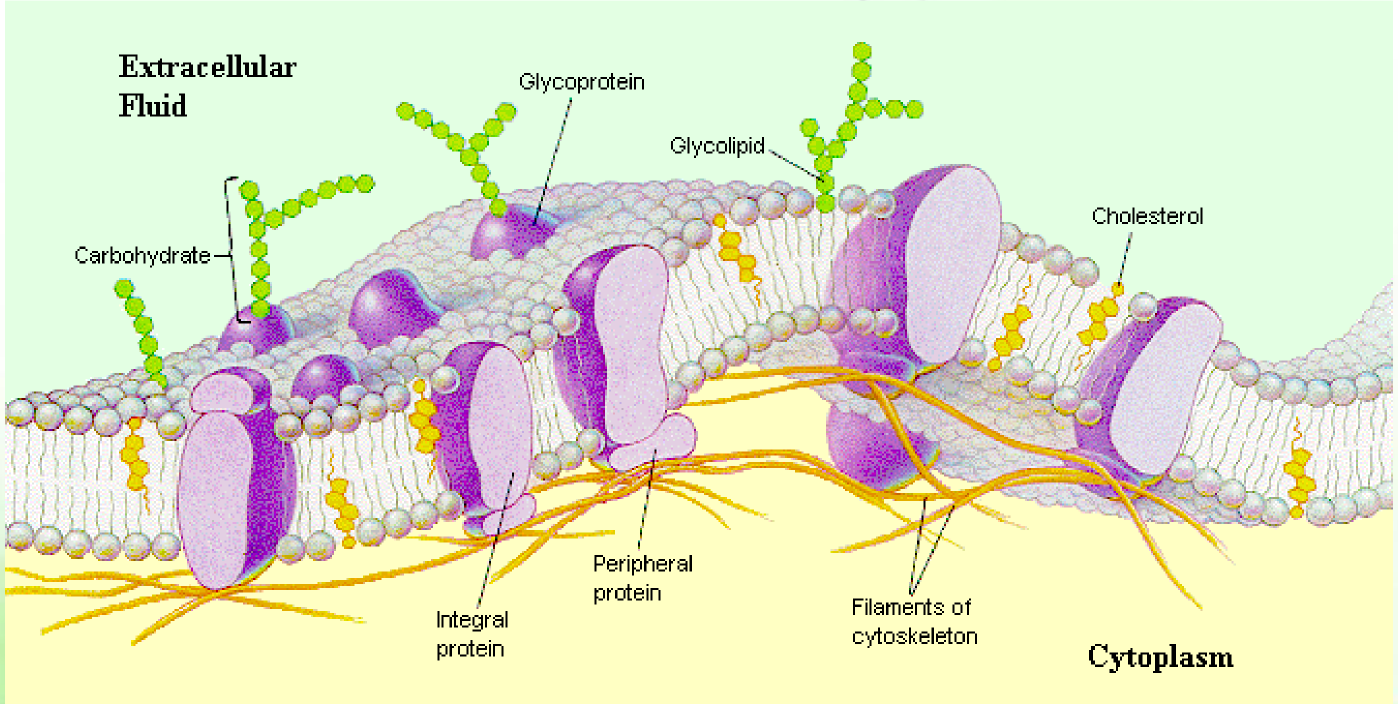


Atherosclerosis



Cell membranes

- The membrane is hypothesized in a model known as the fluid mosaic model.
- Components: 45% lipid, 45% protein and 10% carbohydrate
- They exist side by side without forming some other substance of intermediate nature.

