Lecture :..... 14

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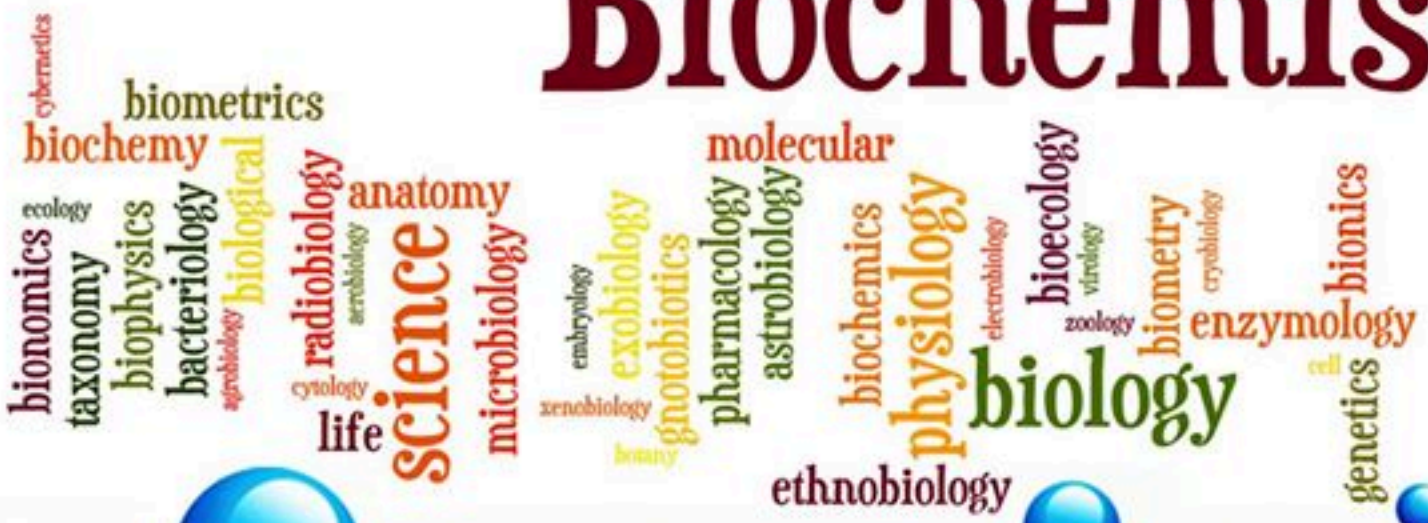
☐ Slide ■ Sheet

Medical Committee
The University of Jordan

Biochemistry



Mousa Suboh

Lipids (2)

Please memorize this sheet with the slides and study the pictures and structures carefully. ☺

***Structures of phospholipids** :

Phospholipids form different structure when they come in contact with water , such as :

- Micelles
- Liposomes
- Membrane bilayer sheet.

❖ Liposomes differ from micelles that *the interior of micelles is hydrophobic , but in liposomes is hydrophilic* .

What is the importance of Liposomes ?

Delivery.

-You can inject a drug in a liposome and mark this liposome , for example by attaching a molecule on its surface to guarantee that the liposome will go to the organ you want to treat.

The liposome then fuses with the plasma membrane of the target cell and empty its cargo.

Sphingophospholipids :

These phospholipids are membrane lipids , their alcohol is **sphingosine**.

What is sphingosine ?

-It is an amino alcohol , containing **one amino group** , **two hydroxyl groups** (diol) and an unsaturated hydrocarbon chain (18 carbon with one double bond).

-It is synthesized in the body from **palmitic acid and serine.**

Ceramides :

They are N-acylsphingosine (acyl means more than two carbons) , a sphingosine molecule that has a fatty acid connected to the amino group that is attached to carbon # 2 of sphingosine, by an **amide bond.**

-It is a component of sphingomyelin, so when you hydrolyze sphingomyelin , you get ceramides.

-Ceramides are important in cell-cell recognition , as in blood typing.

Remember :

In blood typing : we have glycolipid antigens on the RBCs' cell membranes , these are composed of a ceramide

molecule (N-acylsphingosine) that is connected to an oligosaccharide .

The Core oligosaccharide :

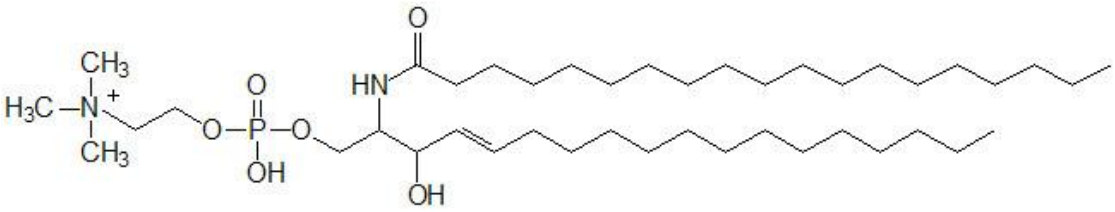
Glu-Gal – N-acetylgalactosamine –Gal- fucose.

- In O type : ceramide + a core oligosaccharide.
- In A type : ceramide + a core oligosaccharide +N-acetylgalactosamine.
- In B type : ceramide + a core oligosaccharide+galactose.

Sphingomyelin:

They are sphingophospholipids that are found in large amounts in brain & nerves.

