Doctor 022

Biochemistry

Sheet no. 11

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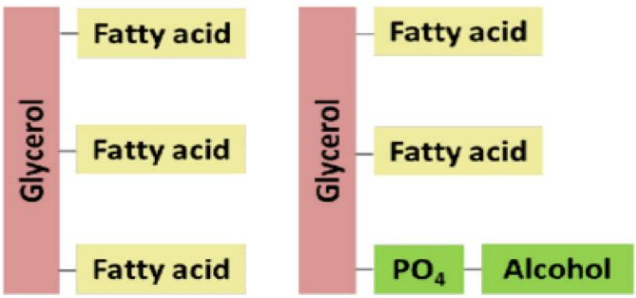
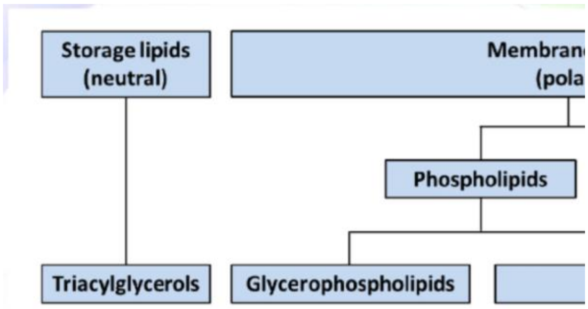
Quick revision:

- The backbone of the Complex lipids in the table below is glycerol (an alcohol with 3 hydroxyl groups). 3 fatty acids bind to Glycerol making a structure called <u>triacylglycerol (storage lipid).</u> If a phosphate group binds to the 3rd carbon of a fatty acid, we'll have another structure called <u>Glycerophospholipid</u>.

- Glycerophospholipids have different functions and tissue distributions depending on the functional group attached to the phosphate group (e.g.ethanolamine, choline and serine).

***Glycerophospholipids are the predominant lipids in the plasma membrane.**





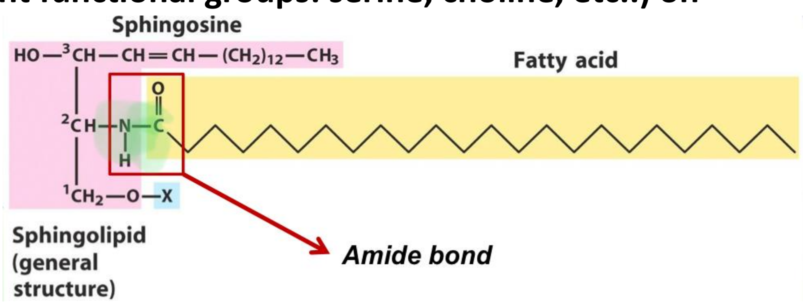
<u>Sphingolipids</u>:

- Sphingolipids play an important role in the formation of the plasma membrane but at a lower rate compared to Glycerophospholipids.

-The core (backbone) of sphingolipids is <u>Sphingosine</u> which is a long-chain amino alcohol (composed of: the amino-acid serine + and the fatty acid palmitate).

**Important features of sphingolipids structure:

1. **A backbone of 3 carbons**
2. **Long hydrocarbon chain containing an alkene group on the <u>3rd carbon</u>**
3. **Amino group on the <u>2nd carbon</u> that becomes an amide group -amide bond- when it is bonded to the fatty acid (amino group, carboxyl group and a fatty acid)**
4. **An oxygen and X (different functional groups: serine, choline, etc..) on the <u>1st carbon</u>**



note: we have to recognize the lipids by their structure

- Sphingolipids are found in the plasma membranes of all eukaryotic cells and is highest in the cells of the central nervous system

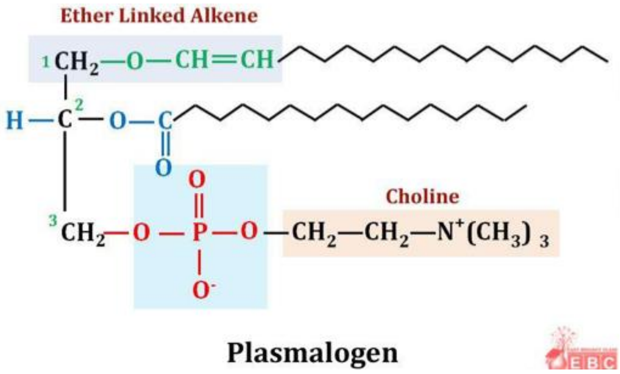
Sphingolipids vs. Plasmalogens:

Q: How can we differentiate between Sphingolipids and Plasmalogens since both of them have an alkene group?

-Plasmalogens have an unsaturated hydrocarbon on C1 (a double bond) and an ether group before the alkene (Ether linked) while in Sphingolipids it is a normal carbon-carbon bond on C3.

-Plasmalogens have an ester group (ester bond) on C2 while Sphingolipids have an amide group (amid bond) on C2.

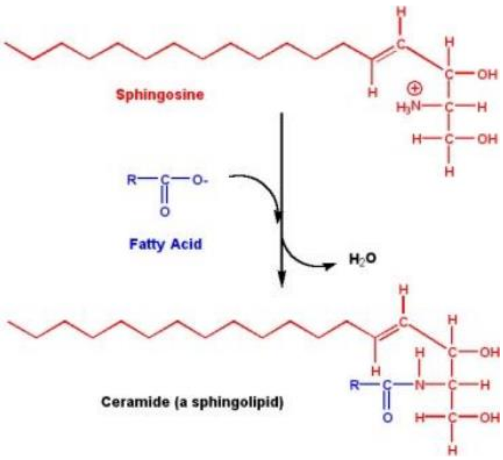
(so simply, look at C2)



note: *Mysterious Lipids* concept isn't required for the midterm. If you want to read about it, go back to the slide and nourish your mind.