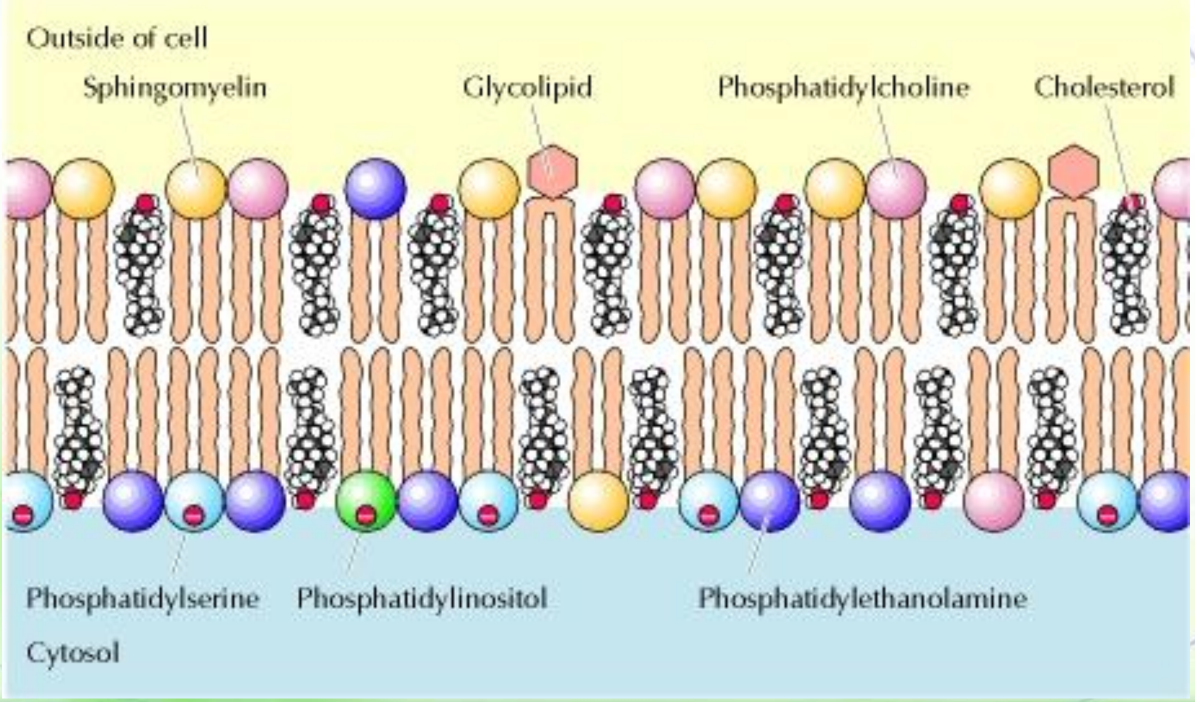


Phospholipids

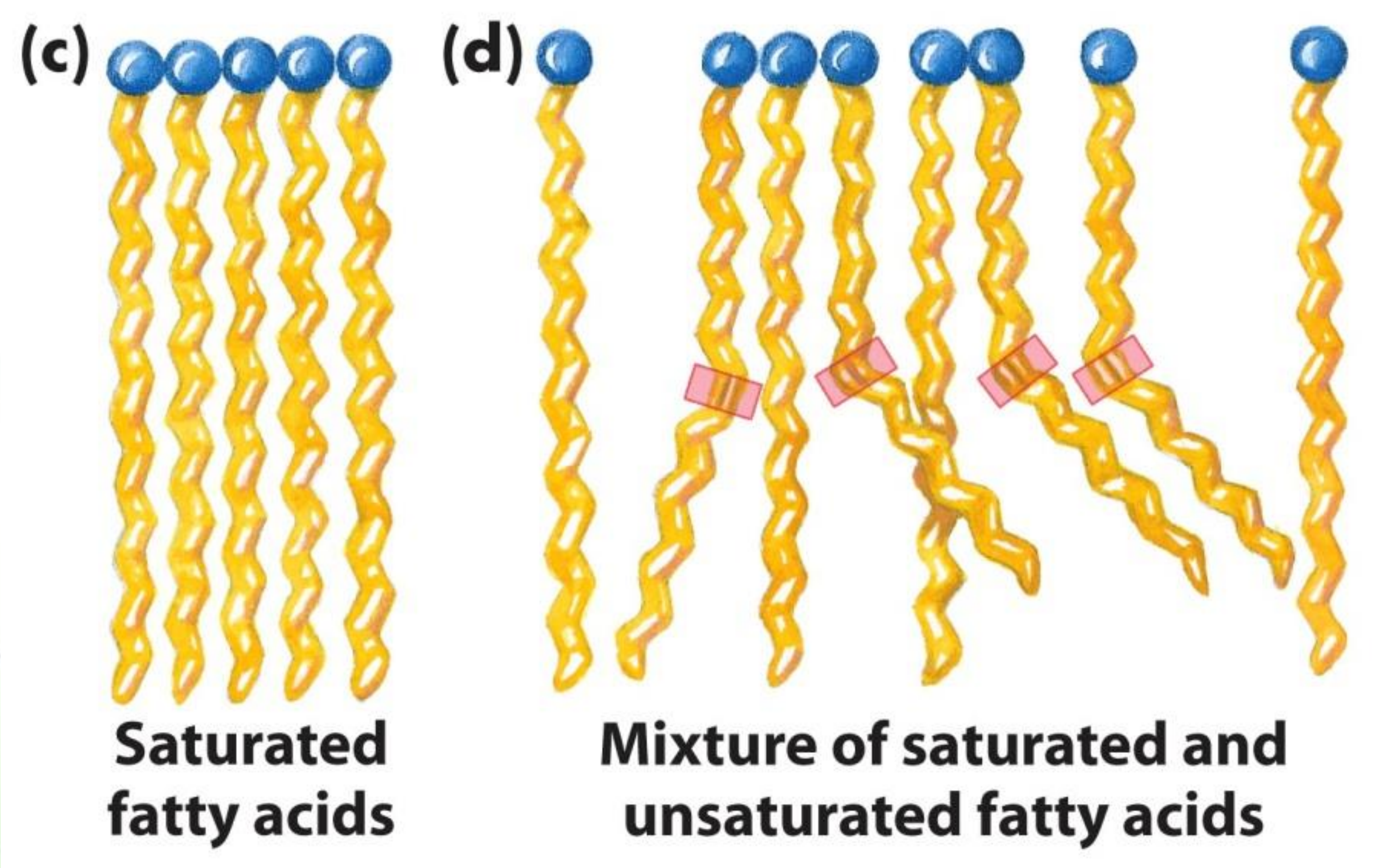
- The outer: phosphatidylcholine, sphingomyelin, and glycolipids(cell recognition)