Composition :



1-Sphingosine is the alcohol.

2-At carbon #1 of sphingosine ,we have the attachment of a *phosphate group* by a phosphoester bond and a *choline* molecule (a nitrogenous base) to that phosphate group .(phosphocholine)

3-At the amino group that is attached to c#2 of sphingosine , there is a long chain fatty acid that is connected to the N atom by an Amide bond. (like in ceramide)

How many nitrogenous bases do we have in sphingomyelin?

Two , the Sphingosine itself (as it is an amino alcohol) and choline.

Glycolipids :

*(they are *Sphingolipids* with a carbohydrate linked to them)

*The alcohol is ***sphingosine*** .

*The lipid part is a long chain fatty acid.

- We have many subclasses . Classification is according to the number & nature of carbohydrate present.

✓ **Cerebrosides :**

*If this glycolipid contains only glucose or galactose molecule as the sugar part , it is named **cerebroside.**

✓ So, We have two types of cerebrosides :

* Glucocerebrosides * Galactocerebrosides

❖ Cerebrosides are found in the myelin sheath of nerves and in the white matter of the brain.

Sulfatides :

They are sulfated galactocerebrosides.

* Galactose is sulfated at carbon # 3.

They are abundant in the myelin sheath.

Gangliosides :

-They are sphingolipids that are connected to an oligosaccharide.

-The sugar part has several sugar & sugaramine residues.

-They are found in the Brain, ganglion cells, & RBCs.

What is important about the ganglioside in the slides (refer to the slides) that galactose is connected to sialic acid .

What is the function of these gangliosides ?

They are receptors for cholera toxin in the human intestine.

Summary :

You have a sphingosine molecule , like the one in the figure, Ok ?

Now , put a fatty acid on the amino group of carbon # 2 ,and :

- A phosphocholine molecule on the OH of carbon # 1 →sphingomyelin
- A glucose or galactose on the OH group of C#1 → cerebroside.
- A Galactose molecule on the OH group of C#1 of sphingosine and a sulfate group on C#3 of galactose → sulfatide.
- An Oligosaccharide with one or more sialic acid → ganglioside.

Lipoproteins:

- What are lipoproteins?

Lipids attached to proteins (which are called apolipoproteins)

-They have irregular shape.

- As the fat content increases:

- The density decreases as lipids are light.
- the diameter increases because lipids can't be tightly packed as proteins

Increasing the lipid content →increasing the diameter→decreasing the density →more dangerous and vice versa.

- Chylomicrons are the most dangerous as they contain 99% lipids and 1% proteins.
- HDL are good for health as they have large amount of proteins. (50% lipids .50% proteins)

What is the function of lipoproteins?

Transport of different types of lipids in blood plasma

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We talked about simple lipids, compound lipids and today we are going to talk about cyclic lipids ☺

*Cyclic lipids (Steroids):

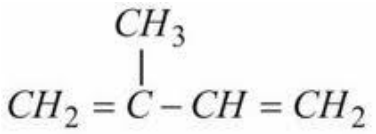
Examples: Cholesterol, bile salts, and steroid hormones.

*All these compounds share a general structure.

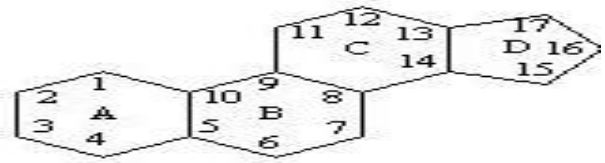
Structure:

1-They have four fused rings with certain connections. These rings are: three 6-membered rings with one 5-membered ring (notice the two methyl groups at carbons # 10 and # 13 of the rings and an -OH group on carbon #3) .Any additions on the structure participate in the naming and the function of these molecules.

2-They are derived from the precursor "isoprene unit" (which is important in synthesis of vitamins as we will discuss thoroughly)



3-This is their nucleus after cyclization:



Steroid nucleus

*The most common steroid: cholesterol

STEROIDS:

*What are steroids?

They are group of cyclic lipids

*Structure: three 6-membered rings and a 5-membered ring with –OH group on carbon #3

*they exist usually with fats and oils (either in membranes or not)

*they are derivatives of cholesterol

Types of steroids:

A- Sterols : most common steroids (and cholesterol is one of them)

B- Adrenal cortical hormones

C- Male and female sex hormones :

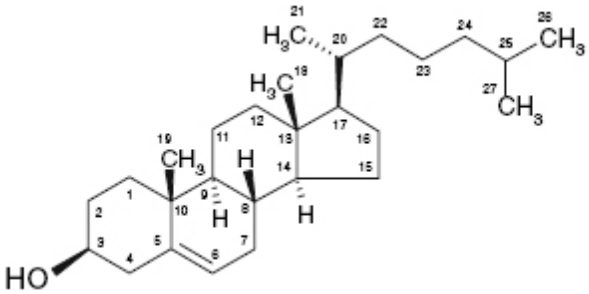
- ❖ Androgens: male 2º sex characteristics
- ❖ Estrogens: female 2º sex characteristics & control of menstrual cycle.
- ❖ Estradiol ,progesterone and testosterone

D- Vitamin D group and its subtypes.

E- Bile acids which are responsible for emulsification of fats within the GI tract.