Ceramide

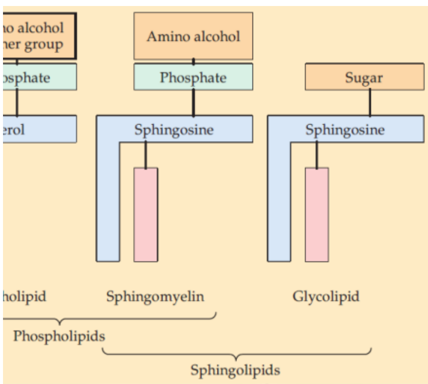
The simplest sphingolipid. It is composed of sphingosine and the fatty acid on the 2nd carbon (no X group).



*Reminder: The simplest Glycerophospholipid is Phosphatidate. (the glycerophospholipid with no attachment at the phosphate) It then differentiates by binding to other groups on the phosphate group.

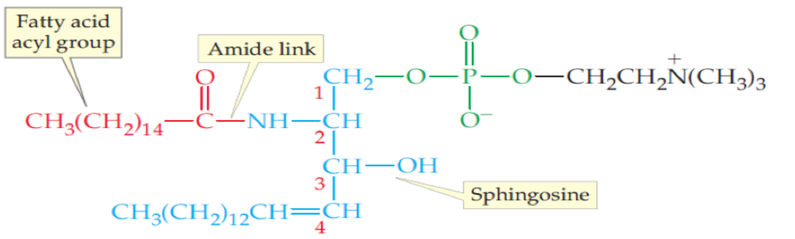
Sphingolipid types:

Sphingolipids can be either linked to a phosphate: Sphingophospholipids OR linked to sugars: Glycolipids.



-**The only sphingophospholipid is Sphingomyelin** (so you will find most sources referring to sphingophospholipid as sphingomyelin) **which is a sphingolipid that is a major component of the coating around nerve fibers (myelin sheath).**

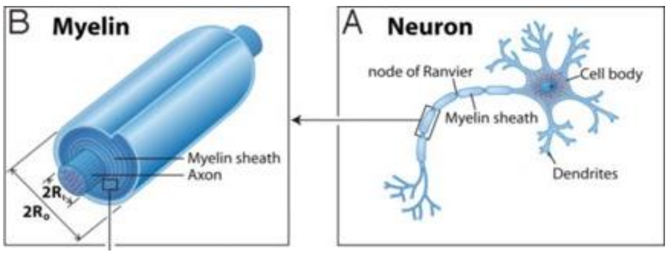
Phosphocholine binds to C1, so it is called sphingocholine (or sphingomyelin).

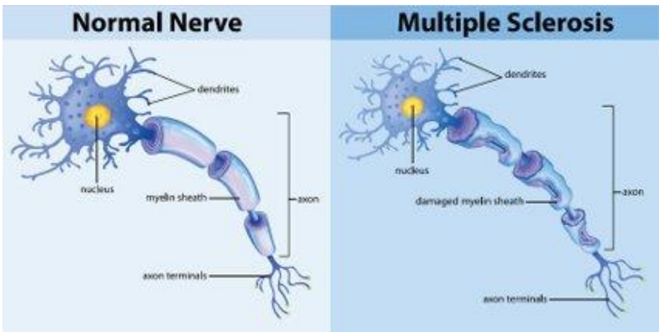


A sphingomyelin (a sphingolipid)

-Myelin sheath is important in action potential transduction and is full of Sphingolipids.

-Multiple Sclerosis is a disease that happens when the myelin sheath is not intact (has gaps), so the signal transduction is unstable.





Glycosphingolipids(Glycolipids):

-Glycolipids are composed of sphingosine, a fatty acid and a sugar molecule (mono- or oligosaccharide).

- **Glycolipids are present on cell membranes and act as cell surface receptors that can function in cell recognition (e.g., pathogens) and chemical messengers.**

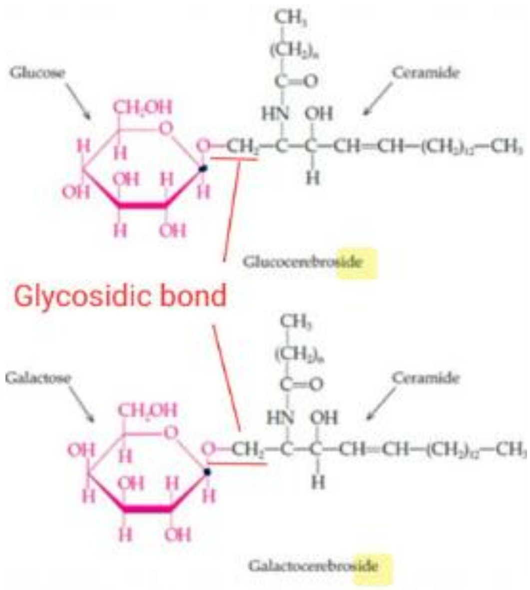
****There are 3 types of Glycolipids:** (depending on the complexity of the sugar molecules that are attached)

1.Cerebroside 2.Globoside 3.Ganglioside

****notice that their names indicate that they're found in the nervous system (it's rich in sphingolipids). The Manifestation of diseases related to synthesis or degradation of Glycolipids is found in the nervous system.**

1.<u>Cerebrosides</u>: The simplest glycolipids, contain a single hexose (Galactose or Glucose).

**So, they're named as Glucocerebrosides or Galactocerebrosides.



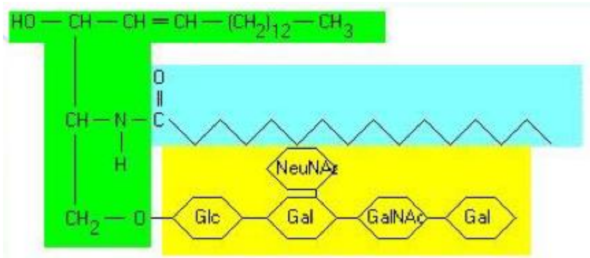
•Notes on the figure: The anomeric carbon makes a Glycosidic bond with Ceramide and it is the reason for the suffix (side) in their names ; they are glycosides.