- The inner: phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol (signaling)

Cholesterol is distributed in both leaflets

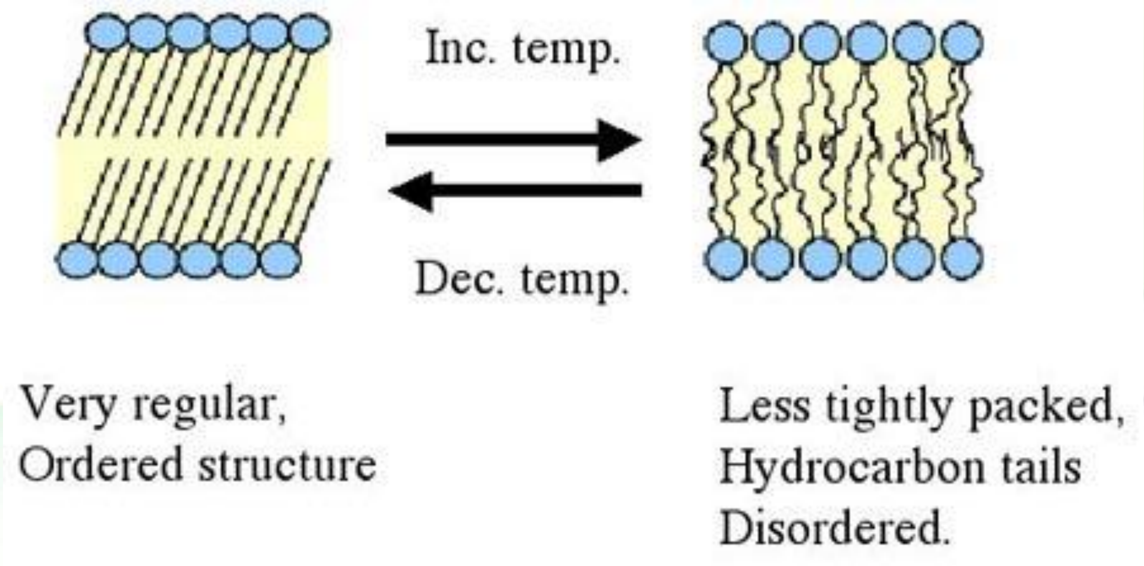
Animal cells vs. plant cells vs. prokaryotic cells

