Lecture 10

Lipids (Pt. 3)

إذا كان يؤذيك حر المصيف و كرب الخريف و برد الشتاء
و يلهيك حسن زمان الربيع فأخذك للعلم قل لي : متى ؟

-أحمد بن فارس الرازي

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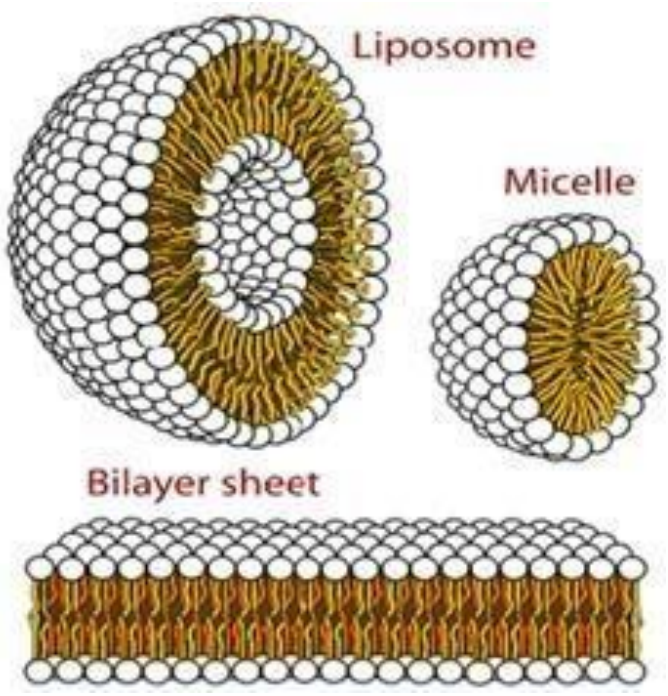
Beginning of the lecture and some notes from previous lectures

- The Doctor clarifies this statement : (protein-linked sugar) means sugar linked to protein regardless of linguistic details ,so it can represent either glycoprotein or proteoglycan.

The different structures of phospholipids



Covalent bonds are very important in biochemistry,but in term of functional biological molecules ,which we study, non-covalent interactions are more important for structure and function(driver of function in the cell).

Phospholipids can form different structures, such as :

- Micelle : phosphate group to the outside, and exposed to the hydrophilic environment .while the hydrophobic tail embedded , buried inside.
- Liposome: we have two layers ,external and internal flipped layer.
- Bilayer sheet : it is actually a liposome but it contains cellular components and organelles .

What is the importance of liposome in medicine and biology ?

Uses of liposomes: delivery

Especially for hydrophilic molecules, like: RNA, DNA.

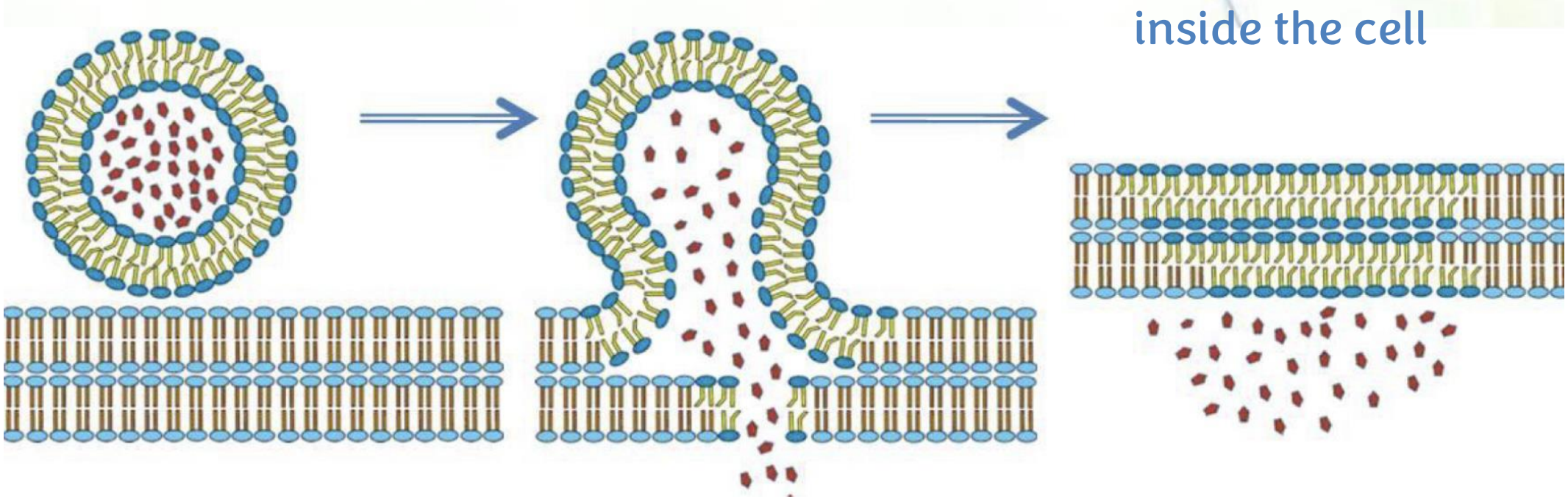
"Some" means object, sac, bag , structure . Chromosome = colored object.

Generally , a hydrophilic molecule interact with the phosphate group of the membrane (which is hydrophilic too), but the obstacle is that the hydrophobic barrier repels that molecule.

Liposome interacts with the membrane

Fuses with the membrane

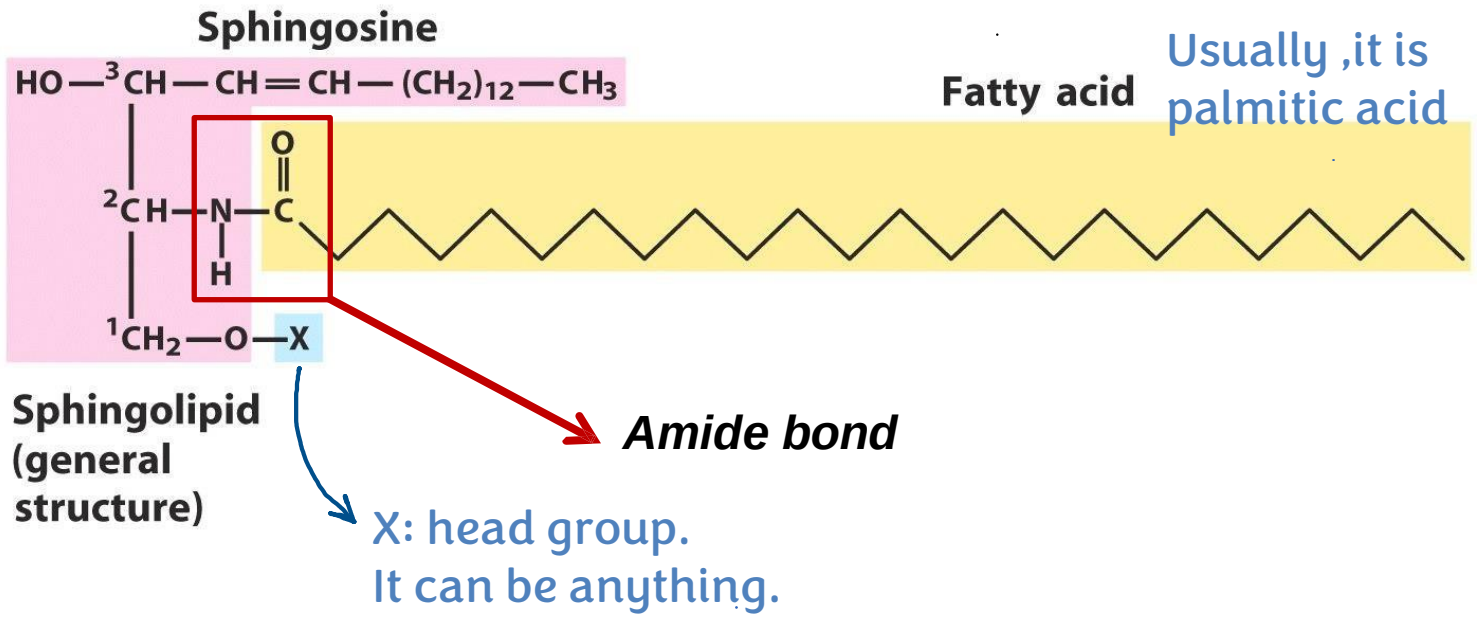
Delivery of the molecule towards inside the cell



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

The backbone of sphingolipids is : sphingosine .
The backbone of glycerophospholipids is glycerol.



How to distinguish sphingolipids?

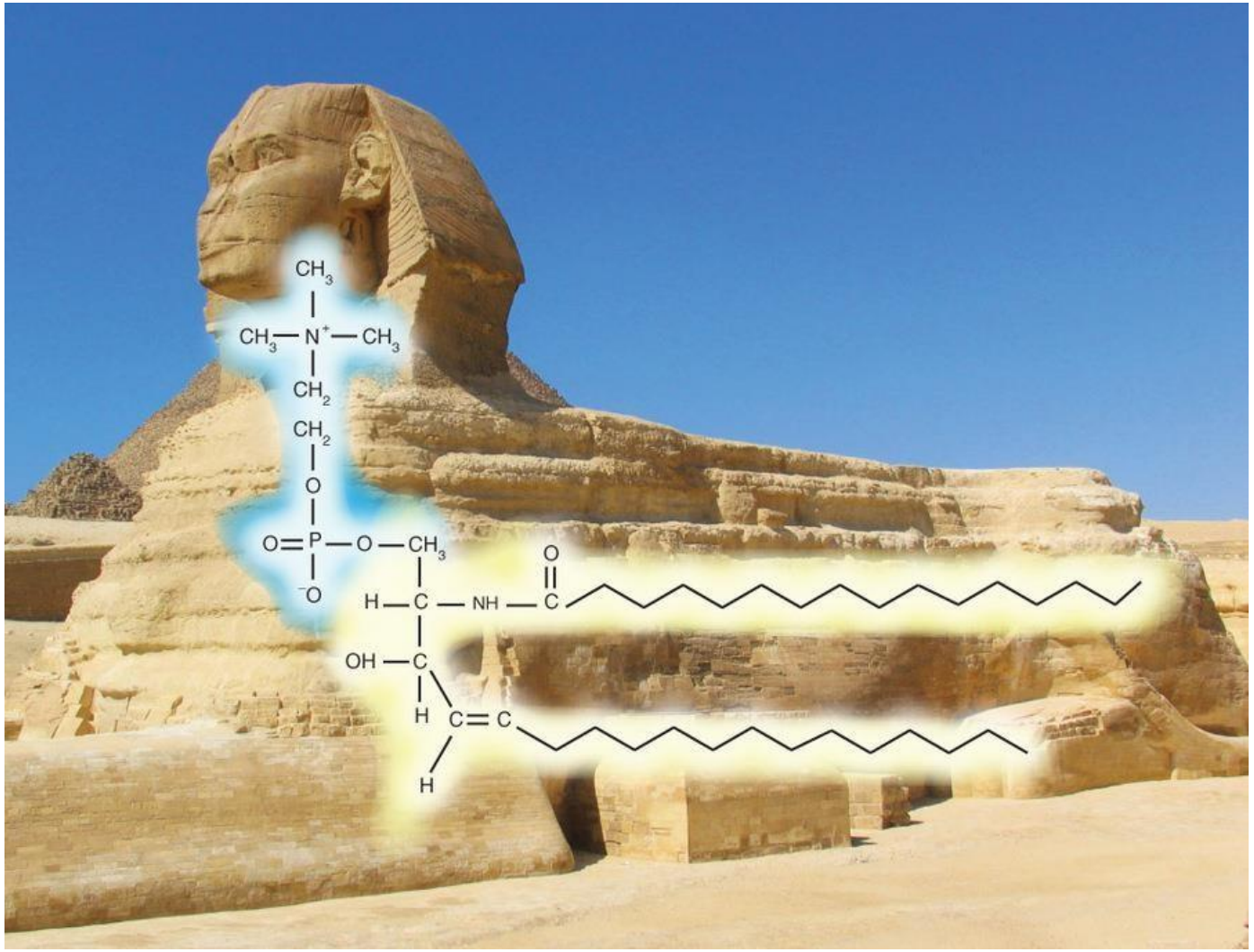
- presence of Alkene group.
- Absences of ester linkage.
- Presence of " Amide bond" comes from an amino acid.