Cholesterol:

Free Cholesterol

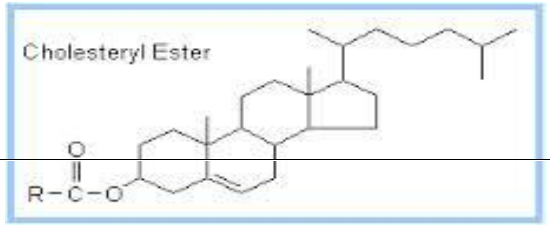


-It is the most important and common ***sterol*** in animal tissues.

-Cholesterol is found in to states:

-Either as **free alcohol** (i.e. at carbon number 3 of the first ring we have a hydroxyl group) and it is called **Free cholesterol**

-OR **esterified** to fatty acid on carbon number 3 "when



hydroxyl group does not exist and a fatty acid links instead of it "(e.g. linoleic, oleic, palmitic)

and we call it **cholesteryl ester .**

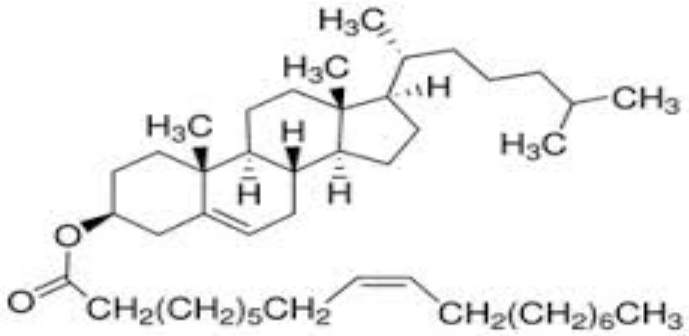
SO , what is the cholesteryl ester ?

Cholesterol esterified at carbon number 3 "no hydroxyl group"

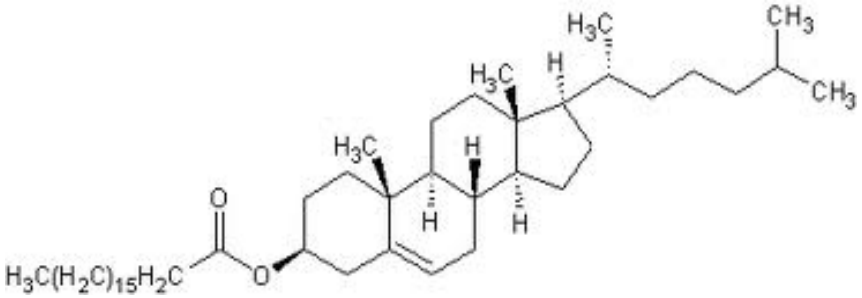
Naming of cholesteryl ester

*According to the fatty acid that is linked to C3 of the four fused rings we name the compounds.

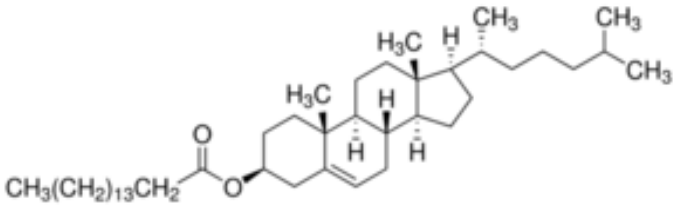
** Cholesteryl oleate (18 carbon units with one double bond)



**cholesteryl strearate(18 carbon units with no double bond)



**cholesteryl palmitate(16 carbon units ,no double bond)



***Does cholesterol exist in plants or prokaryotes?**

No , they are only found in animal cells .

***What is the advantage of cholesterols in membranes** ?

Stabilization of interactions in the membrane though the hydrophobic interactions and the Van Der Waal forces .

***So, do cholesterols increase fluidity of membrane or decrease it ?**

It depends *"we are going to see how later "*

Sources of cholesterol :

1- Synthesized in the body from Acetyl CoA (Co enzyme A +acetyl group "two carbon units")

2- From diet : butter, milk, egg yolk, brain, meat & animal fat (all are animal sources)

→ in plants we have another type of sterols(Phytosterols) but not cholesterol.

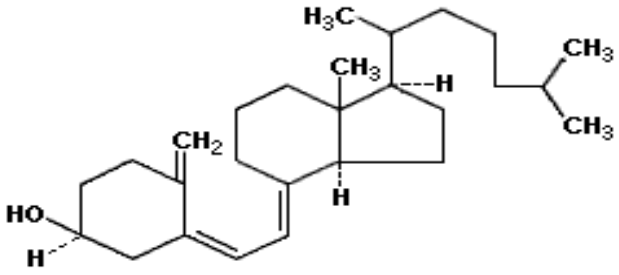
Products of cholesterol :

1- *Sex hormones*: (androgens , estrogens and progestines(like : testosterone, Estradiol and progesterone)

→ *These hormones have the same 4 fused rings*

2- *Certain fat-soluble vitamins* : (A,D,E & K) they are isoprene derivatives.