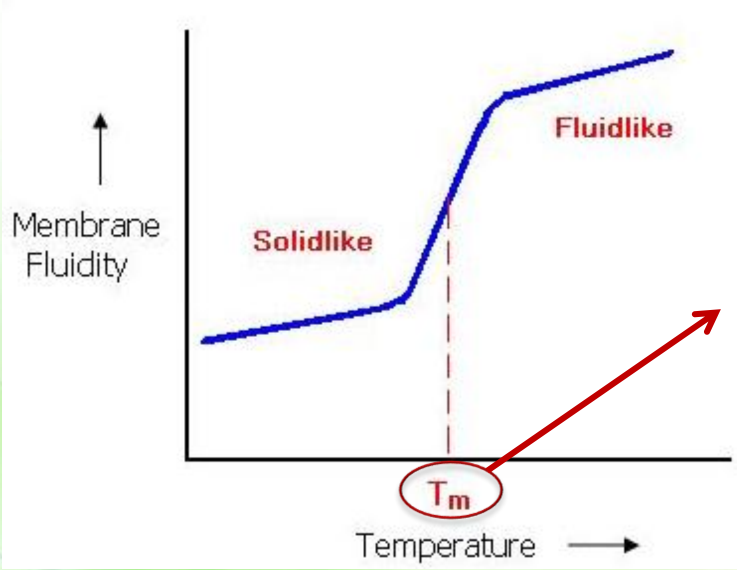


Fatty acids and membrane fluidity



Membrane fluidity and temperature

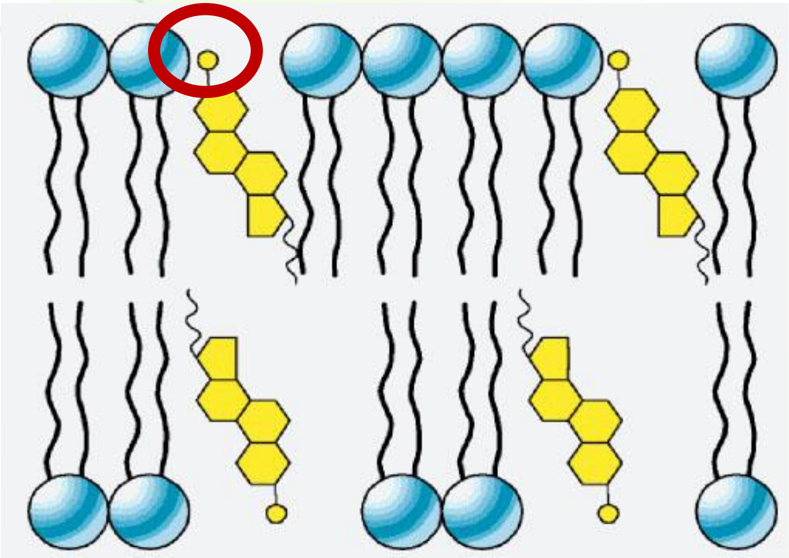




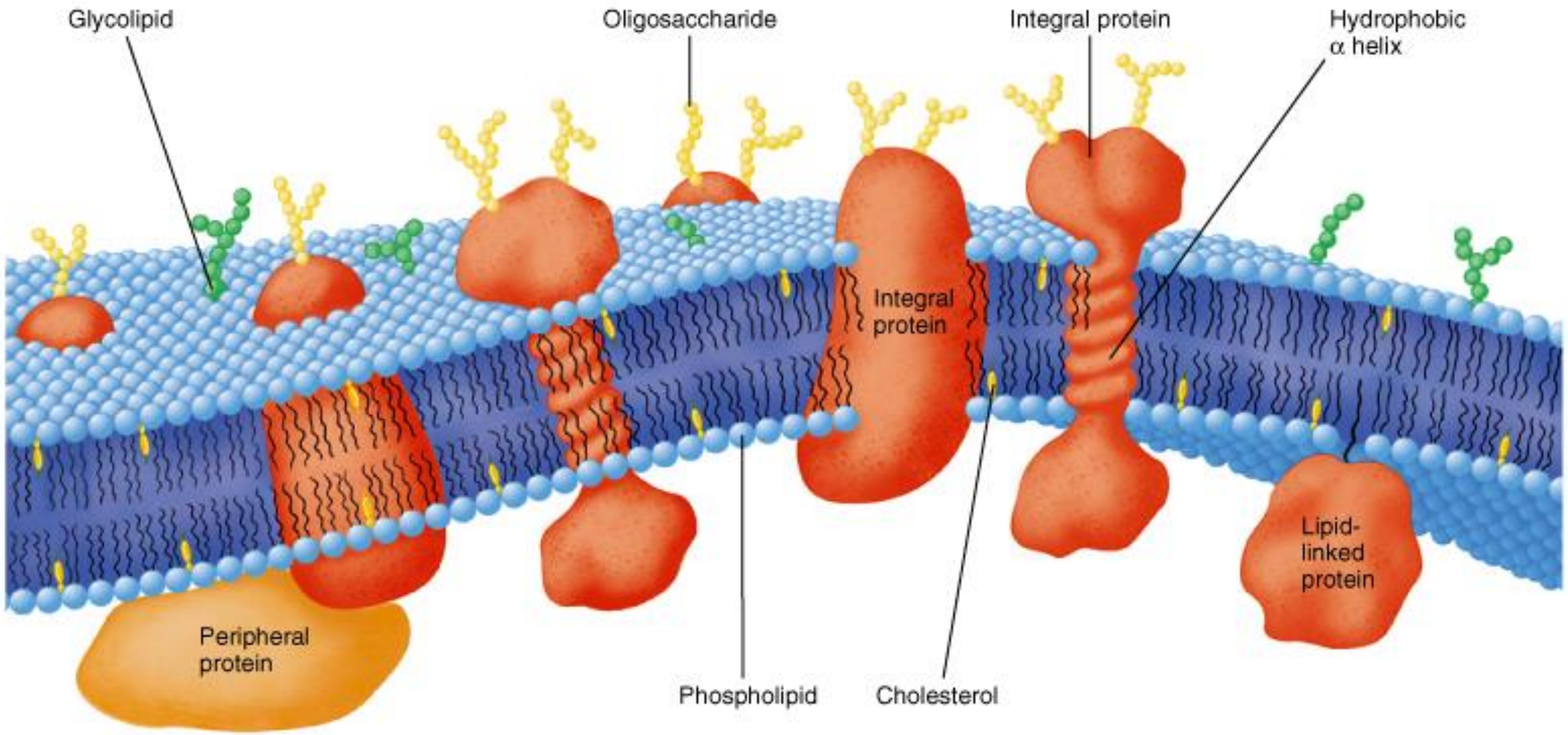
Melting temperature (transition temperature

Cholesterol and membrane fluidity

- The presence of cholesterol and the cis unsaturated fatty acids in the membrane prevent the hydrophobic chains from packing too closely together, allowing free membrane proteins and lipid molecules to move laterally in the plane of the leaflet making the membrane a dynamic environment.
- Cholesterol can also stabilize very fluid membranes by increasing interactions between the fatty acids of phospholipids through hydrophobic interactions with the cholesterol ring structure.