Mysterious lipids

Trivia

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

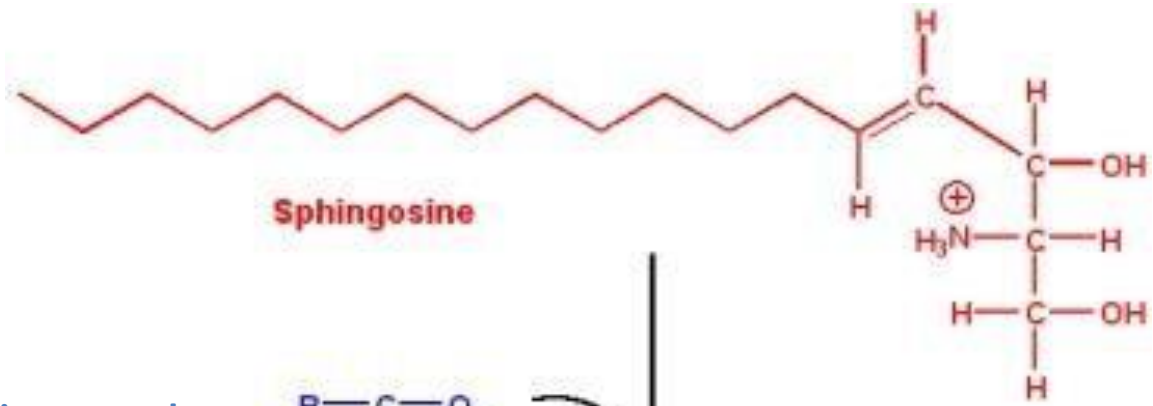
***Sph*ynx → *sph*ingolipids**



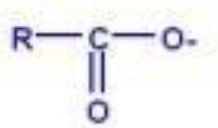
Ceramide

The simplest sphingolipid .

Remember:
The simplest glycerophospholipid is phosphatidic acid.

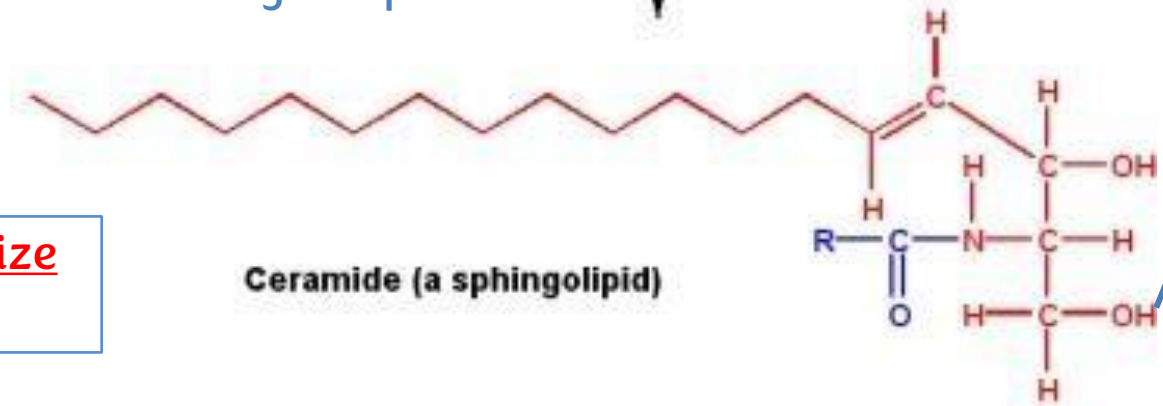


Add it to carbon number 2



Usually it is palmitate

H_2O



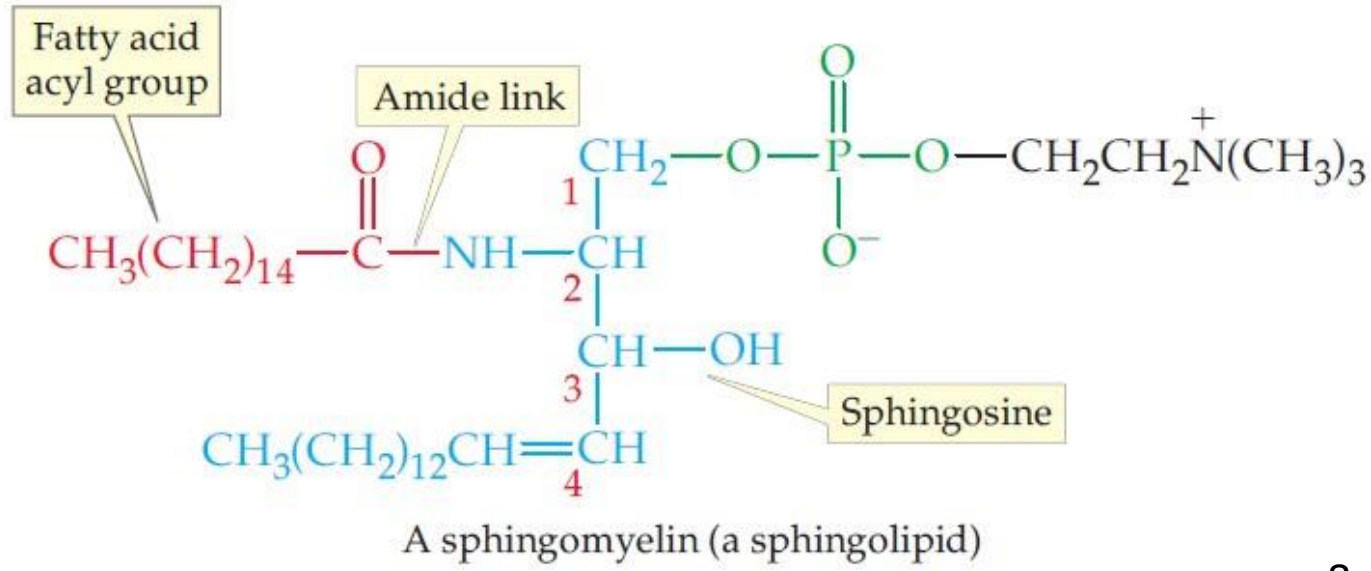
Ceramide does not have a head group; instead, it has a hydroxyl group, which is usually unprotonated (ionized) at physiological PH.

You need to recognize the structure .

Types of sphingolipids : Subclassification of sphingolipids " depending on the X group ".

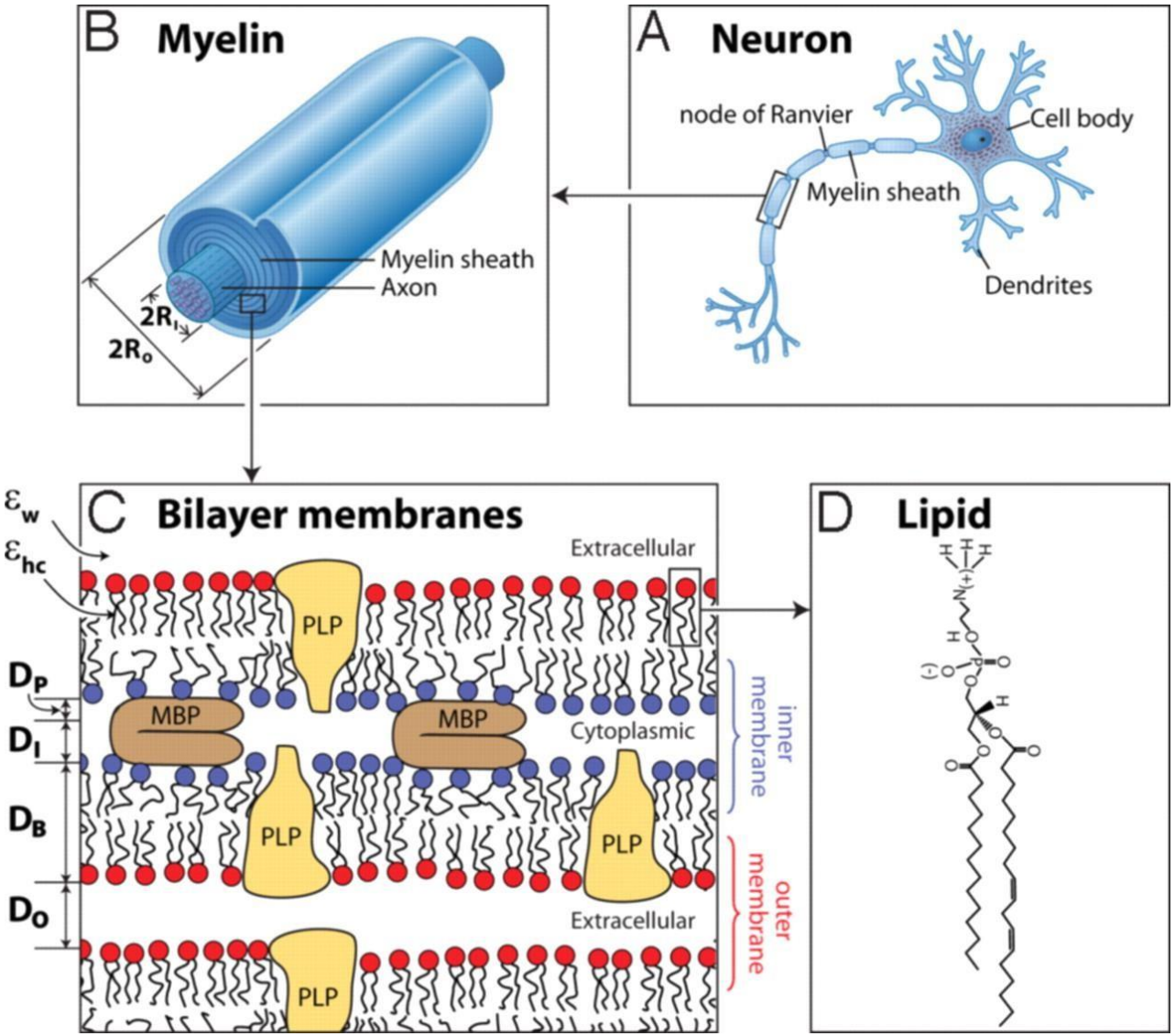
- The sphingolipids are divided into two subcategories:
  - Sphingomyelin It is the only phosphosphingolipid
    - It is a sphingolipid that is a major component of the coating around nerve fibers.
    - The group attached to C1 is a phosphocholine X group = phosphocholine .
  - Glycosphingolipid (or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

