Doctor 022

Biochemistry

Sheet no. 9

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Lipids

We can define lipids as molecules that are water insoluble in a very wide definition because many differences exist among lipids.

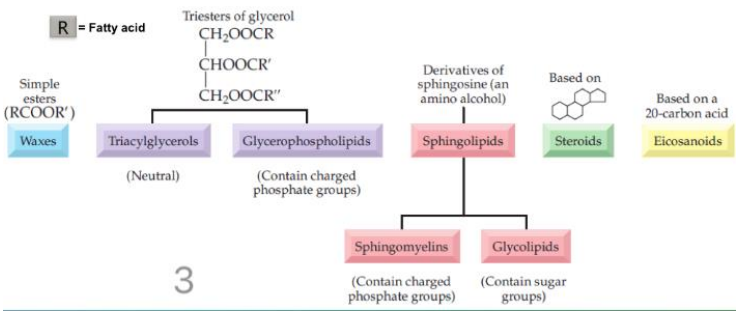
Lipids are a heterogeneous class of naturally occurring organic compounds that share some properties based on structural similarities, mainly a dominance of nonpolar groups.

Lipids molecules generally are water insoluble, but when we look at there structure we can see that many of them are not completely nonpolar. Also, we can see some groups that have polar bonds but their number is small compared to the overall structure so the effect of polar groups will be small that's why we consider their overall structure to be water insoluble .
We classify lipids as amphipathic molecule (they have 2 sides :polar side -smaller- and Nonpolar side -larger-)

***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 of lipids

1)Simple lipids (fats, oils, and waxes)
The difference between oil and fats that oil in liquid state but fats in solid state.They're mixtures of triacylglycerols.
2)Complex lipids (glycerides , glycerophospholipids, sphingolipids, glycolipids, lipoproteins) membrane lipids
3)Derived lipids (fatty acids, alcohols, eicosanoids)
4)Cyclic lipids (steroids) 4 fused rings ,derived from cholesterol.



Triacylglycerols : 3 fatty acids linked to a glycerol molecule

Eicosanoids : a molecule that can mediate inflammatory responses or reactions (inflammation not infection).

A concise explanation of the difference between them (will be explained further in Metabolism) :

***Infection refers to the invasion and multiplication of bacteria or viruses within the body, while inflammation is the body's protective response against infection**

Lipids functions:

One of the most important functions of lipids that they act as a major storage site of energy. Carbohydrates are the major and the first source of energy, so as long as you have sugars in your body you will not use lipids as a source. So lipids are the storage sites of energy but can be used as a source in some cases like fasting or starvation that the body may depend on lipids as a source of energy . Carbohydrates can be stored also but in a very little amount ex. (glycogen).

Let's take an example If someone's weight is 70 kgs and his weight is commensurate with his height, out of these 70 kgs ,the amount of stored lipids is not less than 15kgs. On the other hand, the amount of stored carbohydrates(sugar) may not exceed 0.5 kg. That's why when glycogen is broken down it can last maximally for 12-13 hours, unlike lipids that can last for much longer time.

Why do we use lipids to store energy ?
In addition to its large amounts in the body, there are some other reasons such as :

1) **Lipids don't attract water molecules so water molecules aren't stored along with them.So if the amount of energy stored in the 15 kgs fat- that was mentioned in the previous example- were stored in carbohydrates then our body's volume would be way higher because of the water stored along.**

2) **The amount of energy stored is higher. If we take 1g lipid and 1 g carbohydrates and we want to compare the energy stored in both, carbohydrates will have 4 kcal but lipids will have 9kcal of energy.**

*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)

Phospholipids,sphingolipids and cholesterol are found in membranes, they contribute to the spatial compartmentalization and separation between different structures in the body which is related to regulation of different functions and reactions etc.

*Precursors of hormones and vitamins

1.Lipids can work as hormones and signaling molecules such as sex hormones, Cortisol (a steroid hormone derived from cholesterol and secreted in the state of stress), Aldosterone, ADH etc.
2.Precursors of hormones and vitamins (raw materials that are incorporated in the synthesis of vitamins and hormones). The major vitamin that's synthesized in that way is "Vitamin D" which is made of cholesterol. Generally, many vitamins aren't synthesized through biological pathways in the body and are obtained from the diet, but some vitamins like "D" and "K" are produced in the body.