2.<u>Globosides</u>

3.<u>Gangliosides</u>

-Globosides and Gangliosides are more complex glycolipids (contain two sugar molecules or more).

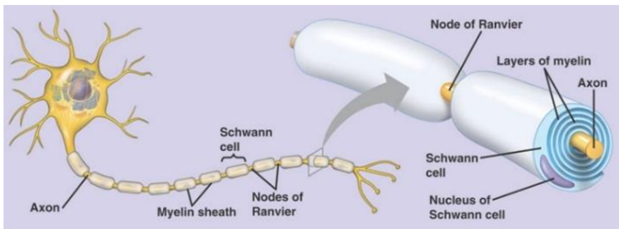
• Both contain glucose, galactose, and N-acetylgalactosamine, but Gangliosides must also contain a modified sugar: <u>sialic acid</u>.



-Sphingolipids are targets for toxins;
Gangliosides are bound by cholera toxin in the human intestine facilitating its endocytosis into the cells (causes Diarrhea, etc...)

<u>Sulfatides:</u>

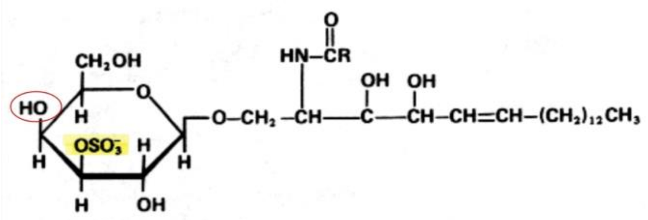
-A type of sphingolipids and glycolipids. This type has a sugar which is attached to a sulfate group.



-Synthesized from Galactocerebrosides.

-Abundant in brain myelin (myelin sheath)

*Check the figure below: Sulfate group and the sugar, notice the position of the circled OH, it is a galactose.



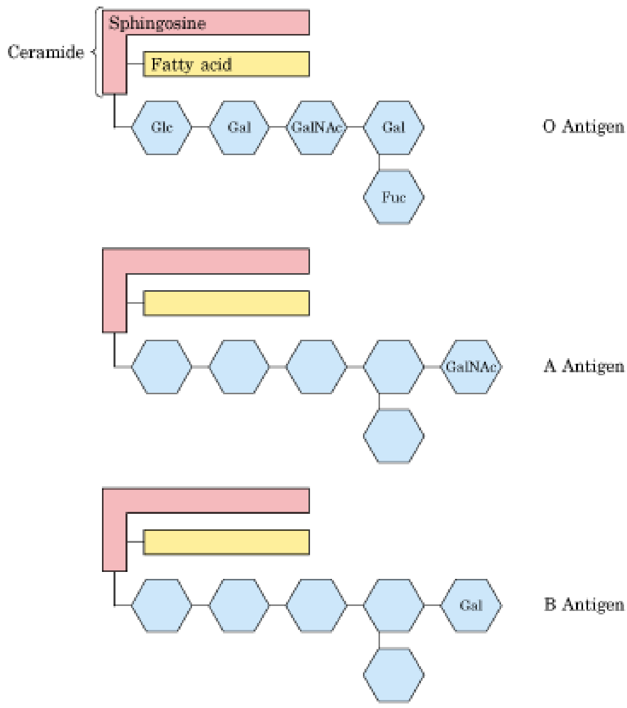
Sphingolipids and blood groups

-Sugars play a role in determining the blood type. They are attached to the Sphingolipids on the plasma membrane of red blood cells (RBCs) surface.

-These sugars can also be attached to proteins (glycoproteins on cell surface).

- 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.

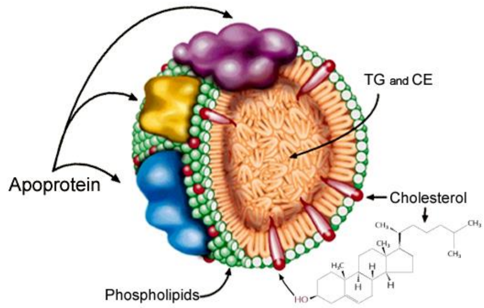


*Check the figure: what is the difference between ABO types?
B: Galactose, A: N-acetylgalactosamine, O: none

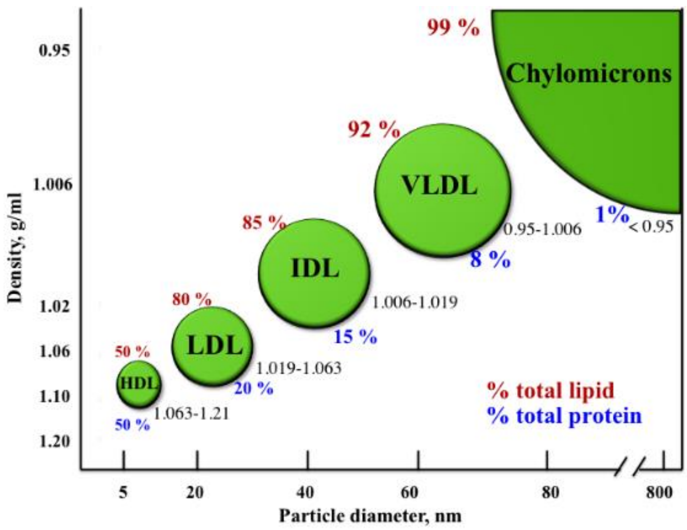
Lipoproteins:

-They are a type of lipid molecules. A combination of two things: lipids and proteins. They look like micelles (phosphate group outside and the fatty acid tails inside).

-So, it's hydrophobic from the inside.



<u>Function</u>: transport of different types of lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) through blood plasma from one place to another.



1.Chylomicrons: transport dietary lipids from intestines to the liver.