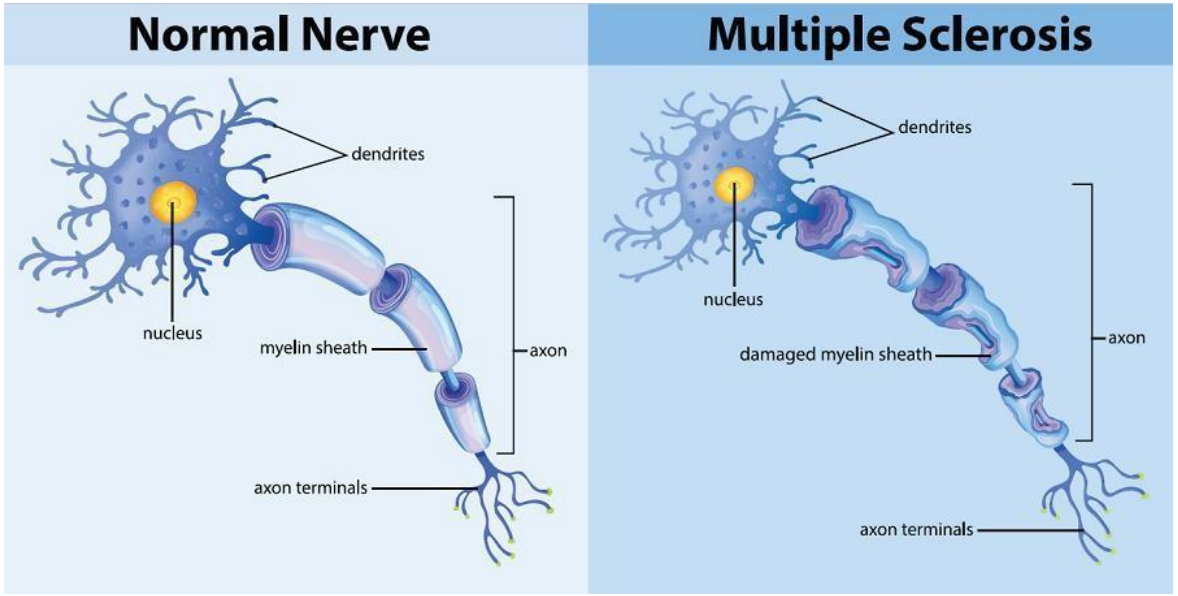
- Sphingomyelin is present in the myelin sheath.
- The myelin sheath resembles the insulating layer (plastic coating)of an electrical wire.
- The myelin sheath must be hydrophobic to isolate the axon and prevent charges from leaking, which helps in the rapid transmission of action potentials.



A sphingomyelin (a sphingolipid)

Zooming into the myelin





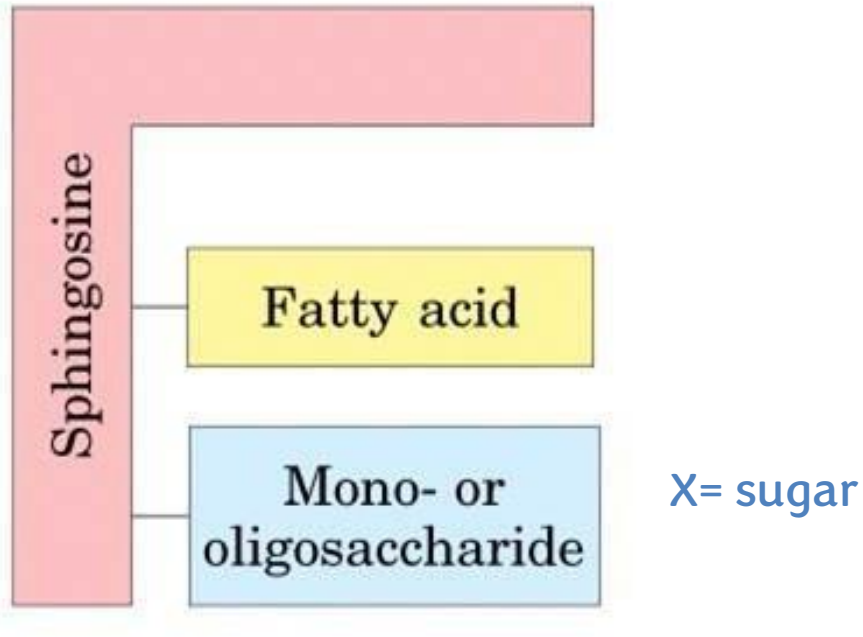
- Multiple Sclerosis (MS) : التصلب اللويحي المتعدد is a disease that occurs when the myelin sheath is destroyed due to the attack by immune cells, leading to gaps in the sheath. This disrupts the transmission of action potentials.
- The axon becomes naked.
- Common among people in their twenties and thirties.

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

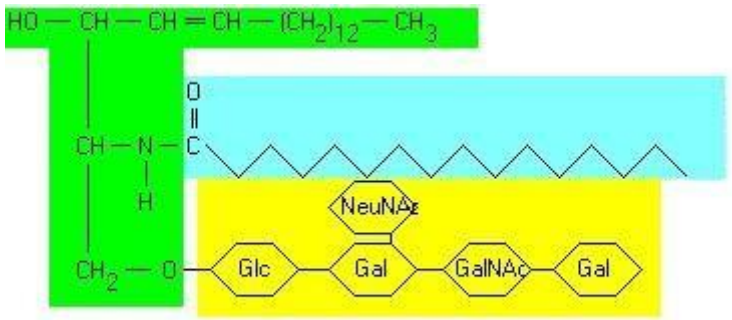
Abundant in CNS .

But they can also be found in other tissues.



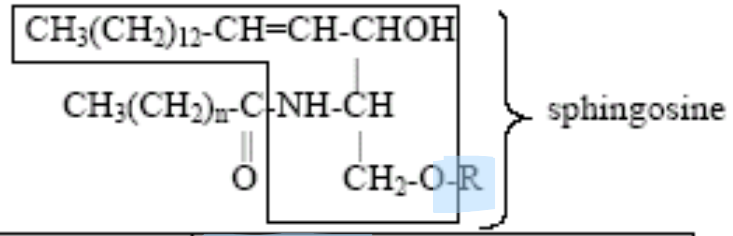
Glycolipids

- **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.**



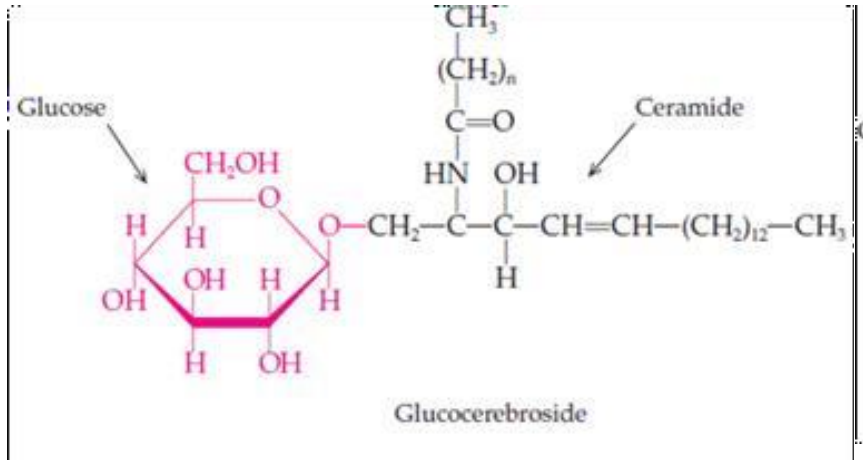
Gangliosides are bound by cholera toxin in the human intestine facilitating its endocytosis into the cells.