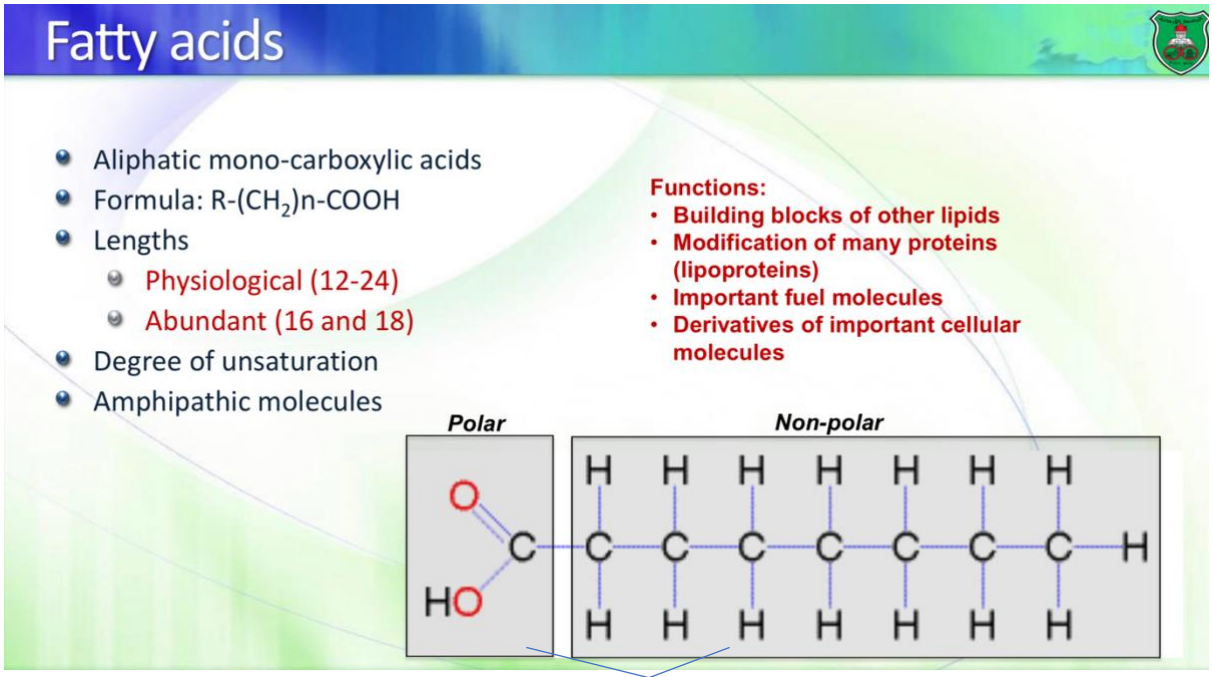
*Shock absorbers and thermal insulators.

Thermal Insulators: Regulate and preserve the body's temperature as lipids make it difficult to lose our body's temperature in addition to its role in thermal regulation.

Shock absorption: Protection of organs, especially superficial ones like the kidneys.Be aware that all of the organs have lipids as a wrapping but the percentage of fat on superficial organs is much higher than organs that are protected with other structures like the heart and the lungs that are protected with the thoracic cage which gives a higher protection than fats. But if the percentage of lipids on internal organs increase, visceral fat will increase which will induce what is known as the belly fat.

Fatty acids (A Class of Lipid Molecule)

Fatty acid in organic chemistry: carboxylic acid with long hydrocarbon chain -Most of them have an even number of carbons (عدد زوجي) but some of them may have odd number of carbons (minority).

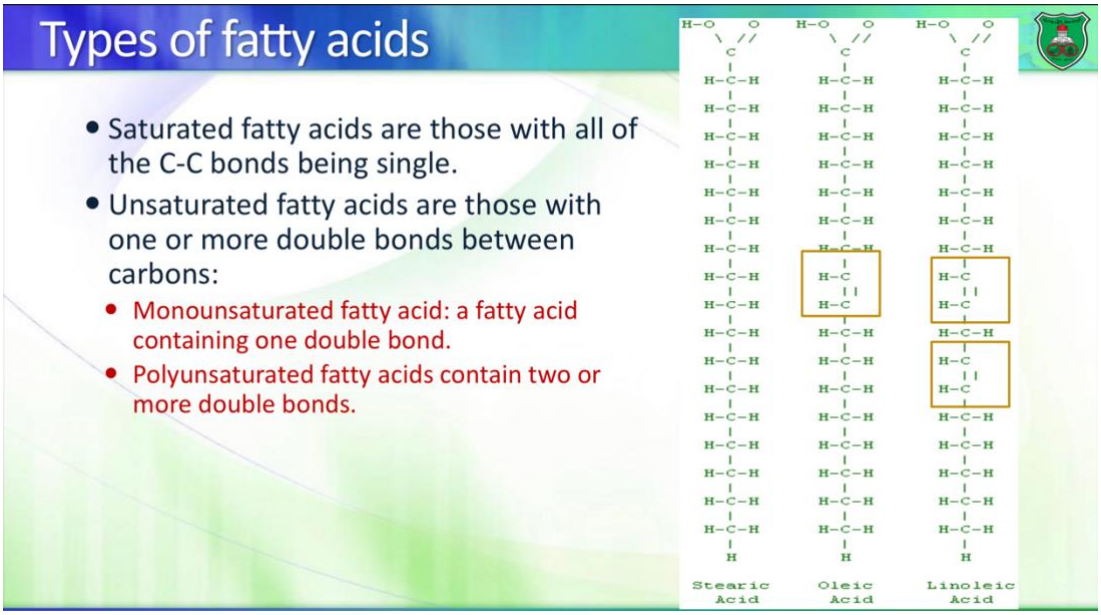


**Notice that the non polar side (hydrocarbon) is greater than the polar side (carboxyl group) but it's a very small part so it's considered an insoluble molecule .