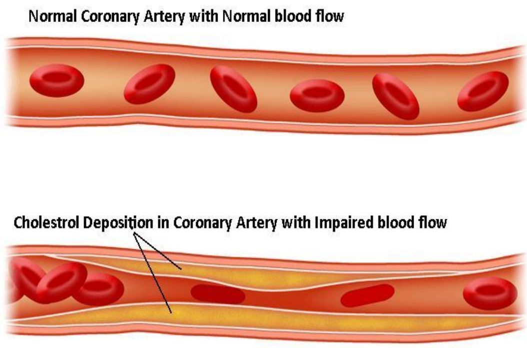
2.VLDL (Very low-density lipoproteins): transport lipids from the liver to the blood.

VLDL and chylomicrons deliver diacylglycerol to tissues

3.IDL (Intermediate density lipoproteins): VLDL are converted to IDL which are converted to LDL in blood by supplying the tissues in its way with lipids.
Intermediate: you can think of it as a transitional state

4.LDL (Low density lipoproteins): during this transition from VLDL to IDL then to LDL the triglycerides are removed and the remaining in the LDL (the Lipoprotein) is Cholesterol, so LDL transport cholesterol to peripheral tissues (muscles, brain…any tissue needs cholesterol).

-LDL is called the Bad Cholesterol; (1) it transports cholesterol from liver to the peripheral tissue, (2) it accumulates in the blood vessels; causing Atherosclerosis (تصلب الشرايين) leading to heart attacks. The figure shows atherosclerosis.



5.HDL (High density lipoproteins): It is known as the Good Cholesterol; it transports the excess cholesterol in peripheral tissue back to the liver, where the liver will get rid of it.
(The sequence of the process is important)

• As lipid content increases, the density decreases (especially triacylglycerol) the density decreases.as the percentage of proteins increases relatively to the lipids, the density increases.

-The Chylomicrons are the hugest but the least dense (little amount of proteins relative to high amounts of lipids). Check the red and blue percentages in the figure above. That's why HDLs are called high dense.

Lipoproteins are different in the origin, the last destination, type of lipids they transport, proteins that are composed of which determine their destinations, size, and densities.

Steroids:

-Steroids are derivatives of cholesterol. The precursor of cholesterol is Isoprene, notice that it is composed of 5 carbons.

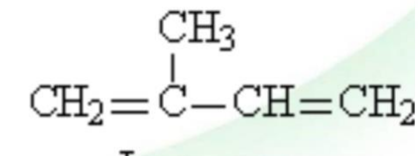
-Cholesterol (steroid) has a core that is called Steroid Nucleus, which is composed of 4 rings, designated as (A, B, C and D)

-A, B and C are six carbons ring while D is a five carbons ring.

-Steroid (27 carbon) = steroid nucleus (17 carbons) + hydrophobic chain of (10 carbons)

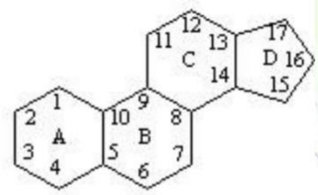
-It is amphipathic molecule; has hydrophobic and hydrophilic side (which is the one that includes (OH))
However, it is very hydrophobic.

The precursor



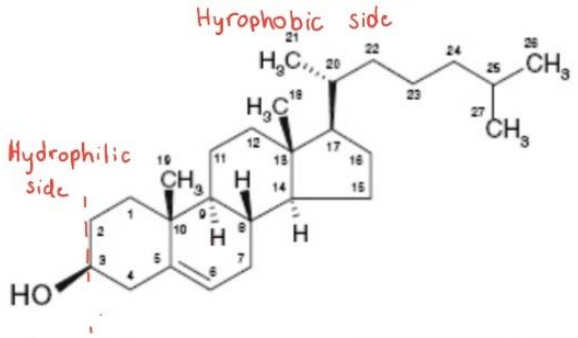
Isoprene

The nucleus



Steroid nucleus

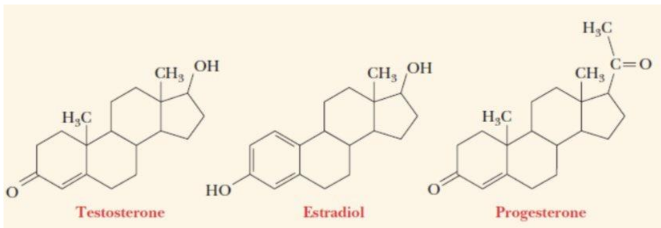
The most common steroid



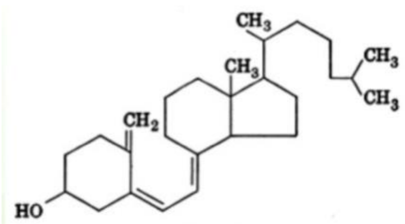
*Products of cholesterol:

-We can derive different molecules from Cholesterol, such as:

1.Hormones: Sex hormones (androgens, estrogens, progestins, cortisol).



2.Vitamin D.

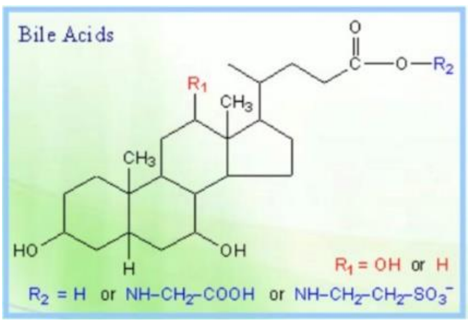


Vitamin D_3

3.Bile acids (intestinal absorption of fat).

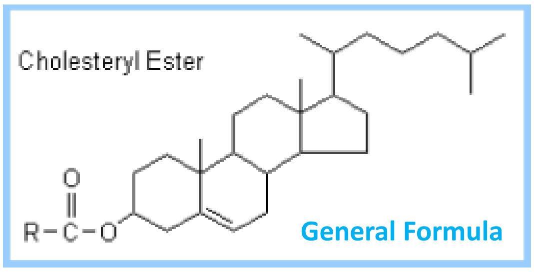
Bile acids (عصارة المرارة أو المادة الصفراء) carry the function of Emulsification or dissolving of dietary lipids. Why?? to facilitate absorption or dissolution of lipids in a hydrophilic environment.