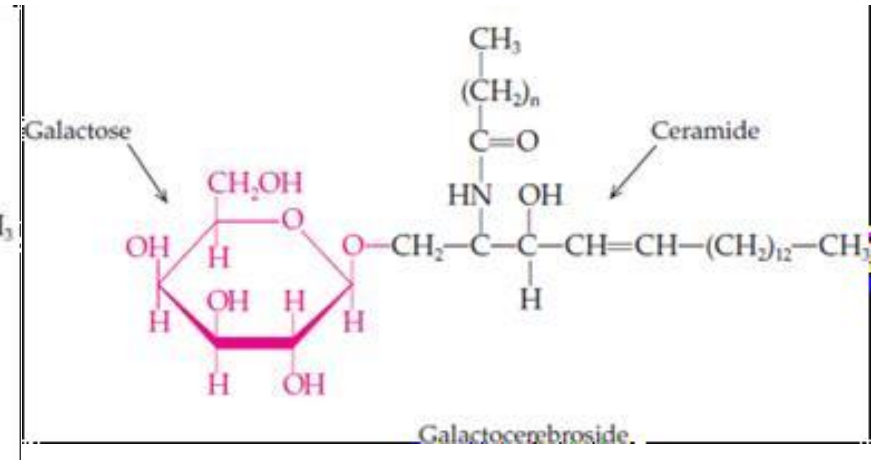
Causes cholera infection



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

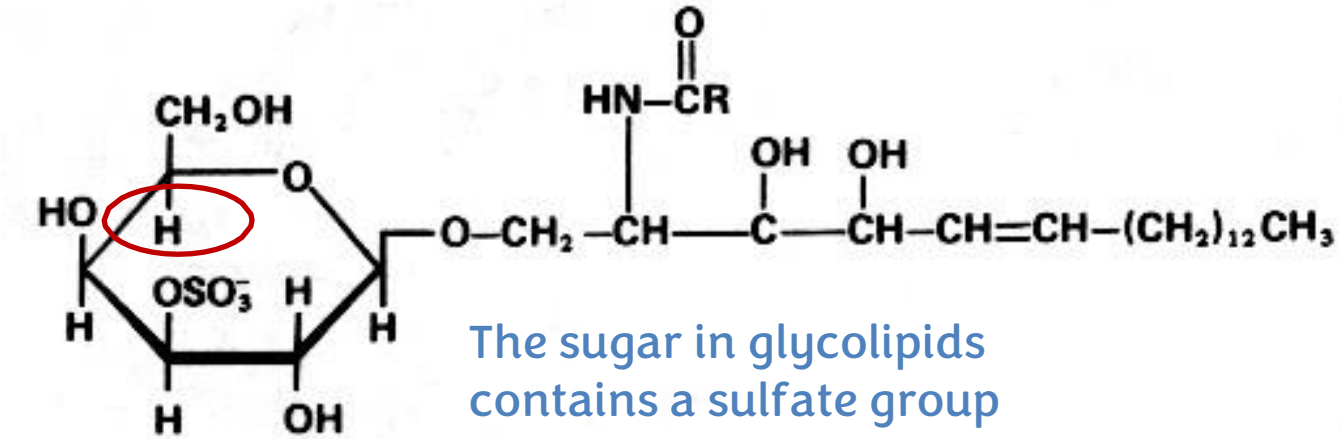
glycolipids



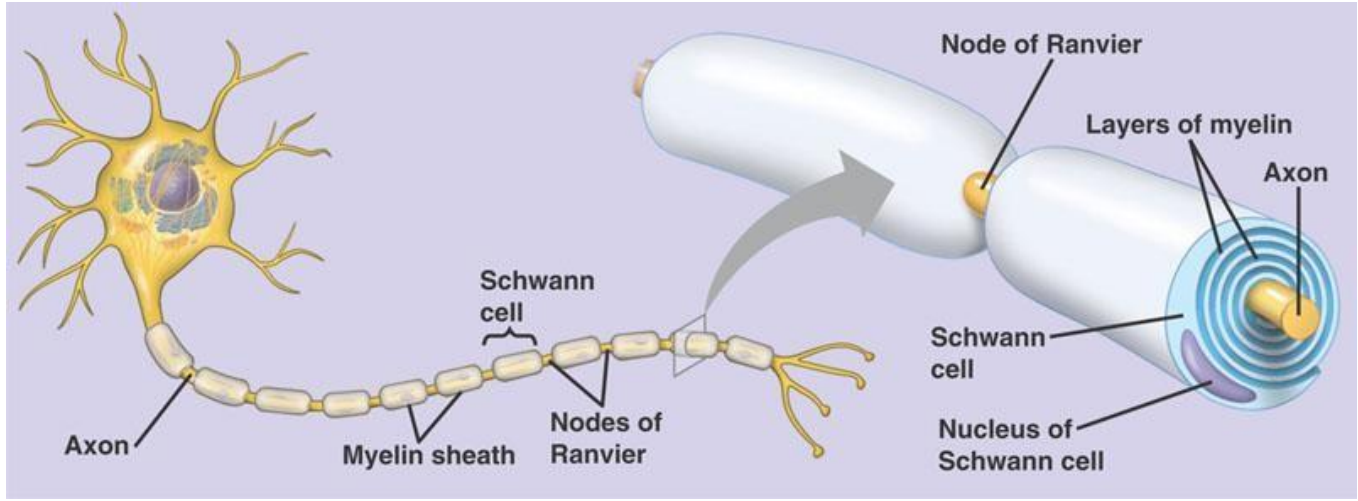


Sulfatides A type of glycolipids

- Synthesized from galactocerebroside
- Abundant in brain myelin

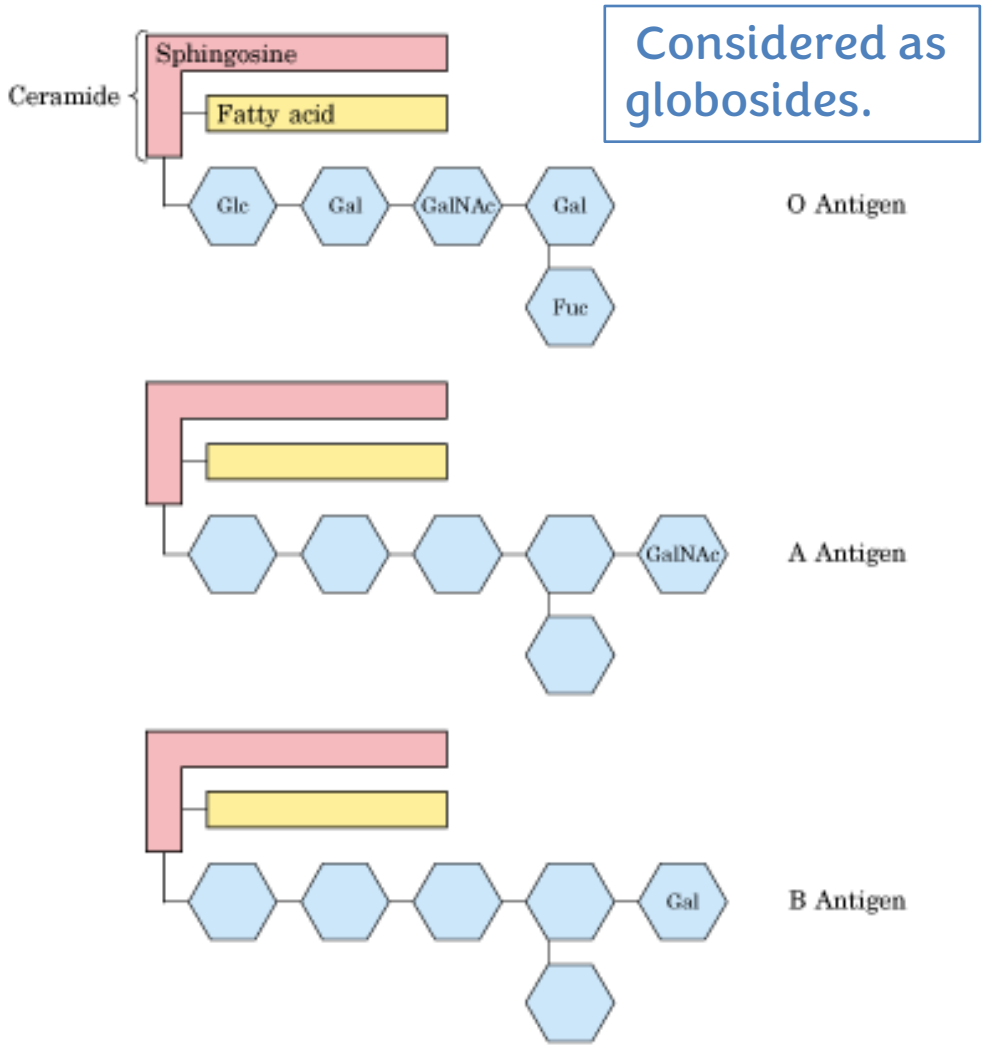


The sugar in glycolipids contains a sulfate group



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

(Transport system of lipid molecule)
A class of molecules responsible for transporting lipids in the blood.

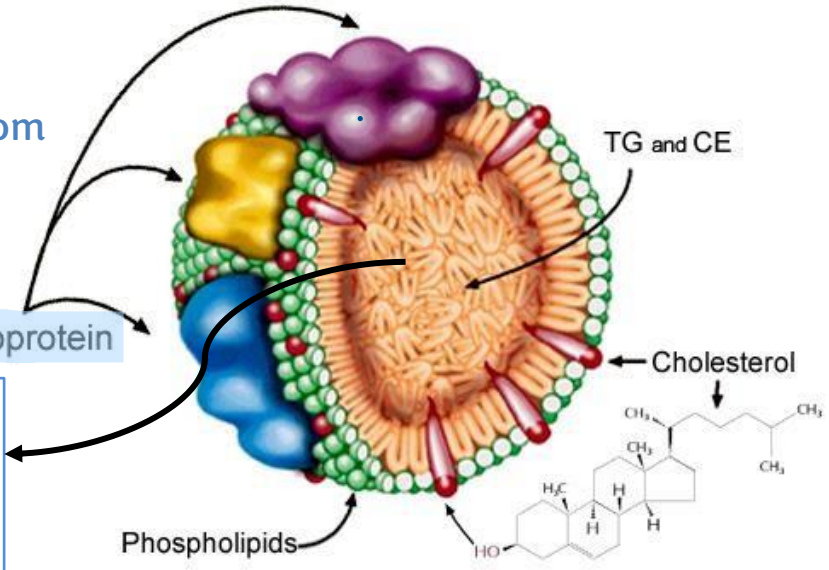
Lipids can be absorbed, but they cannot move in the blood alone (because they're hydrophobic)
They will cluster together.
So there must be a transport system for lipid molecules. It is lipoproteins!

Lipoproteins are a combination of proteins and lipid molecules, such as phospholipids.

They look like **Micelle** :
Outside: phospholipids and proteins are exposed to the blood.
Inside: fatty acids and transported lipids are present .

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

These proteins distinguish lipoproteins from each other and give them their functions.



Inside, there are different types of lipids that can be transported.

Types of lipoproteins

1. Chylomicrons .
2. VLDL (Very low density lipoproteins) .
3. IDL (Intermediate density lipoproteins) .
4. LDL (Low density lipoproteins) .
5. HDL (High density lipoproteins) .

Lipoproteins differ in:

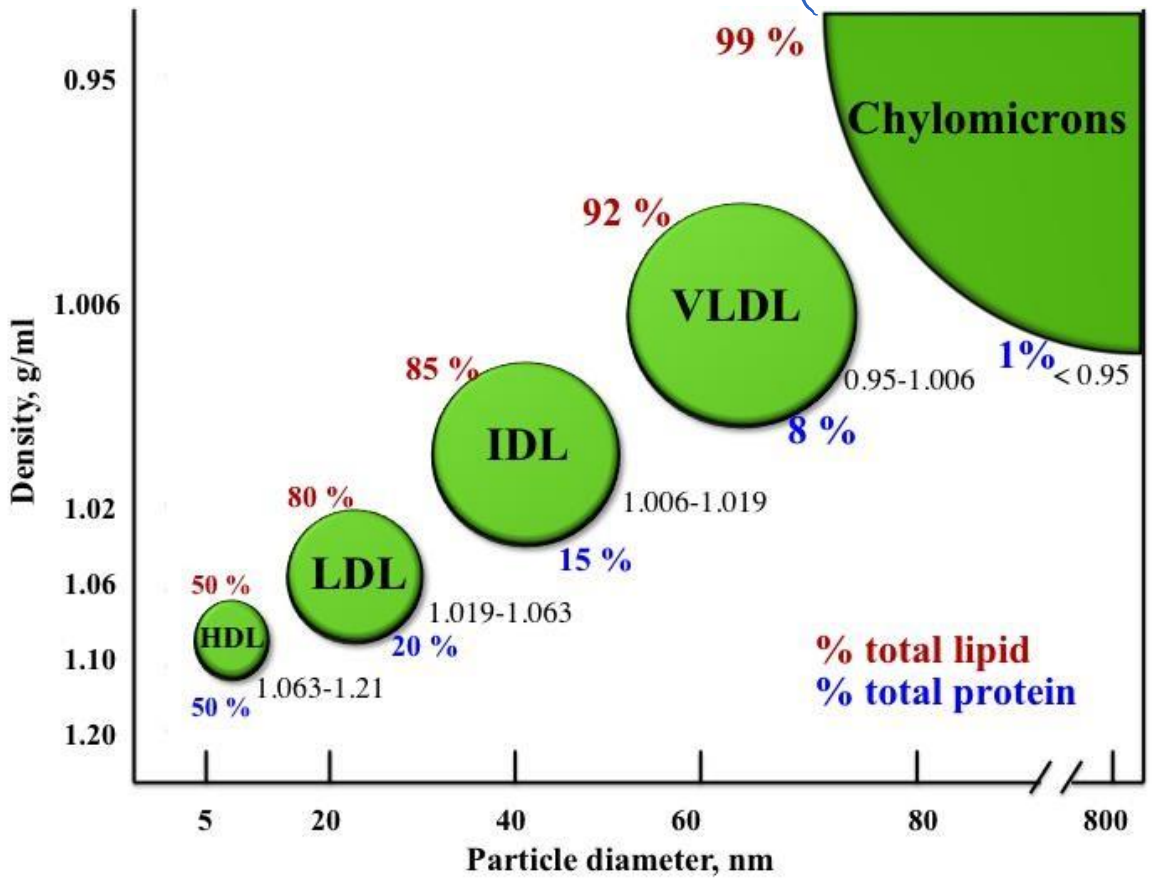
- Apoproteins .
- The size .
- Density (determined by the ratio between protein to lipid content).