Membrane proteins

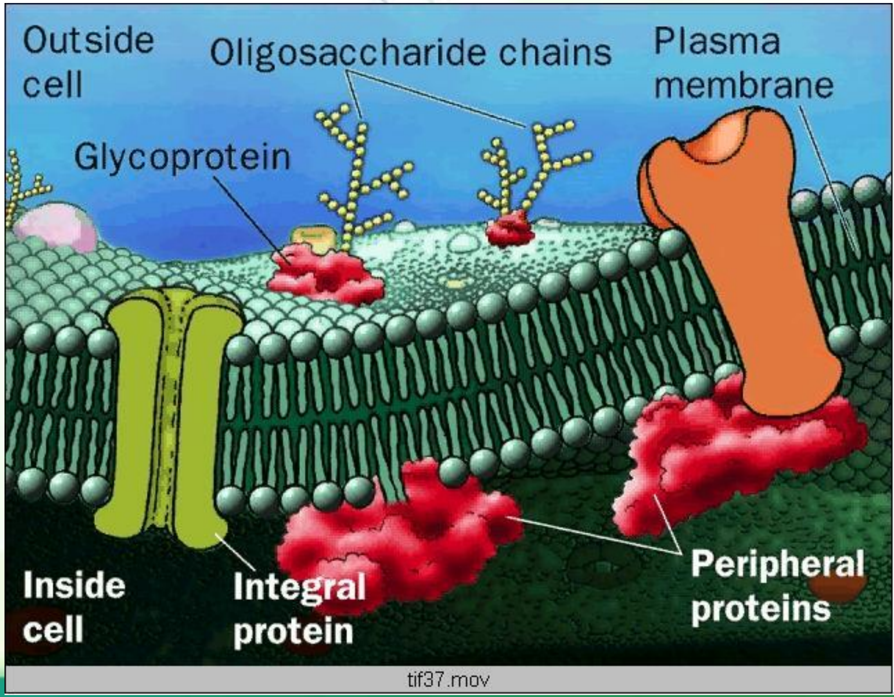


Types of membrane proteins

- Peripheral proteins:
  - are associated with the exterior of membranes via noncovalent interactions
- Integral membrane proteins:
  - anchored into membrane via hydrophobic regions
- Lipid-anchored:
  - associated via a lipid group