→ *isoprene unit : the precursor of the steroids*



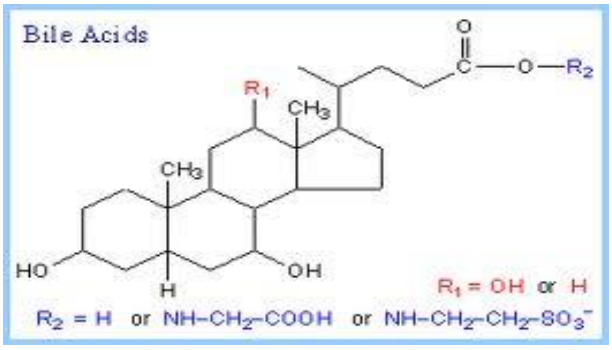
Vitamin D_3

3- ***Bile acids*** : derivatives of cholesterol

*they all share the same 4 fused rings structure with some modifications.

Look to the figure to the right :

*R_1 AND R_2 are different



EICOSANOIDS (ICOSANOIDS):

They have 20 carbon units (eico) and they are *signalling molecules .*

-Made by oxidation of essential polyunsaturated fatty acids (PUFA) that have 20 carbons.

→essential means can't be synthesized in your body .

- The most common one is **Arachidonic acid** "from where we synthesize prostaglandins , prostacyclins and thromboxane and leukotrienes .
- Other fatty acids that can be oxidized to give Eicosanoids : omega-3 and omega-6 fatty acids

**Eicosanoids act as paracrine or autocrine messengers .

**Their half life is from 10sec to 5 min according to the function .

Families of eicosanoids:

Prostaglandins ,Prostacyclins ,Thromboxanes ,Lipoxins and Leukotrienes

Function of Eicosanoids:

1-induction of inflammation

2-mediation of pain signalling.

3-induction of fever (increase in the Temp of the body)

4-smooth muscle contraction

5-smooth muscle relaxation

6-Protection of stomach lining (ulcers in the wall of GI)

7- Stimulation or inhibition of platelet aggregation

8-sodium and water retention

Eicosanoids are divided into types and under each type there are subtypes, so according to the type they do their function (contraction or relaxation, stimulation or inhibition)

For example ,we have several types of prostaglandins: A2, I2, and H2.

So *each one has a certain function* , some may do inhibition and others may do stimulation ,depending on the environment, mediators ,activators and inhibitors in a certain situation ,affecting doing this action or the opposite action.

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- As one of the functions of eicosanoids is to induce inflammation, let's understand how anti inflammatory drugs work.

Anti-inflammatory drugs:

Their function is to inhibit eicosanoids synthesis.

There are two types:

1- Steroids
2- Non Steroidal Anti Inflammatory Drugs.

Let's talk about steroids first. ☺

How do steroids inhibit inflammation?

1) Inflammation process is caused by eicosanoids which are derived from Arachidonic acid
2) Arachicidonic acid is produced from the membrane lipids through the phospholipase A2 enzyme
3) Steroids inhibit phospholipase A2 enzyme action.
4) No Arachidonic acid is produced from the membrane→No metabolism occurs on it → No derivatives of Arachidonic acid are synthesized.
5) Inflammation is inhibited.

❖ Arachidonic acid is converted into Eicosanoids either by:

1-**lipoxygenase** ---give---> leukotrienes which have a relation with WBCs (leukocytes)

2-**cyclo-oxygenase**--give---> prostaglandins and thromboxane →which are mediators of pain

→Preventing the synthesis of these mediators = No pain

2-NSAIDs: Non Steroidal Anti Inflammatory Drugs

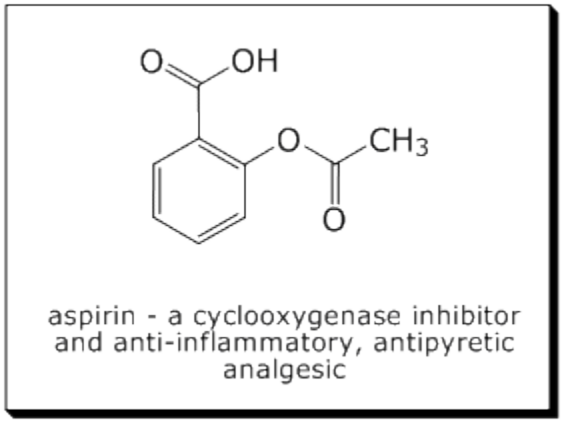
They do the same function of steroids, however they aren't steroids. Also, they have a different mechanism.

→*Analgesics* (المسكنات) *which have side effects on stomach are NSAIDs*

- → ***Examples of NSAIDS :***

_Aspirin, profen (or Brufen), Voltaren.

NOW let's understand **how Aspirin inhibits cyclo-oxygenase enzyme and works as NSAIDS?**

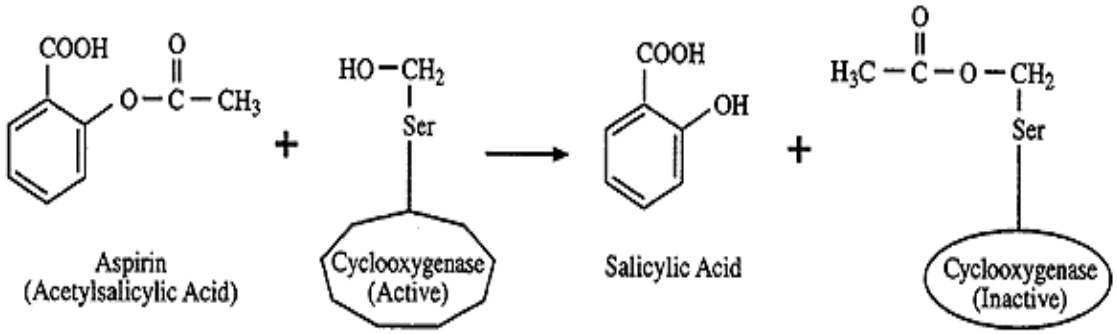


aspirin - a cyclooxygenase inhibitor and anti-inflammatory, antipyretic analgesic

--Aspirin (Acetylsalicylate) has acetyl group "two carbon units" that interacts with the active site of cyclo-oxygenase enzyme giving the enzyme its acetyl group.