If the ratio increases, the density increases

If the density increases, the size decreases

HDL has the highest protein to lipid ratio , and the chylomicrons have the lowest one.

The lowest density.
The largest size.

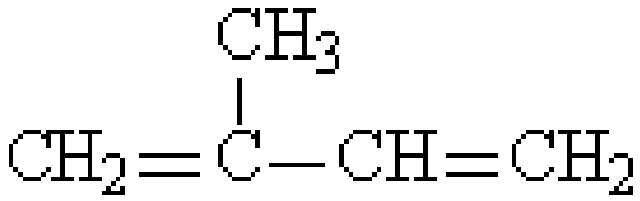


As lipid content increases, the density decreases

Steroids

Steroids are either derived from the steroid nucleus or from another modification of steroids.

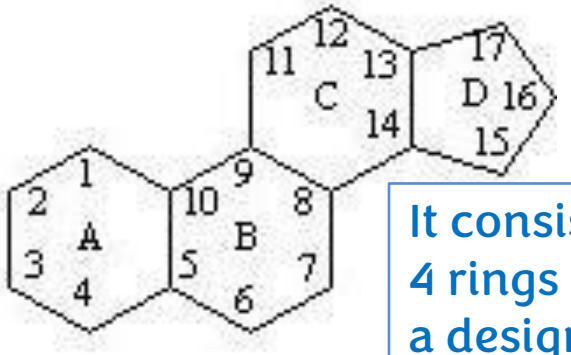
The precursor



Isoprene

5 carbon molecule~> forms the steroid molecules.

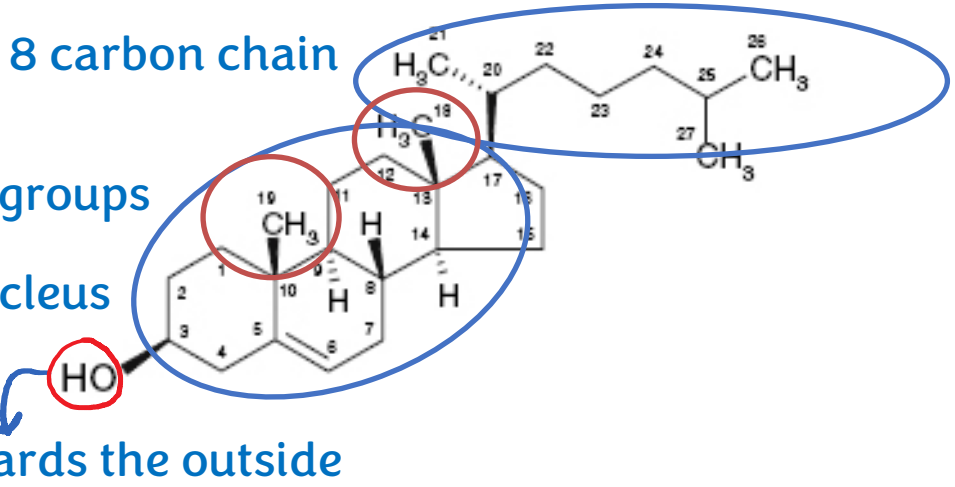
The nucleus



Steroid nucleus

It consists of 17 carbons and 4 rings and each one has a designated letter: ring A, B, C & D

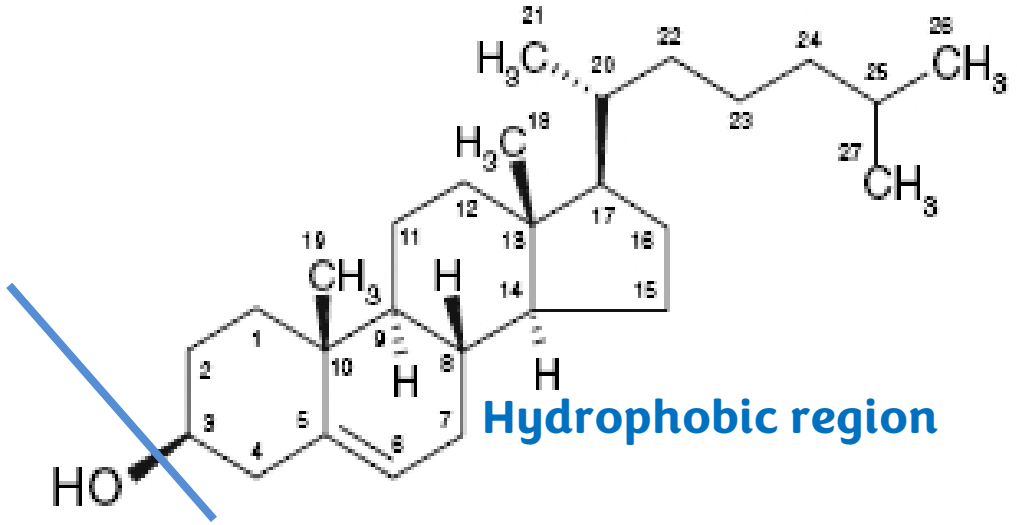
The most common steroid



This is cholesterol, 27 carbons it's the parent steroid; a lot of molecules are synthesized from it, the following structure is a mature steroid.

Steroids

Amphipathic molecule:
If a molecule can be divided into hydrophilic and hydrophobic regions then it's amphipathic.
It has to have both , not just the hydrophilic group.

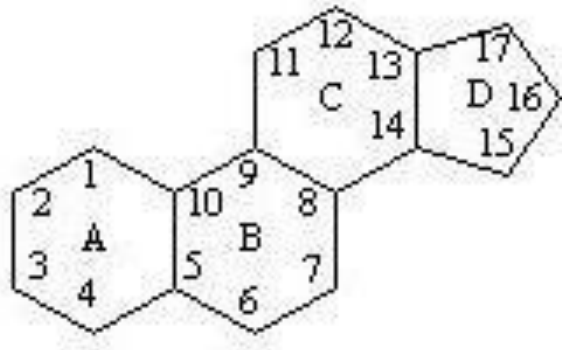


Hydrophobic region

Hydrophilic region

Cholesterol is an amphipathic molecule

Any reaction of the cholesterol molecule would happen at this end because this is the reactive group(OH)



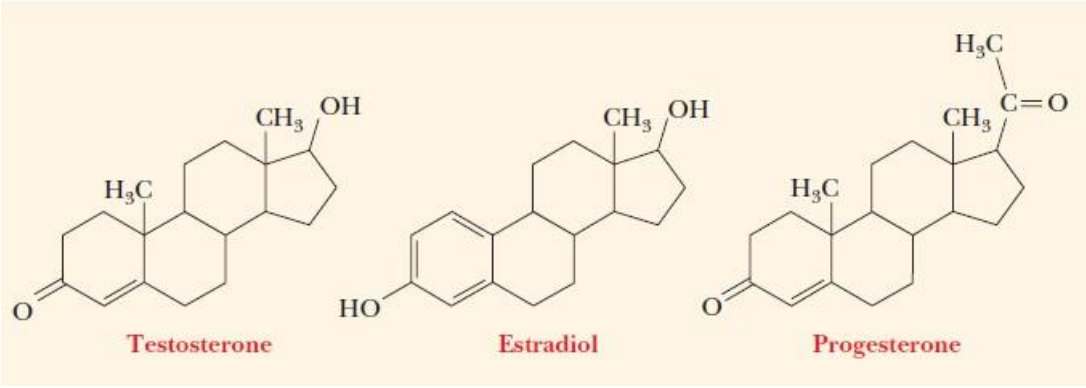
Steroid nucleus

*not all steroid molecules have the nucleus in this structure it can be a derivative of it.

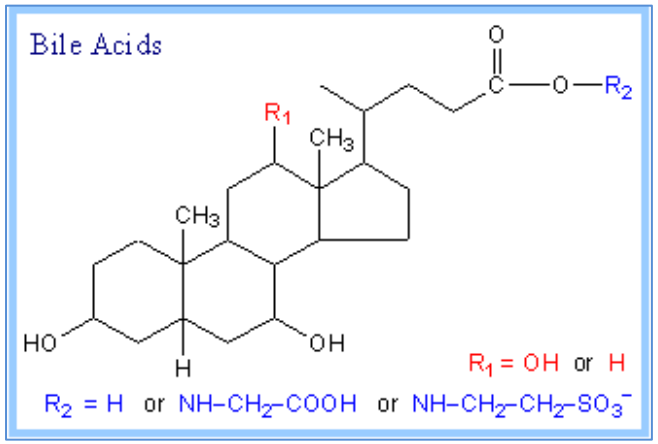
Products of cholesterol

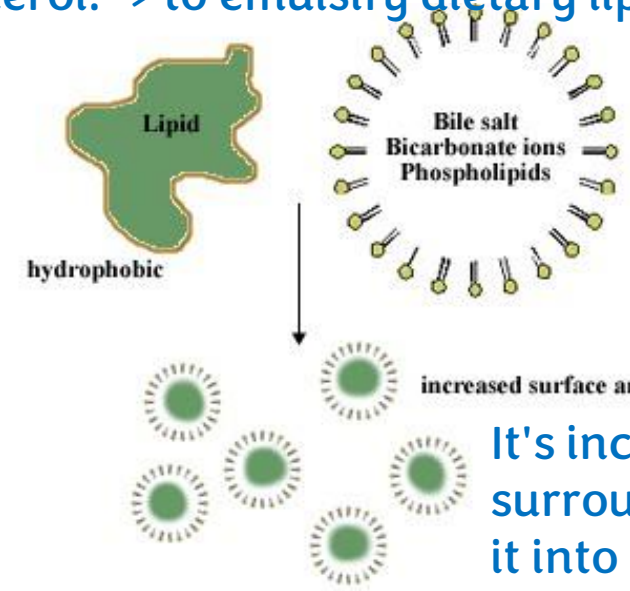
- Hormones
  - Sex hormones (androgens,. estrogens, progestins)
- Vitamin D
- Bile acids (intestinal absorption of fat)

Do not memorize the structures make sure you know what type of molecules they belong to.