Fatty acid has many functions:

1) **Major constituent of phospholipids, sphingolipids, triacylglycerols (the storage form of lipid molecules). Ex. In adipocytes there's a large fat droplet which pushes the nucleus to the periphery and that droplet is triacylglycerol)**
2) **We can use them as a source of energy in starvation and fasting that are the stores in the fatty tissue and those triacylglycerols are broken down to get the fatty acids and then they get oxidized to get acetyl CoA and get energy.**
3) **Form inflammatory mediators (eicosanoids) which are made of arachidonic acid.**
4) **Components of glycoproteins and many other molecules.**

Types of fatty acids

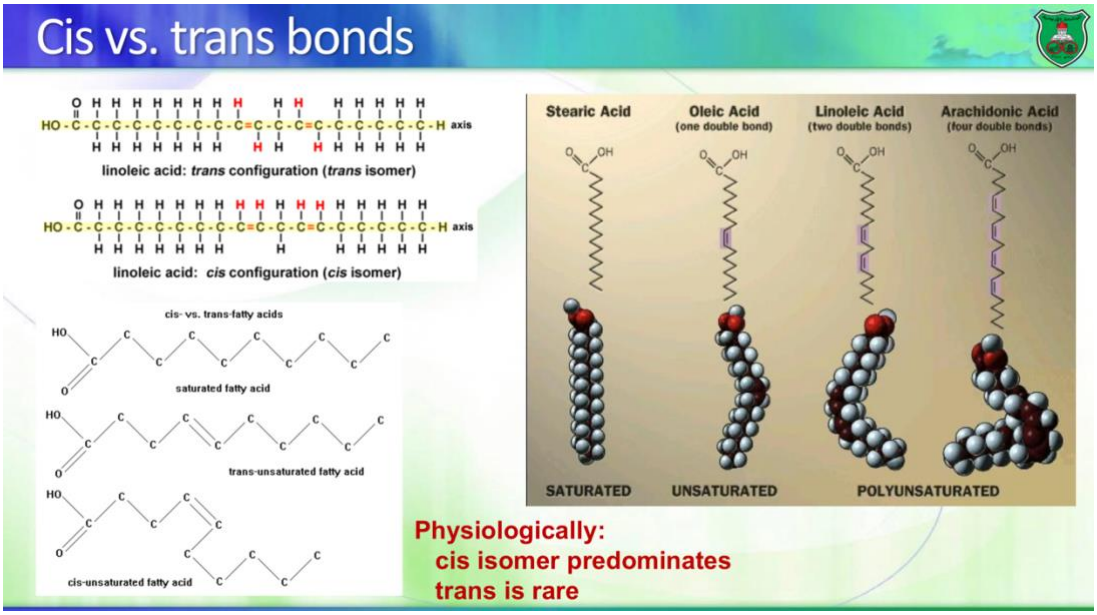


What are the effects of the double bonds on the structure (unsaturated) ?

They <u>change the shape</u> of the molecule " بتطعجه". The hydrogen atoms attached to the carbons that make a double bond may be in cis(hydrogens are on the same direction) or trans(hydrogens are on opposite directions) configuration. If it is cis, it will change the shape of the molecule and kinks will appear so it will give more space for the hydrogens and they will have more than 180 degrees to be found in that's why they take more space and give more a stable structure. On the other hand, if it's trans, it will not kink

(bend) because hydrogens are already in different sides ,trans is similar to saturated fatty acid so there's no need for kinks.

***Cis is a predominant form that means that the majority of fatty acids that have double bonds exhibit the cis configuration and they will be in the liquid form. Trans is rare.**



What are the factors that affect the melting, boiling point and physical properties of fatty acids ?

1) **The existence or absence of double bonds (Saturation)**
2) **The number of double bonds : as the number of double bonds increases,the melting point decreases.**
3) **Number of carbons: as the number of carbons increases, the melting point increases because we have more noncovelant interactions**

-Lipid composition of membranes change. Ex.Fluid mosaic model: the fluidity of membranes is due to their lipid components, formation of vesicles include the outer leaflet(larger) and the inner so the composition of phospholipids change accordingly, also the changes that help cells to move from one site to another is an effect of having lipids in their membranes.

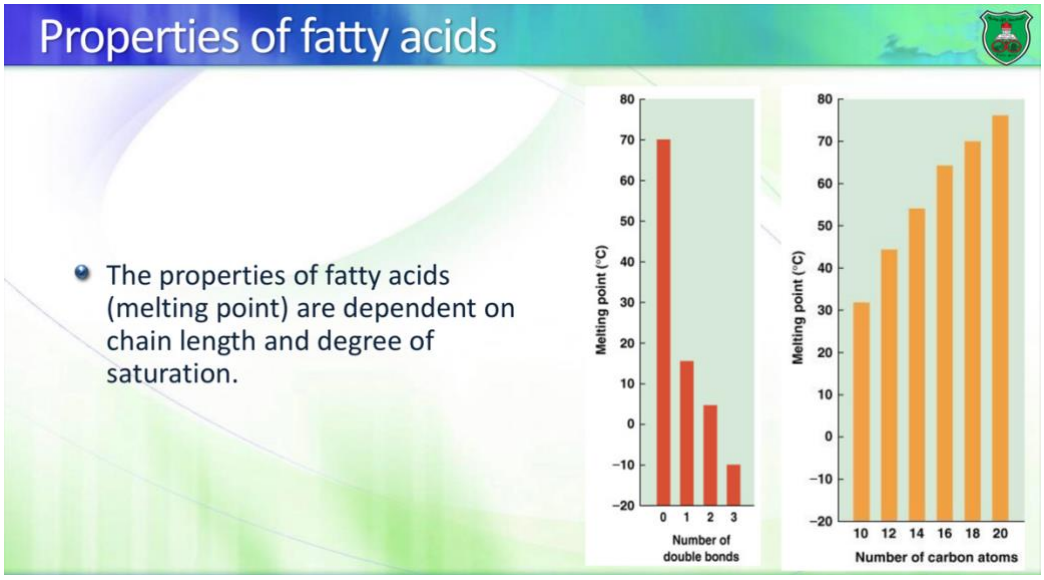
ذو العَقلِ يَشقى في النَعيمِ بِعَقلِهِ	وَأَخو الجَهالَةِ في الشَقاوَةِ يَنعَمُ