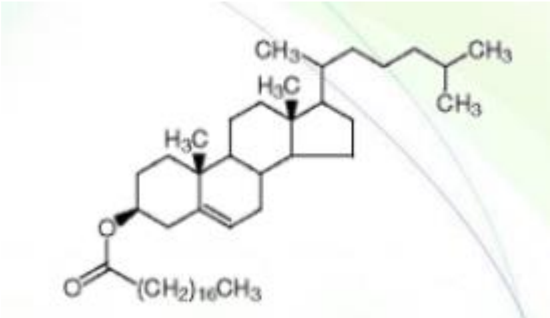
What happens if we don't have bile acids? Lipids that we eat accumulate because they are hydrophobic... But as long as we have bile acids, they break down lipids into smaller droplets, preventing them from clustering. Then they surround those lipid droplets (hydrophilic outside & hydrophobic inside), facilitating absorption in intestines or making it easy.



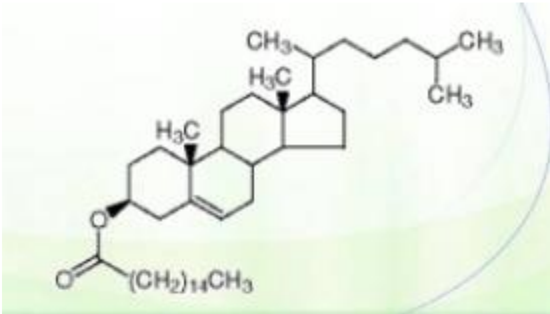
Cholesterol esters:

A cholesterol with a fatty acid attached at (-OH) of C3 so, It becomes a fatty acyl molecule.





Cholesteryl stearate



Cholesteryl palmitate

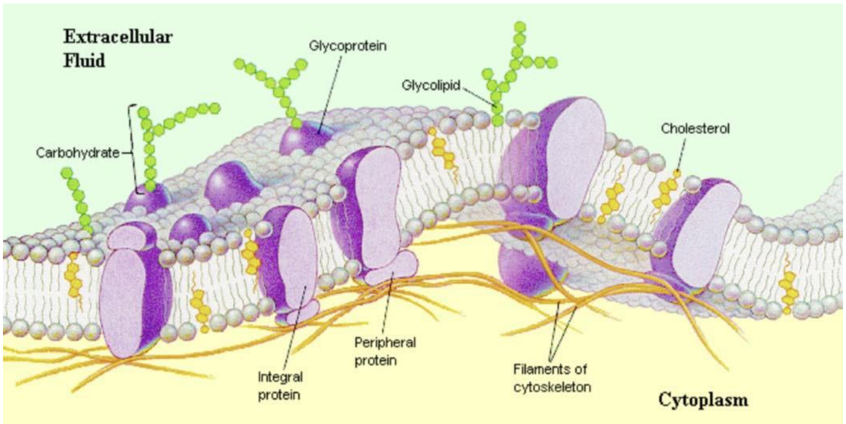
Cell membranes:

-The membrane is hypothesized in a model known as the fluid mosaic model.

**components: 1) 45% lipid 2) 45% protein 3) 10% carbohydrate

-Carbohydrates will be present on the extracellular surface.

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



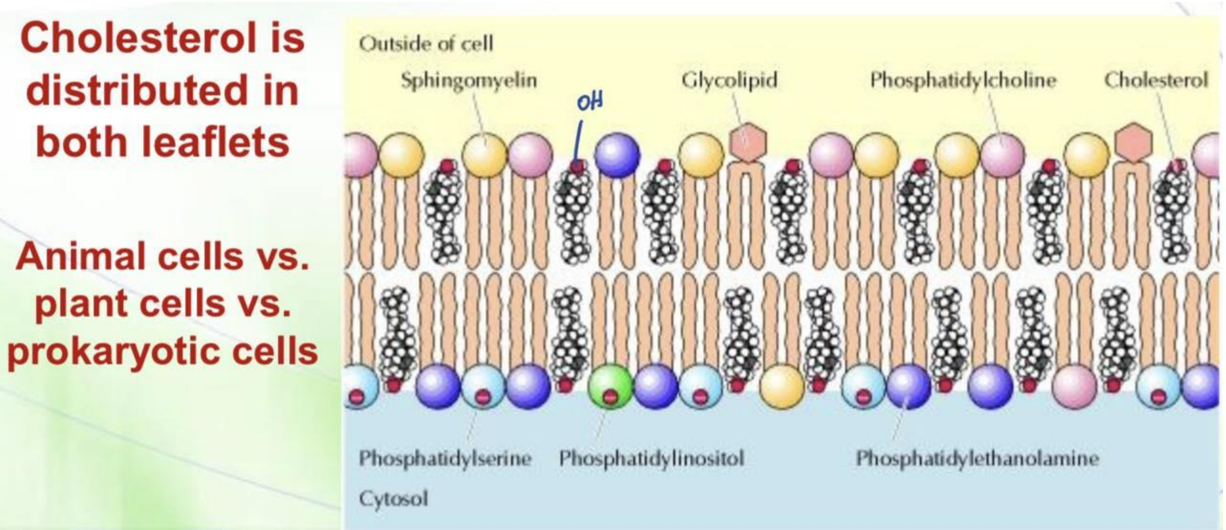
Phospholipids:

• Usually the outer leaflet contains phosphatidylcholine, sphingomyelin, glycolipids (sugar outside, cell recognition).

• Meanwhile, the inner leaflet has more phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol (signalling).

-Inositol is important for signalling, wherever we recive a signal, phosphatidylinositol will be present to produce diacylglycerol and IP3, both of which carry signal transmission inside the cell.

-Cholesterol is equally distributed on BOTH sides of the membrane. (OH) group is exposed outside, next to phosphate groups. But the hydrophobic rings are inside.