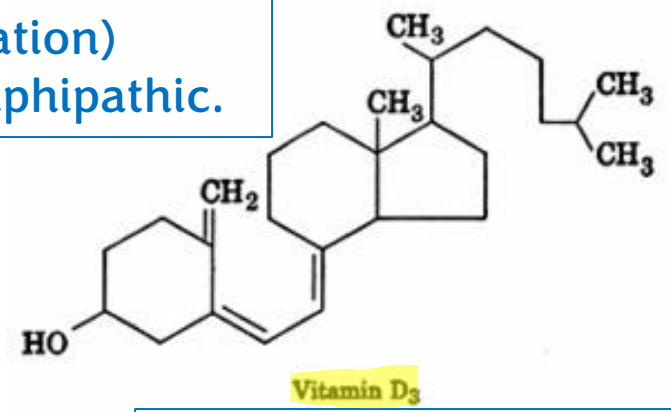
It is produced by the gallbladder from cholesterol!~> to emulsify dietary lipids.





It's increased because the bile surrounds the lipid and breaks it into smaller pieces

It's able to do that (emulsification) because it's amphipathic.



Note :
The intestinal environment is hydrophilic.

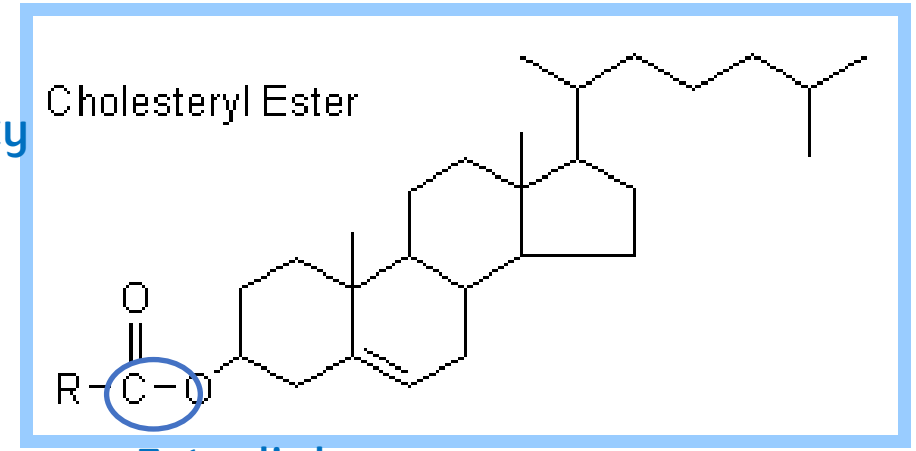
Cholesterol esters

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

- No longer amphipathic.
- It's more hydrophobic.

One more way of storing fatty acids in the cell:
1- glycerol & fatty acid-> stored in adipose tissue.
2- cholesterol & fatty acid.
3- fatty acids in plasma membrane

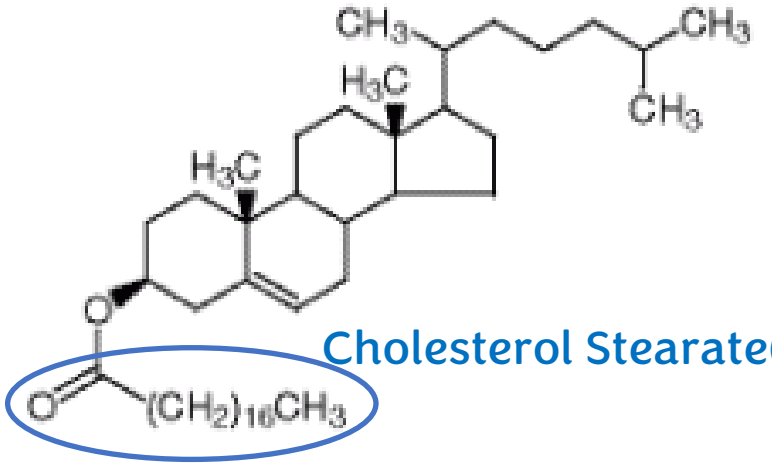
-> whenever the cell needs a certain fatty acid it can take it from the membrane (in certain cases)



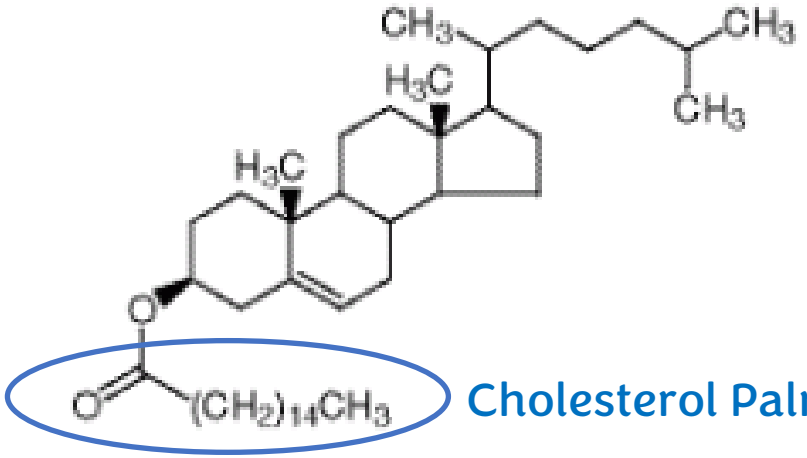
Ester linkage
It's attached to the OH group because it's the reactive group.

Name the molecules?
Cholesterol + fatty acid name.

If you haven't memorized the fatty acids names go study them now >:(



Cholesterol Stearate(18 C)



Cholesterol Palmitate(16 C)

Atherosclerosis

Caused by a build-up of cholesterol and lipoproteins(mainly, especially LDL) in arteries ~> causing blockage~> heart attacks.

↑ Saturation of the BV with cholesterol

↑ Precipitation

↑ Thickness

↓ Diameter

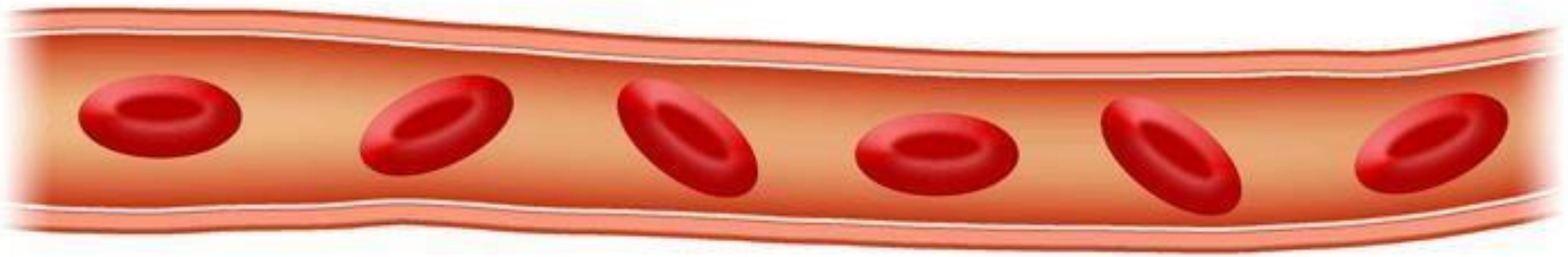
↓ Flexibility

↓ RBCs

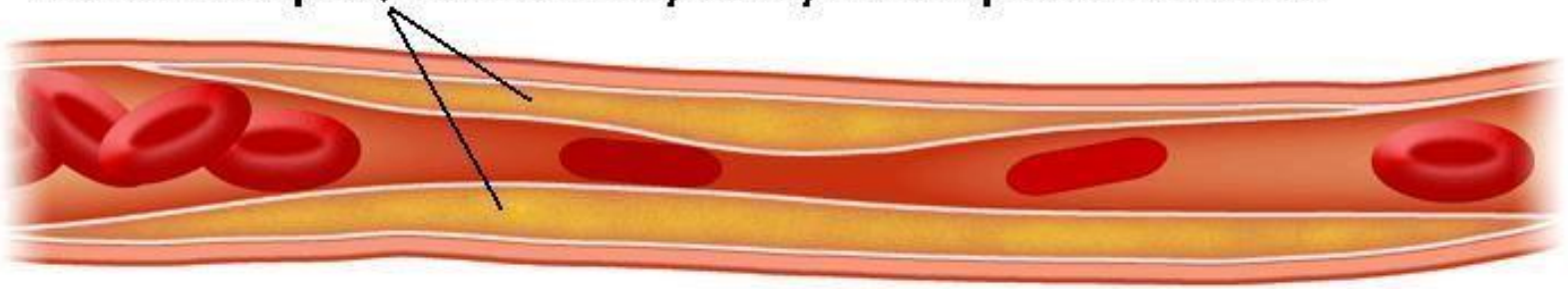
↓ O2 & nutrients

Ischemia

Normal Coronary Artery with Normal blood flow



Cholestrol Deposition in Coronary Artery with Impaired blood flow



Cell membranes

*molecules aren't static, they're dynamic (flexible) & heterogeneous

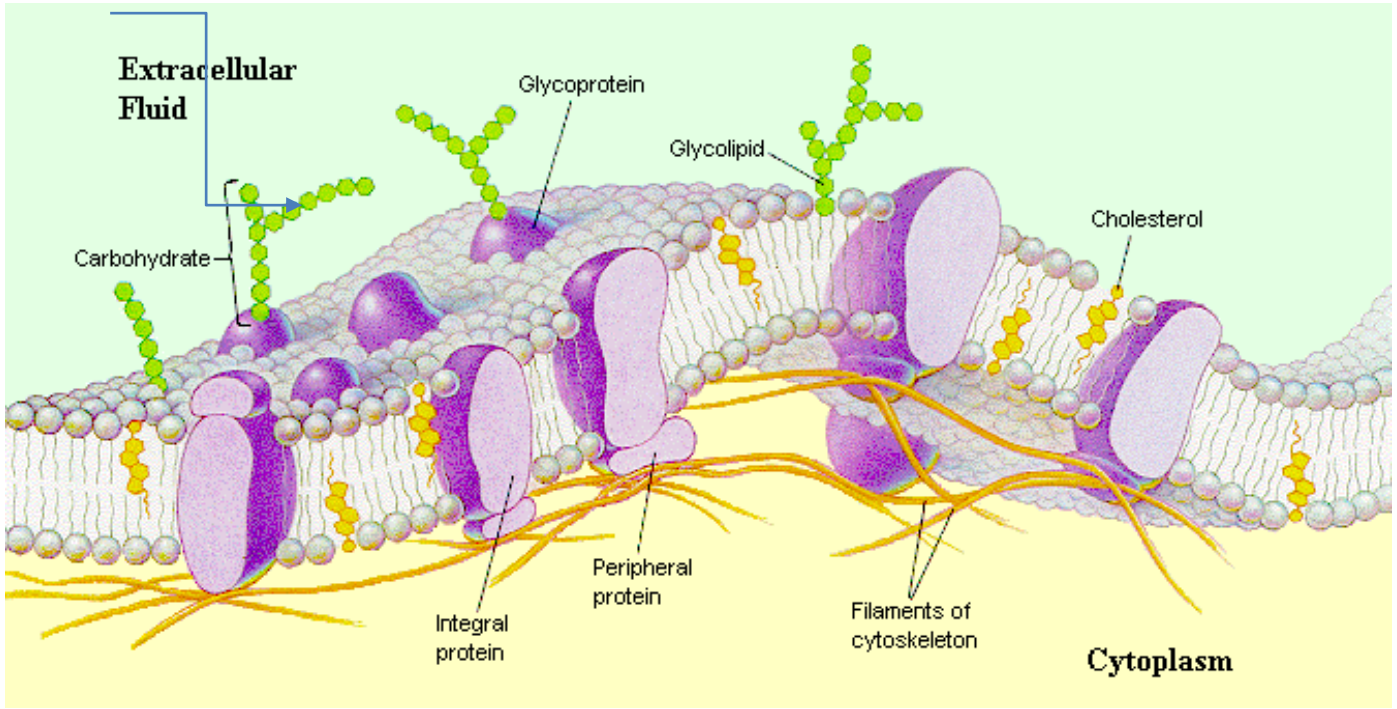
- The membrane is hypothesized in a model known as the fluid mosaic model.
- Components: 45% lipid, 45% protein and 10% carbohydrate

Located externally
Outside of the cell.