--This acetyl group attaches to certain serine residue (now aspirin is salicylic acid without the acetyl group and serine is attached to the acetyl group via the oxygen of its OH group)

-In this way cyclo-oxygenase is inactivated, so no prostaglandins or thromboxanes are produced , and inflammation is relieved .

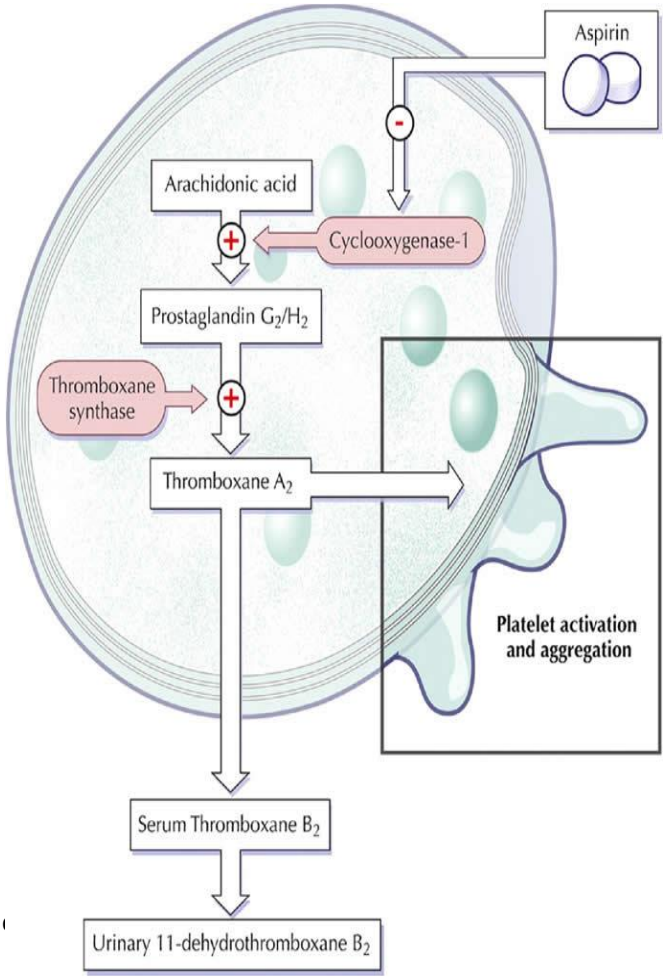


Aspirin is prescribed for patients who suffer from coagulations , or people who have clogged arteries that are treated by putting nets to keep them open , and as blood coagulates on any foreign substance , they prevent it from clotting by taking Aspirin regularly.

why ?!

-Thromboxane A2 responsible for platelet activation and aggregation,

SO, if you give the patient Aspirin, which inhibits the cyclo-oxygenase pathway (prostaglandins and thromboxane synthesis), it will prevent thromboxane A2 (TXA2) generation and there



will be No platelet aggregation.

-Also , Aspirin stops fever and pain by blocking COX enzyme and preventing synthesis of prostaglandin H2 ,which mediates fever and pain.

Specifically:

1. prostaglandin H2 is responsible for fever induction
2. Thromboxane A2 is responsible for platelet activation and aggregation,

COX enzymes:

There are two types COX-1 and COX-2.

*Anti inflammatory drugs inhibit both.

*Inhibition of COX-2 is desirable because COX-2 gives the mediators of Inflammation.

So, inhibition to COX-2 ---> inhibits the Inflammation process.

>>WHILE inhibition of COX-1 is undesirable because it is found in the GI tract, Renal tract and it is important

Good point :

(COX-1) is known to be present in most tissues. In the gastrointestinal tract, COX-1 maintains the normal lining of the stomach. The enzyme is also involved in kidney and platelet function. (COX-2) is primarily present at sites of inflammation.

in platelet function and Macrophage differentiation.

- So , If you take analgesics ,you must eat before taking them. Also, too much analgesics even when your stomach is filled will cause many problems like ulcers. Why ?

-Because these drugs don't differentiate between COX-1 and COX-2 enzymes , and by the inhibition of COX-1 enzyme ,there will be many side effects like ulcers, as COX-1 enzyme is responsible for the protection of stomach lining and the previous mentioned functions.

✓ CELEBREX

*There are drugs that inhibit COX-2 only, like CELEBREX which is very specific. But be careful as it has many side effects and you must be aware of the patient's status. Especially patients with cardiovascular problems.

- Celebrex is also NSAID.
- Celebrex may cause life-threatening heart or circulation problems such as heart attack or stroke.
- What is good about Celebrex that it doesn't affect the stomach.