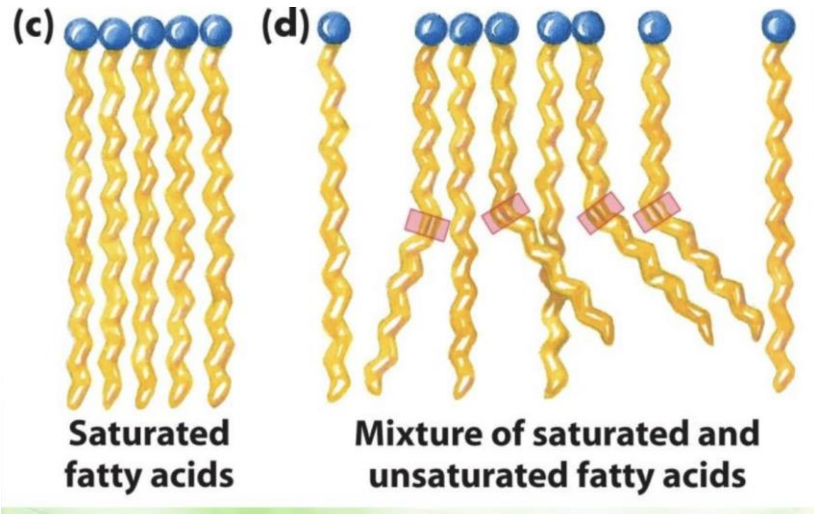
Fatty acid and membrane fluidity:

-Saturated fatty acids are higly packed.

-If we have a double bond in the cis-orientation (unsaturated), there will be spaces between the fatty acids. (the membrane will be more fluid).

-On the right the membrane is more fluid, on the left it is more rigid.

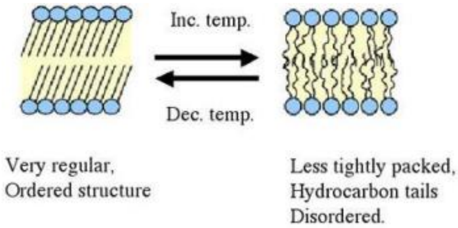
-We mentioned that the cellular membrane contains proteins, why? They are signalling molecules, and they must be dynamic (moving freely in the membrane).



-Signalling is better in the presence of unsaturated fatty acids in the plasma membrane (membrane is less rigid therefore, proteins can move freely).

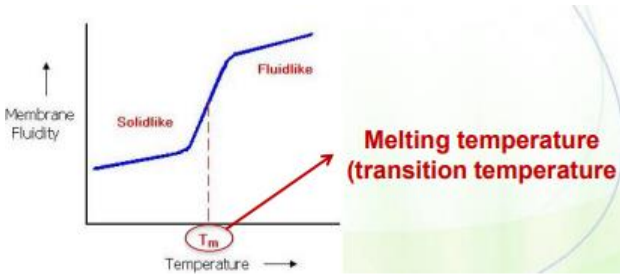
**Membrane fluidity is related to the saturation/unstauration and the temperature.

Membrane fluidity and temperature:



If we put the plasma membrane in a low-temperature environment, the fatty acid chains will become compact, rigid and there will be less dynamic movement. As soon as we raise the temperature, electrons in the fatty acids will start moving (their energy is raised) and the fatty acids will move faster ويصيرو يصطدمو ببعض يمين شمال so the membrane will collapse because the Van Der Waals interactions will be disturbed (the molecules are farther away from each other).

-Melting temperature: the temperature in which the membrane transforms from the stable state into the unstable state.

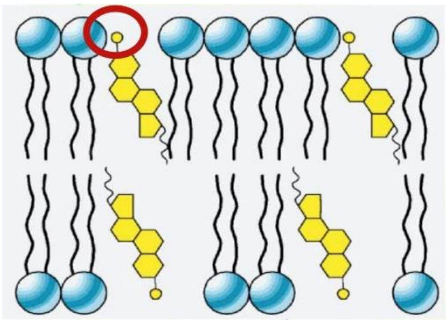


Cholesterol and membrane fluidity:

-The presence of cholesterol and the cis unsaturated fatty acids in the membrane prevent the hydrophobic chains from packing too closely together (it creates spaces and increases fluidity), allowing free membrane proteins and lipid molecules to move laterally in the plane of the leaflet making the membrane a dynamic environment.

-So, it prevents hydrophobic chains from packing too closely together.

-In the case of raising temperature, cholesterol will stabilize very fluid membranes by increasing interactions between the fatty acids of phospholipids through hydrophobic interactions with the cholesterol ring structure, preventing the membrane from collapsing.

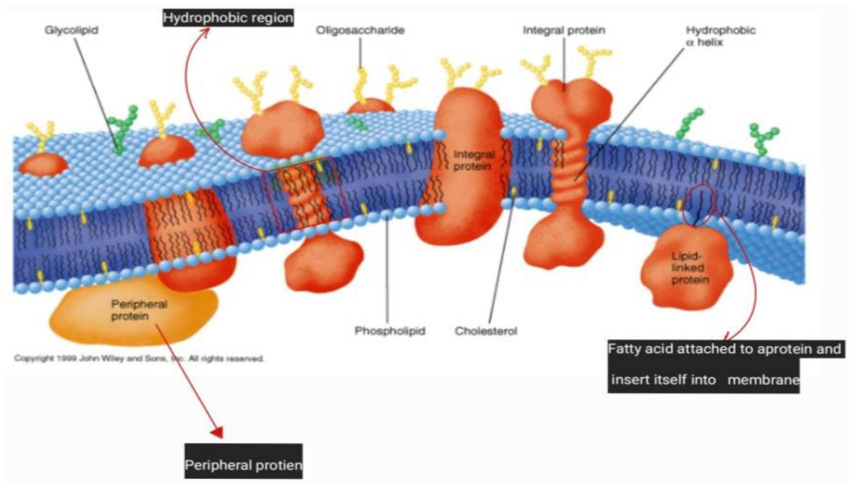


-The role of cholesterol in membrane fluidity is important at every temperature.