The more the kinks are, the greater the thickness becomes and that affects the composition.So in the outer leaflet, thick phospholipids are present and thin ones are in the inner leaflet.

Thick —> Fluid

Thin —> Rigid

-The presence of kinks in an unsaturated molecule(cis) changes the shape of the molecule in a way that makes the atoms away from each other. Thus,they won't be able to make many non covalent interactions so when we want to boil it or melt it we will need lower heat because the number of non covalent interactions is low so they can get broken easily with the consumption of much lower energy.So, the melting and boiling point for unsaturated molecules(cis) are lower. On the other hand, in saturated molecules or the trans form of unsaturated molecules, compaction can occur that they can be very close to each other and can form a very huge number of non covalent interactions , that's why they need more energy to be broken and their melting and boiling point will be higher.
***Although, Trans unsaturated fatty acid's melting point is higher than cis fatty scids but it's lower than saturated ones.**



Important result : The more the kinks are (that arise because of the double bonds) the less the packing (compactness) is, which in turn decreases the physical properties (melting point and boiling point) because it decreases the non-covalent interactions.

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

No. of carbon > 20 : very long chain fatty acid (VLCFA) , solid state at room temperature and the effect of the carboxylic acid is very low so it's water insoluble.

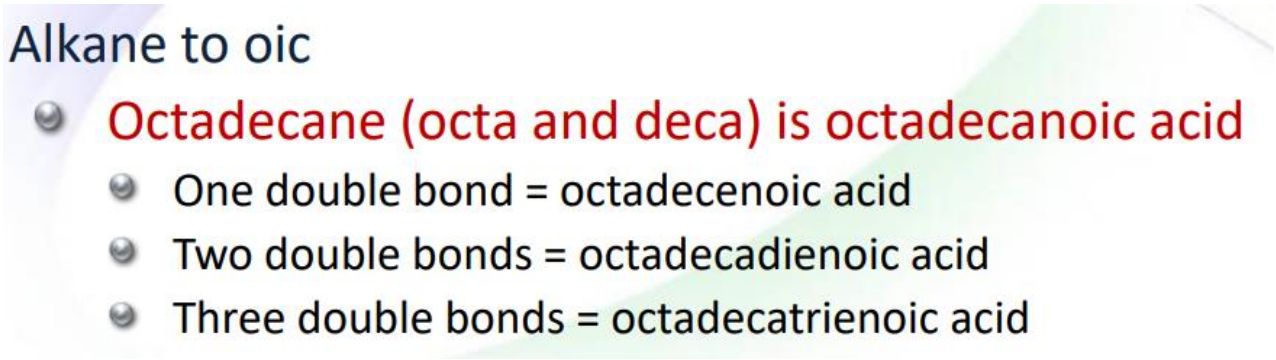
Medium chain is found mainly in the maternal milk , it's solid at room temperature .However, the carboxylic group's effect is still obvious so this in turn makes medium fatty acids water soluble (they require no carriers to move in the bloodstream as they can move on their own since they are water soluble)

The most common ones are long chain F.A. especially (16 and 18)