- They exist side by side without forming some other substance of intermediate nature.

Glycerophospholipids–
> phosphatidylcholine(target of snake venom)

The importance of the protein linked sugars :
- Cell signaling
- Protein folding
- Cell recognition



Phospholipids

function of molecules depend on the noncovalent interactions

- The outer: phosphatidylcholine, sphingomyelin, and glycolipids(cell recognition)

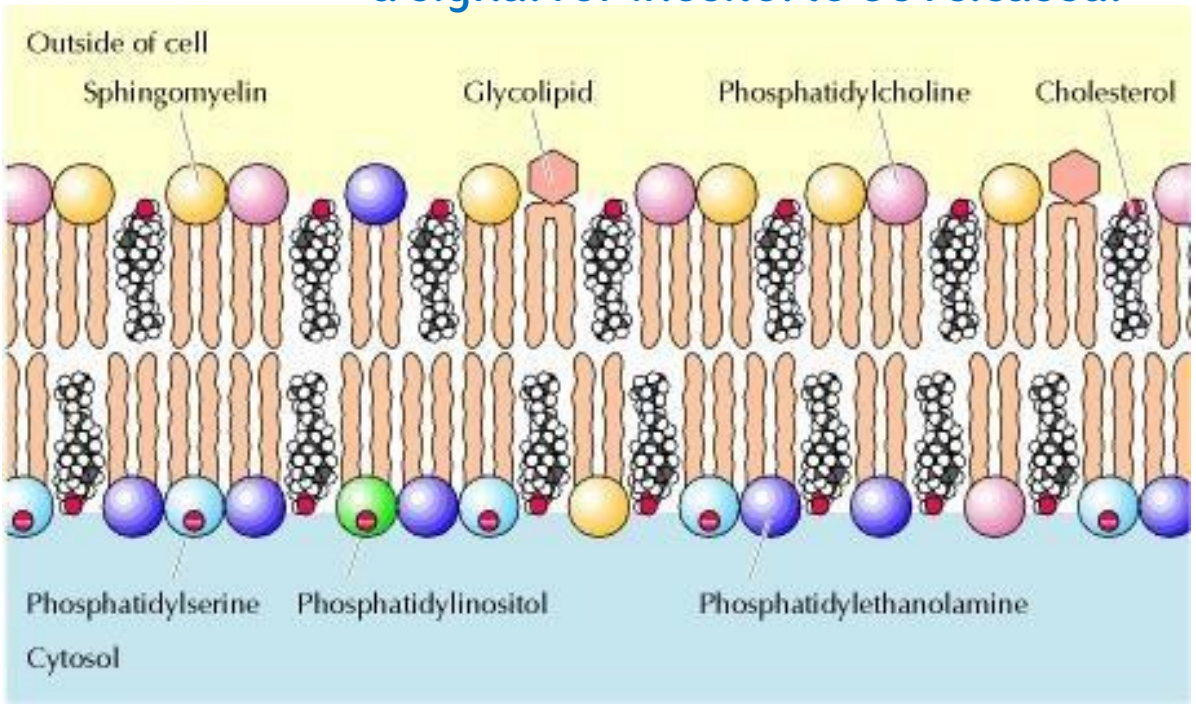
Predominant.

- The inner: phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol (signaling)

~> growth factors, specific molecules, ligand, small molecules..]-> binds with receptor => sending a signal for inositol to be released.

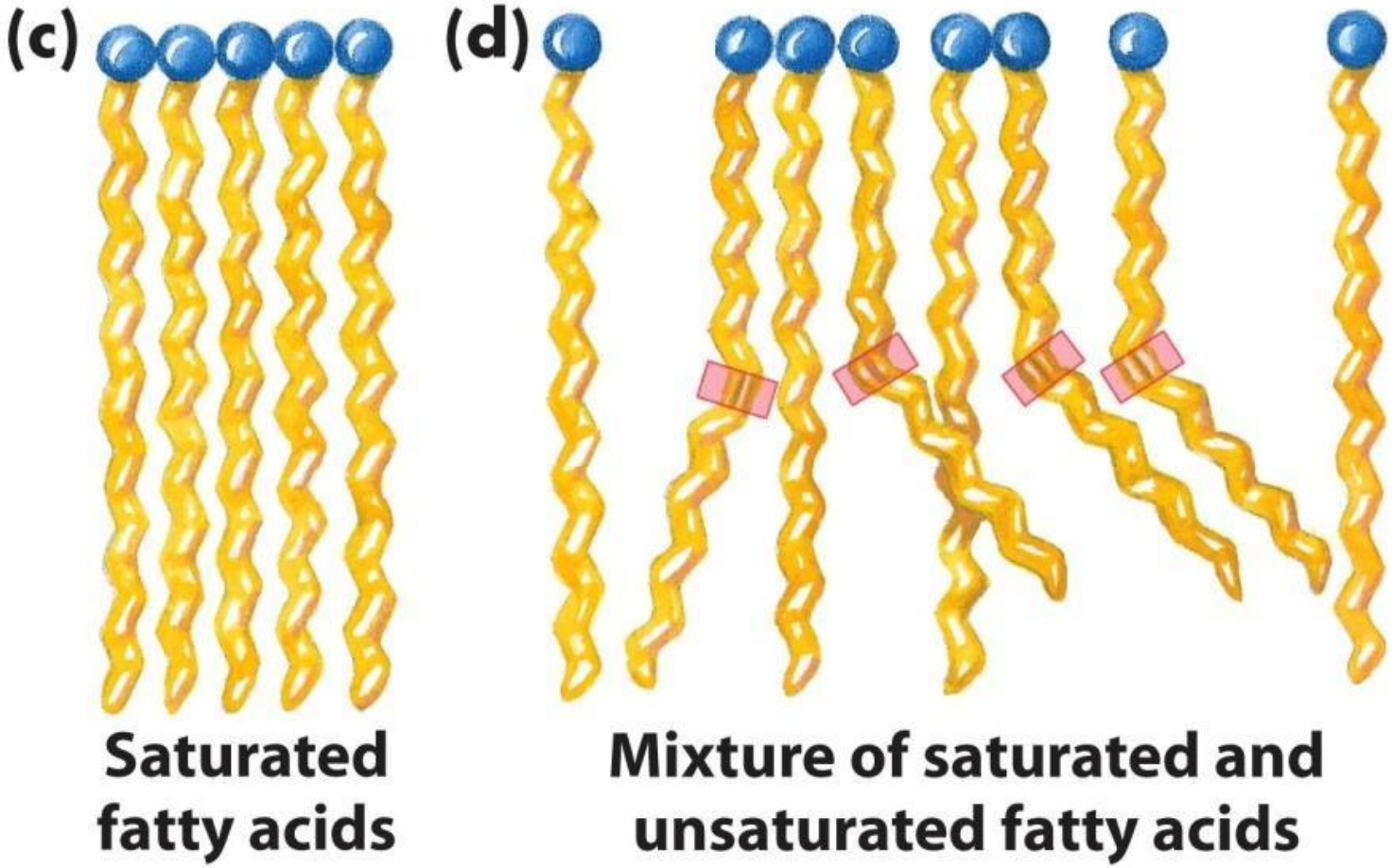
Animal cells vs. plant cells vs. prokaryotic cells

Cholesterol is <u>evenly</u> distributed in both leaflets



Cholesterol is found in animal cells, a similar molecule is found in plant cells, it's not found in bacteria.

Fatty acids and membrane fluidity



rigid

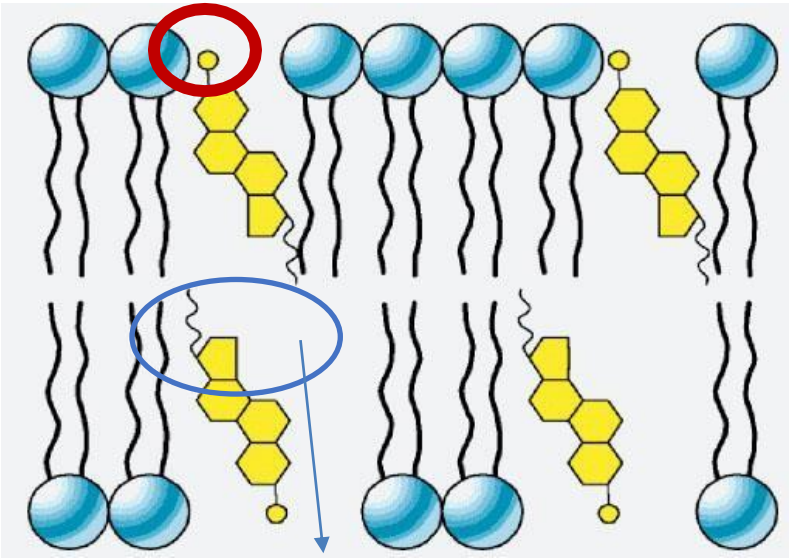
The presence of a cis double bond creates space allowing movement of the molecule-> ore cis double bond more fluidity

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.

-> creates space for fluidity
-> prevents the membrane from colliding with itself- as we've said molecules are dynamic- resulting in its collapse.

Interaction with phosphate group.