-In summary, at low temperature it adds fluidity to the structure and at high temperature it adds stability to the structure.

<u>Membrane proteins</u>

-There are many types of membrane proteins depending on how they interact with plasma membrane:

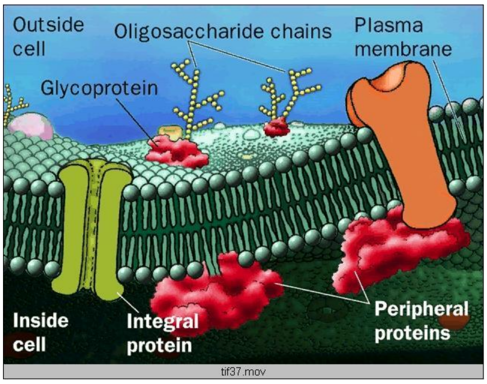


1.Peripheral proteins: are associated with the <u>exterior</u> (outside, not embedded) <u>of membranes</u> via noncovalent interactions (specifically electrostatic interactions and hydrogen bonds) between the negatively charged phosphate groups and the positively charged proteins, same as the interactions between histones and DNA.

2.Integral membrane proteins: anchored into membrane via hydrophobic regions (amino acids), that insert (integrate) itself into the membrane and have hydrophobic interactions with the fatty acid tails. These regions are called transmembrane domains.

3.Lipid-anchored: associated via a lipid group, (lipoprotein). protein attached with fatty acid which is inserted into the plasma membrane.

1.Peripheral membrane proteins



-They are associated with membranes but do not penetrate the hydrophobic core of the membrane.

-They can also be associated with integral membrane proteins. they can interact with phospholipids or integral membrane proteins or both as well.

-They are not strongly bound to the membrane (noncovalent interactions) and can be removed without disrupting the membrane structure. (They can be Dissociated from the plasma membrane easily).

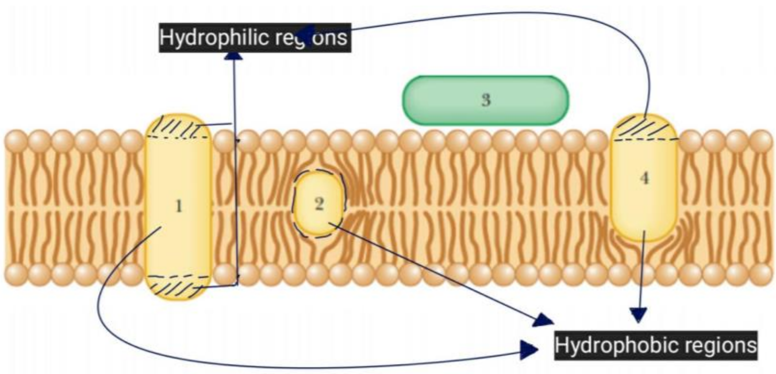
-How can we accomplish that? Will be discussed later in details.

-Treatment with mild detergent, hydrophobic molecules, Hydrophobic solvent (which disrupts the interactions between proteins and plasma membrane.

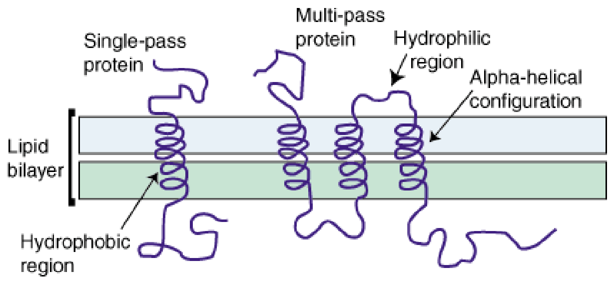
2.Integral membrane proteins

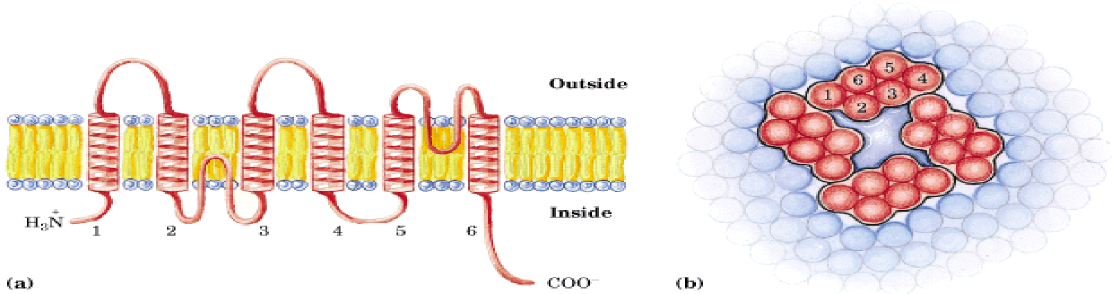
The integral membrane proteins can be associated with the lipid bilayer in several mechanisms. They can be inserted fully in the plasma membrane, they can be exposed from one side of the plasma membrane and they can be exposed at both sides of the plasma membrane.

*check the figure: protein (2) is totally hydrophobic, while proteins (1) & (4) have both hydrophobic and hydrophilic regions and protein (3) is a peripheral protein which is totally hydrophilic



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





-Some can form channels (holes in the plasma membrane that allow ions go out and in). check the figure above, the protein has many domains going in and out and making a hole inside the membrane that allows ion passage.

Structure-function of membranes (these will be discussed in detail in the coming weeks)

1.Transport:
-Membranes are impermeable barrier, transporting nutrients, ions, materials inside and outside cells.

-Proteins can be carriers or channels.

2.Signaling:
-Protein receptors and small molecules (some can be lipids themselves).

3.Catalysis:
-Enzyme-linked receptors.