** **Naming of a fatty acid**:(IUPAC and common)

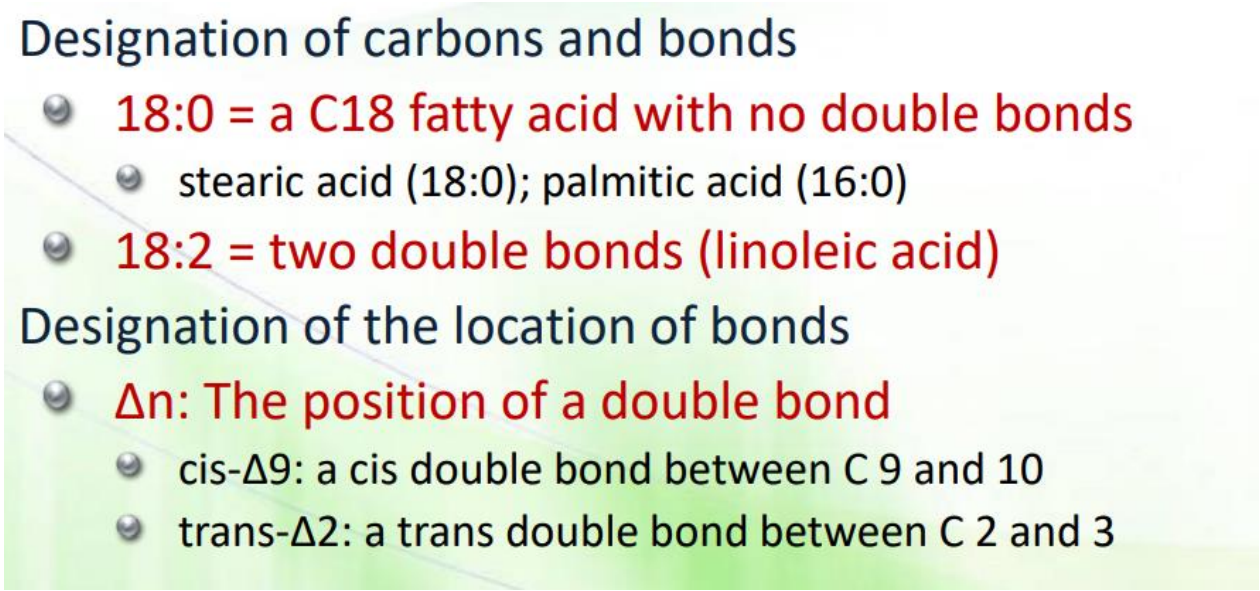
Number	prefix	Number	prefix	Number	prefix
1	Mono-	5	Penta-	9	Nona-
2	Di-	6	Hexa-	10	Deca-
3	Tri-	7	Hepta-	20	Eico-
4	Tetra-	8	Octa-		

When talking about the number of carbons: very similar to organic chemistry (with differences in the first four numbers only)



This IUPAC name (like octadecenoic acid for example) explains the no. of carbons (18 in the mentioned example) and the no. of double bonds (1 in the mentioned example) , (octadecanoic acid for example indicates that we don't have a double bond in the hydrocarbon chain).
(Δ $specifies\ the\ position\ of\ the\ double\ bond$, counted from the carboxylic group side, carbon no.1 is the one in the carbonyl group) for example : a double bond between c9 and c10 is written as $\Delta 9$

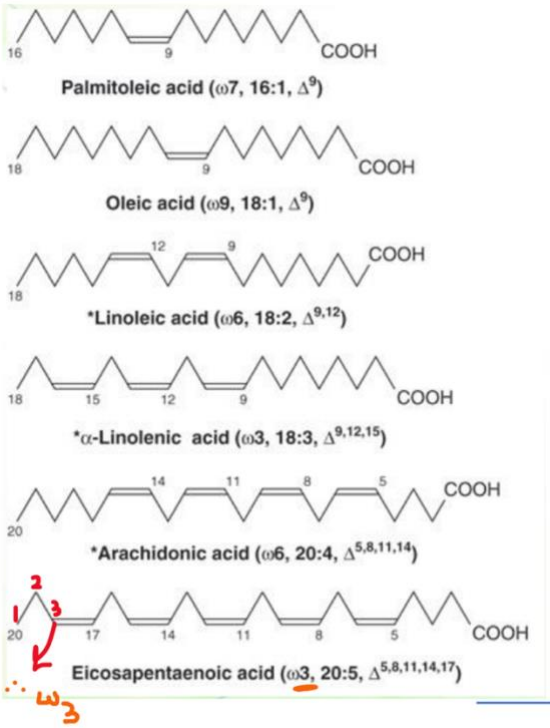
Another example: if we have a double bond between c9 and c10 and another double bond between c12 and c13 , this will be written as: $\Delta 9, 12$



We can also use cis and trans notation for naming.

 # Cis is more abundant in our examples .

**** we need to memorize some common names and know the no. of carbons and double bonds .**



**Arachidonic acid is used in eicosanoids synthesis , it contains 20 carbons and 4 double bonds.

** linoleic and linolenic aren't synthesizable by human bodies , so we consider them to be essential fatty acids because they are obtained from food.

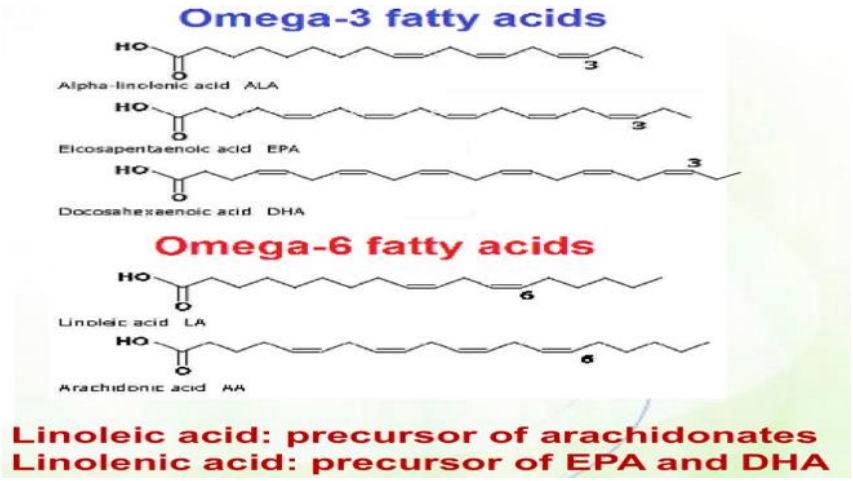
** another classification of fatty acids is dependent on the first double bond from the other side of the carboxyl group(note that this classification doesn't depend on the number of double bonds in the chain).