-

CELL MEMBRANES:

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

-45% LIPIDS, 45%PROTEINS and 10% CARBOHYDRATES.

- Molecules are distributed according to **size and function**.

-The surface from the outside is larger than from the inside, so the bulkier molecules are to the outside .So, the lipid bilayer is not symmetrical.

*__According to function__:

*Molecules which work in recognizing other structures or binding cells to other structures are distributed to the outside, WHILE molecules which are responsible for signaling and sending messages are to the inner side of the membrane.

That's why glycoproteins are to the outside of the membrane as they are responsible for cell -cell recognition.

-Cholesterols are distributed to the both leaflets, mostly to the outer layer.

-Inositides are found at the inner surface of the membrane because they work as second messengers

- *The membrane is a semi-solid structure.

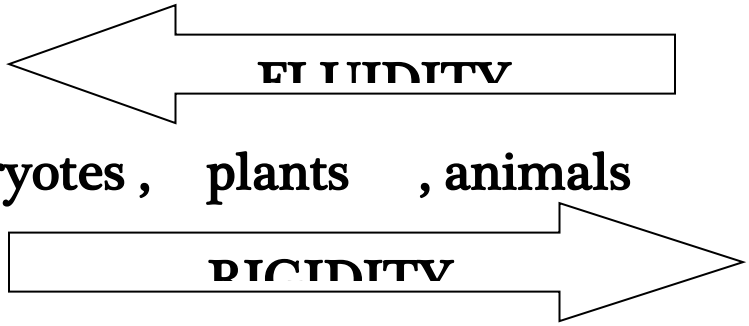
What affects the fluidity of the membrane??

1-Cholestrol content.

2- Fatty acids content .

(Unsaturated-->more fluid --> less rigid)

(Saturated-->less fluid --> more rigid)



Why are the animal cells the most rigid?

1-Because they have more saturated fatty acids

2-Presence of cholesterol, which exists only in animal cell membranes.

- **How does cholesterol work?**

It is found between the long chains of fatty acids ..setting between them and interacting with them via Van Der Waals

and hydrophobic interactions and that's how it stabilizes the membrane.

- **Cholesterol makes the membrane less solid at low temperature and more solid at high temperature , HOW ?**

--At low temperature ,phospholipids tend to pack , but due to the presence of cholesterol , this packing is prevented ,so the fluidity of the membrane increases and the membrane does not solidify.

-**But when the temperature increases** , the fluidity of the membrane increases , so cholesterol helps in the packing of phospholipids via the interactions, making the membrane more solid.

- Membranes have a melting point (either for each molecule or for the whole membrane) : the point at which they become fluid due to the increase in the kinetic energy .

--More kinetic energy will break the bonds , which become elongated and damaged "hydrogen bonding , hydrophobic interactions and Van Der Waals " , so the membrane will be less packed and the hydrophobic tails will be distorted .

Types of membrane proteins :

There are 3 types :

1- **Peripheral proteins** : on the outer surface of the membrane.
2- **Integral membrane proteins** :either spanning the membrane or part of it.
3- **Lipid anchored** : anchored to the membrane via a lipid group .

❖ **peripheral proteins**:

- Peripheral proteins are usually attached to integral proteins .
- They are not strongly bound to the membrane (not covalently bound to it) ,
- We can easily remove them from the membrane without disrupting the membrane *BY Mild detergents*

❖ **Integral proteins :**

-We can't get them without breaking the membrane because they are strongly bound to it.

--Membrane integral domains are

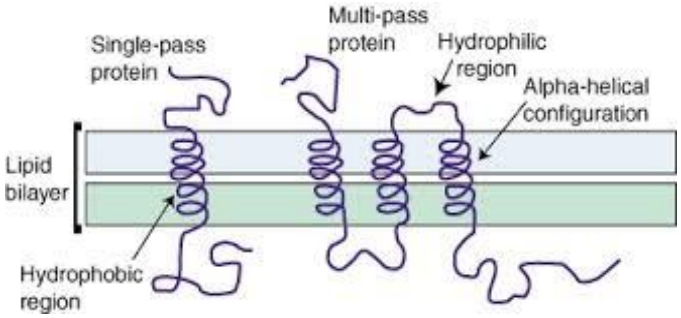
Either α-helix or β sheets

- When we have a channel , it is usually composed of amphipathic α helices . (I.e. that the hydrophilic amino acids (polar)are directed inward to the pore of the channel, while hydrophobic amino acids are facing the membrane phospholipids.

-Also , these proteins may be:

1- **single-pass proteins:**

They have a part that is hydrophilic that is exposed to the cytoplasm or to the ECM. And a hydrophobic region which is anchored in the membrane … if it was a channel ,only the outer part is hydrophobic.



2-**Multi-pass proteins.**

Which inter and exit the membrane at many different points . (Notice the figure to the right)

❖ **Lipid anchored proteins :**

Proteins are anchored in the membrane through lipids. The attachment is covalent.

-**<u>They are 4 types</u> :**

1- Amide-linked myristoyl anchors :

they form ***amide bond* with *myristic acid* (14 carbons) *<u>only</u>* .