(つ◔◡◔つ) the end

فَرَأسُ العِلمِ تَقوى اللَهِ حَقّاً
وَلَيسَ بِأَن يُقالَ لَقَد رَأَستا

(وَلَا تَيْأَسُوا مِن رَّوْحِ اللَّهِ)

وَلَيسَ لِجاهِلٍ في النّاسِ مَعنىً
وَلَو مُلكُ العِراقِ لَهُ تَأَتّى

-زاوية أدبية لمن أراد :

تَفُتُّ فُؤادَكَ الأَيّامُ فَتّا
وَتَنحِتُ جِسمَكَ الساعاتُ نَحتا

وَتَدعوكَ المَنونُ دُعاءَ صِدقٍ
أَلا يا صاحِ أَنتَ أُريدُ أَنتا

أَراكَ تُحِبُّ عِرساً ذاتَ غَدرٍ
أَبَتَّ طَلاقَها الأَكياسُ بَتّا

تَنامُ الدَهرَ وَيحَكَ في غَطيطٍ
بِها حَتّى إِذا مِتَّ اِنتَبَهتا

فَكَم ذا أَنتَ مَخدوعٌ وَحَتّى
مَتى لا تَرعَوي عَنها وَحَتّى

أَبا بَكرٍ دَعَوتُكَ لَو أَجَبتا
إِلى ما فيهِ حَظُّكَ إِن عَقَلتا

إِلى عِلمٍ تَكونُ بِهِ إِماماً
مُطاعاً إِن نَهَيتَ وَإِن أَمَرتا

وَتَجلو ما بِعَينِكَ مِن عَشاها
وَتَهديكَ السَبيلَ إِذا ضَلَلتا

وَتَحمِلُ مِنهُ في ناديكَ تاجاً
وَيَكسوكَ الجَمالَ إِذا اِغتَرَبتا

يَنالُكَ نَفعُهُ مادُمتَ حَيّاً
وَيَبقى ذُخرُهُ لَكَ إِن ذَهَبتا

هُوَ العَضبُ المُهَنَّدُ لَيسَ يَنبو
تُصيبُ بِهِ مَقاتِلَ ضَرَبتا

وَكَنزاً لا تَخافُ عَلَيهِ لِصّاً
خَفيفَ الحَملِ يوجَدُ حَيثُ كُنتا

يَزيدُ بِكَثرَةِ الإِنفاقِ مِنهُ
وَينقُصُ أَن بِهِ كَفّاً شَدَدتا

فَلَو قَد ذُقتَ مِن حَلواهُ طَعماً
لَآثَرتَ التَعَلُّمَ وَاِجتَهَدتا

وَلَم يَشغَلكَ عَنهُ هَوىً مُطاعٌ
وَلا دُنيا بِزُخرُفِها فُتِنتا

وَلا أَلهاكَ عَنهُ أَنيقُ رَوضٍ
وَلا خِدرٌ بِرَبرَبِهِ كَلِفتا

فَقوتُ الروحِ أَرواحُ المَعاني
وَلَيسَ بِأَن طَعِمتَ وَأَن شَرِبتا

فَواظِبهُ وَخُذ بِالجِدِّ فيهِ
فَإِن أَعطاكَهُ اللَهُ أَخَذتا

وَإِن أوتيتَ فيهِ طَويلَ باعٍ
وَقالَ الناسُ إِنَّكَ قَد سَبَقتا

فَلا تَأمَن سُؤالَ اللَهِ عَنهُ
بِتَوبيخٍ عَلِمتَ فَهَل عَمِلتا

فَرَأسُ العِلمِ تَقوى اللَهِ حَقّاً
وَلَيسَ بِأَن يُقالَ لَقَد رَأَستا

وَضافي ثَوبِكَ الإِحسانُ لا أَن
تُرى ثَوبَ الإِساءَةِ قَد لَبِستا

إِذا ما لَم يُفِدكَ العِلمُ خَيراً
فَخَيرٌ مِنهُ أَن لَو قَد جَهِلتا

وَإِن أَلقاكَ فَهمُكَ في مَهاوٍ
فَلَيتَكَ ثُمَّ لَيتَكَ ما فَهِمتا

سَتَجني مِن ثِمارِ العَجزِ جَهلاً
وَتَصغُرُ في العُيونِ إِذا كَبُرتا

وَتُفقَدُ إِن جَهِلتَ وَأَنتَ باقٍ
وَتوجَدُ إِن عَلِمتَ وَقَد فُقِدتا

وَتَذكُرُ قَولَتي لَكَ بَعدَ حينٍ
وَتَغبِطُها إِذا عَنها شُغِلتا

لَسَوفَ تَعَضُّ مِن نَدَمٍ عَلَيها
وَما تُغني النَدامَةُ إِن نَدِمتا

إِذا أَبصَرتَ صَحبَكَ في سَماءٍ
قَد اِرتَفَعوا عَلَيكَ وَقَد سَفَلتا

فَراجِعها وَدَع عَنكَ الهُوَينى
فَما بِالبُطءِ تُدرِكُ ما طَلَبتا

وَلا تَحفِل بِمالِكَ وَاِلهُ عَنهُ
فَلَيسَ المالُ إِلّا ما عَلِمتا

وَلَيسَ لِجاهِلٍ في الناسِ مَعنىً
وَلَو مُلكُ العِراقِ لَهُ تَأَتّى

سَيَنطِقُ عَنكَ عِلمُكَ في نَدِيٍّ
وَيُكتَبُ عَنكَ يَوماً إِن كَتَبتا

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**the sheet was reorganized and these statements were added:

page 5: •*Notes on the figure*: The anomeric carbon makes a Glycosidic bond with Ceramide and it is the reason for the suffix (side) in their names ; they are glycosides.

page 6: VLDL and chylomicrons deliver diacylglycerol to tissues

page 7: Lipoproteins are different in the origin, the last destination, type of lipids they transport, proteins that are composed of which determine their destinations, size, and densities.

**these statements were corrected:

Page 8: hydrophobic (not hydrophilic)

Page 11 -On the right the membrane is more fluid, on the left it is more rigid.

(not the other way around)