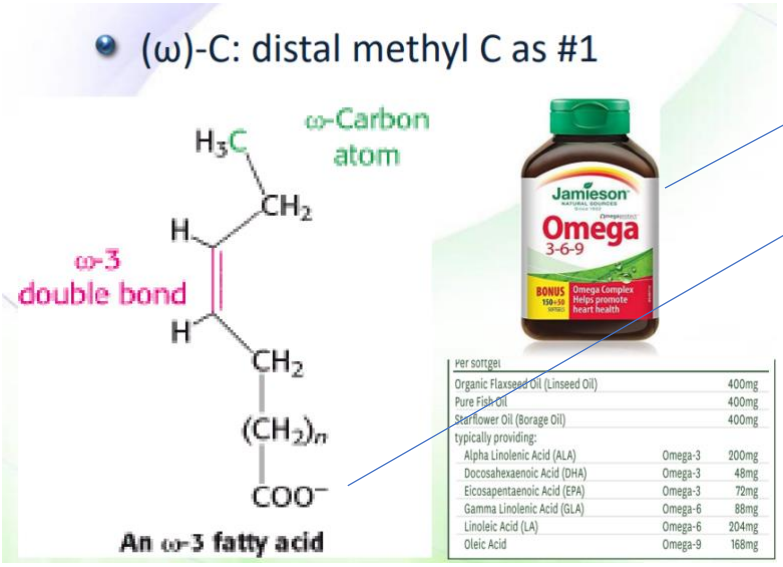
Least important

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-$\Delta^9,\Delta^{12},\Delta^{15}$-Octadecatrienoate	$CH_3CH_2(CH=CHCH_2)_3(CH_2)_6COO^-$
20	4	Arachidonate	all-cis-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-Eicosatetraenoate	$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2COO^-$

-The first 3 columns (from the left) are for memorization, and consequently you'll be able to know the last 2 columns.Also, notice that all of them are cis.The systematic name written as (-ate) instead of (-oic) . It's in the ionized form due to the low pKa in comparison with the

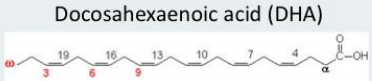
environment(that is basic), so the more abundant state is the deprotonated state (coo-).





Essential for the CNS

Start (carbon 1) but when we deal with omega Ω we start from the opposite side. Ω doesn't give an info about the degree of unsaturation. It's about where the first double bond appears and molecules with Ω3 for example have similar functions.

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 acid: Eicosanoids

→ they are made of fatty acids (Arachidonic Acid) act as inflammatory mediators.

What is the other difference between inflammation and infection?

→ infection includes Microorganisms (bacteria, virus, ...)

→ inflammation doesn't require Microorganisms to happen (for example in Fractures)

Inflammatory changes: (The signs of inflammation)

1- redness and heat (because of the increase in blood supply)

2- swelling (increasing the permeability of Blood Vessels) → Extravasation: Excretion of molecules (Mediators, White blood cells) and fluids from the blood into the inflammation site to mediate some of the reactions and changes that occur during inflammation → causing edema

3- pain (Excretion of pain mediators that stimulate the nerve endings)

Mediator: some molecules that are excreted from the blood into the inflammation site to make these changes.

Effects mediated by Inflammatory Mediators:

- increase the permeability of BV

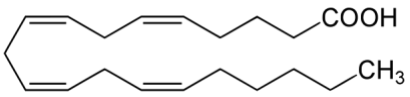
- mediate pain

- relaxation of the smooth muscles in BV (vasodilation) or constriction the smooth muscles in any region not only in BV.

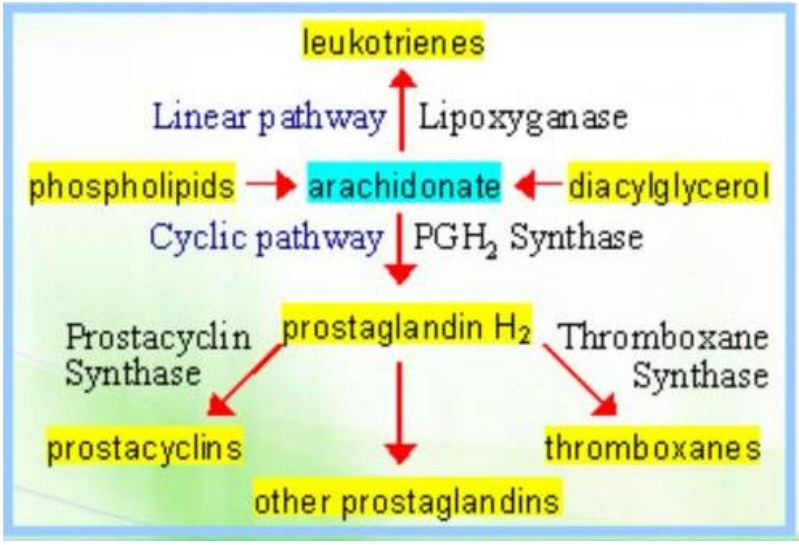
- it can affect the platelet aggregation (عملية تجمع الصفائح في موقع الجرح) which is a preparation of blood clotting.