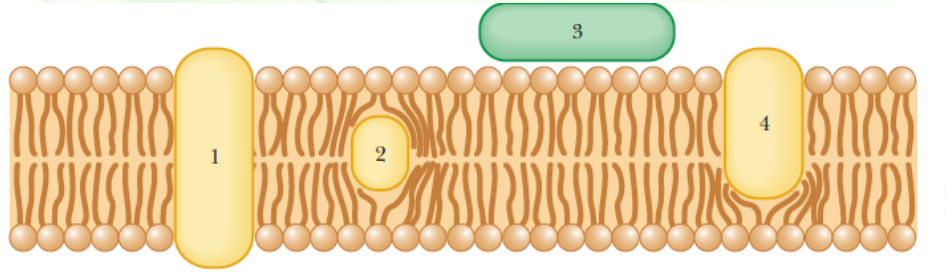
Peripheral membrane proteins

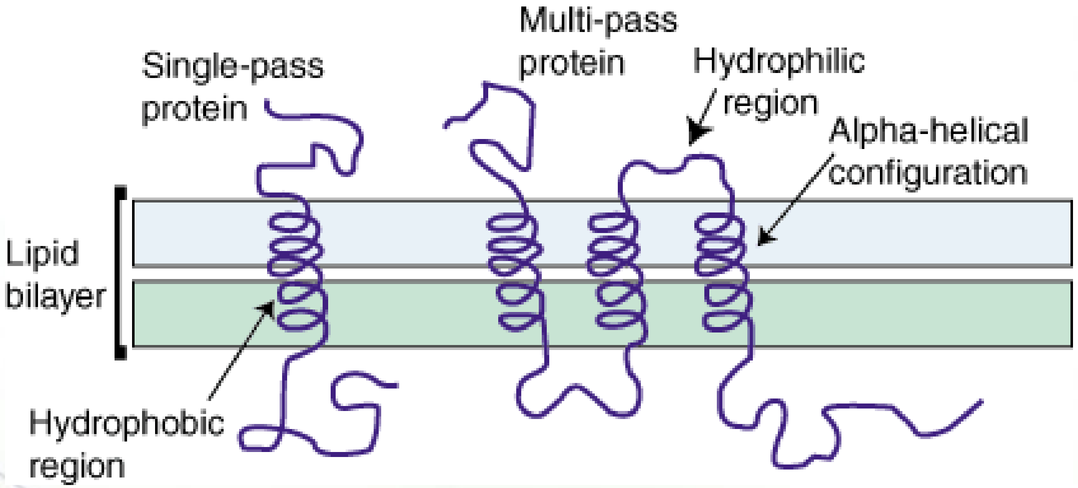
- They are associated with membranes but do not penetrate the hydrophobic core of the membrane.
  - They can be associated with integral membrane proteins.
- They are not strongly bound to the membrane and can be removed without disrupting the membrane structure.
  - Treatment with mild detergent



Integral membrane proteins

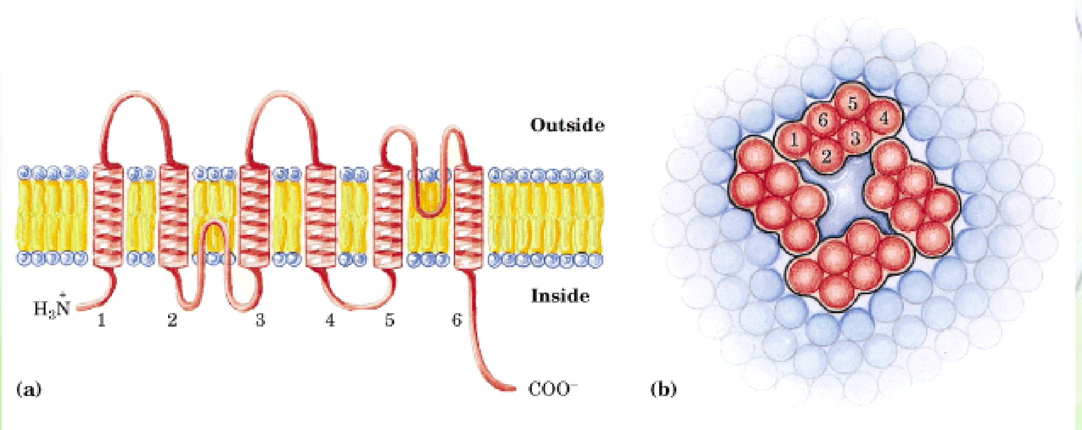
The integral membrane proteins can be associated with the lipid bilayer in several ways.





The membrane integral domains are:
1. Single or multiple
2. α-helix (human) or β-sheet (bacteria)

Some can form channels.



Structure-Function of Membranes

- Transport:
  - Membranes are impermeable barrier
  - Proteins can be carriers or channels
- Signaling
  - Protein receptors and small molecules (some can be lipids themselves)
- Catalysis
  - Enzyme-linked receptors