2- Thioester-linked fatty acyl anchors :

**They make connection through thioester bond " which contains sulfur" with a fatty acid that could be one of the following : myristic acid , palmitic acid ,stearic acid and oleic acid

3- Thioether-linked prenyl anchors :
**Prenylation refers to linking of "isoprene"-based groups (which is the precursor of cholesterol).

4- Glycosylphosphatidyl inositol anchors :
**When you have an oligosaccharide that is

✓ linked to a protein via ethanolamine at one side

✓ And to a phosphatidylinositol via inositol (which is a 6-membered ring with –OH on each carbon) by a glycosidic linkage on the other side .

❖ In other words , the protein is connected to a glycolipid via ethanolamine , and the two fatty acids within the hydrophobic phosphatidyl-inositol group anchor the protein to the cell membrane.

Structure- functions of the membrane :

- -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

❖ Proteins that are peripheral can act as enzymes .

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Lipid-associating substances (Vitamins)

What are vitamins ?

They must be organic compounds that are needed in very small amounts and can't be synthesized in the body to call them vitamins.

-Fat-soluble vitamins -(A,E,D & K) ,which are obtained from cholesteryl esters found in food.

-- If the amount of a vitamin is very high , it will cause hypervitaminosis ……. How this occur ??

1-By taking too much vitamins

2-Because of a great loss of fats, due to a harsh diet or a surgery. So, fat-soluble vitamins are released to the blood causing hypervitaminosis, which may lead to toxic symptoms.

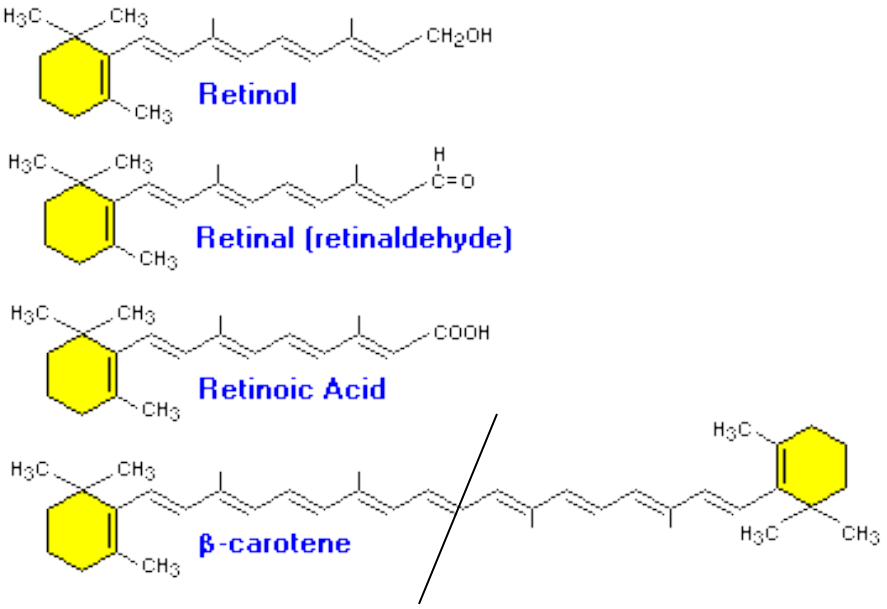
VITAMIN A:

-You can get it from Many sources (like cholesteryl esters or supplements) , *but mainly from β-carotene* that is found in vegetables and fruits that are red , yellow and orange in color.

- β-carotene is mainly found in carrots.

Notice in the figure to the right :

-β-carotene molecule can be broken into two identical molecules /halves by oxidation.



- β-carotene is composed of two retinal molecules that are linked together (look to the dividing line in the figure)

-So, every β-carotene molecule is broken down by oxidation, and two Retinol molecules are produced (alcoholic form),which are further oxidized to aldehyde (retinal) and then to acidic form "Retinoic acid "

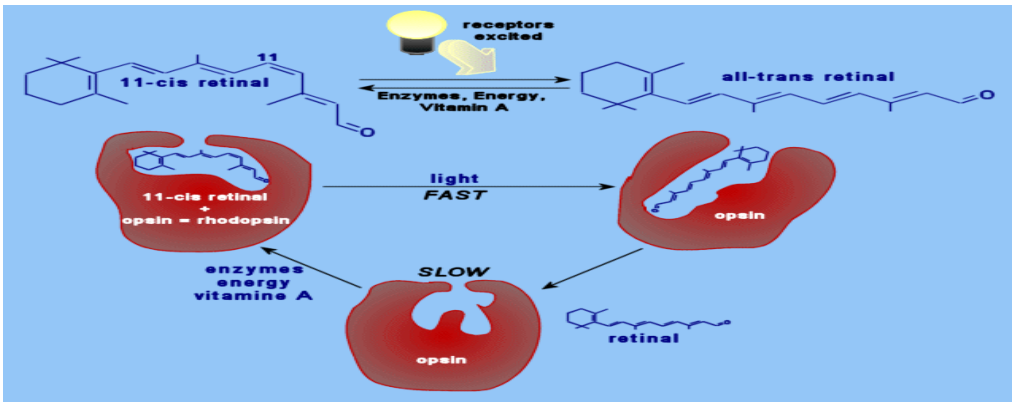
- Each form is important and has a certain function .

β-carotene ----$_{oxidation}$-----> 2 Retinol ----$_{oxidation}$----->2Retinal----$_{oxidation}$----->2 Retinoic acid

What is the importance of vitamin A ?