إن الشتاءَ حبيبٌ كلّه نِعَم....
يا باغي الصيف فلتخرج وتلتهبِ....

- Arachidonic acid



- All cis-Δ^5 ,Δ^8 ,Δ^{11} ,Δ^{14}- eicosatetraenoate, $CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2COO$-



As you can see in the picture, Eicosanoids are derivatives of arachidonate. They separate from phospholipids or diacylglycerols.

بنقصه منهم و بنستخدمه عشان نصنع أنواع كتيرة من ال Eicosanoids .

→ some of them undergo the CYCLIC PATHWAY (formation of a cycle among its structure):

1- prostaglandins

2- prostacyclins

3- Thromboxanes

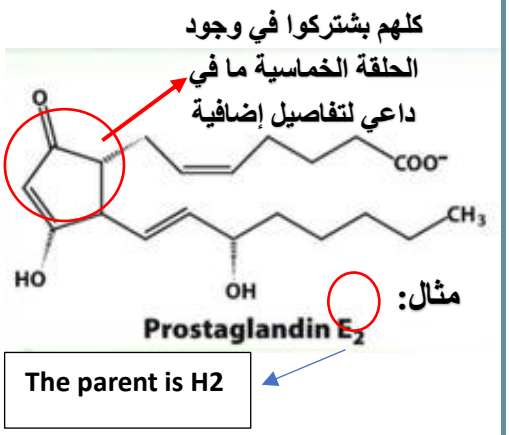
→ others undergo the LINEAR PATHWAY (without cycles):

1- leucotrienes

Eicosanoids and their functions

They control cellular functions in response to injury

(Dr.Mamoun said that you don't have to memorize all of the mentioned functions 👇, just know that all of them control cellular functions in response to injury)



- Prostaglandins

they first discovered them in prostate cells, then they found them in many other cells but there name remained as it is.

Function:

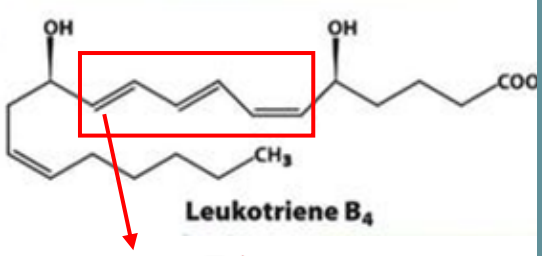
- induction of inflammation
- inhibition of platelet aggregation

when an injury (whether it was small or big) occurs it will cause bleeding which may lead to the death of the patient , why? Because the patient loses a lot of blood leading to a Hypovolemic shock (shock as a result of a decrease in blood volume).The body's response is the formation of the wound. Platelet aggregation is the first step in blood clotting and it's fast, they stick to the injury site and close it. Tissue repair and healing are permanent steps that occur afterwards.

- inhibition of blood clotting

- Leukotrienes

they discovered them first in leukocytes (white blood cells), then they found them in many cells but the name also remained the same.



Leukotriene B_4

leukoTriene: 3 conjugated double bonds كلهم بشتركوا في

- constriction of smooth muscles

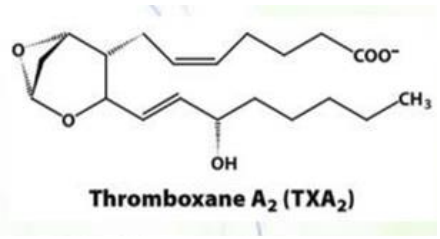
(Especially in Airways)

- Asthma **They are highly synthesized in Asthma patients, that's why Asthma occurs**

One treatment for asthma is leukotrienes blockers (inhibition of the synthesis of leukotrienes and relaxation of the smooth muscles in the airways thus widening them).

- Thromboxanes (cyclic pathway)

Include Cyclic Ether(ROR) in their structures.



Thromboxane A_2 (TXA_2)

- constriction of smooth muscles

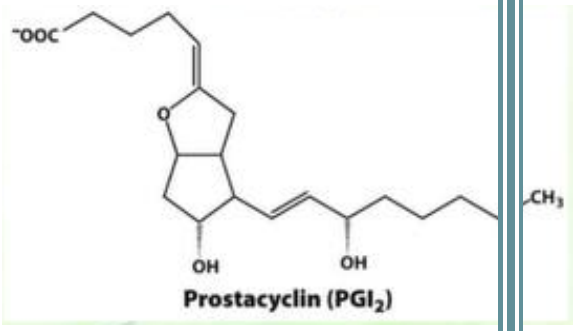
(Especially in Blood Vessels)

- induction pf platelet aggregation

(Opposite to Prostaglandins)

- Prostacyclins (cyclic pathway)

Include cycles.