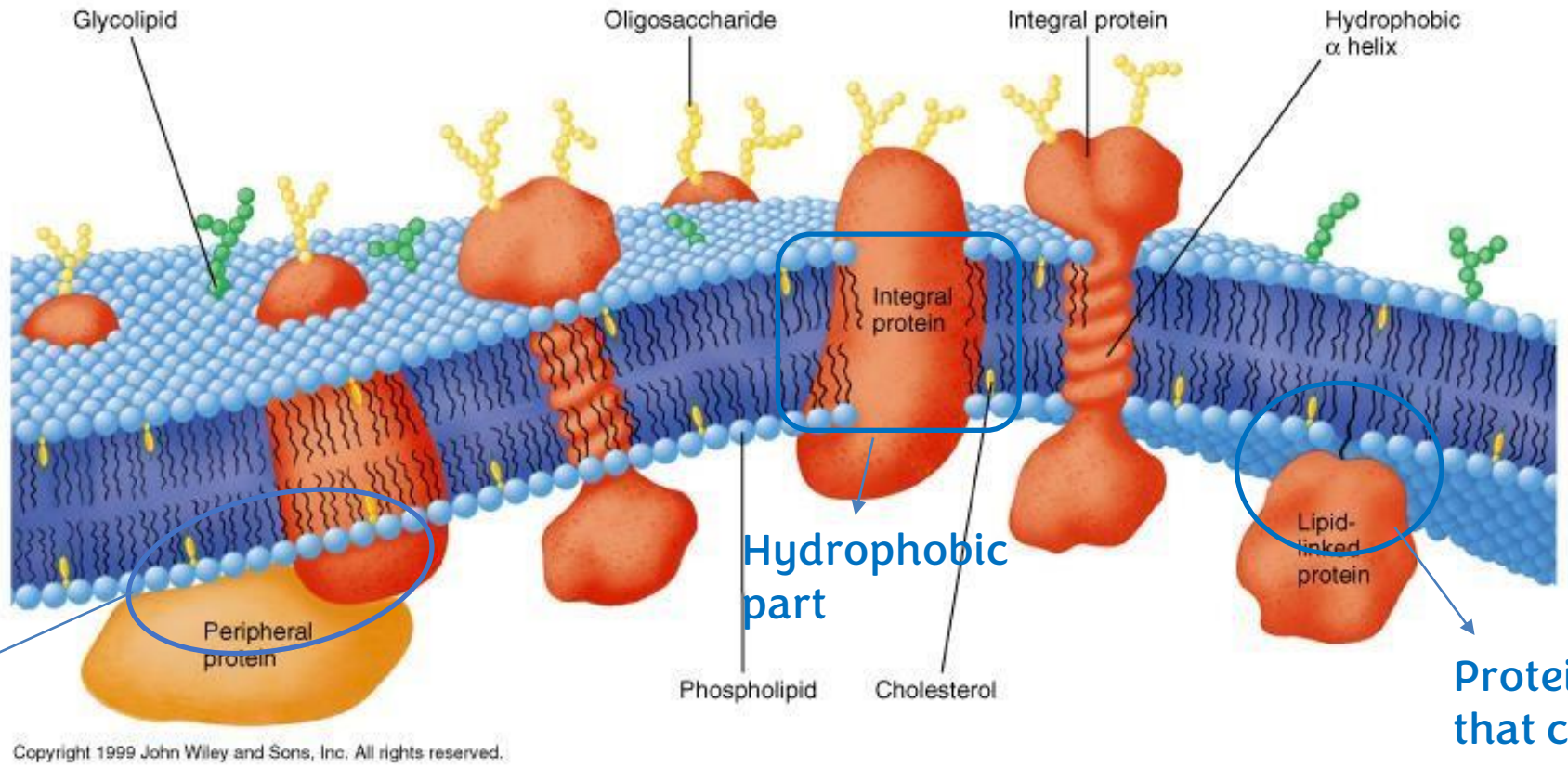


Hydrophobic portion is internal-> hydrophobic interactions with fatty acids
and the OH group is external

- 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

- Integral proteins
- Peripheral proteins
- Lipid linked proteins



Interactions with either phosphate groups of the membrane or another protein (integral one)

Hydrophobic part

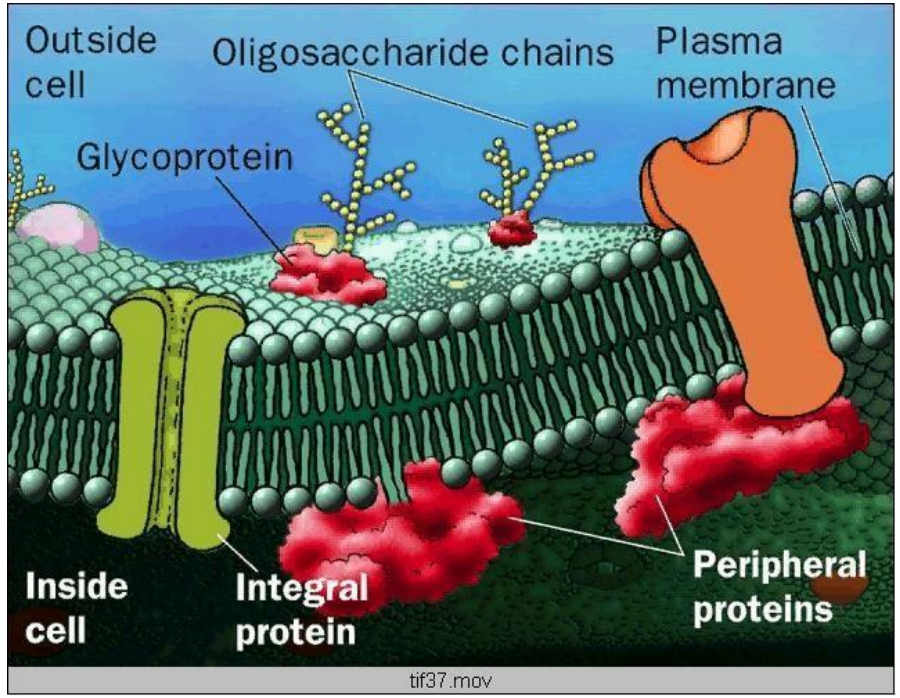
Protein with fatty acid that connects the compound to the membrane.

Types of membrane proteins

- Peripheral proteins: Easy to break because the interaction between them(po4 & protein) is electrostatic= noncovalent
  - are associated with the exterior of membranes via noncovalent interactions
- Integral membrane proteins: We have to break up the entire membrane to release a protein.
  - anchored into membrane via hydrophobic regions
- Lipid-anchored: Easy removal.
  - associated via a lipid group

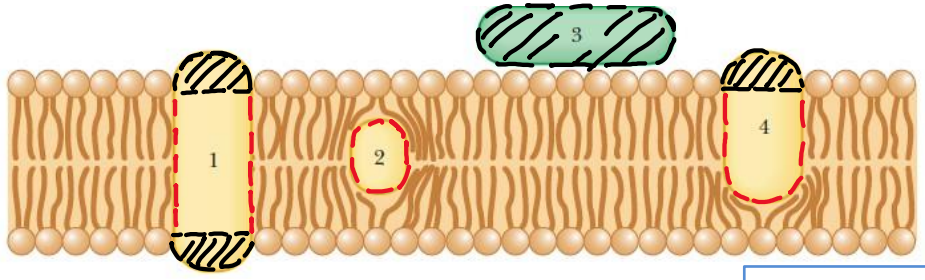
Peripheral membrane proteins

- 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

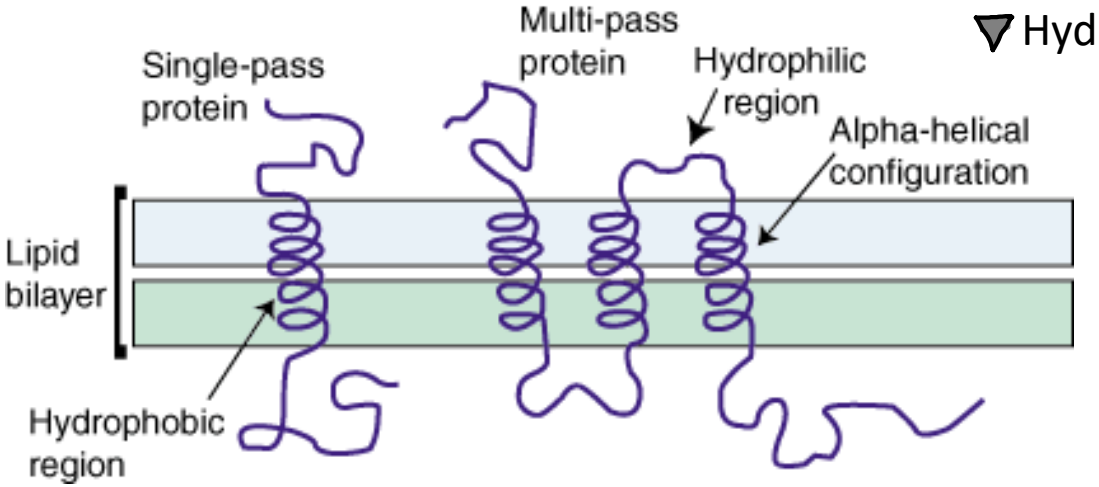
The integral membrane proteins can be associated with the lipid bilayer in several ways.



Hydrophobic region

Hydrophilic region

1- Both ends are exposed.
2- totally embedded.
3- peripheral.
4- one end is exposed.

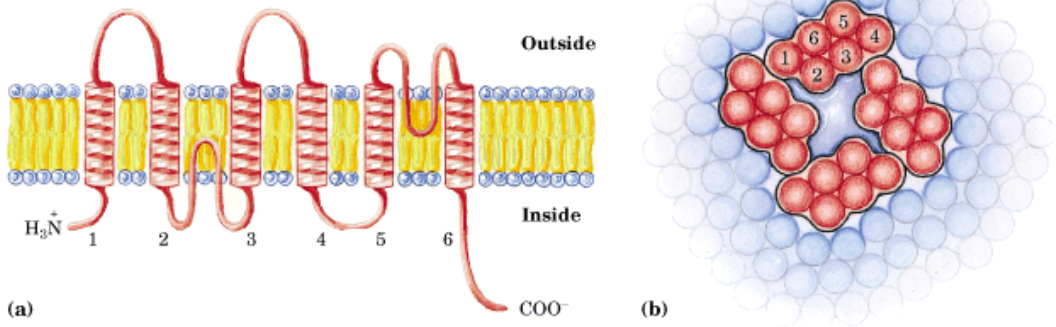


The membrane integral domains are:
1. Single or multiple
2. α-helix (human) or β-sheet (bacteria)

1 transmembrane domain.

Multiple transmembrane domains.

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
  - Enzymes

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V1 → V2	21 –Comment next to the arrow	Glycophospholipids	Glycerophospholipids
V2 → V3	28 –Red and black labels on the top right	Hydrophilic region Hydrophobic region	Hydrophobic region Hydrophilic region
V3 → V4			

Additional Resources:

رسالة من الفريق العلمي:

1. Campbell & Farrell biochemistry
- The chemical natures of lipids type (sec8.2) .
- Biological membrane (sec8.3) .
- The kind of membrane proteins (8.4) .
- The fluid-mosaic model of membrane structure (8.5) .

2. https://youtu.be/wyQi1pw1Vwl?si=NVJ1tEj52xQnf20K

أنتَ مَسؤولٌ عنِ السّعيِ لا عنِ النّتيجةِ

﴿ وَأَنْ لَيْسَ لِلْإِنْسَانِ إِلَّا مَا سَعَى (39)
وأَنَّ سَعْيَهُ سَوْفَ يُرَى (40)
ثُمَّ يُجْزَاهُ الْجَزَاءَ الْأَوْفَى (41)﴾

سُورةُ النّجم