1- Important for vision , spermatogenesis and growth.
2- Without it , Males will be sterile , and the growth is impaired , especially the growth of skin and its appendages .

❖Process of vision:



1) The retinal that is found in the eye cells is *11- cis retinal* (just cis at one bond between C#11 & 12) is bound to a protein called *Opsin* (a protein that is important in the process of vision)
   And their binding produces *Rhodopsin* .
2) In the presence of light,11- cis retinal is converted in to all – trans retinal , which has a higher affinity to the protein Opsin .

3) When the light disappears , all – trans retinal return to ordinary retinal form.
4) By enzymatic processes , ordinary retinal is converted to *11- cis retinal* ,and the affinity decreases and it detaches from the protein .
5) By this way , a message to the brain is delivered that you see something .

- So , all -trans retinal high affinity to Opsin , but 11- cis retinal has low affinity .
- Light causes the isomerization between all- trans retinal and 11- cis retinal.

- The outer segment of rod cells contains flat membrane enclosed discs, the membrane consisting of about 60% Rhodopsin and 40% lipid.

.....

VITAMIN D :

-**Sources**: from skin and dietary intake (fish, meat and supplements)

-Function:

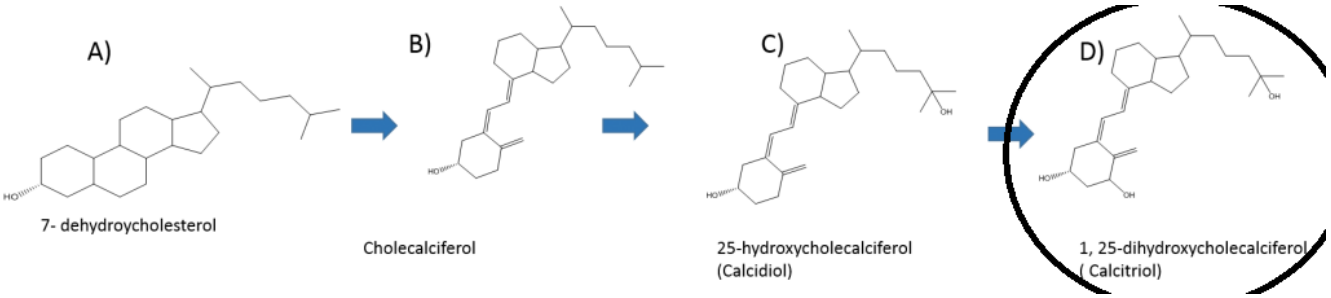
- It is responsible for mineralization of bones and teeth.

-Increases synthesis of ca^{2+} _binding proteins. So, it will increase the absorption of ca^{2+} from intestines and its reabsorption from kidneys (reduces excretion of ca^{2+} by kidneys)

وهنا الدكتور زهق حاله ... وكاتب الشيت عاف حاله والمصحح كمان مات ...
الله يعينكم كملوا كملوا .وعيد سعيد بالمناسبة ^_^

❖ **How it is synthesized?**

1- *7-dehydrocholesterol* exists in skin ,by sunlight (Ultraviolet) ,it it converted to cholecalciferol (vitamin D_3) ***Notice in the figure below***
Some rings of *7-dehydrocholesterol* are opened.



2- Then it goes to the liver where the first hydroxylation occurs at carbon#25 (the last one) via 25-hydroxylase enzyme
3- Then , 25-hydroxy vitamin D_3 goes to kidney where the second hydroxylation takes place at carbon number 1

via 1-hydroxylase enzyme to produce 1,25-dihydroxy vitamin D_3 , or 1,25-dihydroxy cholecalciferol (active form) .

4- Generally ,it has –OH group on carbon # 3 , because it is synthesized from *dehydrocholesterol* .

❖ The active form is responsible for maintaining calcium in the body. (the circled one in the figure)

Note :

-Vitamin D is found in plants (D2) and animals (D3)

-All these forms must be converted to 1, 25-dihydroxy cholecalciferol to be active.

VITAMIN E :

-A group of molecules (called tocopherols)
-α-tocopherol is the most active.
A good reducing agent & an antioxidant (it reacts with oxidizing agents before they can attack other bimolecules)

How does it work as an antioxidant?
It gives the free radical the electron it needs , and they become radicals … but they have a way to deal with their radicals.

****Please look to the figures in the slides.

****

VITAMIN K :

This bicyclic ring system contains two carbonyl groups & a long unsaturated hydrocarbon side chain that consists of repeating ***isoprene Units.***

Types:

*K1--> found in animals.

*K2-->in plants.

*K3-->synthetic one.

***Please look to the figures in the slides.

Bio-function of vitamin K:

Vitamin K is essential for blood clotting .*How is that?*

- In order for a clot to form, we need clotting factors, calcium and vitamin K.
- Vitamin k is important in the carboxylation of glutamate residues that are found in clotting factors/ proteins , like prothrombin , to convert it to γ carboxy glutamate (which has two carboxylic groups on γ carbon)

-The two carboxyl groups bind Ca^{2+} ion to form a bidentate ("two teeth") ligand, which is required for blood clotting. ****Please look to the figures in the slides.

- Without vitamin K → No carboxylation → No bidentate molecule → no clotting.

Good Luck studying this sheet ☺