Prostacyclin (PGI_2)

Function:

- an inhibitor of platelet aggregation

(Same as prostaglandins)

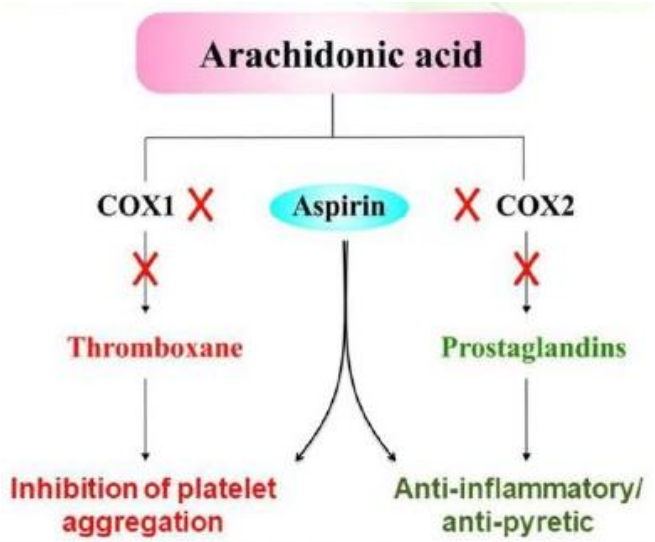
- induction of vasodilation **(relaxation of smooth muscles)**

(Opposite to Thromboxanes)

Different changes during inflammation → need different molecules.

that's why we have different types of molecules with different types of actions.

Aspirin is GOOD



COX: Cyclooxygenase

Aspirin= مميع

- in the past, they used it for reducing pain and decreasing fever for children, but it has side effects.

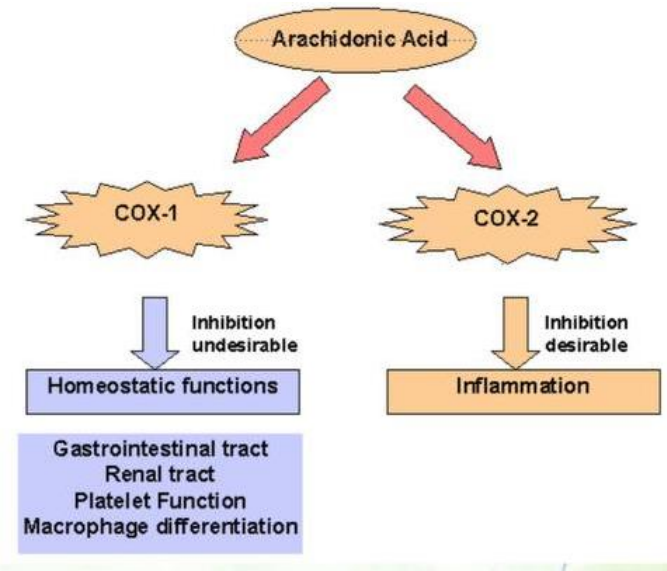
- nowadays they are giving this drug to the elderly as a protective measurement (anticoagulant) for patients with hyper-viscous blood to make blood less sticky and stop blood clots developing .

Targets of Aspirin

- Cyclooxygenase is present in three forms in cells, COX-1, COX-2, COX-3

-Aspirin targets both, but COX-2 should only be the target.

The problem is that COX1 produces these compounds without having an inflammatory necessity (so it affects normal physiological functions in the GI tract, Kidneys etc.)



- **Aspirin inhibits both(COX-1 and COX-2) without recognizing the inflammation. So, aspirin has deprived the body from the COX-1's normal(positive) function.**

So, we need drugs that specifically inhibit COX2 without COX1… for example:

Celebrex

A new generation drug, Celebrex, targets COX2 (to inhibit it), but is prescribed with a strong warning of side effects on the label.

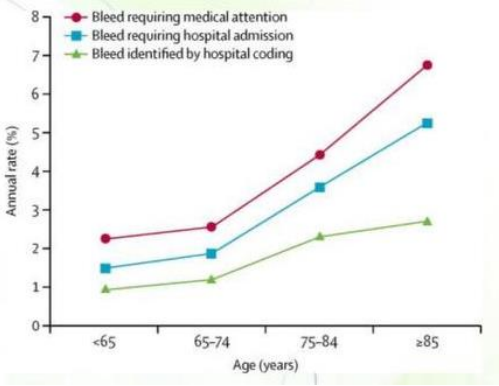
So we don't prescribe this drug very often because of the side effects on the cardiovascular system, so not everyone can take it.

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**).

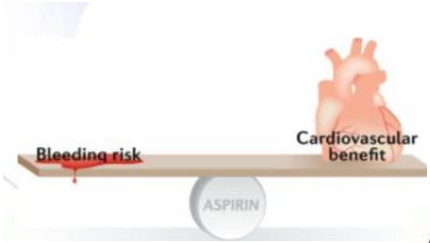
Aspirin is bad

cardiovascular disease vs. bleeding



- Aspirin also cause excessive bleeding among the elderly

As we get older, the viscosity of the blood changes so it becomes more possible to have blood clots and aspirin reduces these effects.But, unfortunately it's linked to some side effects like highly bleeding when a wound occurs.



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

THE END OF SHEET 9

سبحانك اللهم وبحمدك ، أشهد أنا لا إلـه إلا أنت ، أستغفرك وأتوب إليك